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Научно-образовательного и Инновационного центра химико-фармацевтических технологий

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САНТРА СОГАТА

ПРЯМОЕ C-C(X)-СОЧЕТАНИЕ ПРИ АКТИВИРОВАННОЙ СВЯЗИ CHC(Y) В ГЕТЕРО-/КАРБОЦИКЛАХ КАК ИНСТРУМЕНТ ЗЕЛЕНОЙ ХИМИИ ДЛЯ СОЗДАНИЯ ПЕРСПЕКТИВНЫХ БИОЛОГИЧЕСКИ АКТИВНЫХ МОЛЕКУЛ

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Екатеринбург
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SANTRA SOUGATA

DIRECT C-C(X)-COUPLING AT AN ACTIVATED CHC(Y) BOND IN HETERO-/CARBOCYCLES AS A GREEN CHEMISTRY TOOL FOR THE CREATION OF PROMISING BIOLOGICALLY ACTIVE MOLECULES

1.4.3. Organic Chemistry

Thesis for an academic degree
doctor of chemical sciences

Scientific supervisor:
doctor of chemical sciences
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CONTENT

INTRODUCTION

Relevance of the topic. The formation of C-C bonds is fundamental for organic chemistry, as it underlies the processes of constructing carbon frameworks of various classes of organic compounds. The development of modern approaches to organic synthesis has led to the emergence of such methods for the formation of C-C(X) (X = heteroatom) bonds as metal-catalyzed (Pd, Cu, Ni, etc.) cross-coupling reactions of pre-functionalized organic molecules, metal-catalyzed (Pt, Rh, Au, etc.) cross-coupling processes with an activated C-H bond, which have been widely developed in the last 15 years, processes of oxidative cross-coupling with a C-H bond (cross dehydrogenative coupling (CDC)), and also studied for about half a century at the Department of Organic (and Biomolecular) Chemistry of the UrFU and at the Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences under the leadership of Academicians of the RAS O. N. Chupakhin and V. N. Charushin reactions of direct nucleophilic substitution of hydrogen (S_N^H), which is reflected in a huge number of research and review articles, as well as monographs. The advantage of direct C–H functionalization reactions is not only their atom-efficiency (as well as reactor- and stage-efficiency), but also the possibility of using such processes for retro-synthetic analysis, especially using green chemistry approaches.

In the last two decades, along with the term PASE (Pot, Atom, Step Economy), the terms “green” and “sustainable” chemistry are key in search queries. As a rule, these terms mean a more rational organic synthesis, carried out in more gentle/environmentally friendly conditions, with minimal or no destructive impact on the environment, which is determined by lower values of *E*-factors (*E*-factor - environmental factor, ratio mass of waste to mass of products) reactions. It is known that in traditional organic reactions, most of the waste is formed due to chemical transformations of the starting reagents, as well as due to the use of solvents, in most cases, chlorine-containing or aromatic. Therefore, from the view point of “green chemistry” and rational synthesis, reactions in the absence of solvents are more preferable than those in any solvents, even more environmentally friendly ones. Also, chemical transformations carried out in a single reaction flask, including multi-step processes, can be useful for synthetic organic chemistry in the context of minimizing waste, reducing reaction time and simplifying the practical aspects associated with the isolation of products/intermediates at each step. Finally, the application of more environmentally friendly chemical methodologies to traditional organic synthesis protocols, for example, the replacement of some traditional toxic reagents with their more environmentally friendly synthetic equivalents, the use of alternative, more environmentally friendly ways to carry out and/or activate chemical reactions, such as the use of reaction media based on water, ionic liquids or supercritical fluids, processes under microwave heating, sono-, mechanical or

photoactivation, and catalysis of reactions using heterogeneous/solid-phase catalysts (e.g. metal nanoparticles, metal chalcogenides/oxides, metals on inert supports, etc.), as well as bioavailable/biodegradable catalysts, create extensive prospects for the dynamic development of the basic principles and techniques of rational synthesis/green chemistry, applicable both to laboratory, and to industrial processes.

Thus, the development of "green"/rational methods for the synthesis of promising molecules based on the processes of C-C and C-X functionalization (X = heteroatom) of the C(H)C/Y bond (Y ≠ C) in the series of hetero- and carbocyclic substrates is relevant.

The degree of development of the research topic.

Research on the development of "green"/rational methods for the synthesis of promising organic molecules has been carried out for more than two decades by scientific groups of Professors B. Ranu, A. Majee, A. Hajra (India). Oxidative cross-coupling reactions have been developed since 2006 in the works of Professor H.-J. Lee (Canada). Work on the development of reactions of direct nucleophilic substitution of hydrogen in (hetero)arenes has been carried out for about 50 years at the Department of Organic (and Biomolecular) Chemistry of the UrFU, as well as at the Institute of Organic Synthesis, UB of the RAS, under the leadership of RAS Academicians O.N. Chupakhin and V.N. Charushin.

The subject of the study is the processes of direct C-C(X)-functionalization at the activated exo- and endocyclic CHC(Y) bonds in aza- and carbocycles.

The objects of study are small heterocycles (azirines, aziridines and epoxides), carbonyl compounds and their derivatives (diketones, aldehydes, Schiff bases), ethylenes, including those with an activated multiple bond, as well as acetylenes.

The aim of the dissertation work is to study the processes of functionalization of the activated bond C(H)C and C(H)Y (Y = heteroatom) and accompanying transformations in the series of hetero- and carbocyclic substrates for the development of "green"/rational methods for obtaining biologically active molecules/known drugs/precursors, as well as important organic synthons that are hard-to-obtain or inaccessible by other methods.

To achieve the goals of the work, the following tasks must be solved:

• To investigate the processes of functionalization of C(H)C and C(H)Y (Y ≠ C) bonds in small sterically strained heterocycles, namely in azi(ri)dines and epoxides;

• To investigate the processes of functionalization of the C(H) fragment at a multiple bond in acyclic substrates;

• To investigate the processes of functionalization of the C(H) fragment at a multiple bond in cyclic substrates;

• To explore the applicability of new non-conventional media, as well as "green" catalysts for carrying out these transformations;

• To assess the reactivity of the studied objects using quantum chemical methods;

• To evaluate the biological activity of the obtained compounds using *in-silico* methods.

Scientific novelty and theoretical significance. During the work, the following results of scientific novelty were obtained:

- For the first time, direct acyloxylation of the C(sp^3)-H fragment in 2-arylazirines (without opening the three-membered ring) under photoactivation conditions was carried out;

- The possibility of regioselective nucleophilic ring opening in aziridines and azirines under activation conditions with ionic liquids and CuO nanoparticles has been demonstrated for the first time;

- Previously not described in the literature, Cu(II)-catalyzed transformation of aziridines and epoxides under the influence of zinc allyl halides generated *in situ* was discovered, with the formation exclusively of *β*-halogen-substituted *N*-Ts-amines or *β*-halo alcohols or their derivatives, and not allylation products;

- Previously undescribed transformation of *N*-Ts-substituted aziridines under the action of Cu(II) or Zn(II) nitrates in a solvent or its absence (in the case of $Zn(NO_3)_2$*$6H_2O$) was found, leading to the formation of *β*-(nitrooxy)-substituted *N*-Ts-amines;

- For the first time, *self*-catalyzed synthesis of *N*-acyl-/*N*-formyl-*α*-aminoketones was demonstrated in the reactions of 3-aryl-2*H*-azirines/2-Me/Ph-3-aryl-2*H*-azirines with formic acid, as well as other organic acids ;

- For the first time, the possibility of *O*-vinylation of the oxygen atom in 4-hydroxycoumarins under the action of terminal acetylenes was demonstrated;

- For the first time, the possibility of obtaining practically and biologically important selenium esters by the reaction of *α*-aminocarbonyl compounds and diselenides was shown;

- Direct oxidative C(sp^2)–H difunctionalization in 1,4-naphthoquinones under the influence of amines and thiols was carried out for the first time.

Practical significance of the work. Using the processes of direct functionalization of the activated C(H)C and C(H)Y (Y = heteroatom) bond and concomitant transformations in the series of hetero-

and carbocyclic substrates, a wide range of biologically active molecules/drugs/precursors, as well as important organic syntons were obtained:

Effective/green methods have been developed for the synthesis of a number of bioactive substances, drugs or their precursors: malatonin, cathinone, zolimidine, coumarins, antithrombotics such as warfarin, *etc*.;

Effective methods have been developed for the synthesis of *β*-haloalcohols and their derivatives, *β*-functionalized amines and their derivatives of the composition XCCNRR′ (R = H, CH_2OH, R′ = Acyl, Ts; X = (Het)Ar, NHR″, Hal, =O, OR‴ (R‴ = Ac, Alk), ONO_2, SR⁗ (R⁗ = Alk, Ar)), as well as *α*-aminoketones, the latter ones were used as an example to demonstrate the possibility of obtaining potentially bioactive selenoethers that are inaccessible by other methods;

Effective methods for the synthesis of *α,β*-difunctionalized alkanes have been developed; the possibility of obtaining substituted 1,3-dioxolanes and enantiomerically pure substituted 1,4-dioxanes has been demonstrated using the example of ethylene glycol derivatives;

Using the processes of addition of the activated C(H)C and C(H)Y (Y = heteroatom) bond and accompanying transformations in the series of hetero- and carbocyclic substrates, a wide range of compounds with postulated biological activity have been synthesized: substituted oxa- and imidazoles and their annulated derivatives (aza)quinolines and their annelated derivatives, substituted 4-hydroxycoumarins and their annelated derivatives (pyrano[3,2-*c*]coumarins), thioamino-substituted naphthoquinones, as well as derivatives of 2,2'-dipyrromethanes and 3-substituted indoles, including 3,3'-bisindolylmethanes;

Green methods of activation (photo-, mechanical-, activation by metal nanoparticles, activation by ionic liquids, molten salts, etc.) of addition reactions *via* the (non)activated C(H)C/Y bond (Y ≠ C) have been developed and successfully implemented in hetero- and carbocycles, as well as acyclic derivatives. And the reactions are characterized by low values of *E*-factors, reactions take place in the absence of a solvent, and require minimal purification of the products (usually without the use of chromatography).

In general, the results of the dissertation work are of interest for the development of “green”/rational synthetic laboratory and industrial methods for the production of practically valuable molecules: organic synthons, bioactive compounds, as well as potential ligands and fluorophores.

Compliance with the passport of the scientific specialty. The dissertation corresponds to the passport of the scientific specialty 1.4.3. Organic chemistry (chemical sciences) in paragraphs: paragraph 1. “Isolation and purification of new compounds”, paragraph 3. “Development of

rational ways of synthesizing complex molecules", paragraph 7. "Identification of patterns of the "structure-property" type.

The methodology and methods of the dissertation research consist of a systematic study of the processes of functionalization of the C(H)C and C(H)Y bond (Y = heteroatom) and accompanying transformations in the series of hetero- and carbocyclic substrates under the influence of electrophilic and nucleophilic reagents. All obtained products were isolated in pure form and characterized using modern instrumental methods. The starting compounds were prepared according to previously described methods, which were improved or optimized where necessary.

Degree of reliability of the results. The reliability of the methods for the synthesis of new compounds is confirmed by the repeated reproducibility of these syntheses, carried out both by the author and his colleagues. The correct establishment of the structure of the compounds described in this work is confirmed by a complex of physicochemical methods of analysis, such as ^{1}H and ^{13}C NMR and IR spectroscopy, mass spectroscopy, electron microscopy, elemental analysis, and X-ray diffraction analysis.

Provisions submitted for defense:

• Study of the processes of functionalization of C(H)C and C(H)Y (Y ≠ C) bonds in aziridines, azirines and epoxides;

• Study of the processes of functionalization of the C(H) fragment at a multiple bond in acyclic substrates (chalcones, aldehydes, azomethines, alkenes and alkynes);

• Study of the processes of functionalization of the C(H) fragment at a multiple bond in some cyclic substrates (quinones and coumarins);

• Research on the applicability of new non-conventional media, as well as "green" catalysts for carrying out these transformations;

• Comparison of the reactivity of the studied substrates using quantum chemical methods;

• Assessment of the biological activity of the obtained compounds using molecular docking and *in silico* modeling methods.

Approbation of work. The main results of the dissertation work were reported and discussed at the following conferences: III International Scientific Conference "Chemistry in Federal Universities" (Ekaterinburg, 2015), I-V International Conferences "Modern synthetic methodologies for the creation of drugs and functional materials" MOSM 2017-2021 (Ekaterinburg, 2017-2020, Ekaterinburg-Perm, 2021), V All-Russian Conference with international participation on organic chemistry (Vladikavkaz, 2018), 16th CRSI National

Symposium in Chemistry" (Mumbai, India, 2014), National Seminar on "Recent advances in chemistry" (NSRAC 2014) (Santiniketan, India, 2014), International Congress on Heterocyclic Chemistry "KOST-2015" (Moscow, 2015), IV Sino-Russian ASRTU Symposium on Advanced Materials and Processing Technology (Ekaterinburg, 2015), XX Mendeleev Congress on General and Applied Chemistry (Ekaterinburg, 2016), National Seminar on Recent Trends in Chemistry Research (Santiniketan, India, 2017), IV International Young Researchers "Conference Physics, Technologies, Innovation PTI-2017" (Ekaterinburg, 2017), Lecture Workshop on Recent Trends in Interdisciplinary Sciences (Santiniketan, India, 2018), 4th All-Russian Conference on Medicinal Chemistry (Ekaterinburg, 2019), International Conference "Current Problems of Organic Chemistry and Biotechnology" (Ekaterinburg, 2020).

Publications. The main results of the dissertation work are presented in 60 publications, including 27 conference abstracts and 33 articles published in peer-reviewed scientific journals and editions defined by the Higher Attestation Commission of the Russian Federation and the Certification Council of UrFU and indexed in international citation databases such as Scopus.

Structure and scope of the dissertation. The dissertation is presented on 505 pages, contains 88 tables, 414 schemes, 28 figures, 404 bibliographic references. The work consists of an introduction, a literature review (Chapter 1), a discussion of the results (Chapter 2), an experimental part (Chapter 3), a conclusion, a list of symbols and abbreviations, and a list of references.

Personal contribution of the author. The author's contribution consisted of selecting areas of research, determining the goals and objectives of the study, systematizing literature data, planning and conducting experiments, analyzing, interpreting and summarizing the results, and preparing materials for publication. The experimental part of the work was carried out by the author together with employees of the Department of Organic and Biomolecular Chemistry of the UrFU, as well as the Laboratory of Organic Synthesis and the Laboratory of Advanced Materials, Green Methods and Biotechnologies of SE&ICCPT of CEI of the UrFU. Part of the research devoted to the synthesis and study of chemical transformations of aziri(di)nes, as well as the use of ionic liquids, was carried out jointly with members of the laboratory of Prof. A. Majee (Visva-Bharati University, India).

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CHAPTER 1. LITERATURE REVIEW: STUDY OF THE FUNCTIONALIZATION PROCESSES OF C(H)C AND C(H)Y (Y ≠ C) IN HETERO- AND CARBOCYCLES.

As part of this dissertation, we examined the reactivity of aziridines, azirines, epoxides, as well as aldehydes, imines and derivatives of substituted ethylenes. The last three are the most typical precursors, as well as transformation products of the above-mentioned three-membered heterocycles (Figure 1.1). In the frame of current literature review, the most representative examples of the reactions of functionalization processes of C(H)C and C(H)Y (Y ≠ C) in hetero- and carbocycles will be highlighted.

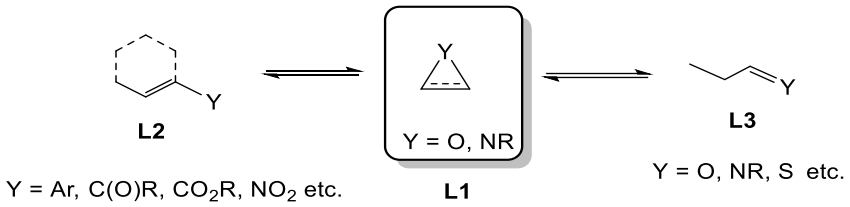


Figure 1.1

1.1. STUDY OF THE FUNCTIONALIZATION OF C(H)C AND C(H)CY (Y ≠ C) BONDS IN AZIRIDINES, AZIRINES AND EPOXIDES

Due to the high ring tension, three-membered heterocycles (for example, aziridines, azirines and epoxides) tend to undergo ring opening reactions under the influence of nucleophilic reagents, and the selectivity of the process is determined by the reaction conditions and the nature of the reagents.

1.1.1. Aziridine ring opening

Aziridine, a three-membered, nitrogen-containing heterocyclic ring is considered as a versatile building block in contemporary synthetic chemistry [1]. In the early days, synthesis of the aziridines was considered as a challenging exertion because of their high reactivity and instability. Owning to the ring strain and the electronegativity of nitrogen atom, aziridines, the smallest *N*-heterocyclic compounds, exhibit intriguing and diverse reactivity, and thus become unique and versatile synthons in many organic transformations. Chemistry based on ring opening of aziridines has been used for an impressive range of synthetic applications. This smallest aza-heterocycles are well known for their tremendous potential in the design of organic synthesis and medicinal chemistry [2,3]. The strained ring structure of aziridines (**L4**) makes them highly reactive towards ring opening. As a consequence, a number of methods are also available to open up the aziridine ring. Thus, under the action of nucleophiles the attack may occur at the unsubstituted (path a) or at the substituted (path b) aziridine carbon atom, leading either to *α*-

branched amines (**L6**, path a) or to *β*-branched amines (**L7**, path b). In addition, nitrogen atom is subjected to quaternization under the action of Lewis or Bronsted acids or silylating, acylating or alkylating agents (Figure 1.2)

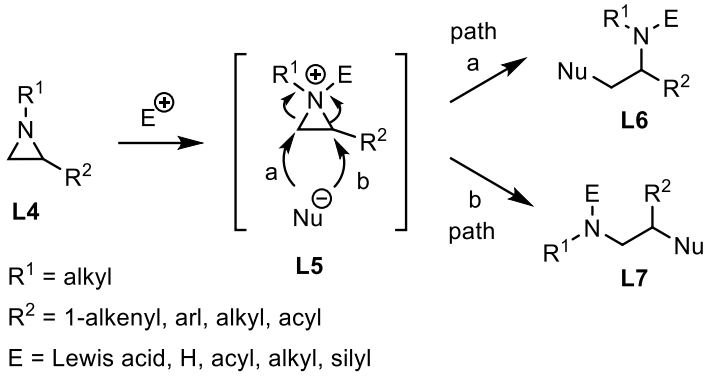
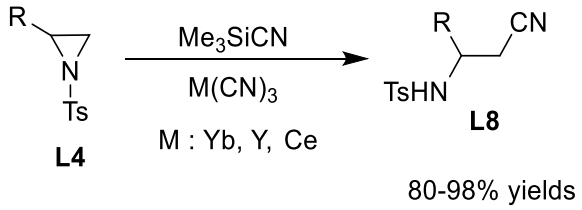


Figure 1.2

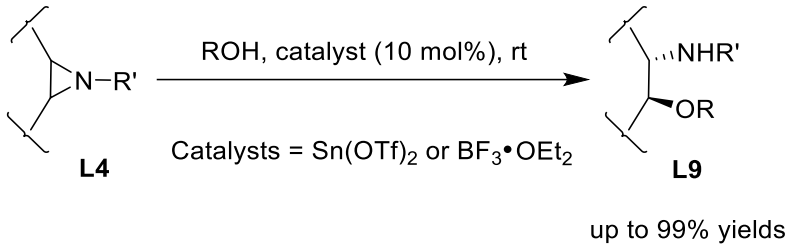
In 1990, Utimoto and co-workers developed that the reaction of *N*-tosylaziridine (**L4**) with cyanotrimethylsilane in the presence of lanthanoid tricyanide catalyst gives *N*-tosyl *β*-aminonitrile (**L8**) in 80-98% yields (Scheme 1.1) [4].



Scheme 1.1

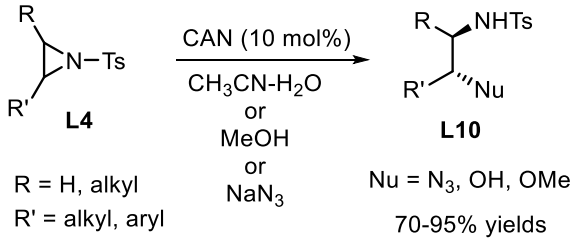
The ring opening product was obtained by selective attack of cyanide at less substituted carbon of the aziridine ring. In this regard the authors have also claimed that optically pure 2-substituted aziridine afforded the corresponding aminonitrile with perfect retention of the stereochemistry of stereogenic center.

A several years later in 2000, Prasad, Sekar and Singh reported [5] an efficient method for the cleavage of aziridines using hydroxyl compounds (Scheme 1.2). They have experimented the cleavage of a variety of aziridines with water, primary, allylic, and propargyl alcohols at room temperature in the presence of a catalytic amount of $Sn(OTf)_2$ or $BF_3{\cdot}OEt_2$. Though the reaction was performed with a variety of alcohols, but the main drawback of this method is that secondary and tertiary alcohols failed to open aziridines under the above conditions. The products (**L9**) were obtain in up to 99% yields. It was also observed that *N*-alkyl substituted azirdines could not be opened with any of these Lewis acids.



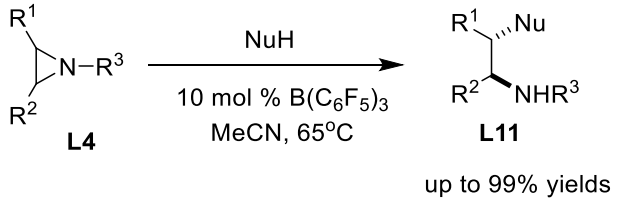
Scheme 1.2

In 2002, Chandrasekhar *et al.* reported a mild protocol for ring cleavage of *N*-tosyl aziridines (**L4**) catalyzed by ceric ammonium nitrate (CAN) [6]. They described that a wide range of *N*-tosylaziridines was cleaved with various nucleophiles like NaN_3, H_2O, MeOH to synthesize corresponding *vicinal* azidoamines, aminoalcohols and aminoethers (**L10**) in good to excellent yields (70-95%) (Scheme 1.3).



Scheme 1.3

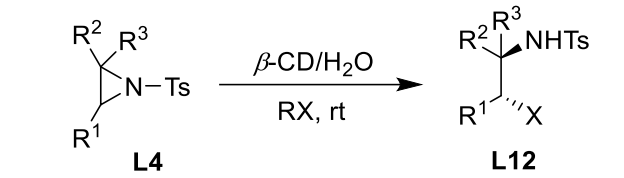
Again, in the next year, a new process for the ring opening of nonactivated aziridines was developed by Watson and Yudin [7] in presence of catalytic amounts of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] in acetonitrile (Scheme 1.4). The reaction proceeded with a variety of amines without any special precautions to exclude water, resulting in the formation of functionalized *trans*-diamines (**L11**) in high yields (up to 99%). They proposed that *in situ* formed [$(C_6F_5)_3B(OH_2)$] H_2O was the catalyst promoting the reaction through a Brønsted acid manifold.



Scheme 1.4

In 2004, Rao and coworkers demonstrated a novel and efficient protocol (Scheme 1.5) for regioselective ring opening of aziridines [8]. They converted only a few cyclic and aryl substituted aziridines to its corresponding *β*-halo amines (**L12**) with easily accessible hydrogen halides using

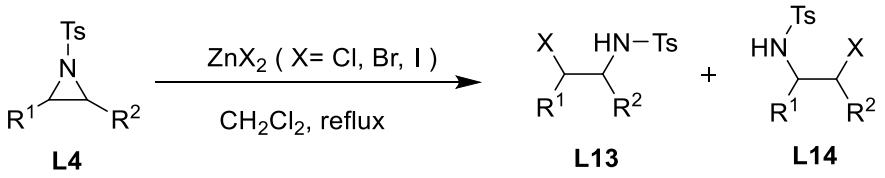
β-cyclodextrin as a catalyst and water as the solvent. Here it should be mentioned that the reaction did not take place in the absence of β-cyclodextrin.



R = H,Li; X = Cl, Br, I
a: R^1, R^2 = $(-CH_2-)_n$ R^3 = H, n = 3,4
b: R^1 = Ph, R^2 = R^3 = H

Scheme 1.5

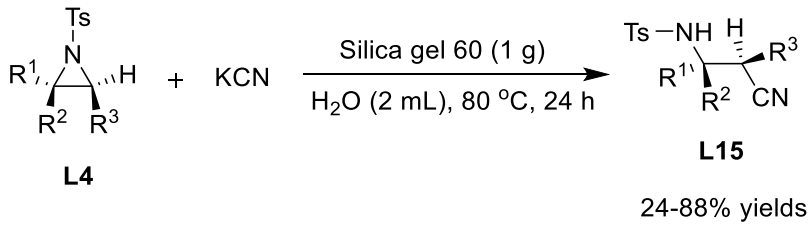
In 2005, Ghorai *et al*. reported another efficient route for highly regio- and stereoselective ring opening of *N*-tosylaziridines to give β-halo amines (**L13,14**) using readily available Zn(II) halides in dichloromethane (Scheme 1.6) [9]. Depending on the solvent and Zn(II) halide, β-halo amines were obtained selectively in up to 88% yields. It is worth mentioning that the reaction of *N*-tosyl-2-phenylaziridine with ZnX_2 was very sensitive to the nature of the solvent used. Thus, in acetonitrile β-chloro- or iodo- amines were isolated as the only products when $ZnCl_2$ or ZnI_2 was used. Surprisingly, the reaction of aziridine with $ZnBr_2$ did not afford the target products.



a : R^1 = Ph, R^2 = H; b : R^1 , R^2 = $-(CH_2)_4-$
c : R^1 = Ph, R^2 = $CH_2OTBDMS$; d : R^1 = CH_2Ph, R^2 = H

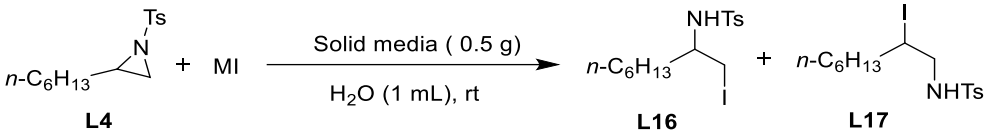
Scheme 1.6

Minakata and Komatsu group developed a unique ring opening reaction [10] between *N*-tosylaziridines and water-soluble nucleophile, such as KCN, in water in the presence of Silica Gel 60. As a result, β-cyano-Ts-amines (**L15**) were obtaines in up to 88% yields (Scheme 1.7).



Scheme 1.7

Also, the same authors performed the ring opening of a certain aziridine with a variety of metal halides (Scheme 1.8) to afford the corresponding ring opening products (**L16-17**). Among the different metal halides, the ring opening reaction did not proceed at all with metal chlorides and bromides, even in the presence of silica, while some metal iodides were found to result in ring opening products under these conditions.



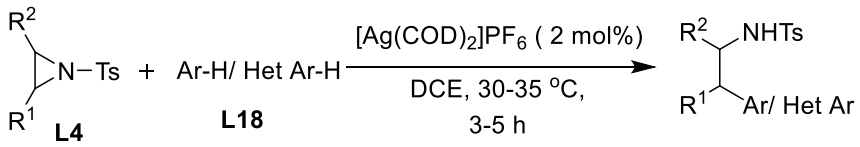
L4 **L16** **L17**

MI = LiI, NaI, KI, CuI, ZnI_2

MI (equiv.)	Time (h)	Yields (%)	
		L16	**L17**
LiI (5)	24	7	15
NaI (5)	24	14	15
KI (5)	24	27	0
CuI (5)	24	0	0
ZnI_2 (2.5)	24	67	6
ZnI_2 (2.5)	48	90	6

Scheme 1.8

Four years later in 2010, Bera and Roy pointed out silver(I)-diene complexes as versatile catalysts for the *C*-arylation of *N*-tosylaziridines (Scheme 1.9) [11]. They revealed that the silver(I) complex $[Ag(diene)_2]^+Y^-$ (where diene = cyclooctadiene, norbornadiene and 1,3-cyclohexadiene; $Y^- = PF_6^-, BF_4^-$) efficiently catalyzed the arylation of *N*-tosylaziridines with arenes and heteroarenes (**L18**) under ambient condition to provide the corresponding *β*-aryl amine derivatives (**L19**) with excellent regioselectivity with good yields (75-85%). In this respect they presented a descriptive mechanistic study of their work to understand the nature of substrate activation and initial bond breaking/making steps. There were some drawbacks also. However, for ring-activated arenes, reactions were complete within shorter reaction times, and product yields were very good, but in contrast, benzene and ring-deactivated arenes were inactive in this reaction condition. In addition, the attempted arylation with aziridine bearing an alkyl substituent such as *N*-tosyl-2-hexylaziridine and *N*-benzyl-2-phenylaziridine failed to make the expected transformation.



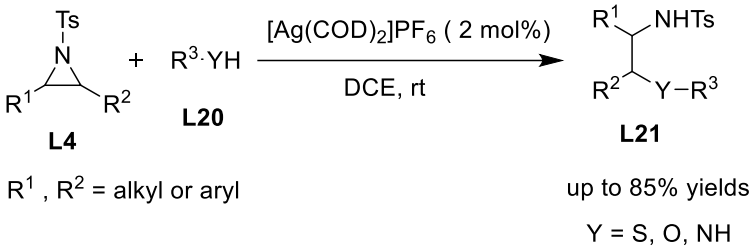
L4 **L18** **L19**

$R^1 = C_6H_5$, 4-ClC_6H_4, 4-MeC_6H_4
R^2 = H, C_6H_5

75-85% yields

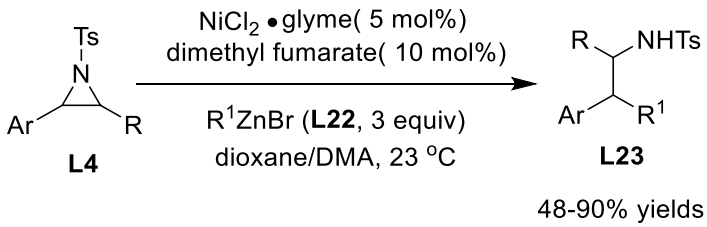
Scheme 1.9

Again in 2011, Bera *et al.* reported another Ag(I) catalyzed ring opening reaction of *N*-tosylaziridines with a variety of *N-, O-,* and *S*-nucleophiles (**L20**) with yields of products (**L21**) up to 85% . They demonstrated that $[Ag(COD)_2]PF_6$ effectively catalyzed the nucleophilic ring opening of *N*-tosylaziridines with various alcohols, amines and thiols (Scheme 1.10) [12]. In this regard here it must be mentioned that, cyclohexyl-*N*-tosylaziridine did not react with aliphatic or aromatic amines even after increasing the catalyst loading and temperature. Also, the authors attempted reaction of *N*-benzyl-2-phenylaziridine and ethanol to give an unidentified complex mixture, while the desired coupling product was not observed.



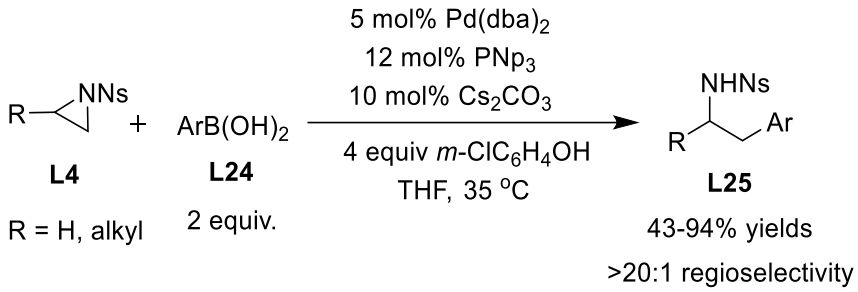
Scheme 1.10

Doyle and group developed a Ni-catalyzed ring opening reaction between *N*-sulfonyl aziridines and a broad range of organozinc reagents (**L22**) (Scheme 1.11) [13]. This method afforded *β*-substituted amines (**L23**) with complete regioselectivity and unconventional diastereoselectivity. The authors have exposed the scope of this protocol with only aromatic aziridines, not for any aliphatic aziridine, which was a major drawback of this protocol.



Scheme 1.11

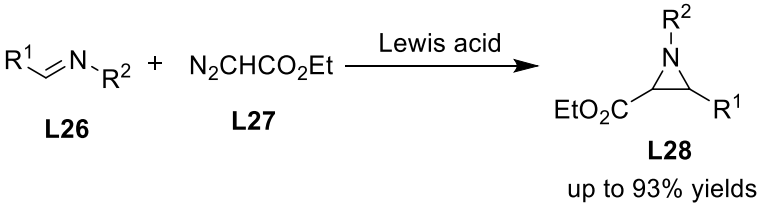
In 2013, Duda and Michael reported another metal catalyzed cross-coupling protocol [14]. Thus, they developed a new palladium-catalyzed procedure for coupling of unsubstituted or 2-alkyl-substituted *N*-tosylaziridines with arylboronic acid (**L24**) (Scheme 1.12). As a result *β*-phenethylamines (**L25**) were obtained in up to 94% yields, and the ring opening reaction was highly regioselective. It must be mentioned that the attempted coupling of alkylboronic acids under these conditions did not give the desired product and also the present conditions did not appear to be applicable to 2,2-disubstituted and 2,3-disubstituted aziridines.



Scheme 1.12

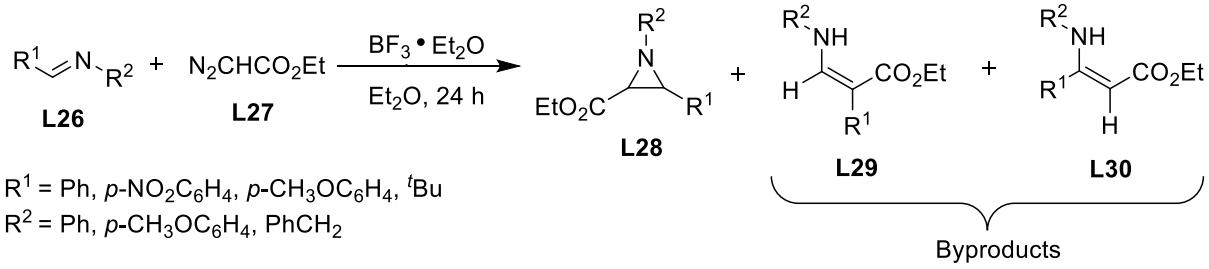
1.1.2. Synthesis of aziridines

There are numerous synthetic routes available for the preparation of aziridines. So, our aim is to highlight some important procedures related to the synthesis of aziridines to get a basic idea about the aziridination. In 1996, Brookhard, Templeton and group reported a convenient synthesis of aziridines (**L28**) from various imines (**L26**) and ethyl diazoacetate (**L27**) catalyzed by readily available Lewis acids (Scheme 1.13) [15].



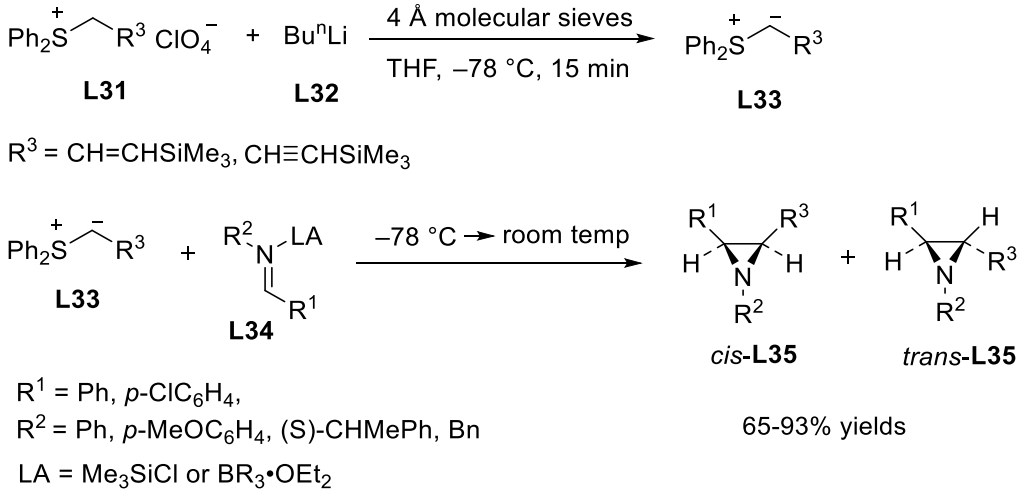
Scheme 1.13

The authors experimented the reaction of an ethereal solution of an imine with variable amounts of $BF_3{\cdot}Et_2O$ in presence of 1.0 equiv. of ethyl diazoacetate (**L27**, EDA) to form the aziridines (**L28**) successfully (up to 93% yields). However, they have also isolated some byproducts (**L29,30**) along with the aziridines (Scheme 1.14) which is one of the main disadvantages of this work. To minimize the formation of these byproducts different solvents were tested and finally they got better result using hexane as a solvent where the aziridine formed as a major product with the formation of the by-products with a very little amount.



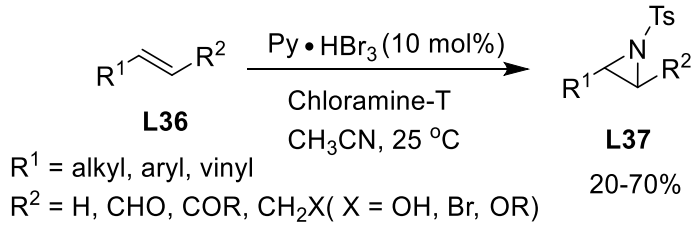
Scheme 1.14

Hou demonstrated another efficient method for the preparation of various α-unsaturated substituted aziridines (**L35**) from *N*-alkyl and *N*-aryl imines and semistabilized prop-2-ynylic and allylic sulfonium ylides in the presence of $BF_3{\cdot}OEt_2$ with high *cis*-selectivity with good yields (65-93%) (Scheme 1.15) [16]. They examined $BF_3{\cdot}OEt_2$ and Me_3SiCl for the activation of imines in the ylide reaction for the preparation of vinyl- and ethynyl-aziridines. Here the major drawback for this aziridination was that either *N*-aryl or *N*-alkyl aldimines, could be aziridinated with satisfactory yield, but the aziridination failed when aliphatic aldimines were used as substrates.



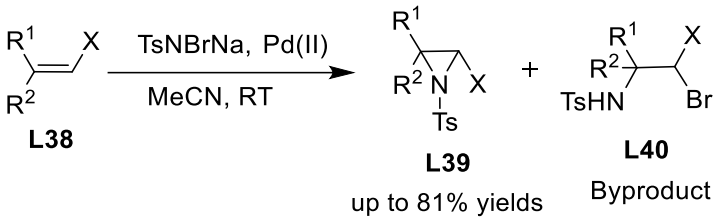
Scheme 1.15

Two years later in 1999, Sudalai *et al.* reported an another method [17] for aziridination of electron-deficient as well as electron-rich olefins (**L36**) using Chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as a nitrogen source to afford the corresponding aziridines (**L37**) in good to moderate yields (20-70%) (Scheme 1.16). Here they used pyridinium hydrobromide perbromide ($Py{\cdot}HBr_3$) as a versatile catalyst to successfully carry out the aziridination. Here it should be noted that when styrene, cyclohexene, and cyclooctene were employed, the corresponding aziridines were obtained in good yields whereas terminal aliphatic olefins such as 1-hexene, 1-dodecene, and a variety of allylic alcohols gave only a moderate yield of aziridinated products.



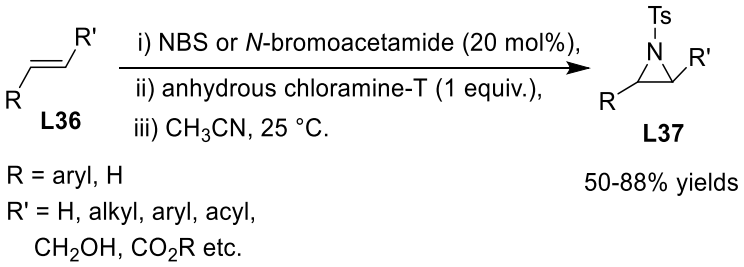
Scheme 1.16

Again, after two years in 2001, Branco and Prabhakar group reported a novel $PdCl_2$-assisted aziridination of a variety of olefins (**L38**) in the presence of bromamine-T, as a nitrogen transfer reagent (Scheme 1.17) [18]. Here it was worthy to mention that in the absence of $PdCl_2$ no significant aziridination takes place which also indicates the positive involvement of the palladium reagent in the aziridine formation reaction. The authors have synthesized aziridines in a good to moderate yield (up to 81% yields) and for some cases they have got bromosulfonamides (**L40**) as by-products.



Scheme 1.17

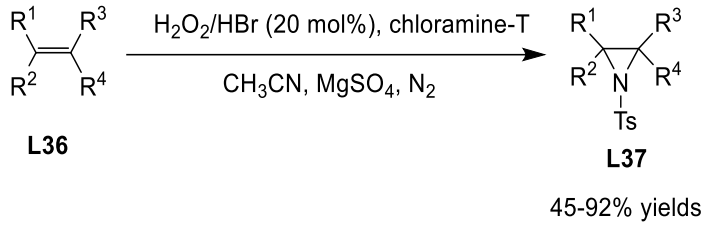
Next in 2003, Thakur and Sudalai described another interesting method for the synthesis of aziridines. They have used *N*-bromoamides as versatile catalysts for aziridination of olefins, and this reagent very effectively catalysed the aziridination of a variety of electron-deficient as well as electron-rich olefins (**L36**) in the presence of chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as a nitrogen source under ambient conditions to afford the corresponding aziridines (**L37**) in good to excellent yields (50-88%) (Scheme 1.18) [19]. This aziridination process seemed to be quite general for a variety of aromatic and aliphatic olefins. However, methyl cinnamate and acrylamide failed to give aziridines under these conditions.



Scheme 1.18

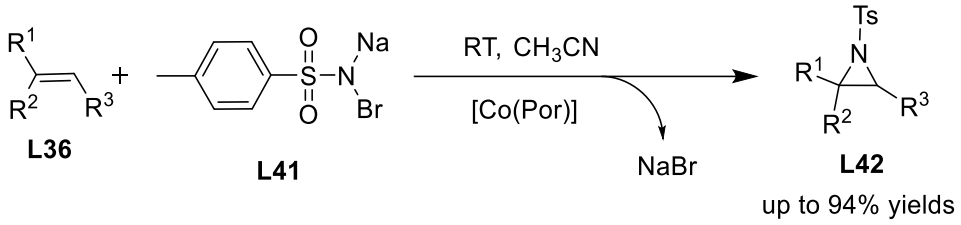
In the next year, Jain, Sharma and Sain reported a transition metal-free approach for the aziridination of alkenes with chloramine-T using the combination of aqueous H_2O_2 and HBr. They successfully converted a variety of alkenes (**L36**) to their corresponding aziridines (**L37**) in very good yields (up to 92%) using chloramine-T and aqueous H_2O_2/HBr (20 mol%) as catalyst in acetonitrile at room temperature, in the presence of $MgSO_4$ as a water-trapping agent under a nitrogen atmosphere (Scheme 1.19) [20]. Relevantly, here it must be mentioned that the presence

of $MgSO_4$ as a water-trapping agent was found to be essential for this reaction as in its absence, aziridines were obtained in lower yields.



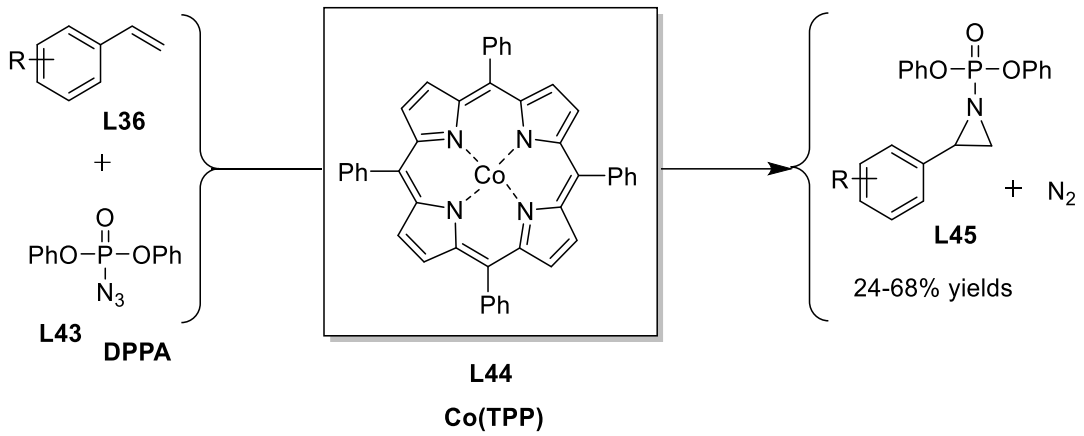
Scheme 1.19

Again in 2005, Zhang *et al.* developed a Co-catalyzed aziridination of various alkenes (Scheme 1.20) [21]. They demonstrated that the Co(Por)/ bromamine-T catalytic system can be effectively aziridinate a wide variety of alkenes (**L36**). The catalytic system can operate at room temperature. The aziridination occurred in a one-pot fashion with alkenes as limiting reagents leading to the formation of the desired *N*-sulfonylated aziridine derivatives (**L42**) in high yields (up to 94%) producing NaBr as the by-product.



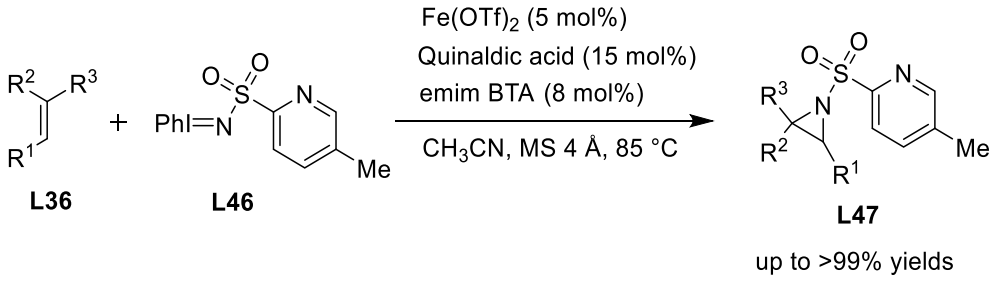
Scheme 1.20

In the next year, Zhang and co-workers reported another cobalt-catalyzed aziridination (Scheme 1.21) with diphenylphosphoryl azide (**L43**, DPPA) [22]. They have demonstrated the application of the common reagent, DPPA, as a nitrene source for the catalytic aziridination by Co(TPP) leading to the formation of synthetically valuable *N*-phosphorylated aziridines (**L45**) directly from the corresponding alkenes (**L36**) with dinitrogen as the byproduct. The authors experimented their aziridination reaction with only styrene and its derivatives as the alkene where they have not studied the generality of the reaction methodology which is the main disadvantage of this work.



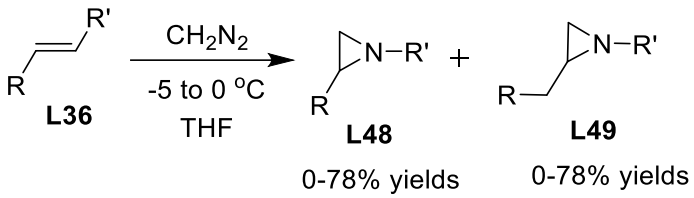
Scheme 1.21

Two years later in 2008, Mayer, Salit and Bolm developed a new method for the aziridination of olefins using iron catalyst [23]. They used a catalytic system based on iron(II) triflate, quinaldic acid and an ionic liquid which allows the aziridination of olefins (**L36**) with equimolar amounts of preformed iminoiodinanes $PhINSO_2Ar$ (**L46**) providing products in good to excellent yields (>99%) (Scheme 1.22). The authors have performed this experiment with a variety of styrene derivatives and only one aliphatic compound cyclooctene as a substrate which was not sufficient to prove the generality of this method.



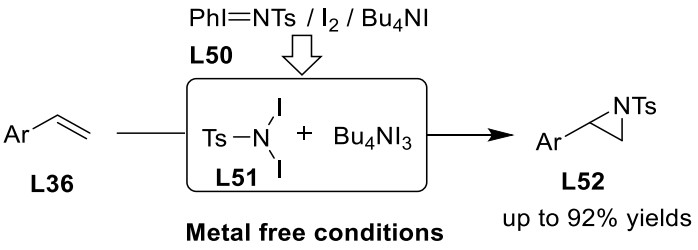
Scheme 1.22

A few years ago in 2010, Branco and Raje group reported a new method of metal-free aziridination without any catalyst (Scheme 1.23) [24] to afford the target products (**L48-49**). The authors demonstrated that the aziridination of *N*-sulfonylimines achieves easily with a very simple, rapid and mild procedure by using diazomethane as the carbene source without any catalyst. The authors have also demonstrated the unexpected homologation of aziridines from imines in the same reaction condition. Actually, this method was an excellent alternative to metal-catalyzed processes due to its lower cost.



Scheme 1.23

In 2013, Minakata *et al.* reported another metal-free catalytic aziridination of alkenes [25]. The aziridination of alkenes (**L36**) with *N*-tosyliminophenyliodinane (PhI=NTs) (**L50**) has been carried out in the presence of a combination of I_2 and tetrabutylammonium iodide (TBAI) (Scheme 1.24). *In situ* generated $TBAI_3$ (from I_2 and TBAI) dramatically promotes the reaction of alkenes with *N,N*-diiodotosylamide (**L51**), which is also formed *in situ*. In this reaction condition, a variety of styrene derivatives including other aromatic alkenes also has been successfully converted to its corresponding aziridine (**L52**) with satisfactory yield. But disappointingly, a very low yield was obtained when aliphatic alkenes were used in the reaction and this limitation really hampered the generality of the reaction.

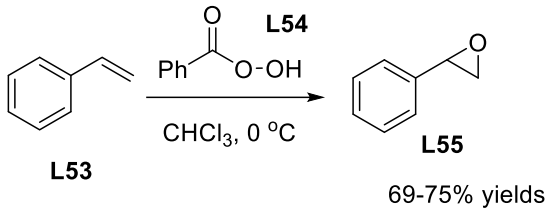


Scheme 1.24

1.1.3. Formation of epoxides from olefines and *α,β*-unsaturated ketones

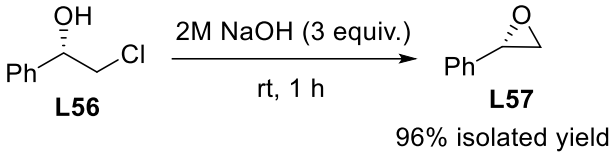
In organic chemistry an epoxides, as cyclic ethers, hold a specific place due to their unique triangular structure with a substantial ring strain, making epoxides highly reactive, more so than other ethers. Due to their various applications, for instance as important reagents for organic synthesis [1, 26] or bioactive compounds/drug candidates [27, 28] epoxides are produced on a large scale by various methods.

The most typical and the oldest one procedure for the preparation of epoxides (**L55**) is the Prilezhaev reaction [29]. This approach involves the oxidation of the alkene (**L53**) with a peroxyacid, such as *m*-CPBA (**L54**) Scheme 1.25) [30].



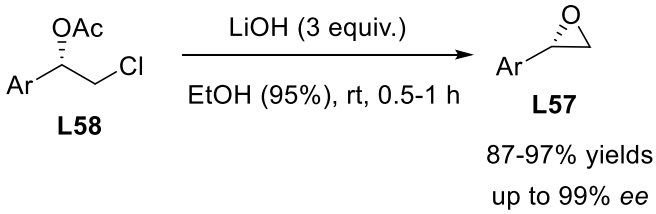
Scheme 1.25

The main disadvantage of the method is no control of stereoselectivity of the reaction. Therefore, for chiral epoxides, such as aryloxiranes (**L57**) enantioselective catalytic reduction of an achiral chloromethyl ketone (**L56**) by means of a chiral oxazaborolidine as catalyst and borane as stoichiometric reductant with following ring closure *via* alkylation reaction can be used (Scheme 1.26) [31].



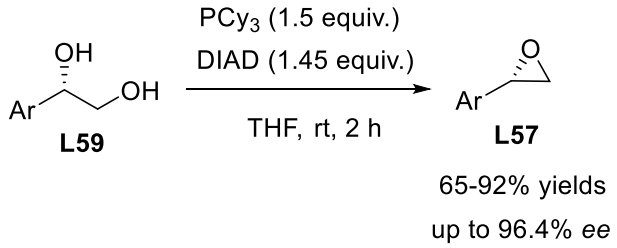
Scheme 1.26

Dynamic kinetic resolution (DKR) of various aromatic chlorohydrins using *Pseudomonas cepacia* lipase (PS-C "Amano" II) and a ruthenium catalyst was reported by Träff *et al.* to afford chlorohydrin acetates in both high yields and high enantiomeric excesses. These optically pure chlorohydrin acetates (**L58**) can be transformed to a wide range of chiral epoxides (**L57**) (Scheme 1.27) [32].



Scheme 1.27

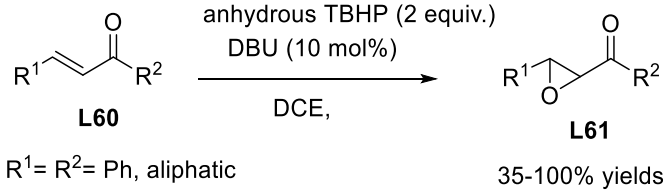
As an another approach, Weissman *et al*. reported the Mitsunobu cyclodehydration of chiral phenethane-1,2-diols (**L59**), which were obtained readily from styrenes to provide the corresponding styrene oxides (**L57**) with high levels of stereoretention for electron-poor substrates (Scheme 1.28). According to the authors, the combination of tricyclohexylphosphine and diisopropylazodicarboxylate in THF provides the best results [33].



Scheme 1.28

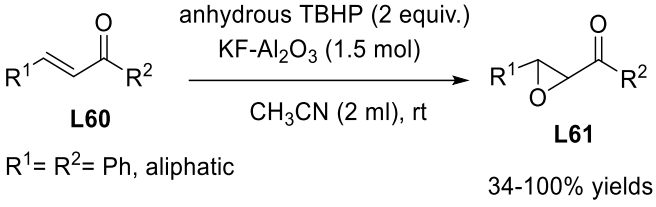
Racemic and optically active epoxyketones are among the most versatile building blocks in organic synthesis. In this compounds, both the ketone and epoxide moieties can be further functionalised to provide promising synthons or bioactive compounds [34]. Therefore. In the frame of this work various synthetic approaches to epoxyketones will be highlighted.

In 1995, Yadav and Kapoor established a method for epoxidation of *α,β*-unsaturated *δ*-lactones and other enones in presence of anhydrous TBHP and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DCE [35] to afford epoxides (**L61**). For TBHP, steric demands are higher than that for alkaline H_2O_2, triethylamine, diisopropylethylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO) which are entirely inefficient for this reaction, but DBU is recognized as a remarkable base in these oxidations (Scheme 1.29).



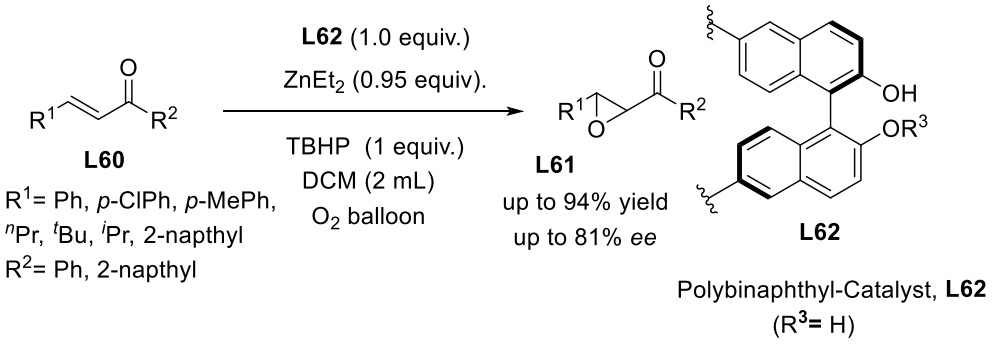
Scheme 1.29

The same authors later developed another method for epoxidation of electron deficient alkene (**L60**) in presence of dichloroethane solution of *tert*-butyl hydroperoxide (TBHP) and KF absorbed on alumina (KF-Al_2O_3) in acetonitrile solvent at room temperature to afford the same products (**L61**) (Scheme 1.30) [36].



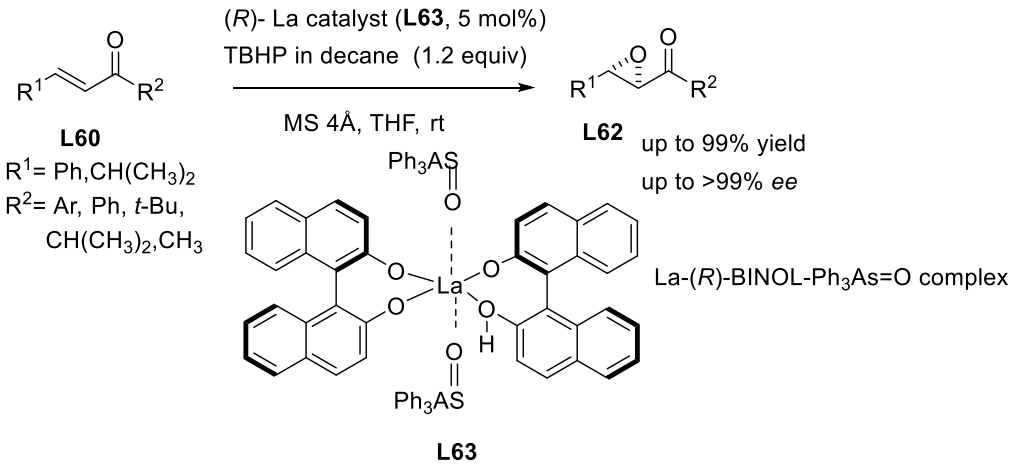
Scheme 1.30

A highly asymmetric epoxidation of *α,β*-unsaturated ketones was described by Pu *et al*. in 1999 using polybinaphthyl zinc catalysts in the presence of *tert*-butyl hydroperoxide and O_2 balloon [37]. For the epoxidation of *α,β*-unsaturated ketones containing *β*-aliphatic substituents has shown up to 81% *ee* using binaphthyl polymer catalyst (**L62**). A variety of *α,β*-unsaturated ketones gave (**L60**) the corresponding epoxy products (**L61**) in up to 94% yields (Scheme 1.31).



Scheme 1.31

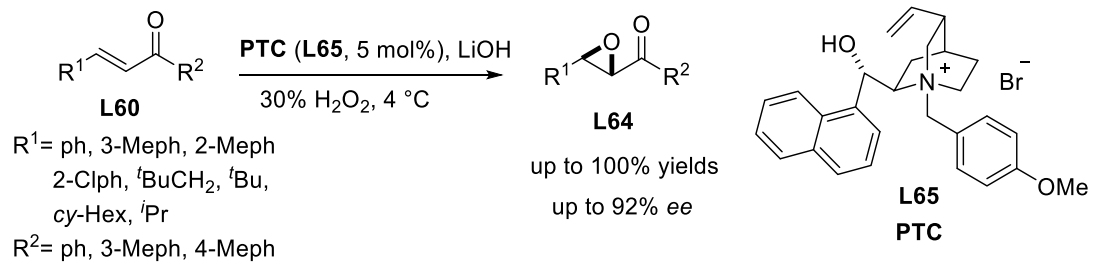
In 2001, Shibasaki and coworker established a method for asymmetric epoxidation of enones in presence of an asymmetric complex catalyst (La-BINOL-Ph_3As=O) (Scheme 1.32) [38] to afford enantiopure epoxides (**L62**). The catalyst (**L63**) was generated by the reaction of La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in the ratio of 1:1:1. A probable mechanism of this reaction has been suggested by the formation of a heterochiral complex for asymmetric amplification. A variety of enones (*trans*-enones and *cis*-enone) and dienone created the corresponding epoxyketones up to 99% yield with more than 99% *ee*.



Scheme 1.32

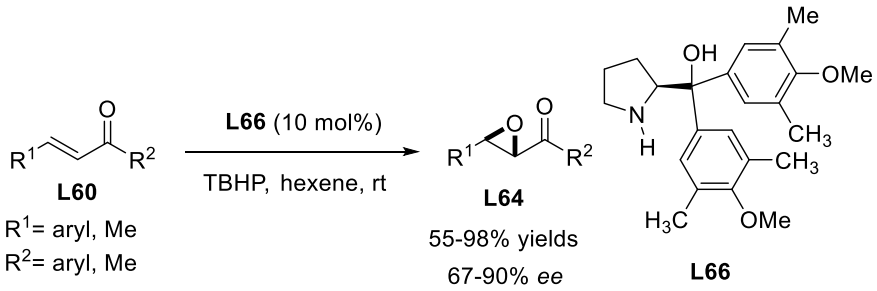
In 2002, Arai *et al*. established a method for catalytic asymmetric epoxidation of enones using phase transfer catalyst (PTC) (**L65**) (Scheme 1.33) [39] to afford enantiopure epoxides (**L64**). The reaction was carried out in the presence of chiral quaternary ammonium salt, PTC **(**5

mol%) and oxidant as 30% H_2O_2 and base (LiOH) to afford the target epoxides in up to 100% yield and up to 92% *ee*.



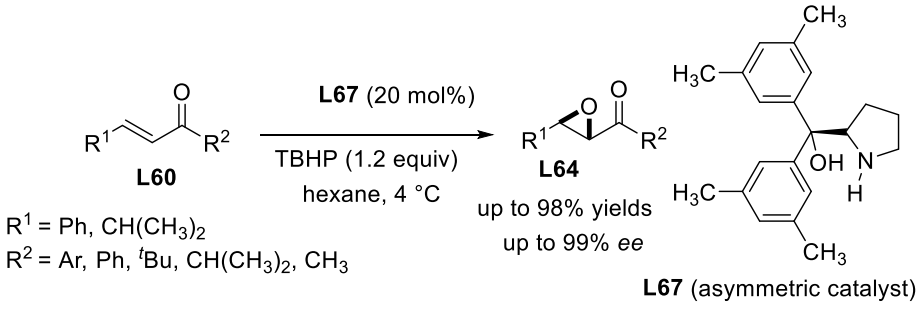
Scheme 1.33

In 2006 an enantioselective protocol for epoxidation of *α,β*-enones was developed by Lattanzi and Russo (Scheme 1.34) [40]. In this reaction diaryl-2-pyrrolidinemethanol (**L66,** 10 mol%) was used as an asymmetric catalyst and *tert*-butyl hydroperoxide (TBHP in 5-6 M decane solution, 33 µL) as oxidant. Various enones afforded the epoxide (**L64**) in up to 98% yield and up to 90% *ee*.



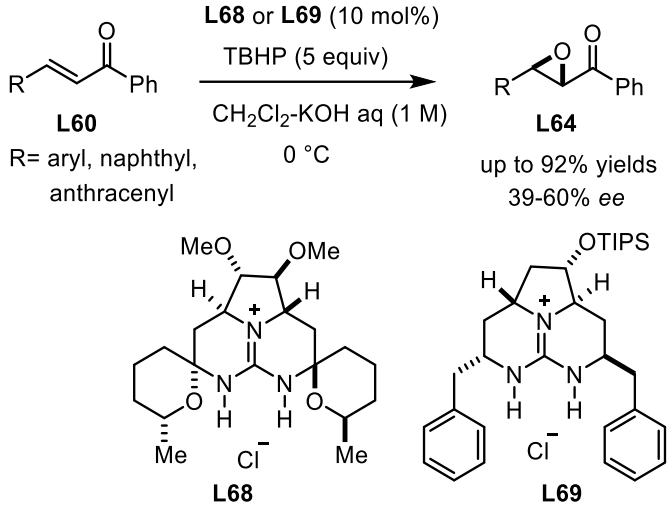
Scheme 1.34

In the same year, Lattanzi described another protocol for asymmetric epoxidation of *α,β*-enones (Scheme 1.35) [41] to afford expoxides (**L64**). The reaction was performed by using bis(3,5-dimethylphenyl)-(*S*)-pyrrolidine-2-ylmethanol catalyst (**L67**) and *tert*-butyl hydroperoxide (TBHP in 5-6 M decane solution) at 4 °C in hexane solvent and different *α,β*-enones afforded the desired epoxy product (**L64**) with maximum *ee* of 99% and up to 98% yield.



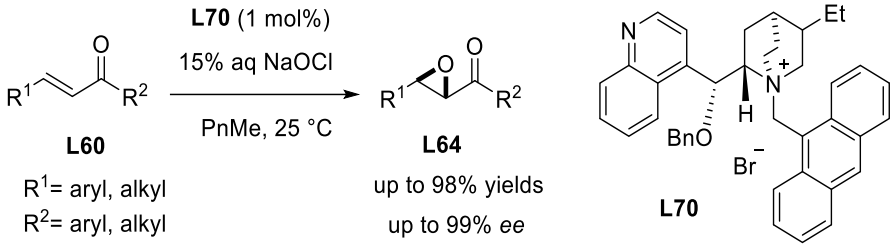
Scheme 1.35

In 2007, Nagasawa *et al*. reported a chiral cyclic guanidine catalyzed asymmetric nucleophilic epoxidation of chalcone and its derivatives with 39-60% *ee* and up to 92% yields [42]. This reaction was obtained in the presence of (guanidine catalyst (**L68**) or (**L69**), 10 mol%) and *tert*-butyl hydroperoxide (TBHP) in 1M CH_2Cl_2-KOH solution at 0 °C temperature (Scheme 1.36).



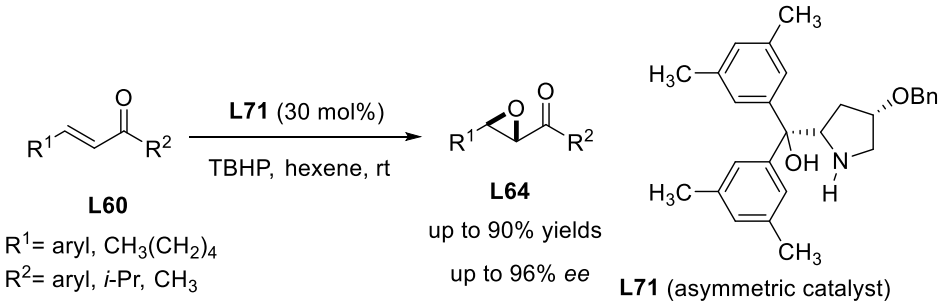
Scheme 1.36

In 2007, Lygo *et al*. developed a new route for the diastereo- and enantioselective synthesis of *α,β*-epoxyketones (Scheme 1.37) [43]. The reaction was carried out in the presence of dihydrocinchonidine derived quaternary ammonium salt phase transfer catalyst, (**L70**) (1 mol%) and aqueous NaOCl in toluene solvent at room temperature. This method has been applied to synthesize *cis*-*α,β*-epoxyketones form *cis*-*α,β*-unsaturated ketones. A library of epoxyketone (**L64**) was obtained with up to 98% yield and up to 99% *ee*.



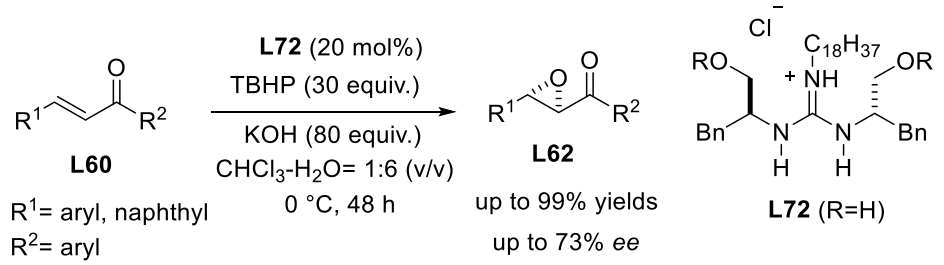
Scheme 1.37

In 2007 a method for enantioselective asymmetric epoxidation of *α,β*-enoSougata Santranes was reported by Zhao *et al*. in the presence of metal-free prolinol organocatalyst (**L71**) (30 mol%) and TBHP (33 μL) at room temperature (Scheme 1.38) [44]. Different enone, containing different steric and electronic properties afforded the epoxy ketones (**L64**) with high yields (up to 90%) and enantioselectivity (up to 96% *ee*).



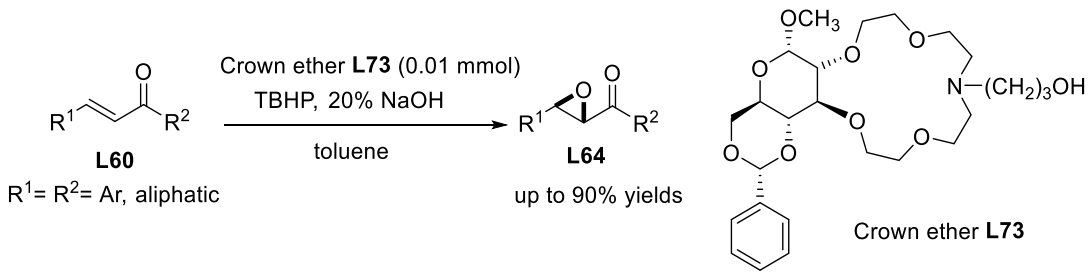
Scheme 1.38

In 2008, Nagasawa and coworkers developed a method for asymmetric epoxidation of *α,β*-unsaturated ketones using a new bifunctional acyclic organocatalyst (**L72**) (Scheme 1.39) [45] to afford epoxides (**L62**) in high yields and acceptable stereselectivity. The reaction was carried out in the presence of catalyst (**L72**) and *tert*-butyl hydroperoxide (TBHP, 5 M in decane solution) as oxidant, KOH as a base in a mixture of $CHCl_3$-H_2O solvent. In catalyst (**L72**) the hydroxyl group played a significant role for the both high yield (up to 99%) and good enantioselectivity (up to 73% *ee* was detected) for this protocol.



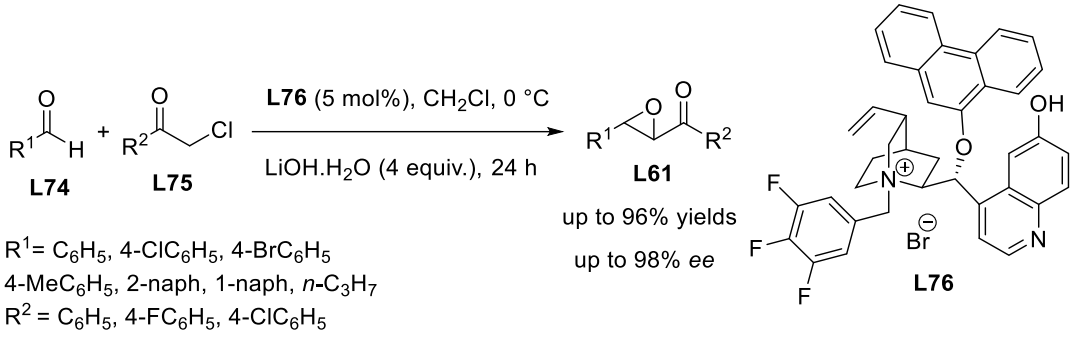
Scheme 1.39

α-D-glucose and *α*-*D*-mannose-based chiral crown ether were used by Bako *et al*. in 2010 as an asymmetric catalyst for asymmetric epoxidation of substituted chalcones and chalcone analogues (Scheme 1.40) [46] to afford epoxides (**L64**). The highest enantioselectivity was observed in the case of *para*-substituted models (83–97% *ee*) *vs*. *ortho*-substituted model compounds (62–83% *ee*). And up to 90% yields were detected.



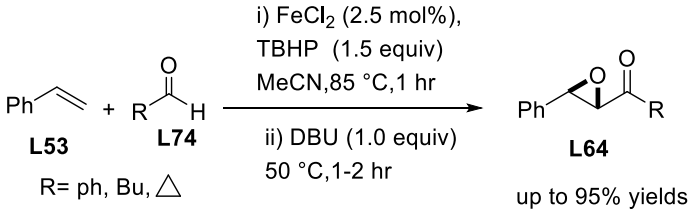
Scheme 1.40

In 2011, Deng *et al*. established a new route for highly enantioselective asymmetric epoxidation **(**Scheme 1.41) [47] affording epoxides (**L61**). The process was developed by the reaction of *α*-halogenated carbonyl compounds (**L75**) and aldehydes or ketones (**L74**) followed by Darzens reaction in the presence of chiral phase transfer catalyst 6′-OH cinchonium salts catalyst, **L76** (5 mol%) at 0 °C. Both electron withdrawing and electron donating substituents produced the epoxides moiety with high yields (up to 96%) and excellent enantioselectivities (up to 98% *ee*).



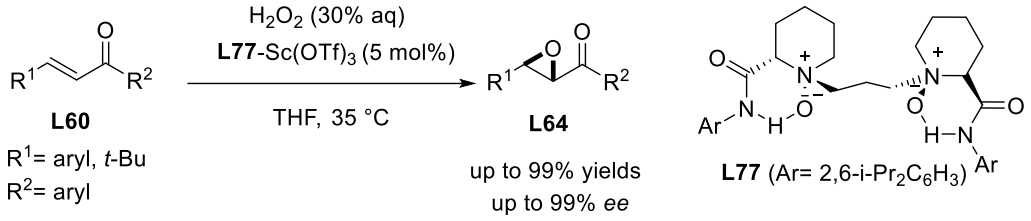
Scheme 1.41

In the same year, Li and coworkers developed a new protocol for preparation of asymmetric carbonyl epoxide (**L64**) by two steps one pot three-component reaction of aldehyde (**L74**), alkene (**L53**) and hydroperoxides in presence of an iron catalyst ($FeCl_2$) and base (DBU) (Scheme 1.42) [48]. The experimental result suggests that the reaction proceeds through a radical pathway. And, the target epoxides were isolated with up to 95% yield.



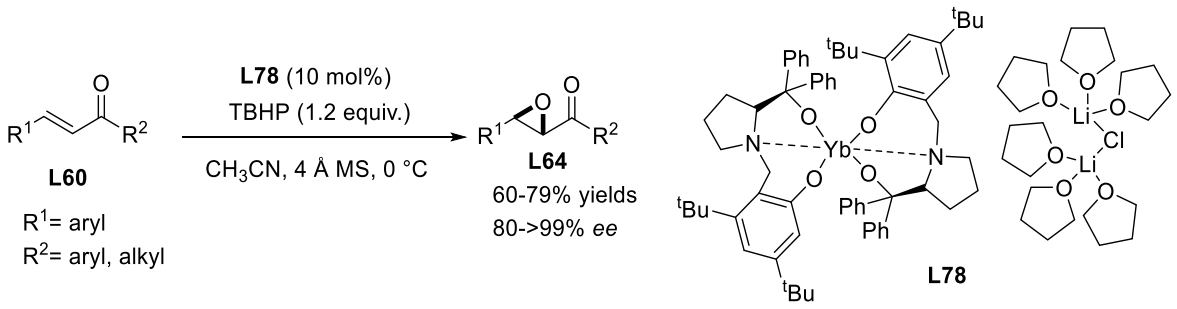
Scheme 1.42

Chiral *N,N*-dioxide-Sc(III) complex [**L77**-$Sc(OTf)_3$] is a chiral catalyst for asymmetric epoxidation of *α,β*-unsaturated carbonyl compound to give enantiopure epoxides (**L64**) was described by Feng *et al*. in 2012 (Scheme 1.43) [49]. Various substituted *α,β*-unsaturated ketone derivatives (both electron-donating and electron-withdrawing, steric substituents,) reacted very well under the optimized reaction conditions to afford epoxide ketones in up to 99% yield and 99% *ee*. The reaction is also applicable for gram-scale synthesis.



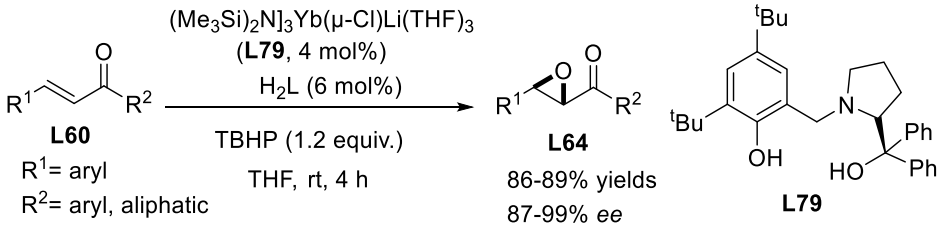
Scheme 1.43

In 2014, Yao and coworkers established a method for asymmetric epoxidation of unsaturated ketones (Scheme 1.44) [50] to afford enantiopure epoxides (**L64**). The reaction was carried out in the presence of heterobimetallic rare earth lithium complexes catalyst (**L78**) and oxidant as a *tert*-butyl hydroperoxide (TBHP, 1.25 equiv.) in acetonitrile solvent at 0 °C. Various substituted *α,β*-unsaturated ketone derivatives reacted very well under the optimized reaction conditions and gave the chiral epoxides in 60-79% yield and 80-99% *ee*.



Scheme 1.44

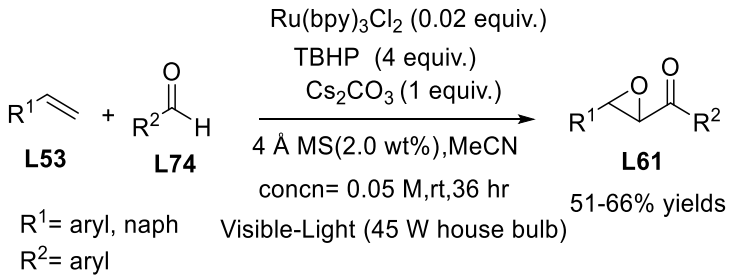
In next year, Yao *et al*. developed a new protocol for preparation of asymmetric carbonyl epoxide using newly modified rare-earth amides catalyst $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$ with phenoxy functionalized chiral prolinols (**L79**) and TBHP as an oxidant at ambient temperature (Scheme 1.45) [51]. This complex gives rise to epoxyketones (**L64**) with good yields (86-89%) and high to good optical purity (87-99% *ee*).



Scheme 1.45

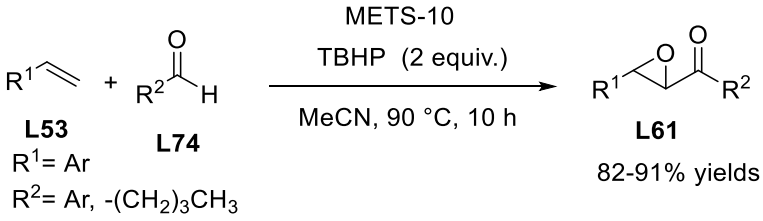
Visible-light promoted synthesis of *α,β*-epoxyketones at ambient temperature was described by Wang and Li in 2015 (Scheme 1.46) [52]. The reaction was carried out by the reaction of styrene (**L53**) and aldehyde (**L74**) in the presence of photocatalyst $Ru(bpy)_3Cl_2$, and oxidant as

a *tert*-butyl hydroperoxide (TBHP) with alkaline conditions (cesium carbonate, Cs_2CO_3), under visible light irradiation to afford the target epoxides (**L61**) in up to 66% yield. Experimental results suggested that the reaction proceeded through a radical pathway and acyl radicals as the key intermediate. The reaction is also applicable for gram scale synthesis.



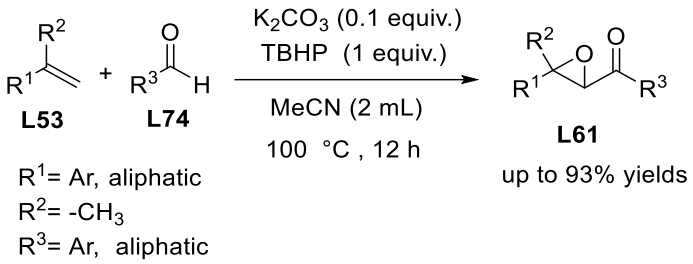
Scheme 1.46

In the same year, Tang *et al*. developed a protocol for preparation of *α,β*-epoxyketones using mesoporous zeolite METS-10 catalysts (33 mg for 1 mmol scale) and TBHP as an oxidant in acetonitrile solvent at 90 °C (Scheme 1.47) [53]. A series of *α,β*-epoxyketones (**L61**) were synthesized with up to 91% yield through the oxidative coupling reaction of alkenes (**L53**) and aldehydes (**L74**). Control experiments suggested that the reaction proceeded through a radical pathway and also investigated by DFT theoretical calculations.



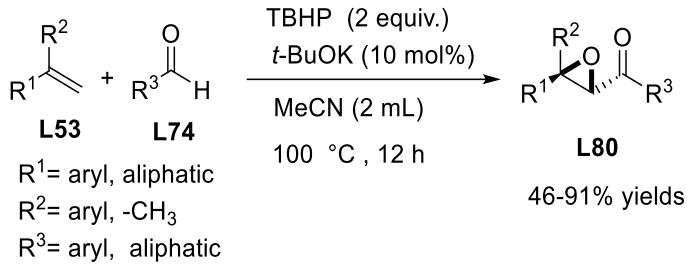
Scheme 1.47

A one pot, transition metal-free strategy for the synthesis of *α,β*-epoxyketones (**L61**) was established by Lu and coworkers in the same year (Scheme 1.48) [54]. The reaction was carried out in the presence of base (K_2CO_3, 0.1 equiv.**)** and oxidant, *tert*-butyl hydroperoxide (TBHP, 1 equiv.) in acetonitrile while reflux. Various substituted alkenes (**L53**) and aldehydes (**L74**) reacted well under optimized reaction conditions and afforded *α,β*-epoxyketones (**L61**) in moderate to good yields (up to 93%). Control experiments suggest that the reaction proceeds through a radical pathway and also confirmed by using radical scavenger like TEMPO (2,2,6,6-tetramethyl piperidine-*N*-oxyl).



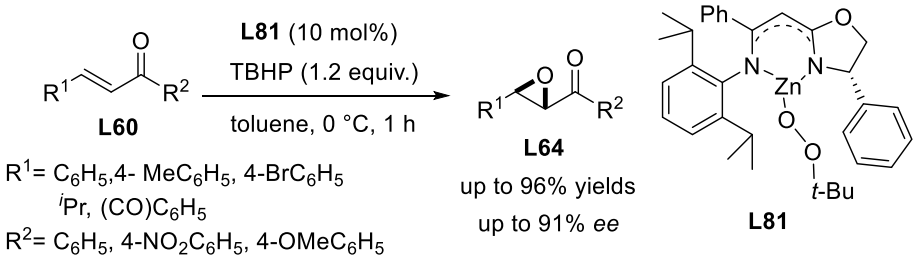
Scheme 1.48

In the same year, Li *et al*. described a protocol for one-pot synthesis of *α,β*-epoxyketones (**L80**) by oxidative coupling reaction of alkene, aldehyde and hydroperoxide (TBHP) in presence 10 mol% potassium *tert*-butanolate (^{t}BuOK) at 100 °C (Scheme 1.49) [55]. The reaction proceeded through the oxidative radical pathway. Various substituted alkenes (**L53**) and also aldehydes (**L74**) (both electron-donating and electron-withdrawing, steric substituents) gave the epoxyketones with high yields (46-91%).



Scheme 1.49

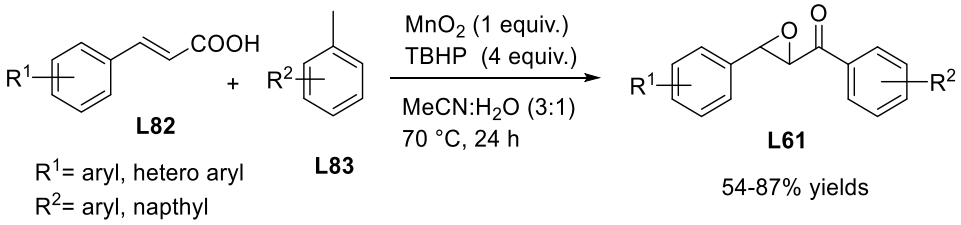
Zinc *tert*-butyl peroxides (cat**4**) complex mediated enantioselective asymmetric epoxidation of enones was described by Jurczak *et al*. in 2016 (Scheme 1.50) [56]. The reaction was carried out in the presence of zinc *tert*-butyl peroxides catalyst (**L81**), and *tert*-butyl hydroperoxide (TBHP) as an oxidant in toluene at 0 °C. The reaction was completed within 1 h and chiral epoxides (**L64**) were formed up to 96% yield and 91% *ee*.



Scheme 1.50

In 2017, Sing and coworkers established a one-pot strategy for the synthesis of *α,β*-epoxyketones (Scheme 1.51) [57]. Different methyl arenes (**L83**) reacted with substituted

cinnamic acids (**L82**) *via* oxidative coupling involving C(sp^3)-H activation and decarboxylative strategy in presence MnO_2/TBHP combination in CH_3CN:H_2O (3:1) solvent system at 70 °C for 24 h and gave the desired product (**L61**) with moderate to good yield (54-87%). The reaction proceeds through a radical pathway and which has been confirmed by using radical scavenger like 2,6-di-tertbutyl-4-methylphenol (BHT) and 2,2,6,6-tetramethyl-1- piperidinyloxy (TEMPO).



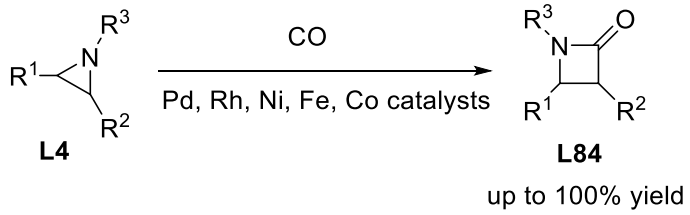
Scheme 1.51

1.1.4. Aziridines ring expansion reactions

Along with the formation of ring opening products the transformations of aziridines may afford the formation of larger size azaheterocycles *via* ring expansion reactions. Below the most typical examples of such transformations will be presented.

1.1.4.1. Formation of azetidines

So far, only one example of such transformations was reported. Thus, Alper and others achieved metal-catalyzed carbonylations of aziridines to yield valuable azetidines, namely *β*-lactams (**L84**) in up to 100% yields (Scheme 1.52) [58]. According to the authors, the regioselectivity of the reaction depends strongly on the substitution pattern of the parent aziridine ring.

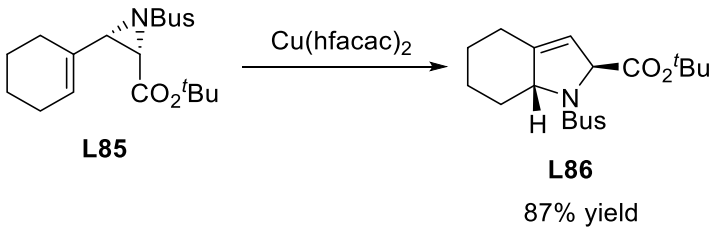


Scheme 1.52

1.1.4.2. Formation of pyrroles

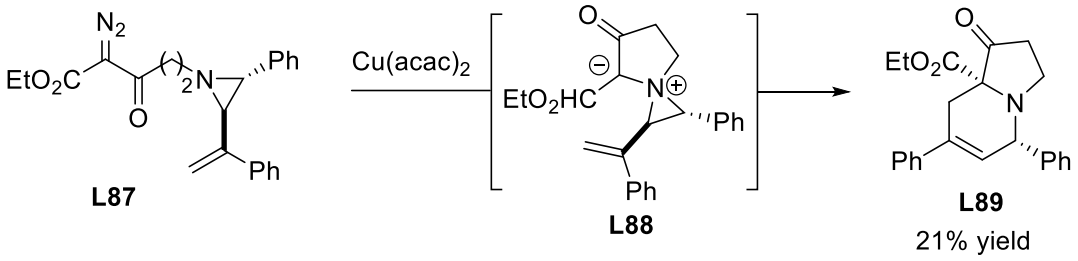
Pyrroles are widely presented in both natural and synthetic bioactive compounds. Therefore, new and efficient synthetic approaches towards these heterocycles, especially cheiral ones, are of high demand.

For instance, Njardarson described a series of Cu-catalyzed transformations of aziridines (**L85**) to pyrrolidines and related rings (**L86**); while these reactions are often stereospecific, they are largely limited to intramolecular examples (Scheme 1.53) [59-61].



Scheme 1.53

Barnes & Rowlands reported the formation indolizidine (**L89**), as [2,3]-Stevens rearrangement product, by means of reaction of aziridinium ylide generated (**L88**) by the intramolecular reaction of a metal carbenoid tethered to a vinylaziridine (**L87**) (Scheme 1.54). It is essential that the correct nitrogen invertomer is used or a competing [1,5]-hydrogen shift predominates [62].

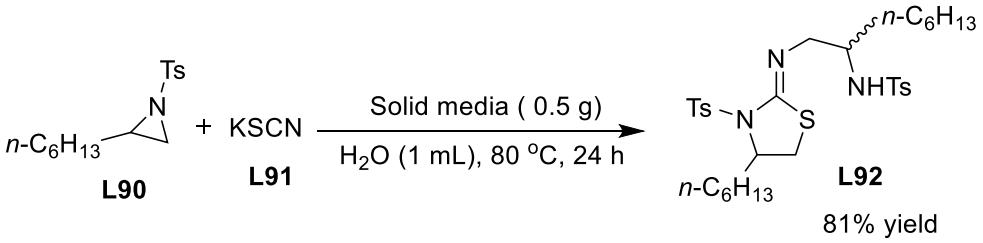


Scheme 1.54

1.1.4.3. Formation of azoles

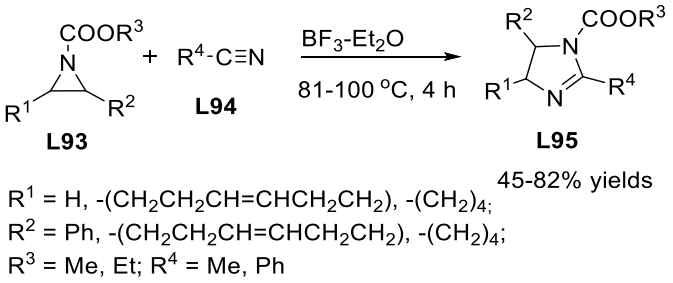
Thiazole moieties are widely presented in various naturally occurring compounds, including thiamine (vitamin B1), which is a key nutrient for humans with a recommended daily dose [63]. And thiazole moiety is one of the key fragment of various synthetic drugs and bioactive compounds [64]. Imidazolines are considered as the most important moiety for their wide applications in various fields of chemistry, such as natural product chemistry, pharmaceutical chemistry, organic synthesis, coordination chemistry and homogeneous catalysis. These are useful intermediates for designing molecules with pharmacological activities such as anti-inflammatory [65], antidiabetic [66] and anticancer [67]. Below some key examples of aziridine ring extension to afford azoles will be presented.

Thus, Minakata and Komatsu group reported “solid media – water” system for the expansion reactions between aziridines and potassium thiocyanate to afford the thiazolidine derivative (**L92**) in 81% yield (Scheme 1.55) [68].



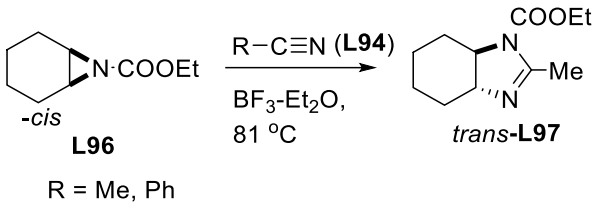
Scheme 1.55

In 1973, Nozaki *et al*. reported the BF_3-mediated reaction of acetonitrile or benzonitrile (**L94**) with *N*-alkoxycarbonylaziridines (**L93**) yielded the corresponding l-alkoxycarbonyl-2-imidazolines (**L95**) [69]. The nitrile-addition possibly proceeds *via* S_N2 type C-N bond cleavage and C-N bond formation (Scheme 1.56).



Scheme 1.56

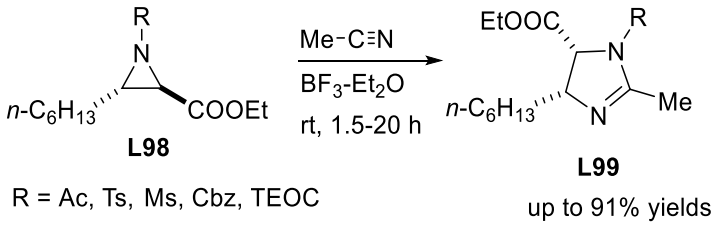
Reaction between *cis*-1,2-dialkyl-substituted aziridines (**L96**) and aliphatic or aromatic nitriles was also reported [68] to give specifically *trans*-product (**L97**). Both acetonitrile and benzonitrile were used in this reaction at 81 °C and 100 °C, respectively. On the basis of this result, an S_N2 mechanism was proposed by the authors (Scheme 1.57).



Scheme 1.57

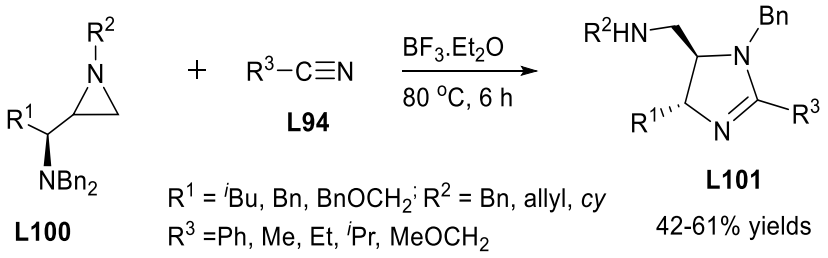
In 1992, Zwanenburg *et al*. expanded the previous method to more substrates such as *N*-protected aziridines derived from ethyl-2-nonenoate [70]. In this work, the reaction took place at

room temperature and the *cis* products (**L99**) were obtained up to 91% yield as single diastereomers (Scheme 1.58).



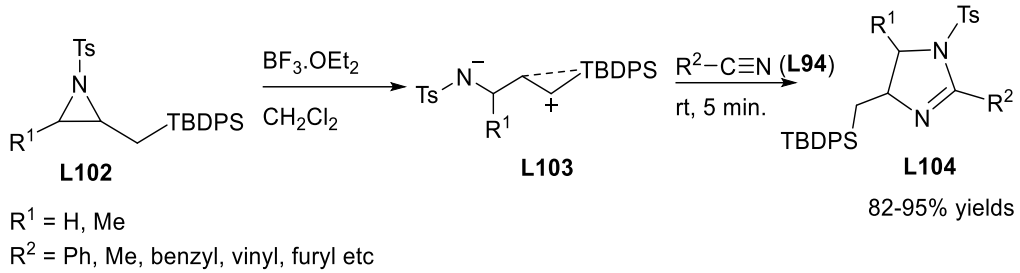
Scheme 1.58

In 2004, Concellon *et al*. [71] investigated the chiral induction in the reaction between enantiopure aziridines (**L100**) with a dibenzylamino group on the *α*-carbon and different nitriles (**L94**) using the catalyst $BF_3.OEt_2$. The *N*-benzyl-4,5-di-substituted imidazolines (**L101**) were obtained in enantiopure form instead of the predicted 5-substituted product with moderate yields (42-61%). In the proposed mechanism, the aziridine ring is opened by the *vicinal* dibenzylamino group using the catalyst $BF_3.OEt_2$ and a new aziridinium species is formed. The newly formed ring is transformed to imidazoline through nucleophilic attack of nitrile followed by ring closure, in which a benzyl group is removed by nitrile as *N*-benzylamide (Scheme 1.59).



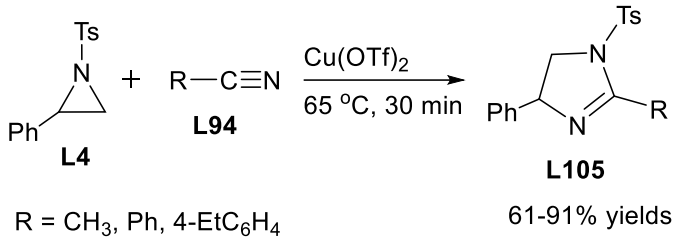
Scheme 1.59

Yadav and co-workers used *tert*-butyldiphenylsilylmethyl-substituted (TBDPS-substituted) aziridines (**L102**) in formal [3+2] cycloaddition with nitriles in the presence of $BF_3{\cdot}OEt_2$ to give imidazoines (**L104**) in good to excellent yields (82-95%) [72]. The presence of silicon stabilizes the *α*-carbocation and allows the formation of the stable zwitterionic intermediates, thus providing an alternative to the typical aryl stabilizing groups. With an increase in the reaction temperature from –78°C to 25°C, the *cis* cycloadduct became the major product (Scheme 1.60).



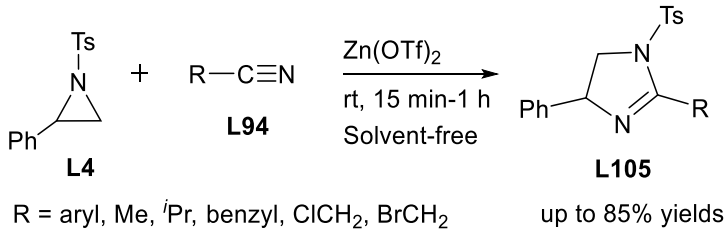
Scheme 1.60

Ghorai and co-workers discovered $Cu(OTf)_2$ mediated [3+2] cycloaddition reactions of various alkyl or aryl substituted *N*-tosylaziridines (**L4**) with nitriles for the syntheses of substituted imidazolines (**L105**) with up to 91% yields [73]. A mechanism for the cycloaddition was proposed to rationalize the formation of a non-racemic imidazoline from optically pure aziridine (Scheme 1.61).



Scheme 1.61

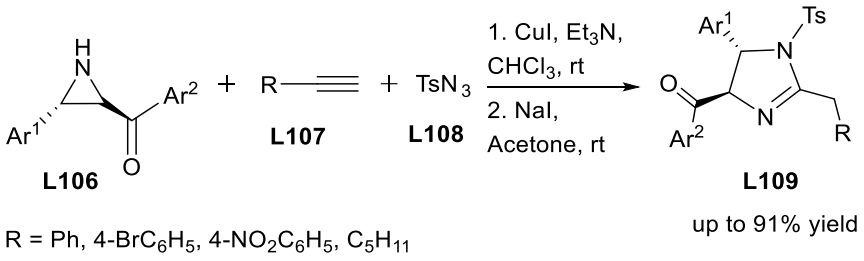
Singh and his group demonstrated that solvent-free reactions of this type can also be achieved with $Zn(OTf)_2$ catalyst, and the corresponding imidazolines (**L105**) were obtained in up to 85% yields (Scheme 1.62) [74].



Scheme 1.62

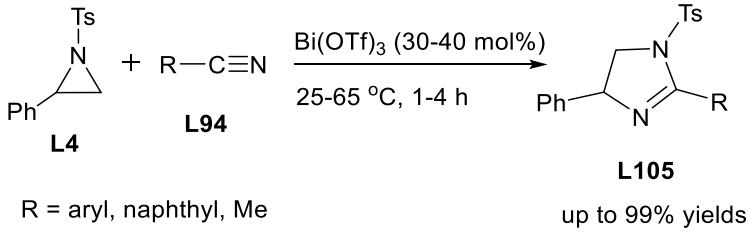
In 2008, Liang *et al*. reported different reaction behaviour of aziridines in reaction with acerylenes affording 2-imidazolines (**L109**) [75]. Thus, from *trans*-*N*-unsubstituted aziridines (**L106**) derived from chalcones, terminal alkynes (**L107**) and tosyl azide (**L108**), the *N*-tosylamidine (**L109**) with the *trans* configuration were obtained as intermediate by the catalysis of CuI in moderate to good yields (up to 91%). These intermediates were transformed to *trans* 4,5-

disubstituted-2-imidazolines through NaI mediated ring expansion with full retention of the configuration (Scheme 1.63).



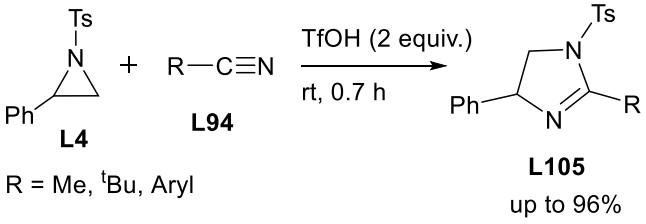
Scheme 1.63

Wei and co-workers used $Bi(OTf)_3$ in formal [3+2] cycloaddition between substituted *N*-tosylaziridines (**L4**) and a variety of nitriles (**L94**) to afford the corresponding imidazolines (**L105**) in up to 99% yields (Scheme 1.64) [76].



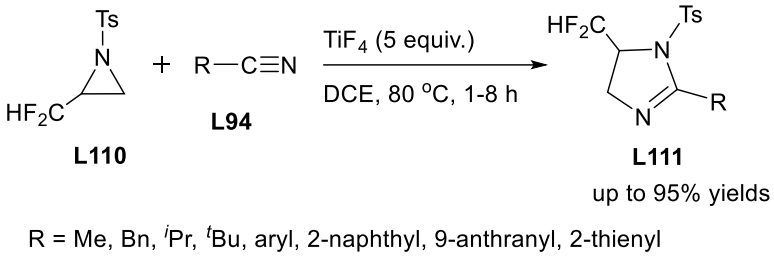
Scheme 1.64

In 2014, Li group used triflic acid for [3+2] cycloadditions between substituted *N*-tosylaziridines (**L4**) and a variety of nitriles (**L94**) to afford the corresponding imidazolines (**L105**) *via* Ritter reaction in excellent yields (up to 96%) [77]. Among the nitriles, pivalonitrile is proven to be better than acetonitrile. The reaction was performed at room temperature (Scheme 1.65).



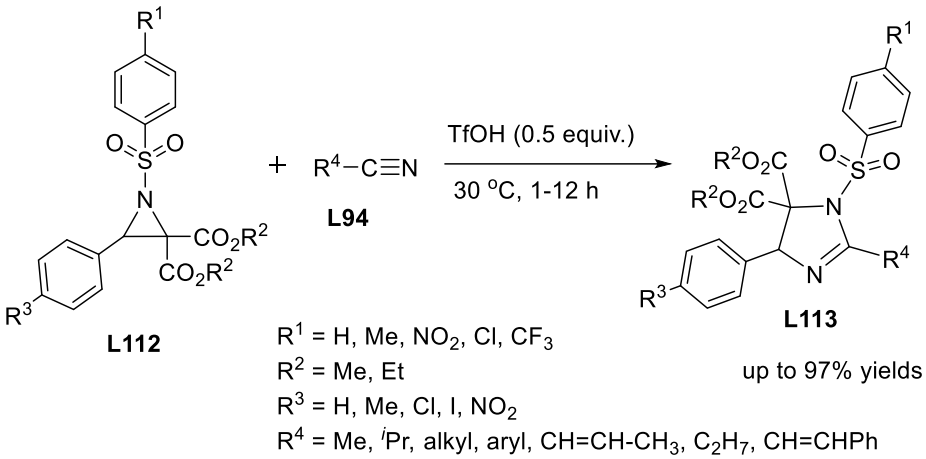
Scheme 1.65

In 2016, Hanamoto *et al*. developed a titanium(IV)fluoride (TiF_4) mediated reaction of 2-(difluoromethyl)-*N*-tosylaziridine (**L110**) with nitriles (**L94**) to synthesize difluoromethylated 2-imidazolines (**L111**) in good to excellent yields (up to 95%) [78]. Both alkyl- and arylsubstituted nitriles underwent reaction smoothly (Scheme 1.66).



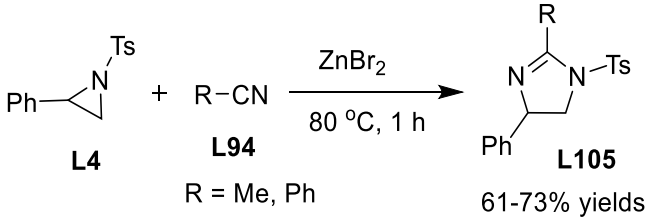
Scheme 1.66

Recently, Zuo and co-workers reported a triflic acid mediated the [3+2] cycloaddition reaction of aziridine dicarboxylates (**L112**) and nitriles (**L94**) to afford tetra-substituted 2-imidazolines (**L113**) in up to 97% yields (Scheme 1.67) [79].



Scheme 1.67

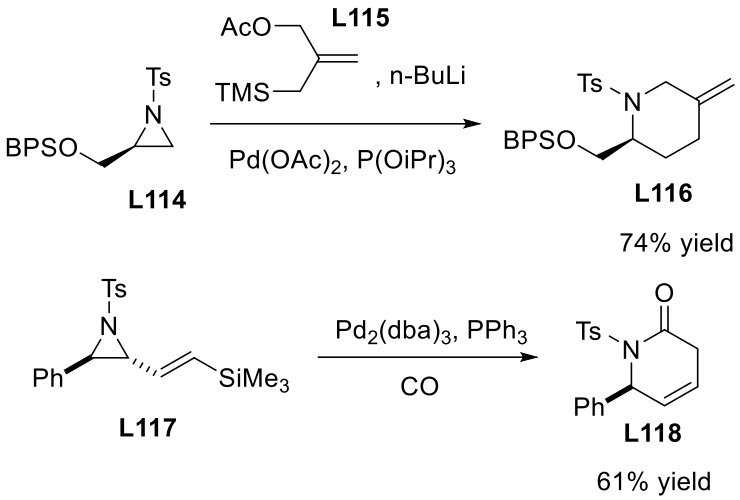
Finally, *N*-Ts aziridines were found to react with methyl- or phenylcyanide in the presence of $ZnBr_2$ as a catalyst to afford substituted imidazolines (**L105**), as [3+2] cycloaddition products, in up to 73% yield (Scheme 1.68) [80].



Scheme 1.68

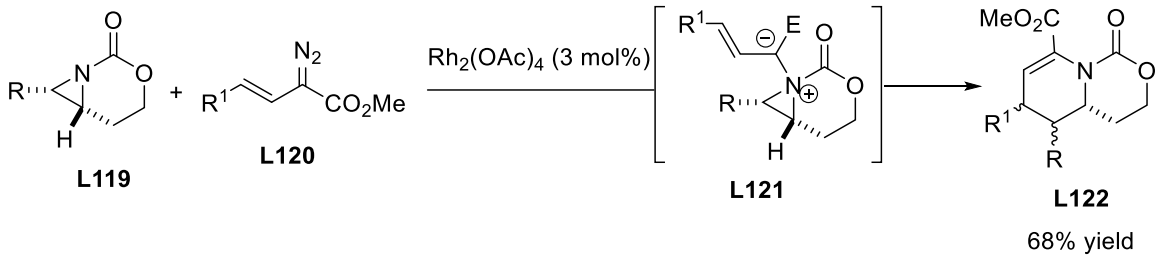
1.1.4.4. Formation of pyridines and azepines

Aziridines [3+3] annelation affording 6-member ring is very rare, and, so far, reported by few examples. Thus, Harrity *et al*. reported Pd-catalysed [3 + 3] annelation between the *N*-Ts-aziridine and Trost's conjunctive allylsilane reagent affording enantiomerically pure piperidine (**L116**) as a key precursor for the stereoselective synthesis of enantiopure indolizidinone. In addition, Pd catalyzed CO insertion reaction was studied to afford chiral pyridone (**L118**) (Scheme 1.69) [81].



Scheme 1.69

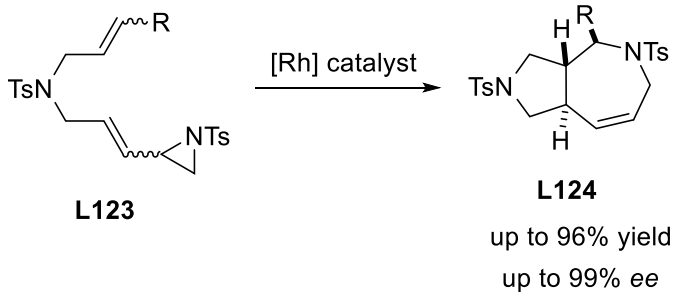
Eshon and co-authors reported the Rh(II)-catalyzed [3+3] stereoselective annelation between oxazine-annelated aziridines (**L119**) and *in situ* formed vinyl carbenes (**L121**) to afford pyrido[1,2-*c*][1,3]oxazines (**L122**) in up to 91% yield and 19:1 *dr* as privileged motifs in bioactive compounds (Scheme 1.70) [82].



Scheme 1.70

Only one example of formation of azepine ring from aziridines was published. Thus, Zhang *et al.* reported a very first case of rhodium-catalyzed intramolecular hetero-[5+2] cycloaddition reaction of vinyl aziridines and alkenes to afford series of unique substituted fused bicyclic azepines (**L124**) bearing multiple stereogenic centers (Scheme 1.71) [83]. The target compounds were obtained in up to 96% yield and up to 99% *ee*. According to the authors, the *E/Z* geometry

of the C-C bonds in the starting vinyl aziridine-alkenes impacts the *cis/trans* stereochemistry of the cycloadducts with up to six stereoisomers delivered.



Scheme 1.71

1.1.5. Reactions of azirines

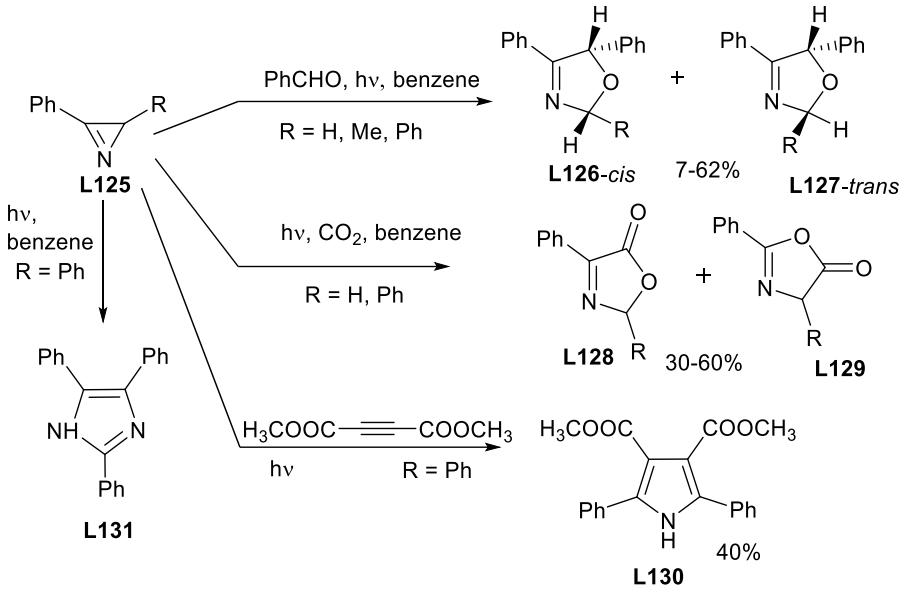
Azirine is probably the most strained molecule as it presents a three-membered heterocycle containing one nitrogen atom and one double bond. The first 2*H*-azirine was reported by Neber *et al*. in 1932 [84, 85]. 2*H*-azirines are naturally occurring antibiotics that have been found in several natural products. Azirinomycin was isolated from *Streptomyces aureus* [86]. Azirine-containing natural products were also isolated from *Dysidea fragilis:* (-)-(*E*)-dysidazirine [87], (*Z*)-dysidazirine, (+)-(*Z*)-antazirine and (+)-(*E*)-antazirine [88] and corresponding chlorinated species [89].

During the last few years the synthetic methodology 'azirine ring opening-intermolecular annulation to multiple bonds' involving UV-induced or visible light photoredox catalyzed azirine bond cleavage has been actively developed for heterocyclic synthesis. Some of the reactions occur under transition metal-free conditions which favor green chemistry and environmental sustainability.

In 1972, Giezendanner and co-workers reported, the irradiation of azirine (**L125**) in benzene solution in presence of equimolar amounts of benzaldehyde, produces oxazolidines where *cis*-(**L126**) and *trans*-(**L127**) isomers are possible, the cis- isomer is favoured [90]. On the other hand, a clean photochemical reaction occurred when azirine was irradiated in benzene solution in the presence of carbondioxide.

Preliminary experiments showed that azirine does not react photochemically with acetophenone or acetone. A photoreaction was observed however, when azirine was irradiated in benzene solution in the presence of two mol-equivalents of dimethyl acetylene dicarboxylate. In this case 2,5-diphenyl-3,4-di-methoxycarhonylpyrrole (**L130**) could be isolated in 40% yield.

2,4,5-triphenyl-imidazol (**L131**) was formed when **L125** was irradiated under the same conditions (Scheme 1.72).

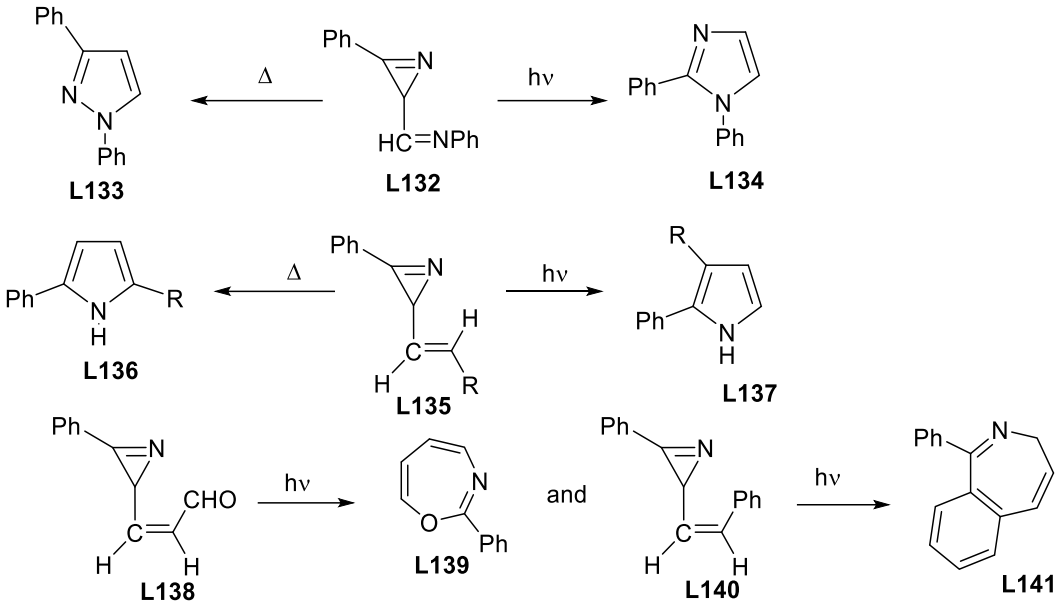


Scheme 1.72

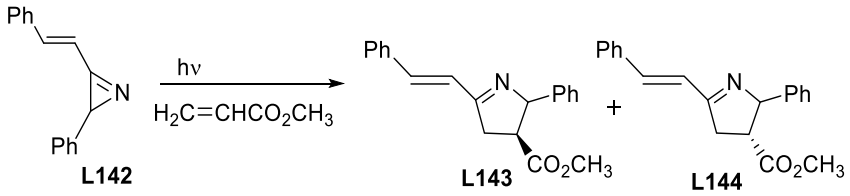
The scope of the thermal and photochemical ring expansion reactions of a number of 2-vinyl-substituted 2*H*-azirines (**L132, L135, L138, L140**) was examined by Padwa *et al.* in 1974 [91]. The azirine derivatives (**L132, L135**) undergo photochemical rearrangement to 2,3-disubstituted pyrroles (**L137**) *via* transient nitrile ylide intermediates which can be trapped with external dipolarophiles. The thermal reactions proceed by a different pathway involving rupture of the azirine C-N single bond giving a butadienyl nitrene which cyclizes to a 2,5-disubstituted pyrrole (**L136**). The photocycloadditions proceed *via* the excited singlet state of the azirine is indicated by the failure of triplet sensitizers and quenchers to sensitize or quench the reaction. Photolysis of 3-phenyl-2-styryl-2*H*-azirine (**L140**) proceeds by a seven-membered transition state and gives l-phenyl-3*H*-2-benzazepine (**L141**) as the major product. A study of the quantum yield for product formation as a function of added dipolarophile shows that the photocyclization to give a seven-membered azepine (**L141**) is significantly faster than cyclization to the five-membered pyrrole ring. The formation of pyrazole (**L133**) and imidazole (**L134**) was also mentioned (Scheme 1.73).

Same group further studied the thermal and photochemical expansion reactions of several unsaturated 2*H*-azirines [92]. The azirine derivatives were found to undergo photochemical reorganization *via* transient nitrile ylide intermediates which can be trapped with external dipolarophiles. Photolysis of the isomeric azirine 3 resulted in the formation of polymeric material.

When the irradiation was carried out in the presence of methyl acrylate, cycloadducts (**L143)** and (**L144)** were isolated in good yield (Scheme 1.74).



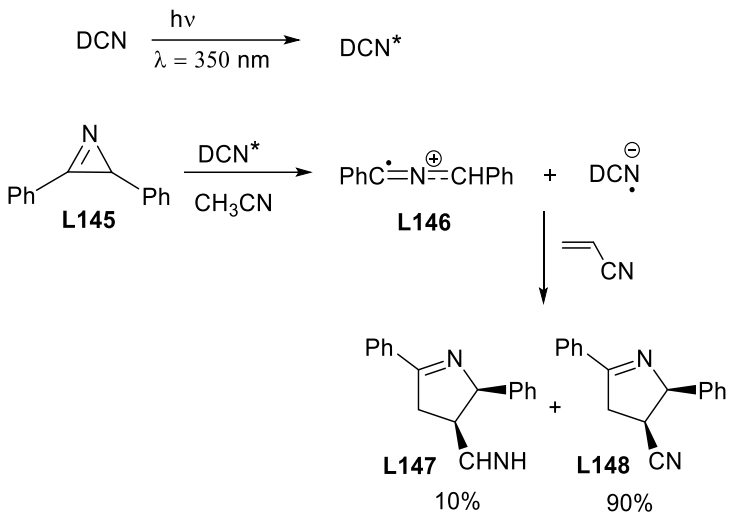
Scheme 1.73



Scheme 1.74

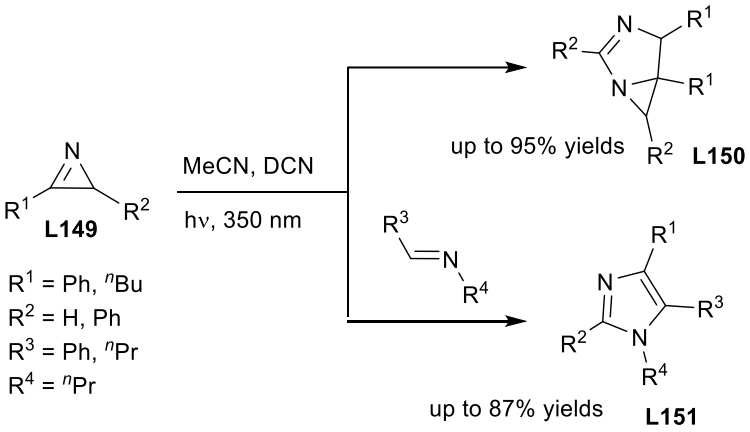
Muller and Mattay focused on the investigation of reactions involving photoinduced electron transfer (PET), especially the PET-catalyzed ring opening of highly strained carbo- and heterocycles [93]. The reactions of azirines, a group of compounds frequently used in 1,3-dipolar cycloaddition reactions, under photosensitized (electron-transfer) irradiation conditions. Since the n-π* transition of azirines occurs at a wavelength of 280 nm, irradiation with light of 350 nm wavelength does not lead to the direct excitation of the substrate.

However, 1,4-naphthalenedicarbonitrile (DCN) is excited and abstracts an electron from the azirine as observed for direct excitation, the C-C bond of azirine is thereby broken. They regard the formation of the 2-azaallenyl radical cation (**L146)** as an intermediate from azirine (**L145**). This species reacts with acrylonitrile under ring closure and back electron transfer to give the five-membered ring**.** The addition thus proceeds *via* a two-step mechanism. Compound (**L148)** is formed in a yield of 90%, whereas that of (**L147)** is just 10%. In contrast, we found a product ratio of 50:50 when DCN catalysis was used (Scheme 1.75).



Scheme 1.75

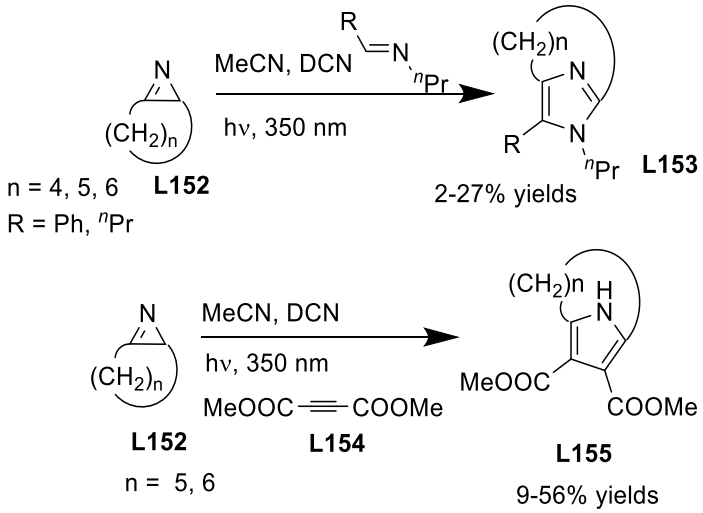
If there is no suitable reaction partner, azirines will dimerize, *via* [3+2] cycloaddition to give fused imidazolines (**L150).** Reaction of azirine (**L149**) with azomethine afforded imidazole **(L151) (**Scheme 1.76).



Scheme 1.76

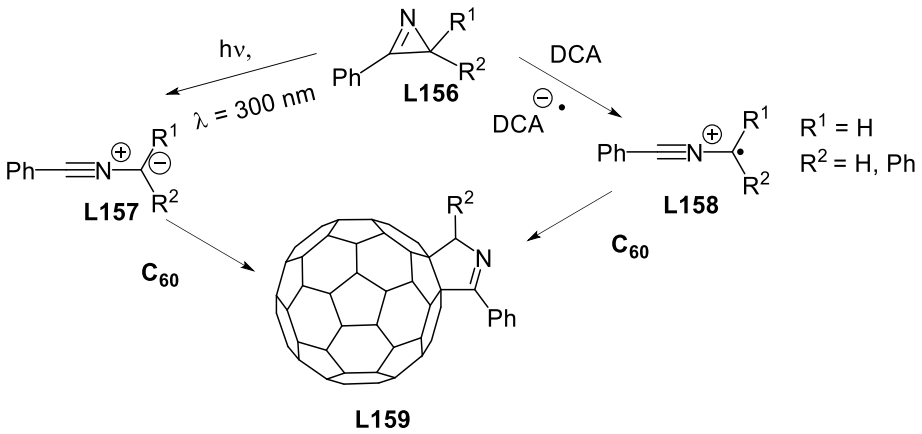
Next year, they also reported the electron acceptor 1,4-naphthalenedicarbonitrile (DCN) is excited by irradiation with light 1 = 350 nm in the presence of azirine (**L125**), leading to the DCN radical anion and a reactive azirine radical cation [94]. This latter species opens to the linear 2-azaallenyl radical cation. Bicyclic azirines (**L152**) react with imines to give [*n*](2,4)imidazolophanes in 2-27% yields.

On the other hand, the PET promoted method, enables the preparation of 3,4-substituted pyrrolophanes in acceptable yields. The reaction of 2-azaallenyl radical ions with acetylenes leads to pyrroles. The azirines react with dimethyl 2-butynedioate (**L154**) to give pyrrolophanes (**L155**) in 9-56% yields (Scheme 1.77).



Scheme 1.77

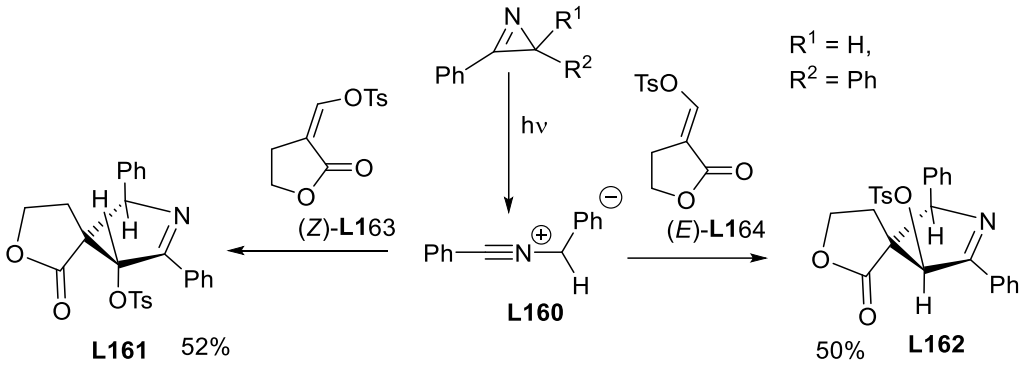
Mattay *et al.* reported an exohedrally functionalized fullerene such as 1,9-(3,4-dihydro-2,5-diphenyl-2*H*-pyrrolo)- [60]fullerene can also be prepared by the [3+2] photocycloaddition of nitrile ylide to C_{60} fullerene [95]. The nitrile ylide (**L157**), which was generated by direct irradiation of 2,3-diphenyl-2*H*-azirine 7 (R^1 = H, R^2 = Ph), added to C_{60} acting as 1,3-dipolamphile with formation of a C_1 symmetrical 1,2-(3,4-dihydro-2,5-diphenyl-2*H*-pyrrolo)-[60]fullerene (**L159**). Mechanistic studies revealed a second reaction pathway, for example, the addition of azirine under photo-induced electron transfer (PET) conditions using 9,l0-dicyanoanthracene (DCA) as a PET sensitizer and light above 400 nm wavelength. In this case the addition obviously occurs *via* a 2-azaallenyl radical cation (**L158**). Aliphatic 2*H*-azirines are not suitable because they have a shorter excitation wavelength than the phenyl substituted 2*H*-azirines with forbidden π-π* transitions of the phenyl group (Scheme 1.78).



Scheme 1.78

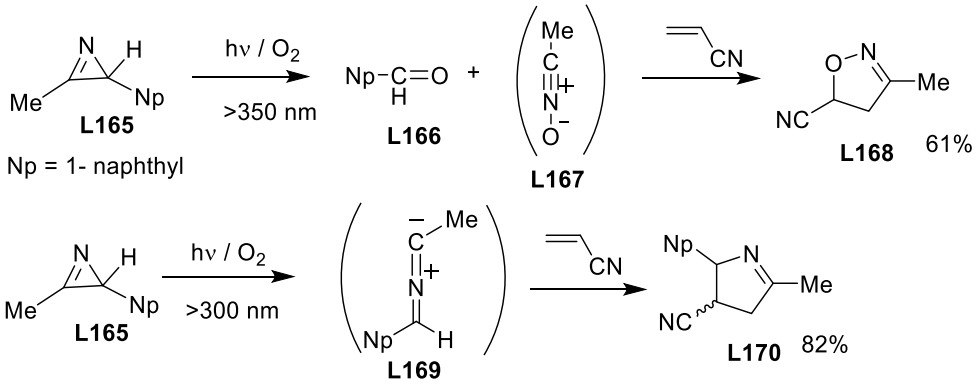
In 2000, Mazal and his group presumed that the nitrile ylide (**L160**) photochemically generated from 2,3-diphenyl-2*H*-azirine adds to both isomers of 3-

(tosyloxymethylene)tetrahydrofuran-2-one with excellent regio- and stereoselectivity giving spiroheterocyclic products (**L161, L162**) in moderate yields (50-52%) [96]. X-Ray structure determination showed dibutolactone to have the *E*-configuration; the corresponding *Z*-isomer was prepared photochemically (Scheme 1.79).



Scheme 1.79

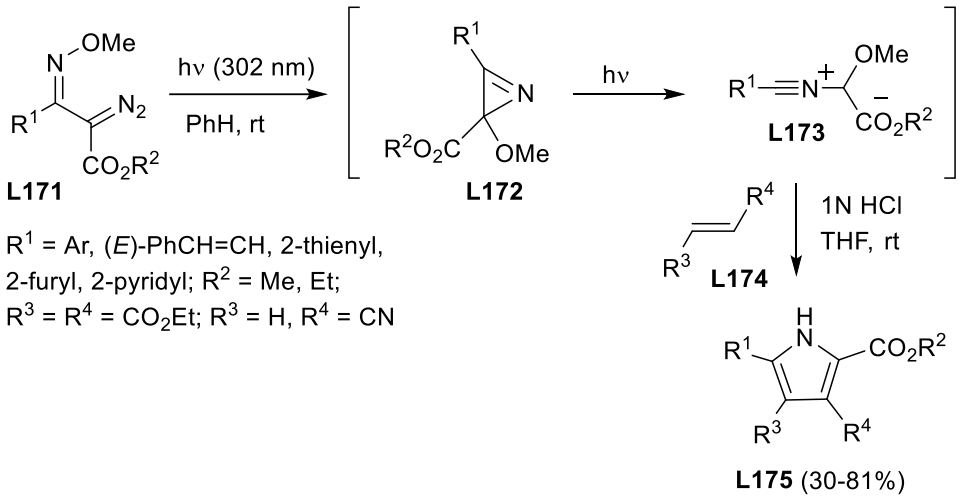
In 2005, Murata and co-workers investigated the photochemistry of 3-methyl-2-(1-naphthyl)-2*H*-azirine by the direct observation of reactive intermediates in matrixes at 10 K and by the characterization of reaction products in solutions [97]. As already reported, the photolysis of the azirine (**L165**) with the short-wavelength light (>300 nm) caused the C-C bond cleavage of the 2*H*-azirine ring to produce the nitrile ylide. However, the products derived from the C-N bond cleavage were exclusively obtained in the irradiation of 1a with the long-wavelength light (366 nm) both in matrixes and in solutions. When azirine (**L165**) was irradiated in the presence of O_2 with the long-wavelength light, acetonitrile oxide (**L167**) was produced through the capture of the biradical generated by the C-N bond cleavage of azirine (**L165**) by action of O_2 (Scheme 1.80).



Scheme 1.80

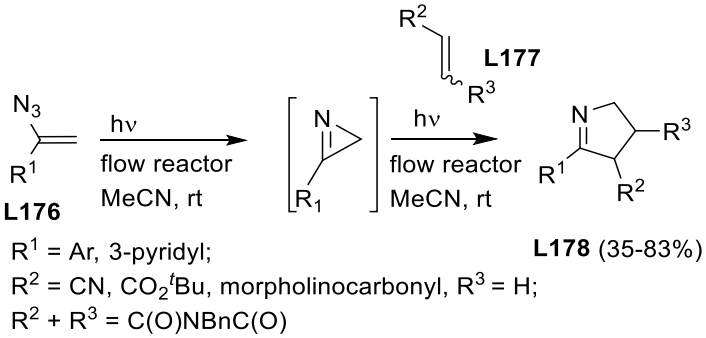
In 2012, Park *et al.* reported 2-methoxyazirine-2-carboxylates (**L172**), formed under photolysis of a diazo oxime ethers (**L171**), to generate nitrile ylides (**L173**) *via* azirine ring opening [98]. These undergo intermolecular 1,3-dipolar cycloaddition to electron-deficient alkenes (diethyl

fumarate and acrylonitrile) and intramolecular cycloaddition to unactivated alkenes (**L174**) to give the corresponding pyrroles (**L175**) in 30-81% yields (Scheme 1.81**)**.



Scheme 1.81

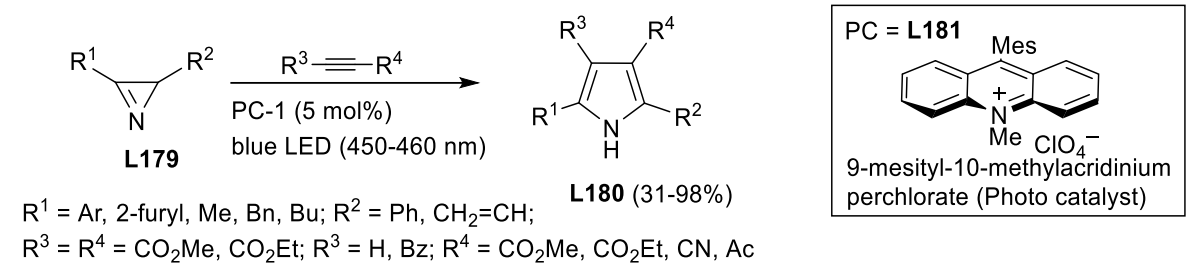
Next year, Kirschning group reported the synthesis of dihydropyrroles (**L178**) under flow conditions starting from aromatic vinyl azides (**L176**) and electron-deficient alkenes [99]. The reaction most likely proceeds *via* photoinduced *in situ* formation of the azirine intermediates. Nitrile ylides formed *via* azirine ring opening under UV-irradiation were trapped directly with electron-deficient alkenes (**L177**) to form (2+3) cycloaddition products. Azodicarboxylates and electron-deficient alkynes as dipolarophiles provided the corresponding 1,2,4-triazole and pyrrole (Scheme 1.82).



Scheme 1.82

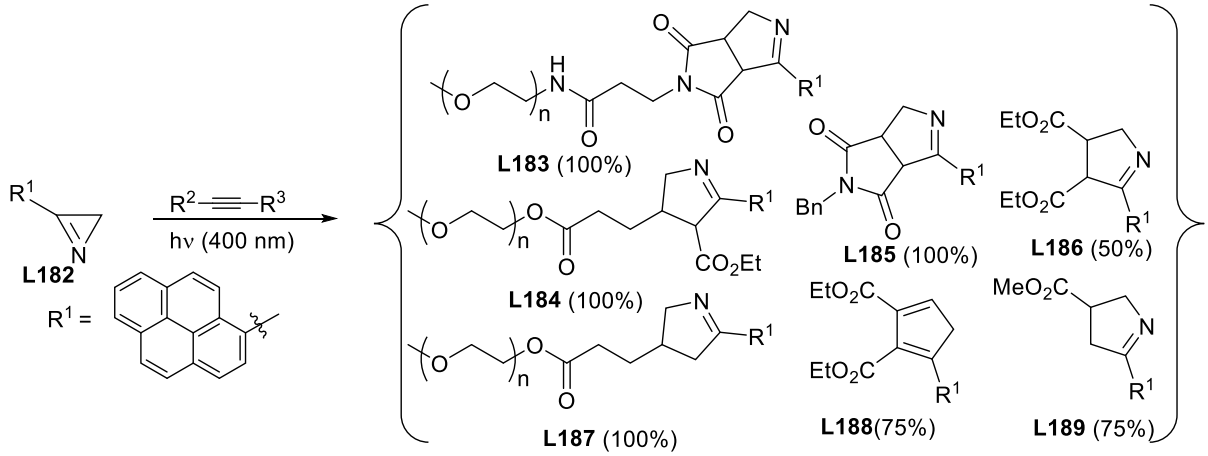
In 2014, Xiao *et al*. reported the photocatalytic formal [3+2] cycloaddition of 2,3-disubstituted azirines (**L179**) with electron-deficient alkynes under irradiation of visible light in the presence of an organic dye photocatalyst (**L181)** led to functionalized pyrroles (**L180**) in 31-98% yields [100]. The highest yields of pyrroles were obtained when dimethyl

acetylenedicarboxylate was used, whereas alkynes having only one activating group, e.g. acrylonitrile as well as alkyl acrylates are less effective in this reaction (Scheme 1.83).



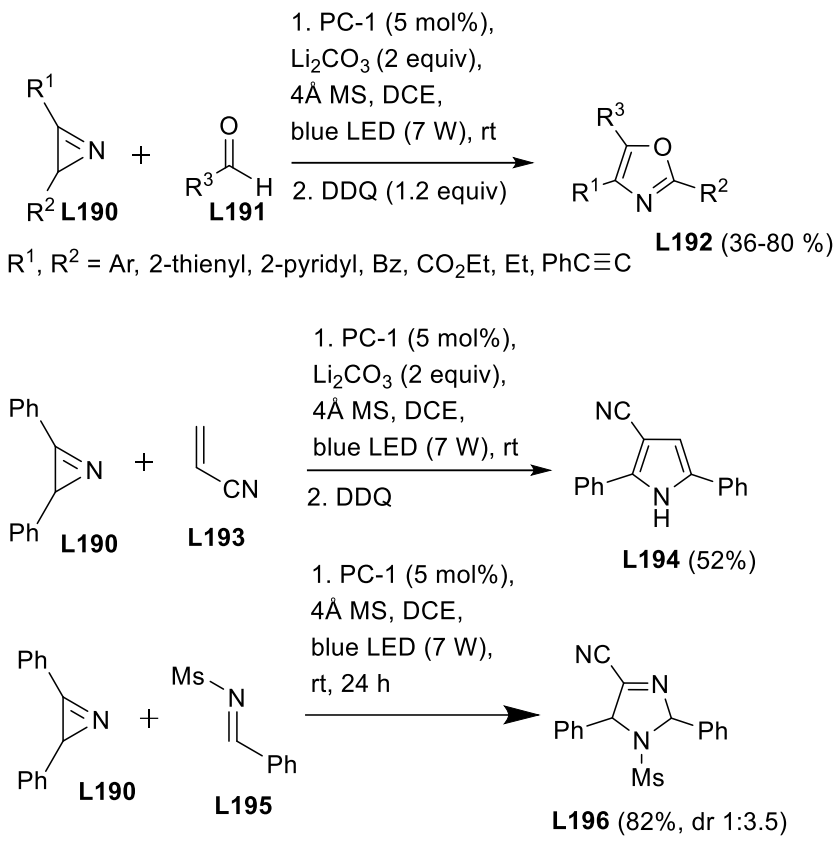
Scheme 1.83

A catalyst-free synthesis of pyrrole derivatives (**L183-L189**) *via* cycloaddition of photoreactive pyrenylazirine (**L182**) which is able to absorb light at wavelengths above 400 nm was developed by Barner-Kowollik group [101]. Irradiation of azirine with low-energy light sources in the presence of a diverse range of electron-deficient alkenes led to the corresponding 3,4-dihydro-2*H*-pyrrole derivatives. Quantitative ligation of the photoactivatable chromophore with functional polymeric substrates was performed and full conversion with irradiation times of only 1 min under ambient conditions was achieved (Scheme 1.84).



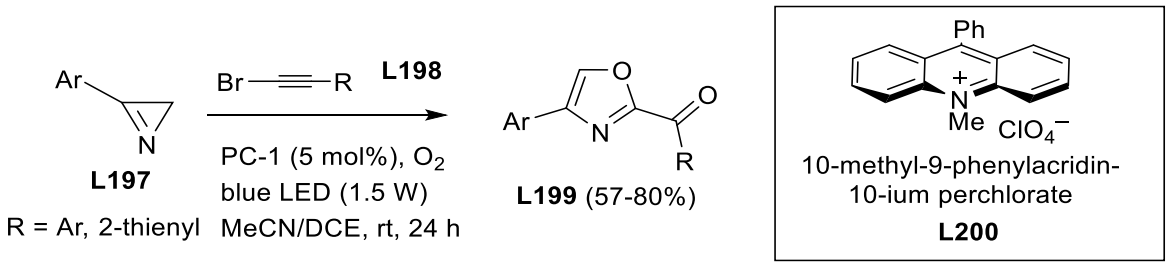
Scheme 1.84

In 2015, Xiao *et al.* reported the synthesis of 2,4,5-trisubstituted oxazoles (**L192**) from azirines (**L190**) and aldehydes (L191) *via* the [3+2] cycloaddition/oxidative aromatization sequence by the use of visible light-induced photoredox catalysis in 36-80% yields [102]. Acrylonitrile (**L193**) can be also used, and *via* the reaction with azirine (**L190**) it affording pyrrole (**L194**) in moderate yield (52%). Imine (**L195**) can also participate in the visible light-photocatalyzed [3+2] cycloaddition with azirine (**L190**) to afford 2,5-dihydroimidazole (**L196)** in 82% yield (Scheme 1.85).



Scheme 1.85

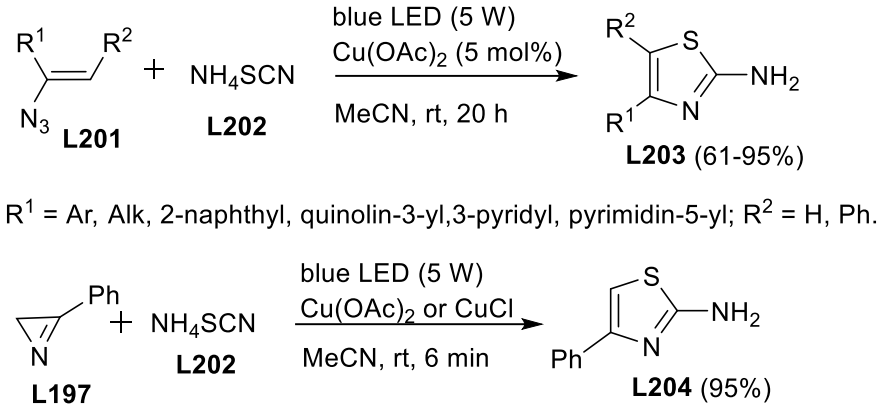
In 2016, Wang and co-workers developed the synthesis of a wide range of 2,4-disubstituted oxazoles (**L199**) in moderate to good yields (57-80%) by three-component annulation of azirines (**L197**) with bromoalkynes (**L198**) in the presence of molecular oxygen at room temperature under visible light irradiation using acridinium salt (**L200**) as an organic photocatalyst (Scheme 1.86) [103].



Scheme 1.86

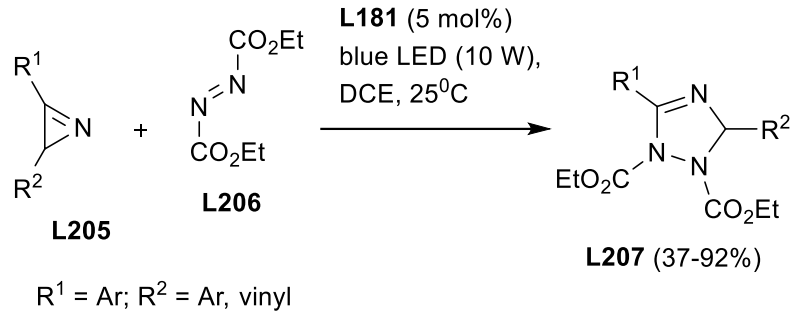
In the next year, W. Lei and his group found, ammonium thiocyanate (**L202**) as an excellent annulations reagent for the preparation of 4-alkyl/aryl-2-aminothiazoles (**L203**) (in 61-95% yields) from vinyl azides (**L201**) [104]. The reaction proceeds smoothly in the presence of $Cu(OAc)_2$ under blue LED irradiation at room temperature. It was demonstrated that other copper salts (CuCl, CuBr, CuSCN) can also catalyze the reaction effectively. The mechanism of this reaction involves

the formation of $Cu(NCS)_2^-$ that works as the photocatalyst to activate vinyl azides and as the Lewis acid catalyst to promote *N*-C2 bond cleavage of the intermediate azirines with thiocyanate. The involvement of the azirine (**L197**) in the reaction is not in doubt since both $Cu(OAc)_2$ and CuCl-catalyzed reactions of 3-phenyl-2*H*-azirine with NH_4SCN produced the 2-aminothiazole (**L204**) in 95% yield (Scheme 1.87).



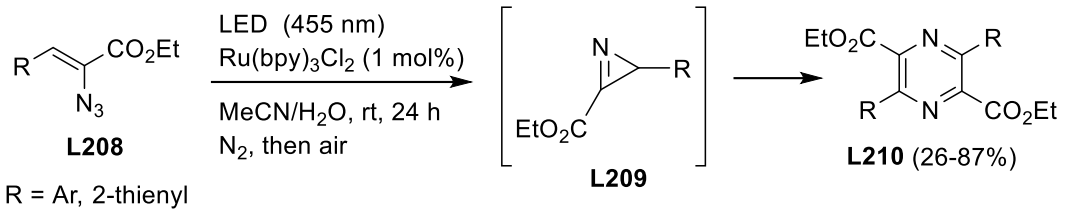
Scheme 1.87

In the same year, Tang and group reported, the reaction of azirines (**L205**) with azodicarboxylates (**L206**) under visible light LED irradiation afforded 1,2,4-triazolines (**L207**) in up to 92% yields [105]. A plausible pathway involves azirine oxidation by the photoredox catalyst (**L181**) under visible light to give 2-azaallenyl radical cation, which reacts with azodicarboxylate. The asymmetric reaction was also attempted using the chiral photosensitizer as the catalyst based on the ion-pair strategy; however, only 20% *ee* was achieved (Scheme 1.88).



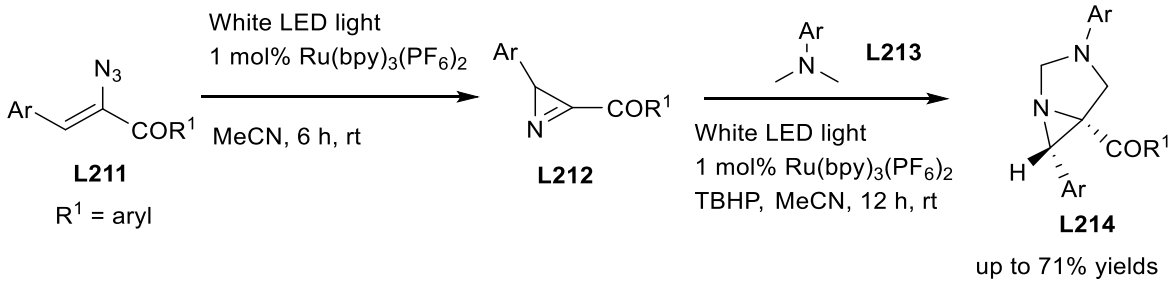
Scheme 1.88

In the year 2017, Reiser and co-workers activated the vinyl azides (**L208**) by a triplet sensitization process from an excited ruthenium photocatalyst in the presence of water to form dihydropyrazines *via* intermediate azirine (**L209**). Further a single-electron transfer process under air atmosphere led to the tetrasubstituted pyrazines (**L210**) in good to excellent yields (up to 87%) (Scheme 1.89) [106].



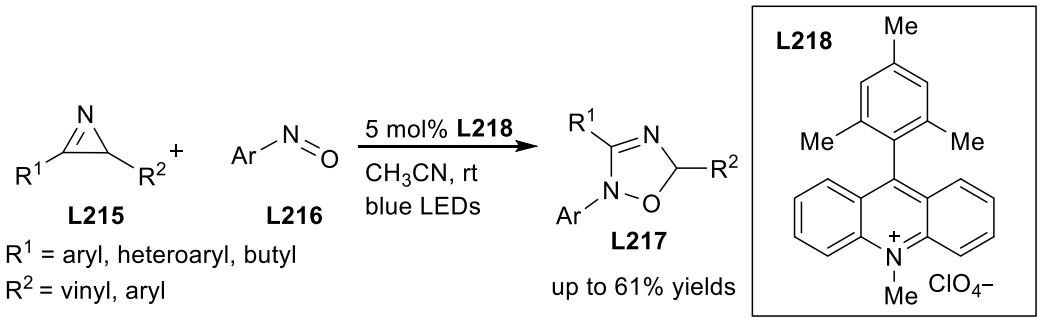
Scheme 1.89

Maurya group reported that *N,N*-dimethylanilines (**L213**) were coupled with *α*-azidochalcones (**L214**) under visible-light driven $Ru(bpy)_3(PF_6)_2$ catalyzed photocascade continuous flow microfluidic approach that involves the creation of one C−C and two C−N new bonds [107]. The reaction involves dual photocatalysis ensuing two sp^3 C−H bond functionalization of *N,N*-dimethylanilines uder the action of azirines (**L212**) formed from (**L211**). To explore the scope of the reaction, 20 different 1,3-diazabicyclo[3.1.0]hexanes (**L214**)were synthesized in up to 71% yields (Scheme 1.90).



Scheme 1.90

Recently, Xiao *et al*. achieved a formal [3+2] cycloaddition reaction of 2*H*-azirines (**L215**) with nitrosoarenes (**L216**) under irradiation by visible light with the assistance of organic dye photoredox catalyst (**L218**). This method utilizes nitrosoarenes as efficient radical acceptors and provides a green and powerful method for a series of biologically important 1,2,4-oxadiazole (**L217**) derivatives in up to 61% yields (Scheme 1.91) [108].



Scheme 1.91

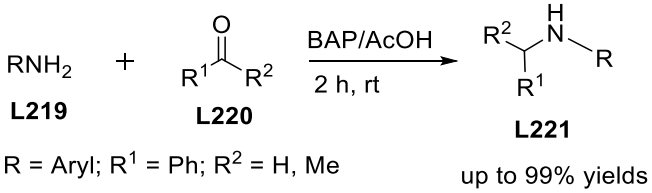
1.2. STUDY OF THE FUNCTIONALIZATION PROCESSES OF C(H)Y (Y≠C) BONDS IN AZOMETHINES

Aziri(di)nes are known to transform into azomethine derivatives. On the other hand, azomethines themselves are capable of cyclizing into these azaheterocycles. As a result, azomethines can be considered both as transformation products of aziri(di)nes and as their synthetic precursors. Therefore, as part of our work, we investigated the synthesis methods and reactivity of azomethines in some key transformations. Below, a brief literature analysis on this topic will be presented.

1.2.1. Reactions between amino- and carbonyl components and some other transformations

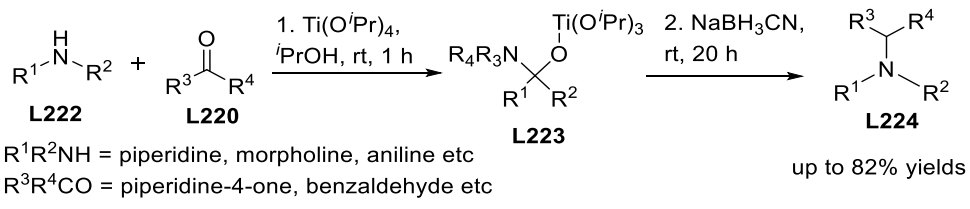
A typical method for the synthesis of azomethines is the interaction of the carbonyl and amino components in various conditions. Reductive amination of aldehydes/ketones is considered as a convenient approach to substituted amines as azomethines are capable of undergoing reduction in the presence of various types of reducing agents, including the presence of formic acid/formates to afford target amines. Due to the widespread applications of amines, several methods have been devised and reported in the literature.

In 1984, Pelter *et al*. reported a borane-pyridine (BAP) system for the reductive amination of a wide variety of carbonyl compounds (**L220**) under the action of amines (**L219**) to afford multisubstituted amines (**L221**) in up to 99% yields (Scheme 1.92) [109].



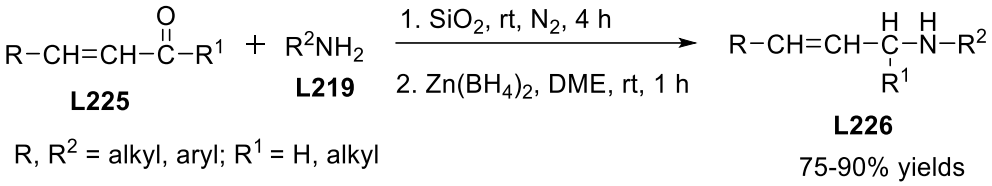
Scheme 1.92

In 1990, Mattson and co-workers observed that in the reductive amonation reaction of ketones (**L220**) with amines (**L222**) titanium(IV)isopropoxide can be used as a Lewis acid to generate complexes (**L223)** which were then reduced by the sodium cyanoborohydride in up to 82% yields (Scheme 1.93) [110].



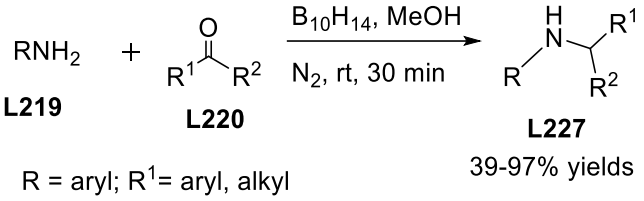
Scheme 1.93

Ranu and co-workers in 1998, reported various examples of reductive amination of conjugated aldehydes and ketones (**L225**) with an aprotic amines (**L219**) in the presence of silica gel followed by the addition of zinc borohydride in a one-pot operation and afforded the target amones (**L226**) in 75-90% yields (Scheme 1.94) [111].



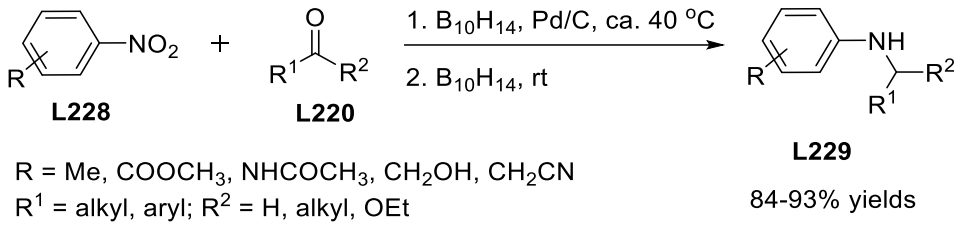
Scheme 1.94

In 2000, Bae *et al*. established a reductive amination of aldehydes and ketones (**L220**) by the reaction of amines (**L219**) in methanol using decaborane ($B_{10}H_{14}$) at room temperature under nitrogen, which afforded amines (**L227**) in up to 97% yields (Scheme 1.95) [112].



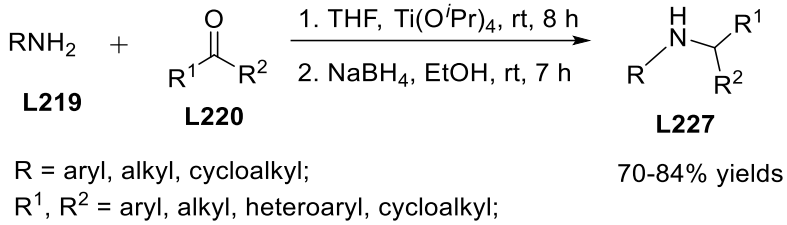
Scheme 1.95

The same group reported the preparation of *N*-alkylaminobenzenes (**L229**, 84-93% yields) by reduction of nitrobenzenes (**L228**) followed by reductive amination of ketones (**L220**) with decaborane ($B_{10}H_{14}$) in the presence of 10% Pd/C catalyst (Scheme 1.96) [113].



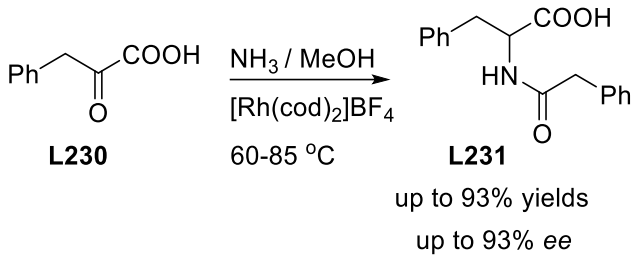
Scheme 1.96

In 2003, Kumpaty and co-workers described reductive amination of aldehydes and ketones (**L220**) by the reaction of amines (**L219**) in THF using a combination of Ti(^{i}PrO)$_4$ and $NaBH_4$ at room temperature and obtained amines (**L227**) in 70-84% yields (Scheme 1.97) [114].



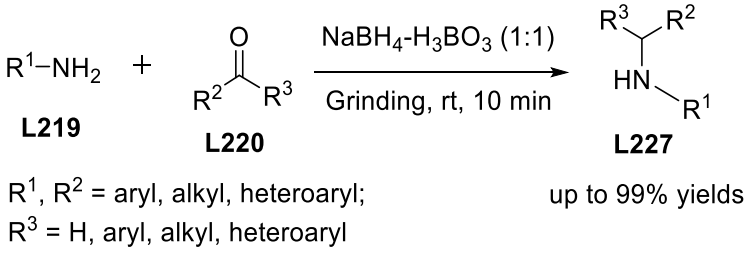
Scheme 1.97

In the same year, Kadyrov and Riermeier reported the reaction of phenylpyruvic acid (**L230**) in methanolic ammonia at 60 °C in the presence of a Rh-catalyst smoothly converted to *N*-(phenylacetyl) phenylalaninamide (**L231**) in up to 93% yields with up to 95% *ee* (Scheme 1.98) [115].



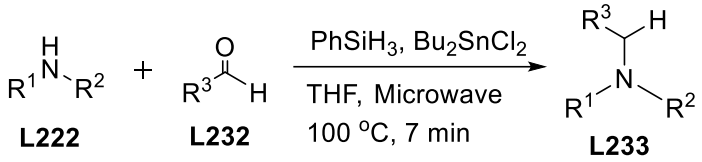
Scheme 1.98

In 2005, Cho and Kang described a reductive amination reaction of aldehydes and ketones (**L220**) uner the action of amines (**L219**) using sodium borohydride activated by boric acid, *p*-toluenesulfonic acid monohydrate or benzoic acid as reducing agent under solvent-free conditions and up to 99% yields were obtained (Scheme 1.99) [116].



Scheme 1.99

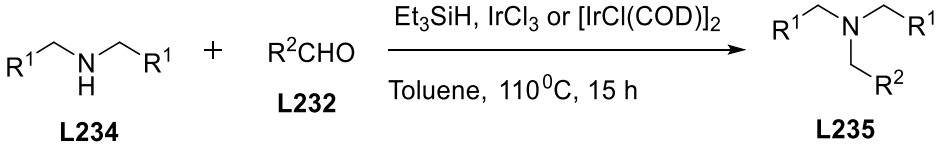
In the same year, Kangasmetsa and Johnson reported a procedure for the direct reductive amination of aldehydes (**L232**) with amines (**L222**) using dibutyltin dichloride as catalyst in the presence of phenylsilane as reductant [117]. Rapid reaction is promoted by the use of microwave conditions with anilines, secondary and primary amines being suitable reactants and afforded target amines (**L233**) in 41-93% yields (Scheme 1.100).



R^1 = aryl, alkyl, cyclohexyl, morpholine, benzyl, *N*-Bocpiperazine;
R^2 = H; R^3 = aryl, alkyl, vinyl

Scheme 1.100

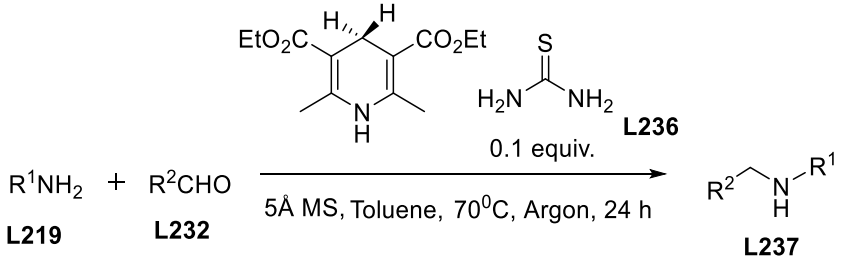
A methodology for the reductive alkylation of secondary amine (**L234**) with aldehyde (**L232**) and Et_3SiH using an iridium complex as a catalyst has been reported in 2005 by Y. Ishii and co-workers [118]. Treatment of amine (**L234**) with aldehyde (**L232**) and Et_3SiH (1:1:1) in 1,4-dioxane at 110 °C under the influence of a catalytic amount of $[IrCl(COD)]_2$. In this reaction, no reduction of aldehyde took place. It was found that $IrCl_3$, which is a starting material for preparation of iridium complexes such as $[IrCl(COD)]_2$, acts as catalyst for the present reductive alkylation of amine (Scheme 1.101).



R^1 = alkyl, benzyl, piperidine, morpholine
R^2 = alkyl, benzyl

Scheme 1.101

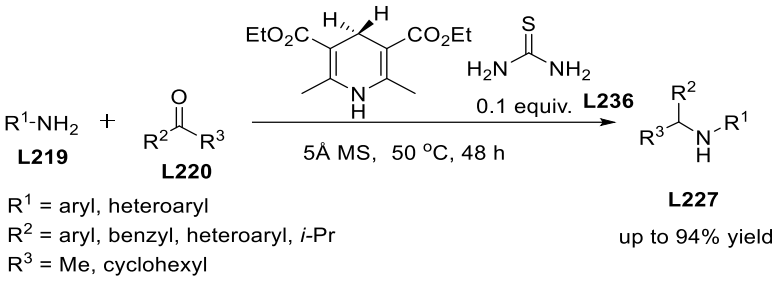
In the next year, Menche and Arikan observed a hydrogen-bond-catalyzed direct reductive amination of aldehydes (**L232**) with amines (**L219**) [119]. The acid- and metal-free process used thiourea as organocatalyst (**L236**) and the Hantzsch ester for transfer-hydrogenation and allows for the high-yielding synthesis (up to 93%) of diverse amines (**L237**) (Scheme 1.102).



R^1 = aryl, heteroaryl; R^2 = aryl, alkyl

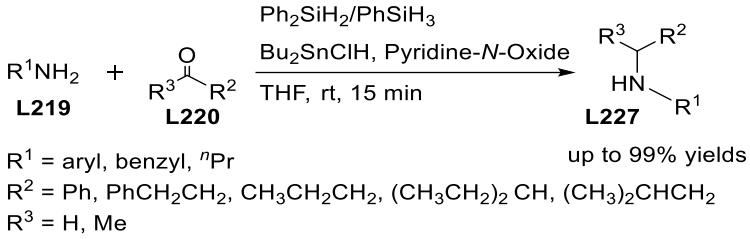
Scheme 1.102

A direct reductive amination of ketones (**L220**) with amines (**L219**) that relies on selective imine activation by hydrogen bond formation has also been reported in 2006 by same the group [120]. The mild, acid- and metal-free process requires only catalytic amounts of thiourea (**L236**) as hydrogen bond donor and utilizes the Hantzsch ester for transfer hydrogenation. The method allows the efficient synthesis of structurally diverse amines (**L227**) in up to 94% yields (Scheme 1.103).



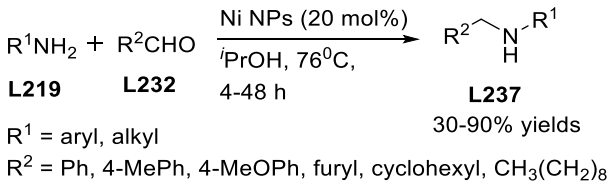
Scheme 1.103

In the same year, Baba and co-workers reported the reductive amination of aldehydes or ketones (**L220**) with amines (**L219**) using Ph_2SiH_2 or $PhSiH_3$ promoted by the direct use of Bu_2SnClH–pyridine *N*-oxide as a catalyst. This method has advantages in terms of its mild conditions and wide application to various carbonyls and amines, including aliphatic examples as well as excellent yields (up to 99%) of target amines (**L227**) (Scheme 1.104) [121].



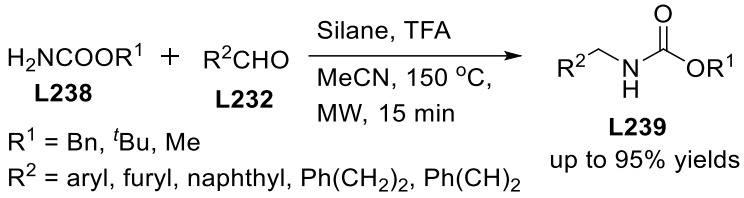
Scheme 1.104

Alonso and his group in 2008 used nickel nanoparticles as a catalyst for the reductive amination of aldehydes (**L232**) with amines (**L219**) utilized *iso*-propanol for transfer hydrogenation in absence of any added base. Target amines (L237) were obtaines in 30-90% yields (Scheme 1.105) [122].



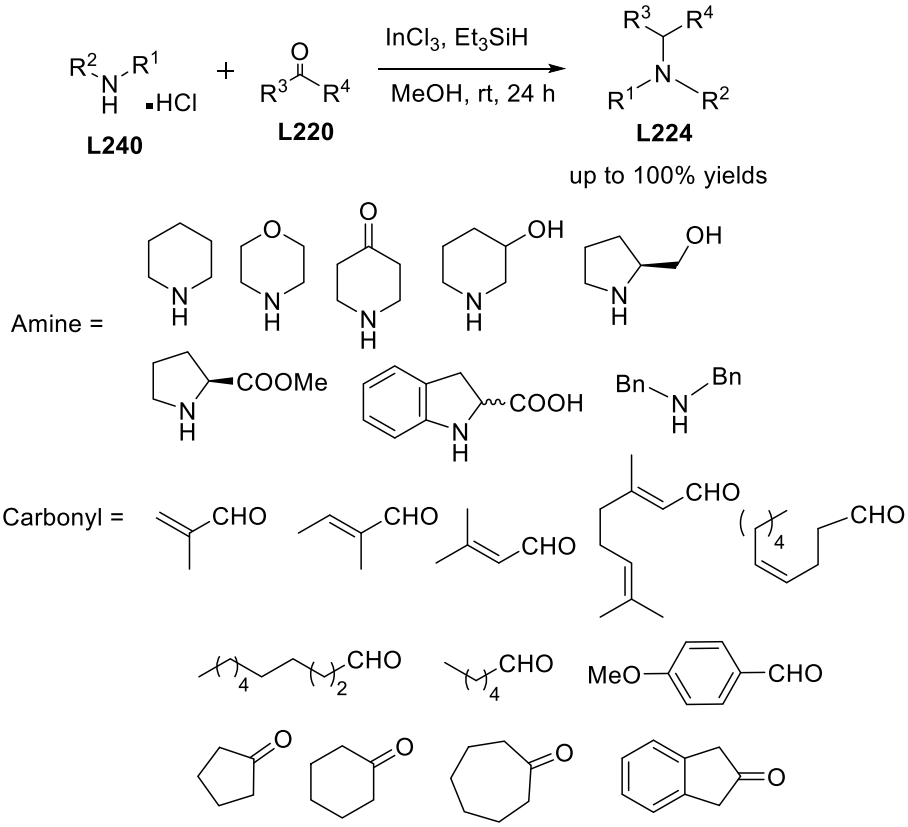
Scheme 1.105

In the same year, Lehmann and Scobie reported microwave-assisted reductive alkylation of methyl carbamate (**L238**) with a range of aldehydes (**L232**) with excellent yields of target amines (**L239**) (up to 95%) by using *tert*-butyldimethylsilane (TBDMSH) as a reducing agent [123]. This is a rapid functional group inter-conversion of structurally diverse aldehydes into primary amines (Scheme 1.106).



Scheme 1.106

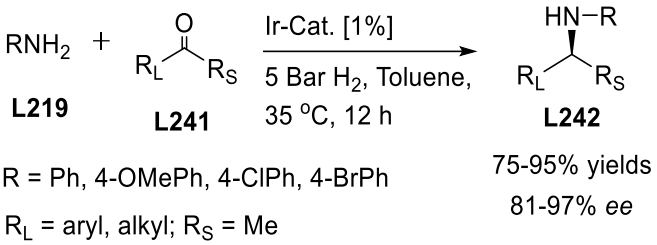
Yang and his group in 2008 conveyed a concept for the reductive amination of aldehydes and ketones (**L220**) with various secondary amines (**L240**), including *L*-proline, in the presence of $InCl_3/Et_3SiH$/MeOH system, which was nontoxic, highly chemoselective, high yielding (up to 100% target amines (**L224**)) and water-tolerating one (Scheme 1.107) [124].



Scheme 1.107

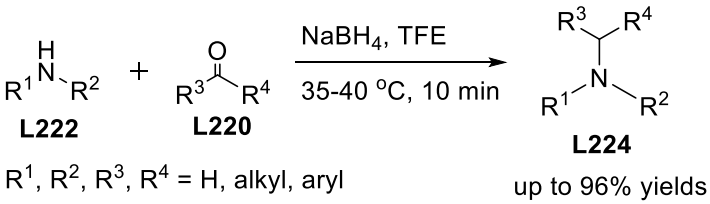
In the next year, Xiao and his group used a half-sandwich Cp*M(III)-diamine (M=Rh,Ir) catalysts for the direct asymmetric reductive amination (DARA) of prochiral ketones (**L241**) with

aniline (**219**) and its electron-deficient analogues [125]. This half-sandwich catalyst enables highly enantioselective (up to 97% *ee*) hydrogenation of both cyclic and acyclic imines, and reaction afforded target amines (**L242**) in 75-95% yields (Scheme 1.108).



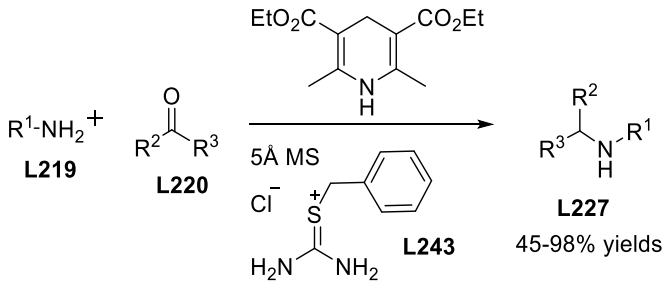
Scheme 1.108

In 2011, Tajbakhsh and co-workers reported a convenient procedure for the reductive alkylation of primary and secondary amines (**L222**) and *N*,*N*-dimethylation of amino acids in up to 96% yields by using sodium borohydride as a reducing agent in 2,2,2- trifluoroethanol without use of a catalyst or any other additive (Scheme 1.109) [126].



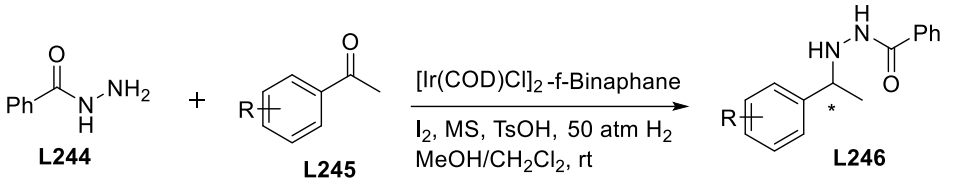
Scheme 1.109

Kim and co-workers in 2012 discussed about the direct reductive amination of ketones (**L220**) with amines (**L219**) using the Hantzsch ester in the presence of *S*-benzyl isothiouronium chloride (**L243**) as a recoverable organocatalyst [127]. A wide range of ketones as well as amines were found to give the expected products (**L227**) in moderate to excellent yields (45-98%) (Scheme 1.110).



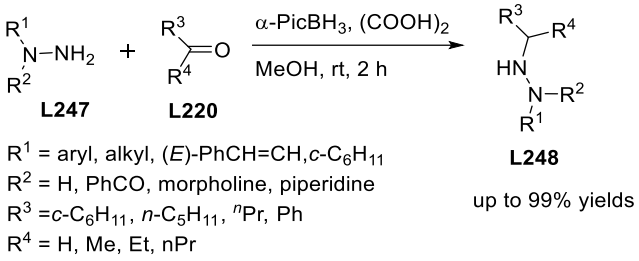
Scheme 1.110

In 2013, Zhang and co-workers reported a green method for the preparation of chiral amine (**L246**) synthesis and the direct catalytic asymmetric reductive amination using ketones (**L245**) and phenylhydrazide (**L244**) which is an ideal nitrogen source for reductive amination. Molecular sieves play dual roles in this reaction [128]. The reaction afforded up to >99% yields with 94% *ee*. *f*-Binaphane minimizes the inhibition effect from amines and helps the coordination of sterically demanding imines to the iridium center (Scheme 1.111).



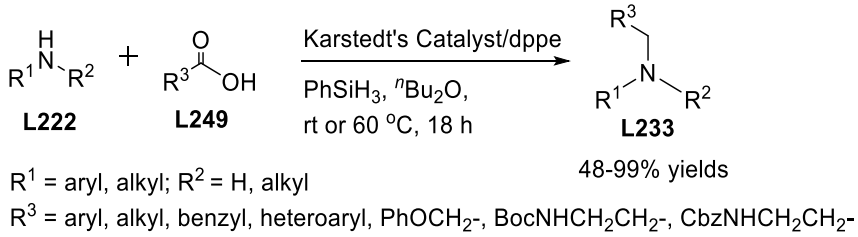
Scheme 1.111

In the same year, Yokomatsu and group reported an efficient method for the direct reductive alkylation of hydrazine derivatives (**L247**) of ketones (**L220**) with α-picoline-borane to synthesize a variety of *N*-alkylhydrazine derivatives (**L248**) in up to 99% yields [129]. This method provided *N*,*N*-dialkylhydrazine derivatives and *N*-monoalkylhydrazine derivatives upon fine-tuning of the substrates and the reagent equivalency in a one-pot manner (Scheme 1.112).



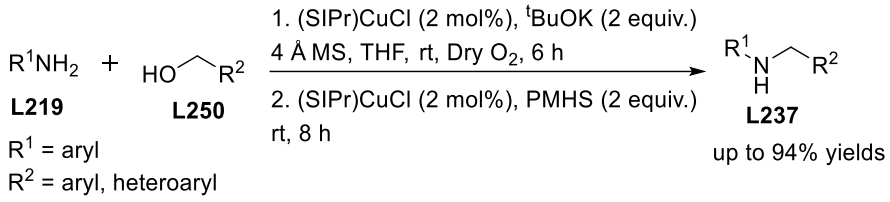
Scheme 1.112

In 2014, Beller and co-workers described a straightforward process for the *N*-alkylation of amines (**L222**) applying carboxylic acids (**L249**), phenylsilane as the hydride source, commercially available Karstedt catalyst ([Pt(CH_2=$CHSiMe_2$)$_2$O]) and 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand which has a slightly higher selectivity for the monoalkylation affording the target amines (**L233**) with 48-99% yields (Scheme 1.113) [130].



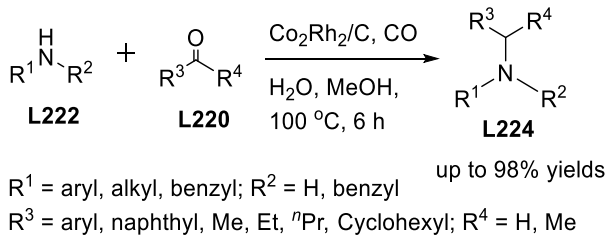
Scheme 1.113

In the next year, Jiang and his group reported a one-pot tandem synthetic strategy for the amination of alcohols (**L250**) with amines (**L219**), which provided useful imines and secondary amines (**L237**) *via* an oxidation-reduction strategy [131]. Copper *N*-heterocyclic carbene complex was used as catalysts for both aerobic oxidation of alcohols to aldehydes and reduction of imines to amines with up to 94% yields (Scheme 1.114).



Scheme 1.114

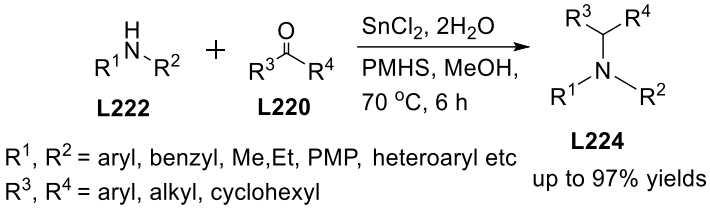
In 2015, Park and Chung reported cobalt−rhodium heterobimetallic nanoparticle catalyst for the reductive amination of aldehydes and ketones (**L220**) with amines (**L222**) afforing the target amines (**L224**) in up to 98% yields. Reaction was carried out in the presence of 5 atm carbon monoxide without any external hydrogen source [132]. Water was added to the reaction mixture to produce hydrogen *in situ via* a water-gas-shift reaction. According to the authors, the reaction can be extended to the tandem reduction of aldehydes and ketones with nitroarenes. The catalytic system was stable under the reaction conditions and could be reused eight times without losing any catalytic activity (Scheme 1.115).



Scheme 1.115

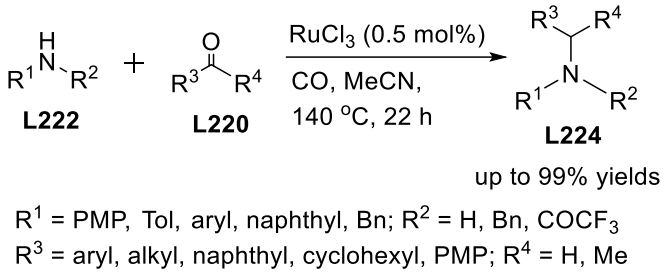
In the same year, Kumar and his group reported stannous chloride catalyzed chemoselective reductive amination of a variety of carbonyl compounds (**L220**) with aromatic

amines (**L222**) for the synthesis of a diverse range of tertiary amines (**L224**) in up to 97% yields using inexpensive polymethylhydrosiloxane as reducing agent in methanol [133]. This method is also applicable for the synthesis of secondary amines including heterocyclic ones (Scheme 1.116).



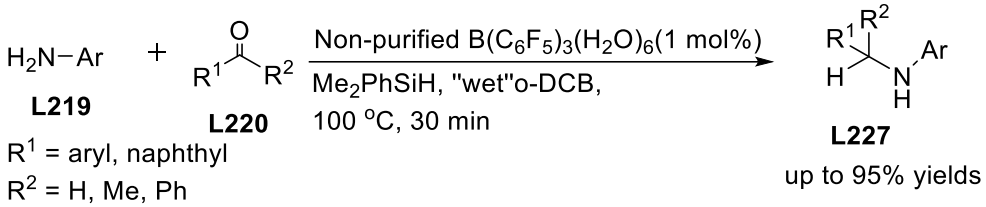
Scheme 1.116

Chusov and his group also investigated in the same year a ruthenium-catalyzed reductive amination of ketones (**L220**) with amines (**L222**) affording the target products (**L224**) in up to 99% yields without an external hydrogen source using carbon monoxide as the reductant and ruthenium(III) chloride as the catalyst (Scheme 1.117) [134].



Scheme 1.117

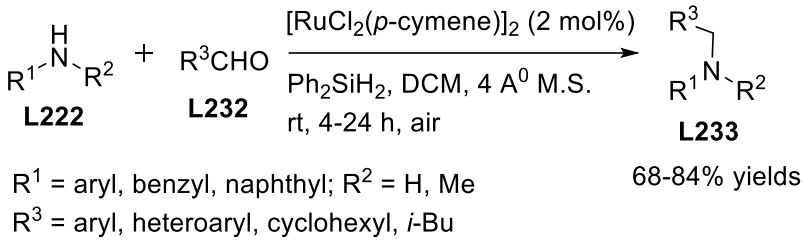
In 2016, Ingleson and co-workers reported a reductive amination of carbonyl compounds (**L220**) with amines (L219) using 1 mol% non-purified $B(C_6F_5)_3$ as catalyst, dehydrosilylation and 'wet solvents' for the production of secondary and tertiary arylamines (**L227**) in high yield (up to 95% yields) (Scheme 1.118) [135].



Scheme 1.118

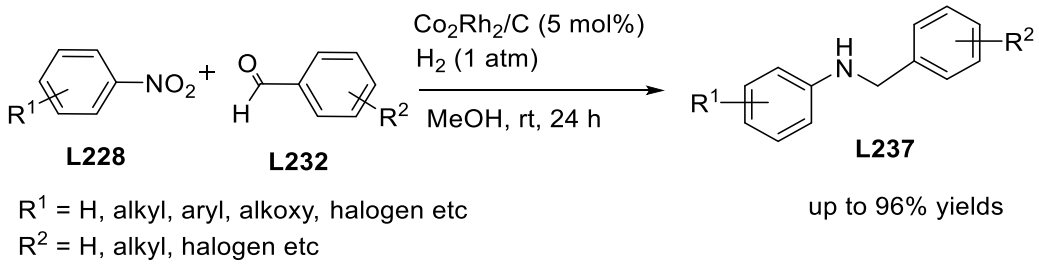
Li and co-workers in the same year also used a $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalyst for the direct reductive amination of aldehydes (**L232**) with anilines (**L222**) affording the target amines (**L233**) in 68-84% yields [136]. The $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system was

very efficient for the synthesis of secondary and tertiary amines in good yields, and this system was highly chemoselective, tolerating a wide range of functional groups, such as NO_2, CN, CO_2Me, F, Cl, Br, OMe, Me, furyl and alkyl (Scheme 1.119).



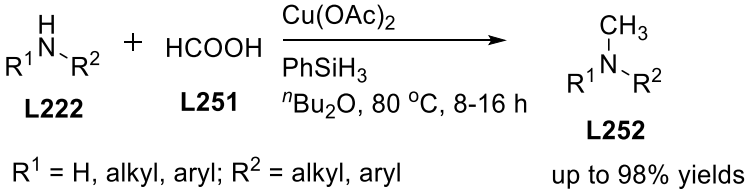
Scheme 1.119

In 2017, Chung and co-workers reported cobalt-rhodium heterobimetallic nanoparticle (Co_2Rh_2/C)-catalyzed tandem reductive amination of aldehydes (**L232**) with nitroaromatics (**L228**) affording the target secondary amines (**L237)** in up to 96% yields [137]. The tandem reaction proceeds without any additives under mild conditions (1 atm H_2 and 25 °C) (Scheme 1.120).



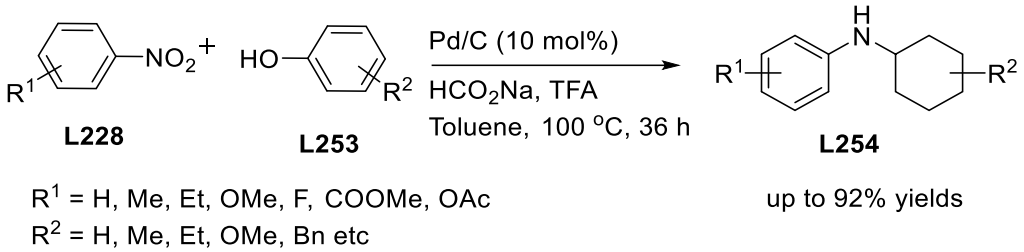
Scheme 1.120

He *et al*. in 2017 reported a copper-catalyzed protocol for reductive methylation of amines (**L222**) and in situ formed imines with formic acid (**L251**) as a C1 source and phenylsilane as a reductant, affording the corresponding methylamines (**L252**) in up to 98% yields [138]. This protocol offers an alternative method for indirect utilization of CO_2, as formic acid can be readily obtained from hydrogenation of CO_2 (Scheme 1.121).



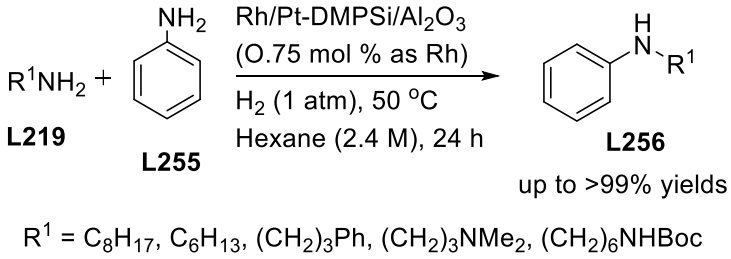
Scheme 1.121

In the next year, He and co-workers explored a direct and efficient palladium-catalyzed reductive coupling reaction of nitroarenes (**L228**) with phenols (**L253**) [139]. A series of *N*-cyclohexylaniline derivatives (**L254**) was obtained in up to 92% yields *via* C–N bond formation by the use of inexpensive sodium formate as the hydrogen donor (Scheme 1.122).



Scheme 1.122

Recently, Kobayashi and co-workers discussed a highly selective reductive cross-amination using aniline (**L255**) or nitroarenes and alkylamines (**L219**) catalyzed by heterogeneous Rh/Pt bimetallic nanoparticles under mild conditions for obtaining *N*-alkylated cyclohexylamine derivatives (**L256**) in up to >99% yields [140]. The catalyst was recovered and reused for five runs, keeping high activity. In this reaction, imine intermediates generated during the course of partial hydrogenation of aniline derivatives were trapped immediately by strongly interacting primary alkylamines with the catalyst, which caused a highly selective transformation to give the desired products, while suppressing dicyclohexylamine formation (Scheme 1.123).



Scheme 1.123

1.2.2. Azomethines and aldehydes as building blocks for the preparation of azaheterocycles

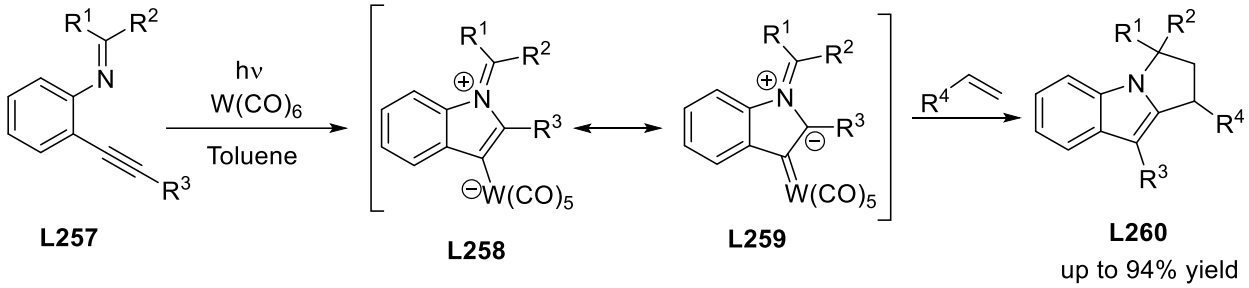
In heterocyclic chemistry azomethines are common donors of C-C-N moieties. Below some typical examples of such reactions will be discussed.

1.2.2.1. Synthesis of indoles

Indoles and isoindoles are among the most abundant and relevant heterocycles in natural products and pharmaceuticals [141, 142]. The synthesis of indole systems is among the topic of research worldwide for over 100 years, and a variety of well-established classical methods are now

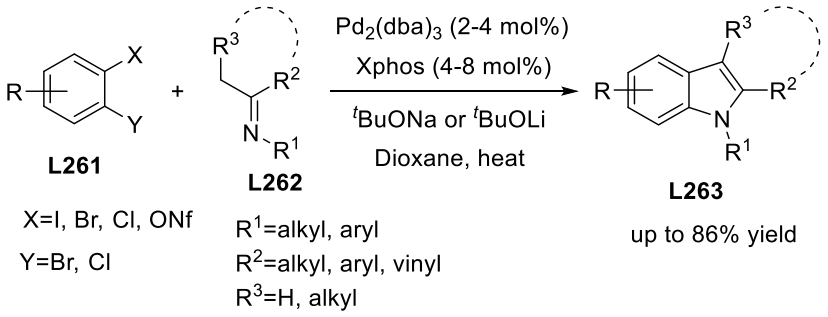
available. Herein, we will highlight the most common methods for the synthesis of indoles involving azomethines.

Kusama and co-authors reported a method for the preparation of cyclopentane-fused indole deriavatibes, by means of reaction between *N*-(*o*-alkynylphenyl)imine derivatives (**L257**) with $W(CO)_5$ (L) (Scheme 1.124). The cyclization of the imine nitrogen onto the electrophilically activated alkyne moiety afforded a metal-containing azomethine ylide (**L258-259**). [3+2] Cycloaddition of this ylide species with various electron-rich alkenes resulted in unstable carbene complexes, which afforded tricyclic indoles (L260) substituted with aryl or alkyl moieties at the 3-position of the indole nucleus [143].



Scheme 1.124

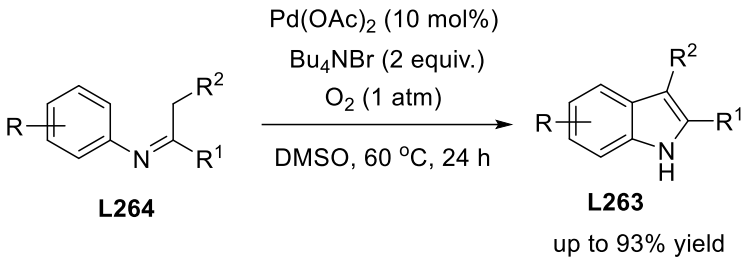
Barluenga and co-authors reported a detailed research on the application of new Pd-catalyzed synthesis of indoles from 1,2-dihaloarenes and *o*-halobenzene sulfonates (**L261**) and imines (**L262**) is described (Scheme 1.125). The synthesis was based on the cascade reaction, involving *α*-arylation of imines followed by an intramolecular C–N bond-forming reaction promoted by the same Pd catalyst. Using the model reaction with 1,2-dibromobenzene the authors confirmed its applicability for a wide scope of aryl, alkyl, and vinyl substituents to be introduced to different positions of the target indoles (**L263**) [144].



Scheme 1.125

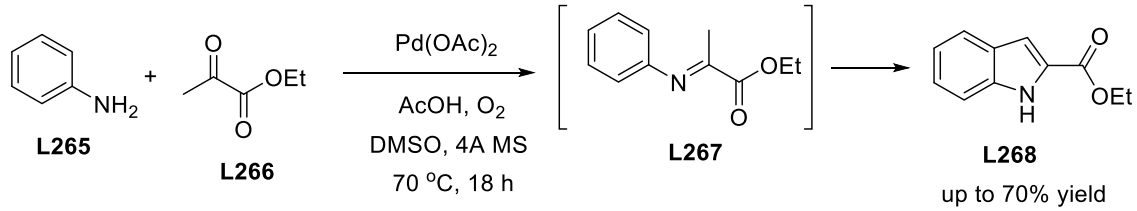
Wei and co-authors reported a simple, palladium-catalyzed cyclization reaction of *N*-aryl imines (**L264**), to afford 2,3-disubstituted indoles (**L263**) (Scheme 1.126) [145]. The key step of

the reaction is the oxidative linkage of two C–H bonds in the presence molecular oxygen as the sole oxidant. This process is quick, atom-economical and tolerates a broad range of functional groups with up to 93% yield of target indoles.



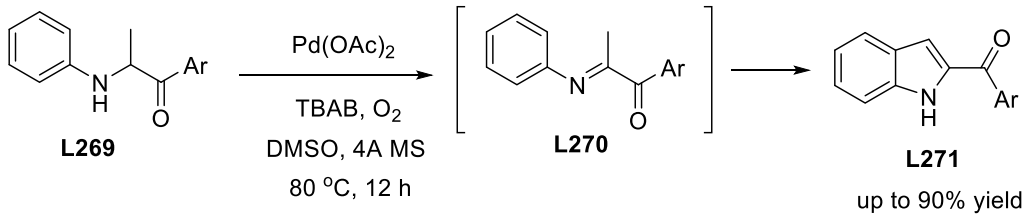
Scheme 1.126

Ren *et al.* developed a single-step synthesis of indoles from simple anilines (**L265**) and ketones (**L256**) by using organic acid catalysis under aerobic oxidation (using ambient oxygen) conditions in the presence of $Pd(OAc)_2$ (Scheme 1.127) [146]. The reaction affords a broad substrate scope in up to 70% yields. According to the authors, the *in situ* formed imine was involved in the first ligand exchange and later carbopalladation of the *α*-Me to afford the target products (**L268**).



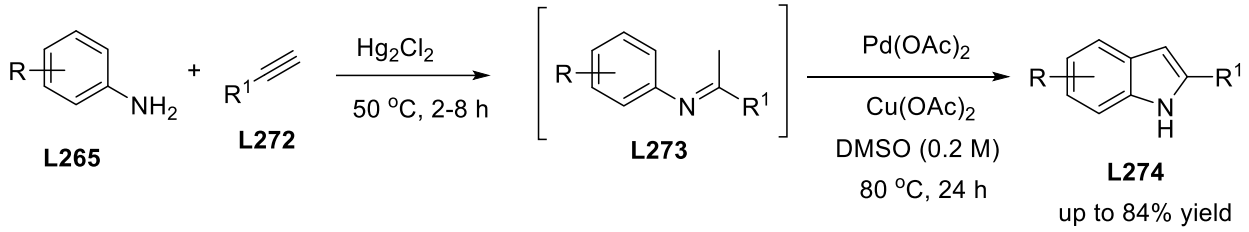
Scheme 1.127

Zhang and co-authors reported an exxicient synthesis of 2-aroylindoles (**L271**) *via* palladium-catalyzed tandem oxidative annulation of *α*-aminoketones (**L269**) (Scheme 1.128). According to the authors the two-step reaction takes place, which involves initial oxidation of *α*-aminoketones to generate imine, and the subsequent palladium-catalyzed aerobic annulation of last ones afforded desired 2-aroylindoles in one pot in up to 90% yield [146].



Scheme 1.128

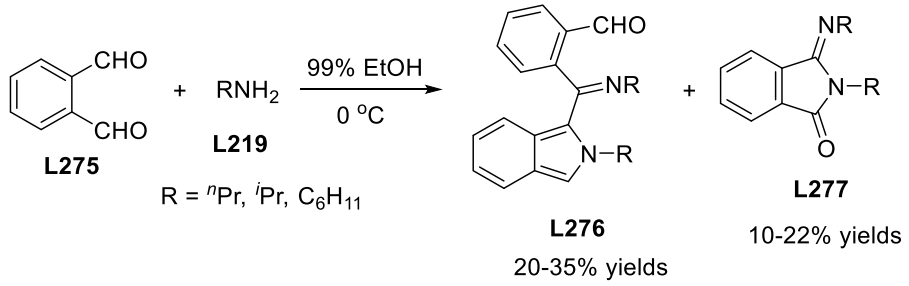
Rsuini *et al.* reported an efficient synthetic approach to various 2-substituted inoles (**L274**) through a regioselective Hg(I)-catalyzed hydroamination of terminal acetylenes (**L272**) in the presence of anilines affording ketimines (**L273**) with their following Pd(II)-catalyzed cyclization vis C-H activation (Scheme 1.129). The target products were obtained in up to 84% yields. According to the authors, the arylacetylenes proved to be more effective than the alkyl derivatives [147].



Scheme 1.129

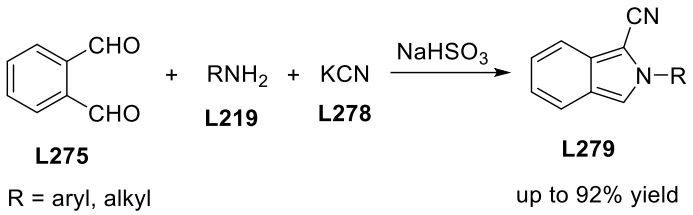
1.2.2.2. Synthesis of isoindoles and their fused derivatives

The most common method for the preparation of isoindoles is the condensation reaction between *o*-phenylenedialdehyde (OPD, *o*-terephthalic aldehyde) or its derivatives with aminicomponents. Thus, Nanya and co-authors reported the synthesis of isoindoles (**L276)** together with the imines (**L277)** by reaction of *o*-phenylenedialdehyde (**L275**) with amines (**L219**) in 99% alcohol at 0 °C (Scheme 1.130). The presence of tertiary butyl alcohol, the yield of the isoindoles 44 is somewhat better. *tert*-Butylamines does not react with OPD. The use of aniline affords mainly 1-phenylimino-2-phenylisoindoline (79%) [148].



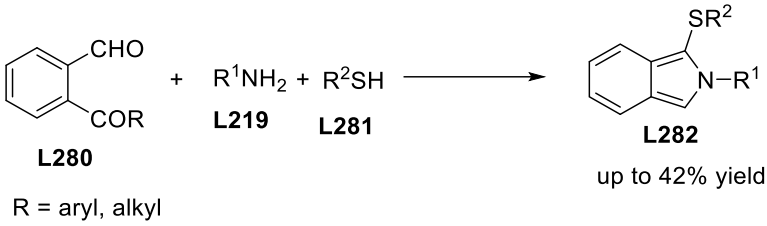
Scheme 1.130

D'Amico *et al.* reported a method for the synthesis of isoindole (**L279**) (up to 92%) involving the interaction of *o*-phenylenedialdehyde (**L275**) with methylamine hydrochloride (**L219**) and cyanide (**L278**) in methanol (Scheme 1.131) [149]. The molar reactant ratios were OPD: ($MeNH_2$ + HC1): KCN = 1:2.2:2.54.



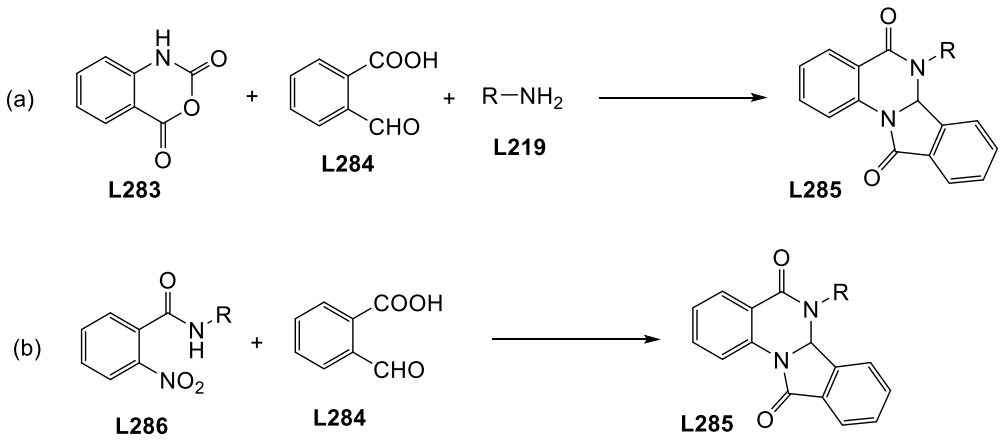
Scheme 1.131

Stenson *et al.* reported the synthesis of isoindoles (**L282**) by means of reaction *o*-acylbenzaldehydes (**L280**) with thiols (**L281**) and amines (**L219**) (Scheme 1.132) [150].



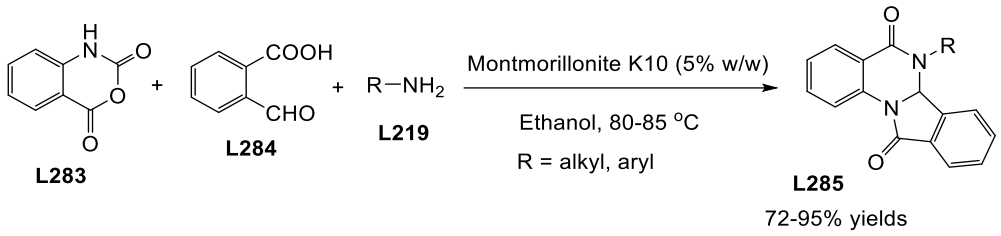
Scheme 1.132

Isoindolo[2,1-*a*]quinazolines are the potent inhibitors of TNF-*α* (Tumour Necrosis Factor-*alpha*) which is one of the key cytokine mediators involved in the inflammatory response is used as a marker for many inflammatory disorders [151]. Due to their immense biological activities, synthesis of isoindolo[2,1-*a*]quinazoline derivatives is a demanding task. To the best of our knowledge only very few different methods are available to synthesize this moiety. In fact there are two methods which are generally used for the synthesis of isoindolo[2,1-*a*]quinazoline derivatives (**L285**). One is the three-component reaction of isatoic anhydride (**L283**), an amine (**L219**) and 2-formylbenzoic acid (**L284**) (Scheme 1.133, a). The other involves the reductive one-pot reaction of *N*-substituted 2-nitrobenzamides (**L286**) and 2-formylbenzoic acids (**L284**) (Scheme 1.133, b).



Scheme 1.133

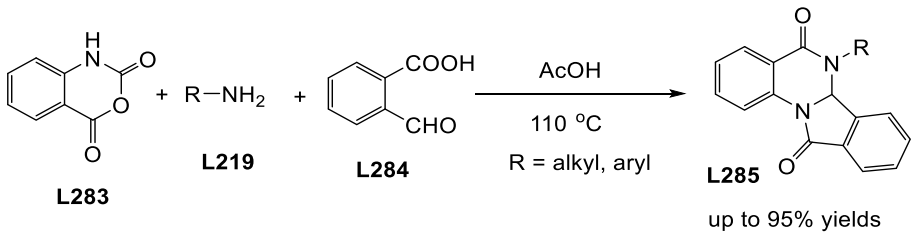
In 2011, Pal *et al*. first synthesized 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione derivatives (**L285**) by employing a new three component reaction of isatoic anhydride (**L283**), an amine (**L219**) and 2-formylbenzoic acid (**L284**), using montmorillonite K10 as the catalyst in refluxing ethanol (Scheme 1.134) The target products were isolated in up to 95% yield [152].



Scheme 1.134

During optimization of the reaction conditions the authors have observed that treatment of isatoic anhydride with aniline and 2-formylbenzoic acid in the presence of commercially available anhydrous (+)-camphor-10-sulfonic acid (CSA) in ethanol at 80–85 ºC produced 6-phenyl-6,6*a*-dihydroisoindolo-[2,1-*a*]quinazoline-5,11-dione as the only sole product. To develop an environmentally friendly process they examined the use of montmorillonite K10 as a catalyst as it could be reused and observed that MCR proceeded well. Employing this methodology they have synthesized a range of 6-substituted derivatives with a variety of aliphatic and aromatic amines. The main disadvantage of this method is that the yield is low and as well as the reaction time is very long in case of some compounds.

Recently, Sashidhara *et al*. reported a procedure for the construction of 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione and 5-phenylisoindolo[2,1-*a*]quinazolin-11(6*aH*)-one (**L285**) derivatives by means of three component reaction between isatoic anhydride (**L283**), amines (**L219**) and 2-formylbenzoic acid (**L284**) in acetic acid at 110 ºC. Up to 95% yields of target products were observed (Scheme 1.135) [153].

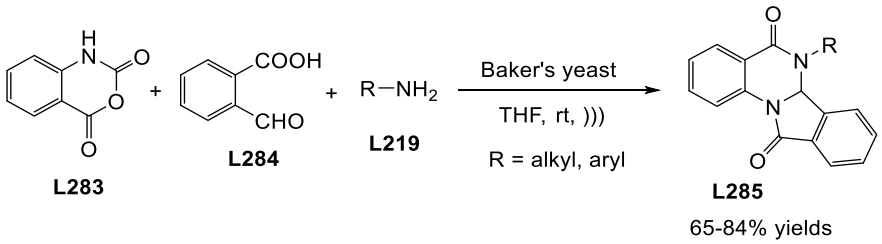


Scheme 1.135

The authors examined the solvent effects by carrying out the reaction with various other common solvents like ethanol, *iso*-propanol, DMF, DMSO, acetonitrile, 1,4-dioxane etc. The yields were not so good like acetic acid. More interestingly they have observed that in presence of

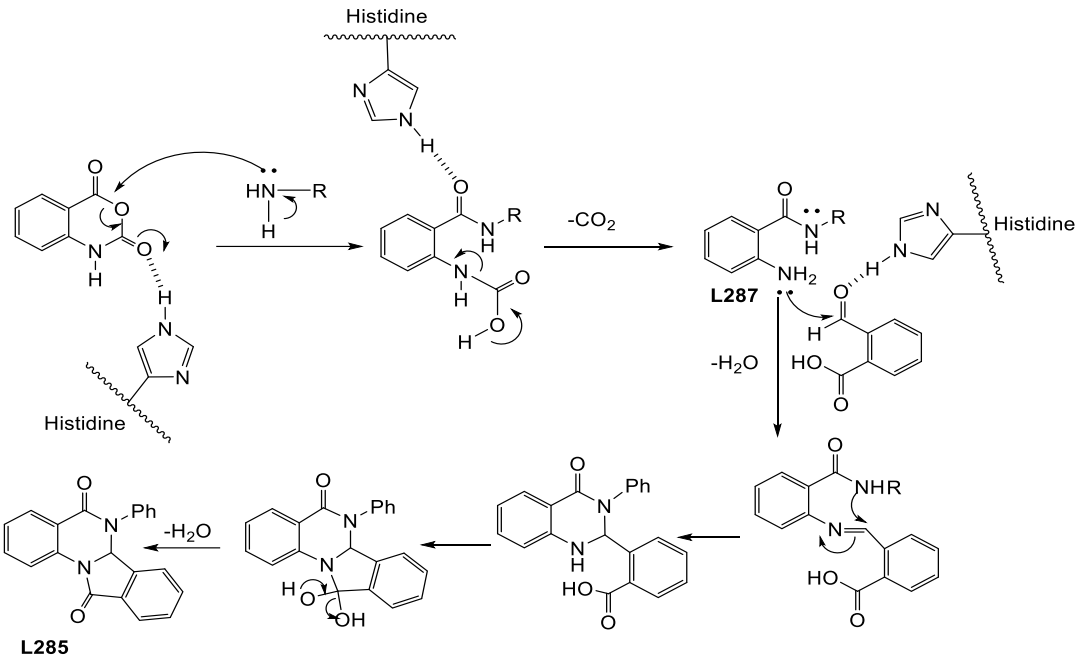
CF_3COOH the reaction did not proceed at all. The scope of this one-pot three-component was next investigated by employing a variety of substituted aliphatic and aromatic amine derivatives. The yields were better for the more nucleophilic aliphatic amines than aromatic amines. The main disadvantage of this method is that the use large amount of toxic solvent.

Raval *et al.* reported the catalytic application of *Saccharomyces cerevisiae* (Baker's yeast) for the synthesis of isoindolo[2,1-*a*]quinazolines (**L285**) by the reaction between isatoic anhydride (**L283**) and 2-formylbenzoic acid (**L284**) under ultrasonication in THF solvent in up to 84% yields (Scheme 1.136) [154].



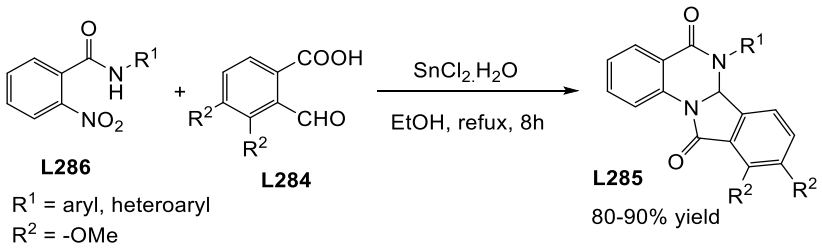
Scheme 1.136

The authors have introduced a reaction mechanism to prove the role of the catalyst (Scheme 1.137). The cell of baker's yeast produces a variety of enzymes. According to their hypothesis, among these enzymes, lipase available in baker's yeast might be responsible for accelerating the reaction. It is well known that lipase contains variety of different amino acid residues. The amino acid residues like aspartic acid, histidine and serine might be interacting with the substrate. NH proton of histidine may be considered responsible for enhancing electrophilic character of carbonyl carbon of isatoic anhydride and 2-carboxybenzaldehyde. Then decarboxylation occurs resulting in generation of 2-amino-*N*-substituted-benzamide (**L287**). The intermediate (**L287**) reacts with 2-carboxy benzaldehyde generating imine intermediate, which is converted into the final product with loss of water molecule. The mechanism is schematically presented in Scheme 1.137.



Scheme 1.137

Foroumadi *et al.* developed the direct preparation of isoindolo[2,1-*a*]quinazoline-5,11-dione derivatives (**L285**) in 80-90% yields *via* reaction of 2-nitrobenzamides (**L286**) and 2-formylbenzoic acids (**L284**) in the presence of $SnCl_2.2H_2O$ under reflux conditions in EtOH (Scheme 1.138) [155]. The reductive reaction of 2-nitrobenzamides in the presence of $SnCl_2$ with diverse substrates has been investigated.



Scheme 1.138

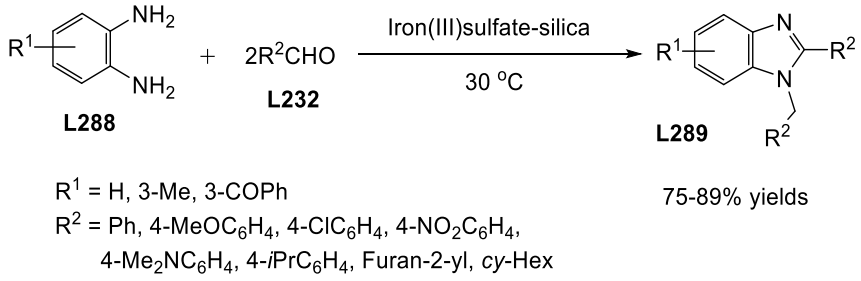
The reaction proceeded in two steps, first the reduction of the NO_2 group of 2-nitrobenzamides and then ring closure by nucleophilic addition of the NH_2 group to both the CHO and COOH groups of 2-formylbenzoic acids. The main disadvantage of their procedure is the limitation of substrates scope.

1.2.2.3. Synthesis of benzimidazoles

Benzimidazole and its derivatives are very important compounds due to their immense biological and pharmacological activities and are used as selective neuropeptide YY1 receptor antagonists, factor Xa inhibitors, smooth muscle cell proliferation inhibitors, antitumor, antiviral,

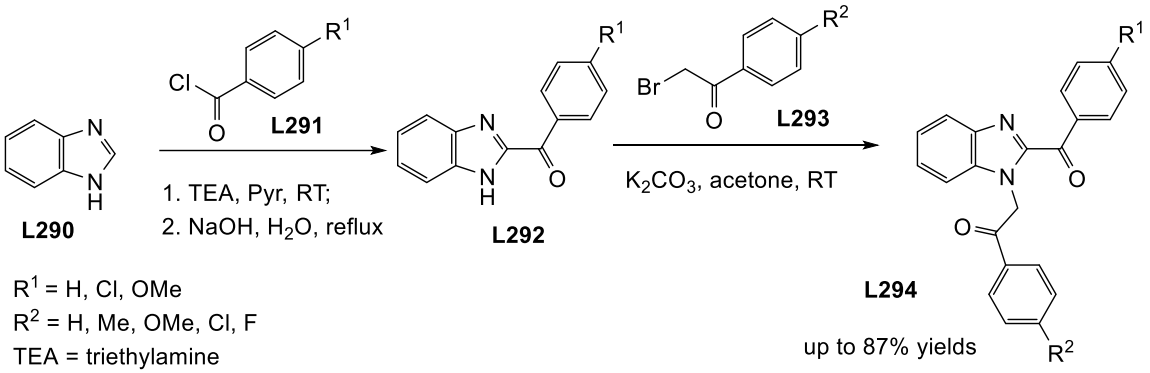
antimicrobial agents, and for HIV, herpes (HSV-1), influenza, and human cytomegalovirus (HCMV) [156, 157]. In addition, there have also been reports of their use as possible precursors for aminoboronic acids with an interest as bifunctional organic catalysts [158].

The reported works are typically limited to the optimization of the reaction conditions. An example is the condensation of *o*-phenylenediamine (**L288**) with aldehydes (**L232**), one of the most studied approaches for the preparation of simple 1,2-disubstituted structures (**L289**). The employment of several catalysts under mild conditions such as poly(*N,N*'-dibromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS) or *N,N,N,N*-tetrabromobenzene-1,3-disulfonamide (TBBDA) [159], L-proline [160], $SiO_2/ZnCl_2$ [161], or ferric sulfate soaked with silica [iron(III)sulfate–silica] [162] under solvent-free conditions usually provides the products in good yields (75-89%) (Scheme 1.139).



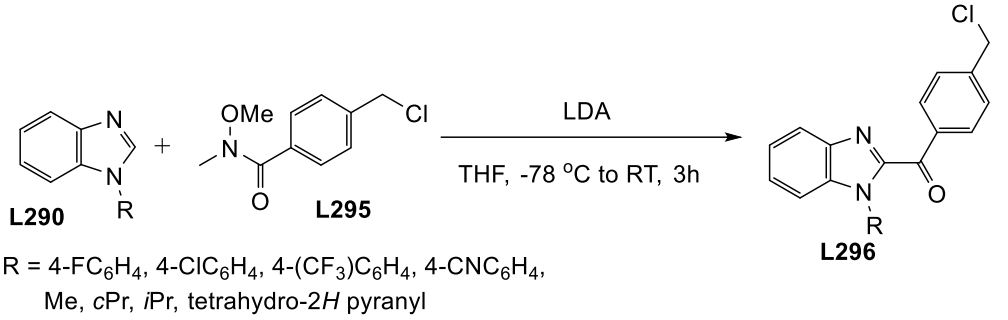
Scheme 1.139

Kayalgil and co-workers reported the synthesis of 1,3-diarylpyrazino[1,2-*a*]benzimidazole derivatives. The reaction of a benzimidazole moiety (**L290**) with acyl chlorides (**L291**) gave the corresponding 2-aryloylbenzimidazole derivatives (**L292**), which were then treated with 2-bromoacetophenones (**L293**) to give 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles (**L294**) in up to 87% yields (Scheme 1.140) [163].



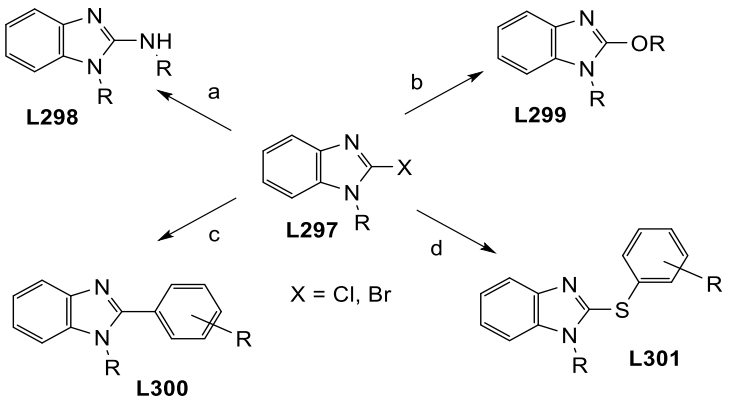
Scheme 1.140

Functionalization of C-2 position is another possible method to achieve 1,2-disubstituted benzimidazoles. Högberg and co-workers described the synthesis of some benzimidazole intermediates (**L290**) by acylation of the 2-position of imidazoles (**L290**) with the Weinreb amide (**L295**) in the presence of LDA (lithium diisopropylamide) to afford the desired compounds (**L296**) (Scheme 1.141) [164].



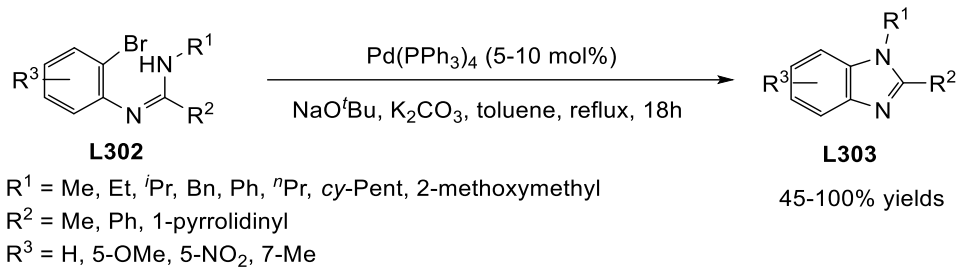
Scheme 1.141

2-Halo-substituted benzimidazoles (**L297**), such as 2-chloro- or 2-bromobenzimidazoles, are important intermediates for functionalization of the benzimidazole scaffold at the 2-position (Scheme 1.142). These compounds are versatile intermediates to prepare of 2-heterobenzimidazoles (**L298**, **L299** & **L301**) (Scheme 1.142, paths a, b and d) and 2-arylbenzimidazoles (**L300**) (Scheme 1.142, path c).



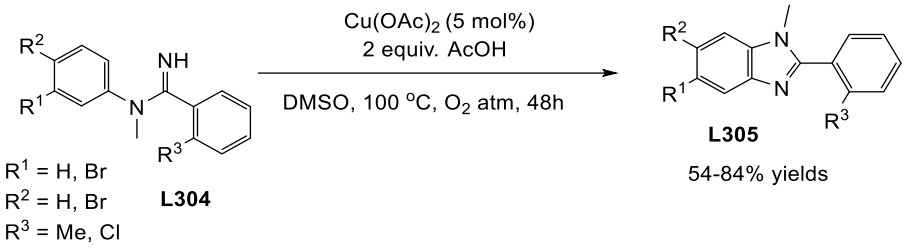
Scheme 1.142

In order to improve the regioselectivity of the synthesis of *N*-substituted benzimidazoles, novel methods have been developed, as explained below. The development of a metal-catalyzed intramolecular aryl-amination/cyclization approach was an elegant way to allow the construction of complex benzimidazoles in a regioselective way. Firstly reported by Brain and co-workers, this method was readily adopted with high success by several groups that used several metal salts such as palladium-, copper- or cobalt-based catalysts (Scheme 1.143) [165, 166]. The target imidazoles (**L303**) were obtaines in 45-100% yields.



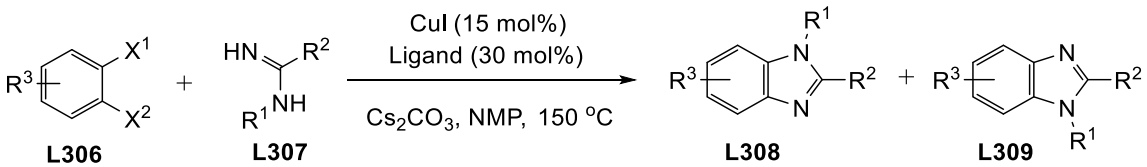
Scheme 1.143

In 2008, Buchwald and co-workers developed a copper-catalyzed amination for the synthesis of substituted 2-arylbenzimidazoles (**L305**) in good yields (up to 84%) from the corresponding amidines (**L304**), also demonstrating that the procedure could be extended to the preparation of *N*-methylated benzimidazoles (Scheme 1.144) [167].



Scheme 1.144

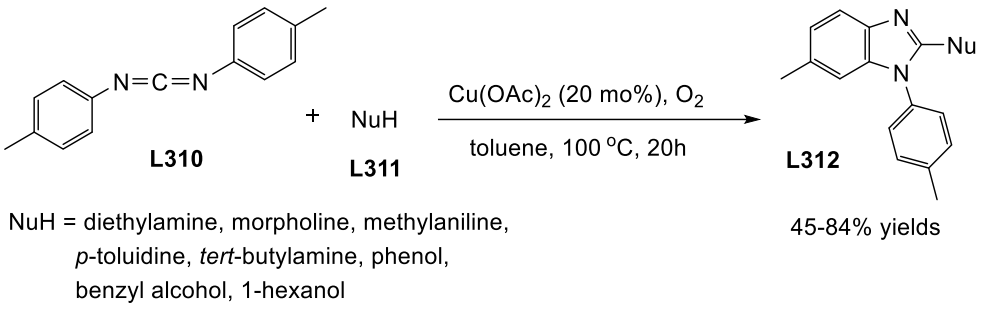
Mani and co-worker have previously reported on the CuI-catalyzed amination reaction of 1,2-dihaloarenes with guanidines and amidines, to achieve 2-substituted 1-*H*-benzimidazoles [168]. Recently, the group developed a comprehensive study of the regioselectivity of the reaction of 1,2-dihaloarenes (**L306**) with *N*-substituted amidines (**L307**) to obtain 1,2-disubstituted benzimidazoles (**L308** & **L309**) (Scheme 1.145). Several factors and its influence on the regioselectivity were investigated, such as: the chemoselectivity of nitrogen atoms in the first amination step; the steric and electronic effect of the substituent on the arene ring; the reactivity control between differentiated halides or even the reaction with different amidines.



Scheme 1.145

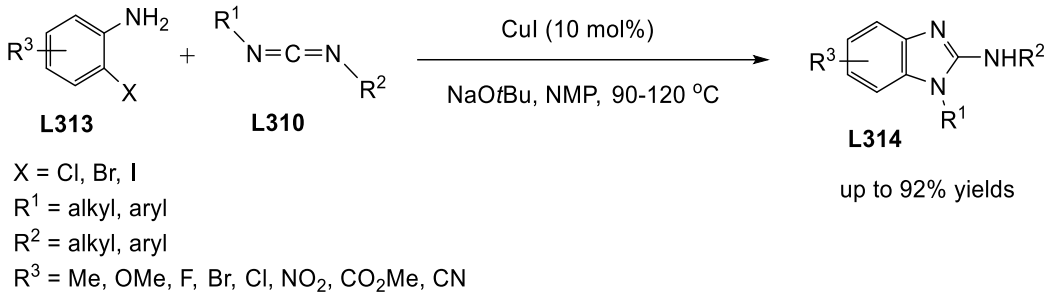
Bao and co-workers reported the use of $Cu(OAc)_2/O_2$ system to prepare benzimidazole derivatives directly in 45-84% yields from the reaction of diarylcarbodiimides (**L310**) with

different nucleophiles, through addition/C-H activation in a one-pot cascade procedure (Scheme 1.146) [169].



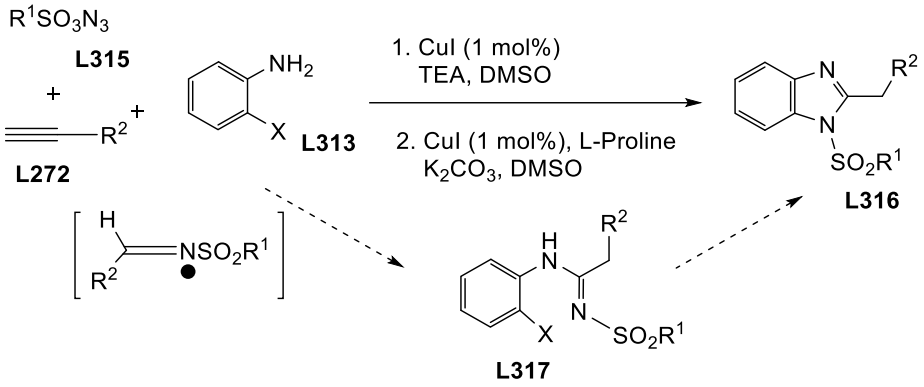
Scheme 1.146

The same approach was adopted by Cai and co-workers, who synthesized a variety of 2-aminobenzimidazoles (**L314**) from *o*-haloanilines (**L313**) and carbodiimides (**L310**) by means of a copper-catalyzed reaction, in the presence of NaO^{t}Bu and by using *N*-methyl-2-pyrrolidinone (NMP) as solvent in a "ligand-free" manner in up to 92% yields (Scheme 1.147) [170].



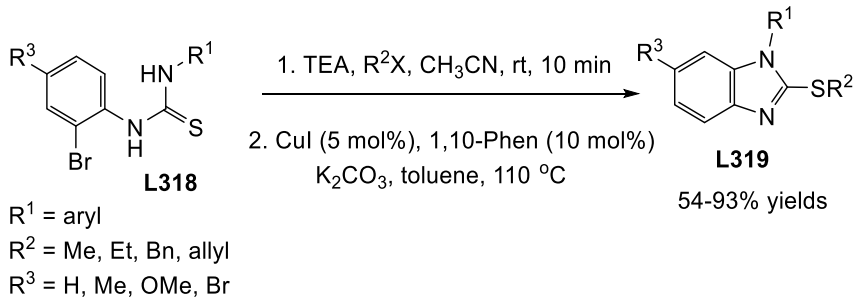
Scheme 1.147

Wang and co-workers developed a three-component reaction of sulfonyl-azides (**L315**), terminal alkynes (**L272**) and 2-bromoaniline (**L313**) to achieve 2-substituted 1-sulfonylbenzimidazoles (**L316**). The proposed mechanism involves the copper-catalyzed azide/alkyne addition to form a ketenimine intermediate (**L317**) that is attacked by the amine to generate the corresponding *N*-sulfonylamidine. The copper-catalyzed intramolecular C-N coupling afforded the products (**L316**) in moderate to good yields (Scheme 1.148) [171].



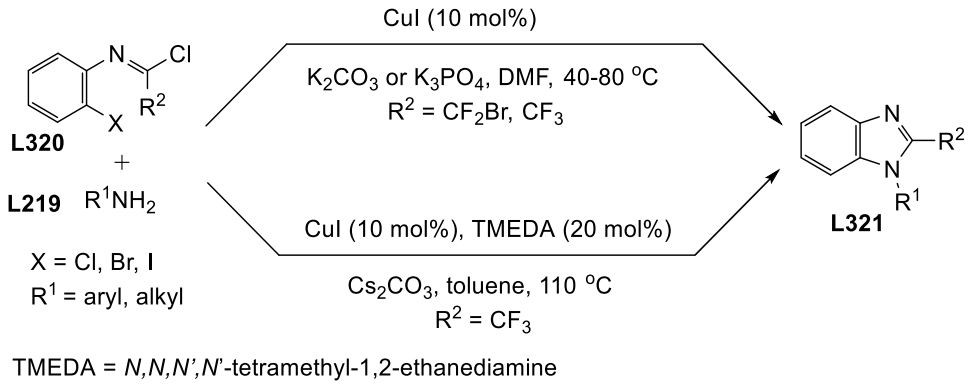
Scheme 1.148

The intramolecular copper-catalyzed arylamination can also be applied to the synthesis of *N*-substituted 2-mercaptobenzimidazoles (**L319**) in 54-93% yields. The preparation of these compounds was described by Muzart *et al*., who attained the desired products by the *S*-alkylation of thiourea derivatives (**L318**), followed by the intramolecular C-N coupling (Scheme 1.149) [172]. They also demonstrated that benzimidazole ethiones could be obtained from 2-mercaptobenzimidazoles substituted with a *p*-methoxybenzyl group.



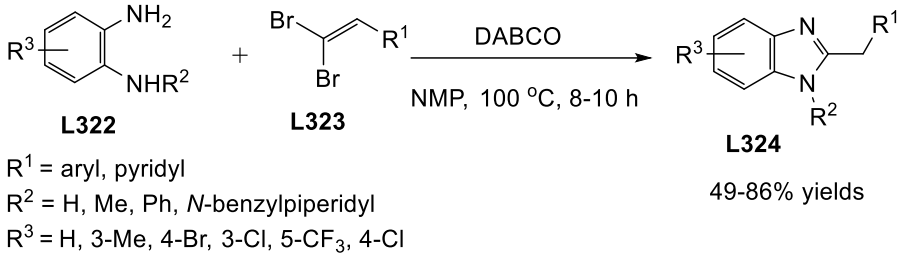
Scheme 1.149

The Wu [173] and Zhang [174] groups have independently developed similar procedures to assemble *N*-substituted 2-fluoro-methylbenzimidazoles (**L321**). Both groups reported the double amination of fluorinated acetimidoyl halides (**L320**) with primary amines (**L219**) catalyzed by CuI. While the Wu group applied a ligand-free approach, Zhang and co-workers used a CuI/TMEDA (Scheme 1.150). Wu approach consisted on a Cu-catalyzed coupling of imidoyl chlorides and primary amines under mild conditions.



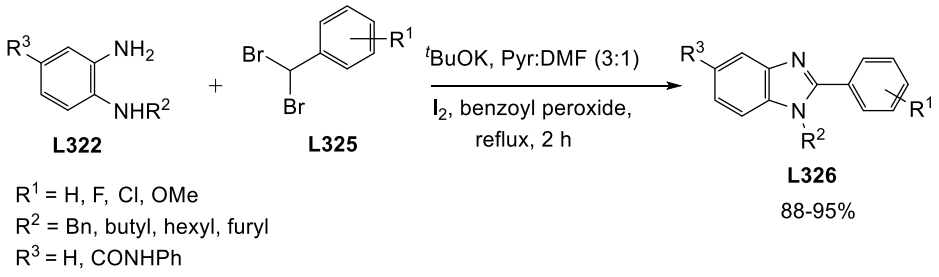
Scheme 1.150

Schmidt and co-workers [175] described the preparation of substituted benzimidazoles (**L324**) from 1,1-dibromoethenes (**L323**) and *o*-diaminobenzenes (**L322**). The reaction proceeds in the presence of 1,4-diazabiclyco[2.2.2]octane (DABCO), using NMP as solvent at 100 ºC and 49-86% yields were obtained (Scheme 1.151). The proposed mechanism, based on experimental observations, involves the generation of an alkynyl bromide intermediate upon treatment of dibromide with base. Reaction of the generated intermediate with a corresponding diamine provides an alkynylamine compound, which subsequently cyclizes to give the desired substituted benzimidazoles.



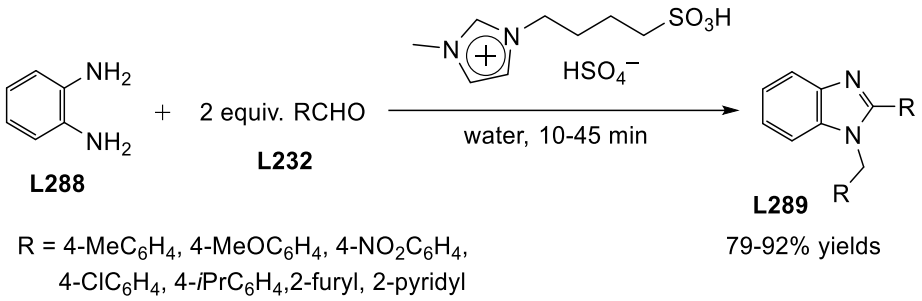
Scheme 1.151

Siddapa *et al*. used dibromomethylarenes (**L325**) and o-phenylendiamines (**L322**) to access substituted benzimidazoles (**L326**) in 88-95% yields in the presence of KO^{t}Bu as base followed by the addition of iodine and catalytic amount of benzoylperoxide under reflux conditions (Scheme 1.152) [176].



Scheme 1.152

Beheshtiha *et al.* reported 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate ([$(CH_2)_4SO_3$HMIM][HSO_4]) [177] and 1-methylimidazolium trifluoroacetate ([Hmim]TFA) [178] (Scheme 1.153) used to catalyze one-pot condensations between aldehydes (**L232**) and *o*-phenylenediamine (**L288**) in water at room temperature to afford benzimidazoles (**L289**) in 79-92% yield. These procedures seem to have advantages from the use of a water soluble catalyst, allowing its easy recovery and reutilization.



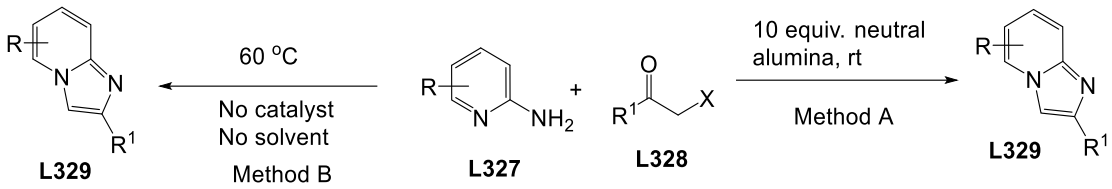
Scheme 1.153

Chakraborti group reported that the fluorous alcohols trifluoroethanol and hexafluoro-2-propanol efficiently promote the cyclocondensation of *o*-phenylenediamine with aldehydes to afford selectively the 1,2-disubstituted benzimidazoles at room temperature in short times [179].

1.2.2.4. Synthesis of imidazo[1,2-*a*]pyridines

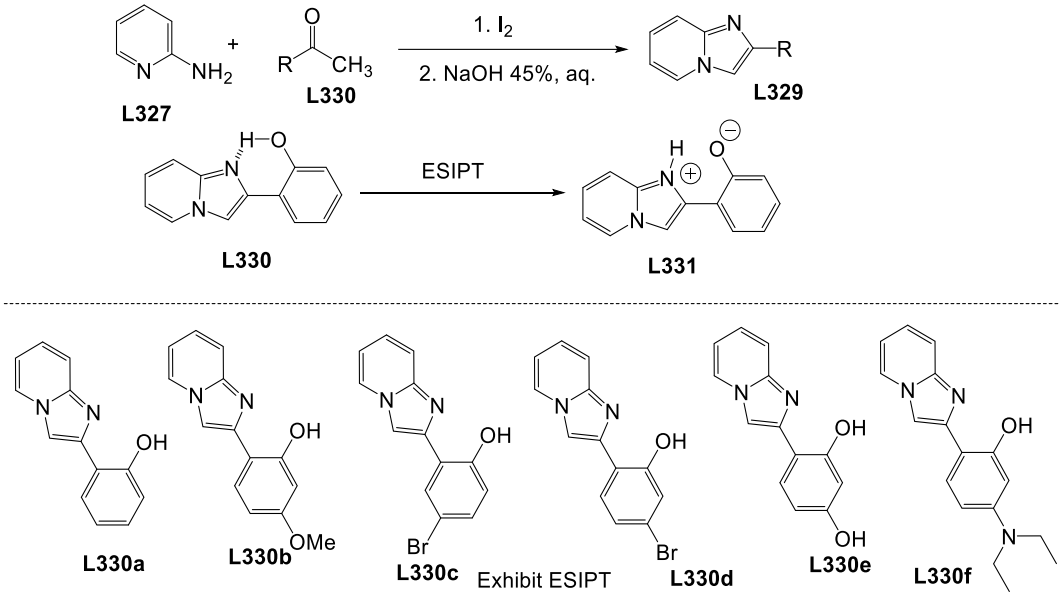
Imidazopyridines are important class of biologically active nitrogen containing heterocycles. Among the various imidazopyridine derivatives, imidazo[1,2-*a*]pyridine moiety is the most important in the field of natural products and pharmaceuticals. These derivatives show a wide range of biological activities such as antifungal, antiinflammatory, antitumor, antiviral, antibacterial, antiprotozoal, antipyretic, analgesic, antiapoptotic, hypnoselective, and anxioselective activities [180, 181].

Condensation reaction between α-haloketones (**L328**) with the 2-aminopyridines (**L327**) is the oldest approach for the synthesis of imidazo[1,2-*a*]pyridine derivatives (**L329**) [182]. Over the years various catalytic and non-catalytic systems have been employed to this strategy by the different groups. We are discussing few of them in this review. Sahu *et al.* reported that the neutral alumina is an efficient medium for this transformation under room temperature (Scheme 1.154, Method A) [183]. They synthesized various imidazopyridine derivatives employing this method. The Chen and Wu group showed that the imidazo[1,2-*a*]pyridines could be synthesized from α-bromo/chloroketones and 2-aminopyridines under catalyst and solvent-free conditions at 60 ºC (Scheme 1.154, Method B) [184].



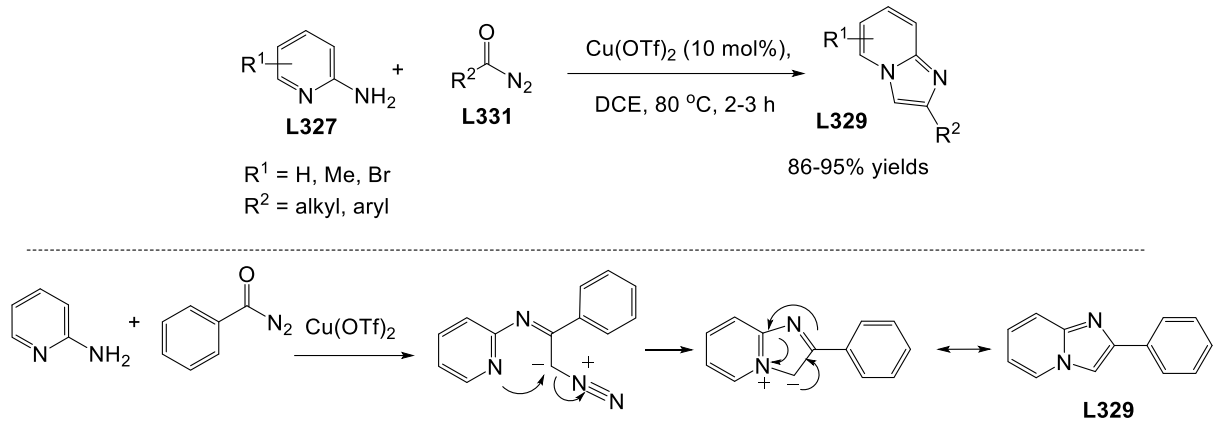
Scheme 1.154

Cyrański and Gryko *et al.* reported the synthesis of a library of imidazo[1,2-*a*]pyridines (**L329**) from 2-aminopyridine (**L327**) and ketones (**L330**) (Scheme 1.155) [185]. Reaction proceeds *via in situ* generation of *α*-iodoketones, the following Ortoleva-King reaction and ring closure. The thus obtained imidazo[1,2-*a*]pyridines possessing a 2-hydroxyphenyl substituent at position C2 were found to exhibit an excited-state intramolecular proton transfer (ESIPT) ro form cationic form (**L331**) According to the authors, imidazo[1,2-*a*]pyridines possessing aryl substituents at the position of C2 display strong emission bands in the blue region.



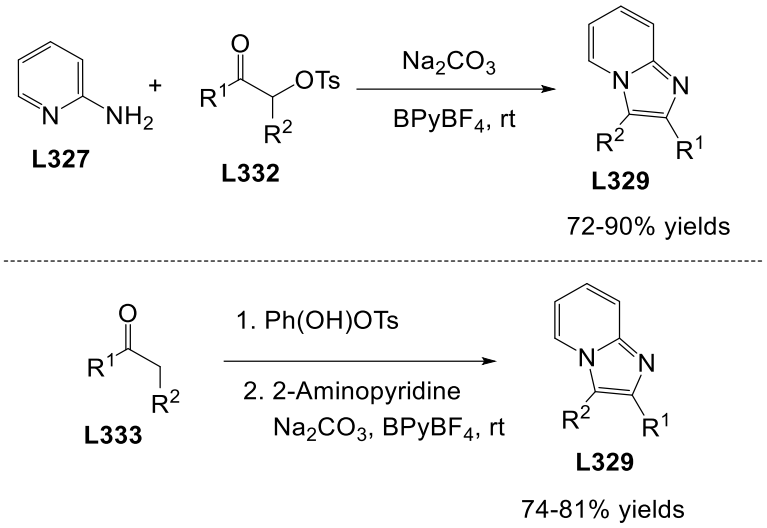
Scheme 1.155

$Cu(OTf)_2$-Catalyzed reaction between *α*-diazoketones (**L331**) and 2-aminopyridines (**L327**) also afforded the imidazo[1,2-*a*]pyridines (**L329**) with good selectivity and good yields (Scheme 1.156) [186]. This reaction is equally suitable for both the aromatic and aliphatic diazoketones and undergoes *via* the imine formation followed by the nitrogen insertion.



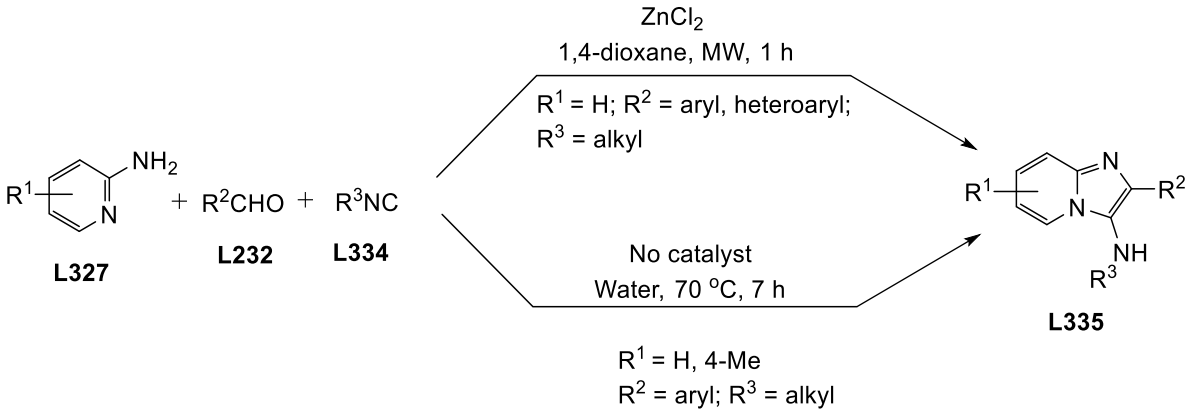
Scheme 1.156

Reaction between *α*-tosyloxyketones (**L332**) and 2-aminopyridine (**L327**) in ionic liquid $BPyBF_4$ at room temperature afforded the imidazopyridine derivatives (**L329**) within an hour [187]. The ionic liquid is more preferable for this condensation reaction as longer reaction time and higher temperature is required for the organic solvent. The imidazopyridines have been synthesized from direct ketone by *in situ* generation of the *α*-tosyloxyketones (Scheme 1.157).



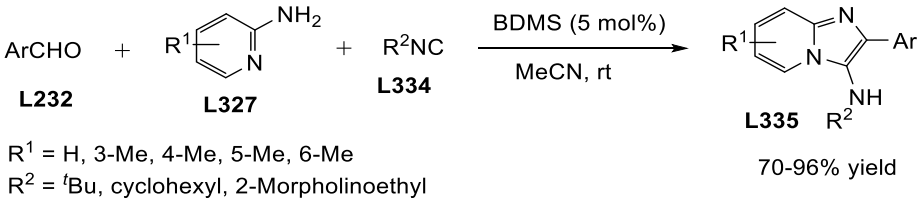
Scheme 1.157

In 2007, the Rousseau *et al*. and Adib *et al*. independently reported the multicomponent synthesis of imidazo[1,2-*a*]pyridines (**L335**) using 2-aminopyridine (**L327**), aldehyde (**L232**) and isonitrile (**L334**) (Scheme 1.158) [188, 189].



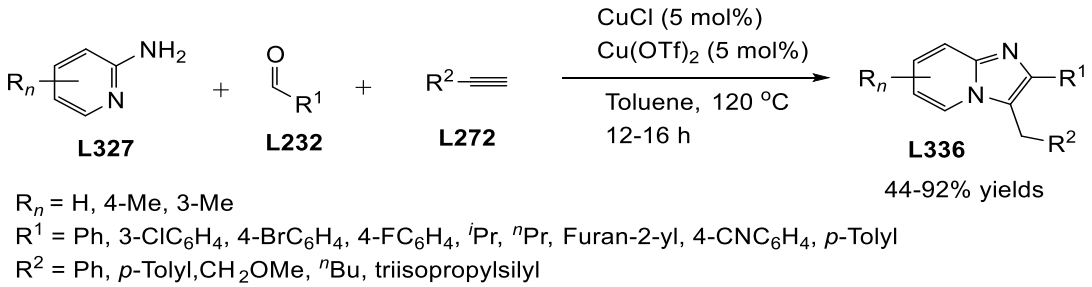
Scheme 1.158

A convenient synthetic protocol for the synthesis of imidazo[1,2-*a*]pyridines (**L335**) has been developed by Khan group employing one-pot three-component Ugi reaction by employing aromatic amidine (**L327**), aromatic aldehyde (**L232**), and isocyanide (**L334**) using 5 mol% of bromodimethylsulfonium bromide (BDMS) at room temperature with 70-96% yields (Scheme 1.159) [190]. In addition, they also studied the fluorescence properties of the synthesized imidazopyridine derivatives.



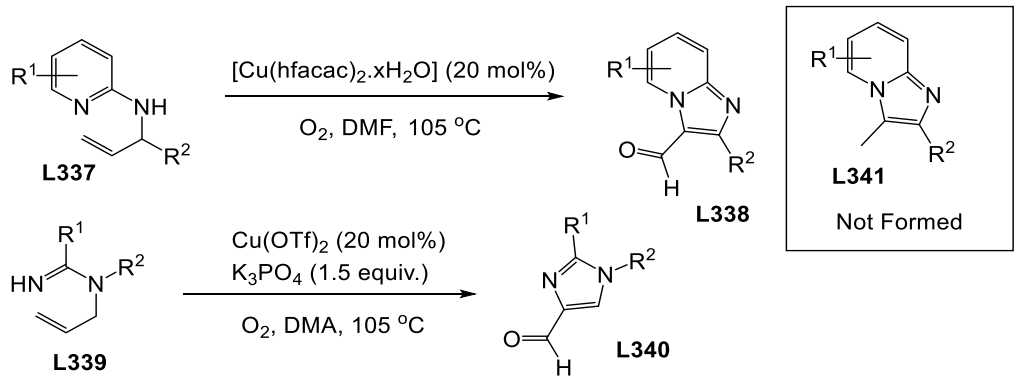
Scheme 1.159

Gevorgyan and his co-worker have first time developed a general method for the synthesis of imidazopyridine derivatives (**L336**) in up to 92% yields by the copper-catalyzed three-component coupling reaction of aldehydes (**L232**) with 2-aminopyridines (**L327**) and terminal alkynes (**L272**) (Scheme 1.160) [191].



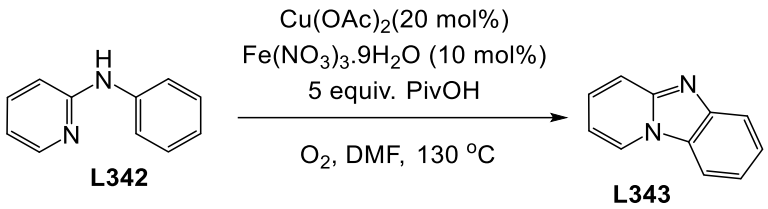
Scheme 1.160

Zhu group described an unexpected and novel intramolecular dehydrogenative aminooxygenation reaction in *N*-allylpyridin-2-amines (**L337**) and *N*-allyl-*N*-R^2-acetimidamides (**L339**) for the construction of imidazopyridines (**L338, L340**) containing a formyl group (Scheme 1.161) [192]. This unprecedented copper catalyzed (20 mol%) reaction in DMF or DMA was carried out under oxygen atmosphere employing simple acyclic precursors. Copper salts are essential for this transformation and the other solvents like DMSO, NMP were not so fruitful. A library of imidazo[1,2-*a*]pyridine-3-carbaldehydes (**L338**) with broad substrates scope were synthesized in moderate to good yields and this process is also applicable for the synthesis of 1,2-disubstituted imidazole-4-carbaldehydes.



Scheme 1.161

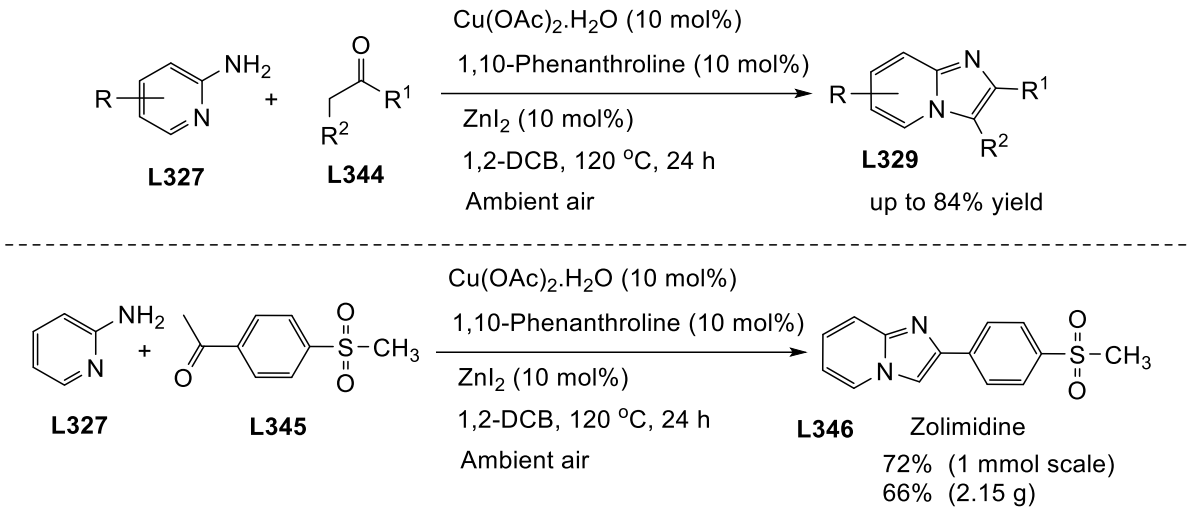
Pyrido[1,2-*a*]benzimidazoles (**L343**) were synthesized by the Zhu *et al.* through the direct the intramolecular aromatic C-H amination in pyridine (**L342**) co-catalyzed by the copper and iron-salts in DMF under dioxygen atmosphere (Scheme 1.162) [193]. The pivalic acid is required as an additive for this reaction to improve the yield. The iron salt promoted the reaction itself but increased the yield of the reaction significantly by its ability to facilitate formation of the more electrophilic Cu(III) species required for the S_EAr (electrophilic aromatic substitution). In this process, the pyridinyl nitrogen in the substrates acts as both a directing group as well as nucleophile.



Scheme 1.162

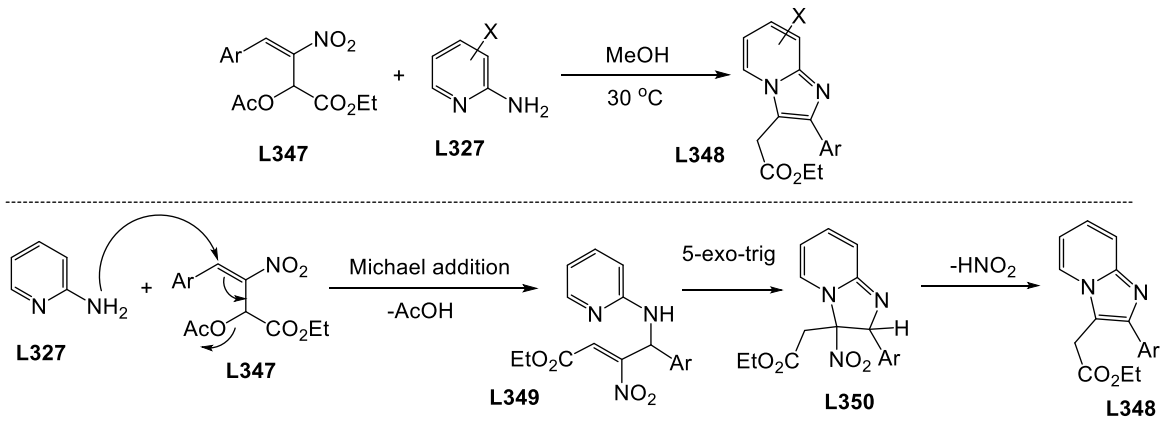
Our group developed a copper-catalyzed direct oxidative cyclization *via* C–H amination between 2-aminopyridines (**L327**) and methyl aryl/heteroaryl ketones (**L344**) under ambient air

[194]. A library of functionalized imidazo[1,2-*a*]pyridines has been synthesised in good yields (up to 84%) from basic and easily available starting materials. This one-pot simple reaction protocol has been utilized for the direct preparation of zolimidine (**L346**), a marketed antiulcer drug in large scale (Scheme 1.163).



Scheme 1.163

Namboothiri group synthesized functionalized imidazo[1,2-*a*]pyridines by the reaction between Morita-Baylis-Hillman (MBH) acetates of nitroalkenes (**L347**) and 2-aminopyridines (**L327**) under room temperature in MeOH (Scheme 1.164) [195]. This reagent-free one-pot reaction proceeds through cascade inter-intramolecular double aza-Michael addition of 2-aminopyridines to MBH acetates. They synthesized a library of imidazo[1,2-*a*]pyridine (**L348**) derivatives employing different 2-aminopyridines and MBH acetates within short reaction time but this methodology was ineffective for the aminoheterocycles like 2-aminopyrimidine, 2-aminopyrazine and 2-aminothiazole. Marketed drug Alpidem and Zolpidem has been prepared by them employing this strategy with 72% and 78% overall yield respectively.

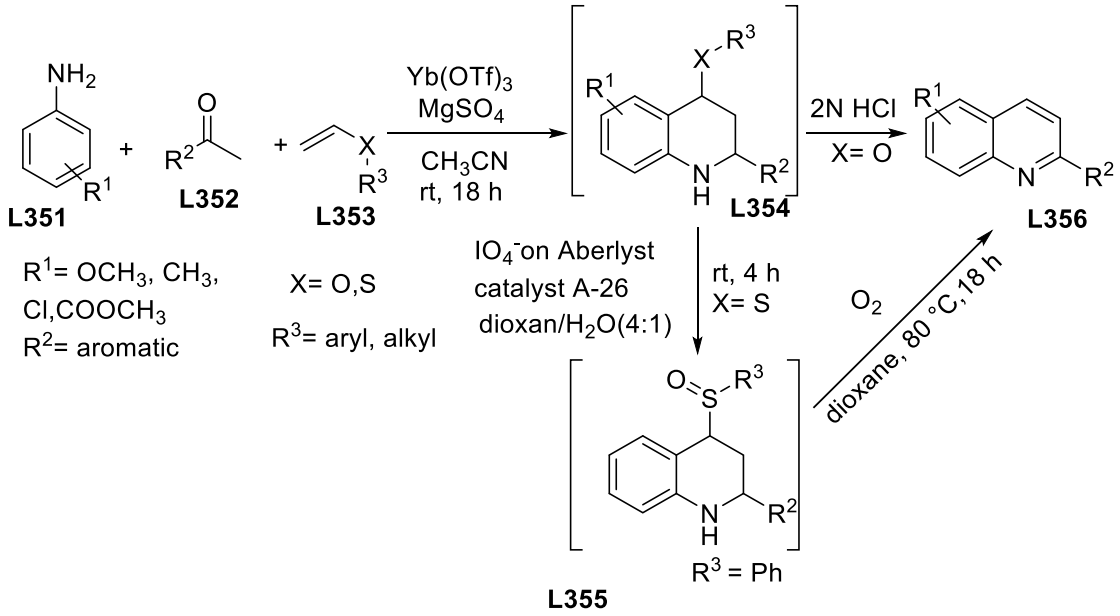


Scheme 1.164

1.2.2.5. Synthesis of quinolines

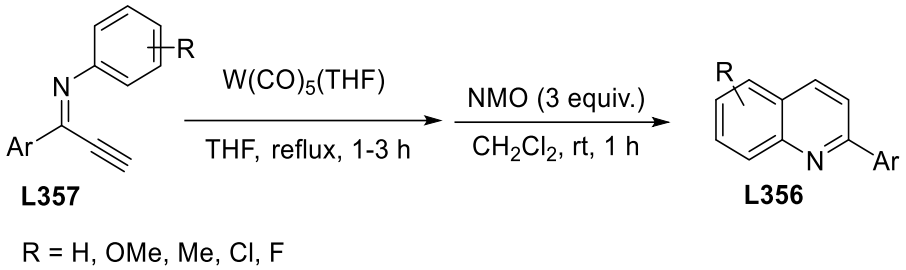
Quinoline and its derivatives are important structural scaffolds in many pharmaceuticals and they have been shown a diverse range of biological activities [196, 197], including *P*-selectin antagonism, antimalarial, and antitumor activities [198]. Below, a most common synthetic approaches towards quinolines will be reported.

In 2004, Pasau *et al*. established a method for the synthesis of 2-substituted quinolines (**L365**) derivatives *via* multicomponent reaction (Scheme 1.165) [199]. As a first step ytterbium triflate, $Yb(OTf)_3$ (0.05 equiv.) was used as a catalyst, and, as a second step, the intermediate [**L354**] (X=S) was oxidized by using IO_4^- on amberlyst A-26 in dioxane/water (4:1, v/v) solution at room temperature. Then the intermediate [**L355**] provided the corresponding quinoline derivatives (**L356**). This protocol was extended to liquid-phase and also solid-phase chemistry.



Scheme 1.165

In the same year, Akiyama and coworkers reported a protocol for the synthesis of 2-arylated quinolines (**L356**) by [4+2] electrocyclization of alkynyl imines (**L357**) *via* vinylidene complexes (Scheme 1.166) [200]. In this reaction 20 mol% of tungsten vinylidene complex, $[W(CO)_5(THF)]$ has been used as a catalyst. After the oxidative treatment on the crude mixture which was reacted with 3 equiv. NMO (*N*-methylmorpholine *N*-oxide) at ambient temperature in dichloromethane solvent, provided the desired product in good yields.

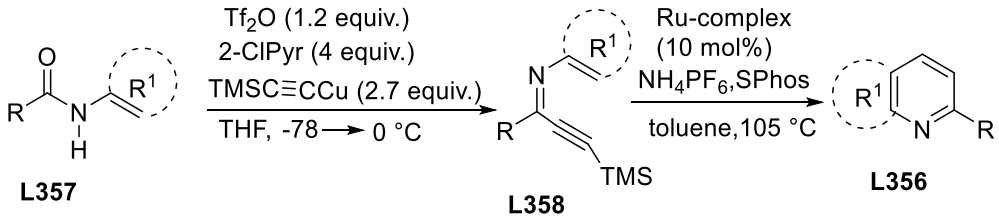


L357 **L356**

R = H, OMe, Me, Cl, F

Scheme 1.166

Ruthenium-catalyzed synthesis of pyridine and quinoline derivatives (L356) by two-steps reaction *via* cycloisomerization of 3-azadienynes was described by Movassaghi and Hill in 2006 (Scheme 1.167) [201]. As a first step, the formation of azadienyne (**L358**) in at -78 to 0 °C in presence of trifluoromethane sulfonic anhydride (Tf_2O, 1.2 equiv.) and 2-chloropyridine (4 equiv.) as base. Azadienyne afforded the corresponding product (**L356**) in presence of chlorocyclopentadienyl bis(triphenylphosphine) ruthenium complex catalyst, [$CpRu(PPh_3)_3Cl$, 10 mol%] and 2-dicyclohexyl-phosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos, 10 mol%), and ammonium hexafluorophosphate (1 equiv.) in toluene at 105 °C after 19 h.



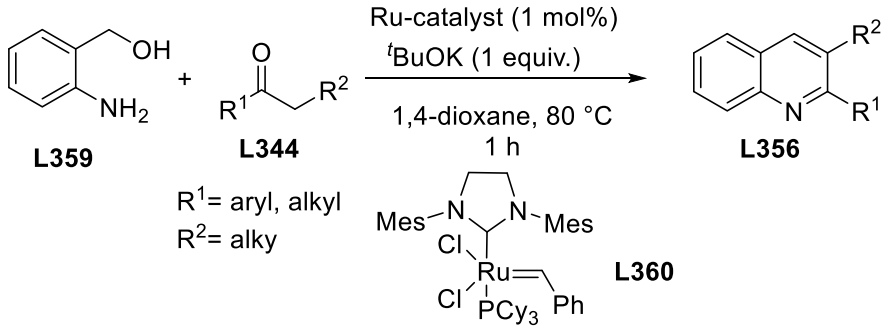
L357 **L358** **L356**

R= aryl, ^{t}Bu, $N(CH_2CH_2)_2O$

R^1= aryl, heteroaryl, napthayl

Scheme 1.167

In 2008, Verpoort *et al*. reported the synthesis of quinolines (**L356**) by the reaction of 2-aminobenzylalcohol (**L359**) and a variety of ketones (**L344**) *via* modification of the Friedländer reaction using Ru-catalyst (Scheme 1.168) [202]. This reaction was developed by using the second generation Grubbs catalyst (Ru-catalyst, **L360**, 1 mol%) and base (^{t}BuOK, 1 equiv.) for 1 h to give different quinoline derivatives with high yields.



L359 **L344** **L356**

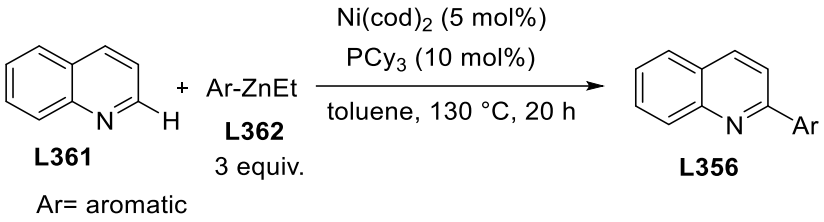
R^1= aryl, alkyl

R^2= alky

L360

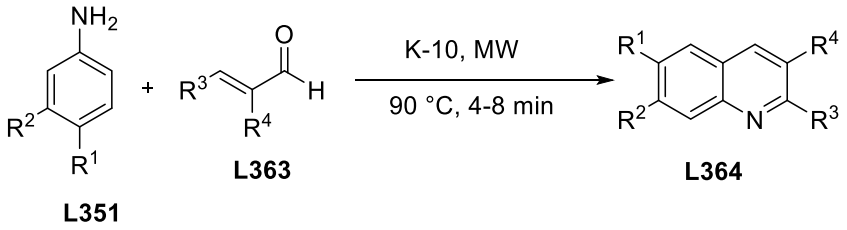
Scheme 1.168

Another approach by means of Ni-complex-mediated reaction to synthesise 2-substituted quinoline derivatives (**L356**) followed by C-H arylation was established by Chatani *et al*. in 2009 (Scheme 1.169) [203]. Here, quinoline (**L361**) reacted with the various acrylic compounds in the presence of Ni-complex, bis(1,5-cyclooctadiene)nickel(0) [$Ni(cod)_2$, 5 mol%], and tricyclohexyl phosphine (PCy_3, 10 mol%) in toluene at 130 °C. Arylzinc (**L362**) was prepared by treatment of readily available aryl boronic acids with diethylzinc and used as a source of an aryl group.



Scheme 1.169

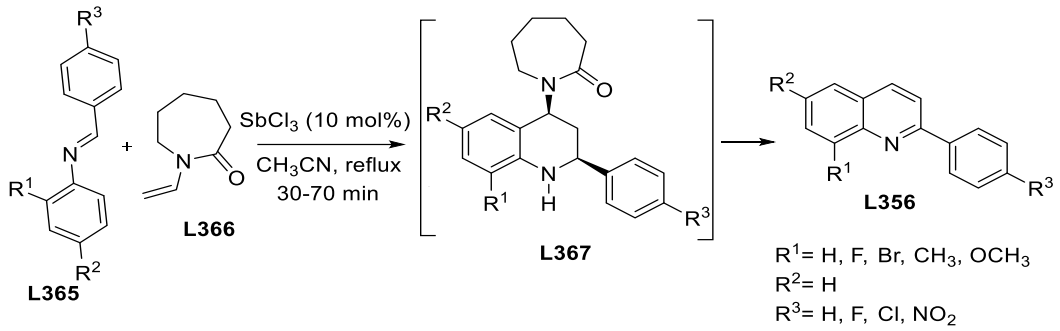
In the same year, Torok *et al*. described a method for the synthesis of quinoline derivatives (**L364**) *via* a domino cyclization–aromatization approach, where cyclization and oxidation step occurs readily (Scheme 1.170) [204]. In this reaction montmorillonite K-10 was used as a catalyst and the reaction proceeded under solvent-free conditions under microwave irradiation. Different substituted anilines (**L351**) reacted well with substituted *α,β*-unsaturated carbonyl compounds (**L363**) and gave the respective quinoline moiety (**L364**) in high yields.



R^1= H, CH_3, CH_3CH_2, F, Cl, Br, CH_3O, R^2= H, CH_3, Cl
R^3= C_6H_5, 2-NO_2-C_6H_4, 2-CH_3O-C_6H_4,4-CH_3O-C_6H_4, 4-NO_2-C_6H_4
R^4= H, CH_3

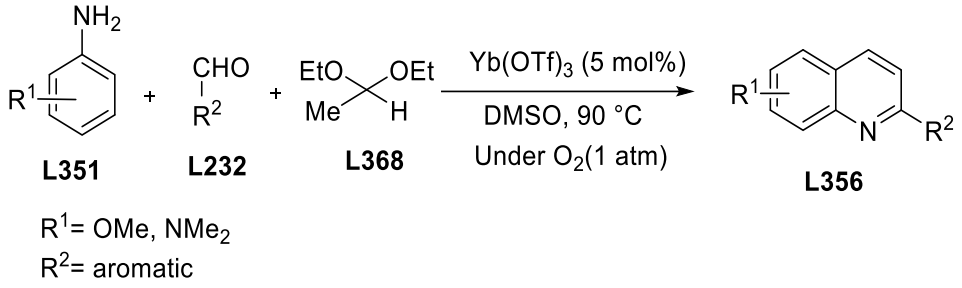
Scheme 1.170

Synthesis of quinoline (**L356**) derivative was reported by Varma and coworkers in 2010 by multicomponent imino-Diels-Alder reaction between azomethines (**L365**) and *N*-vynilazepinone (**L366**) (Scheme 1.171) [205]. This reaction was expanded by using antimony(III) chloride ($SbCl_3$, 10 mol%) catalyst in acetonitrile under reflux. The formayion of intermediate [**L367**] was postulated.



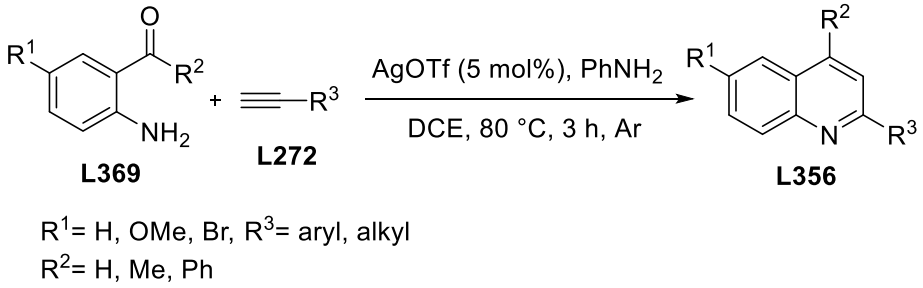
Scheme 1.171

One-pot synthesis of 2-arylquinoline (**L356**) was developed by Furukawa *et al*. in 2010 by the reaction between arylamines (**L351**), arylaldehyde (**L232**) and 1,1-diethoxyethane (**L368**) (Scheme 1.172) [206]. This reaction was carried out by using ytterbium triflate catalyst, $Yb(OTf)_3$ (5 mol%) in DMSO under oxygen atmosphere at 90 °C in moderate to good yields. The authors synthesized various 2-arylquinolines in high yields and also investigated theirfluorescence properties.



Scheme 1.172

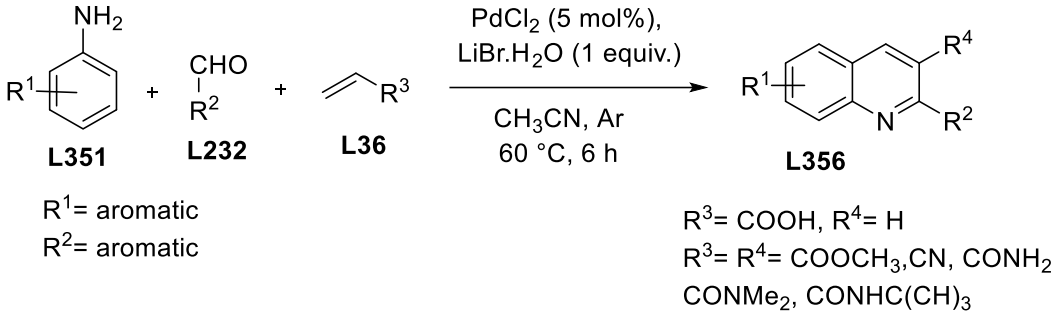
In 2011, a silver catalyzed synthesis of 2-substituted quinolines (**L356**) *via* cascade reaction of 2-aminoaryl (**L369**) with alkyne (**L272**) was established by Li *et al*. (Scheme 1.173) [207]. Here, silver triflate, AgOTf (5 mol%) was used as catalyst and aniline as solvent. Different *o*-aminoaldehydes and a terminal alkynes were tested to explore the hydroamination-cyclization reactions and produced the corresponding 2-substituted quinolines in moderate yields.



Scheme 1.173

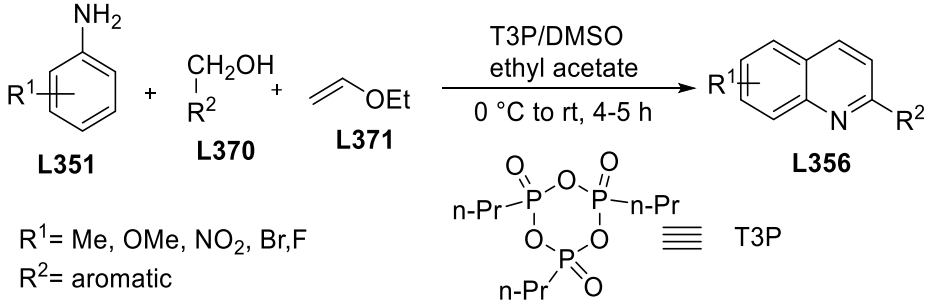
In 2012, Jiang and coworkers developed a protocol for the synthesis of 2-substituted as well as and 2,3-disubstituted quinolines (**L356**) *via* MCR between anlines (**L351**), aldehydes

(**L232**) and alkenes (**L36**) in the presence of palladium catalyst ($PdCl_2$, 5 mol%) and $LiBr.H_2O$ (1 equiv.) in acetonitrile under an argon atmosphere at 60 °C (Scheme 1.174) [208]. Various electron withdrawing and electron-donating substituents in 2-substituted and 2,3-disubstituted quinolines have been synthesized by using this approach in good yields.



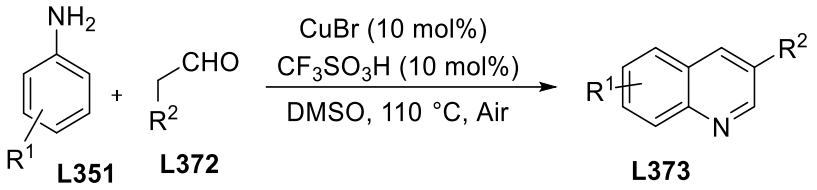
Scheme 1.174

In 2013, Rangapa *et al*. described a synthetic route for the synthesis of 2-arylquinolines (**L356**) *via* one-pot three-component reaction of aniline (**L351**), benzyl alcohol (**L370**) and ethyl vinyl ether (**L371**) (Scheme 1.175) [209]. This reaction was carried out in the presence of propylphosphonic anhydride (T3P, 2 equiv.) which is used as a coupling reagent in EtOH/DMSO (2:1) solvent. This method tolerates a variety of benzyl alcohols and different anilines to provide substituted 2-arylquinolines in good yields.



Scheme 1.175

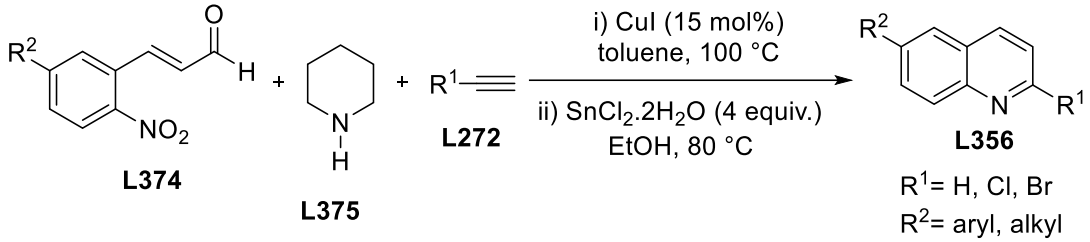
Copper-catalyzed synthesis of 3-substituted quinolines (**L373**) was established by Li *et al*. in 2013 by means of the reaction of aldehyde (**L372**) and aniline (**L351**) (Scheme 1.176) [210]. This reaction was developed in the presence of copper catalyst like copper(II) bromide (CuBr, 10 mol%) and trifluoroacetic acid in DMSO solvent at 100 °C. Different substituted quinolines were synthesized by this route in moderate yields.



R^1= EWG, EDG, cyclo
R^2= aromatic, aliphatic

Scheme 1.176

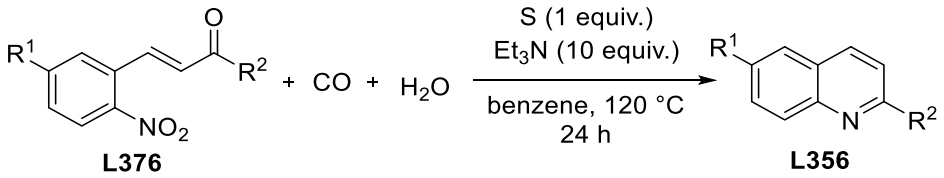
$SnCl_2$ mediated synthesis of 2-substituted quinolines (**L356**) using A^3-coupling between acetylenes (**L272**), chalcones (**L374**) and piperidine (**L375**) followed by reductive cyclization in one pot was established by Perumal *et al*. in 2014 (Scheme 1.177) [211]. Here copper(I) Iodide (15 mol%) was used as a catalyst for the formation of *N*-propargylamine in the first step *via* A^3-coupling and in the second step $SnCl_2.H_2O$ (4 equiv.) was used for cyclization. Different ortho nitroaldehydes and aryl, alkyl alkynes have been examined to explore the reactions and produced the corresponding 2-substituted quinolines in moderate yields.



R^1= H, Cl, Br
R^2= aryl, alkyl

Scheme 1.177

Nishiyama and coworkers in 2014 reported a synthetic route for sulfur assisted synthesis of substituted quinolines (**L356**) (Scheme 1.178) [212]. This reaction was achieved by the reaction of *β*-(2-nitrophenyl)-*α*,*β*-unsaturated ketones (**L276**) with carbon monoxide (50 atm) and water (40 equiv.) in presence of sulfur (1 equiv.) and base (Et_3N, 10 equiv.) at 120 °C for 24 h. A variety of quinolines were synthesized by this route in moderate yields.

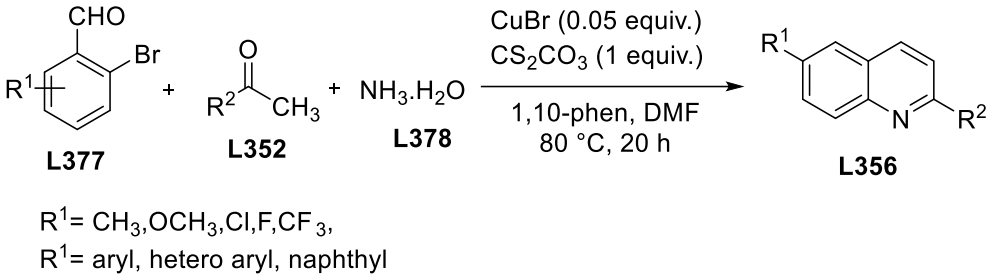


R^1= H, OCH_3, Cl, R^2= aryl, CH_3

Scheme 1.178

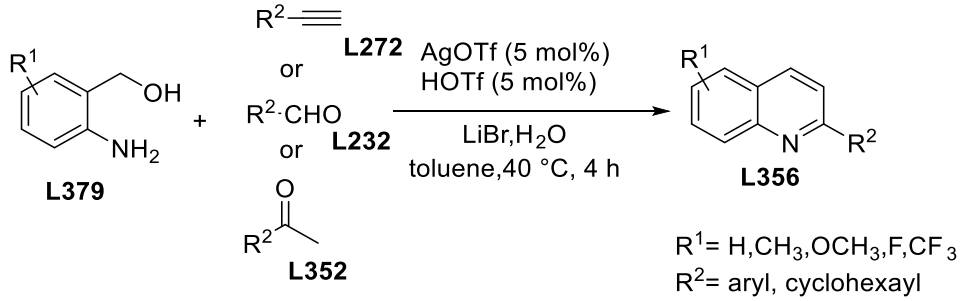
Synthesis of substituted quinolines (**L356**) was developed by Fan *et al*. in 2014 *via* one-pot cascade reaction between 2-bromobenzaldehyde (**L377**), aryl methyl ketone (**L352**) and aqueous ammonia (**L378**) (Scheme 1.179) [213]. This reaction was performed in presence of

copper bromide (CuBr, 0.05 equiv.) as a catalyst, Cs_2CO_3 (1 equiv.) as base and 1,10-phenanthroline (0.1 equiv.) as a ligand in DMF solvent at 80 °C. With the optimized reaction conditions, the different substituted aldehyde and aryl methyl ketones afforded the corresponding quinoline derivatives in high yields.



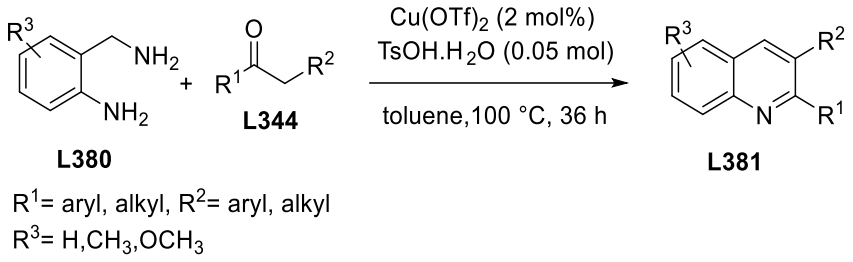
Scheme 1.179

In 2015, Zhang *et al*. described a protocol for the synthesis of 2-substituted quinolines (**L356**) by the reaction between 2-aminobenzyl alcohol (**L379**) and alkyne (**L272**)/ketone (**L232**)/ aldehyde (**L352**) (Scheme 1.180) in the presence of AgOTf (5 mol%), LiBr (10 mol %), HOTf (10 mol%), and H_2O (0.2 mL), in toluene (3 mL) at 40 °C under air for 8 h [214]. This method tolerates a variety of benzyl alcohols and different alkyne/ketone/ aldehyde to provide 2-substituted quinolines in high yields.



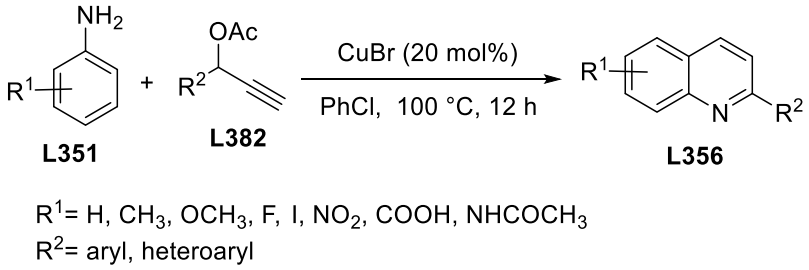
Scheme 1.180

Another copper-catalyzed synthesis of 2-substituted and 2,3-disubstituted quinolines (**L381**) were developed by You and coworkers in 2015 by condensation reaction between 2-amino benzylamine (**L380**) with ketones (**L344**) (Scheme 1.181) [215]. This reaction was carried out in presence of copper(II) triflate [$Cu(OTf)_2$, 2 mol%) as a catalyst and $TsOH{\cdot}H_2O$ (0.05 mmol) in toluene solvent at 100 °C. A wide range of quinoline derivatives has been synthesized in high yields.



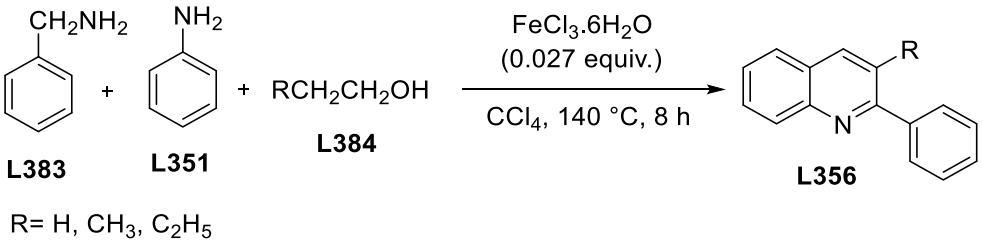
Scheme 1.181

In 2016, Liang *et al*. described a route for the synthesis of quinolines (**L356**) by intermolecular cyclization reaction between anilines (**L351**) with terminal alkyne ester (**L382**) using copper catalyst (Scheme 1.182) [216]. Copper bromide (CuBr, 20 mol%), in chlorobenzene solvent at 100 °C for 12 h provide quinoline derivatives in high yields. Another copper catalyst like CuCl, CuI, $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$ were not suitable for this reaction.



Scheme 1.182

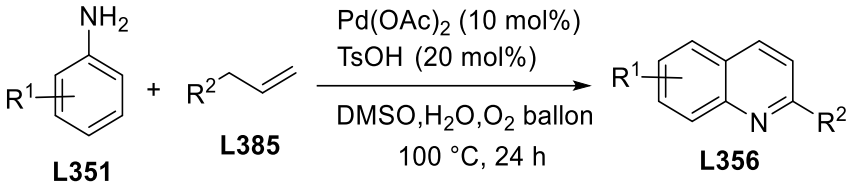
In the same year, Khusnutdinov *et al*. reported a method for the synthesis of 2-substituted quinolines by the multicomponent reaction of aniline (**L351**), benzylamine (**L383**), alcohols (**L384**) (Scheme 1.183) [217]. This reaction was extended in the presence of an iron catalyst, $FeCl_3.9H_2O$ (0.027 equiv.) in carbon tetrachloride at 140 °C. The reaction probably goes through *in situ* generation of *N*-benzylideneaniline which afforded the desired product.



Scheme 1.183

Palladium-catalyzed synthesis of 2-substituted quinoline (**L356**) *via* allylic C-H oxidative annulation between anilines (**L351**) and alkenes (**L385**) was reported by Jiang and coworkers in 2016 (Scheme 1.184) [218]. This reaction was performed in presence of palladium(II) acetate [$Pd(OAc)_2$, 10 mol%) as a catalyst and additive as a TsOH (20 mol%) in DMSO at 100 °C under

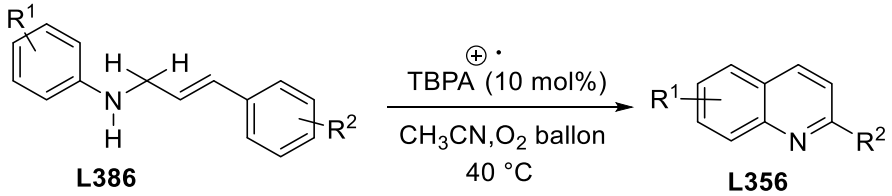
oxygen (using a ballon). This reaction tolerates a range of functional groups which furnished the corresponding quinoline derivatives (**L356**) in high yields after 24 h.



R^1= FG, R^2= aryl, -$(CH)_2CH_3$

Scheme 1.184

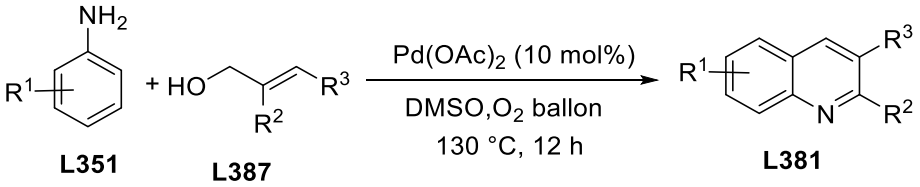
In the same year, Jia *et al*. developed an approach for the synthesis of 2-arylquinolines (**L356**) *via* sp^3 C-H aerobic oxidation induced by a catalytic radical cation salt from *N*-cinnamylanilines (**L386**) (Scheme 1.185) [219]. This reaction was carried out in the presence of radical cation salt, [tris(4-bromophenyl)aminium hexachloroantimonate, $TBPA^{+\cdot}$] (10 mol%) in acetonitrile at 40 °C under oxygen atmosphere. Variety of *N*-cinnamylanilines (**L386**) provided a series of corresponding 2-arylquinolines in moderate yields.



R^1= H, CH_3, OCH_3,OEt, Cl, Br, napth
R^2= OCH_3, Cl, Br

Scheme 1.185

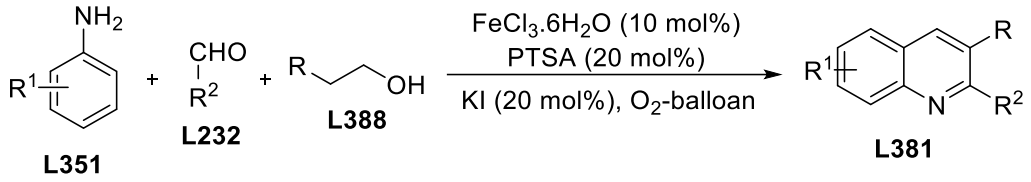
Palladium-catalyzed synthesis of quinoline (**L381**) from allyl alcohol (**L387**) and aniline (**L351**) *via* oxidative cyclization was established by Zhao and coworkers in 2017 (Scheme 1.186) [220]. In this reaction, palladium(II) acetate [$Pd(OAc)_2$, 10 mol%) was used as a catalyst and DMSO as a solvent. A variety of allylic alcohols reacted well with different anilines to provide quinoline derivatives in high yields after 12 h.



R^1= H,CH_3,OCH_3,Ph,F,Cl, Br,CN,CF_3,OCF_3,napth
R^2= aryl, heteroaryl, R^3= H

Scheme 1.186

In the same year, Li *et al*. developed a method for the synthesis of 2-arylquinolines (**L381**) through a three-component Povarov reactions between aniline (**L351**), aldehyde (**L232**) and alcohol (**L388**) (Scheme 1.187) [221]. This reaction was achieved in the presence of iron chloride [$FeCl_3.H_2O$, 10mol%], *p*-toluenesulfonic acid (PTSA, 20 mol%), KI (20 mol%) under an oxygen atmosphere. A series of 2-arylquinolines were synthesized by this methodology in moderate to high yields.

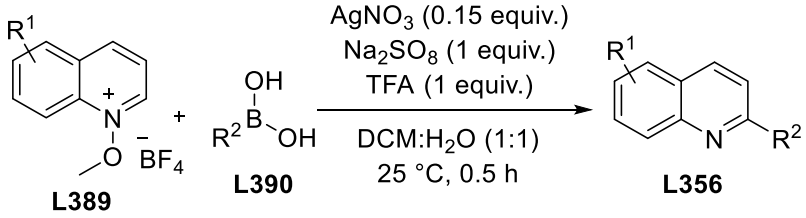


L351 **L232** **L388** **L381**

R^1= H, Me, OMe, NO_2, OPh, COOEt
R^2= aryl, heteroaryl, R= H, CH_3

Scheme 1.187

In 2018, Wu and coworkers described a protocol for the synthesis of 2-arylquinolines (**L356**) by the reaction between *N*-methoxyquinoline-1-ium tetrafluoroborate salts (**L389**) with aryl boronic acids (**L390**) using silver catalyst (Scheme 1.188) [222]. This reaction was developed in the presence of silver nitrate ($AgNO_3$, 0.15 equiv.), an oxidant like $Na_2S_2O_8$, trifluoroacetic acid (TFA, 1 equiv.) as an additive, in dichloromethane:water (1:1) at room temperature. A wide range of functionalities could be tolerated under the optimized reaction conditions to provide the corresponding 2-arylquinolines in high yields. The reaction proceeded *via* a radical pathway.

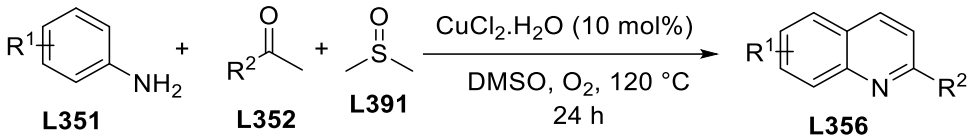


L389 **L390** **L356**

R^1= OCH_3, OEt, Cl, Br, Ph, CN
R^2= aryl

Scheme 1.188

Another copper-catalyzed synthesis of 2-arylquinolines (**L356**) by the reaction between aniline (**L351**), aryl methyl ketone (**L352**) and DMSO (**L391**) *via* aerobic oxidative cyclization was established by Guo and coworkers in 2018 (Scheme 1.189) [223]. In this reaction, copper chloride [$CuCl_2.H_2O$, 10 mol%) was used as a catalyst, DMSO as a carbon source and oxygen as an oxidant. Using this protocol, a number of anilines and ketones easily converted to corresponding 2-arylquinolines in high yields after 24 h.



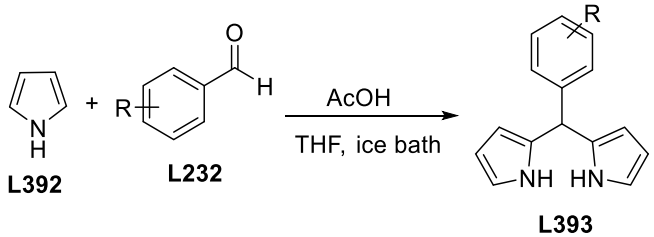
R^1= CH_3,$CH(CH_3)_2$, F,Cl, Br, CF_3, COOMe
R^2= aryl, alkyl

Scheme 1.189

1.2.2.6. Synthesis of dipyrromethanes and their fused derivatives

Dipyrromethanes are considered as important precursors in organic synthesis, namely, in the preparation of porphyrins and porphyrin analogs such as *meso*-substituted corroles, chlorins, expanded porphyrins, and calixpyrroles and also other important compounds such as fluorescent markers or coordination compounds [224]. In particular, these compounds have a wide range of applications for the preparation of asymmetric polypyrrolic polymers [225] and in materials science, medicine and optics [226, 227]. In recent developments, dipyrromethanes involving the one-pot condensation of 2 equiv. of pyrrole with a suitable electrophile have been introduced for the synthesis of BODIPYs dyes having photophysical properties to make them the ideal fluorescent scaffolds for the development of high-performance imaging probes [228]. On the other hand, bis(indolyl)methanes represent variety of molecules with diverse and complex structures, which are present in terrestrial and marine natural sources such as tunicates and sponges and exhibit significant bioactivities [229].

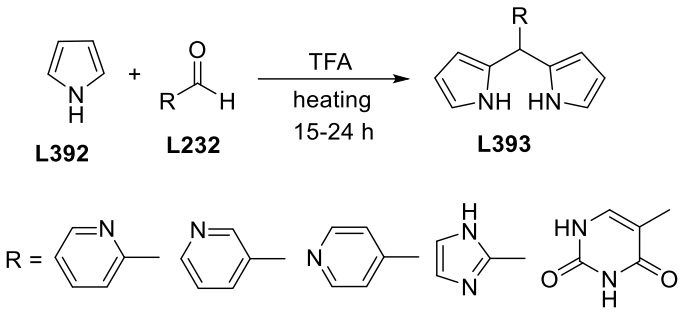
In 1994, Thompson and group synthesized the aryldipynomethanes (**L393**) from the direct condensation of excess amount of pyrroles (**L392**) with aromatic aldehydes (**L232**) dissolved in a solution of THF and acetic acid (9: l) stirred for 30 min to 2 hours at room temperature (Scheme 1.190) [230].



R = H, 4-Me, 4-NMe_2, 4-Cl, 4-CN, 4-NO_2

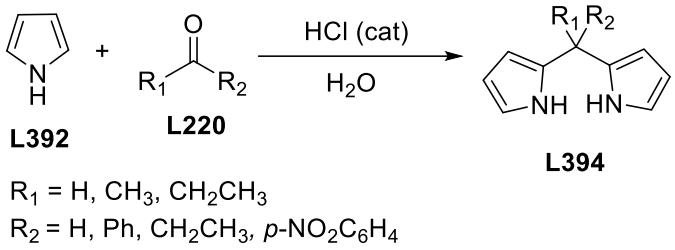
Scheme 1.190

In 2000, Lindsey *et al.* obtained dipyrromethane by the condensation reaction of carbonyl compounds (**L232**) with excess pyrrole (**L392**) in the presence of trifluoroacetic acid or BF_3-etherate under solvent-free conditions (Scheme 1.191). This method is useful to prepare dipyrromethanes bearing a wide variety of substituents [231].



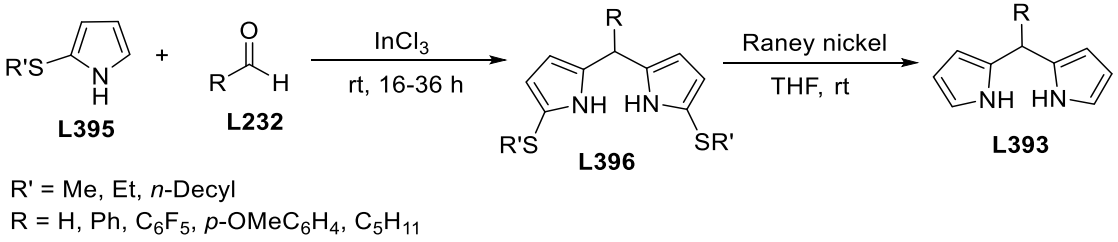
Scheme 1.191

Sobral's group in 2003 described a synthesis of *β*-free-dipyrromethanes in the presence of aqueous HCl. This is one-step reaction procedure for the synthesis of dipyrromethanes (**L394**) from pyrrole (**L392**) and carbonyl compounds (**L220**) and it affords products in moderate to high yields (Scheme 1.192) [232].



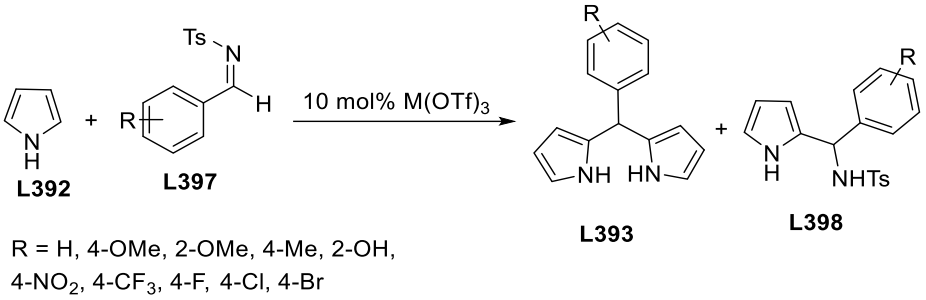
Scheme 1.192

In 2005, Lindsey *et al.* established a protocol involving the use of a 2:1 ratio of 2-SR'-pyrroles (**L395**) and benzaldehyde (**L232**) with a catalytic amount of $InCl_3$ at room temperature in the absence of any solvent. The *α*-SR' group was removed by hydrodesulfurization using Raney nickel or nickel complexes and dipyrromethane (**L393**) were obtained (Scheme 1.193) [233].



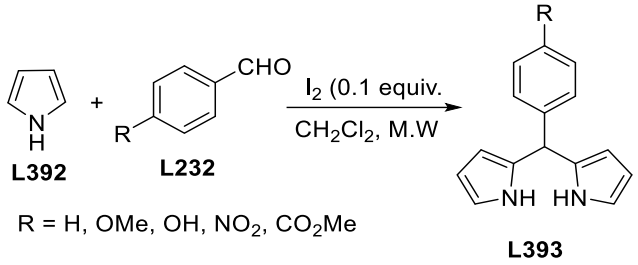
Scheme 1.193

In 2006, Unaleroglu and coworkers described a protocol for the synthesis of dipyrromethanes (**L393**) by the reaction of *N*-tosyl imines (**L397**) with an excess amount of pyrrole in the presence of metal triflates [234]. They used various types of metal triflates like $Cu(OTf)_2$, $Gd(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$, $Nd(OTf)_3$ (Scheme 1.194).



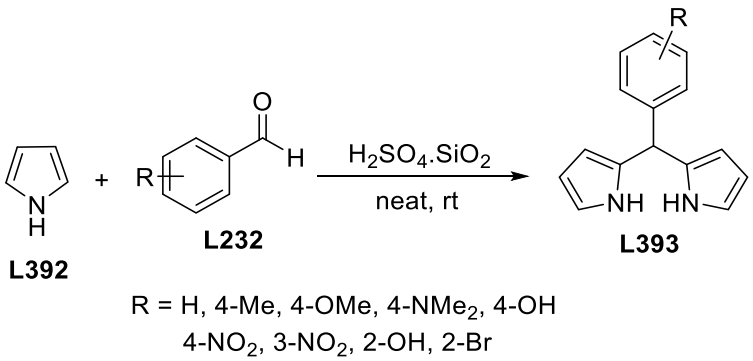
Scheme 1.194

In 2010, Zerrouki *et al.* reported a method for synthesis of *meso*-substituted dipyrromethanes (**L393**) by the reaction of pyrroles (**L392**) and aldehyde (**L232**) using molecular iodine as the catalyst [235]. Various aromatic dipyrromethanes were produced after a preliminary reaction of nitrobenzaldehyde and pyrrole catalyzed by I_2 in CH_2Cl_2 solvent on microwave heating (Scheme 1.195).



Scheme 1.195

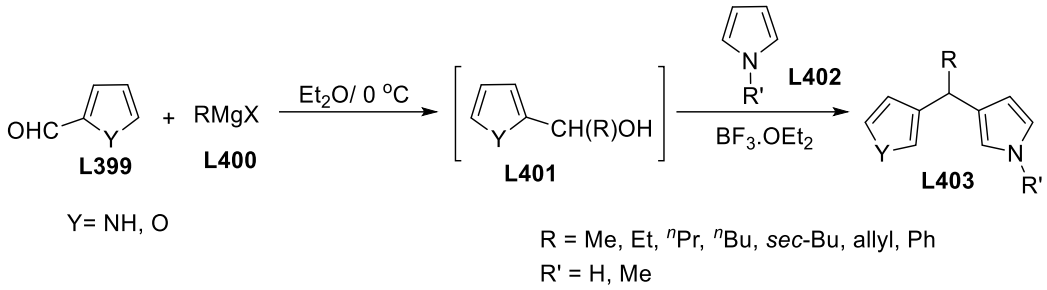
In the same year, Shang and co-workers proposed a silica-supported sulfuric acid (H_2SO_4•SiO_2) as a heterogeneous and efficient catalyst to give the corresponding dipyrromethanes (**L393**) resulted from the condensations reaction between pyrrole (**L392**) and aldehyde (**L232**) at room temperature (Scheme 1.196) [236].



Scheme 1.196

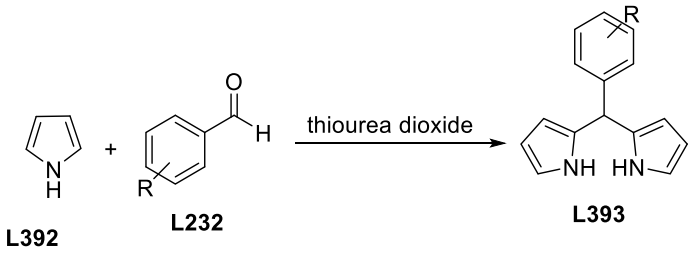
The reaction of furan aldehyde (**L399**) with Grignard reagent (**L400**) followed by the reaction of pyrrole or *N*-methylpyrrole (**L402**) in the presence of $BF_3.OEt_2$ resulting in *meso*-

elaborated bis(heterocyclyl)methanes (**L403**) has been reported by Sharma *et.al.* in 2011 (Scheme 1.197) [237].



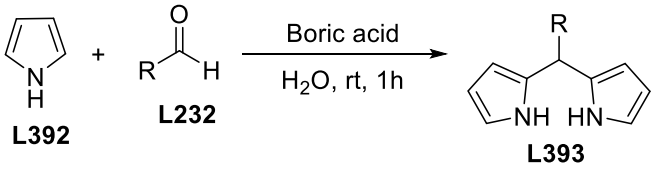
Scheme 1.197

In the same year, Sain and his group described thiourea dioxide as an organocatalyst for the synthesis of novel heterocyclic compounds including dipyrromethanes (**L393**) from pyrrole (**L392**) and aldehydes (**L232**) (Scheme 1.198) [238].



Scheme 1.198

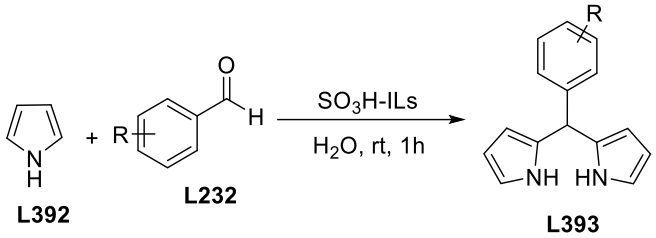
In 2016, Chauhan and coworkers reported the synthesis of dipyrromethanes (**L393**) by the condensation reaction of aldehydes (**L232**) and pyrrole (**L392**) using boric acid (Scheme 1.199) [239]. The reaction was carried out at room temperature in aqueous media to afford dipyrromethanes in good to excellent yields. They also prepared new compound analogue, *meso*-acetyldipyrromethane in moderate to good yield.



Scheme 1.199

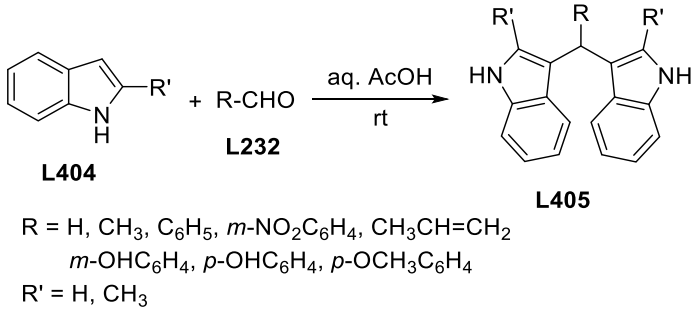
In the same year, Sirion *et al.* reported a metal-free method for the green synthesis of dipyrromethanes (**L393**) from aldehydes (**L232**) and unsubstituted pyrrole (**L392**) catalyzed by

SO_3H-functionalized ionic liquids (SO_3H-ILs) in aqueous media and at room temperature (Scheme 1.200) [240].



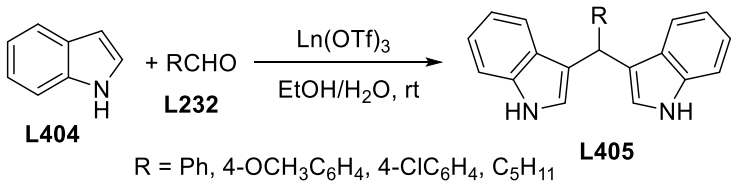
Scheme 1.200

In 1963, Kamal and Qureshi developed a method for the synthesis of substituted bis(indolyl)methanes compounds (**L405**) by the condensation process occurring between various aldehydes (**L232**) and indoles (**L404**) in an aqueous medium containing acetic acid or malonic acid or urea (Scheme 1.201) [241].



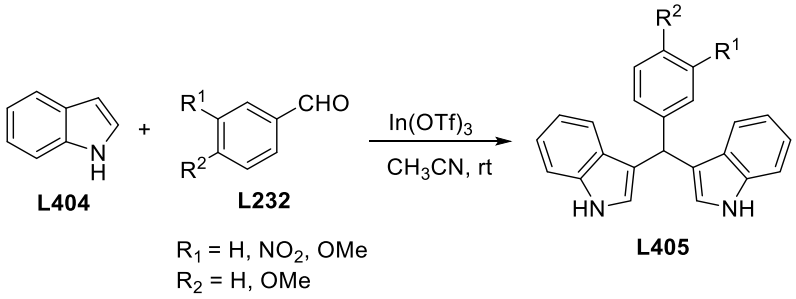
Scheme 1.201

In 1996, Wang *et al.* found lanthanide triflates as effective catalysts for reactions of indoles (**L404**) with aromatic and aliphatic aldehydes or ketones (**L232**) in aqueous solution [242] to afford bisindoles (**L405**). The authors used a variety of lanthanide triflates, $Ln(OTf)_3$ [Ln= La, Pr, Nd, Gd, Dy, Er, Yb] for the reaction and observed different amounts of yields (Scheme 1.202).



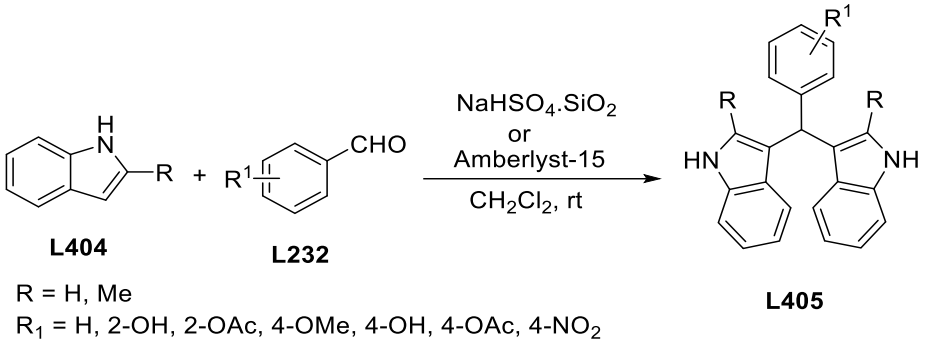
Scheme 1.202

Permul and group in 2002, reported that $InCl_3$ and $In(OTf)_3$ to be effective catalysts for the acetylation of indole (**L404**) to 3-acetylindoles (**L232**) affording bisindoles (**L405**) in good yield. They also found $In(OTf)_3$ (5 mol%) to be an efficient catalyst for the synthesis of bis-indolylmethane and indolylquinoline derivatives (Scheme 1.203) [243].



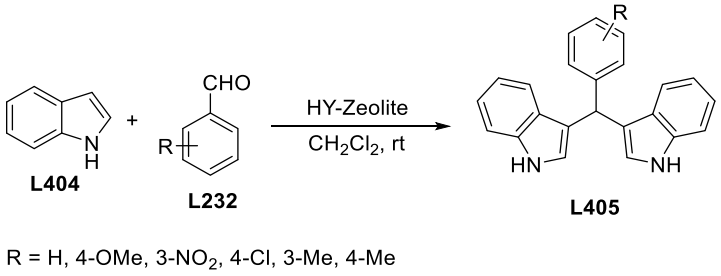
Scheme 1.203

In the next year, Das *et al.* reported silica supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) as heterogeneous catalyst for facile synthesis of bis- and tris(1*H*-indol-3-yl)methanes (**L405**) from the reaction of indoles (**L404**) and carbonyl compounds (**L232**) [244]. They used DCM as a solvent for the reaction in room temperature (Scheme 1.204).



Scheme 1.204

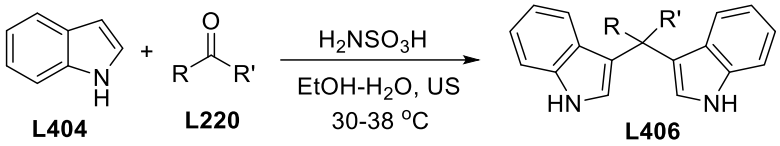
In 2004, Murugesan and group reported Zeolites-catalyzed reaction between indole (**L404**) and aromatic aldehydes (**L232**) affording bis(indolyl)methanes (**L405**) at room temperature [245]. Dichloromethane was taken as solvent and various Zeolites such as Hβ, HY and H-ZSM-5 were used as catalysts to check their catalytic activities in the synthesis of bis(indolyl)methanes (**L405**) (Scheme 1.205).



Scheme 1.205

In 2006, Li *et al.* reported a protocol for the synthesis of bis(indolyl)methanes (**L406**) through the reaction between indoles (**L404**) and aromatic aldehydes and ketones (**L220**) (Scheme

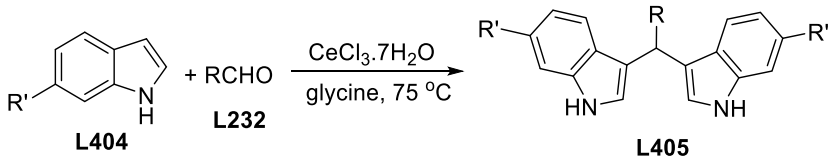
1.206) [246]. The reactions were catalyzed by aminosulfonic acid (H_2NSO_3H) and carried out at 30–38 ºC in EtOH aqueous solution under ultrasound irradiation to afford the products in 23–96% yield.



R = C_6H_5, 3-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4
R' = H, CH_3

Scheme 1.206

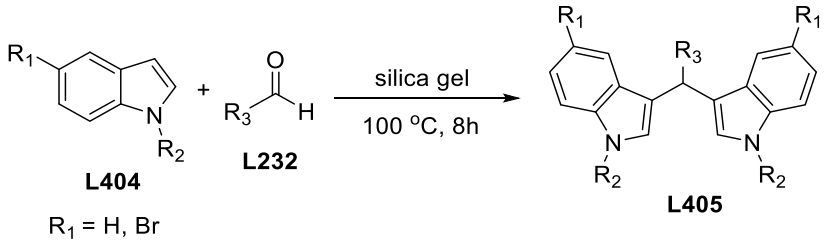
Few years later, in 2009, Silveira and co-workers used catalytic amount of glycerin and $CeCl_3.7H_2O$ to synthesize several bis(indolyl)methanes (**L405**) in good yields by the reaction of indoles (**L404**) with aldehydes (**L232**) occurred at 75 ºC (Scheme 1.207) [247]. They showed that the method is applicable to aliphatic and aromatic aldehydes.



R = C_6H_5, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, 2-ClC_6H_4, 4-$OCH_3C_6H_4$, 3-$NO_2C_6H_4$, 2-$CH_3C_6H_4$, 2-furyl
R'= H, Br

Scheme 1.207

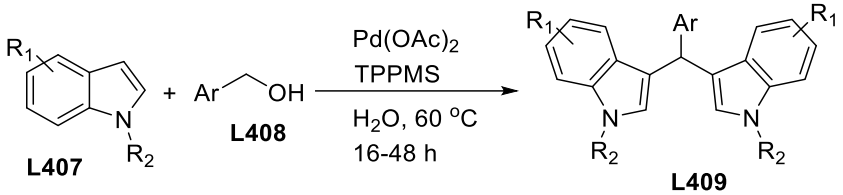
In 2012, Mendesin and group described a methodology for the synthesis of bis(indolyl)methanes (**L405**) from indoles (**L404**) and aldehydes (**L232**) promoted by silica gel under the solvent-free conditions at 100 ºC stirred for 8 h (Scheme 1.208) [248]. The products were obtained through the reaction of indoles with carbonyl compounds. The silica gel was easily recycled and utilized for further reactions.



R_1 = H, Br
R_2 = H, Ts
R_3 = C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 2-BrC_6H_4

Scheme 1.208

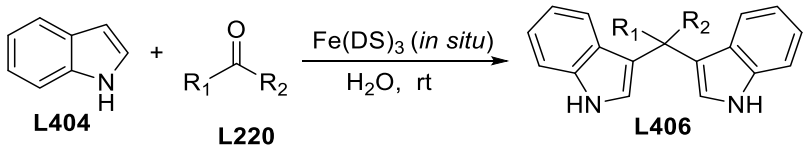
In 2013, Hikawa *et al.* reported a method for the synthesis of bis(indolyl)methanes (**L409**) *via* domino reactions of indoles (**L407**) with benzyl alcohols (**L408**) using 5 mol% of $Pd(OAc)_2$ (Scheme 1.209) [249]. The reported protocol involved C3-benzylation of indoles and benzylic C–H functionalization in water medium and the reactions were performed under 60 °C temperature for 16-48 h.



R_1 = H, 5-Me, 5-OMe, 5-F, 5-CN
R_2 = H, Me
Ar = C_6H_5, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-FC_6H_4, 4-$CH_3OC_6H_4$, 2-EtC_6H_4

Scheme 1.209

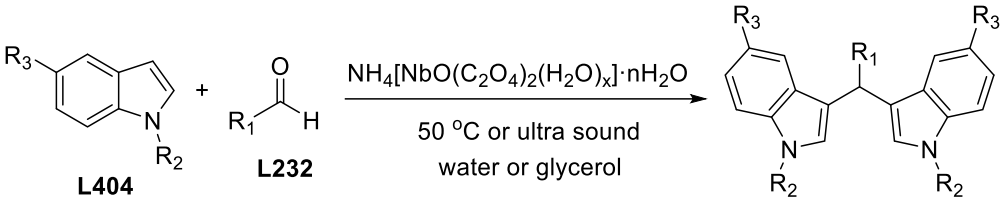
Maleki *et al.* in 2014, developed a method where a Lewis acid-surfactant iron(III) dodecyl sulfate was prepared *in situ* and was effectively used as a catalyst in the synthesis of bis(indolyl)methanes (**L406**) and Michael reactions of indoles (**L404**) with *α,β*-unsaturated carbonyl compounds in an aqueous medium. This method produced these corresponding products in good to excellent yield at room temperature (Scheme 1.210) [250].



R_1: C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4
R_2: H, Me

Scheme 1.210

In 2015, Lenardão and group developed a green procedure for the synthesis of bis(indolyl)methanes (**L405**) from indoles (**L404**) and aldehydes (**L232**) using ammonium niobium oxalate (ANO) $NH_4[NbO(C_2O_4)_2(H_2O)_x]\cdot nH_2O$ as the catalyst and water or glycerol as the solvent (Scheme 1.211) [251]. The desired products were formed under conventional heating or under sonication.

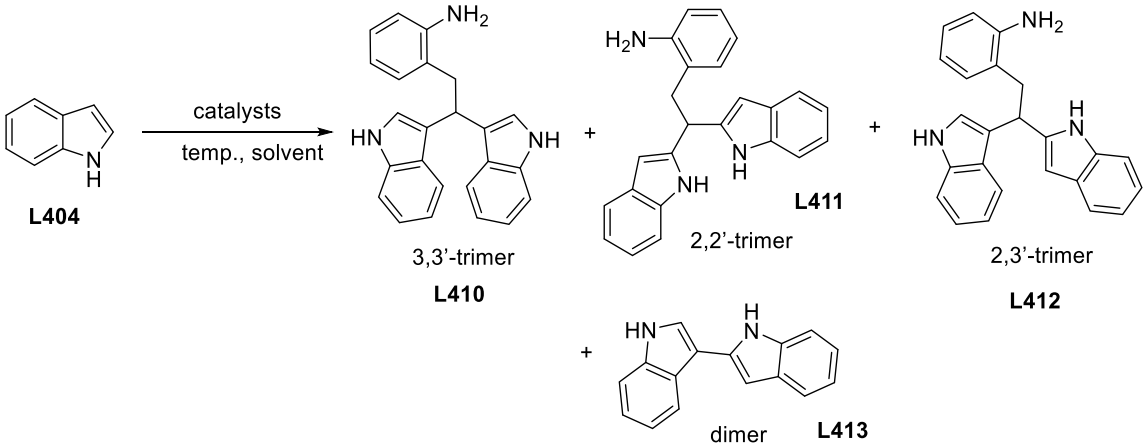


R_1 = C_6H_5, 4-$CH_3C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 2-furyl
R_2 = H, Me
R_3 = H, Br

Scheme 1.211

1.2.2.7. Formal trimerization of indoles

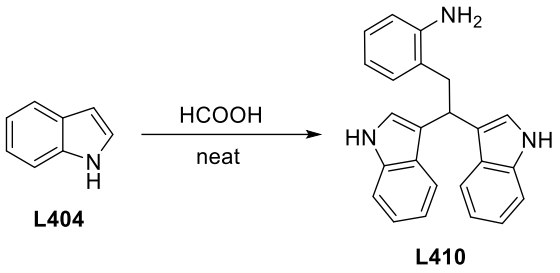
Long before, in 1977, Ishii *et al.* showed that indole (**L404**) itself is polymerized under various acidic conditions to give various polymeric products (dimer (**L413**) and trimers (**L410**-L**412**)) of indole. Different types of acid catalysts and solvents were used for these transformations such as TsOH-PhH, $ZnCl_2$-AcOH, HCl gas-PhH, TFA-Et_2O, *etc*. (Scheme 1.212) [252].



Catalysts	Conditions	Yields of 3,3'-Trimer
TsOH-PhH	Reflux, 8 h	3.3%
$BF_3.Et_2O$	Room temp., 5 days	9.6%
$ZnCl_2$-AcOH	105 °C, 4 h	15.3%
$ZnCl_2$-AcOH	Room temp., 21 h	92.9%
0.5M HCl	Room temp., 24 h	92.8%
0.5M HBr gas	Room temp., 1.5 h	44.2%
CF_3CO_2H, Et_2O	Room temp., 48 h	68.4%

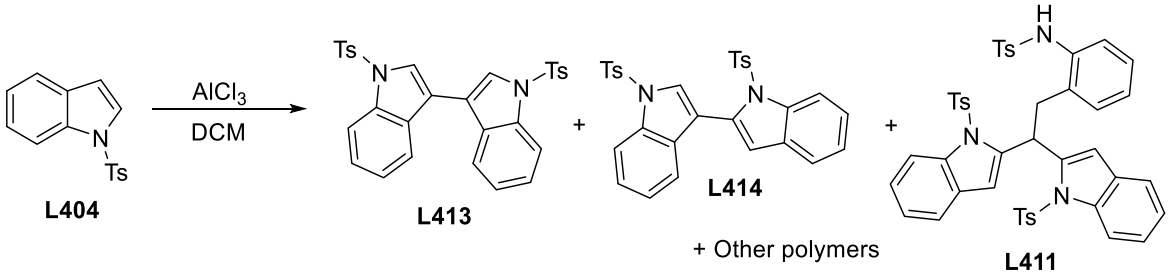
Scheme 1.212

In 2000, Konda group reported that neat formic acid singly efficient for the synthesis of bisindoles (**L410**) along with *N*-formylates carbazoles, diphenylamine and even moderately weak nucleophilic anilines to furnish the corresponding *N*-formyl derivatives (Scheme 1.213) [253].



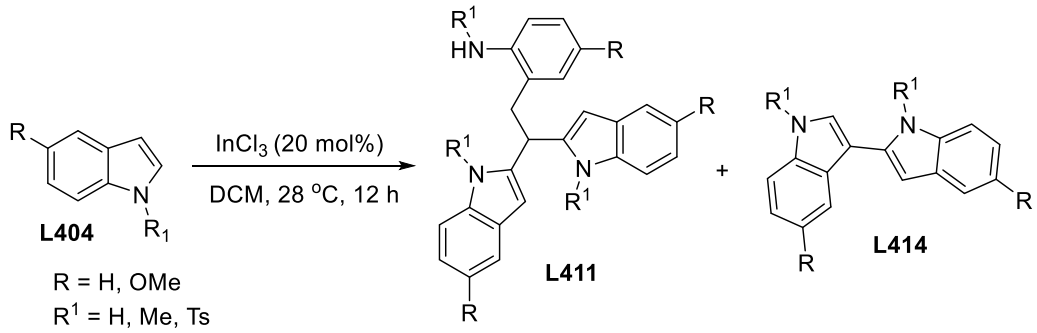
Scheme 1.213

Nakatsuka *et al.* studied the reactivity of *N*-tosylindole (**L404**) in the presence of $AlCl_3$ in CH_2Cl_2 solvent for 25 min and found two types of trimerization products. One type of product was formed by condensation between both pyrrole parts (dimers (**L413,L414**) and trimer(**L411**)) and the other was between a pyrrole part and a benzene part of indole (Scheme 1.214) [254].



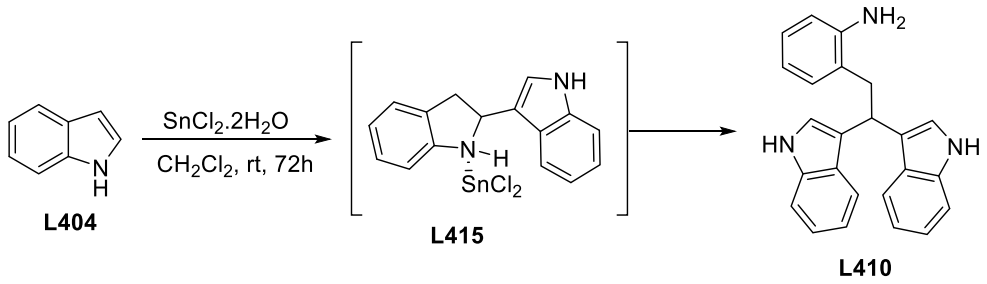
Scheme 1.214

Just one year later, in 2005, Jaisankar *et al.* developed a procedure for the synthesis of *N*-substituted derivatives of indole (**L404**) which underwent self-addition to afford indolylindoline compounds (**L411, L414**) using $InCl_3$ in dichloromethane solvent for 12 h (Scheme 1.215) [255].



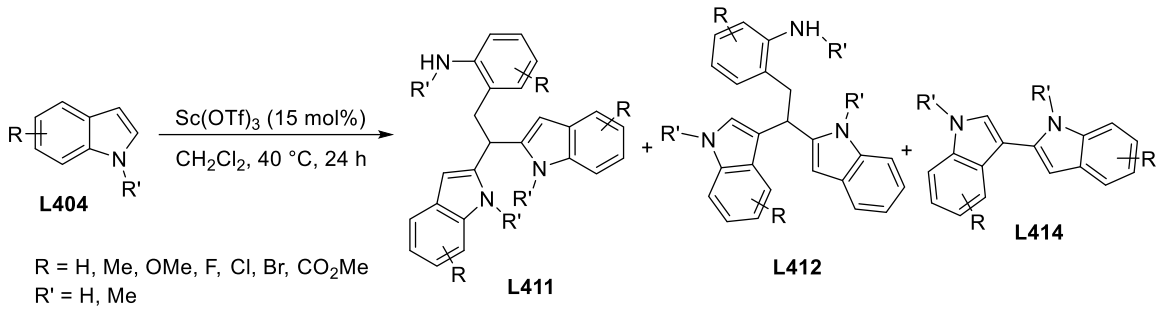
Scheme 1.215

In 2011, Cachet group developed a method where Lewis acid $SnCl_2 \cdot 2H_2O$ catalyzed indole dimerization affording bis-indole (**L410**) through the formation of intermediate 3-(indolin-2-yl)-1*H*-indole (**L415**). (Scheme 1.216) [256].



Scheme 1.216

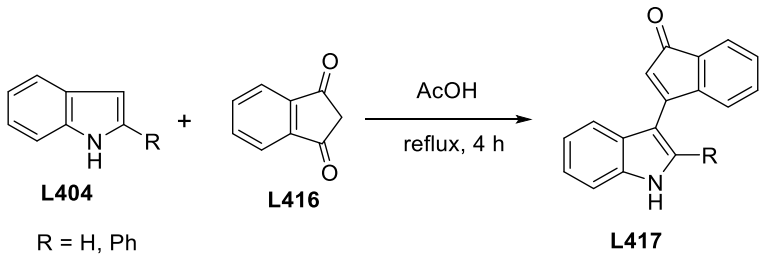
In 2017, Kumar *et al.* reported the trimerization of indole that is the one-pot synthesis of 2-[2,2-bis(indol-3-yl)ethyl]anilines (**L411**, **L412**) and 3-(indolin-2-yl)indoles (**L414**)catalyzed by $Sc(OTf)_3$ at 40 °C in CH_2Cl_2 for 24 hours (Scheme 1.217) [257].



Scheme 1.217

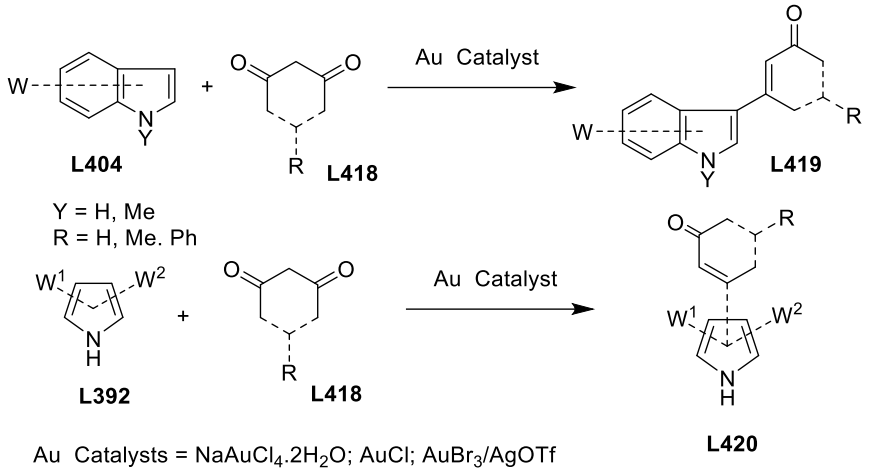
1.2.2.8. Alkenylation of indoles

In 1993, Hammoda reported the reaction of indan-1,3-dione (**L416**) with indole, indole derivatives (**L404**) and other heterocycles [258] to afford the aalkenylation product (**L417**). The author experimented the reaction of indole and indole derivatives with only indan-1,3-dione as 1,3-dicarbonyl compound only and they not studied the generality of the reaction methodology (Scheme 1.218) which is the most disadvantage of his work.



Scheme 1.218

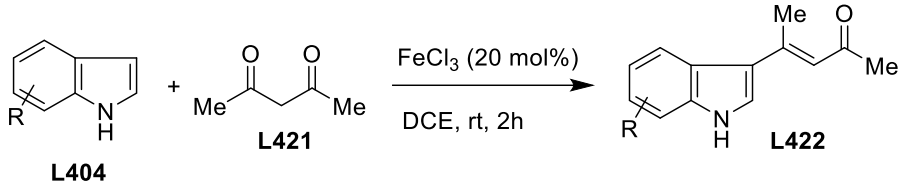
In 2006, Arcadi *et al.* investigated that gold(III) derivatives are efficient catalysts for the direct selective alkenylation reaction of indoles (**L404**) and pyrroles (**L392**) with 1,3-dicarbonuyl compounds (**L418**) (Scheme 1.219) [259] to afford product (**L419**). This method allowed high functional group tolerance, regioselectivity, and scope under relatively mild conditions.



Scheme 1.219

According to the authors, the 3-alkenylindoles could be readily available through gold-catalyzed sequential cyclization / alkenylation reaction of 2-alkynylanilines with 1,3-dicarbonyl compounds. But explanation was given for the mechanism of these transformations.

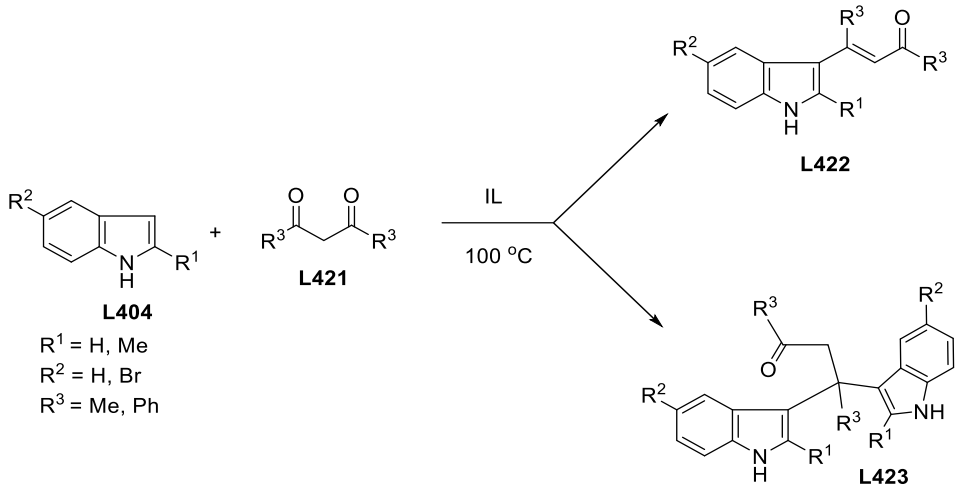
Next, in 2008, Jadav *et al.* reported a direct $FeCl_3$-catalyzed selective 3-alkenylation of indoles with 1,3-dicarbonyl compounds under mild conditions [260]. They attempted the coupling of indole (**L404**) with acetylacetone (**L421**). The reaction was carried out using 20 mol % anhydrous $FeCl_3$ in dichloroethane, and went to completion in 2 h at room temperature giving product (**L422**) in 88% yield with complete *E*-selectivity (Scheme 1.220).



Scheme 1.220

In 2009, the Rad-Moghadam group reported that, two ionic liquids, *N,N,N,N*-tetramethylguanidinium trifluoroacetate (TMGT) and the unprecedented *N,N,N,N*-tetramethylguanidinium triflate (TMGTf), are effective catalysts and solvents for condensations between indoles (**L404**) and arylaldehydes or 1,3-diketones (**L421**) providing a simple and

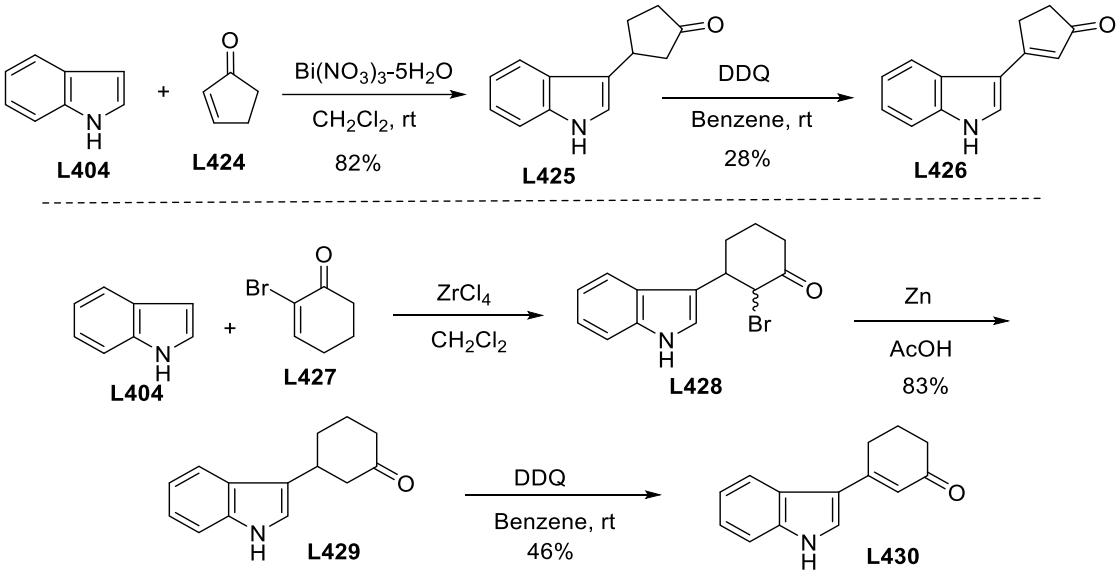
efficient method for synthesis of bis(3-indolyl)methanes (**L423**) or casually 3-alkenylindoles (**L422**) due to stereoelectronic concerns of reactants (Scheme 1.221) [261].



Scheme 1.221

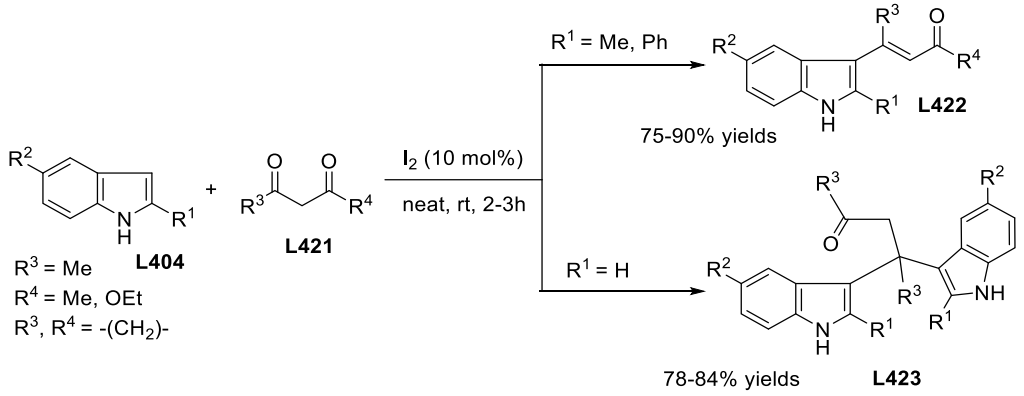
The authors could not synthesize only alkenylated product selectively. And in this reaction scheme the bis-indole also formed, which is the main disadvantage of their work.

Saracoglu *et al.* described the synthesis of new 3-vinylindole derivatives (**L426**, **L430**) [262]. 3-Vinylindoles as precursors of carbazole and *bis*-indole derivatives were synthesized. Then, aiming to form new carbazoles, Diels-Alder reactivity of these vinylindoles was studied with various dienophiles. Only three 3-vinyl or 3-alkenylated indole derivatives were synthesized in 28-46% yield through multistep reaction (Scheme 1.222).



Scheme 1.222

In 2012, Singh group demonstrated the use of iodine as catalyst for C-3 alkylation/alkenylation of various indoles (L404) with 1,3-dicarbonyl compounds (L421) at room temperature affording the desired alkenylindoles (**L422**) in up to 90% yields or bisindoles (**L423**) (Scheme 1.223) [263].



Scheme 1.223

1.3. STUDY OF THE FUNCTIONALIZATION PROCESSES OF C(H)C BONDS

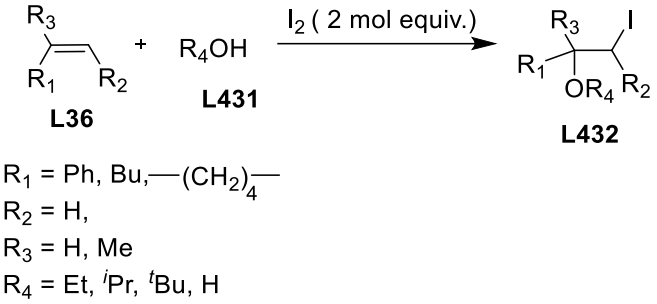
As part of our work, we examined the reactivity of styrene, including those activated by electron-withdrawing groups, in some key transformations for aziridines, as well as in new transformations that are not available in the series of aziridines.

1.3.1. Regioselective 1,2-difunctionalization of olefins

The 1,2-difunctionalization of olefins become very interesting to organic chemists when the selective addition of two different functional groups, like water or alcohols or acetic acid and halogens (halohydroxylation or haloalkoxylation or haloacetoxylation) occurs in a highly selective manner. The reaction of alkenes mainly this difunctionalization has been widely studied and utilized in various techniques for functional group interconversions. Among them the halohydrin, *β*-iodoether and *β*-iodoacetoxy compounds play a crucial role in the fields of drug scaffolds, synthetic organic chemistry, medicinal and industrial chemistry as well as material sciences. They are also the key intermediates in the synthesis of several halogenated marine natural products.

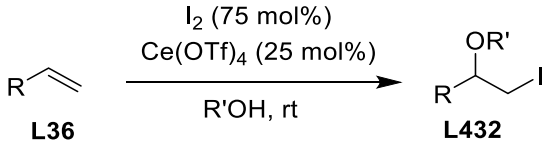
In 1998, Sanseverino and de Mattos reported the reaction of alkenes (**L36**) with I_2 and alcohols (EtOH, ^{i}PrOH, ^{t}BuOH) (**L431**) or water for the preparation of diverse *β*-iodoethers and iodohydrins (**L432**) respectively in a efficient manner [264]. They experimented the reaction of different alkenes with 2 equivalents of iodine and different alcohols or water to prepare a variety of *β*-iodoethers or iodohydrins in good yields and high purity (Scheme 1.224). But only in the case

of hex-1-ene the reaction gave predominantly the secondary ether mixed with some of its regioisomer (85:15 by HRGC).



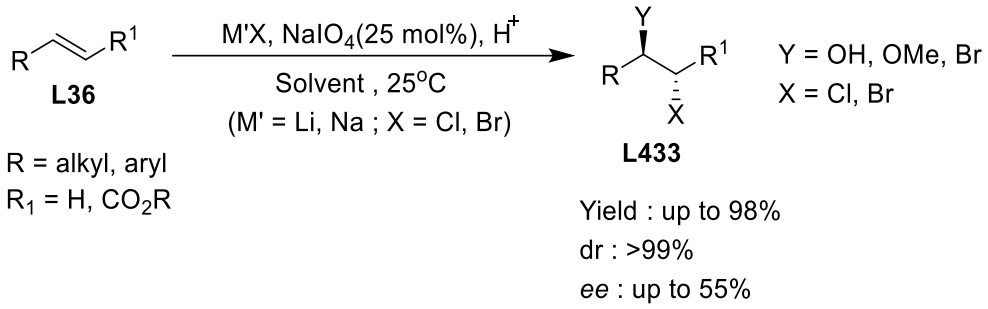
Scheme 1.224

After two years in 2000, Iranpoor and Shekarriz investigated that $Ce(OTf)_4$ was a efficient catalyst for the regioselective 1,2-alkoxy, hydroxy, and acetoxy iodination of alkenes (**L36**) with I_2 (Scheme 1.225) [265]. Actually in this work they reported a very simple, efficient and general method for alkoxy, acetoxy and hydroxy iodination of alkenes addording products (**L432**). But here it must be mentioned that the reaction of *trans*-stilbene in methanol under similar reaction conditions was also studied, but no reaction occurred under these conditions. Also, the high regioselectivity of the products was not observed in the case of 1-octene and 1-octadecane.



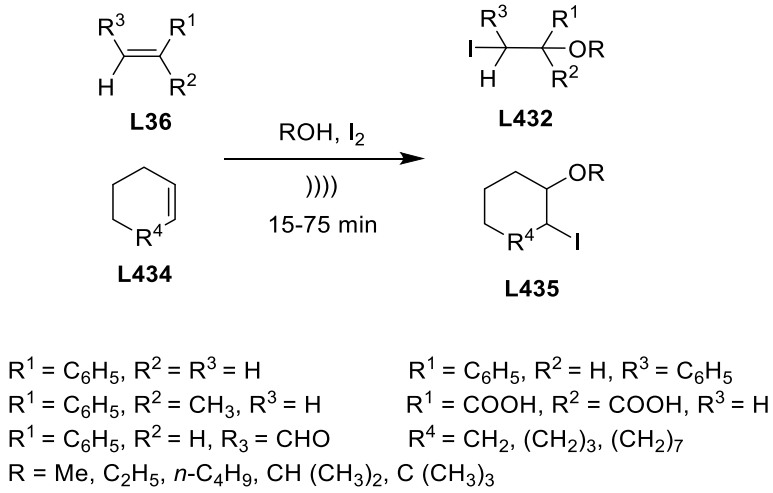
Scheme 1.225

In 2003, Dewkar and coworkers reported a method where $NaIO_4$ oxidatively halogenates a variety of olefins (**L36**) and aromatics with alkali metal halides as halogen source under mild conditions, in a highly regio- and stereoselective fashion [266]. The reaction was carried out using 25 mol% $NaIO_4$ in presence of different solvent systems like CH_3CN/H_2O (2:1), AcOH, $MeOH/H_2O$ (3:1) to give the corresponding halogenated product (**L433**) with good yields (up to 98%) and up to 55% *ee* (Scheme 1.226). In the absence of $NaIO_4$, no reaction took place and lowering the molar ratio of $NaIO_4$ also resulted in the reduced yield.



Scheme 1.226

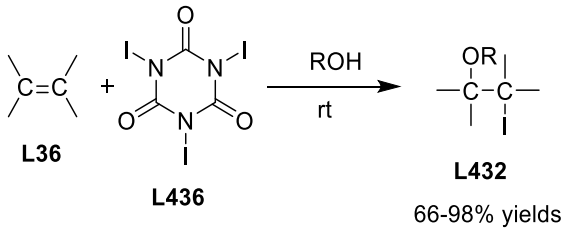
In 2005, Rama and Pasha reported their findings on the effect of ultrasound on the regioselective preparation of *β*-iodoethers from a mixture of olefin (**L36**) or cuclohexenes (**L434**), I_2 and alcohol [267]. The reaction was studied with a set of nine different alkenes and five different alcohols in presence of varied amounts of iodine. They have found that, the metal salt or excess of iodine is not required when the reaction proceeded under the influence of ultrasound to obtain *β*-iodoethers (**L432**) or iodo-alkoxy cycloalkanes (**L435**) in high yields (Scheme 1.227). The main disadvantage of this protocol is the alkenes with electron withdrawing groups such as maleic acid and cinnamaldehyde did not react even after sonication for 8 h.



$R^1 = C_6H_5$, $R^2 = R^3 = H$ $R^1 = C_6H_5$, $R^2 = H$, $R^3 = C_6H_5$
$R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = H$ $R^1 = COOH$, $R^2 = COOH$, $R^3 = H$
$R^1 = C_6H_5$, $R^2 = H$, $R_3 = CHO$ $R^4 = CH_2$, $(CH_2)_3$, $(CH_2)_7$
R = Me, C_2H_5, *n*-C_4H_9, CH $(CH_3)_2$, C $(CH_3)_3$

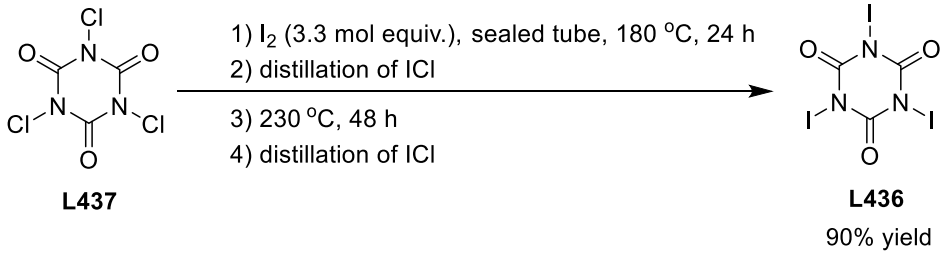
Scheme 1.227

In 2007, Ribeiro, Esteves and de Mattos reported a new method using triiodoisocyanuric acid (TICA) (**L436**) which reacted with alkenes (**L36**) in the presence of oxygenated nucleophilic solvents (alcohols, AcOH and H_2O) leading to the formation of corresponding *β*-iodoethers, *β*-iodoacetates and iodohydrins (**L432**) in 66-98% isolated yield (Scheme 1.128) [268]. In this study, different alkenes and activated alkenes that possess an enolethers moiety were used as substrates. However, among the enolethers if the reaction was performed with 1-methoxycyclohexene in water, the hemiacetal was very unstable and 2-iodocyclohexanone was obtained as a product.



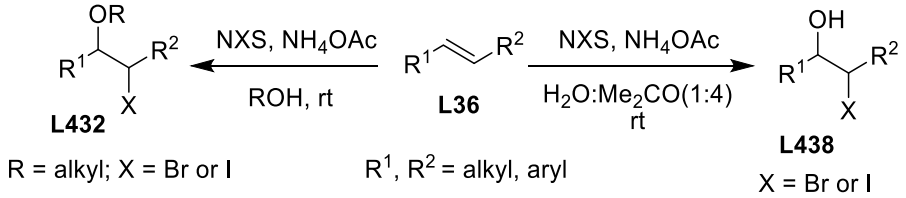
Scheme 1.228

TICA can be prepared by substituting the readily available and inexpensive trichloroisocyanuric acid (**L436**) employing 3.3 mol equiv. of I_2. The product (brown solid) was obtained in 90% yield after 24 h at 180 °C followed by 48 h at 230 °C in a sealed tube and distillation of ICl under reduced pressure (Scheme 1.229).



Scheme 1.229

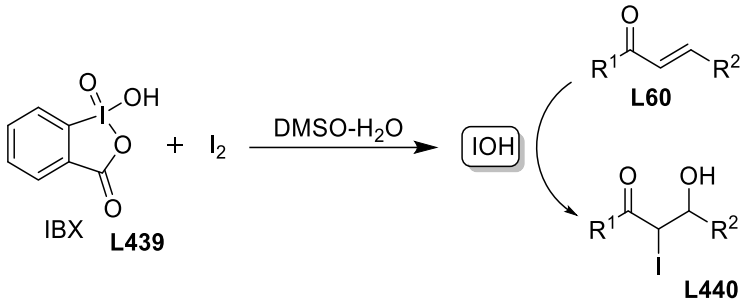
In the same year, Das and his group developed an efficient and rapid method for the synthesis of *vicinal* halohydrins (**L438**) and haloethers (**L432**) from alkenes (**L36**) and *N*-halosuccinimides employing ammonium acetate (NH_4OAc) in water or alcohols (Scheme 1.230) [269]. The authors used catalytic amount of NH_4OAc (10 mol%) for this conversion. The conversion proceeded at room temperature and the reaction took place within short time to afford the products in moderate to excellent yields. Here the presence of NH_4OAc was very important as it accelerated the completion time of the reaction.



Scheme 1.230

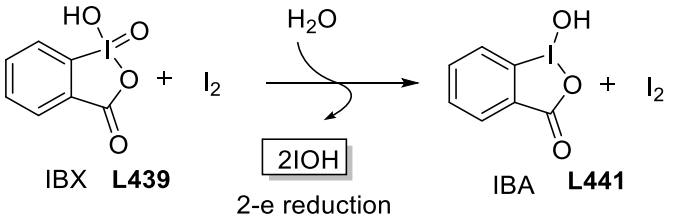
In 2009, a new protocol for the iodohydroxylation of olefins (Scheme 1.231) was reported by Moorthy, Senapati, and Kumar using the redox chemistry between the IBX-I_2 couple for facile generation of IOH [270]. The authors described that the redox reaction between IBX and I_2 in DMSO-H_2O leads to the formation of IOH, which can be further exploited to convert a variety of

electron rich olefins as well as electron deficient *α,β*-unsaturated carbonyl compounds (**L60**) to their corresponding iodohydrins (**L440**) with anti stereochemistry in very good isolated yields.



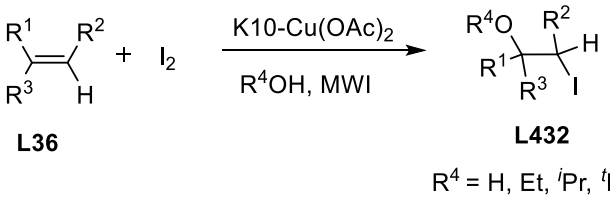
Scheme 1.231

It was concluded that *o*-iodoxybenzoic acid or 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (**L439**) is readily reduced to *o*-iodosobenzoic acid (IBA) in the presence of molecular iodine in DMSO-H_2O to generate hypoiodous acid (IOH) (**L441**). The reaction between IBX and I_2 is shown in Scheme 1.232.



Scheme 1.232

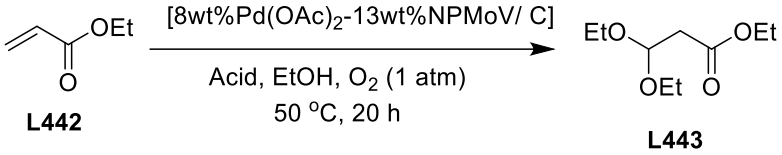
In 2012, the Shallu group described that the envirocats (K10-MX), act as efficient catalysts for the iodination of olefines (**L36**) with iodohydrin and *β*-iodoethers (**L432**) formation (Scheme 1.233) in excellent yields under microwave irradiation (MWI) without making use of high-boiling solvents and long reaction times [271]. The reaction was also found to be very efficient in both internal and terminal alkenes. But it was found that the conversions were very efficient for all the substrates except for undec-10-en-1-ol and undec-10-en-1-oic acid. Also, comparatively great selectivity of the terminal double bond over the internal has been observed.



Scheme 1.233

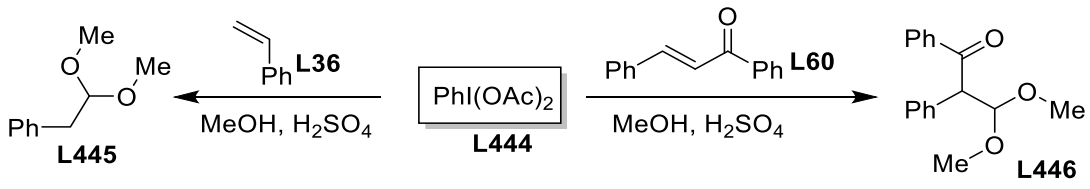
1.3.2. Formation of acetals

A very few methods are available in literature for the preparation of terminal acetals. Thus, in 2000, Kishi, Sakaguchi, and Ishii reported a reaction using chloride free $Pd(OAc)_2$-NPMoV system, namely, $Pd(OAc)_2$ supported on activated carbon combined with molybdovanadophosphate (NPMoV)] in mild conditions for the acetalization of terminal alkenes bearing an electron-withdrawing substituent (such as ethyl acrylate and acrylonitrile) [272]. As an example, ethyl acrylate (**L442**) was converted to ethyl 3,3-diethoxypropionate (**L443**) in satisfactory yield through the acetalization with EtOH acidified by CH_3SO_3H under O_2 (1 atm) in the presence of 8 % wt. $Pd(OAc)_2$/C and NPMoV (Scheme 1.234). However, a very low yield of ethyl 3,3-diethoxypropionate was obtained in the absence of CH_3SO_3H.



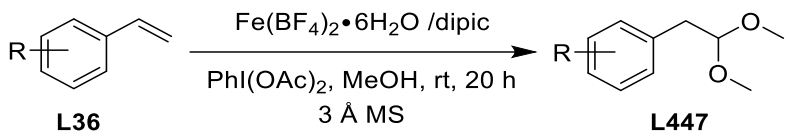
Scheme 1.234

Next year Yusubov and Zholobova investigated that the reaction of iodosobenzene diacetate (**L444**) in methanol in the presence of sulphuric acid with styrene (**L36**) or chalcone (**L60**) gave rise to oxidative rearrangement (Scheme 1.235) resulting in their corresponding acetals (**L445-L446)** [273]. This oxidative rearrangement occurred under mild conditions affording in high isolated yields. The main disadvantage is that the method was applied to some specific olefinic systems (chalcones or styrenes), which actually hampered the generality of this method.



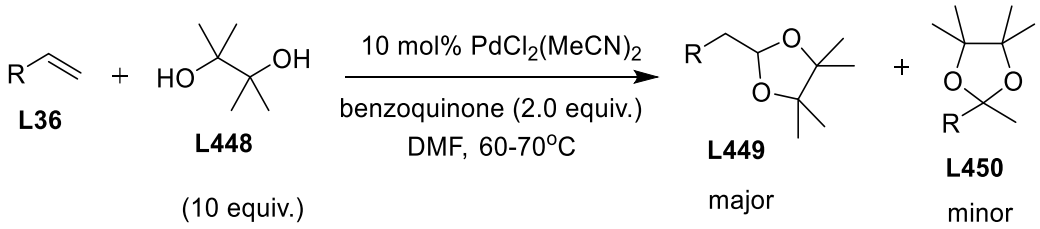
Scheme 1.235

In 2012, Chowdhury and Lahiri reported a generalized approach for iron-catalyzed chemo- and regioselective formation of anti-Markovnikov acetals (**L447**) from styrene derivatives (**L36**) [274]. They observed that $Fe(BF_4)_2{\cdot}6H_2O$ in the presence of *dipic* (pyridine-2,6-dicarboxylic acid) and $PhI(OAc)_2$ can efficiently catalyze the formation of anti-Markovnikov dialkyl acetals from styrene derivatives with chemo- and regioselectivity in good yields under mild reaction conditions (Scheme 1.236). Unfortunately, poor yield of anti-Markovnikov acetals was obtained from the long-chain alcohol, such as 1-pentanol.



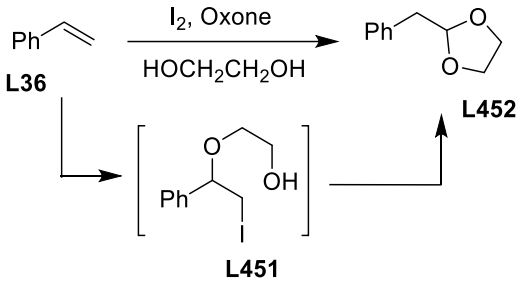
Scheme 1.236

In the same year, Yamamoto and co-workers demonstrated another method for the synthesis of terminal acetals (**L449**) and (**L450**) *via* highly selective anti-Markovnikov nucleophilic attack of pinacol (**L448**) at alkenes (**L36**) using a palladium catalyst [275]. The authors reported the synthesis of terminal acetals from different olefinic systems (vinylarenes, allyl aryl ethers, and 1,5-dienes) by using a bulky tertiary diol, pinacol (Scheme 1.237). In this reaction mainly the nature of the substrates and the steric bulkiness of the pinacol cooperatively controlled the regioselectivity in an anti-Markovnikov manner. Here it must be mentioned that the reaction of 2- and 4-vinylpyridines did not proceed. As a substrate *α*-methylstyrene was also tested. However, in that case, no terminal acetal was observed, and a large portion of the substrate remained unreacted. Dienes such as diethyl diallylmalonate and 1,7-octadiene resulted in no formation of terminal acetals.



Scheme 1.237

Very recently, Narender *et al.* reported a new metal-free protocol for the synthesis of terminal acetals by tandem oxidative rearrangement of olefins using oxone as an oxidant in the presence of iodine (Scheme 1.238) [276]. They investigated that the olefin (**L36**) at first underwent nucleophilic ring opening by ethylene glycol leading to the formation of a co-iodo intermediate (**L451**) which further rearranged in presence of oxone to provide the corresponding cyclic acetal (**L452**) predominantly. Acetal was not observed in the absence of oxone, which indicates that it plays a crucial role in formation of acetal. Here it must be mentioned that in the case of cyclic olefins, ring contraction product was observed.

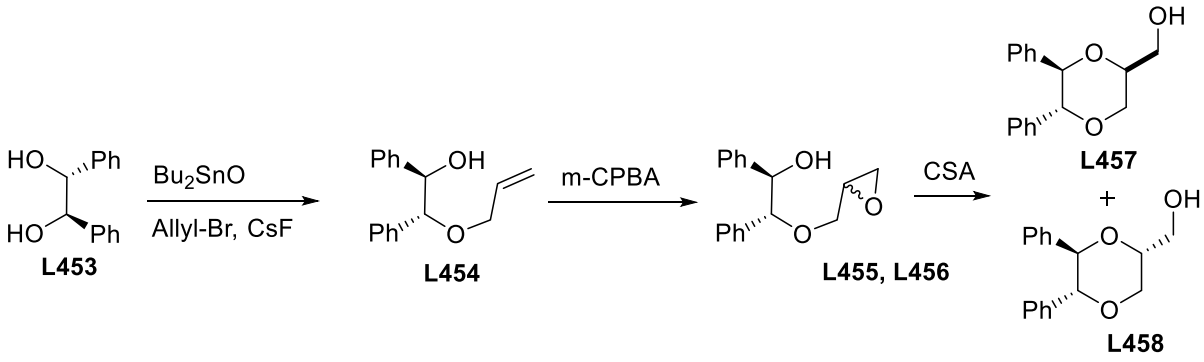


Scheme 1.238

1.3.3. Synthesis of substituted 1,4-dioxanes

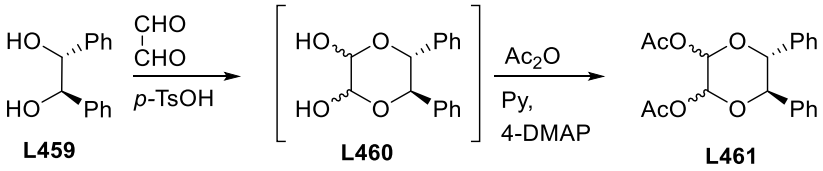
Besides using as a solvent, 1,4-dioxane-based scaffolds occur in a large number of natural products and bioactive compounds [277].

In 1992, Aube group reported monoallylation of 1,2-diphenylethane-1,2-diol (**L459**) most conveniently using the tin-mediated protocol [278]. High-temperature epoxidatlon of 2-(allyloxy)-1,2-diphenylethan-1-ol (**L454**) in the presence of a radical scavenger yielded a mixture of isomeric epoxides in good yield. Interestingly, epoxides (**L455-L456**) were obtained with a modest level of steteoselectivity. Ring closure was achieved by treatment with camphorsulfonic acid (CSA) in benzene, affording a separable mixture of 1,4-dioxanes (**L457**) and (**L458**) **(**Scheme 1.239**)**.



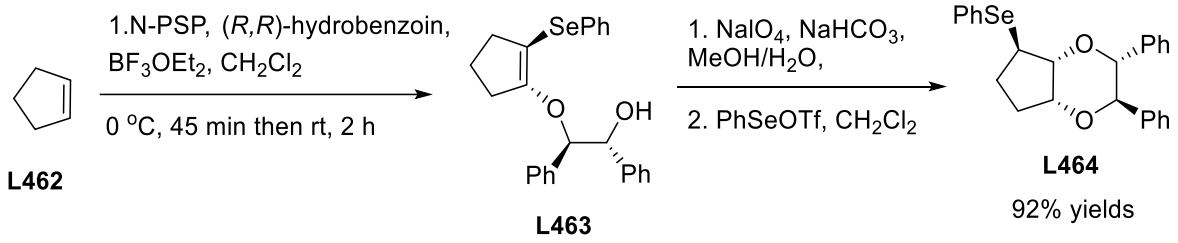
Scheme 1.239

Fujioka *et al*. in 1995 reported a new route for the synthesis of chiral diol (**L460**) based on the reaction between glyoxal and (1*R*,2*R*)-1,2-diphenylethane-1,2-diol (**L459**) using chiral hydrobenzoin as an auxiliary (Scheme 1.240) [279].



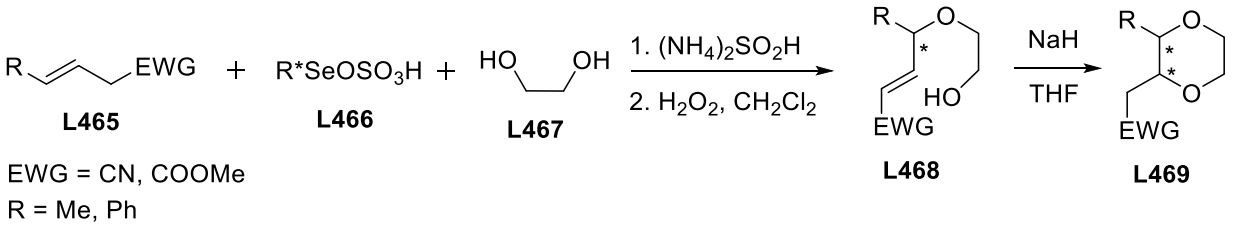
Scheme 1.240

In 1998, Kim and co-workers reported oxyselenylation of cyclopentene (**L462**) with (*R*, *R*)-hydrobenzoin and subsequent oxidation-elimination of the resulting oxyselenide afforded olefin (**L463**) and its (1*S*)-diastereomer in 1:1 ratio in 92% yield [280]. After separation from its diastereomer by column chromatography, compound was treated with PhSeOTf to give only *cis*-fused bicyclic dioxane (**L464**) (Scheme 1.241).



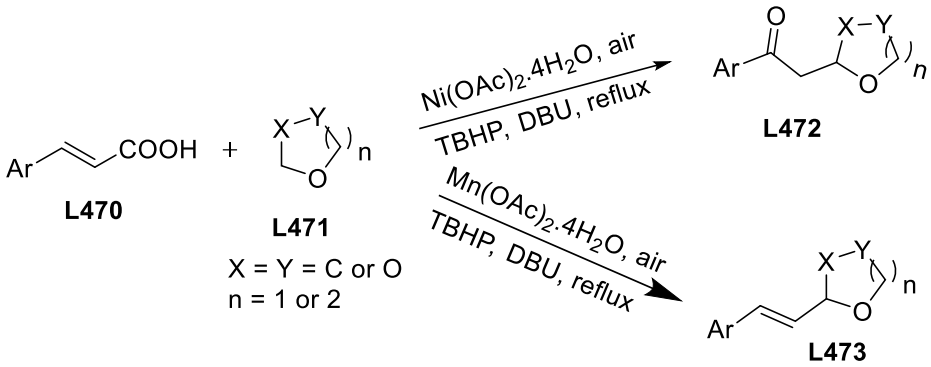
Scheme 1.241

An alkene (**L465**) was converted into two enantiomerically pure diastereomeric selenoethers in 2002, by Tiecco and group through a regio- and stereospecific anti addition reaction mediated by *N*-(phenylseleno)phthalimide (**L466**) in the presence of ethylenglycol (**L467**) [281]. This alkoxyselenylation reaction can be employed as the key step to allow the synthesis of several isomeric tetrasubstituted 1,4-dioxanes (**L469**) in enantiomerically pure form (Scheme 1.242).



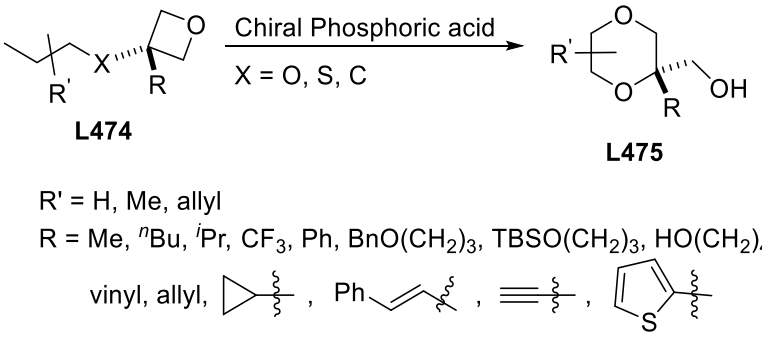
Scheme 1.242

In 2014, Zhang *et al*. reported a nickel- and manganese-catalyzed decarboxylative cross coupling of *α,β*-unsaturated carboxylic acids (**L470**) with cyclic ethers (**L471**) such as tetrahydrofuran and 1,4-dioxane to synthesize functionalized diether [282]. Oxyalkylation was achieved when nickel acetate was used as catalyst, while manganese acetate promoted the reaction of alkenylation (Scheme 1.243). Products (**L472**) or (**L473**) were obtained accordingly.



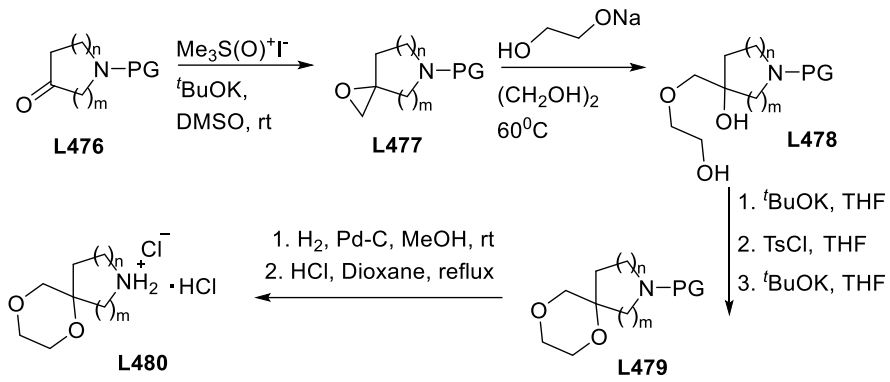
Scheme 1.243

Yang and Sun, in 2015, reported a new asymmetric synthesis of chiral 1,4-dioxanes and other oxa-heterocycles (**L475**) by means of organocatalytic enantioselective desymmetrization of oxetanes (**L474**) [283]. This process proceeds with enantioselectivity to establish the quaternary stereocenters. This method complements the existing, yet limited, strategies for the synthesis of these oxa-heterocycles (Scheme 1.244).



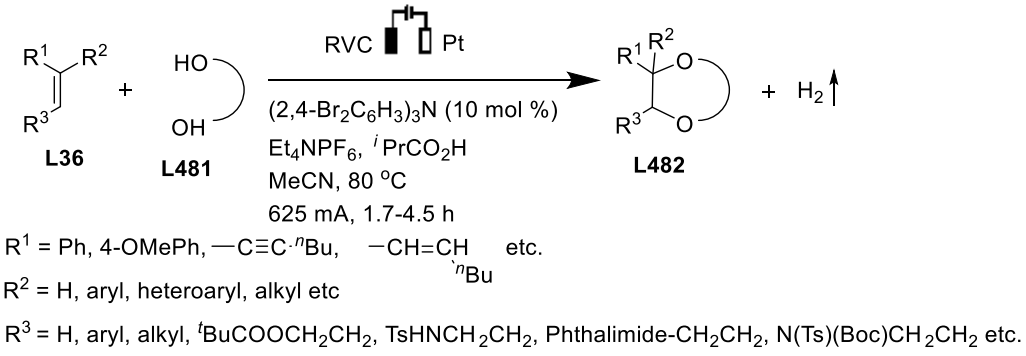
Scheme 1.244

In 2018, Grygorenko *et al*. reported an approach for the preparation of 2-mono-, 2,2- and 2,3-disubstituted 1,4-dioxanes (**L479-L480**). The reaction sequence commences from readily available epoxides, in most cases prepared *via* the Corey–Chaikovsky reaction of the corresponding aldehydes and ketones [284]. The key step of the method is epoxide (**L477**) ring opening with ethylene glycol monosodium salt, followed by further cyclization of the diols (**L478**) obtained. The utility of the approach was demonstrated by multigram preparation of novel functionalized 1,4-dioxanes bearing additional cycloalkane, piperidine or pyrrolidine rings, mostly spirocyclic compounds, which are advanced building blocks for medicinal chemistry (Scheme 1.245).



Scheme 1.245

Cai and Xu reported an electrochemical dehydrogenative annulation of alkenes (**L36**) with 1,2- and 1,3-diols (**L481**) using a redox catalyst for the synthesis of 1,4-dioxane and 1,4-dioxepane derivatives (**L482**) [285]. The combination of electrochemistry and redox catalysis using an organic catalyst allows the electrosynthesis to proceed under transition metal- and oxidizing reagent-free conditions. The electrolytic method has a broad substrate scope and is compatible with many common functional groups, providing an efficient and straightforward access to functionalized 1,4-dioxane and 1,4-dioxepane products with diverse substitution patterns (Scheme 1.246).

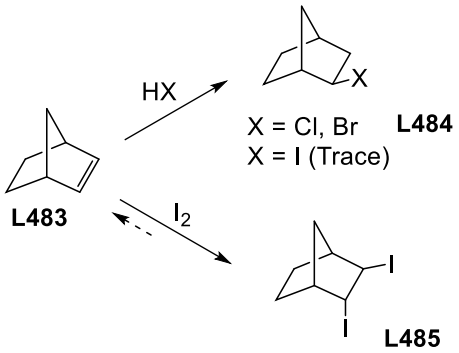


Scheme 1.246

1.3.4. Formation of diiodine-substituted derivatives

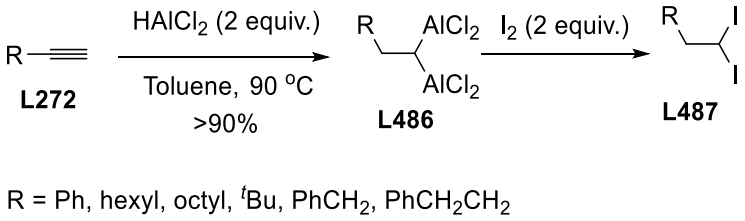
Organic haloalkanes are extensively used for carbon-heteroatom bond forming reactions as well as the carbon-metal atom bond formation such as Grignard's reagent [286], carbenoids [287] etc. Specifically, carbenoids are preferentially prepared from iodoalkanes since they are more reactive than the corresponding other haloalkanes [288]. The preparation of the iodoalkanes is more difficult due to the high C–I bond reactivity [289] and diiodo alkane is even more difficult. Few methods have been achieved to prepare *gem*-diiodo alkane, but to the best of our knowledge there is no such general method to prepare *vicinal*-diiodo compounds.

In 1993, the Kropp group found that silica gel and alumina mediated the addition of HCl, HBr, and HI to alkenes. Further investigation of the treatment of 2-norbornene (**L483**) with I_2 and alumina revealed that the major product is the *vicinal*-diiodide (**L485**) (Scheme 1.247) [290]. This *vicinal*-diiodo compound is stable due to the relief of strain.



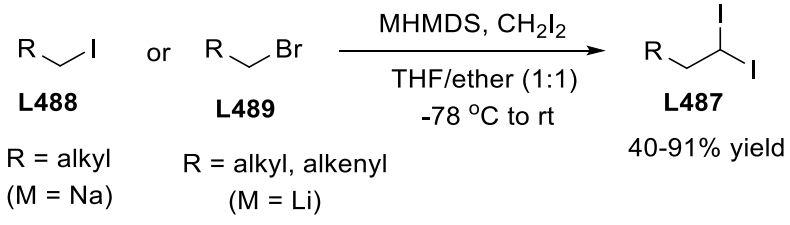
Scheme 1.247

Marek *et al*. reported a new and straightforward approach for the one-pot synthesis of sp^3 1,1-diiodoalkanes (**L487**) in good yields *via* the synthesis of 1,1-bis(dichloroalumino)alkanes (**L486**) at 90 °C for the bismetallic synthesis and 0 °C for the reaction with I_2 and the method has been applied to large scale preparations (Scheme 1.248) [291].



Scheme 1.248

In 2008, Charette and his co-worker developed a synthetic procedure for functionalized *gem*-diiodoalkanes (**L487**) using $NaCHI_2$ and $LiCHI_2$ at -78 °C from alkyl iodides (**L488**) and benzyl/allyl bromides (**L489**) in high yield, providing complete conversion of the starting material (Scheme 1.249) [292].

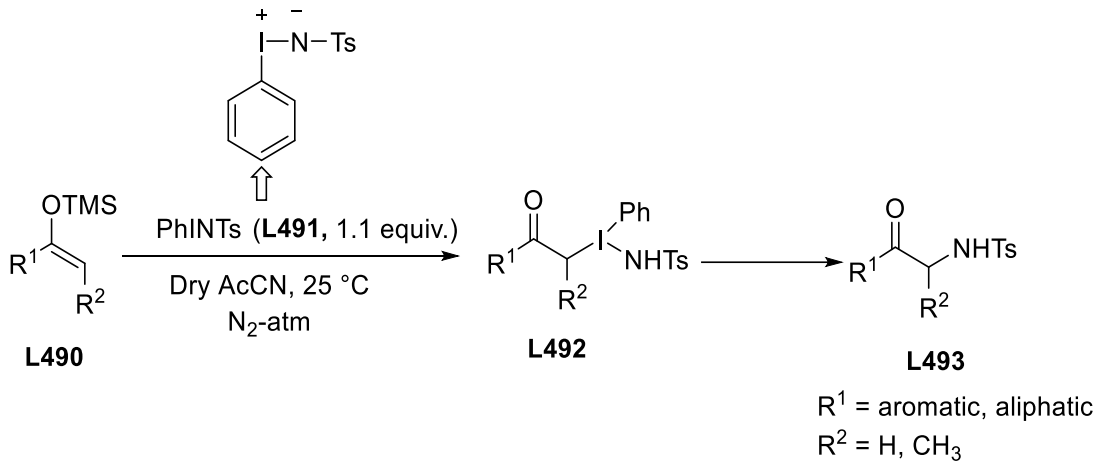


Scheme 1.249

1.3.5. Synthesis of *α*-aminoketone derivatives

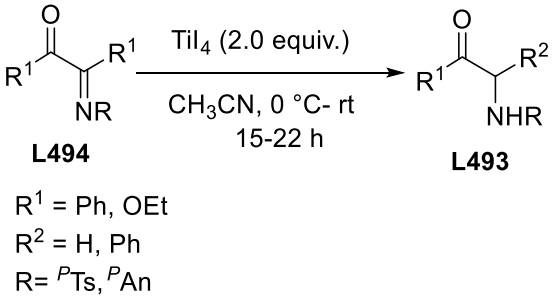
Among other nitrogen-containing heterocyclic skeletons, synthesis of *α*-aminoketones has gained considerable attention due to the significance of this structural motif. In recent time, the development of environmentally benign and clean synthetic procedures is one of the goals in organic synthesis with high atom economy. So the development of efficient approaches from readily available starting material is highly desirable.

In 1996, Ahn *et al*. reported a method for the synthesis of *α*-tosylamino carbonyl compounds (**L493**) by using [(*N*-(*p*-toluenesulfonyl)imino)phenyliodinane)], PhINTs (**L491**) which was found to be a good aminating reagent in dry acetonitrile solvent (Scheme 1.250) [293]. Different substituted phenyl ring provided the desired products in moderate yields.



Scheme 1.250

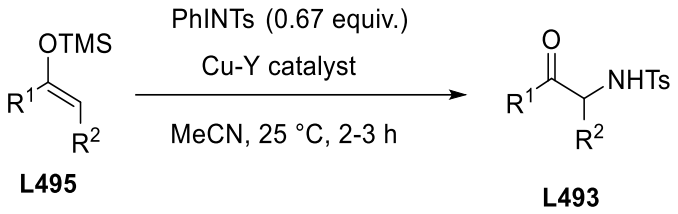
In 2001, Shimizu *et al*. established a method for the synthesis of *α*-aminocarbonyl compounds (**L493**) by the reduction of *α*-iminocarbonyl compounds (**L494**) where titanium tetraiodide (TiI_4) was used as a reducing reagent (Scheme 1.251) [294]. TiI_4 reduced different type of imine substrate to corresponding amino compound after 15-22 h in moderate yields.



Scheme 1.251

In the same year, Phukan and Sudalai demonstrated a synthesis of *α*-aminocarbonyl compounds (**L493**) using heterogeneous catalyst from silyl enol ether (**L495**) at room temperature

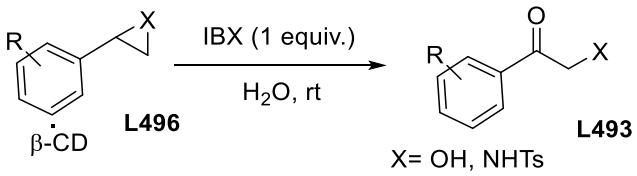
in acetonitrile as solvent (Scheme 1.252) [295]. Cu-exchanged Y-zeolite was used as a heterogeneous catalyst which provided the desired product in good yields.



$R^1 = R^2$= aryl, cycloalkyl

Scheme 1.252

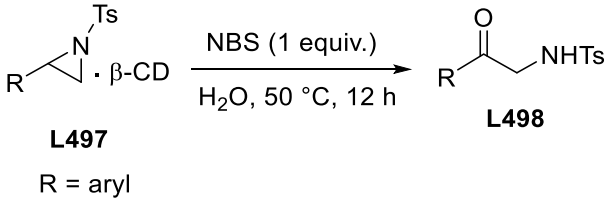
In 2003 Rao *et al*. described a procedure for oxidative cleavage of *β*-cyclodextrin (*β*-CD) of aziridines and epoxide complex (**L496**) to produce *α*-hydroxyketones and *α*-aminoketones (**L49**3) with high yields (Scheme 1.253) [296]. This reaction was mediated in presence of IBX (2-iodoxybenzoic acid) and water medium. Cyclodextrins, which are cyclic oligosaccharides and has a cavity like structure which binds substrates selectively and catalyzes chemical reactions. In the absence of cyclodextrin, the reaction does not proceed.



R = H,Br,Cl,Me,OMe,NO_2
X= O,NTs

Scheme 1.253

Synthesis of *α*-tosylaminoketones (**L498**) from aziridines in the presence of *β*-CD was reported by Rao *et al*. in 2005 (Scheme 1.254) [297]. In this reaction NBS has been used for the first time for oxidative cleavage reaction of *β*-cyclodextrin-aziridine complexes (**L497**) which give the corresponding *α*-tosylaminoketones (**L498**) in water medium with high yields.

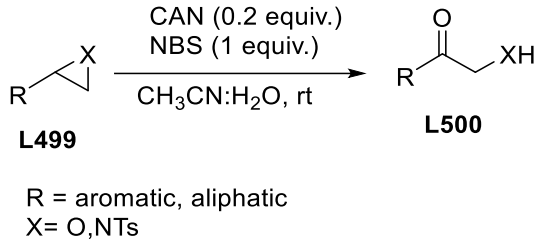


R = aryl

Scheme 1.254

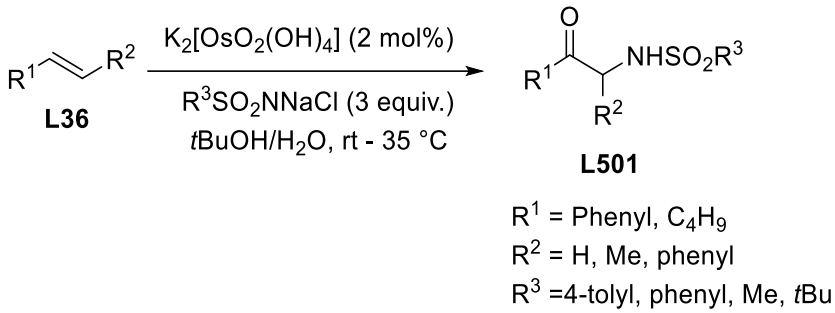
In the same year, Rao and coworkers established another procedure for synthesis of *α*-hydroxyketones and *α*-aminoketones (**L500**) by oxidation of epoxides and aziridines (**L499**) at ambient temperature (Scheme 1.255) [298]. This reaction was carried out in the presence of

cerium(IV) ammonium nitrate (CAN, 0.2 equiv.) and NBS (1 equiv.) to give the corresponding product after 4-12 h in acetonitrile-water solvent (9:1) in good yields.



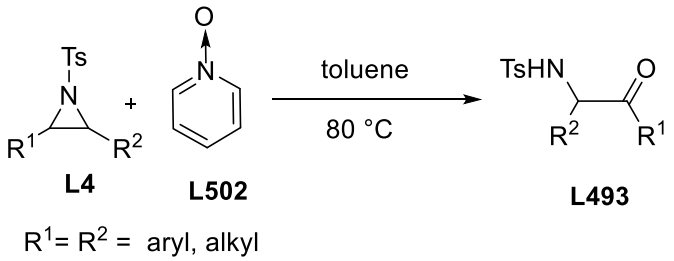
Scheme 1.255

Osmium complex catalyzed synthesis of *α*-aminoketones (**L501**) by oxidation of alkene (**L36**) was described by Muniz *et al*. in 2005 (Scheme 1.256) [299]. This reaction was enlarged in the presence of 2 mol% of osmium complex, $K_2[OsO_2(OH)_4]$ and tert-butyl alcohol/water mixture and provided the desired product in moderate yields.



Scheme 1.256

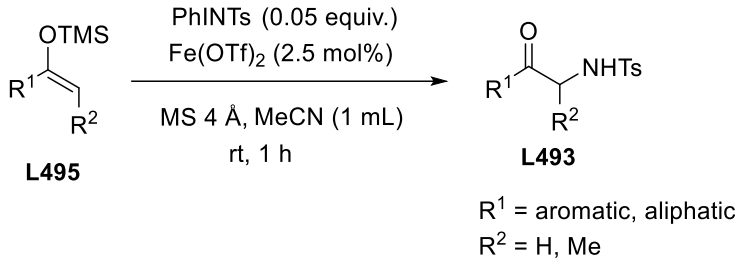
Synthesis of *α*-tosylaminoketones (**L493**) by means of oxidative ring opening of aziridines (**L4**) in presence of pyridine *N*-oxide (**L502**) was reported by Hao and coworkers in 2007 (Scheme 1.257) [300]. In this reaction pyridine *N*-oxide (1.2 equiv.) has been used as a stoichiometric amount and various aziridine provided the corresponding carbonyl products with high yields.



Scheme 1.257

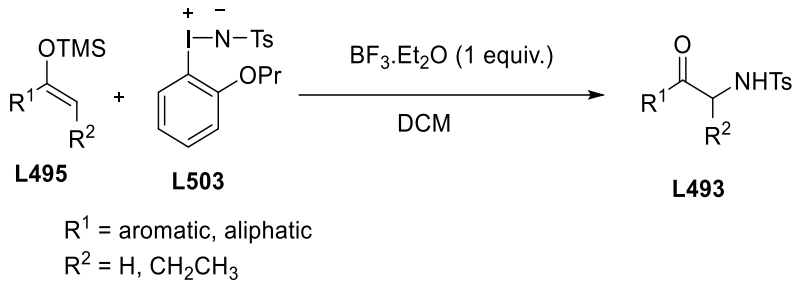
In 2008, Bolm *et al*. developed a method for aziridination reaction of various enol silyl ethers (**L495**) in ambient temperature. The reaction was extended using iron catalyst in acetonitrile solvent at room temperature (Scheme 1.258) [301]. Various enol silyl ether effectively reacted

with tosylimino(iodo)benzene (PhINTs) to provide the desired products (**L493**) in moderate to good yields.



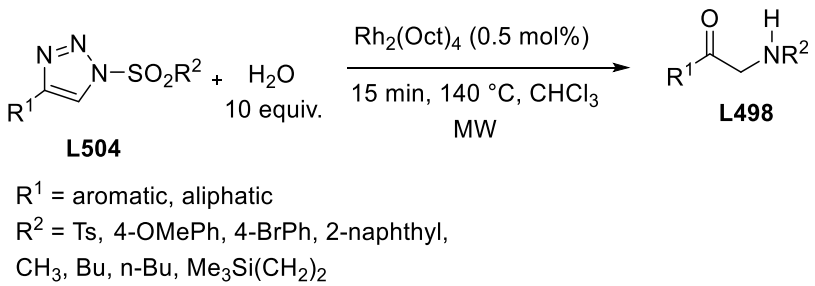
Scheme 1.258

In 2011, Zhdankin reported a method for the metal-free amination of sifferent silyl enol ethers (**L495**) by using *o*-alkoxyphenyliminoiodanes (**L503**) and boron trifluoride diethyl etherate as an additive in dichloromethane solvent at 0.2-24 h (Scheme 1.259) [302]. Reaction afforded the desired products (**L495**) in moderate yields.



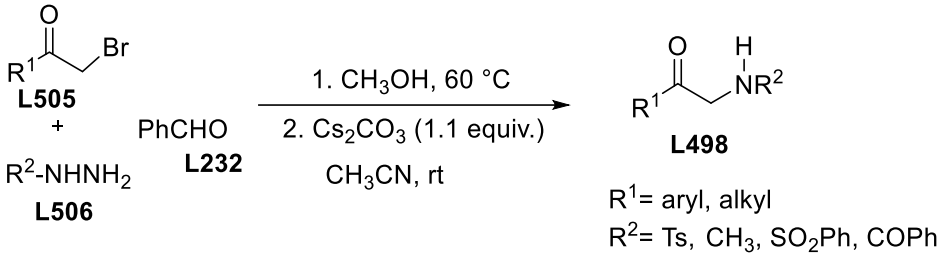
Scheme 1.259

Rhodium-catalyzed the synthesis of *α*-aminoketones (**L498**) from terminal alkyne *via* denitrogenetive hydration *N*-sulfonyl-1,2,3-triazoles (**L504**) was described by Murakami *et al*. in 2012 (Scheme 1.260) [303]. They carried out the reaction by using 0.5 mol% of $Rh(Oct)_4$, (Oct = Octanoate) catalyst and water (10 equiv.) in chloroform solvent and the reaction mixture was heated at 140 °C for 15 min under microwave irradiation. Different type of triazoles was varying with both phenyl moiety afforded the desired product with high yields. Not only aryl sulfonyl group also but also the simple alky groups like methyl, *n*-butyl, benzyl etc. were suitable for this reaction.



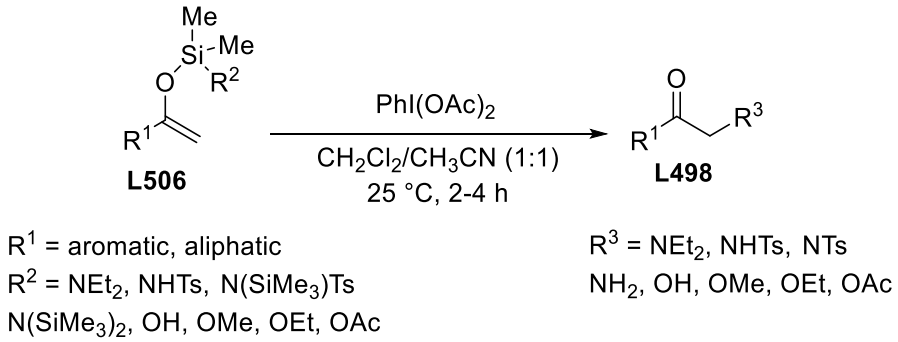
Scheme 1.260

Cs_2CO_3 promoted two steps one-pot synthesis of α-aminoketones (**L498**) was developed by Zhan and coworkers in the year 2014 (Scheme 1.261) [304]. This reaction was carried out by using hydrazines (**L506**), aldehydes (**L232**), and α-haloketones (**L505**) as starting materials *via* a cascade condensation, nucleophilic substitution and also N-N bond cleavage pathway. α-Halo ketones and hydrazine with different steric and electronic group reacted smoothly and afforded the α-aminoketones with moderate to good yields.



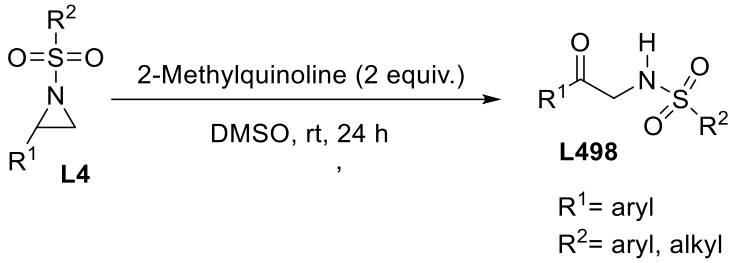
Scheme 1.261

In the same year, Wirth and Mizar developed a method for functionalization of carbonyl compounds at α-position as well as the synthesis of α-aminoketones (**L498**) through umpolung reaction of silyl enol ethers (**L506**) in presence of hypervalent iodine, like PIDA (Scheme 1.262) [305]. This reaction proceeded very smoothly at ambient temperature in the presence of PIDA and in the absence of any Lewis acid. Different nucleophile produced the corresponding desired products in moderate to good yields.



Scheme 1.262

In 2016, Liu *et al*. established an approach for the facile synthesis of α-amino aryl ketones (**L498**) *via* oxidative ring opening of *N*-sulfonyl aziridines (**L4**) at ambient temperature (Scheme 1.263) [306]. Here, 2-methylquinoline has been used as a catalyst and promoted the ring opening of different substituted *N*-sulfonyl aziridines which provided the analogous α-aminoketones after 24 h in high yields. The reaction is also applicable for gram-scale synthesis.



Scheme 1.263

1.3.6. Reactions of 4-hydroxycoumarins

Over the years, many methods have been developed in order to synthesize various derivatives of 4-hydroxycoumarins due to their immense biological as well as biochemical activities. Due to its unique structure 4-hydroxycoumarins (**L507**) are capable to react with both nucleophiles and electrophiles (Figure 1.3). In the next paragraph, a brief review has been discussed about the chemical transformations of 4-hydroxycoumarins.

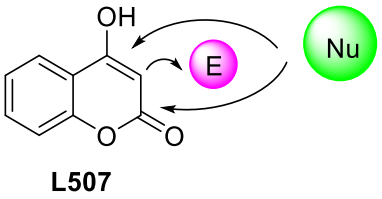
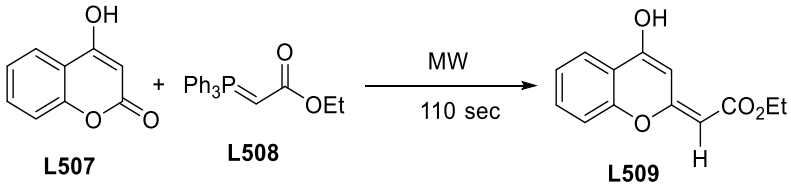


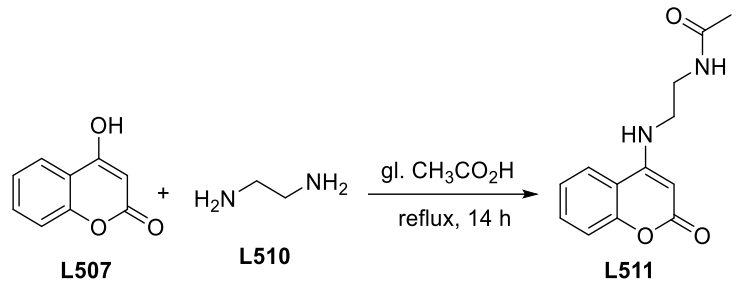
Figure 1.3

In the year 1999, Sabitha *et al.* reported an efficient stereoselective Wittig olefination of 4-hydroxycoumarin (**L507**) with ethoxy-carbonyl methylene-(triphenyl) phosphorene (**L508**) heated to 90 ºC in microwave irradiation for 1-2 mins afforded (*E*)-ethyl 2-(4-hydroxy-2*H*-chromen-2-ylidene)-acetate (**L509**) in good yields (Scheme 1.264) [307].



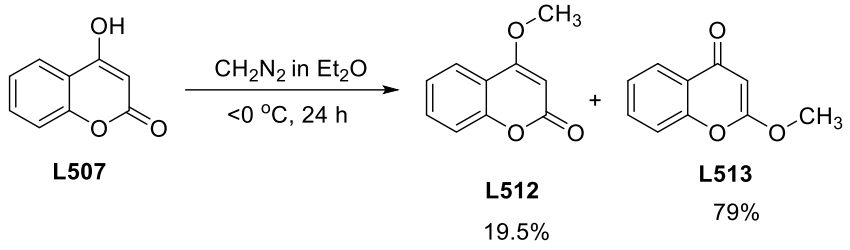
Scheme 1.264

In the same year, Ivanov and group successfully developed a method for the synthesis of *N*-{2-[(2-oxo-2*H*chromen-4-yl)amino]ethyl} acetamide (**L511**) *via* the reaction of 4-hydroxycoumarin (**L507**) with ethylenediamine (**L510**) in boiling glacial acetic acid and refluxing for 14 h [308]. In next stage, *N*-acetylation of the second amino group happened simultaneously (Scheme 1.265).



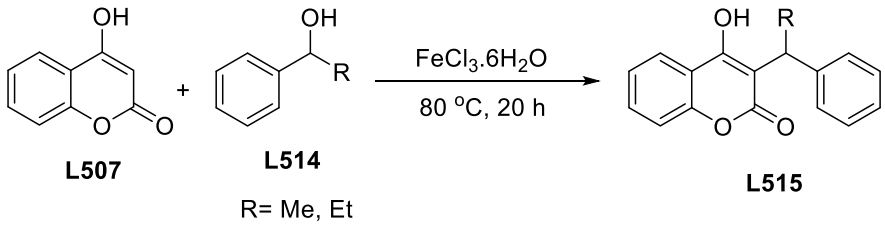
Scheme 1.265

In the very next year 2000, Sulko and co-workers reported *O*-alkylation reaction of 4-hydroxycoumarin with diazomethane in the presence of a catalytic amount of trimethylamine [309]. By the result of this reaction, 4-methoxycoumarin and 2-methoxychromone was obtained as a product. 2-Methoxychromone (**L513**) was produced with 79% yield (Scheme 1.266).



Scheme 1.266

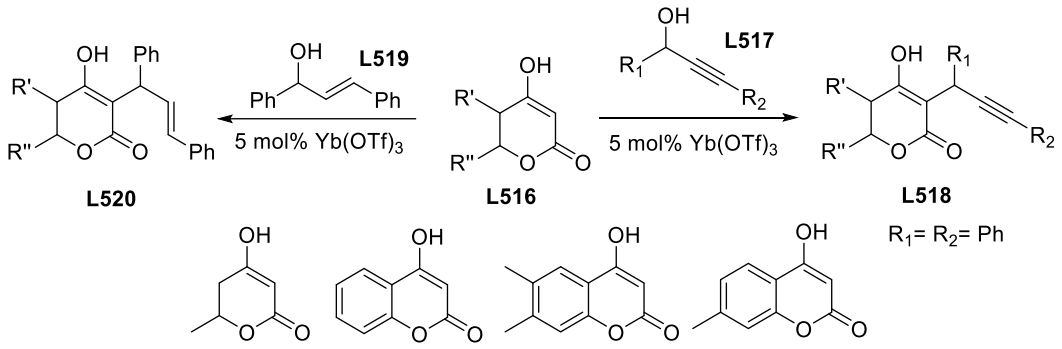
In 2007, Beller *et al.* developed a general and efficient iron-catalyzed benzylation of 1,3-dicarbonyl compounds. Various types of 1,3-dicarbonyl compounds, 4-hydroxycoumarins (**L507**) get reacted with benzylic alcohols (**L514**) to give the corresponding benzylated products (**L515**) in good to excellent yield [310]. 4-hydroxycoumarin also underwent benzylation and gave 4-hydroxy-3-(1-phenylethyl)-2*H*-chromen-2-ones which are pharmaceutically interesting (Scheme 1.267).



Scheme 1.267

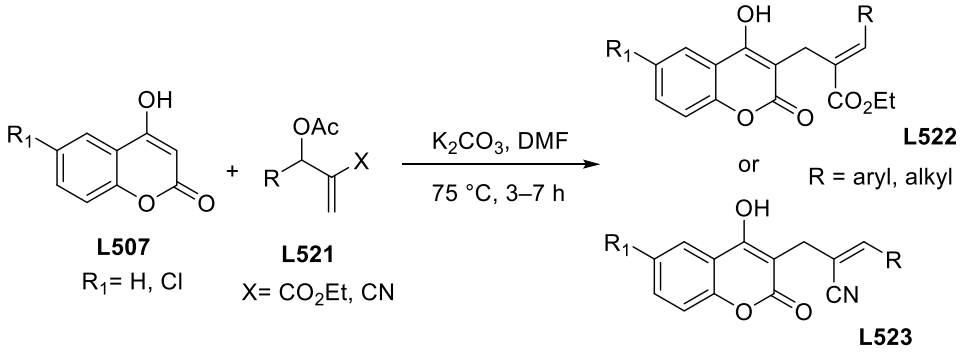
In the same year, Zhou group established a highly efficient and mild Lewis acid-catalyzed coupling reaction of 1,3-dicarbonyl compounds, including 4-hydroxycoumarins (**L516**). with propargylic alcohols using catalytic amount of $Yb(OTf)_3$ effectively promoted the propargylation (**L518**) and allylation of 4-hydroxycoumarins (**L520**) at the 3-position [311]. By the application

of this reaction as a key step in a one-pot procedure, a multi-substituted furocoumarin can easily be synthesized (Scheme 1.268).



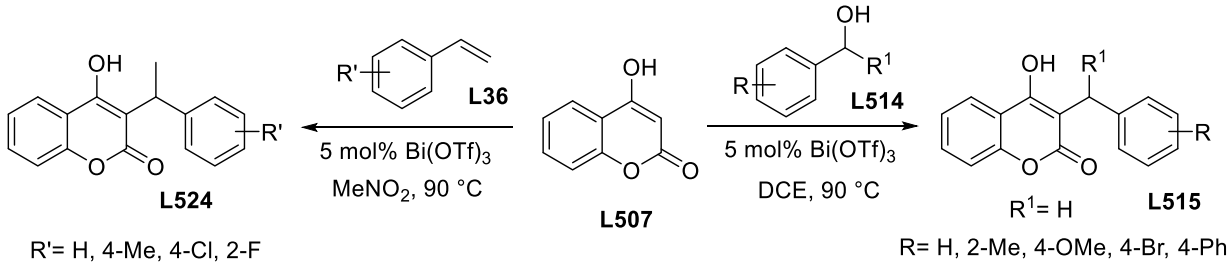
Scheme 1.268

In 2009, Reddy *et al.* did the exploration of 4-hydroxycoumarin (**L507**) for nucleophilic addition as Baylis–Hillman acetate adducts has been described [312]. Initially, the reaction of Baylis–Hillman acetate adduct (**L521**) reacted with 4-hydroxycoumarin in the presence of potassium carbonate in anhydrous DMF at 75 °C afforded the corresponding 3-substituted 4-hydroxycoumarins (**L522** or **L523**) in good yields (Scheme 1.269).



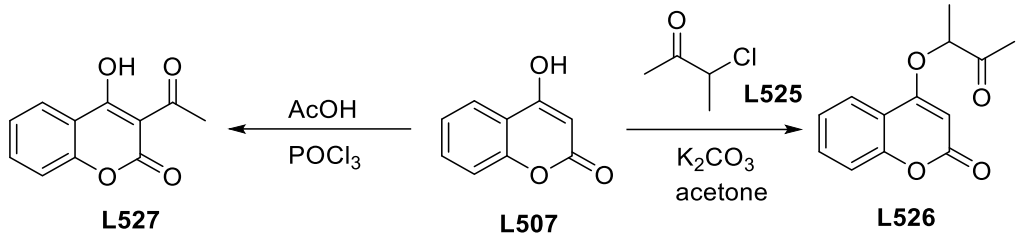
Scheme 1.269

In the year 2010, Rueping and group developed an effective metal-catalyzed benzylations of 4-hydroxycoumarin (**L507**) employing a low amount of $Bi(OTf)_3$ [313]. They found the catalyst was cheap, non-toxic, and air-stable. The 3-alkylated hydroxycoumarins (**L524** and **L515**) were obtained in high yields after short reaction times. Two widely used anticoagulants phenprocoumon and coumatetralyl were synthesized applying this new methodology (Scheme 1.270).



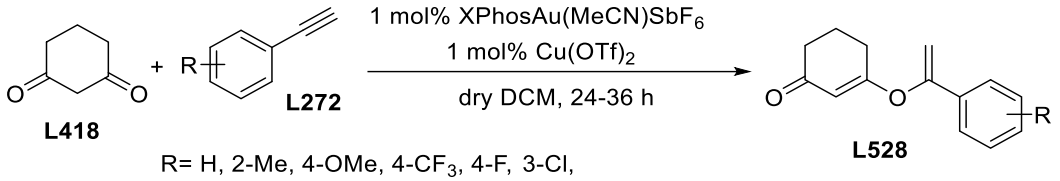
Scheme 1.270

In 2012, Samehi *et al.* reported a method for *O*-alkylation of 4-hydroxycoumarin (**L507**) upon reaction with 3-chloro-2-butanone (**L525**) in acetone in the presence of anhydrous K_2CO_3 [314] to afford product (**L526**). Additionally they also showed the treatment of 4-hydroxycoumarin with glacial acetic acid and phosphorous oxychloride ($POCl_3$) afforded 3-acetyl-4-hydroxy-2*H*-chromen-2-one (**L527**) (Scheme 1.271).



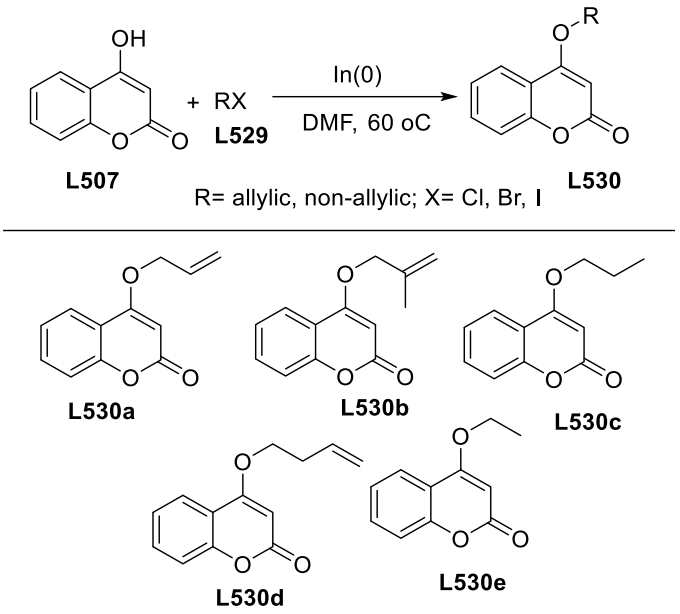
Scheme 1.271

In 2013, Shi and co-workers reported *O*-vinylation of cyclic 1,3-diketones (**L418**) ubder the action of arylacetylenes (**L272**) in the presence of gold-catalyst [*t*-BuXPhosAu(MeCN)SbF_6], and reaction leads to various vinyl ethers (**L528**) [315]. A catalytic amount of copper triflate and DCM solvent was needed as a significant additive for promoting this transformation (Scheme 1.272).



Scheme 1.272

In 2014, Singh and the group studied the indium(0)-mediated cross-coupling of alkylindium species, generated from alkylhalides (**L529**) with 4-hydroxycoumarin (**L507**) [316]. Surprisingly, a regioselective enolic *O*-alkylation (**L530**) took place at 60 °C in *N*,*N*-dimethylformamide (DMF) solvent when alkyl or allyl halide were employed and the synthetically useful enol-ether linkage was formed in excellent yields within 6–12 h (Scheme 1.273).

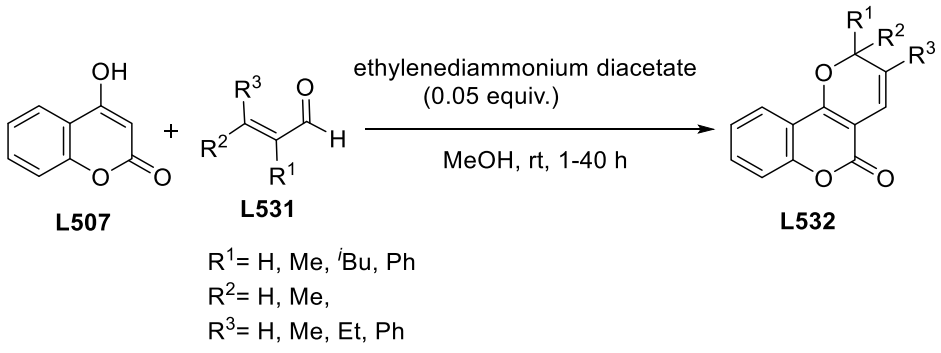


Scheme 1.273

1.3.7. Synthesis of pyrano[3,2-*c*]coumarins

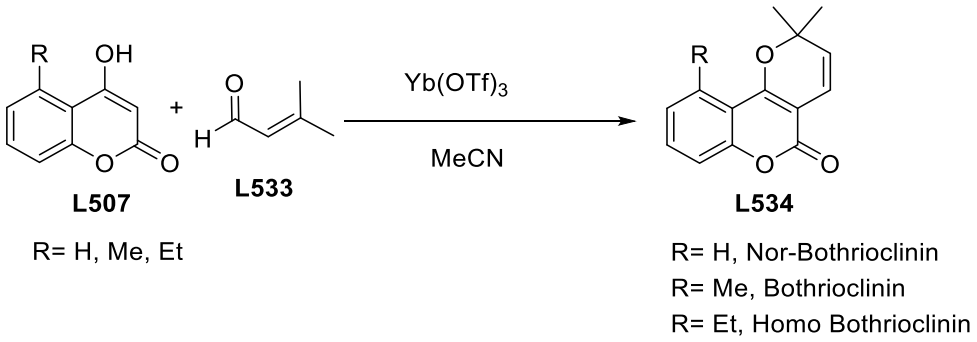
Pyranocoumarin derivatives are a class of fused oxygen containing heterocycles that constitute building blocks for many natural products found across the plant kingdom [317]. It has drawn much attention due to their potential biological and pharmaceutical activities including antifungal, insecticidal, anti-cancer, anti-HIV, anti-inflammatory, antioxidants, and antibacterial activities [318, 319]. Considering these important uses, their syntheses have been received much attention in the field of medicinal and pharmaceutical chemistry.

In 1990, Appendino *et al*. reported a method for synthesis of pyranocoumarin derivatives (**L532**) by the reaction of 4-hydroxycoumarin (**L507**) and *α*,*β*-unsaturated aldehyde (**L531**) in presence of ethylenediammonium diacetate (0.05 equiv.) in methanol as solvent at room temperature (Scheme 1.274) [320]. 4-Hydroxycoumarin effectively reacted with different enals to provide the desired products in moderate to good yields.



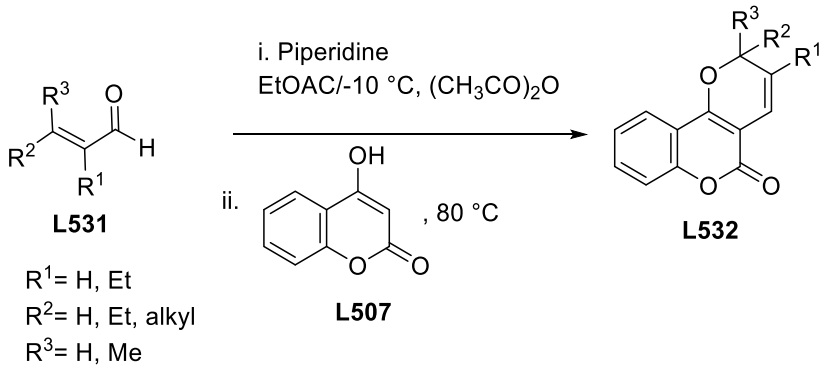
Scheme 1.274

Palmisano's group discovered ytterbium triflate [$Yb(OTf)_3$] catalyzed reaction for the synthesis of pyranocoumarin (**L534**) derivative *via* a domino Knoevenagel-electrocyclic reaction between coumarins (**L507**) and 3-methylbut-2-enal (**L533**) in acetonitrile solvent (Scheme 1.275) [321]. The authors showed that the spectroscopic data of bothrioclinin and homo bothrioclinin were identical with the reported the natural products.



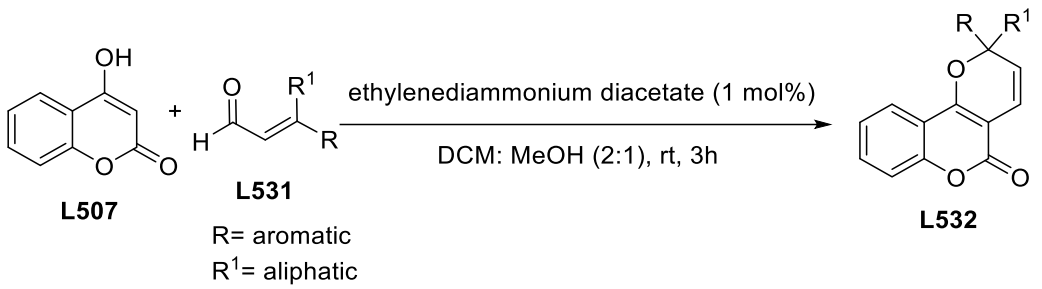
Scheme 1.275

A regioselective method for preparation of pyranocoumarin derivatives (**L532**) was developed by Cravotto *et al*. in the year 2001 [322]. The reaction was a one pot two steps reaction of *α,β*-unsaturated carbonyl compound (**L531**) and piperidine (406 µL) in ethylacetate and acetic anhydride [$(CH_3O)_2O$, 400 µL] at -10 ºC. Then the temperature of the reaction system has been increased to 80 ºC and 4-hydroxycoumarin was added to the reaction mixture by portion wise (Scheme 1.276). Various enal afforded the desired products in moderate to good yields.



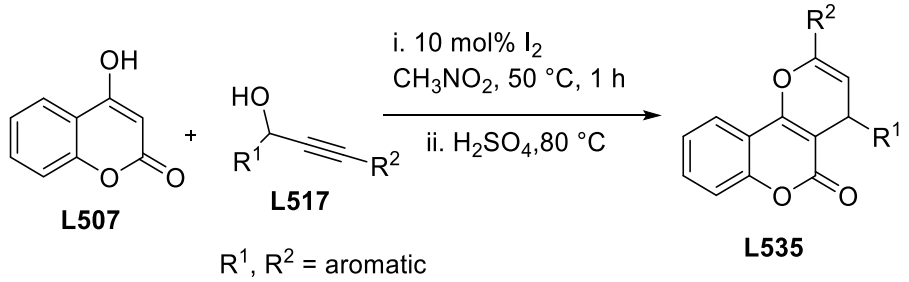
Scheme 1.276

In 2007, Yang *et al*. established a new approach for the synthesis of pyranocumarins (**L532**) by the reaction between 4-hydroxycoumarin (**L507**) and *α,β*-unsaturated aldehyde (**L531**) at room temperature (Scheme 1.277) [323]. Ethylenediammonium diacetate (1 mol%) was used as a catalyst and a mixture of methylene chloride and methanol (2:1) as a solvent.



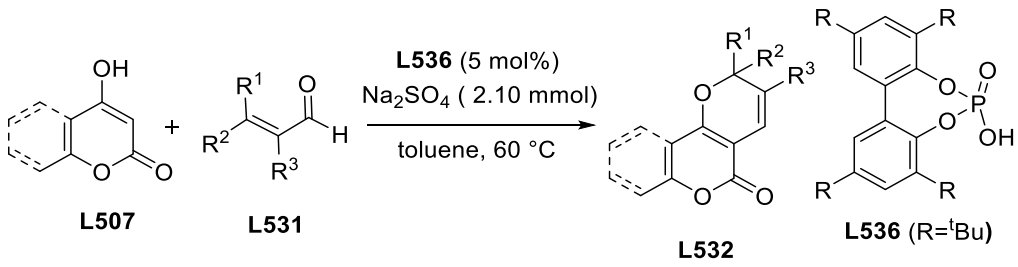
Scheme 1.277

In 2009, Lin and coworkers reported a method for synthesis of multi-substituted pyranocoumarin derivatives (**L535**) by two steps reaction, using molecular iodine and sulfuric acid (Scheme 1.278) [324]. 4-Hydroxycoumarin (**L507**) was effectively reacted with different secondary propargylic alcohols (**L517**) to provide the desired products in moderate to good yields.



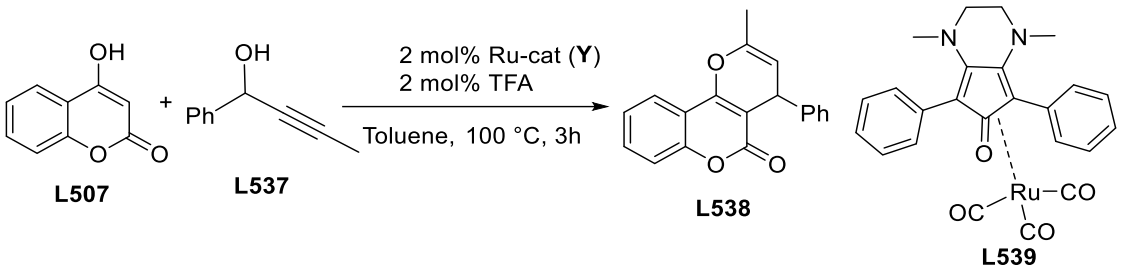
Scheme 1.278

In the same year, Renaud *et al*. demonstrated a phosphoric acid (**L536**) catalyzed pyranones ring formation by the reaction of 4-hydroxycoumarin (**L507**) with *α*,*β*-unsaturated aldehydes (**L531**) (Scheme 1.279) [325]. The present method proceeds through phosphoric acid catalyzed formal [3+3] cycloaddition reaction in the presence of sodium sulphate in toluene solvent at 60 ºC to provide the corresponding pyrano products (**L532**, **L536**) in moderate to high yields.



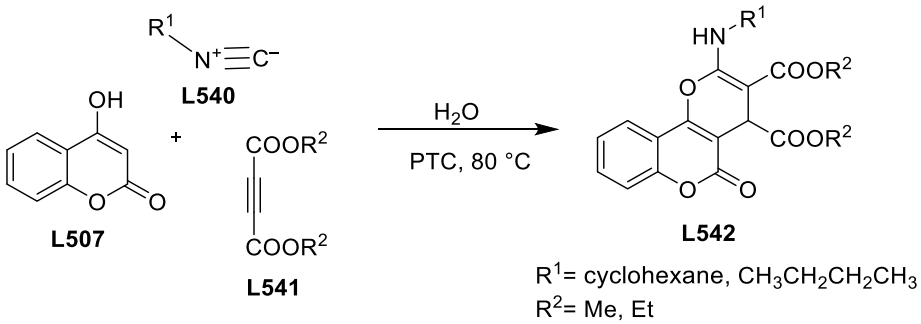
Scheme 1.279

In 2010, Haak *et al*. described a synthesis of pyrano[3,2-*c*]coumarins (**L538**). The synthesis was carried out by the reaction of propargyl alcohols (**L537**) with 4-hydroxycoumarin (**L507**) in presence of 2 mol% ruthenium salt (**L539**) and 2 mol% trifluoroacetic acid as the catalysts in toluene (Scheme 1.280) [326].



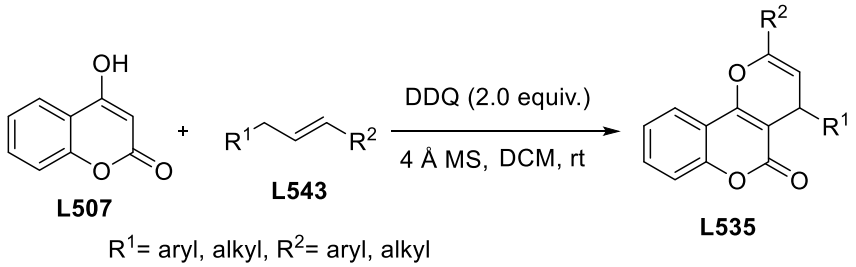
Scheme 1.280

Prajapati *et al.* demonstrated a protocol for the synthesis of pyrano[3,2-*c*]coumarins (**L542**) by using isocyanide (**L540**), dialkyl acetylenedicarboxylate (**L541**), and 4-hydroxycoumarn (**L507**) in water solvent at 80 °C (Scheme 1.281). Here 10 mol% tetrabutylammonium bromide (TBAB) used as a phase-transfer catalyst [327].



Scheme 1.281

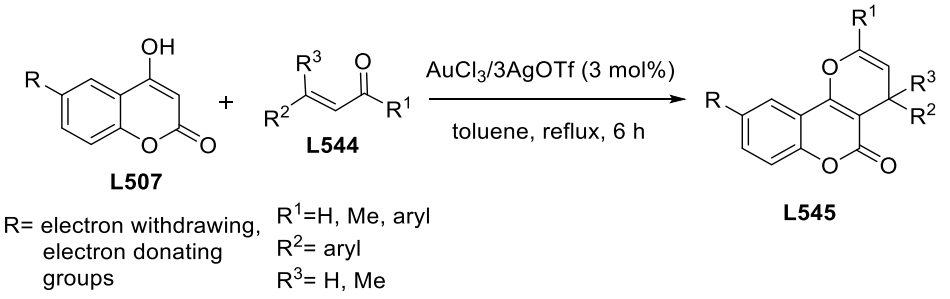
In 2010, Lin *et al*. established a new approach for the synthesis of functionalized pyranocoumarin (**L535**) through direct conjugate addition/annulations reaction of 4-hydroxycoumarin (**L507**) with 1,3-diarylallylic compounds (**L543**) (Scheme 1.282) [328]. They used DDQ as a catalyst and added by portion to the reaction mixture. A wide range of functionalities could be tolerated under the mild reaction conditions to provide the corresponding pyrano products in good to high yields.



Scheme 1.282

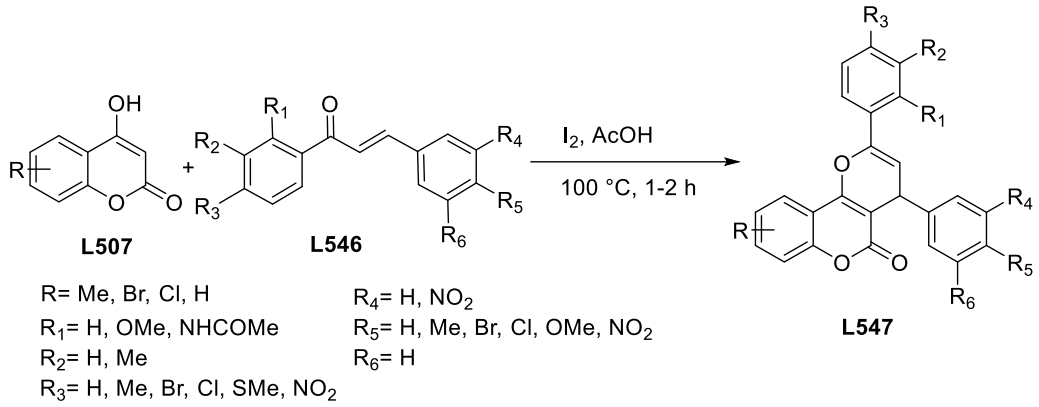
In 2011, Liu and coworkers reported a selective approach for the synthesis of pyranocoumarin derivatives (**L545**) *via* a tandem reaction of 4-hydroxycoumarins (**L507**) with *α*,*β*-unsaturated ketones (**L544**) in presence of gold(III) catalyst (Scheme 1.283) [329]. The reaction was carried out in the presence of $AuCl_3$/3AgOTf (3 mol%), in toluene solvent at reflux

conditions and gave the desired product by removal of water. A variety of functionalized pyrano[3,2-*c*]coumarins were synthesized with good yields.



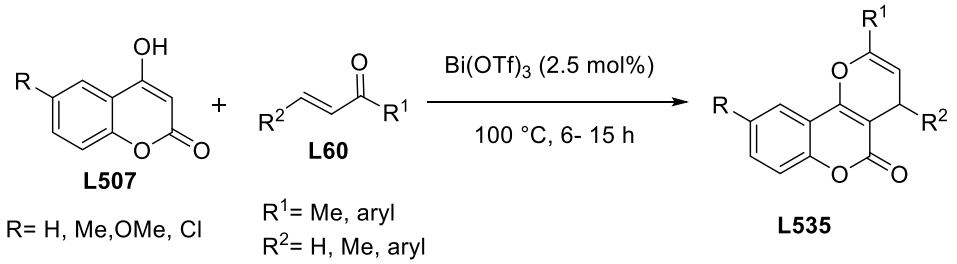
Scheme 1.283

In 2013, Ahmed and Babu developed a method for the regioselective synthesis of the multi-substituted pyranocoumarin derivatives (**L547**) by means of the reaction between 4-hydroxycoumarins (**L507**) and chalcones (**L546**) using molecular iodine (Scheme 1.284) [330]. The reaction was carried out in the presence of molecular iodine (1 equiv.), in acetic acid as solvent at 100 °C for 1-2 h. The desired products were obtained in high yields.



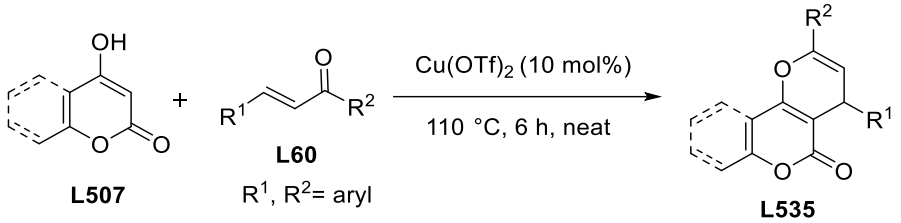
Scheme 1.284

In 2013, Bezuidenhoudt *et al*. described another method to synthesize pyrano[3,2-*c*]coumarins (**L535**) under solvent-free conditions (Scheme 1.285) [331]. Various 4-hydroxycoumarins (**L507**) with substituted/unsubstituted *α,β*-unsaturated carbonyl compounds (chalcones) (**L60**) were expediently reacted in presence of $Bi(OTf)_3$ (2.5 mol%) at 100 °C to produce the desired product (**L535**) by removal water as the only side product.



Scheme 1.285

In the same year, Hajra *et al.* demonstrated copper(II) triflate catalyzed the tandem reaction of 4-hydroxycoumarin (**L5o7**) with *α,β*-unsaturated carbonyl compounds (**L60**) for the efficient regioselective synthesis of pyrano[3,2-*c*]coumarins (**L535**) at 100 °C under solvent-free conditions (Scheme 1.286) [332]. Various pyranocoumarins were synthesized using this method with good to excellent yields. This present protocol was also explored to synthesise 4-hydroxy-6-methyl-2-pyrone successfully which suggest the synthetic potential of this methodology.



Scheme 1.286

CONCLUSION FOR THE CHAPTER 1

Aziridines, azirines and epoxides are capable to participate in ring opening reactions upon the action of *N-,O-,S-,C*-nucleophilic reagents as well as halogenating agents along C(H)C and C(H)Y (Y = heteroatom) bonds to afford ring opening products or other heterocyclic systems, including drug candidates, fluorophores or ligands. The selectivity of such processes is determined by the reaction conditions, including the catalyst type, and/or the nature of starting synthons and/or the nature reagents used. Most commonly these reactions are carried out in solution and using TM-based catalysts, which affects strongly the *E*-factor of the reaction. In a very rare cases the above-mentioned reactions were carried out using green/PASE (pot, atom, step economic) conditions, such as solvent-free methods, by using TM-free catalysts, under mechanochemical conditions, *etc*. Finally, the methods for the synthesis of the above mentioned three-member heterocycles are quite limited and may involve hardly available reagents. Therefore, more advanced synthetic protocols involving cheaper/easily available reagents, greener reactions conditions, lower *E*-factors protocols, and less expensive catalysts/greener catalysts need to be developed. Reactions, involving the formation of C-C(X) bonds in the three-member ring without ring opening are quite rare in these heterocycles and need to be explored as well.

Azomethines and their carbonyl-containing synthetic precursors are subjected for transformations along C(H)C and C(H)Y (Y = heteroatom) bond, which is widely used for the synthesis of various heterocyclic systems, including the above mentioned aziri(di)nes and epoxides, quinolines, fused imidazoles *etc*., as well as substituted amines and dipyrromethanes and their fused derivatives. However, for these synthons greener reaction conditions, such as solvent-free methods, TM-catalyst free approaches, mechanochemical methods *etc.*, need to be developed to provide both lower *E*-factors and higher reaction yields.

Alkenes and their derivatives under the action of *N-,O-,S-,C*-centered synthons as well as halogenationg reagents are subjected for transformations along C(H)C bond, which makes these compounds useful synthons for the preparation of various heterocyclic scaffolds, including aziri(di)nes and epoxides, as well as various aliphatic and heterocyclic compounds. Most commonly these reactions are carried out in conventional reaction conditions, while using of non-conventional ones or using greener methods might lower *E*-factors and/or result in unexpected products.

Based on all mentioned above, the ultimate aim of this dissertation work is to study the processes of functionalization of the activated C(H)C and C(H)Y bond (Y = heteroatom) and accompanying transformations in the series of small heterocycles (azirines, aziridines and

epoxides), carbonyl compounds and their derivatives (diketones, aldehydes, Schiff bases), ethylenes, including those with an activated multiple bond, as well as acetylenes for the development of “green”/rational methods for obtaining biologically active molecules/known drugs/precursors, as well as important organic synthons that are difficult or inaccessible by other methods.

To achieve the goals of the work, the following tasks must be solved:

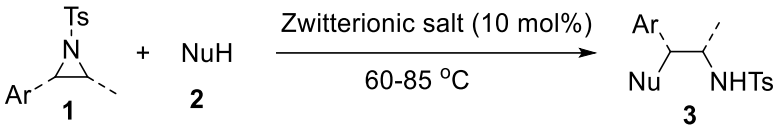
- To investigate the processes of functionalization of C(H)C and C(H)Y (Y ≠ C) bonds in small sterically strained heterocycles, namely in azi(ri)dines and epoxides;
- To investigate the processes of functionalization of the C(H) fragment at a multiple bond in acyclic substrates;
- To investigate the processes of functionalization of the C(H) fragment at a multiple bond in cyclic substrates;
- To explore the applicability of new non-conventional media, as well as “green” catalysts for carrying out these transformations;
- To assess the reactivity of the studied objects using quantum chemical methods;
- To evaluate the biological activity of the obtained compounds using *in silico* methods.

CHAPTER 2. RESULTS AND DISCUSSION

2.1. RING OPENING OF AZIRIDINES IN PRESENCE OF AN APROTIC IMIDAZOLIUM ZWITTERIONIC MOLTEN SALT

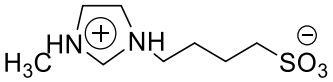
Based on the literature data analysis, three-membered heterocycles, due to the high steric strain of the cycle, tend to enter into ring opening reactions under the action of nucleophilic reagents, while the selectivity of the process can be directed by the reaction conditions and/or the nature of the reagents. And ionic liquids/molten salts can be considered as promising catalyst for such reactions.

Therefore, in the frame of the dissertation work we have developed of a simple and efficient procedure for regioselective ring opening of aziridines by various nucleophiles under mild and solvent-free conditions by using a zwitterionic-type molten salt, 4-(3-methylimidazolium) butane sulfonate as a catalyst (Scheme 2.1).



NuH = indole, pyrrole, methanol, ethanol, acetic acid, *N,N*-diisopropylamine

Zwitterionic salt:



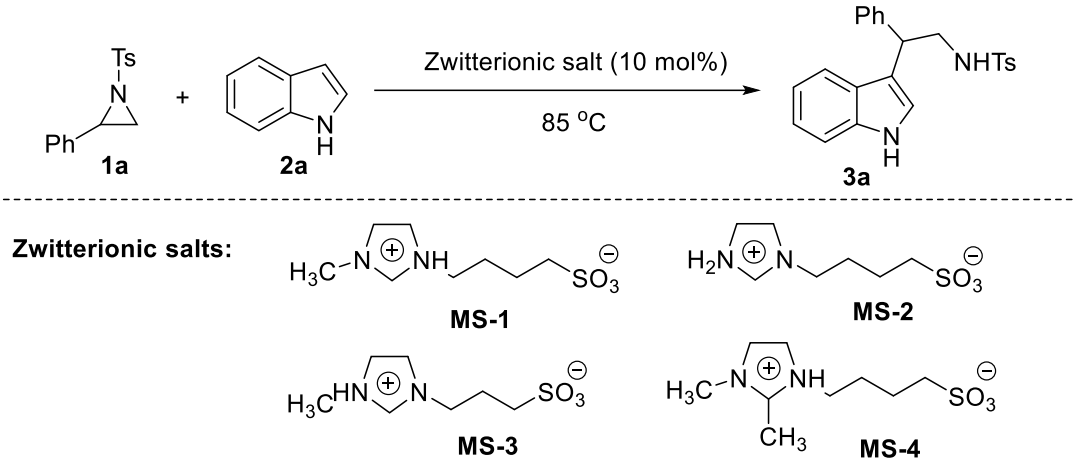
4-(3-Methylimidazolium)butane sulfonate (**MS-1**)

Scheme 2.1

At initial stage, we have taken a mixture of readily available indole (**2a**) and 2-phenyl-1-tosylaziridine (**1a**) as model substrates using 10 mol% of 4-(3-methylimidazolium)butane sulfonate (**MS-1**) as catalyst where the indole acts as a nucleophile. The reaction proceeded smoothly at 85 °C and the desired product *N*-(2-(1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (**3a**) was obtained in 84% yield within 3 h. We have performed our experiment with some other molten salts also and the results were shown in the Table 2.1. It has been observed that other molten salts (**MS-2**, **MS-3** and **MS-4**) are not effective like (**MS-1)** for this nucleophilic ring opening process. When we have used 4-(1-imidazolium)butane sulfonate (**MS-2**) as a catalyst (entry 2, Table 2.1) the yield was considerably lower (70%) than (**MS-1)** (84%) as a catalyst. Similarly, we have found that the molten salt 3-(1-imidazolium) propane sulfonate (**MS-3**, entry 3, Table 2.1) was also less effective by giving the desired product with only 64% yield and lastly, when we used 4-(2,3-dimethylimidazolium)butane sulfonate (**MS-4**, entry 4, Table 2.1) no formation of desired product was observed. According to these observations, we

have selected the aprotic zwitterion (**MS-1)** for this nucleophilic ring opening. Effect of temperature has also been studied as shown in the table (entry 5-7, Table 2.1) and it has been observed that at higher temperature as well as at lower temperature the yields are not satisfactory. Finally, the amount of catalyst loading was checked under this reaction conditions using catalyst (**MS-1)** for the same reaction. It was observed that 10 mol% of catalyst **(MS-1)** can afford better yield (84%) compare to that of 5 mol% (70% yield). Similarly, when we have used 15 mol% of the catalyst no considerable improvement was observed (85% yield) and finally, when the reaction was carried out in absence of any catalyst no conversion has been detected (entry 10, Table 2.1).

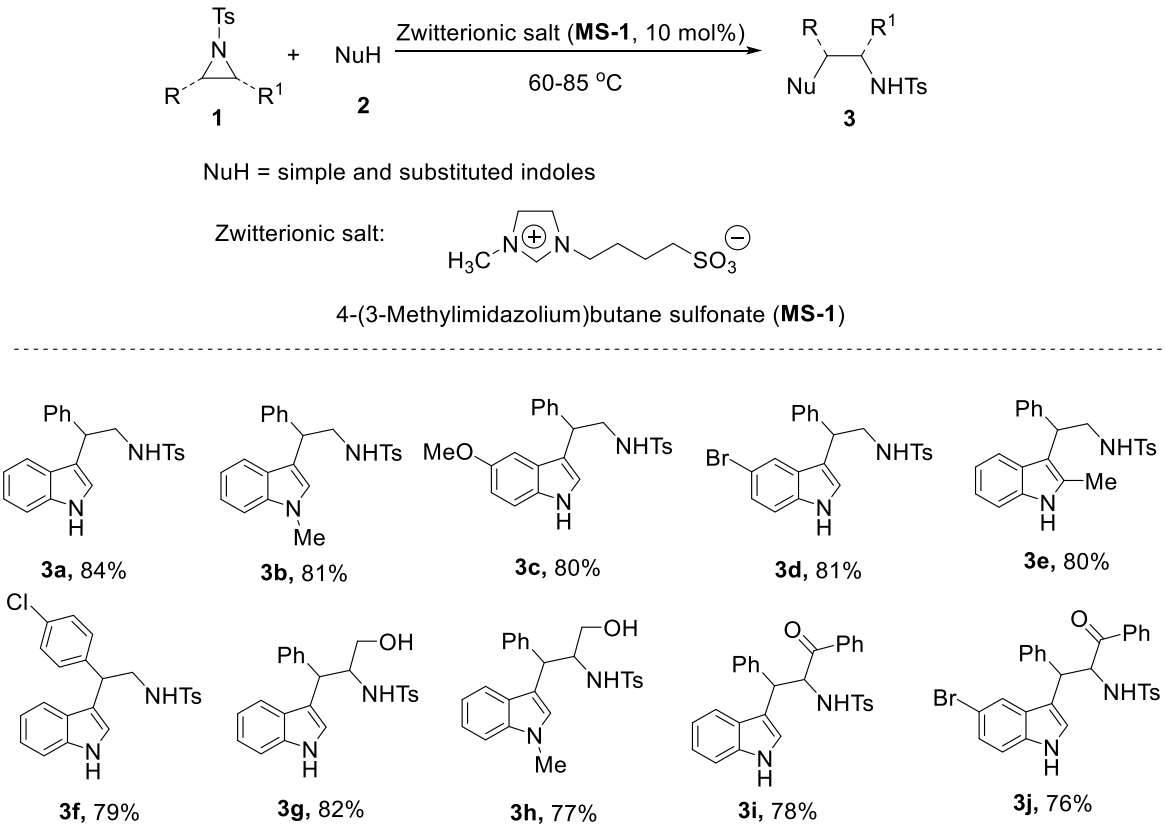
Table 2.1. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Temp (°C)	Time (h)	Yields[b] (%)
1	**MS-1** (10)	85	3	84
2	**MS-2** (10)	85	3	70
3	**MS-3** (10)	85	3	64
4	**MS-4** (10)	85	3	ND[c]
5	**MS-1** (10)	100	3	76
6	**MS-1** (10)	50	5	45
7	**MS-1** (10)	rt	10	Trace
8	**MS-1** (5)	85	3	70
9	**MS-1** (15)	85	3	85
10	--	85	3	ND

[a]***Reaction conditions:*** Carried out with 0.5 mmol of **1a** and 0.5 mmol of **2a** in the presence of 10 mol% catalyst in neat conditions. [b]Isolated yields. [c]ND = Not detected in TLC.

Inspired by this result we further explored the scope of this reaction. First of all, we have focused on the use of different aziridine systems with various substituted indoles to prove the general applicability of the reaction conditions, and the obtained results are summarized in Scheme 2.2. It was observed that electron-rich and electron-deficient indoles afforded the desired products efficiently with very good yields under the present reaction conditions when reacted with various aziridines. *N*-Substituted indole also acted as an excellent nucleophile to this ring opening course and gave satisfactory yield (**3b**). The indole containing an electron donating -methoxy group at the 5-position also gave the desired product with good efficiency (**3c**). The bromo-substituted indole gave the corresponding product (**3d**) in 81% yield without forming any dehalogenated products. Simple 2-phenyl-1-tosylaziridine (**1a**) reacted with indole very well to give the desired product with high yield (**3a**). Similarly, aryl *N*-tosylaziridine substituted with chloro- group at the benzene ring was efficiently afforded the desired product (**3f**) with good yield. The general applicability of this reaction was highlighted through the reaction of a variety of aziridines, substituted by different functional groups with various nucleophiles. In this regard, the effect of a hydroxy group as well as carbonyl functionalities in the aziridine system was also investigated where both of these functionalities were reacted smoothly with indole as well as the substituted indoles under the present reaction conditions to give the desired products (**3g-3j**) without affecting the functional groups.



Scheme 2.2

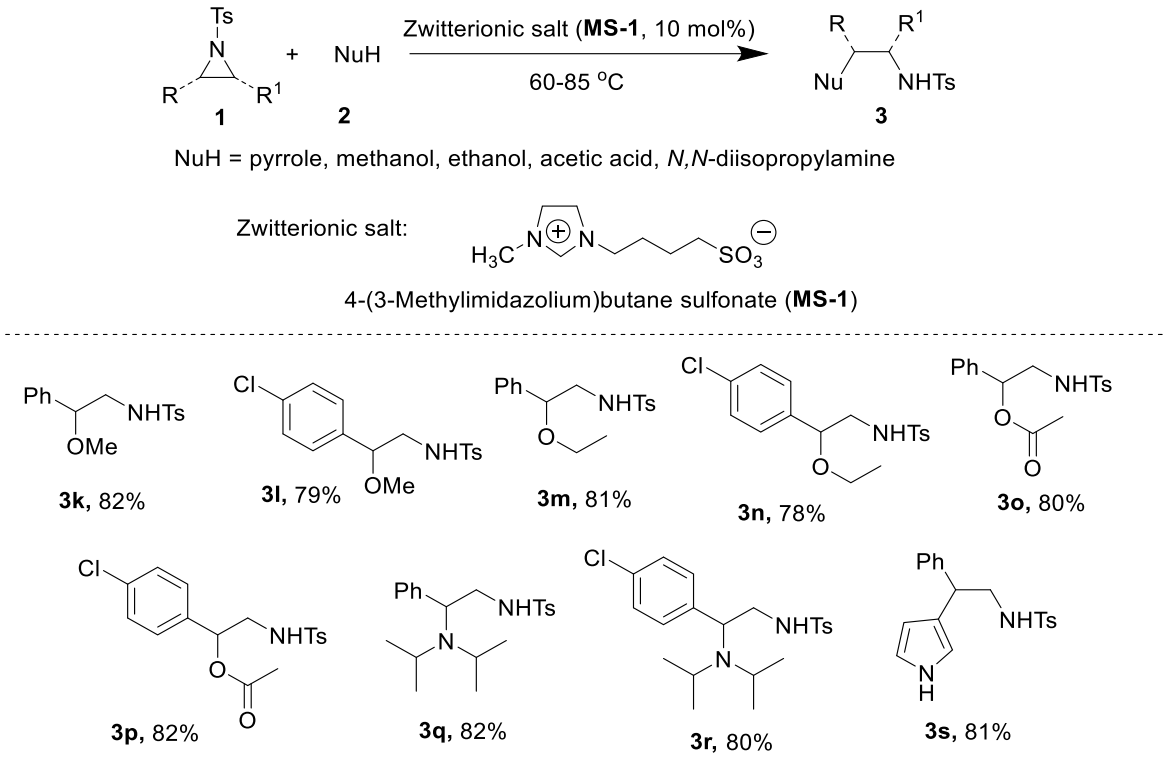
The other aziridine systems, in spite of simple aryl *N*-tosylaziridine did not affect the efficiency and the regioselectivity of the reactions. Among our synthesized compounds, the known synthesized compounds have been characterized by only spectral data and the new compounds by both spectral data and analytical data. The reaction conditions were really mild and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all of the reaction combinations which are supported with high yields and regioselectivity of this protocol.

Next, the general applicability of our present methodology has been investigated by using some other nucleophiles to react with aziridines regioselectively. To our delight, the corresponding ring opening products (**3**) were obtained regioselectively in good yields and the results are summarized in Scheme 2.3. We have successfully employed methanol and ethanol to synthesize the corresponding compounds (**3k–3n**) with satisfactory yields which increases the scope of this transformation. Both 2-phenyl-1-tosylaziridine (**1a**) and 2-(4-chlorophenyl)-1-tosylaziridine (**1b**) reacted smoothly with the other nucleophiles to produce the corresponding products with good yields. Also we have observed that the aziridine ring opening was possible by using acetic acid (**2h**) as a good nucleophile to give the corresponding products (**3o**) and (**3p**) in 80% and 82% yields, respectively.

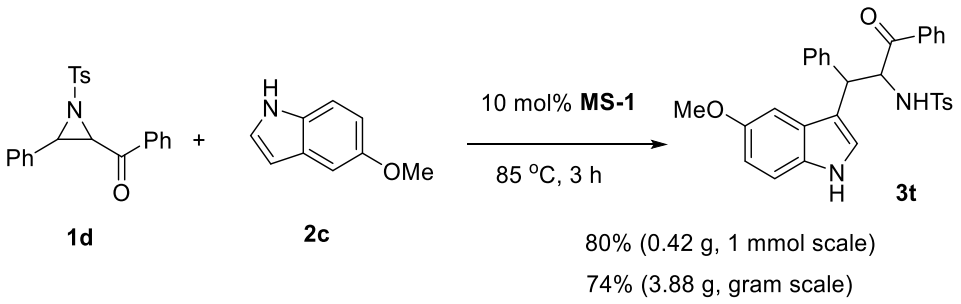
Moreover, the most representative secondary amine such as diisopropylamine (**2i**) was also used, and the reaction afforded the desired products (**3q** and **3r**) with good yields. This is one of the important advantages of the adopted methodology as amines are not a suitable as a nucleophile under mild acidic conditions. In addition, 2-phenyl-1-tosylaziridine (**1a**) underwent ring cleavage by pyrrole (**2j**) with preferential attack at the benzylic position resulting in the formation of desired 3-alkylated pyrrole derivatives (**3s**) with 81% yield. In general, all of the reactions were clean and gave the corresponding ring opening products with good regioselectivity. During our study we have not observed the formation of any product by terminal attack. The phenyl groups substituted with electron-donating or electron withdrawing groups did not affect the efficiency or the regioselectivity of the reactions. Here it must be mentioned that the reactions with other nucleophiles (Scheme 2.4) required longer time (14 h) compared to that for indoles and pyrrole (**3h**).

Here we have also demonstrated the applicability of this methodology on gram scale synthesis. For this purpose the key starting material phenyl(3-phenyl-1-tosyl--aziridin-2-yl)methanone (**1d**) was prepared in 52% yield by the reaction of chalcone with 1 equiv. of anhydrous chloramine-T in the presence of 20 mol% of NBS (*N*-bromosuccinimide) in acetonitrile at room temperature. The treatment of aziridine (**1d**) with 5-methoxy indole (**2c**) (1 equiv) at 85

°C for 3 h in the presence of MBS under neat conditions afforded the corresponding ring opening product (**3t**) in 80% yield in one-pot. Whereas the same reaction for the preparation of this compound (**3t**) on the gram-scale afforded 74% of isolated product (Scheme 2.4).



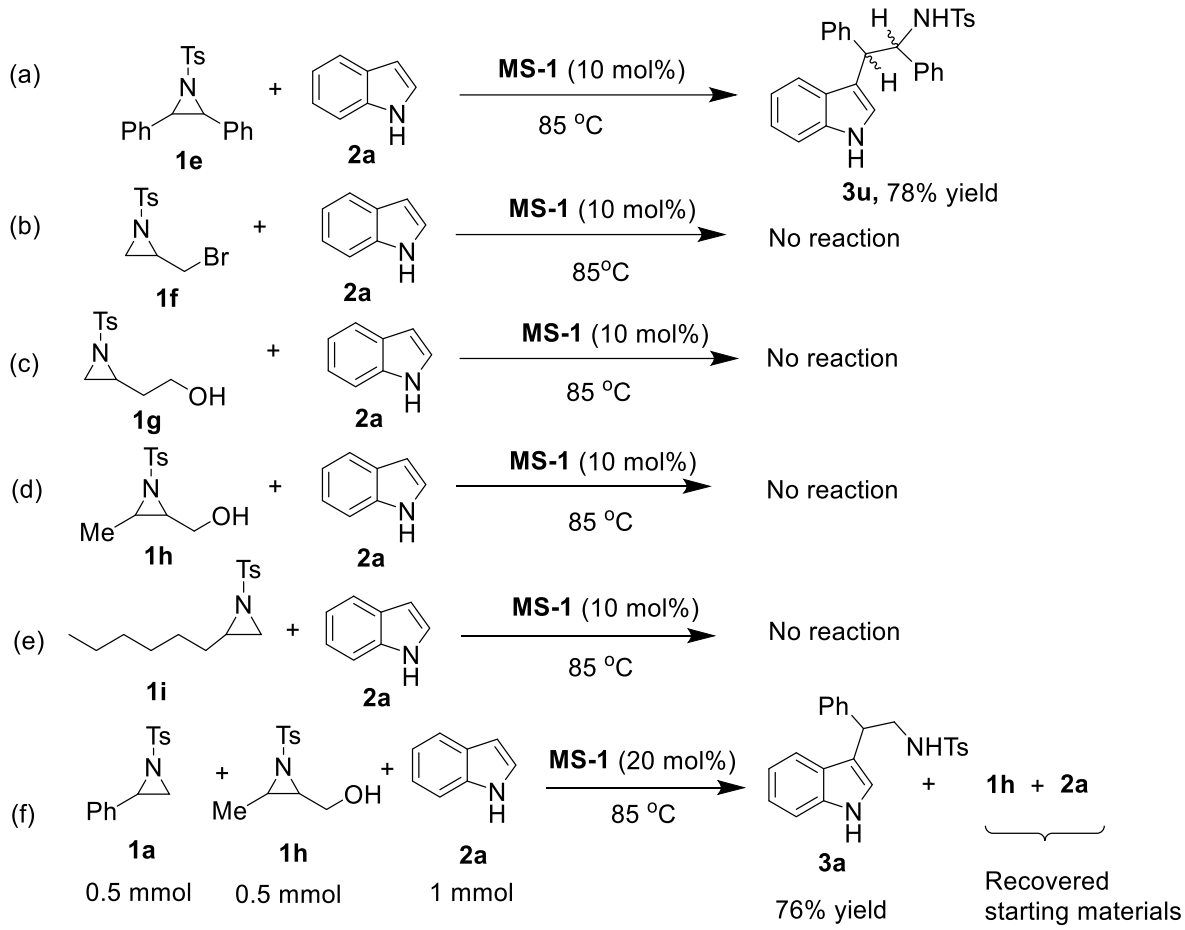
Scheme 2.3



Scheme 2.4

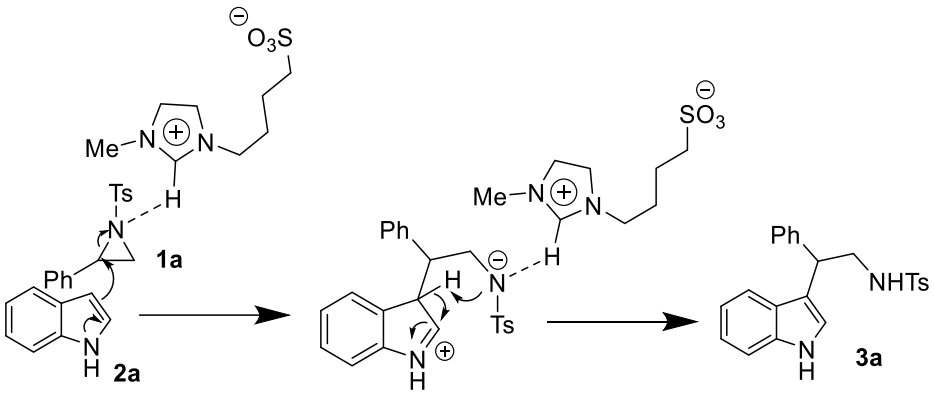
As we have observed the regioselective ring opening products from only attack at the benzylic C-atom, we have further examined it by using different aliphatic aziridines for more conclusive results as shown in the Scheme 2.5, and we have not found any ring opening product. Here it is important to say that in case of aziridine (**1e**) where there are two symmetric benzylic C-atoms for the attack, and we have got a mixture of *syn*/*anti* product (**3u**) with 1:1 ratio. However, we were not able to synthesize the unsymmetrical aziridine bearing two different phenyl moieties at both of the aziridine ring carbons and have not been tested them. Relevantly, we have treated a mixture (1:1) of aziridines with benzylic moiety (**1a**) and aziridine containing no benzylic moiety

(**1h**) under the same reaction conditions for ring opening. As a result, we have noticed that only the former (**1a**) undergoes smooth reaction to afford the desired product (**3a**) whereas the later one (**1h**) was remain unchanged and recovered as starting material (Scheme 2.5).



Scheme 2.5

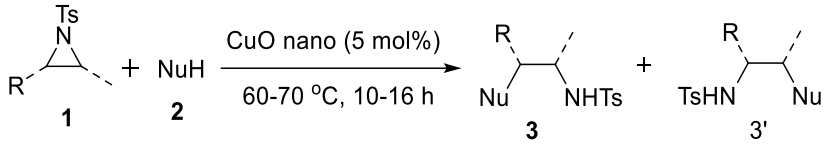
Though we have not studied the mechanism in details but based on literature [333] as well as our previous observations [334, 335] we can predict the possible mechanistic pathway according to Scheme 2.6 where the aziridine (**1a**) is activated through hydrogen bond formation between C2–H of imidazolium cation (**A**) and nitrogen atom of aziridine group. Similar to our previous observations the role of the SO_3^- is not clear; it may stabilize the transition state of the reaction through electrostatic interaction which facilitates the nucleophilic ring opening by different nucleophiles in an S_N2 fashion to provide the final product (**3**).



Scheme 2.6

2.2. RING OPENING OF AZIRIDINES IN PRESENCE OF CuO NANO PARTICLES

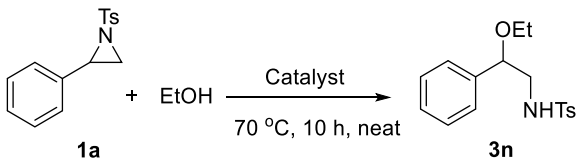
In order to study the effect of the type of activating agent on the structure of the resulting product, the transformation described above was investigated in the presence of copper(II) oxide nanoparticles (CuO nanoparticles). We have developed an efficient method for ring opening of aziridines by various nucleophiles under mild and neat reaction conditions using copper oxide nanoparticles as a reusable catalyst (Scheme 2.7). Our ring opening method involves different types of nucleophiles like alcohols, thiols, indole etc.



Scheme 2.7

We commenced our study taking readily available ethanol as the nucleophile and phenyl *N*-tosylaziridine (**1a**) as the model substrates in the presence of catalytic amount of CuO nano (5 mol%) at 80 °C for 10 h under neat conditions (Table 2.2, entry 1). To our delight, desired *N*-(2-ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3n**) was obtained in 80% yield after 10 h and no further improvement was noticed by increasing reaction time. Encouraged by this initial result, we proceeded to optimize the reaction conditions which are summarized in Table 2.2. CuO nano was found to be the most effective catalyst among the various metal nanocatalysts tested (In_2O_3, NiO, ZnO) (Table 2.2, entries 2-4) and 5 mol% CuO nano proved to be optimal. Lower conversions were obtained when CuO powder was used (Table 2.2, entry 5). Other copper salts (such as $Cu(OAc)_2$, CuBr, $CuCl_2$, CuI, Cu_2O, $Cu(OTf)_2$) were not so effective for this conversion (Table 2.2, entries 6-11). With respect to the quantity of the catalyst, there was no significant enhancement in yields when the amount of catalyst was increased from 5 to 10 mol% while decreasing the amount of catalyst decreased the yield. In the absence of catalyst, negligible amount of desired product was observed. As well we did not carry out the reaction in the presence of any solvent as we got satisfactory result under neat conditions. Thus, optimal reaction conditions were obtained using phenyl *N*-tosylaziridine (**1a**, 1 mmol) and ethanol (2 mmol) in the presence of 5 mol% of CuO nano at 70 °C for 10 h under neat conditions (Table 2.2, entry 1).

Table 2.2. Optimization of the reaction conditions.[a]



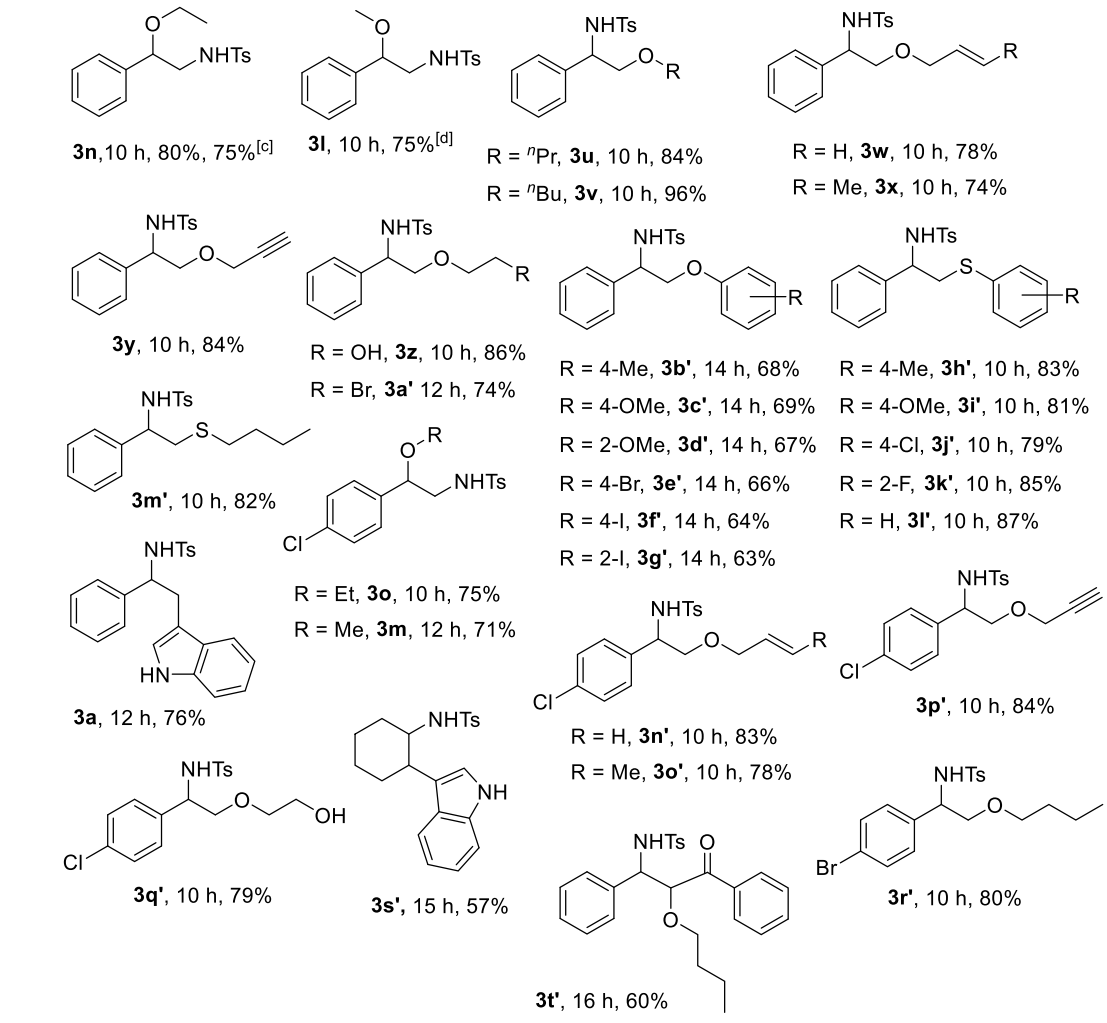
Entry	Catalyst (mol%)	Yield[b] (%)
1	CuO nano (5)	80
2	In_2O_3 nano (5)	35
3	NiO nano (5)	44
4	ZnO nano (5)	48
5	CuO (5)	65
6	$Cu(OAc)_2$ (5)	38
7	CuBr (5)	40
8	$CuCl_2$ (5)	32
9	CuI (5)	51
10	Cu_2O (5)	70
11	$Cu(OTf)_2$ (5)	68
12	CuO nano (10)	80
13	CuO nano (3)	62
14	-	30

[a]***Reaction conditions:*** A mixture of **1a** (1 mmol) and ethanol (2 mmol) was stirred at 70 °C in the presence of catalyst under neat conditions for 10 h. [b]Isolated yields.

After optimization we focused on the use of different aziridine systems with various nucleophiles such as alcohols, thiols, indoles to prove the general applicability of the reaction conditions and the results are summarized in Table 2.3. Simple aryl *N*-tosylaziridine (**1a**) reacted with methanol to give the corresponding product (**3l**) in 75% yield. Similarly, *n*-propanol gave the corresponding ring opening product (**3u**) in 84% yield. For methanol and ethanol we observed that the reactions afforded the products resulting from a benzylic attack, whereas, for *n*-propanol and other nucleophiles, the attack occurred overwhelmingly at the least-hindered *β*-carbon. Simple aryl *N*-tosylaziridine (**1a**) reacted with a number of aliphatic and aromatic alcohols to give the corresponding products (**3v-3g'**) with satisfactory yields. Allylic, as well as propargylic alcohols, reacted with compound (**1a**) without any difficulty (**3w**-**3y**). Aromatic alcohols containing electron-donating groups (-Me,–OMe) have shown also good efficiency (**3b'**- **3d'**). Aromatic alcohols substituted with halogens such as -I and -Br (**3e'**-**3g'**) smoothly reacted with *N*-tosylaziridine (**1a**) without forming any dehalogenated products. Next, we turned our attention to use other nucleophiles such as thiols and indoles. Phenyl *N*-tosylaziridine (**1a**) reacted smoothly with aliphatic and aromatic thiols to give the corresponding products (**3m'-3l'**) in good to excellent yields. The thiophenols bearing electron-donating substituents such as –Me, –OMe (**3h'** & **3i'**) and

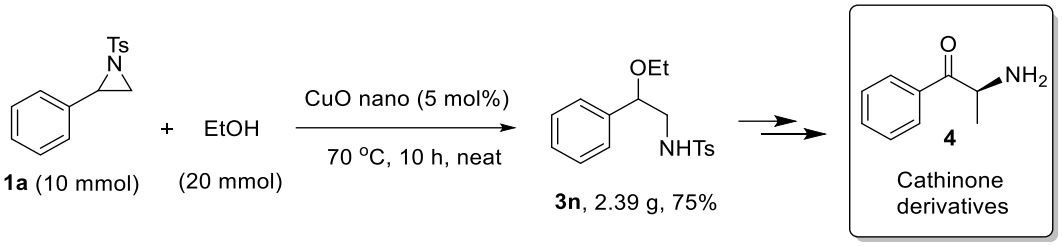
electron-withdrawing substituents such as –Cl, –F reacted well to afford the corresponding ring opening products (**3j'** & **3k'**). Simple aryl *N*-tosylaziridine (**1a**) also reacts with indole to give the corresponding product (**3a**) in 76% yield. Other substrates of aziridines like 2-(4-chlorophenyl)-1-tosylaziridine (**1b**) and 2-(4-bromophenyl)-1-tosylaziridine (**1c**) gave the same type of nucleophilic ring opening reactions. 2-(4-Chlorophenyl)-1-tosylaziridine (**1b**) reacted with a number of aliphatic alcohols to give corresponding benzenesulfonamides (**3o-3q'**) with good yields. 2-(4-bromophenyl)-1-tosylaziridine (**1c**) also reacts with butan-1-ol to give the product (**3r'**) in 80% yield. The effect of carbonyl functionality in the aziridine system was also investigated where carbonyl functionality was unaffected under the present reaction conditions and reacted smoothly with ^{n}BuOH to afford the product (**3t'**). It is worthy to mention that aliphatic aziridine also reacted smoothly with indole to afford the desired product (**3s'**).

Table 2.3. Ring opening of aziridines with various nucleophiles.[a,b]



[a]***Reaction conditions:*** aziridines **1** (1 mmol), nucleophiles **2** (2 mmol for aliphatic alcohols, 1 mmol for aromatic alcohols as well as thiols and indole), CuO nano (5 mol%) at 70 °C. [b]All are isolated yields. [c]Phenyl N-tosylaziridine (**1a**, 10 mmol) and EtOH (20 mmol) in the presence of CuO nano (5 mol%) at 70 °C for 10 h. [d]Reaction was carried out at 60 °C.

All of the synthesized compounds have been characterized by spectral and analytical data. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported with high yields. *N*-(2-ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3n)** is a valuable precursor for the preparation of aminoalcohol derivatives, as well as *α*-aminoketones, in particular, analogues of the neurostimulator cathinone (**4)**. So, the potential synthetic applicability of this method was investigated on the gram scale using the model reaction. The reaction could afford 2.39 g of product (**3n**) in 75% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of ring opening product *N*-(2-ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3n**) (Scheme 2.8).

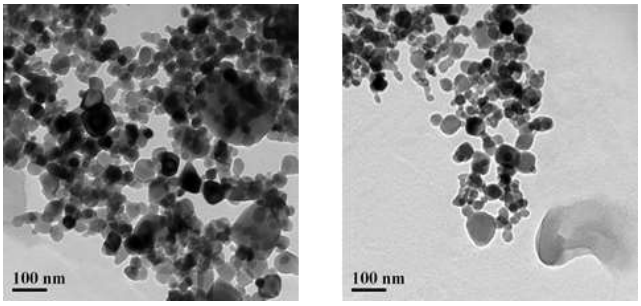


Scheme 2.8

The reusability of the catalyst was also studied to make this protocol more effective in a greener way. After completion of the reaction, ethyl acetate (10 mL) was added to the reaction mixture. Then the insoluble CuO nanoparticles were filtered by Teflon membrane (PTFE, 0.2 mm pore size). The CuO nanoparticles were thoroughly washed with the ethanol, dried and reused for the next cycle. The catalyst maintained its high level of activity even after being recycled five times for synthesizing product (**3aa**) as shown in Table 2.4. The morphology of CuO nano was determined by HRTEM. A comparative study of the HRTEM of the fresh catalyst and the recovered catalyst after six cycles (Figure 2.1) showed that the catalyst did not undergo agglomeration during the recycling process.

Table 2.4. Recycling of CuO nano for synthesizing of product (**3n**).[a]

No. of cycle	Yields (%)[b]	Catalyst recovery (%)
1	80	95
2	78	91
3	75	87
4	72	85
5	69	82

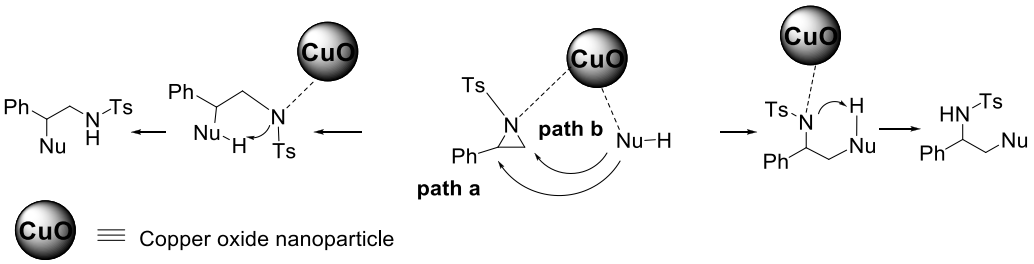


A **B**

Figure 2.1 HRTEM image of CuO catalyst before (A) and after six cycles (B)

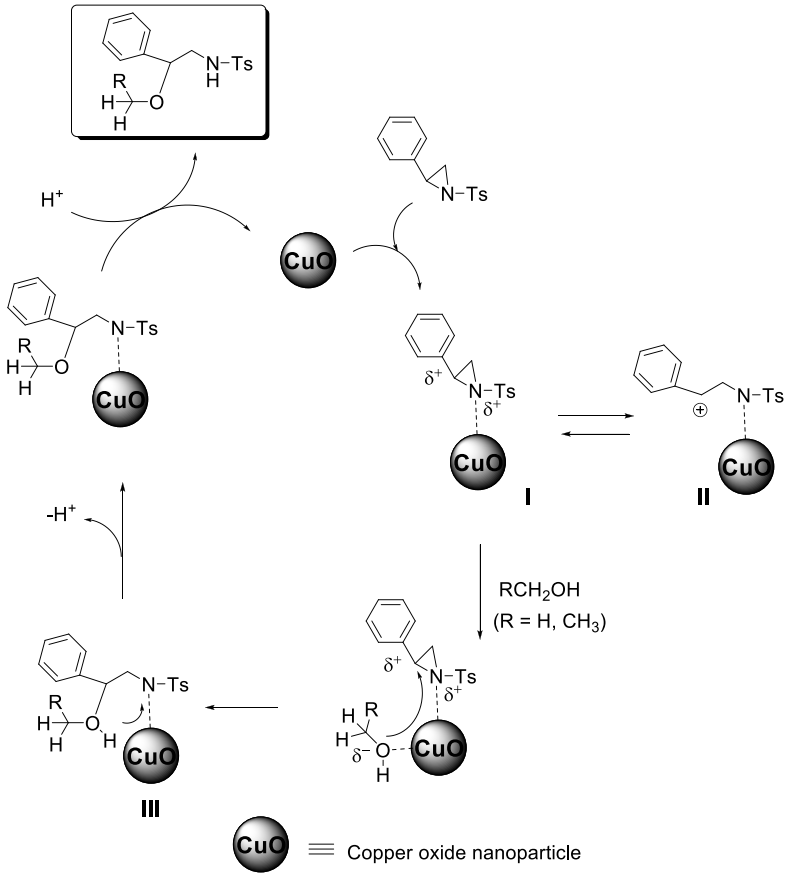
In addition, we have developed a greener reaction condition bearing lower *E*-factors [336] in cases of this CuO nano-catalyzed aziridine ring opening reaction which is consistent with the principles of the atom economy.

Though the mechanistic details have not been studied but based on literature as well as our previous observations [337] we can predict the possible pathway according to (Scheme 2.9) where the aziridine is activated by CuO nano through the co-ordination with nitrogen atom of aziridine group. It is well reported that highly dispersed CuO particles to possess the acidic properties [338], in particular, they can catalyze the ring opening of phenyl-substituted epoxides under the action of *O*- and *N*-nucleophiles [339]. This acidity (Lewis type of Brønsted type) [340] is associated with a high content of broken metal-oxygen bonds in highly dispersed metal-oxide particles, which are obtained when the surface of bigger crystal of metal oxide as an ideal lattice plane, to become exposed by cutting/breaking this bigger crystal to the ultra-small ones (or NPs) to result in exposed metal centers which are coordinatively unsaturated and, thus, highly reactive, *i.e.* acidic. Thus, the CuO NPs might both to catalyze the aziridine ring towards the nucleophilic attack and to stabilize the transition state of the reaction during the attack of different nucleophiles (*via* path a or path b) in an S_N2 fashion to provide the ring opening final products.



Scheme 2.9

Based on these experimental results and literature reports, a reaction mechanism can be postulated for the ring opening reactions of aziridines under the action of various nucleophiles in the presence of Lewis acids-like CuO NPs (Scheme 2.10). Thus, as a first step, the azaphilic activation of aziridines [341] by CuO NPs catalyst reversibly produces an activated complex [**I**]. The intermediacy of the open-chained carbocation [**II**] is also possible [342]. In case of hard small nucleophiles, such as MeOH and EtOH they react with complex [**II**] *via* the S_N2-type mechanism with high regioselectivity at the most positively charged benzylic carbon of complex [**I**] to produce new intermediate [**III**]. Again, the intermediacy of a zwitterionic specie [**III**] could not be disregarded and in this case the reaction would provide intermediate [**III**] by S_N1-type mechanism.



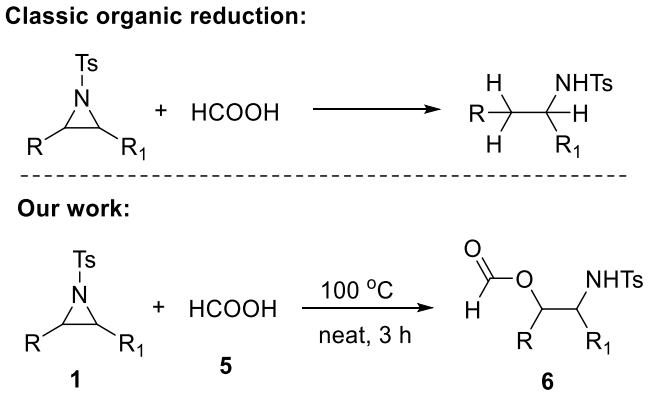
Scheme 2.10

The similarity of the results observed for the methanol and ethanol as nucleophiles could be attributed to their better adsorption on the surface of CuO catalysts [339], and this phenomenon is widely studied on metallic copper surface [19] where methoxy- and ethoxy species are better stabilized and, thus, can be easier delivered to the mostly positively charged reaction site of the aziridine. In case of other nucleophiles, such as longer chained or aryl alcohols, thiols and indole the reaction outcomes are driven by either steric or electronic issues.

2.3. RING OPENING OF AZIRIDINES USING FORMIC ACID

In synthetic organic chemistry, formic acid was often used as a source of proton and hydride ion from the formate ion [343]. It can also act as a source of formyl group in the formylation reaction of amines [344]. An interesting result was obtained by the interaction of aziridines (**1**) with formic acid (**5**), which in classical organic reactions is used as a source of proton and hydride ion from the formate ion, as well as as a source of the formyl group in the amine formylation reaction. When heating aziridines (**1**) at 100 °C temperature, no reduction products were observed in formic acid, but the products of the ring opening of the aziridine were regioselectively formed (**6**). However, to the best of our knowledge there is no such report where formic acid has been used as nucleophiles on the regioselective ring opening of aziridines. So, in continuation of our research on aziridines, we are very much interested to report our method for ring opening of aziridines by formic acid.

In our present protocol we have taken a mixture of aziridines and formic acid in the absence of any catalyst and solvent. The reaction mixture was then treated at 100 °C temperature to get the desired products (Scheme 2.11). In this work the ring opening of aziridines with formic acid is a little bit different from general expectations. Here formic acid is not acting as reducing agent in the ring opening process as classical organic reactions (Scheme 2.11**)**. The formic acid initially activates the aziridines whereas the formate group generated from formic acid acts as a nucleophile itself instead of the source of hydride ion leading to the formation of nucleophilic ring opening products.

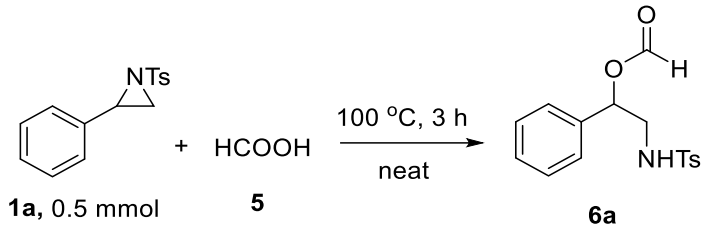


Scheme 2.11

Initially we have optimized our conditions by varying the amount of formic acid using 2-phenyl-1-tosylaziridine (**1a**) as a model substrate. The results of optimization are summarized in Table 2.5. We have started our experiment by mixing 2-phenyl-1-tosylaziridine (**1a**) and formic acid (**5**) in 1:1 ratio at 100 °C temperature and stirred the mixture for 3 h. At this temperature and

time limit the reaction proceeded smoothly and the product 2-(4-methylphenyl)sulfonamido-1-phenylethyl formate (**6a**) was isolated in 86% yield (entry 1, Table 1). Further increment in the amount of formic acid to 1.25 equiv, 1.5 equiv, 1.75 equiv and 2 equiv; we did not observe any significant changes of yields and were in the range 85-86% (entries 2-5, Table 1). The reaction did not proceed well at room temperature even after 12 h (entry 6, Table 1). So, we have considered the final optimized conditions using 1 equiv of formic acid with respect to 1 equiv of 2-phenyl-1-tosylaziridine (**1a**) at 100 °C for 3 h.

Table 2.5. Optimization of the reaction conditions

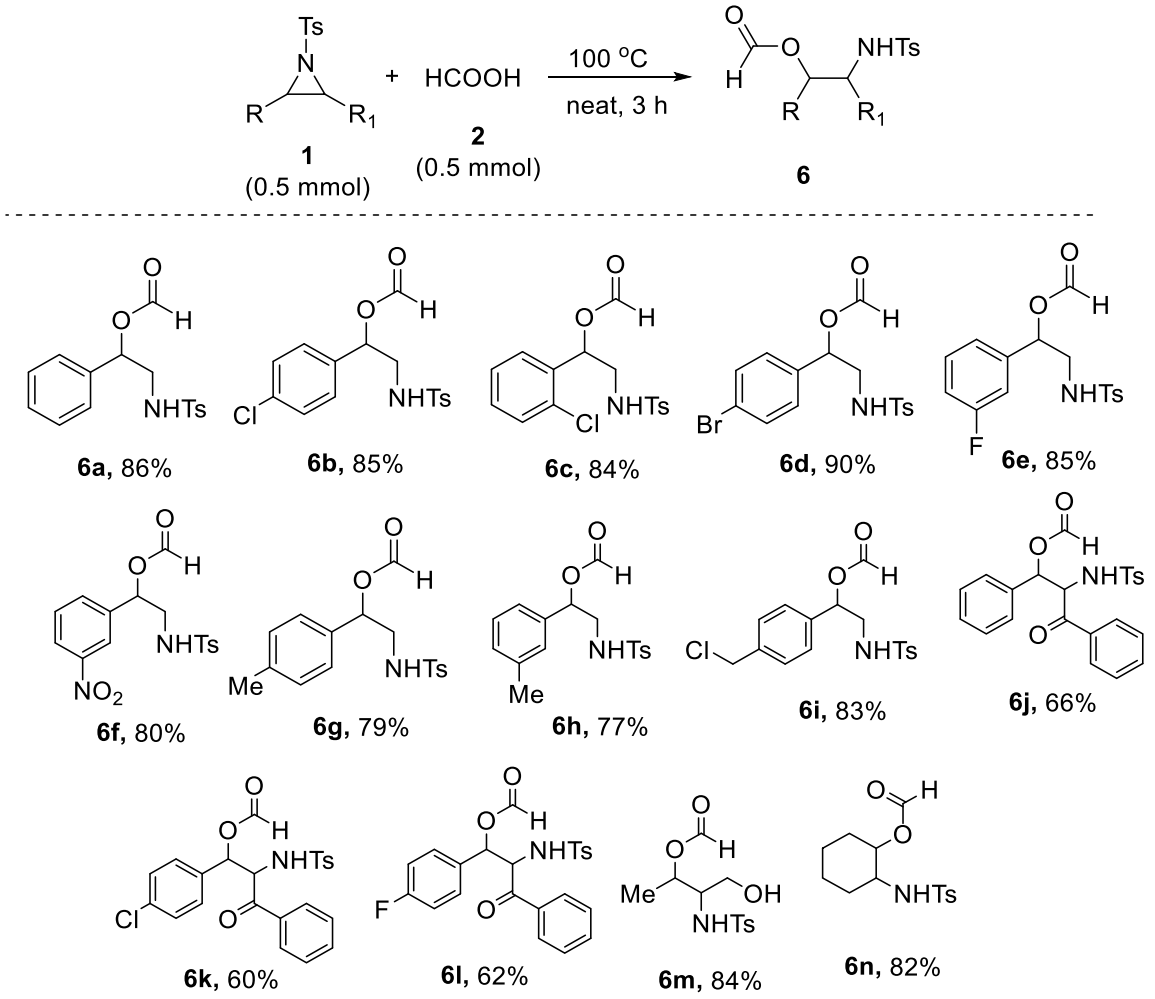


Entry	Aziridines (**1a**, equiv)	Formic acid (**5**, equiv)	Isolated yields (%)
1	1	1	86
2	1	1.25	86
3	1	1.5	85
4	1	1.75	85
5	1	2	86
6[a]	1	1	20

[a]Reaction was carried out at room temperature for 12 h.

After optimizing the reaction conditions, we have further explored our methodology by varying different aziridine systems switching to the general applicability of the reaction conditions and the results are summarized in Scheme 2.12. It was observed that 2-phenyl-1-tosylaziridine (**1a**) containing electron withdrawing groups (chloro-, fluoro-, bromo-, nitro-) at the phenyl moiety (as found effective to afford the desired products (**6b-6f**) in good yields. Also 2-phenyl-1-tosylaziridine (**1a**) substituted with some electron donating groups like -Me, -CH_2Cl at the benzene ring effectively afforded the desired products (**6g-6i**) in good to excellent yields. The effect of carbonyl functionality in the aziridine system was also investigated where carbonyl functionality was unaffected under the present reaction conditions and reacted smoothly with formic acid to give the corresponding ring opening products (**6j-6l**). Aliphatic aziridines underwent smooth

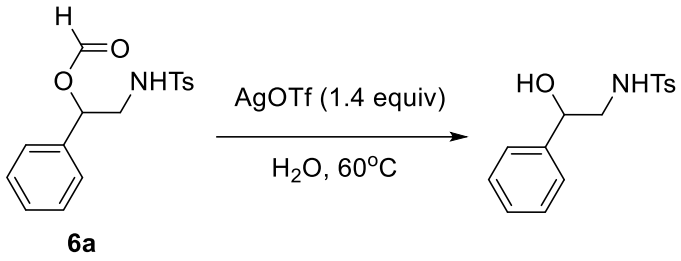
reaction with formic acid in present conditions yielding the corresponding products (**6m**) and (**6n**) in 84% and 82% yields, respectively. All of the synthesized compounds have been characterized by spectral and mass-spectroscopy. The reaction conditions were mild and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported with high yields and regioselectivity of this protocol. A single crystal X-ray analysis of compound (**6n**, CCDC 1569124**)** was performed to confirm the structure of the ring opening products (Figure 2.2).



Scheme 2.12

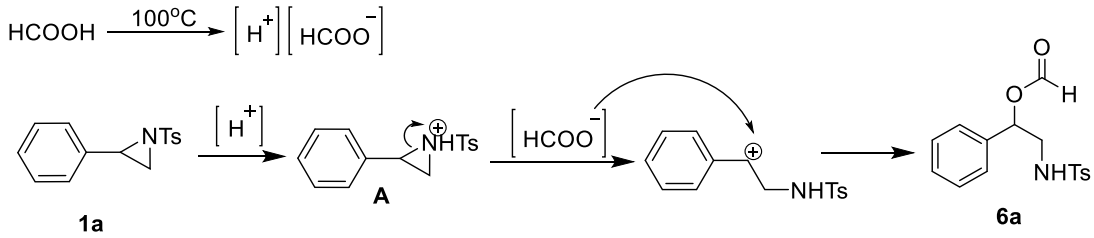
Figure 2.2. X-Ray crystallographic data for the structure of compound (**6n**)

It was also proved that by utilising this method, the ring opening product (*i.e.* formate ester **6a**) could be transformed to the corresponding hydroxyl compound without any difficulty by applying a common hydrolysis method (Scheme 2.13).



Scheme 2.13

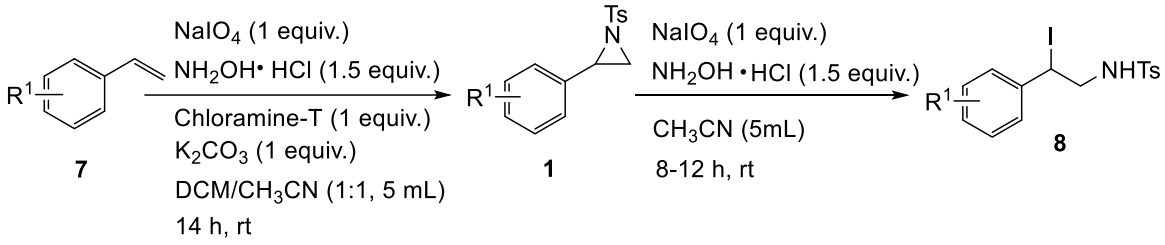
A probable mechanism of our present protocol has been depicted in Scheme 2.14. Initially the proton from the formic acid itself can activate the aziridine ring system to form specie [**A**] followed by the ring opening. The nucleophilic attack occurs in an S_N1 fashion in our predicted mechanism to provide the final ring opening product (**6a**).



Scheme 2.14

2.4. SYNTHESES AND RING OPENING OF AZIRIDINES IN PRESENCE OF $NH_2OH·HCl$ AND $NaIO_4$

Next, we investigated the possibilities of ring opening of the aziridine cycle under the action of halogenating agents under various conditions. We have found that the treatment of styrenes **7** with the combination of hydroxylamine hydrochloride and sodium periodate in presence of Chloramine-T/K_2CO_3 combination with olefins using DCM/acetonitrile as solvent afforded smoothly to aziridines (**1**) (Scheme 2.15). It was also found that the same system in the absence of Chloramine-T/K_2CO_3 affords smoothly aziridine ring opening products, such as β-iodoethylamines (**8**). We have observed that aziridine ring opening occurs regioselectively.



Scheme 2.15

Mainly we have optimized the reaction conditions by varying the amount of $NaIO_4$ and $NH_2OH·HCl$, Chloramine-T, K_2CO_3 and solvent as shown in Table 2.6 using simple styrene (**1a**) as a model substrate. All reactions were carried out on 1 mmol scale in room temperature. Initially we have taken 1 equiv. of $NaIO_4$, $NH_2OH·HCl$, Chloramine-T, K_2CO_3 in 5 mL of dichloromethane (DCM) and no desired product (**1a**) was observed after 14 h (entry 1, Table 2.6). Further increment in the amount of all of these reagents same results were obtained in each case (entries 2-6, Table 2.6). Then we turned our attention to change the solvent and we have seen that the use of a mixture of DCM and acetonitrile (1:1 v/v) as the solvent yielded compound (**1a**) in 52% in presence of 1 equiv. of all the reagents (entry 7, Table 2.6). It indicated that the binary solvent system might play an important role for this conversion. Then by increasing the proportion of $NH_2OH·HCl$ from 1 to 1.5 we got the desired product (**1a**) in 74% yield (entry 8, Table 2.6). Further increasing the amount of all the reagents in different ratios the yields did not improve significantly (entries 9-11, Table 2.6) but by decreasing yields decreased (entries 12-14, Table 2.6). In absence of Chloramine-T or K_2CO_3 the reaction did not proceed at all (entries 15 and 16, Table 2.6). We have also investigated the role of solvent for this reaction and observed that solvent plays a crutial role in the reaction. Only DCM and acetonitrile mixture act as a good solvent for these particular reactions. Here it must be mentioned that the reaction did not proceed at all when only DCM or acetonitrile was used (entries 4 and 17, Table 2.6). In presence of some common solvents such as toluene, DCE, DMSO

the formation of desired product was not observed (entries 18-22, Table 2.6). So finally, we have considered optimized reaction conditions using 1 equiv. of $NaIO_4$, 1.5 equiv. of $NH_2OH{\cdot}HCl$, 1 equiv. of Chloramine-T and 1 equiv. of K_2CO_3 with respect to the 1 equiv. of styrene (**7a**) in 5 mL of DCM and acetonitrile mixture (1:1 v/v) at room temperature for 14 h (entry 8, Table 2.6).

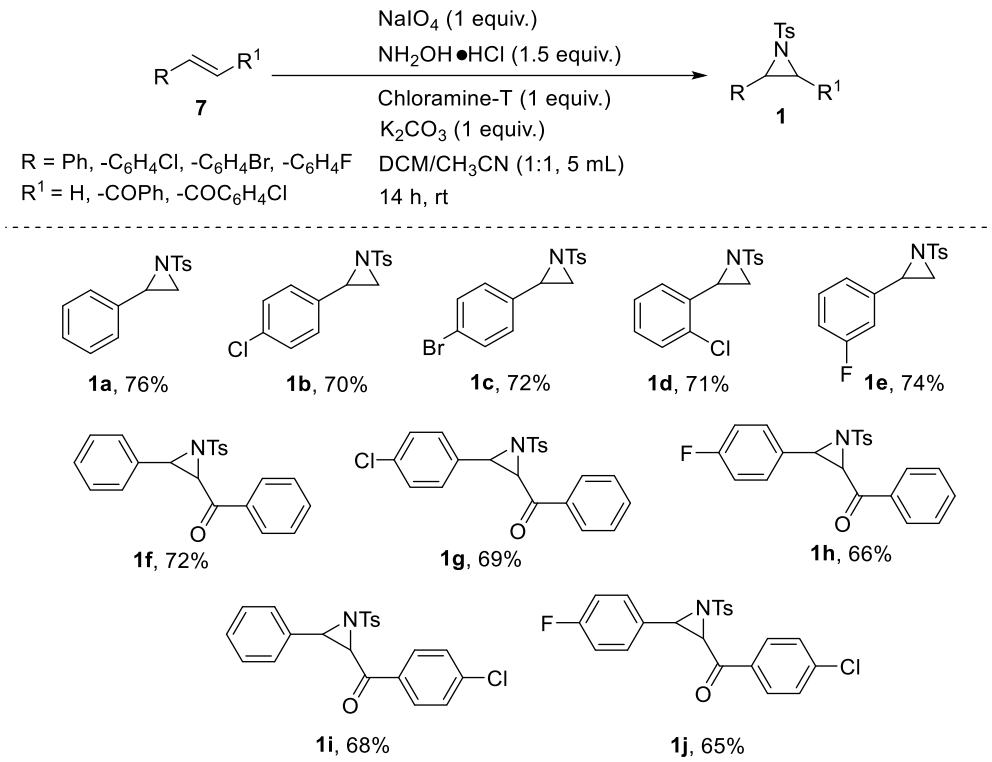
Table 2.6. Optimization of the reaction conditions.[a]

Entry	$NaIO_4$ (equiv.)	$NH_2OH{\cdot}HCl$ (equiv.)	Chloramine-T (equiv.)	K_2CO_3 (equiv.)	Solvent (5 mL)	Yield[b](%)
1	1	1	1	1	DCM	0%
2	1	1	2	1	DCM	0%
3	1	1	1	2	DCM	0%
4	1	1.5	1	1	DCM	0%
5	1	2	1	1	DCM	0%
6	1.5	1	1	1	DCM	0%
7	1	1	1	1	DCM:CH_3CN (1:1)	52%
8	1	1.5	1	1	DCM:CH_3CN (1:1)	76%
9	1.5	1.5	1	1	DCM:CH_3CN (1:1)	72%
10	1	1.5	1	2	DCM:CH_3CN (1:1)	71%
11	1	1.5	2	1	DCM:CH_3CN (1:1)	72%
12	1	1.5	1	0.5	DCM:CH_3CN (1:1)	58%
13	1	1.5	0.5	1	DCM:CH_3CN (1:1)	56%
14	0.5	1.5	1	1	DCM:CH_3CN (1:1)	35%
15	1	1.5	-	1	DCM:CH_3CN (1:1)	0%
16	1	1.5	1	-	DCM:CH_3CN (1:1)	0%
17	1	1.5	1	1	CH_3CN	0%
18	1	1.5	1	1	Toluene	0%

19	1	1.5	1	1	DCE	0%
20	1	1.5	1	1	DCE:CH_3CN (1:1)	20%
21	1	1.5	1	1	DMSO	0%
22	1	1.5	1	1	DMSO:CH_3CN(1:1)	0%

[a]***Reaction conditions:*** 1 mmol of styrene (**7a**) with various proportions of $NaIO_4$, $NH_2OH{\cdot}HCl$, Chloramin-T and K_2CO_3 in solvent (5 mL). [b]Isolated yields.

After getting the optimized reaction conditions in hand, we have investigated the substrates scope of this protocol and the results are presented in Scheme 2.16. At first, our attention was focused on the use of different olefinic systems with various substitutions to prove the general applicability of the reaction conditions. It was observed that the simple styrene including the styrene containing an electron withdrawing halogen group on the aromatic ring showed good efficiency (**1a**-**1e**). Among them the 4-chloro- and 2-chloro-substituted styrenes gave the corresponding products (**1b**) and (**1d**) in 70% and 71% yields respectively without forming any dehalogenated products. Other electron withdrawing substituents like bromo- and fluoro- group on styrene moiety also afforded the desired products with satisfactory yields (**1c** and **1e**). In addition, different *α,β*-unsaturated carbonyl compounds were also subjected to this reaction condition which obviously increased the efficiency of the present protocol. Aziridination of chalcones is of great interest because such aziridines can act as synthons for the synthesis of biologically active compounds. The present method is equally effective for simple chalcone as well as substituted chalcones to produce the corresponding aziridines (**1f-1j**). Chalcones containing halogen groups like -Cl and -F in phenyl ring successfully gave the desired products without any difficulties (**1g**, **1h**, **1i** and **1j**) under the present reaction conditions. All of the known synthesized compounds have been characterized by spectral data and the new compounds by both spectral data and analytical analysis. The single crystal X-ray analysis of the compound (**1f**, CCDC 1494352) was performed to confirm the structure by X-ray (Figure 2.3). The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials.

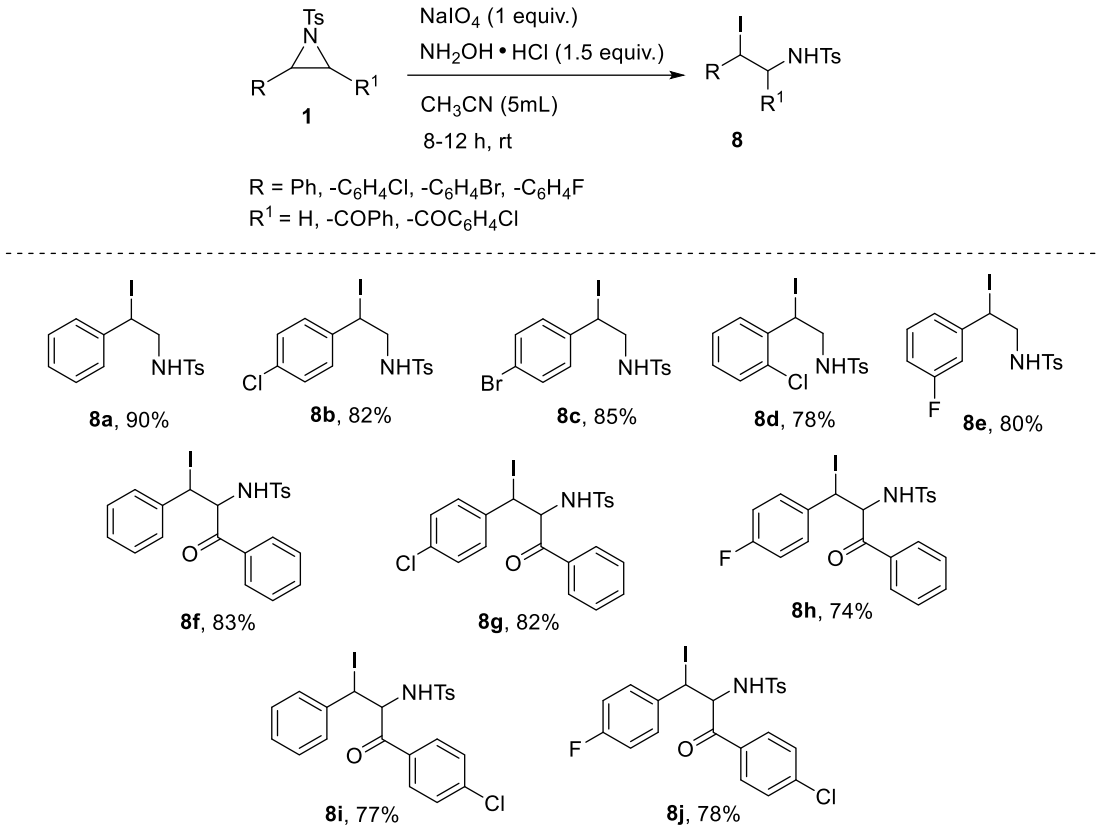


Scheme 2.16

Figure 2.3. X-Ray crystallographic data for the structure of compound (**1f)**

$NaIO_4$ and $NH_2OH{\cdot}HCl$ system was mentioned previously as good and mild oxidizing agent and a very good source of *in situ* generator of iodine, and this was demonstrated in case of aziridine synthesis starting from styrenes. Next the attention was focused for the regioselective ring opening of the synthesized aziridines (**1**) as products of transformation of styrenes under the developed conditions. We have found that the above mentioned system can be used for the aziridines ring opening using $NaIO_4$ and $NH_2OH{\cdot}HCl$ as iodine source. As a result we have obtained the corresponding ring opening products (**8**) in good yields, and the ring opening occurred in a regioselective manner and all the results are summarized in Scheme 2.17.

All the synthesized aziridines gave the desired ring opening products without any difficulties. The general applicability of this reaction was highlighted through the smooth reactions of simple and substituted aziridines towards ring opening (**8b**-**8e**). Also the aziridines from chalcone and substituted chalcones underwent smooth ring opening reaction regioselectively using the same reagents combination (**8f-8g**). We have used only acetonitrile as a solvent for this ring opening reactions. We have not studied much about the optimization of this ring opening step but found that no need to use DCM, only acetonitrile is effective. For all reaction combinations we have not observed the formation of any by-products and also the protocol was supported with high yields and high regioselectivity.

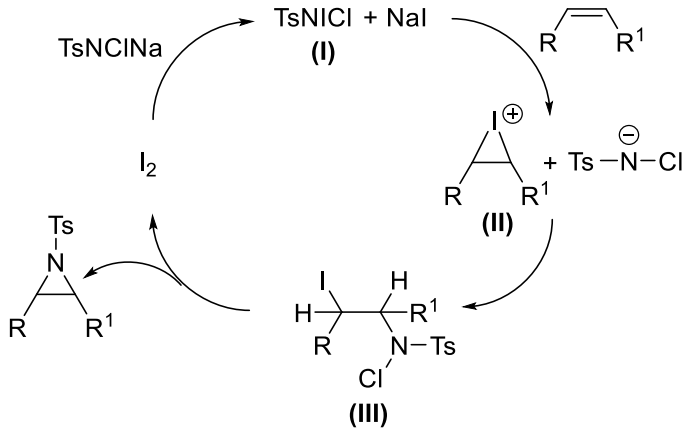


Scheme 2.17

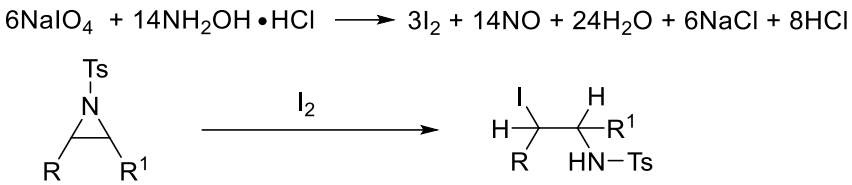
We have assumed a possible mechanistic pathway for the both synthesis and ring opening of aziridine (Scheme 2.18). Thus, as a first step, the *in situ* generated iodine acts as the source for the generation of the I^+ ion. Initially, I^+ may react with the chloramine-T to produce specie [**I**], which then reacts with the olefin to afford the iodonium ion [**II**]. Then the reaction of the TsNCl $^{\ominus}$ with iodonium ion [**II**] produces *β*-iodo-*N*-chloro-*N*-toluenesulfonamide (**III**). Finally, cyclization of (**III**) leads to the formation of the desired aziridine in presence of basic medium. The reaction between chloramine-T and regenerated iodine forming species [**I**] completing the

suggested pathway. Whereas the ring opening is a simple nucleophilic ring opening of aziridines using *in situ* generated iodine as nucleophile in the same reaction conditions.

For aziridination:



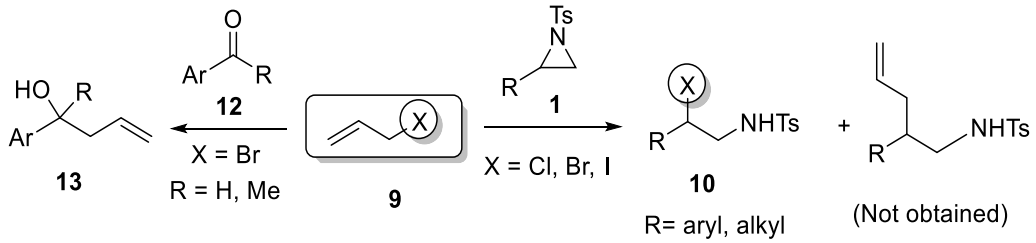
For ring opening of aziridine:



Scheme 2.18

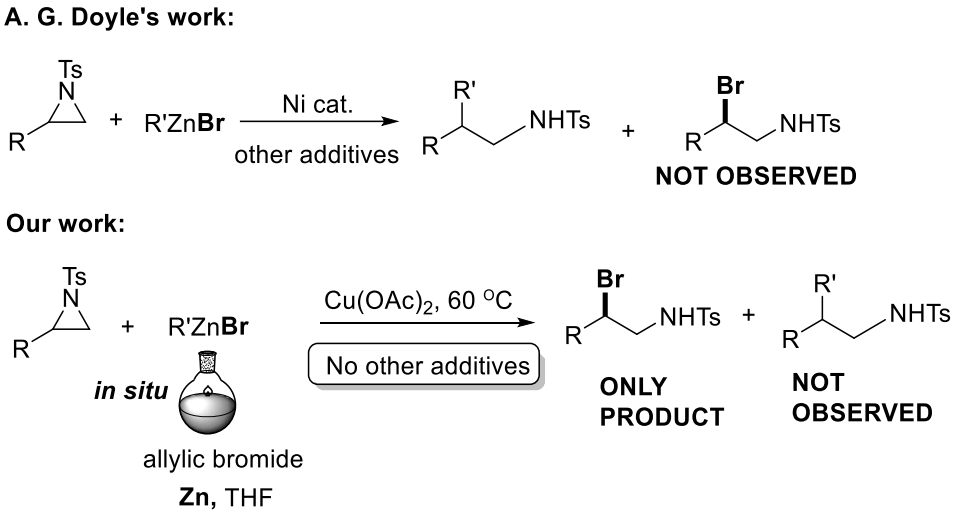
2.5. DIFFERENTIAL ADDITION OF NUCLEOPHILES TO AZIRIDINES AND ALDEHYDES UNDER SIMILAR REACTION CONDITIONS BY USING ALLYLZINC HALIDE AS A SOURCE OF HALIDE

In order to expand the range of nucleophiles, we studied the interaction of *N*-Ts-aziridines with C-nucleophiles, namely allylic zinc halide generated *in situ* by the interaction of allyl halides with zinc dust. Thus, instead of formation expected allylation products (**13**) as it can be observed for the carbonyl compounds under the allylation conditions azyridines formed the corresponding *β*-halogenetated-*N*-ethylsulphamides (**10**) (Scheme 2.19). In this case, the allylic zinc halide is the source of halide acting as a nucleophile. The main advantages of the present procedure are easy to handle, no need for inert atmosphere, mild reaction conditions, and applicability to a wide variety of substrates for aziridines and carbonyl compounds.



Scheme 2.19

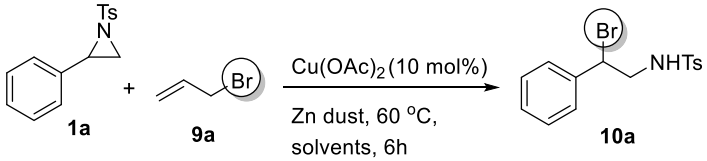
Initially, we were studied the possibility of nucleophilic ring opening of aziridine by allylation for which, *N*-tosylaziridines (**1a**) (1 mmol) and allylic bromide (**9a**) (3 mmol) were taken as substrates in presence of zinc dust (1 mmol) as reported by Doyle *et al.* [13] at room temperature using $Cu(OAc)_2$ as additive. We have observed in the change of the starting material after 12 h. Afterwards we carried out the same reaction at 60 °C and observed a considerable conversion of aziridine to our expected ring opening product. After careful workup and purification, surprisingly we found that the corresponding ring opening product of aziridine under these conditions using the additive $Cu(OAc)_2$ is not the allylation product but it is the ring opening product of aziridine by bromide as a nucleophile **(**Scheme 2.20**)**.



Scheme 2.20

In view of complete understanding and optimizing this observation the reaction was carried out in various organic solvents such as THF, DMSO, DMF, acetonitrile, 1,2-DCE, toluene, 1,4-dioxane, ethanol, etc. at 60 °C temperature. The results are summarized in Table 1. Either moderate or trace amount of the desired product was observed in DMSO, DMF, acetonitrile, 1,2-DCE, toluene, 1,4-dioxane and ethanol (Table 2.7, entries 2 to 8) as a solvent. Whereas the targeted product was obtained with maximum yield (84%) in THF solvent at 60 °C for 6 h (Table 2.7, entry 1), no significant amount of the desired product was formed when the reaction was carried out at room temperature (Table 2.7, entry 10). The best effective reaction temperature was found to be 60 °C (Table 1, entry 1) and the yield of the reaction did not improve by increasing the reaction time from 6 h to 9 h (Table 1, entry 11). The increase of the temperature was not beneficial (Table 2.7, entry 12) while decreasing the reaction temperature decreased the yield of the reaction (Table 2.7, entries 13). The use of $Cu(OAc)_2$ (10 mol%) gave the best result with excellent yield.

Table 2.7. Screening of the solvent effects.[a]



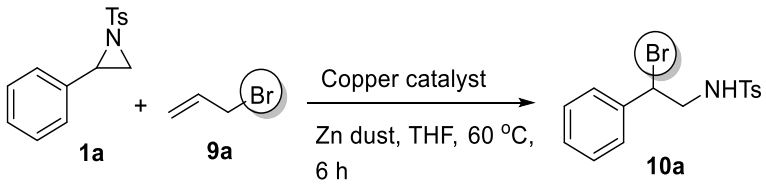
Entry	Solvents (2 mL)	Yields[b] (%)
1	THF	84
2	DMSO	32
3	DMF	Trace
4	CH_3CN	29
5	1,2-DCE	51

6	Toluene	35
7	1,4-Dioxone	42
8	EtOH	18
9	-	0
10[c]	THF	Trace
11[d]	THF	83
12[e]	THF	80
13[f]	THF	62

[a]***Reaction condition:*** A mixture of **1a** (1 mmol) and **9a** (3 mmol) was heated at 60 °C for 6 h in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of Zn dust. [b] Isolated yields. [c] Reaction was carried out at room temperature. [d] Reaction time 9 h. [e] Reaction was carried out at 80 °C. [f] Reaction was carried out at 50 °C.

The reaction has also been carried out by using other copper salts (10 mol% each) such as $CuCl_2$, CuI, $CuBr_2$, $Cu(OTf)_2$, Cu_2O, CuO nano, etc. (Table 2.8**)** and they were not so efficient like $Cu(OAc)_2$. Increasing the amount of $Cu(OAc)_2$ from 10 to 20 mol% resulted in no significant change in the formation of the product (Table 2.8, entry 8). On decreasing the amount from 10 mol% to 5 mol% there was a notable decrease in product formation (Table 2.8, entry 9). The reaction did not proceed at all without any catalyst (Table 2.8, entry 10). In addition, in presence of other catalyst such as $AgNO_3$, no formation of (**10a**) was observed rather some other compound was obtained (Table 2.8, entry 10).

Table 2.8. Effects of various copper catalysts.[a]



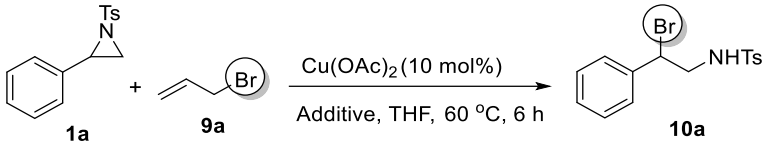
Entry	Catalyst (mol%)	Yields[b] (%)
1	$Cu(OAc)_2$ (10)	84
2	$CuCl_2$ (10)	67
3	CuI (10)	56
4	$CuBr_2$ (10)	69
5	$Cu(OTf)_2$ (10)	48
6	Cu_2O (10)	40
7	CuO nano (10)	62
8	$Cu(OAc)_2$ (20)	84
9	$Cu(OAc)_2$ (5)	65

10	-	0
11	$AgNO_3$	0

[a]***Reaction condition:*** A mixture of **1a** (1 mmol) and **9a** (3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of different copper catalysts and 1 mmol of Zn dust. [b] Isolated yields.

In addition, Zn dust also made a vital contribution to the reaction to proceed (Table 2.9, entry 1). No reaction was observed without zinc dust (Table 2.9, entry 2), and the use of indium powder instead of Zn dust did not afford any product (Table 2.9, entry 3).

Table 2.9. Effects of other metal on the halogenation reaction.[a]

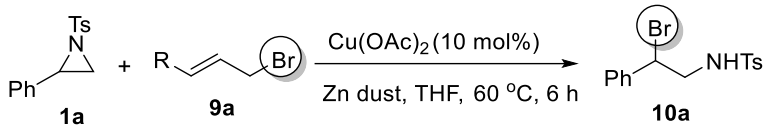


Entry	Metal	Yields[b] (%)
1	Zn dust	84
2	-	0
3	Indium dust	Trace

[a]***Reaction conditions:*** A mixture of **1a** (1 mmol) and **9a** (3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of different additives.

The use of other allylic bromides like crotyl bromide or cinnamyl bromide gave no response as a source of bromine (Table 2.10, entry 2, entry 3). Accordingly, our final optimized reaction condition was achieved using *N*-tosylaziridine (1 mmol) with allylic bromide (3 mmol) in the presence of 10 mol% copper acetate, Zn dust (1 mmol) and THF solvent at 60 °C temperature to give the corresponding halogenated product under ambient air.

Table 2.10. Effects of different allylic bromides on the halogenation reaction.[a]



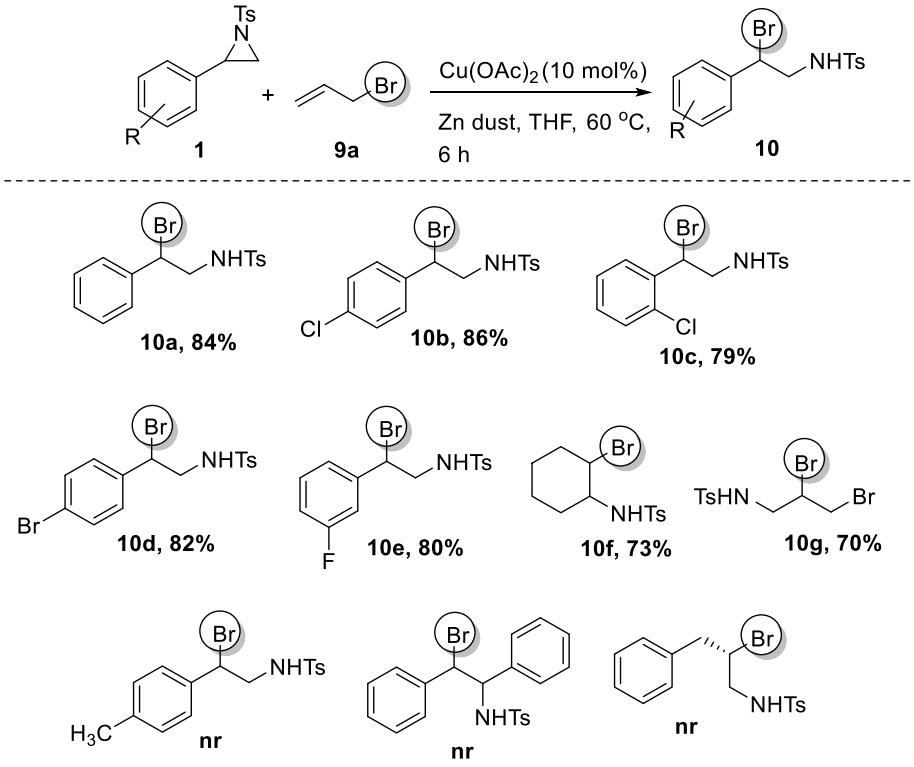
Entry	R	Yields[b] (%)
1	H	84
2	CH_3	NR
3	Ph	NR

[a] ***Reaction conditions:*** A mixture of **1a** (1 mmol) and **9** (3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of Zn dust. [b] Isolated yields. NR = No reaction.

After optimizing the reaction conditions, we explored the scope of this reaction (Table 2.11). At first, our attention was focused on the use of different aziridine systems with various

allylic halides to prove the general applicability of the reaction conditions and the results are summarized in Table 2.11. It was observed that allylic bromide, allylic chloride, and allylic iodide reacted efficiently with various aziridines to afford the desired products with good yields under the present reaction conditions. Simple phenyl *N*-tosylaziridine (**1a**) reacted well with allylic bromide to give the desired product with good yield (**10a**). Similarly, aryl *N*-tosylaziridine substituted with chloro in the benzene ring was found quite effective to afford the desired products (**10b** and **10c)** with excellent yield. Aziridines, substituted by other halogens (such as –Br, -F) underwent smooth reactions with allylic bromide which highlighted the general applicability of this reaction (**10d** and **10e**). In addition, the aliphatic aziridine systems were also investigated under the present reaction conditions and reacted smoothly with allylic bromide to afford the brominated amines (**10f** and **10g**).

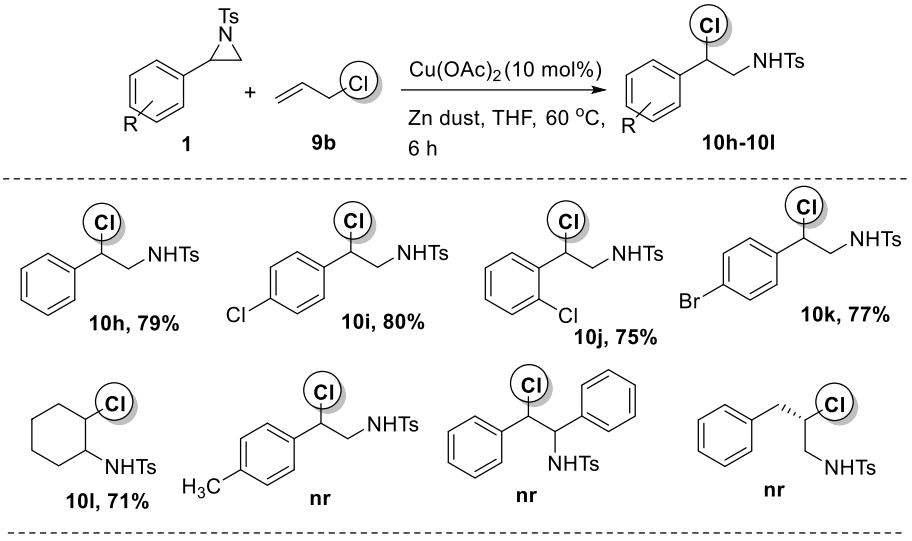
Table 2.11. Scopes and limitations of the present protocol.



Reaction conditions: A mixture of aziridine (**1**, 1 mmol) and allylic bromide (**9a**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of Zn dust.

Next, we turned our attention using another allylic halide namely allylic chloride (**9b**) with various substituted aziridine systems (Table 2.12). *N*-Tosylaziridine substituted with various functionalities (such as –Cl, -Br) at the benzene ring underwent smooth reaction (**10h-10k**). Aliphatic aziridine also reacted smoothly with allylic chloride to give the desired chlorinated amine (**10l**) with good yield.

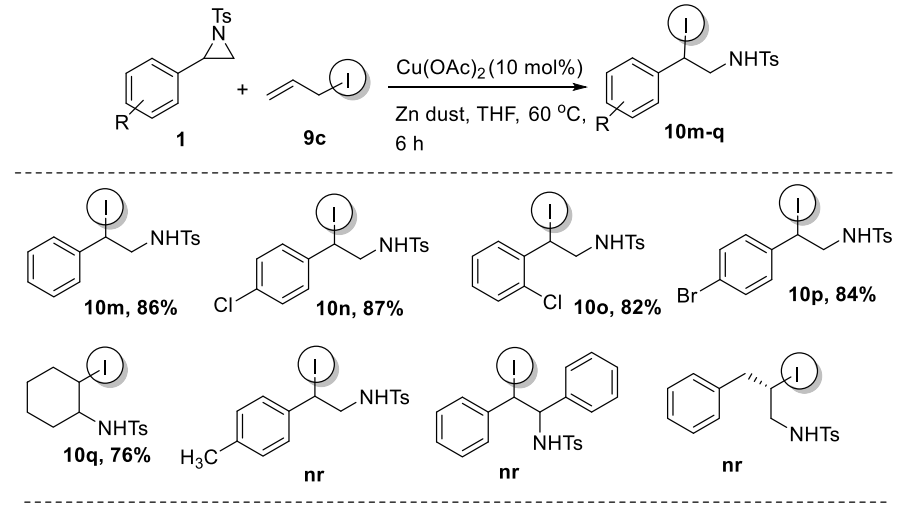
Table 2.12. Scopes and limitations of the present protocol.



Reaction conditions: A mixture of aziridine (**1**, 1 mmol) and allylic chloride (**9b**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of Zn dust.

We have successfully used allylic iodide to synthesize the corresponding compounds (**10m-q**) which increases the scope of this transformation (Table 2.13). Both aryl *N*-tosylaziridine (**1a**) and chloro- and bromo-substituted aryl *N*-tosylaziridine reacted smoothly with good yields (**10n-p**). The aliphatic aziridine system also gave the desired product (**10q**). *N*-Tosylaziridine with electron-donating group like methyl did react with all three halides under the optimized reaction conditions. Again, *N*-tosylziridines derived from *cis*-stilbene and another enantiomerically pure (*S*)-2-benzyl-1-tosylaziridine were also inert under the present reaction condition.

Table 2.13. Scopes and limitations of the present protocol.



Reaction conditions: A mixture of aziridine (**1**, 1 mmol) and allylic iodide (**9c**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% Cu(OAc)2 and 1 mmol of Zn dust.

All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. X-Ray crystallographic analysis of *N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (**10l,** CCDC 1835222) was performed to confirm the structure of the product as shown in Figure 2.4. The reaction conditions are mild enough and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations giving rise to high yields of desired products and regioselectivity of the protocol. In all the cases the halide part has been introduced as a nucleophile.

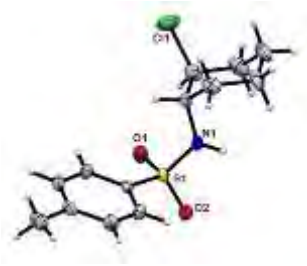
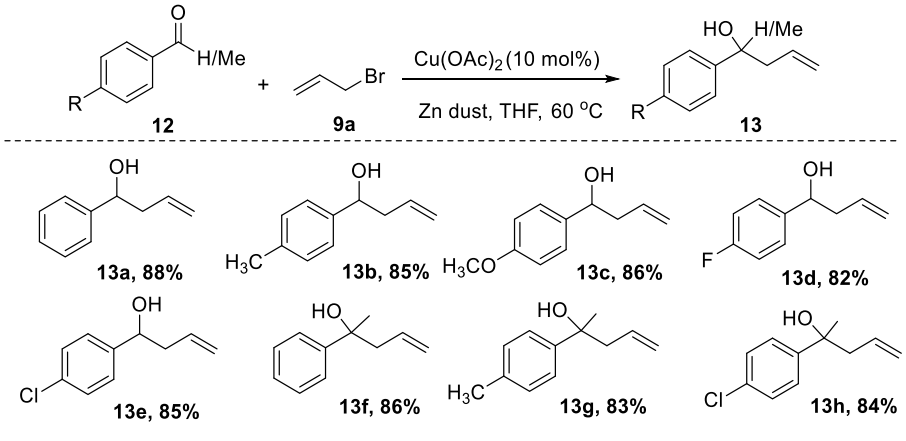


Figure 2.4. X-Ray crystallographic data for the structure of compound (**10l**).

Before coming to any conclusion based on the above observation, we thought to explore the same reaction conditions using the carbonyl compounds where the halide addition in the carbonyl functionality is not usual. To our delight, we observed the expected result and got the homoallylic alcohol as the sole product (Table 2.14). First, we have tested various aryl aldehydes substituted with various functionalities. Both electron-donating, as well as electron-withdrawing substituents, afforded the desired allylation products (**13a**-**13e**) with excellent yields. Next, we have also examined a few acetophenone derivatives which underwent allylation reaction in very good yields (**13f**-**13h**).

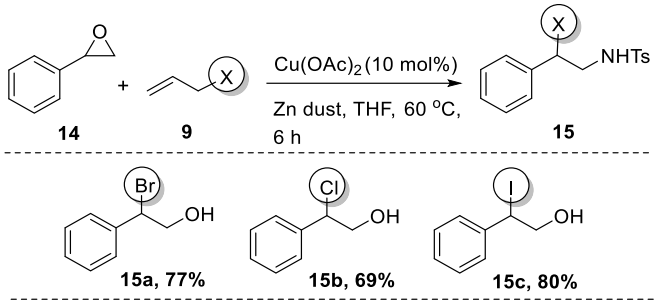
Table 2.14. Reaction of aldehydes and ketones with allylic bromide.



Reaction conditions: A mixture of aldehyde or ketone (**12**, 1 mmol) and **9a** (3 mmol) was heated in THF (2 mL) at 60 °C in presence of 10 mol% $Cu(OAc)_2$ and 1 mmol of Zn dust.

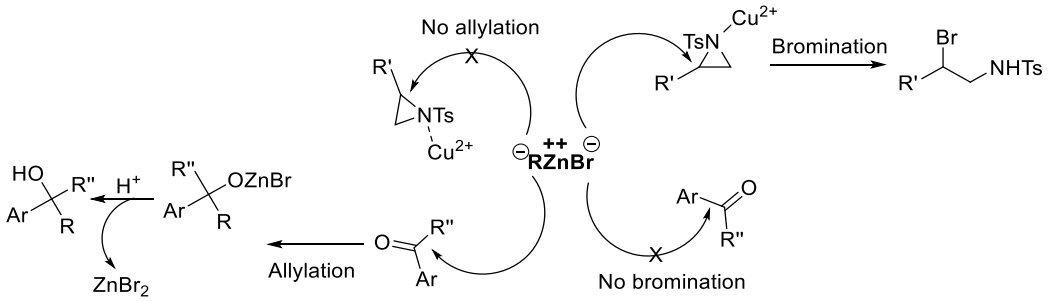
The present protocol has also been examined for epoxides and it is worthy to mention that styrene epoxide (**14**) reacted smoothly with these three allylic halides (Table 2.15); yielding the corresponding products (**15a**), (**15b**) and (**15c**) in 77%, 69%, and 80% yields, respectively.

Table 2.15. Scope of the epoxide in the reaction with allylic halides.



Reaction conditions: A mixture of epoxide (**1**, 1 mmol) and allylic halide (**2**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% Cu(OAc)2 and 1 mmol of Zn dust.

It is worthy to mention that we have optimized the reaction time using only allyl bromide and within 6h the reaction completed. We have found the same reaction time for allyl chloride as well as iodide also. So, from this observation, we may conclude that under the reaction conditions zinc allylic halide possesses ambident nucleophilic character where both the allylic and halide are active nucleophiles which is not observed usually. The zinc allylic halide is formed under the experimental conditions and the $Cu(OAc)_2$ acts as the catalysis to activate the carbonyl group as well as aziridine ring. In the case of carbonyl compound, two competitive nucleophiles may add but as the addition of halide is not thermodynamically favorable due to the elimination of hydrogen halide from the *gem* halohydrin, the resulting product is the homoallylic alcohol; whereas, in case of aziridines, the halide ion is a better nucleophile. Thus the halide ion readily attacks the available electrophilic carbon in the aziridine as the zinc allylic species is relatively bound and produces the corresponding nucleophilic ring opening [19] product of aziridine in presence of Lewis acid. The probable mechanism of this observation is described in Scheme 2.21.

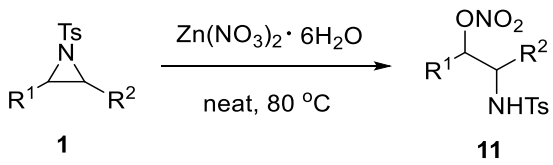


Scheme 2.21

2.6. SYNTHESIS OF *β*-(NITROOXY)-SUBSTITUTED AMINES BY REGIOSELECTIVE RING OPENING OF AZIRIDINES

It should be noted that, for the above-mentioned reaction, in the case of 2,3-tetramethylenaziridine (aziridine condensed with cyclohexane), when using other salts instead of copper(II) acetate, for example, copper(II) triflate, silver(I) triflate, a significant decrease in the yield of the target product was observed (as low as 15%). In the case of the use of copper(II) nitrate, as well as silver(I) nitrate, an unexpected product (**11j)** was observed in the reaction mass, the structure of which was determined by the X-ray method (Figure 2.5). Based on the higher yield of product (**11j)** (up to 20%) in the case of silver(I) nitrate, we assumed that the reaction proceeds due to the *in situ* formation of zinc(II) nitrate, as the reaction between Zn dust and $AnNO_3$ can be used for the obtaining of $Zn(NO_3)_2$. In confirmation of this, a reaction was carried out with commercially available zinc(II) nitrate (in the form of hexahydrate) in the absence of allylic halides, and as a result, an increase in the yield to 90% of the expected *β*-(nitrooxy)-amine product (**11j)** was observed.

Eventually, we were interested to develop a convenient and environment friendly method for regioselective ring opening of aziridines with $Zn(NO_3)_2 \cdot 6H_2O$ to afford *β*-(nitrooxy)-amines (Scheme 2.22). The reactions proceeded under neat conditions with high regioselectivity.

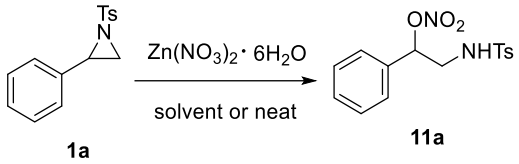


Scheme 2.22

For the initial study, 1 mmol of 2-phenyl-1-tosylaziridine (**1a**) was used as the model substrate to optimize the reaction conditions employing 1 equiv. of $Zn(NO_3)_2 \cdot 6H_2O$ as the nitrate source. Initially the reaction was carried out in various organic solvents such as 1,2-DCE, DCM, 1,2-DCB, THF, 1,4-dioxane, acetonitrile, DMF, toluene, etc., as well as in aqueous medium. The results are summarized in Table 2.16. First of all, the desired product (**11a)** was obtained in 80% yield in 1,2-DCE solvent after heating at 80 °C for 1 h (Table 2.16, entry 1). Further increasing the reaction time no increase in yield was observed (Table 2.16, entry 2). Either no formation or trace amount of the desired product was observed in 1,2-DCB, THF, 1,4-dioxane, acetonitrile, DMF, toluene and in water (Table 2.16, entries 5–11). In the case of DCM the desired product was obtained in 63% yield (Table 2.16, entry 4). No result was obtained at room temperature in 1,2-DCE (Table 2.16, entry 3). The targeted product was obtained in maximum yield (90%) under

solvent-free conditions at 80 °C for 1 h (Table 2.16, entry 12). By further increasing the amount of $Zn(NO_3)_2 \cdot 6H_2O$ no increase in yield was observed (Table 1, entries 13 and 14). Next the effects of reaction time and temperature on the reaction were also investigated. No significant amount of the desired product was formed when the reaction was carried out at room temperature (Table 2.17, entry 1). The best effective reaction temperature was found to be 80 °C (Table 2.17, entry 4) and the yield of the reaction did not improve by increasing the reaction time from 1 h to 3 h (Table 2.17, entry 5). Increasing the temperature was not beneficial (Table 2.17, entry 6) while decreasing the reaction temperature decreased the yield of the reaction (Table 2.17, entries 2 and 3).

Table 2.16. Screening of solvent effects.[a]



1a **11a**

Entry	Amount of $Zn(NO_3)_2 \cdot 6H_2O$	Solvent	Time (h)	Temp (°C)	Yields[b] (%)
1	1 equiv.	1,2-DCE	1	80	80
2	1 equiv.	1,2-DCE	2	80	80
3	1 equiv.	1,2-DCE	1	rt	nd
4[c]	1 equiv.	DCM	1	50	63
5	1 equiv.	1,2-DCB	1	80	nd
6	1 equiv.	THF	1	80	<10
7	1 equiv.	1,4-Dioxane	1	80	nd
8	1 equiv.	CH_3CN	1	80	<10
9	1 equiv.	DMF	1	80	nd
10	1 equiv.	toluene	1	80	nd
11	1 equiv.	H_2O	1	80	nd
12	1 equiv.	neat	1	80	90
13	1.5 equiv.	neat	1	80	90
14	2 equiv.	neat	1	80	88

[a]***Reaction conditions:*** 1 mmol of **1a** was reacted with $Zn(NO_3)_2 \cdot 6H_2O$ in various solvents or neat conditions. [c]Reaction was carried out under reflux condition. nd = Not detected in TLC.

Table 2.17. Temperature effect on the ring opening reaction.[a]

Entry	Temp. (°C)	Time (h)	Yields[b] (%)
1	rt	12	<10
2	40	1	35
3	60	1	64
4	80	1	90
5	80	3	87
6	100	1	85

[a]***Reaction conditions:*** 1 mmol of **1a** was reacted with $Zn(NO_3)_2 \cdot 6H_2O$ in various solvents or neat conditions. [b]Isolated yields.

We have examined a few other metal salts as shown in Table 2.18 in both in 1,2-DCE and neat conditions. It has been observed that other metal salts such as $Cu(NO_3)_2 \cdot 3H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$ are not such effective as $Zn(NO_3)_2 \cdot 6H_2O$ for this ring opening process. When 1 equiv. of $Cu(NO_3)_2 \cdot 3H_2O$ was used in neat as well as in 1,2-DCE; 60% and 63% yields were observed respectively (Table 2.18, entries 2 and 3). $Fe(NO_3)_3 \cdot 9H_2O$ was also not so effective like $Zn(NO_3)_2 \cdot 6H_2O$; 40% and 72% yield were obtained in neat and 1,2-DCE (Table 2.18, entries 4 and 5). Thus the optimal yield (90%) was obtained when the reaction was carried out employing 1 equiv. of $Zn(NO_3)_2 \cdot 6H_2O$ with respect to compound (**1a**) at 80°C under solvent-free conditions for 1 h.

Table 2.18. Effects of various nitrate sources.[a]

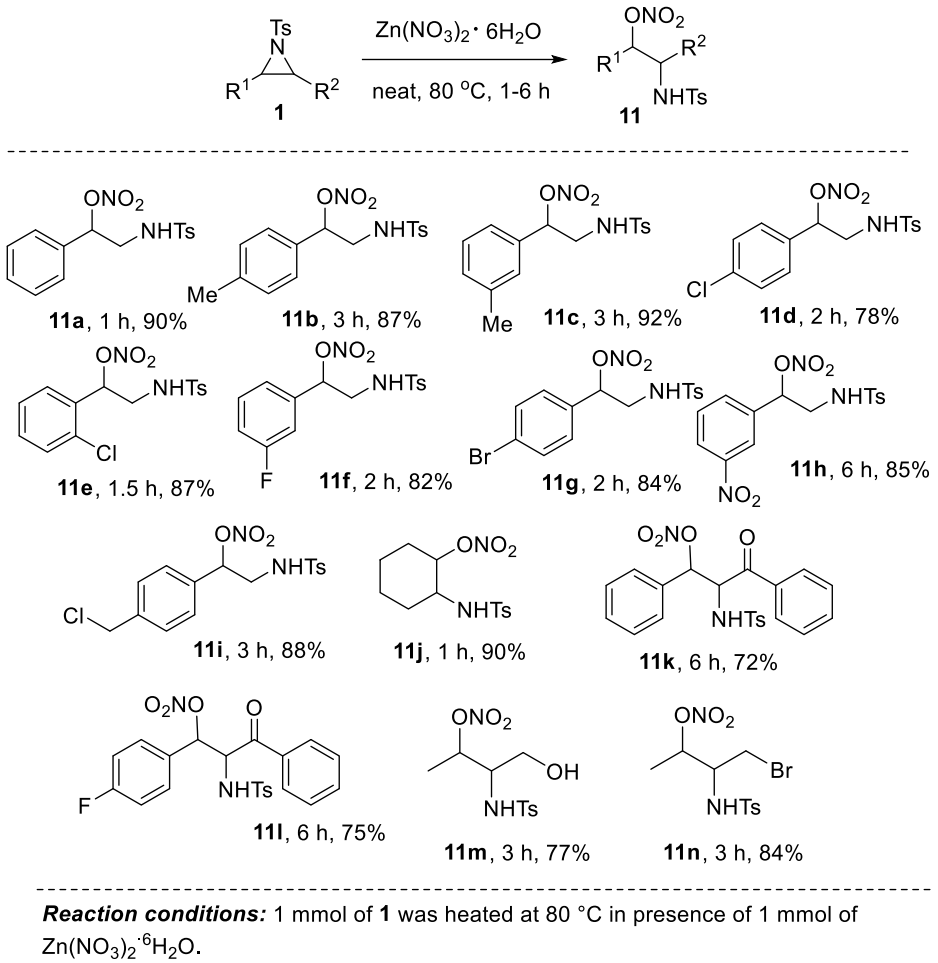
Entry	Metal salts (amount)	Solvent	Yield[b] (%)
1	$Zn(NO_3)_2 \cdot 6H_2O$ (1 equiv.)	neat	90
2	$Cu(NO_3)_2 \cdot 3H_2O$ (1 equiv.)	neat	60
3	$Cu(NO_3)_2 \cdot 3H_2O$ (1 equiv.)	1,2-DCE	63
4	$Fe(NO_3)_3 \cdot 9H_2O$ (1 equiv.)	neat	40
5	$Fe(NO_3)_3 \cdot 9H_2O$ (1 equiv.)	1,2-DCE	72

[a]***Reaction conditions:*** 1 mmol of **1a** was heated at 80 °C in presence of 1 mmol of various nitrate sources. [b]All are isolated yields. nd = Not detected in TLC.

After having the optimized reaction conditions in hand, various aziridines (**1**) were introduced to react with $Zn(NO_3)_2 \cdot 6H_2O$ to prove the general applicability of this methodology. The results are summarized in Table 2.19. In most of the cases the desired products were obtained in good to excellent yields (**11a**–**11n**). It was observed that electron-rich and electron-deficient aziridines reacted efficiently with $Zn(NO_3)_2 \cdot 6H_2O$ to afford the desired products with good yields under the present reaction conditions. Simple aryl *N*-tosylaziridine as well as methyl-substituted aziridines reacted well to give the desired products with high yields (**11a-11c**). Similarly, aryl *N*-tosylaziridines substituted with halogens such as chloro-, fluoro-, bromo- at the benzene ring was found to be effective to afford the desired products (**11d-11g**) in good yields. Aryl *N*-tosylaziridine substituted with nitro group as well as chloromethyl group underwent smooth reaction to afford high yield (**11h** and **11i**). It is noteworthy to mention that this present protocol is applicable to aliphatic aziridines also and gave satisfactory yields (**11j-11n**). Aziridines, substituted by different functional groups underwent smooth reactions which highlighted the general applicability of this reaction. In this regard, the effect of carbonyl functionalities as well as hydroxyl group in the aziridine system was also investigated where both of these functionalities were unaffected under the present reaction conditions and reacted smoothly $Zn(NO_3)_2 \cdot 6H_2O$ (**11k-11m**). To the best of our knowledge this is the first report for the synthesis of carbonyl-substituted nitrate derivatives. The other aziridine system such as 2-(bromomethyl)-3-methyl-1-tosylaziridine did not affect the efficiency and the regioselectivity of the reaction.

All these reactions were performed under an aerobic condition and are not sensitive to air and moisture. In addition, the reaction is highly *regio*-selective. We have observed that the product is very much regioselective for benzylic attack. No other regio-isomer was isolated under the present reaction conditions. After completion of the reaction, water and minimum amount of ethylacetate were added to the reaction mixture; by sequential separation and evaporation of solvent obtained the crude products. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported by high yields and *regio*-selectivity of the protocol. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data and X-ray crystallographic analysis of 2-(4-methylphenylsulfonamido)cyclohexyl nitrate (**11j**, CCDC 1549293) was performed to confirm the structure of the product as shown in Figure 2.5.

Table 2.19. Substrates scope.



Reaction conditions: 1 mmol of **1** was heated at 80 °C in presence of 1 mmol of $Zn(NO_3)_2{\cdot}^6H_2O$.

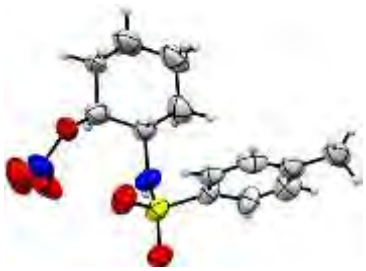
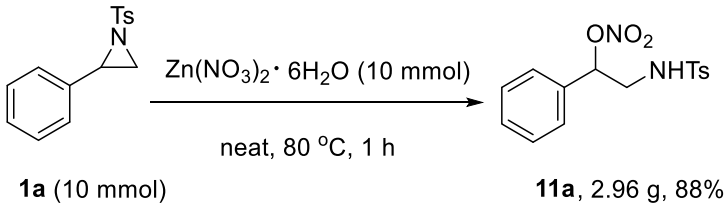


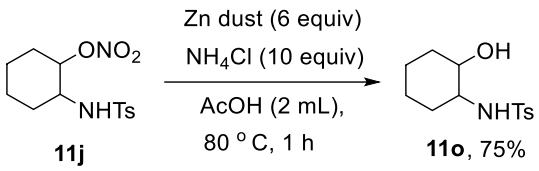
Figure 2.5. X-Ray crystallographic data for the structure of compound (**11j**).

Furthermore, the potential synthetic applicability of this method was investigated on the gram scale using the model reaction. As shown in Scheme 2.23, the reaction could afford 2.96 g of product (**11a)** in 88% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large scale synthesis of *β*-(nitrooxy)-substituted amine derivatives.



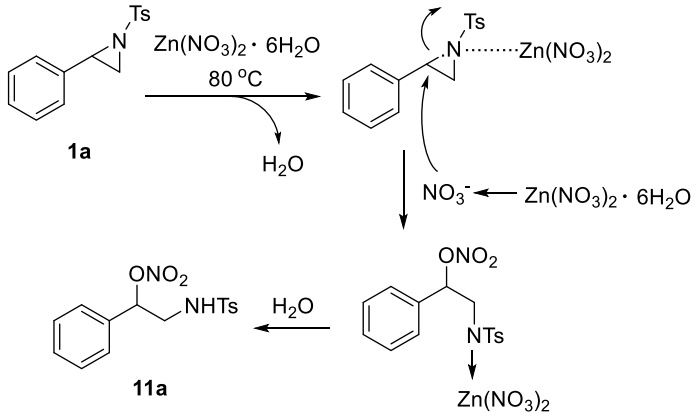
Scheme 2.23

The nitrooxy derivative could be easily transformed to a hydroxy derivative by applying a common reductive method (Scheme 2.24). The prevalence of 1,2-aminoalcohol motif has inspired the development of numerous synthetic approaches to this structural unit and its derivatives [345]. The 1,2-aminoalcohol motif is frequently found in a wide range of natural products, biologically active molecules, and important intermediates in many organic syntheses [346]. The desired *N-(*2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (**11o**) was obtained in 75% yield in presence of zinc dust and ammonium chloride in acetic acid medium.



Scheme 2.24

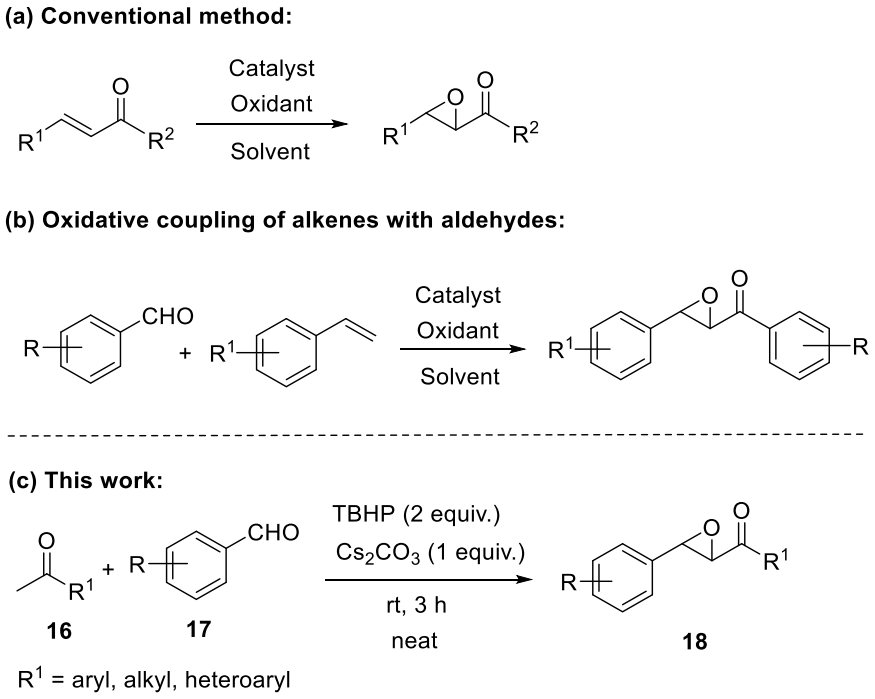
A probable pathway of the reaction may be explained by the dual role of the zinc nitrate (Scheme 2.25). The initial activation of the aziridine ring followed by the nucleophilic ring opening with nitrate ion where oxygen anion is the effective nucleophile gives the final product.



Scheme 2.25

2.7. A DOMINO APPROACH FOR THE SYNTHESIS OF *α,β*-EPOXYKETONES FROM CARBONYL COMPOUNDS

As part of the work, another type of model compounds were synthesized, namely *α,β*-epoxyketones. These heterocycles were also used as model substrates in the above mentioned reactions with allylhalides in the presence of Zn dust. In the frame of our work we have developed an efficient method for the synthesis of *α,β*-epoxyketones by one pot reaction between aldehydes and ketones in presence of cesium carbonate and *tert*-butyl hydrogen peroxide (TBHP) under neat conditions. In our methodology, we have used the one-pot domino type reaction with aldehydes and ketones to get *α,β*-epoxyketones without presynthesized chalcone precursors (Scheme 2.26c). So, in addition to the existing approaches, we have constructed the epoxide moiety through one pot two component coupling from readily available and simple starting materials employing metal-free catalysts with environmentally benign oxidants under solvent-free conditions.

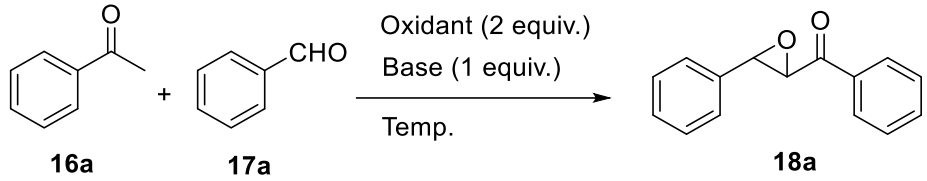


Scheme 2.26

Initially, we commenced our study by taking acetophenone (**16a,** 1 mmol) and benzaldehyde (**17a,** 1 mmol) as model substrates using *tert*-butyl hydrogen peroxide (TBHP, 2 equiv., 5.0-6.0 M in decane) as oxidant, cesium carbonate (Cs_2CO_3,1 equiv.) as a base at room temperature without using any solvent (Table 2.20, entry 1). To our delight, the reaction proceeded smoothly under these neat conditions and the desired product (**18a**) was isolated in 96% yield within 3 h. Then, to examine the efficiency of the oxidant we have tested different peroxides as shown in Table 1. When benzoyl peroxide was used a trace amount of desired product was isolated (Table 2.20, entry 2), whereas, no conversion has been detected in TLC in case of di-*tert*-butyl

peroxide (DTBP) and *tert*-butyl peroxybenzoate (TBPB) (Table 2.20, entries 3 & 4). As a result, TBHP was found to be an effective oxidant for this domino epoxidation. Other common bases like KOH, K_2CO_3 and Na_2CO_3 were not effective for this conversion (Table 2.20, entry 5, 6 & 7). Next, the effects of temperature and reaction time on the reaction were also investigated. No considerable changes have been found with respect to yield when the reaction was carried at higher temperature up to 80 °C (Table 2.20, entries 8 & 9) and the yield of the reaction did not improve by increasing or decreasing the reaction time (Table 2.20, entries 10 & 11).

Table 2.20. Optimization of the reaction conditions.[a]



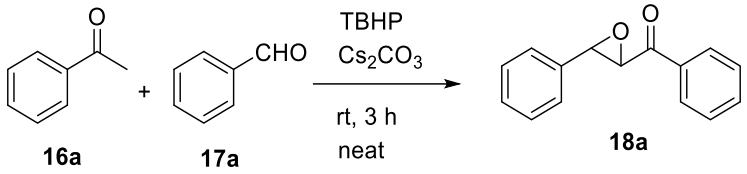
Entry	Oxidant	Base	Time (h)	Temp. (°C)	Yield[b](%)
1	**TBHP**	**Cs_2CO_3**	**3**	**rt**	**96**
2	Benzoyl peroxide	Cs_2CO_3	3	rt	trace
3	DTBP	Cs_2CO_3	3	rt	ND[c]
4	TBPB	Cs_2CO_3	3	rt	ND[c]
5	TBHP	KOH	3	rt	56
6	TBHP	K_2CO_3	3	rt	75
7	TBHP	Na_2CO_3	3	rt	trace
8	TBHP	Cs_2CO_3	5	50	75
9	TBHP	Cs_2CO_3	5	80	78
10	TBHP	Cs_2CO_3	1	rt	54
11	TBHP	Cs_2CO_3	5	rt	94

[a]***Reaction conditions:*** **16a** (1 mmol), **17a** (1 mmol) and various oxidants (2 equiv.), different bases (1 equiv.) at different temperatures under neat conditions, [b]Isolated yield, [c]ND = Not detected in TLC.

Next, we investigated the loading effect of oxidant (TBHP) and base (Cs_2CO_3) in different ratio as shown in Table 2.21. Using 0.5 equiv. of TBHP the yield was significantly lower (62%) (Table 2.21, entry 1) and when the amount was increased to 2 equiv. the desired product was obtained in 96% yield (Table 2.21, entry 3). Again, by using 4 equiv. of the oxidant no enhancement of the yield was noticed (Table 2.21, entry 4). Similarly by increasing the amount of Cs_2CO_3 from 1 to 2 equiv. no significant improvement of yield was observed (Table 2.21, entries 3, 6 & 7). With lowering the amount of base the yield was significantly changed (Table 2.21, entry 5). Even in the absence of TBHP and also Cs_2CO_3 no conversion has been detected in TLC (Table

2.21, entry 8 & 9). It is noteworthy to mention that in the presence of only base (Cs_2CO_3) we have observed the formation of only chalcone (Table 2.21, entry 9). So, from the above observations, we can conclude that using 2 equiv. of TBHP and 1 equiv. of the Cs_2CO_3 gave the best result (Table 2.21, entry 3).

Table 2.21. Loading effects of oxidant and base on the reaction.[a]

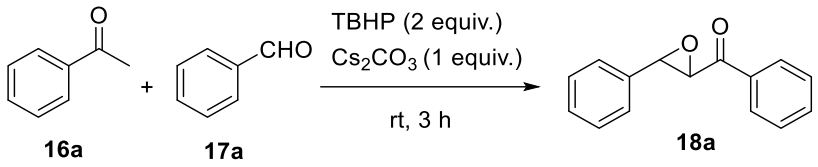


Entry	TBHP (equiv.)	Cs_2CO_3 (equiv.)	Yields[b] (%)
1	0.5	1	62
2	1	1	77
3	**2**	**1**	**96**
4	4	1	94
5	2	0.5	55
6	2	2	97
7	2	3	95
8	2	-	ND[c]
9	-	1	ND[d]

[a]***Reaction conditions:*** **16a** (1 mmol), **17a** (1 mmol) and TBHP (as stated amount,5.0-6.0 M in decane), Cs_2CO_3 (1 equiv.) at room temperature for 3 h under neat conditions, [b] Isolated yield, [c]ND = Not detected in TLC, [d]Chalcone was formed as sole product.

Though we have observed that the reaction underwent smoothly in absence of any solvent, a series of experiments have been carried out to examine the role of solvents if any (particularly for enhancement) which are summarized in Table 2.22. A nonpolar non-protic solvent like toluene showed the very small conversion of this reaction (Table 2.22, entry 1) and surprisingly in polar non-protic solvent DMSO, the reaction did not proceed significantly (Table 2.22, entry 2). In other non-protic polar solvents like DMF, 1,2-DCE, 1,4-dioxane and THF, the desired product was obtained in 40-64% yields (Table 2.22, entries 3,4,5 & 6). Whereas in the case of MeCN and DCM, the desired product was obtained in 68% and 76% yield respectively (Table 2.22, entries 7 & 8). The targeted product was obtained with maximum yield (96%) under solvent-free conditions at room temperature for 3 h (Table 2.22, entry 9). Thus the optimal yield (96%) was obtained when the reaction was carried out employing 2 equiv. of TBHP and 1 equiv. of Cs_2CO_3 at room temperature under solvent-free conditions for 3 h.

Table 2.22. Screening of the solvent effects.[a]



Entry	Solvent	Temp (°C)	Yield[b] (%)
1	Toluene	rt	15
2	DMSO	rt	<6
3	DMF	rt	40
4	1,2- DCE	rt	64
5	1,4- Dioxane	rt	52
6	THF	rt	58
7	MeCN	rt	68
8	DCM	rt	76
9	**Neat**	**rt**	**96**

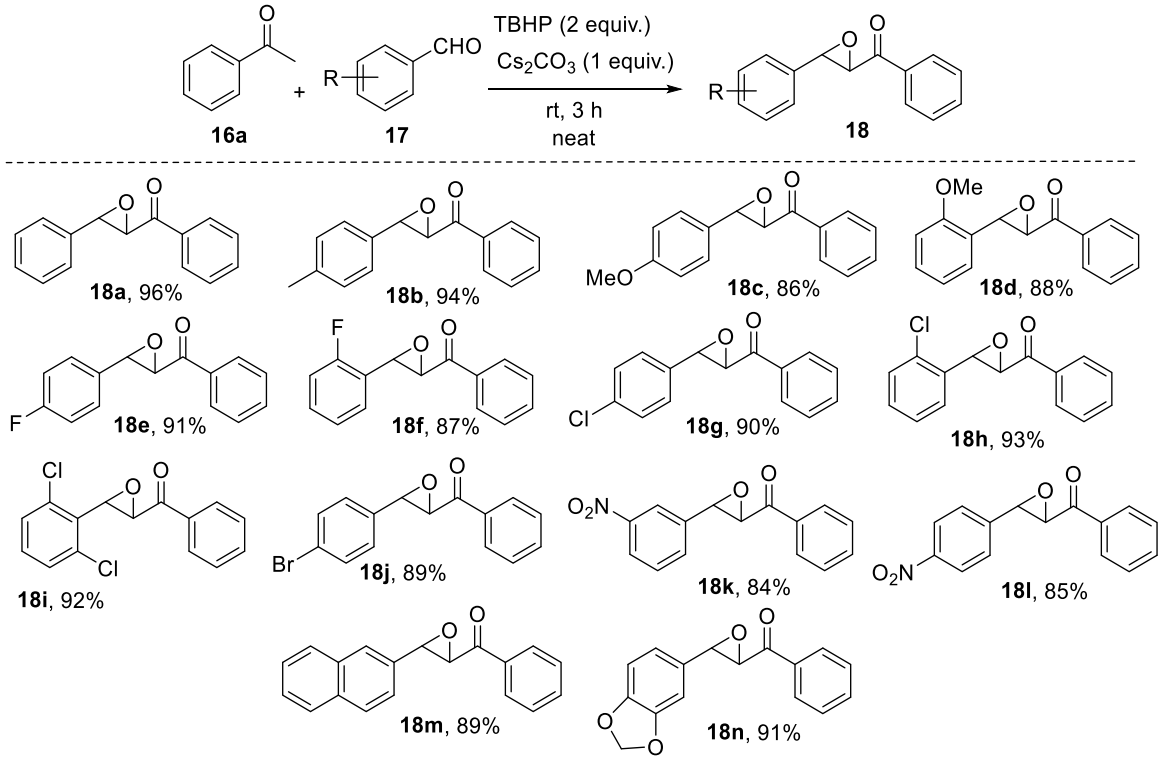
[a]***Reaction conditions:*** **16a** (1 mmol), **17a** (1 mmol) and TBHP (2 equiv.), Cs_2CO_3 (1 equiv.) at room temperature in different solvents (3 mL), [b]Isolated yields

With the optimized reaction conditions in hand, the substrate scope of this protocol was investigated. At first, our attention was focused on the use of different aldehydes to react with acetophenone and the results are presented in Table 2.23. It has been observed that a library of *α,β*-epoxyketones have been synthesized by varying different substituents. Different electron donating substituents such as methyl (**18b**), methoxy (for products (**18c, 18d**)) afforded the desired products in excellent yields (86-94%). Similarly, various electron withdrawing groups like halogens (F, Cl, Br) (for products (**3e, 3f, 18g, 18h, 18i, 18j**)) and nitro (for products (**18k, 18l**)) produced the desired products with very good to excellent yields. Naphthyl substituent also gave good result (**18m**). The acid sensitive group containing aldehyde (piperonal) was unaffected under the present reaction conditions which signify the mildness of the reaction conditions (for product (**18n**)).

Next, under the same reaction conditions, we have synthesized various *α,β*-epoxyketones by changing the ketone moiety and the results are depicted in Table 2.24. Different electron donating substituents such as methyl (**18o**), methoxy (**18p**) underwent smooth conversion in excellent yields (97% and 96% respectively). As well as electron withdrawing groups like halogens -Cl (**18q**), -Br (**18r**), I (**18s**) and -NO_2 (**18t**) produced the desired products in 85% to 93% yields. In addition, methyl sulfonyl group remained unaffected under this reaction conditions producing the desired product (**18u**) in 88% yield.

Next, the effect of substituents on both the aldehyde as well as acetophenone was tested as shown in Table 2.25. Methyl substituents on both the phenyl moieties (**18v**) as well as a combination of methyl and methoxy (**18w**) substituents underwent smooth reaction in good to excellent yields. Similarly, various electron withdrawing groups like chloro (**18a′**), bromo (**18b′**) produced the desired products in 92% & 90% yields respectively. Combination of electron withdrawing group and electron donating in alternate positions showed very good conversion (**18x**, **18y** & **18z**).

Table 2.23. Substrates scope of aldehydes.

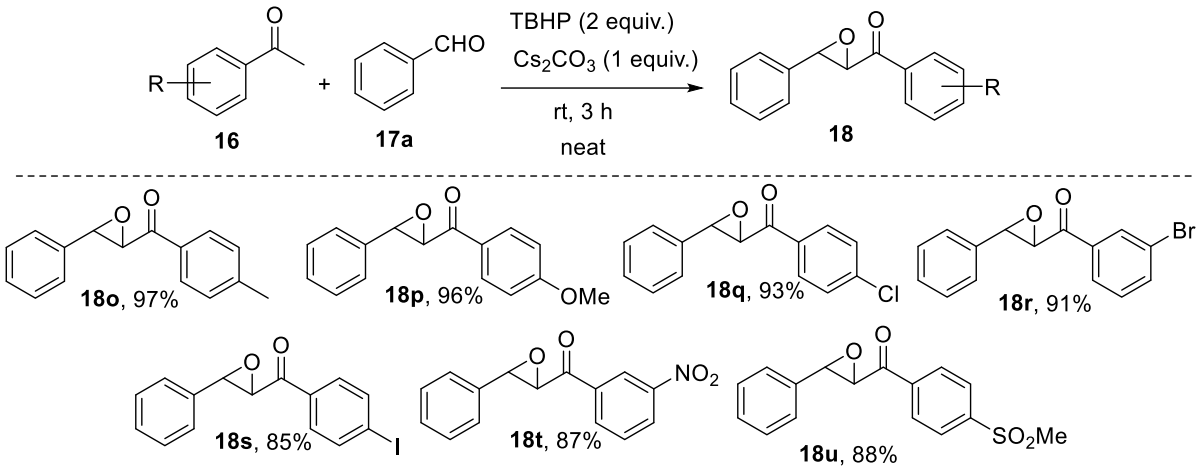


Reaction conditions: **16a** (1 mmol), **17** (1 mmol) and TBHP (2 equiv.), Cs_2CO_3 (1 equiv.), at room temperature under neat condition for 3 h

Then our attention was turned to the use of heterocyclic moieties adjacent to ketone like thiophene (**18c′-18h′**) and furan (**18i′**) which are summarized in Table 2.26. Very good yields (81-94%) were obtained in each case. Various functionalities were also unaffected under the present reaction conditions which proved the general applicability of this present procedure.

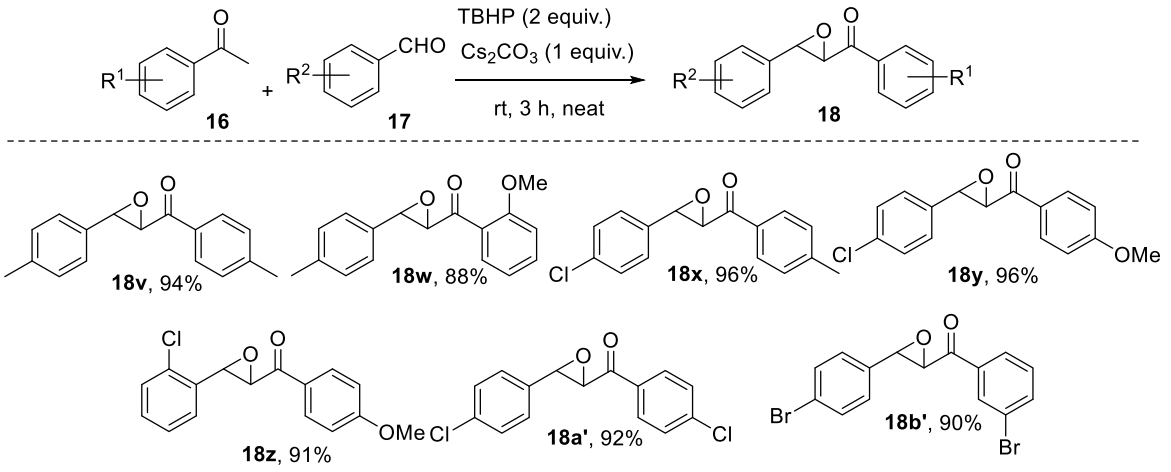
Finally, we proceeded to use aliphatic moieties adjacent to ketone to prove the wider substrates scope in Table 2.27. The *α,β*-epoxyketones have been synthesized having aliphatic moieties (**18j′**, **18k′**) with 94% and 92% yield respectively. Here, the cyclopopanone system remains unaffected under present reaction conditions which again showed the mildness of our procedure.

Table 2.24. Substrates scope of acetophenones.



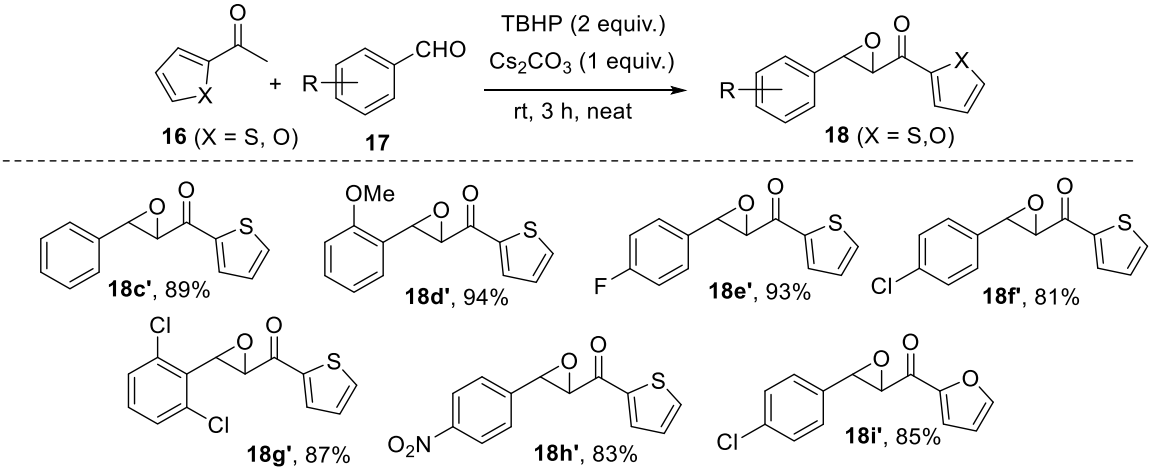
Reaction conditions: **16** (1 mmol), **17a** (1 mmol) and TBHP (2 equiv.), Cs_2CO_3 (1 equiv.), at room temperature under neat condition for 3 h.

Table 2.25. Substrates scope on both aryl aldehydes and acetophenones.



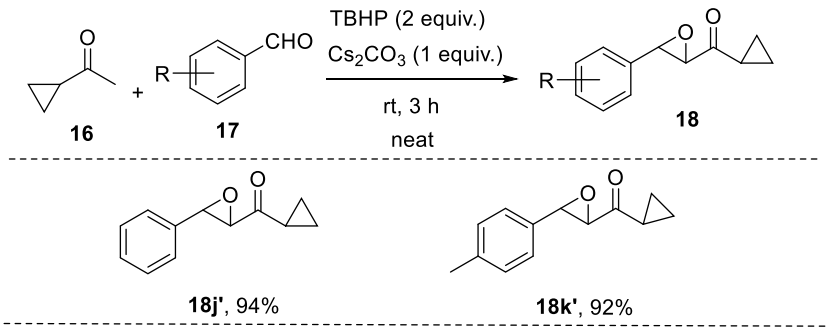
Reaction conditions: **16** (1 mmol), **17** (1 mmol) and TBHP (2 equiv.), Cs_2CO_3 (1 equiv.), at room temperature under neat condition for 3 h.

Table 2.26. Substrates scope of heteroarylketones.



Reaction conditions: 16 (1 mmol), 17 (1 mmol) and TBHP (2 equiv.), Cs2CO3 (1 equiv.), at room temperature under neat condition for 3 h.

Table 2.27. Substrates scope using aliphatic ketones.



Reaction conditions: **16** (1 mmol), **17** (1 mmol) and TBHP (2 equiv.), Cs_2CO_3 (1 equiv.), at room temperature under neat condition for 3 h.

The structures of the products synthesized in the current study were identified using ^{1}H NMR, ^{13}C NMR spectroscopies as well as elemental analysis. The structure of compound (**18v**, CCDC 1814755) was confirmed by using single-crystal X-ray diffraction analysis (Figure 2.6).

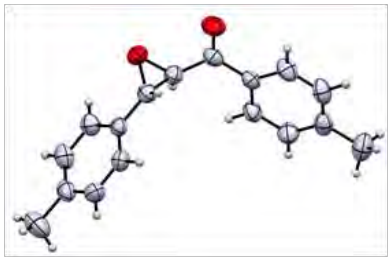
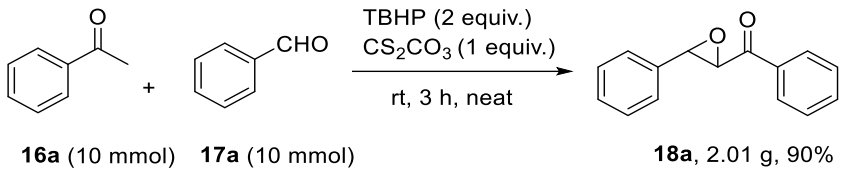


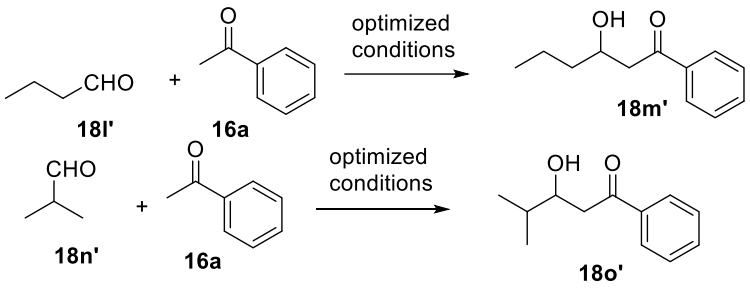
Figure 2.6. X-Ray crystallographic data for the structure of compound (**18v**).

The synthetic application of this present methodology was further demonstrated through a gram-scale preparation of *α,β*-epoxyketone. As illustrated in Scheme 2.27, under the optimized reaction conditions, acetophenone (**16a,** 1.20 g) and benzaldehyde (**17a,** 1.06 g) were smoothly reacted to the desired product (**18a**, 2.01g) in 90% isolated yield without any significant loss of its efficiency. This delegate conversion helps clear practical value that this method may offer for rapid and consistent access of *α,β*-epoxyketone substances and under very mild reaction conditions.



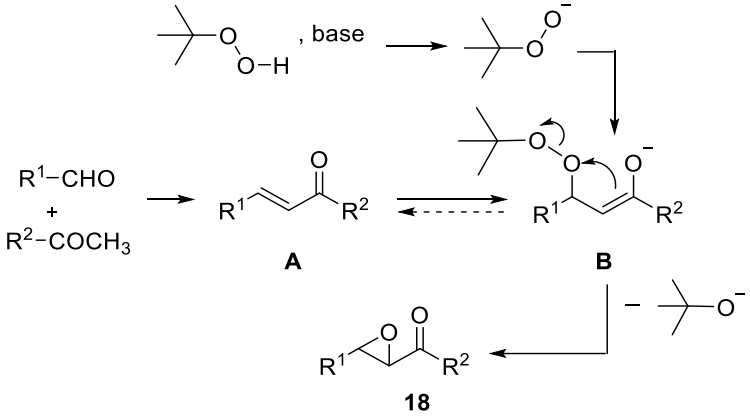
Scheme 2.27

The reactions with aliphatic aldehydes and acetophenone gave interesting results. We have tested two different aliphatic aldehydes such as butyraldehyde (**18l'**) and isobutyraldehyde (**18n'**) with acetophenone (**16a**). Here instead of the desired product (epoxide) we have isolated the *β*-hydroxy ketones (**18m', 18o'**) (Scheme 2.28).



Scheme 2.28

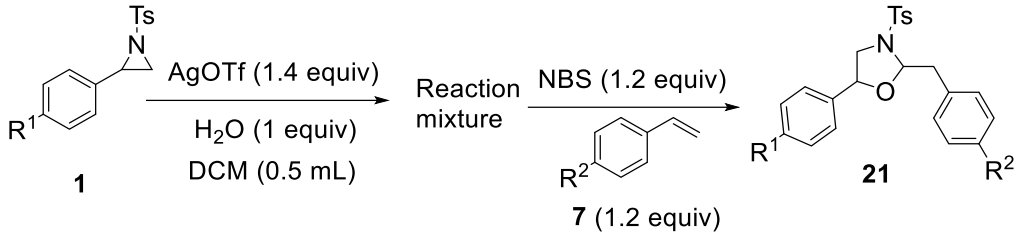
Based on this above observation (as stated in Scheme 2.28) and literature [347, 348], we have proposed a mechanism for this one-pot procedure (Scheme 2.29). The first step is the formation of corresponding *α,β*-unsaturated ketone (**A**) in the presence of a base. Conjugate addition of a peroxy anion generated from *tert*-butyl hydrogen peroxide under basic conditions at the *β*-position of the *α,β*-unsaturated ketone (**A**) affords *β*-peroxyenolate (**B**). Subsequent intramolecular nucleophilic displacement at the proximal oxygen atom breaks the weak O-O single bond with concomitant ejection of a leaving group -alkoxide to furnish the desired epoxide (**3**). The reaction for aliphatic aldehyde under the present reaction conditions gives the *β*-hydroxyketone not the *α,β*-unsaturated ketone which is the necessary intermediate (**A**) before the formation of an epoxide. Thus we can predict the reaction pathway which may be the formation of chalcone followed by the epoxide formation.



Scheme 2.29

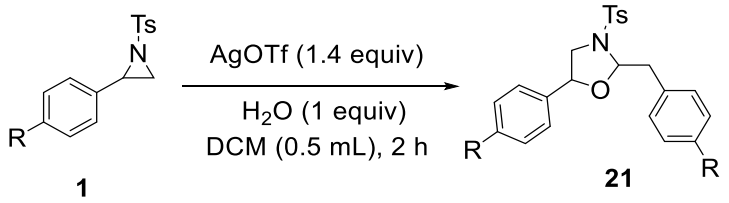
2.8. CONVERSION OF AZIRIDINES TO OXAZOLIDINES

In addirion to ring opening reactions azyridines can be involved in recyclization reactions to form other heterocycles. Based on practical applicability of such prosesses, within the framework of the dissertation work, we studied the possibilities of expansion reactions of aziridine cycles, for example, to obtain multi-substituted oxazoles (**21**). We have developed one pot nucleophilic ring opening of *N*-Ts-aziridines (**1**) by water to the corresponding ring opening product (*N*-Ts-phenylalaninol) followed by its addition to the double bond to get the 5-membered oxazolidine derivatives (**21**) by geminal functionalization of alkene by non-Wacker process (Scheme 2.30). We also carried out the reaction under similar conditions using *N*-Ts-aziridine (**1**) without adding any styrene (**7**) and NBS as shown in Scheme 2.31 and tried to isolate the intermediate. Surprisingly the isolated product was the same (**21**) as observed in the Scheme 2.30 where the benzylic part is also coming from the aziridine itself.



* When R^2 = electron donating group, then the styrene part does not takes part in the reaction course and the product should be like the product obtained in absence of styrene but yield was very low.

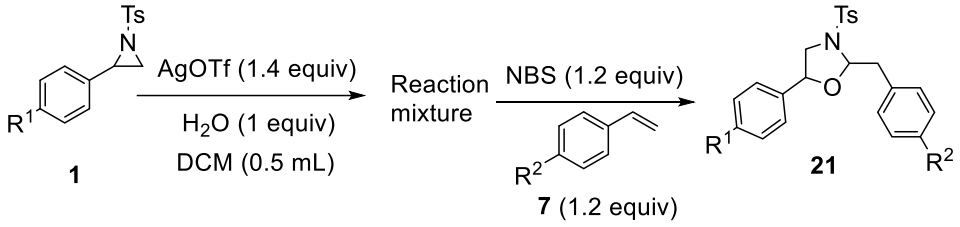
Scheme 2.30

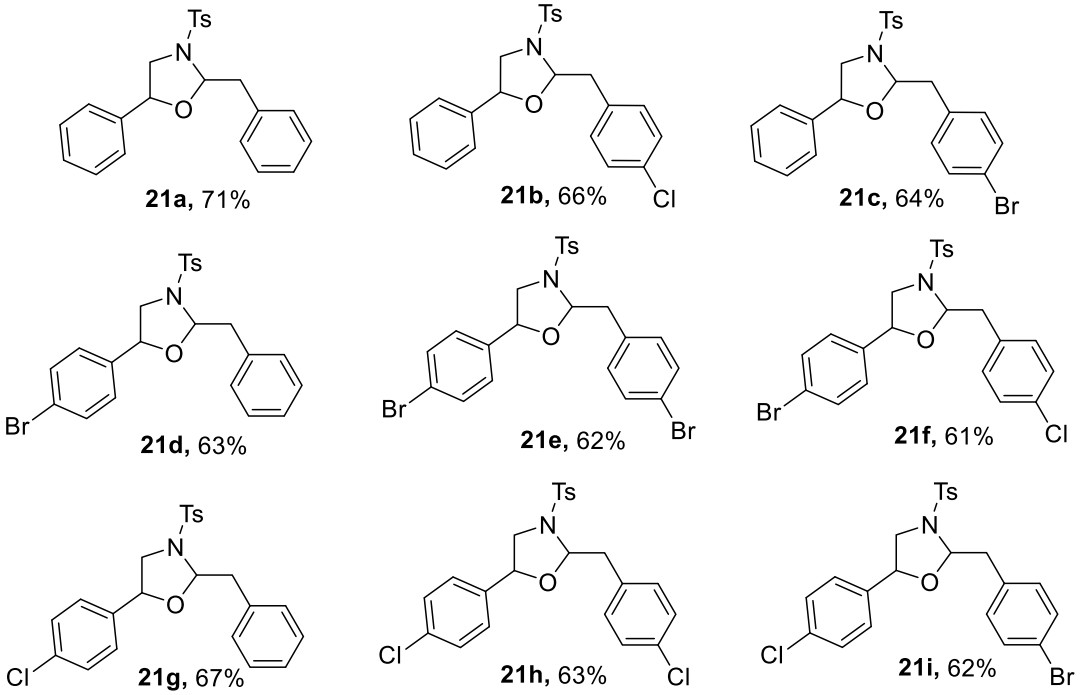


Scheme 2.31

Initially we have chosen 2-phenyl-1-tosylaziridine (**1a**) instead of *N*-Ts-phenylalaninol and simple styrene (**7a**) as the model substrate. A mixture of 2-phenyl-1-tosylaziridine (**1a**, 0.5 mmol), AgOTf (0.7 mmol), H_2O (0.5 mmol) and 0.5 mL of DCM was taken in a sealed tube in an one pot procedure and stirred at room temperature for 1 h. After that NBS (0.6 mmol) and styrene (**7a**, 0.6 mmol) were added to the reaction mixture and stirring continued for another 4 h to get the corresponding 5-substituted oxazolidine derivative (**21a**) with 70% yield.

We have examined nine different substrate combinations to confirm our observation as summarized in the Scheme 2.32. We have got the 5-substituted oxazolidine derivatives as the addendum in our methodology. The variation of the aziridines with different substitution in the phenyl ring as well as different styrene showed comparable reaction under similar reaction conditions. The reactions are very much selective for simple styrene and for the styrene containing electron withdrawing groups in the phenyl ring. Also the reaction proceeded smoothly in a selective way for those aziridines having electron withdrawing group in the phenyl ring.



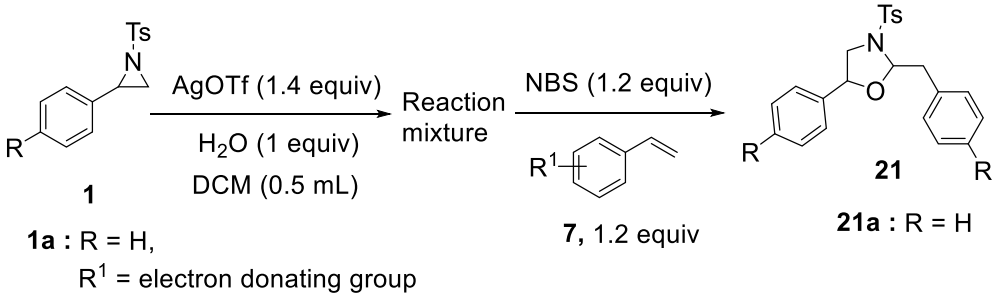


The reaction was carried out on 0.5 mmol scale.

Scheme 2.32

Also we have observed that styrene with electron donating substituents like 4-methoxy styrene and 2,4-dimethyl styrene are not effective for this reaction as no desired oxazolidines were isolated under this reaction conditions. This observation was very interesting and obviously most important part of our method. When we were trying to carry out the reaction using 2-phenyl-1-tosylaziridine (**1a**) under similar reaction conditions (Scheme 2.32) with styrenes having electron donating group there was no expected oxazolidine derivatives obtained with substituted phenyl

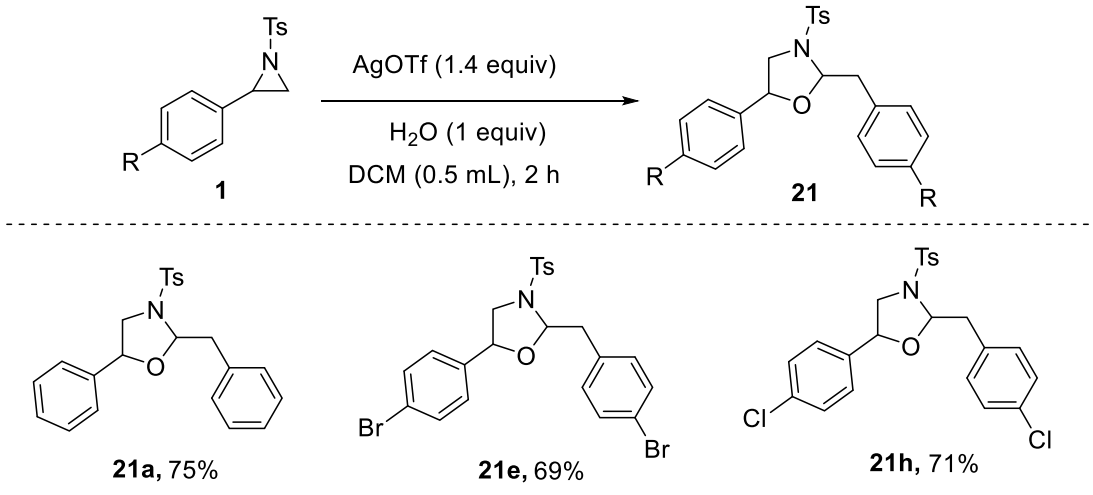
ring in the benzylic moiety but each time we have isolated the same oxazolidine (**21a**) as shown in the Scheme 2.33 but the yields of the oxazolidines were very poor (<10%).



The reaction was carried out on 0.5 mmol scale.

Scheme 2.33

Based on this repeated observation (Scheme 2.33) we have decided to examine our possible reaction path and carried out the reaction under similar conditions using 2-phenyl-1-tosylaziridine without adding any styrene (**7**) and NBS as shown in Scheme 2.34. We have actually tried to isolate the intermediate, but surprisingly the isolated product was the same (**21a**) as observed in the Scheme 2.32 and Scheme 2.33 where the benzylic part was also coming from the aziridine itself. To get more decisive results we have examined the general applicability and scope of this unusual ring opening followed by addition of this ring opening product with aziridine itself to afford the final product as oxazolidine derivatives. We have tested another three different aziridine derivatives and observed the expected oxazolidines with good yields as shown in the Scheme 2.34.

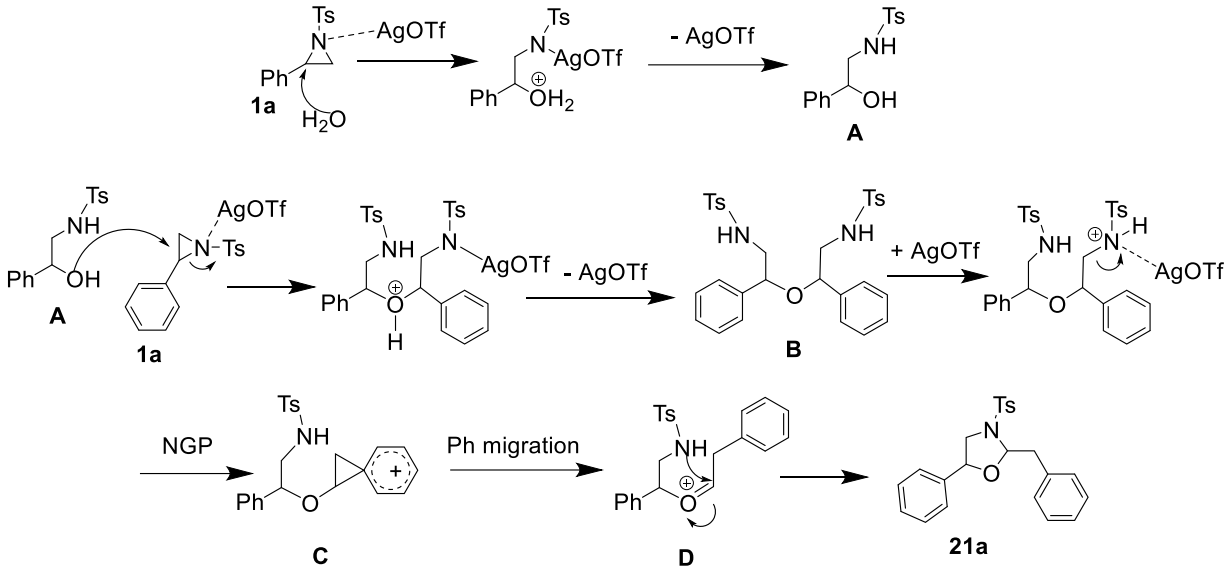


The reaction was carried out on 0.5 mmol scale.

Scheme 2.34

We have proposed a possible mechanistic pathway (Scheme 2.35) based on the literature [349] and our previous work [350]. The ring opening product (**A**) of 2-phenyl-1-tosylaziridine (**1a**)

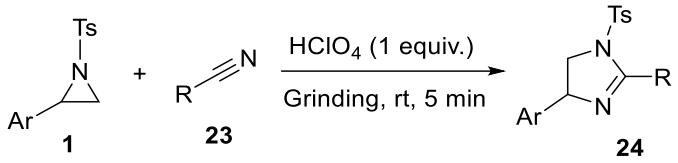
by water reacted with the aziridine **(1a)** itself to give the intermediate **B**. In presence of AgOTf this intermediate (**B**) produced another intermediate (**C**) which was stabilized by neighbouring group participation (NGP) in which intramolecular phenyl migration (**D**) followed by cyclization gave the final oxazolidine product (**21a**).



Scheme 2.35

2.9. MECHANOCHEMICAL SYNTHESIS OF 2-IMIDAZOLINES

To explore the practical applicapability of aziridine ring opening reactions we have also developed a simple and convenient process for the synthesis of 2-imidazoline derivatives by [3+2] cycloaddition reactions by simple grinding of *N*-tosylaziridines in neat in the presence of perchloric acid ($HClO_4$) (Scheme 2.36).



Scheme 2.36

The study was initiated with the reaction of 0.25 mmol of 2-phenyl-1-tosylaziridine (**1a**) and 0.25 mmol of benzonitrile (**23a**) by simply grinding them together in presence of 1 equiv of sulfuric acid at room temperature under ambient air for 10 min. Gratifyingly, the desired cycloaddition product, 2,4-diphenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (**24a**), was obtained in a 36% yield after 10 min (Table 2.28, entry 1). This result encouraged to optimize the reaction in different conditions, and the results are summarized in Table 2.28. First, the reaction was carried out individually in presence of other mineral acids such as HCl, $HClO_4$ and HBr (entries 2-4, Table 2.28); where $HClO_4$ gave the best result (92% yield). Other common acids like phosphoric acid (H_3PO_4), acetic acid (CH_3COOH), trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (PTSA) did not afford the desired product (entries 5-8, Table 2.28). In presence of triflic acid (TfOH) the reaction underwent smoothly yielding 84% yield (entry 9, Table 2.28). The best result was obtained in presence of 0.5 mmol of $HClO_4$ after grinding for 5 min (95% yield, entry 10, Table 2.28). By decreasing the amount of $HClO_4$ the yield was decreased significantly (entry 11, Table 2.28). Therefore, on the basis of the series of experiments (entries 1−11, Table 2.28), the optimized reaction conditions were considered by using 0.25 mmol (1 equiv) of $HClO_4$ under solvent-free conditions for 5 min grinding of aziridine (**1a)** (0.25 mmol) and nitrile (**23a**) (0.25 mmol) at room temperature under ambient air (entry 10, Table 2.28).

Table 2.28. Optimization of the reaction conditions.[a]

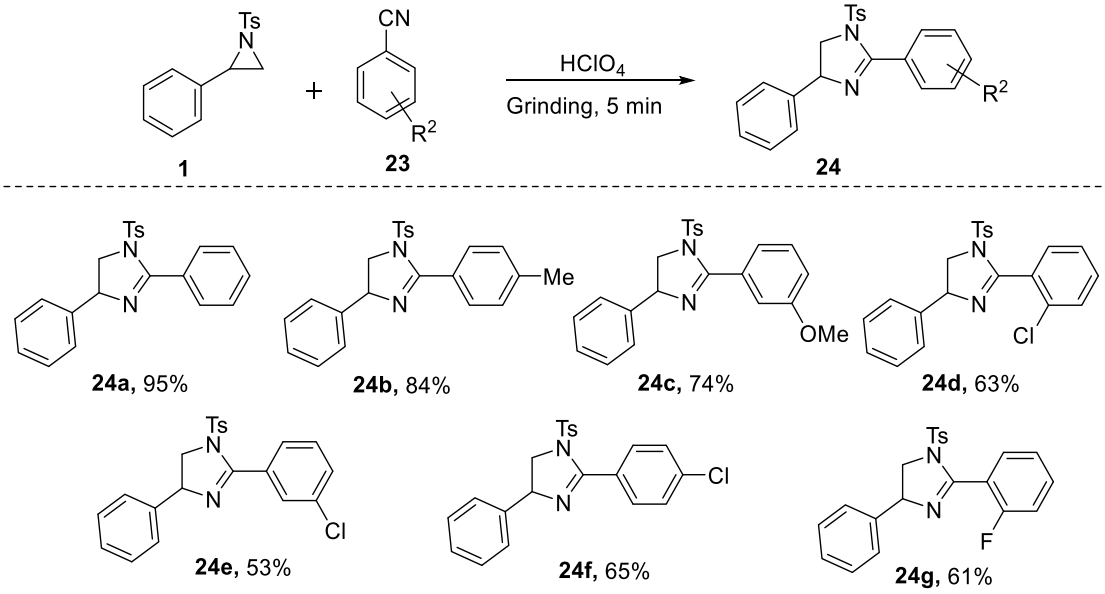
Entry	Acid (1 equiv.)	Time (min.)	Yields[b] (%)
1	H_2SO_4	10	36
2	HCl	10	15

3	$HClO_4$	10	92
4	HBr	10	Trace
5	H_3PO_4	10	ND
6	CH_3COOH	10	ND
7	TFA	10	ND
8	PTSA	10	ND
9	TfOH	10	84
10	$HClO_4$	5	95
11[c]	$HClO_4$	5	64

[a]***Reaction conditions:*** 0.25 mmol of **1a** and 0.25 mmol of **23a** were ground on a mortar at room temperature in presence of 1 equiv. of different acids. [b]All are isolated yields. [c]0.5 equiv of $HClO_4$ was used.

After having the optimized reaction conditions in hand, various substituted benzonitrile (**23**) were introduced to react with 2-phenyl-1-tosylaziridine (**1a**) as well as other with substituted tosylaziridines to prove the general applicability of this methodology. First, the effect of substituents of aryl nitriles was tested. The results are summarized in Table 2.29 & 2.30.

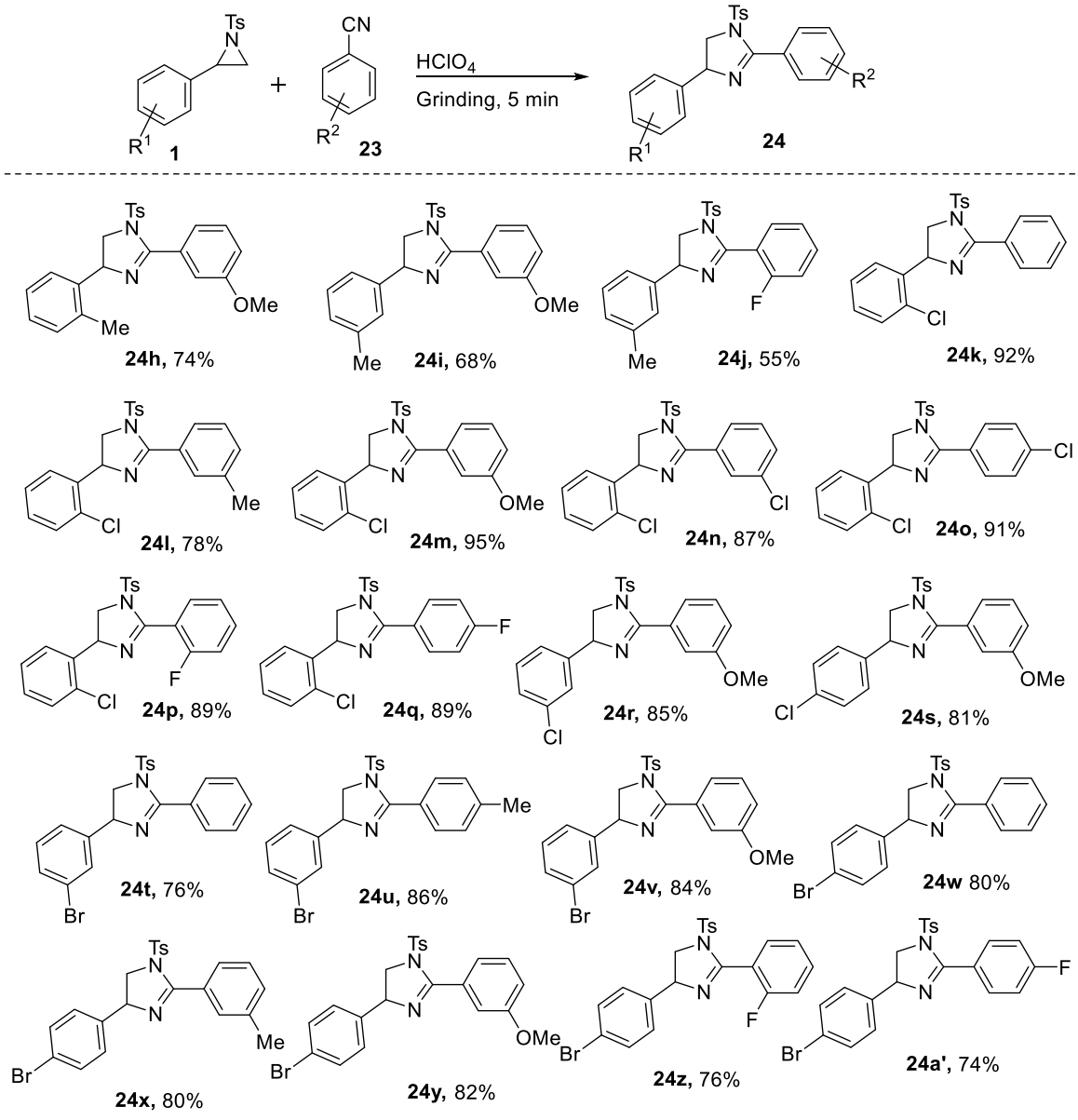
Table 2.29. Substrates scope.



Reaction conditions: All reactions were performed on 0.25 mmol scale. 0.25 mmol aziridine (**1**) and 0.25 mmol nitrile (**23**) grinding with a mortar and pestle followed by perchloric acid for 5 min. All are isolated yields.

In most cases, the desired products were obtained in good yields (**24a**-**24g**). During the optimization of reaction conditions it has been observed that simple benzonitrile gave the desired product (**24a**) in excellent yield. Other benzonitriles bearing electron-donating substituents such as -Me, -OMe (**24b** and **24c**) and electron withdrawing substituents such as -Cl and -F reacted well to afford the corresponding 2-imidazoline derivatives (**24d**, **24e**, **24f** and **24g**).

Table 2.30. Substrates scope of the reaction between substituted tosylaziridine and substituted benzonitrile.

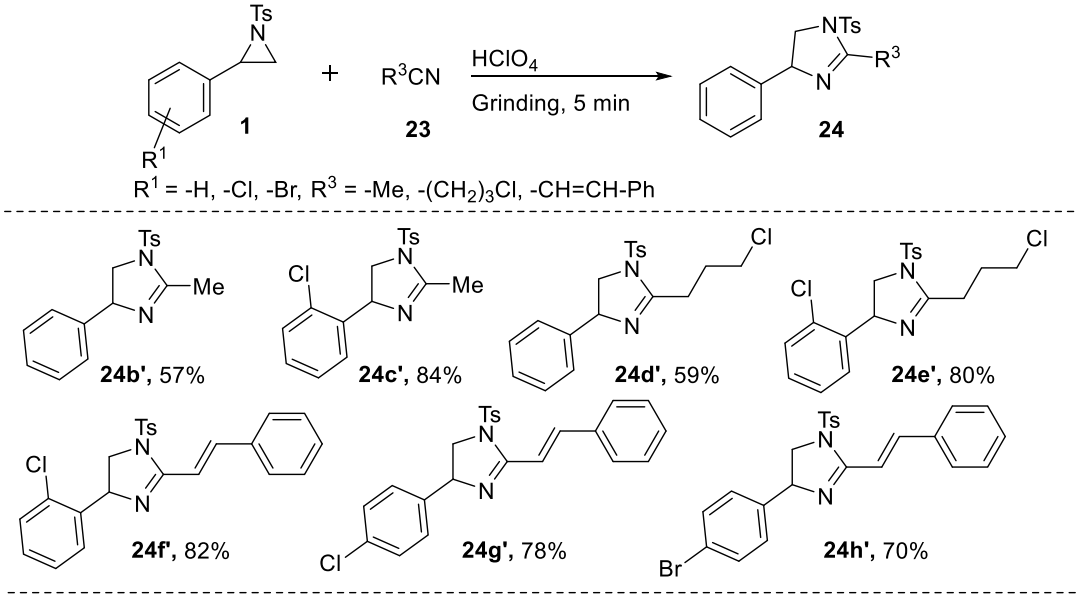


Reaction conditions: All reactions were performed on 0.25 mmol scale. 0.25 mmol aziridine (**1**) and 0.25 mmol nitrile (**23**) grinding with a mortar and pestle followed by perchloric acid for 5 min. All are isolated yields.

Next the effect of substituents on both the aziridine as well as benzonitrile was tested as shown in Table 2.31. Combination of methyl and methoxy substituents on the phenyl ring of the aziridine moiety and phenyl ring of the benzonitrile moiety respectively underwent smooth

reaction in good yields (**24h** and **24i**). Combination of electron withdrawing groups (such as -F, -Cl and -Br) and electron donating substituents (such as -Me and -OMe) in alternate positions showed very good conversion (**24j**, **24l**, **24m**, **24r**, **24s**, **24u**, **24v**, **24w**, **24x** and **24y**). Similarly, various electron withdrawing groups like -Cl, -F and -Br at the aziridine as well as both of the phenyl rings of aziridines and aryl nitriles produced the desired products in excellent yields (**24k, 24n**, **24o**, **24p**, **24q**, **24t**, **24z** and **24a'**).

Table 2.31. Substrates scope of the reaction between substituted tosylaziridine and aliphatic as well as cinnamyl nitriles.



Reaction conditions: All reactions were performed on a 0.25 mmol scale. 0.25 mmol aziridine (**1**) and 0.25 mmol nitrile (**23**) grinding with a morter and pestle followed by perchloric acid for 5 min.

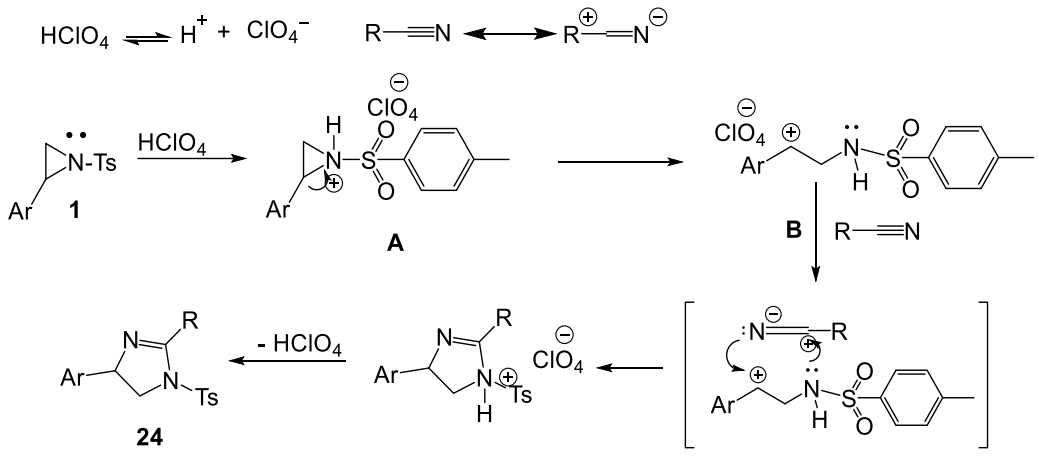
Then aliphatic nitriles as well as cinnamyl nitriles have been tested and are summarized in the Table 4. Simple acetonitrile gave the desired products (**24b'** and **24c'**) in 57% and 84% yields. Another aliphatic nitrile such as 4-chlorobutyronitrile also underwent smooth reactions with different benzonitriles with moderate to good yields (**24d'** and **24e'**). It is worthy to mention that cinnamyl nitrile (**2l**) was also good substrate to afford the desired products (**24f'**, **24g'** and **24h'**) with different substitutions; yielding 70% to 82% yields.

All these reactions were performed under an open atmosphere and are not sensitive to air and moisture. In addition, the reaction is highly *regio*-selective. No other *regio*-isomer was isolated under the present reaction conditions. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported by high yields and *regio*-selectivity of the protocol. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data and X-ray crystallographic analysis of 4-(2-

chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (**24m**, CCDC 1910227) was performed to confirm the structure of the product as shown in Figure 2.7.

Figure 2.7. X-Ray crystallographic data for the structure of compound (**24m**).

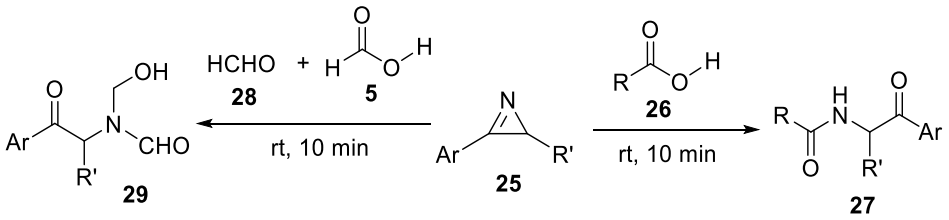
Based on our previous works on aziridine and literature examples [73, 74], a probable mechanistic pathway has been proposed in Scheme 2.37. Thus, in the presence of perchloric acid protonated form (**A)** was formed and underwent ring opening to form a stable benzylic carbocation (**B**), which on further reaction with nitrile (**23**) in S_N1 mode and subsequent [3+2]-cycloaddition led to the formation of imidazoline (**24**).



Scheme 2.37

2.10. SELF-CATALYZED SYNTHESIS OF *N*-ACYL-/*N*-FORMYL-*α*-AMINOKETONES BY THE REACTION OF 3-ARYL-2*H*-AZIRINES/2-Me/Ph-3-ARYL-2*H*-AZIRINES WITH FORMIC ACID, AS WELL AS OTHER ORGANIC ACIDS

High reactivity of unsaturated analogues of aziridines, for example, 2*H*-azirines, is determined by the higher steric strain of the three-membered cycle, due to the presence of a reactive π bond, shorter than that in aziridines.This determines the high ability of azirines to undergo regioselective ring opening under the action of nucleophiles and electrophiles, most commonly under mild conditions. Within the framework of our work, we have studies some previously undescribed reactions of 2*H*-azirines. Thus, for the first time, we developed a simple protocol for *N*-trifluoroacetylated *α*-aminoketones synthesis by a simple ring opening reaction of various aryl 2*H*-azirines with trifluoroacetic acid (TFA). In addition, this method is also effective to synthesize *N*-acylated *α*-aminoketones by using other carboxylic acid derivatives. The reaction takes 10 min for completion at room temperature (Scheme 2.38).



Scheme 2.38

Initially, the study was initiated by investigating the reaction of 3-phenyl-2*H*-azirine (**25a**, 1 mmol) in dichloromethane (DCM) at room temperature in the presence of 1 equiv. of trifluoroacetic acid (TFA). The desired product 2,2,2-trifluoro-*N*-(2-oxo-2-phenylethyl)acetamide (**27a**) was formed in 78% yield within 10 min (Table 2.32, entry 1). Encouraged by this observation the optimization of the reaction conditions has been established. The results are summarized in Table 2.32. No improvement of the yield was observed by increasing the reaction time up to 15 to 30 min. To interpret the solvent effects, a variety of aprotic polar solvents like 1,2-DCE, DCB, DMSO, DMF, CH_3CN, acetone, THF, 1,4-dioxane, benzene, chlorobenzene (Table 2.32, entries 2-11) as well as few protic polar solvents like MeOH, EtOH and H_2O (Table 2.32, entries 15-17) have been tested for this reaction. Among them, toluene was found to be the best choice in which 94% yield was obtained (Table 2.32, entry 13). The reaction did not proceed under the neat conditions (Table 2.32, entry 18). By decreasing the amount of TFA (0.5 equiv.) decreased the yield, in addition increasing the amount of TFA to 2 equiv. also decreased the yield (Table 2.32, entries 12-14). Thus, the optimized yield (94%) was achieved by treating 1 equiv. of TFA in toluene for only 10 min at room temperature under aerobic conditions (Table 2.32, entry 14).

Table 2.32. Optimization of the reaction conditions.[a]

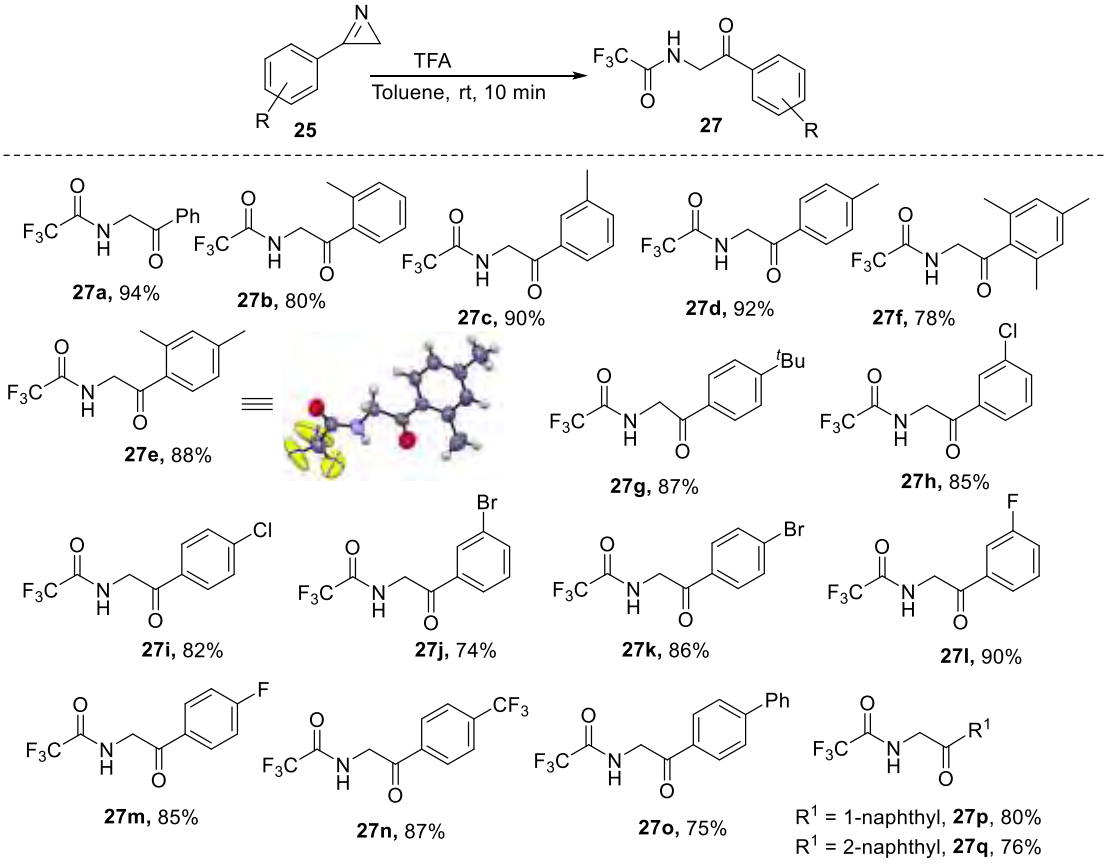
Entry	TFA (equiv.)	solvents (3 mL)	yields (%)
1	1	DCM	78
2	1	1,2-DCE	65
3	1	DCB	55
4	1	DMSO	nd[b]
5	1	DMF	nd[b]
6	1	CH_3CN	70
7	1	acetone	30
8	1	THF	nd[b]
9	1	1,4-dioxane	20
10	1	benzene	88
11	1	chlorobenzene	86
12	1	toluene	94
13	0.5	toluene	40
14	2	toluene	75
15	1	methanol	nd[b]
16	1	ethanol	nd[b]
17	1	water	nd[b]
18	1	neat	nd[b]
19[c]	1	toluene	93

[a]***Reaction conditions:*** **25a** (1.0 mmol), TFA (different equiv. amount), solvent (3 mL), at room temperature in different solvents (3 mL) for 10 min. [b]nd = not detected in TLC. [c]The reaction was carried out under argon atmosphere.

After optimizing the reaction conditions, the substrates scope of this TFA-mediated ring opening reaction with various substituted aryl 2*H*-azirines have been explored. The results are

depicted in Table 2.33. A series of *N*-trifluoroacetylated *α*-aminoketone derivatives were obtained (**27a-27q**) in good to excellent yields. The simple 3-phenyl-2*H*-azirine (**25a**) produced the desired 2,2,2-trifluoro-*N*-(2-oxo-2-phenylethyl)acetamide (**27a**) in 94% yield. 3-Aryl-2*H*-azirines bearing electron-donating substituent (like -methyl) at -*ortho*, -*meta* and -*para* positions of the phenyl ring reacted efficiently with TFA to provide the corresponding products in good to excellent yields (**27b**, 80%; **27c**, 90%; **27d**, 92%). As well as, reactions with disubstituted and trisubstituted electron-donating methyl substituent also underwent smooth reaction (**27e**, 88%; **27f**, 78%). Substrate containing strong electron-donating substituent (like *tert*-butyl) underwent a smooth reaction under the optimal reaction conditions (**27g**, 87%). Similarly, 2*H*-azirines with electron-withdrawing groups like chloro-, bromo-, fluoro- took part in the reaction and afforded the products in very good yields (**27h**, 85%; **27i**, 82%; **27j**, 74%; **27k**, 86%; **27l**, 90%; **27m**, 85%). Furthermore, the reaction proceeded smoothly in case of a strong electron-withdrawing group (–CF_3) containing aryl-2*H*-azirine which afforded the desired product in excellent yield (**27n**, 87%). Aryl-2*H*-azirine with 4-biphenyl, 1- and 2-naphthyl moieties produced the desired products (**27o**, **27p**, **27q**) with 75%, 80%, 76% yields respectively.

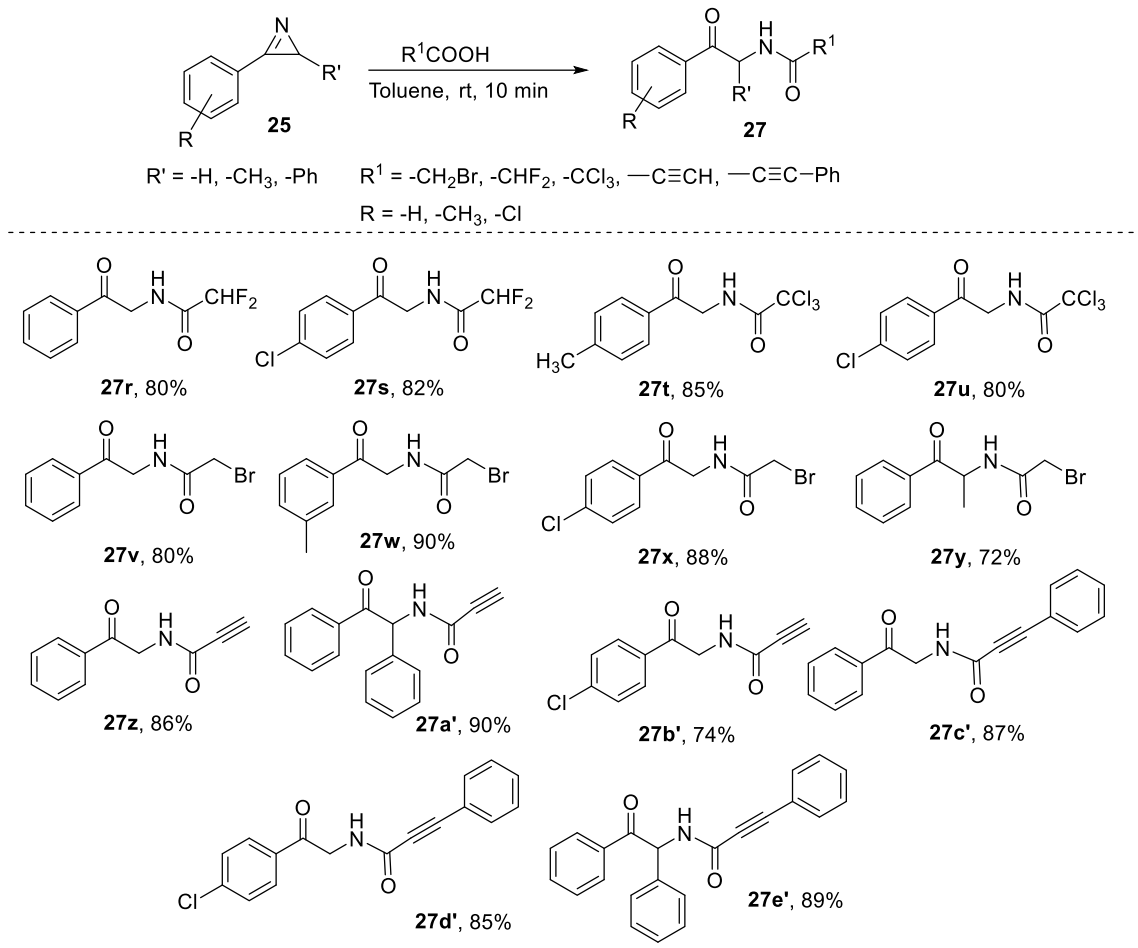
Table 2.33. Substrates scope for the synthesis of *N*-trifluoroacetylated *α*-aminoketones.



Reaction conditions: 3-aryl-2*H*-azirine (**25**, 1 mmol), TFA (1 mmol), toluene (3.0 mL) under ambient air for 10 min, room temperature.

Most interesting observation of this methodology is that when several other acids such as difluoroacetic acid, trichloroacetic acid, bromoacetic acid, propiolic acid and phenylpropiolic acid have been tested for the reaction under similar conditions the corresponding desired products (**27r-27e'**) were obtained in good to excellent yields (Table 2.34). However, acetic acid, benzoic acid, propionic acid and pivalic acid were unable to give desired products.

Table 2.34. Substrates scope by varying other acids.

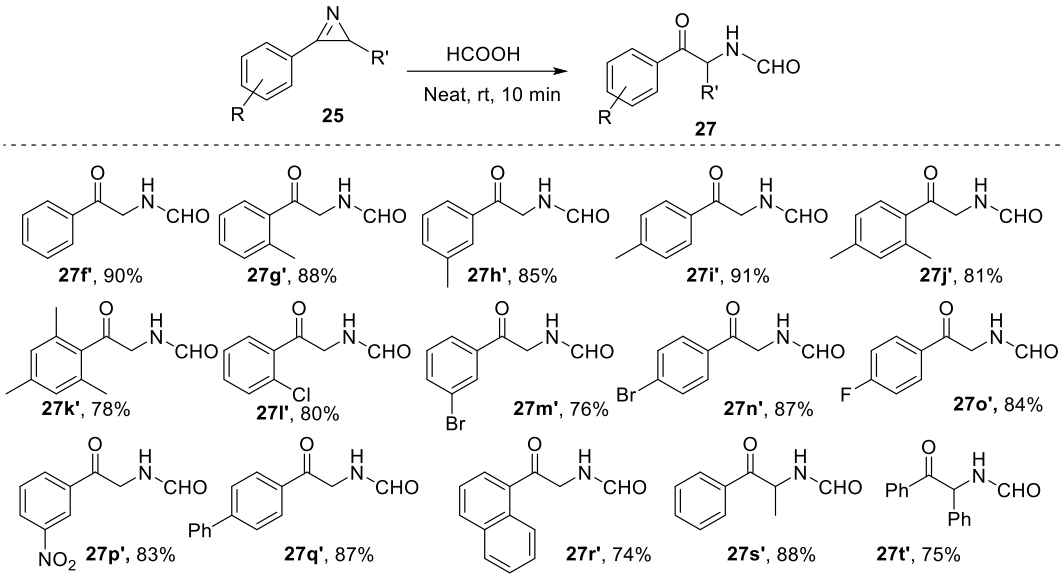


Reaction conditions: 3-aryl-2*H*-azirine (**25**, 1 mmol), acid (1 mmol), toluene (3.0 mL) for 10 min, ambient air, room temperature.

It is worthy to note that formic acid instead of TFA under neat conditions underwent smooth reaction to give *N*-formylated *α*-aminoketones. Using this strategy, a series of *N*-formylated *α*-aminoketone derivatives (**27f'-27r'**) have been synthesized in good to excellent yields by ring opening of azirines (Table 2.35). It has been observed that simple 3-phenyl-2*H*-azirine (**25a**) produced the desired *N*-(2-oxo-2-phenylethyl)formamide (**27e'**) in 90% yield. 3-Aryl-2*H*-azirines bearing electron-donating substituent (like -methyl) at -*ortho*, -*meta* and -*para* positions of the phenyl ring efficiently reacted with formic acid to provide the corresponding products in excellent yields (**27g'**, 88%; **27h'**, 85%; **27i'**, 91%). As well as, reactions with disubstituted and trisubstituted electron-donating methyl substituent proceeded efficiently (**27j'**,

81%; **27k'**, 78%). Further, 2*H*-azirines with electron-withdrawing groups like chloro-, bromo-, fluoro- and -nitro underwent smooth reaction and afforded the products very smoothly (**27l'**, 80%; **27m'**, 76%; **27n'**, 87%; **27o'**, 84%; **27p'**, 83%). In addition, aryl-2*H*-azirine with 4-biphenyl and 1-naphthyl moieties produced the desired products **27q'**and **27r'**in 87% and 74% yield respectively. This method is also applicable for highly substituted (-methyl and -phenyl) 2*H*-azirines and afforded the corresponding products in good yields (**27s'**, 88%; **27t'**, 75%).

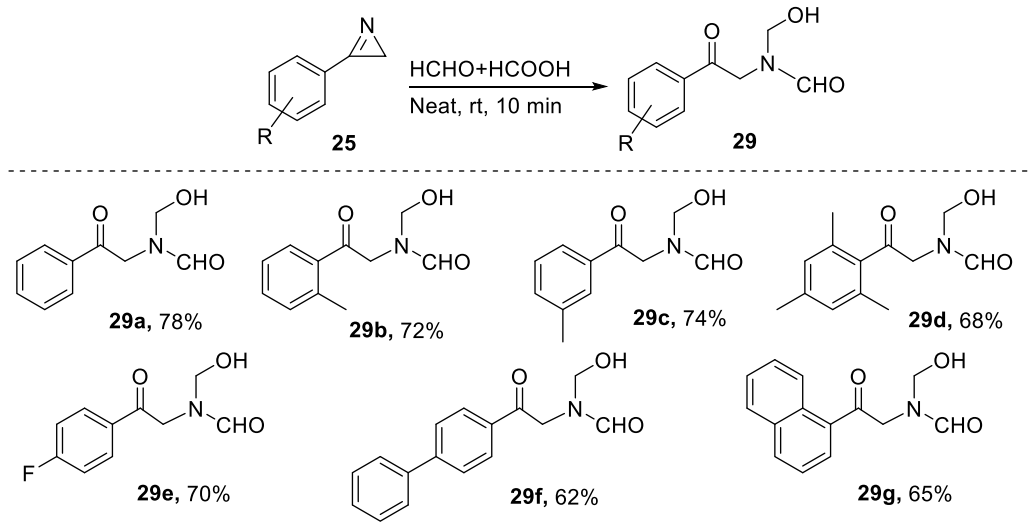
Table 2.35. Substrates scope for the synthesis of *N*-formylated *α*-aminoketones.



Reaction conditions: 3-aryl-2*H*-azirine (**25**, 1 mmol), HCOOH (1 mmol) under neat conditions for 10 min, ambient air, room temperature.

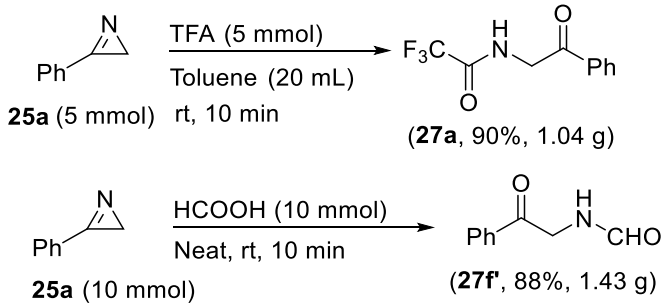
In addition, 2*H*-azirine with formic acid and formaldehyde in 1:1:1 ratio under similar reaction conditions gives *N*-hydroxymethylated formamide (Table 2.36). A series of desired products has been synthesized (**29a-29g**) in moderate to good yields using this protocal. It was observed that simple 3-phenyl-2*H*-azirine (**25a**) produced the desired *N*-(hydroxymethyl)-*N*-(2-oxo-2-phenylethyl) formamide (**29a**) in 78% yield. 3-Aryl-2*H*-azirines bearing methyl substituent at -*ortho*, and -*meta* positions as well as trimethyl-substituted phenyl ring afforded the products very smoothly (**29b**, 72%; **29c**, 74%; **29d**, 68%). Also, electron-withdrawing group (fluoro-) at the phenyl moiety was found efficient to afford the desired product (**29e**, 70%) in good yields. In addition, aryl-2*H*-azirine with biphenyl and naphthyl moieties produced the desired products 5f and 5g in 62% and 65% yield respectively.

Table 2.36. Substrates scope for the synthesis of *N*-hydroxymethyl formamide.



Reaction conditions: 3-aryl-2*H*-azirine (**25**, 1 mmol), HCOOH (1 mmol), HCHO (1 mmol) under neat conditions for 10 min, ambient air, room temperature.

No other external additives or oxidants are needed for this reaction. All these reactions were carried out under the open atmosphere and are not sensitive to air and moisture. An inert atmosphere is not required. No decomposition or polymerization has been observed under the present reaction conditions. No by-products have been observed in any reaction. The reactions are regioselective and high yielding. Characterization of the synthesized known compounds was made by the comparison of spectral data and new compounds by spectral and analytical data. Finally, the X-ray crystallographic analysis of *N*-(2-(2,4-dimethylphenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (**27e**) was performed to confirm the structure (CCDC 1978555).

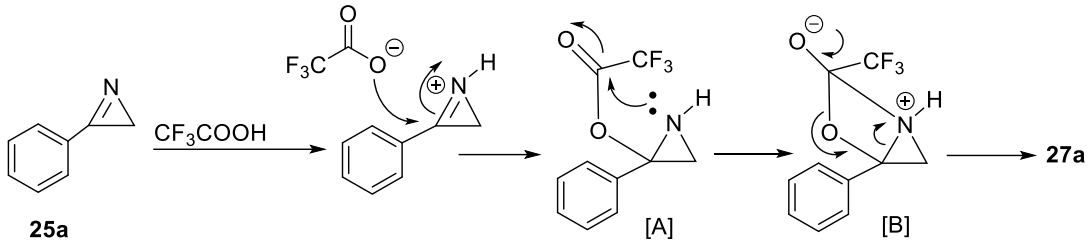


Scheme 2.39

The potential synthetic applicability of this method was investigated on the gram-scale using the model reaction in our laboratory setup for the synthesis of *N*-trifluoromethylated *α*-aminoketones and *N*-formylated *α*-aminoketones. As shown in Scheme 2.39, the reaction could afford 1.04 g of product (**27a**) in 90% yield and 1.43 g of product (**27f'**) in 88% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for

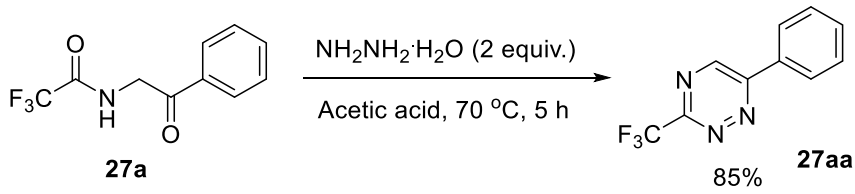
a large-scale synthesis of *N*-trifluoromethylated *α*-aminoketone derivatives and *N*-formylated *α*-aminoketone derivatives.

The mechanism of the formation of *N*-trifluoromethylated *α*-aminoketone derivatives has been explained based on the literature [351]. Here, the strong trifluoroacetic acid plays the role of activation of azirine by the proton. On the other hand, the trifluoro acetate acts as a nucleophile and attacks the activated azirine to form the intermediate [**A**] as shown in Scheme 2.40. This intermediate is not stable and the lone pair of nitrogen attacks the carbonyl carbon of ester to give the 1,3-oxazitidine ion [**B**]. This 1,3-oxazitidine ion [**B**] gives the stable desired product (**27a**) *via* the ring opening of aziridine.



Scheme 2.40

As an extension, a cyclization reaction was carried out taking *N*-trifluoroacetyl *α*-aminoketone (**27a**) with hydrazine hydrate and substituted 1,2,4-triazine (**27aa**) has been isolated in excellent yield (Scheme 2.41). These 1,2,4-traizine derivatives exhibit a broad spectrum of biological activities with antiinflammatory, antitumor, antibacterial, anticonvulsant, and antiviral properties.

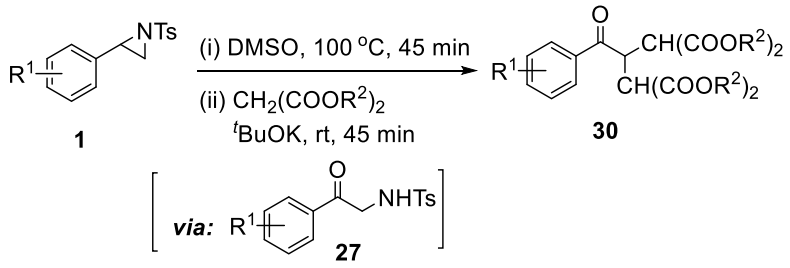


Scheme 2.41

Some other transformations of *α*-aminoketones were studied and results are presented below.

2.11. SYNTHESIS OF BIS(*β,β′*-DIALKOXY CARBONYL) COMPOUNDS BY OXIDATIVE CLEAVAGE OF AZIRIDINES

We have mentioned above that *α*-aminoketones (**27**) can be easily synthesized from aziridine (**1**) by short-term heating in DMSO (see Scheme 2.45). In addition, we have observed that subsequent interaction of *α*-aminoketones (**27**) with dialkylmalonates led to the formation of 2-benzoyl malonates (**30**) with yields of 70-88% (Scheme 2.42). This approach can be considered as a convenient and simple way for the synthesis of bis(*β,β′*-dialkoxy carbonyl) derivatives through the reaction between *N*-tosylaziridines and malonate esters under ambient air using ^{t}BuOK in DMSO solvent (Scheme 2.42). In this procedure *α*-aminoketones were путукфеув *in situ* from aziridines in DMSO solvent and, at the second step were transformed to the target bis(*β,β′*-dialkoxy carbonyl) derivatives *via* tandem process. The reaction conditions are mild, metal-free, and the products are obtained in good yields with very short reaction time at room temperature. To the best of our knowledge this is the first report where aziridines have been introduced to synthesize bis(*β,β′*-dialkoxy carbonyl) derivatives.

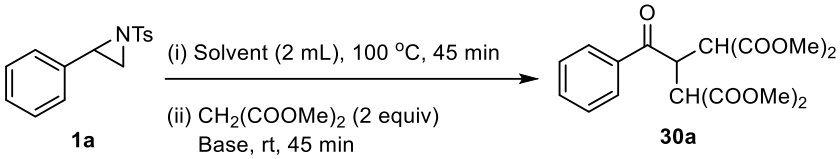


Scheme 2.42

We started our study by mixing 2-phenyl-1-tosylaziridine (**1a**, 1 mmol) in DMSO (2 mL), and the reaction mixture was stirred at 100 °C temperature for 45 min. Next, 2 equiv. of dimethyl malonate and 1 equiv. of K_2CO_3 were added to the reaction mixture and stirred for another 45 min at room temperature. Gratifyingly, the expected bis(*β,β′*-dimethoxy carbonyl) compound (tetramethyl 2-benzoylpropane-1,1,3,3-tetracarboxylate, **30a**) was obtained in 55% yield. Encouraged by this result, we carried out the reaction under different conditions to optimize the reaction conditions, and the results are summarized in Table 2.37. First, we fixed the solvent and temperature. In presence of 1 equiv. of mild bases like K_2CO_3 and Cs_2CO_3 55% and 70% yield of the desired product was obtained respectively (entries 1 & 2, Table 2.37), whereas by using Et_3N (1 equiv.) only 23% yield was isolated (entry 3, Table 2.37). By using other organic bases like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) the yield increased up to 72% and 74% respectively (entries 4 & 5, Table 2.37). The best result was obtained by using 1 equiv. very strong bulky base ^{t}BuOK and 88% yield was isolated (entry 6, Table 2.37).

By decreasing amount of the base the yield decreased (76%) as well as by increasing the amount of base to 2 equiv. the yield again decreased (85%) (entries 7 & 8, Table 2.37). Other common organic solvents (such as CH_3CN, toluene, 1,2-DCE, DCM) were not so effective for this conversion (entries 9–12, Table 2.37). Further, we have observed that the reaction did not proceed without base in DMSO (entry 13, Table 2.37). Finally, the optimized reaction conditions were achieved by carrying out the reaction in DMSO at 100 °C for 45 min and then in presence of malonate ester (2 equiv.) with 1 equiv. of ^{t}BuOK at room temperature for another 45 min under ambient air (entry 6, Table 2.37).

Table 2.37. Optimization of the reaction conditions[a]

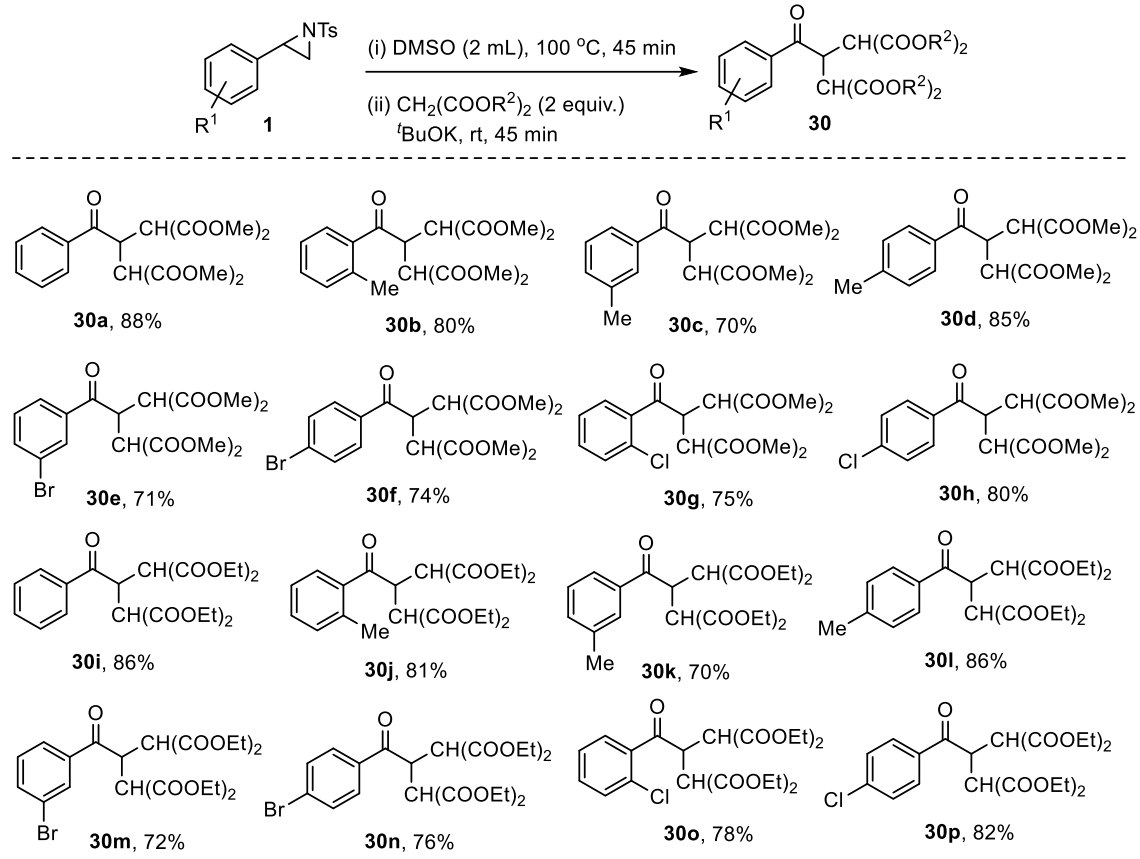


1a 30a

Entry	Solvent	Base	Yield[b] (%)
1	DMSO	K_2CO_3 (1 equiv.)	55
2	DMSO	CS_2CO_3 (1 equiv.)	70
3	DMSO	Et_3N (1 equiv.)	23
4	DMSO	DBU (1 equiv.)	72
5	DMSO	DABCO (1 equiv.)	74
6	**DMSO**	**^{t}BuOK (1 equiv.)**	**88**
7	DMSO	^{t}BuOK (0.5 equiv.)	76
8	DMSO	^{t}BuOK (2 equiv.)	85
9	CH_3CN	^{t}BuOK (1 equiv.)	32
10	Toluene	^{t}BuOK (1 equiv.)	20
11	1,2-DCE	^{t}BuOK (1 equiv.)	25
12	DCM	^{t}BuOK (1 equiv.)	27
13	DMSO	-	ND[c]

[a]***Reaction conditions***: 1 mmol of **1a**, 2 mmol of malonate ester in presence of solvent (2 mL) and bases (as stated). [b]All are isolated yields. [c]Not detected in TLC.

With the optimized reaction conditions in hand, the substrate scope of this tandem protocol was investigated, and the results are presented in Scheme 2.43. Substrate scopes were achieved by using various substituted aziridines (**1**) with different active methylene containing nucleophiles like dimethyl malonate (DMM) and diethyl malonate (DEM). During optimization we have observed that 2-phenyl-1-tosylaziridine (**1a**) reacted with DMM to afford excellent yield (**30a**, 88%).



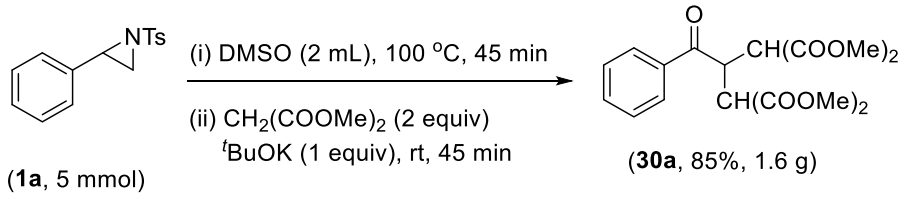
Reaction conditions: All reactions were carried out in 1 mmol scale; **1** (1 mmol), malonate esters (2 mmol), and ^{t}BuOK (1 equiv.) in DMSO (2 mL). All are isolated yields.

Scheme 2.43

N-Tosyl aziridine with electron-donating substituent (such as –Me) at the *ortho*- and *para*-position of the phenyl ring reacted with DMM to afford the corresponding bis(*β*-dimethoxycarbonyl) in excellent yields (**30b**, **30d**). But -Me substituent at the *meta*- position the yield slightly decreased (**30c**, 70%). Electron-withdrawing groups (such as −chloro, and –bromo) on the phenyl ring of the aziridine moiety at different positions efficiently reacted with DMM and offered good yields. For example, bromo- substituted aziridines at *meta*- (**30e**) and *para*- (**30f**) positions gave the desired products in 71% and 74% yields respectively (**30e** & **30f**). On the other hand, for chloro- substituted aziridines at *ortho*- and *para*- positions the yields were better (75% and 80% for **30g** and **30h** respectively). This strategy was also extended to another malonate ester

(such as DEM) to prove the general applicability of this present procedure which was disadvantage of the previous methods.[4b] Simple 2-phenyl-1-tosylaziridine (**1a**) reacted with DEM very smoothly and gave excellent yield (**30i**, 86%). Compounds having electron-donating substituents at *ortho*- and *meta*- positions 81% and 70% yields of the products respectively (**30j** and **30k**). It is also notable that for the electron-donating substituent (-Me) at *para*- position the yield amusingly increased (**30l**, 86%). Electron withdrawing group like -bromo at *meta*- and *para*- positions of the phenyl ring of the aziridine moiety 72% and 76% yields were obtained (**30m** and **30n**) whereas in case of -chloro substituent at *ortho*- and *para*– positions gave better yields (78% for **30o** and 82% for **30p**).

Moreover, the impending synthetic applicability of this protocol was investigated on the gram scale using the model reaction in our laboratory setup. As shown in Scheme 2.44, the reaction could afford 1 g of product (**30a**) in 85% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of bis(*β*-dimethoxy or *β*-diethoxy carbonyl) derivatives.

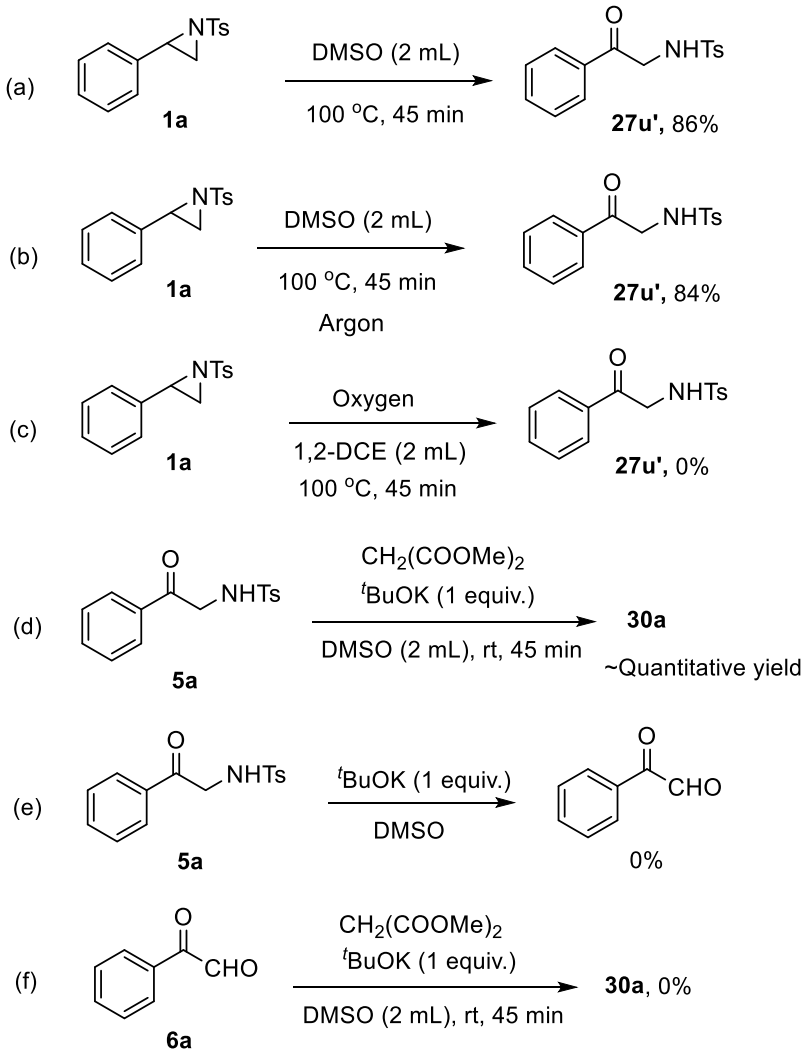


Scheme 2.44

It is worth mentioning that all these reactions were performed in an open atmosphere and are not sensitive to air and moisture. All the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. The reaction conditions were mild enough and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all the reaction combinations giving rise to high yields of the desired products and regioselectivity of the protocol.

A few control experiments were carried out to obtain a better understanding of the mechanistic pathway of the reaction (Scheme 2.45). First of all, we synthesized the corresponding *α*-aminoketone (**27u′**) according to our previously reported method [352]. In addition, when 2-phenyl-1-tosylaziridine (**1a**) was treated with dry DMSO at 100 °C for 45 min *α*-aminoketone (**27u′**) was obtained in 86% yield (Scheme 2.45a). The same reaction under an argon atmosphere also gave a satisfactory yield (Scheme 2.45b) which proves that the oxygen comes from the DMSO solvent. But the reaction of aziridine (**1a**) using molecular oxygen in 1,2-DCE produced no *α*-aminoketone (**27u′**) (Scheme 2.45c). Next, when *α*-aminoketone (**27u′**) was subjected to the

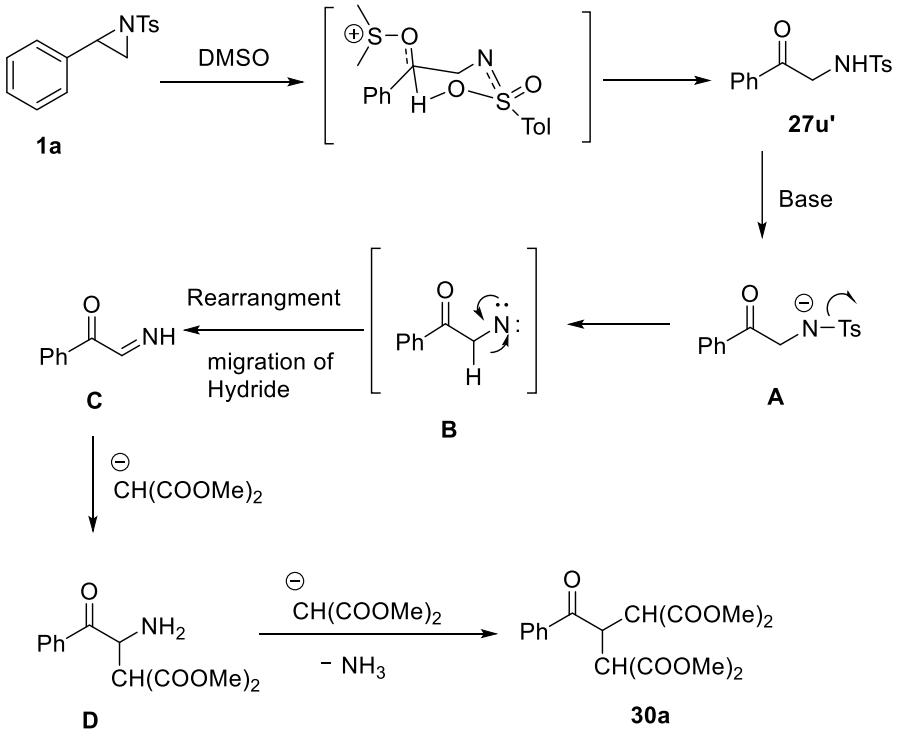
optimized reaction conditions, the corresponding desired final product **30a** was obtained in a quantitative yield (Scheme 2.45d). Furthermore, *α*-aminoketone (**27u′**) was isolated from the reaction mixture by quenching the reaction after 45 min. These results indicate that the reaction proceeds through the formation of *α*-aminoketone (**27u′**). In addition, we did not observe the formation of phenylglyoxal when *α*-aminoketone (**27u′**) was treated with a base in DMSO (Scheme 2.45e). Even under the standard reaction conditions, phenylglyoxal did not afford the desired condensed product (**30a**) by reacting with DEM (Scheme 2.45f) which indicated that no such intermediate (phenylglyoxal) was formed during the reaction.



Scheme 2.45

Based on the literature data [353, 354] and our control experiments, a probable mechanism was proposed (Scheme 2.46). In the first step, 2-phenyl-*N*-tosylaziridine (**1a**) forms *α*-aminoketone (**27u′**) as an intermediate by oxidative cleavage in the presence of DMSO according to the literature [353]. In the presence of a base this *α*-aminoketone (**27u′**) releases a proton to produce an anionic intermediate [**A**]. In the next step a nitrene intermediate [**B**] [354] is formed by

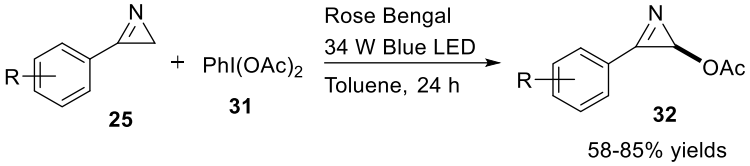
the elimination of a –tosyl (Ts) group from the intermediate [**A**]. This nitrene intermediate [**B**] produces imine [**C**] by rearrangement. This intermediate imine [**C**] is the key component of the reaction, where, in the first step the nucleophilic addition of the active nucleophile of malonate ester produces another intermediate [**D**]. The final step involves the substitution of the amino group of the intermediate [**D**] by another nucleophile which gives the desired product (**30a**).



Scheme 2.46

2.12. VISIBLE-LIGHT-INDUCED REGIOSELECTIVE C(sp^3)-H ACYLOXYLATION OF ARYL-2*H*-AZIRINES WITH (DIACETOXY)IODOBENZENE

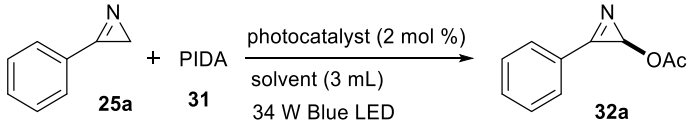
In 2*H*-azirines, selective C-H-functionalization in the cycle is a non-trivial task, since it can be accompanied by an easy opening of the ring. It is known from the literature that (diacetoxy)iodobenzene (PIDA) can be successfully used to activate the C(sp^3)-H bond in oxidative cross dehydrogenative coupling reactions (CDC), including in 2*H*-azirines under conditions of catalysis by transition metals. On the other hand, photo-catalyzed direct C-H functionalization using organic photooxidation-reduction catalysts is of interest for synthetic organic chemistry. As a follow-up to these studies, a combined effort has been applied involving 2*H*-azirines and PIDA as the reagent for selective C(sp^3)-H oxidation using an organophotoredox catalyst (Scheme 2.47). According to literature, this is the first approach for the synthesis of acyloxylated aryl-2*H*-azirines using an organophotoredox catalyst.



Scheme 2.47

Initially, the reaction with 3-phenyl-2*H*-azirine (**25a**, 1 mmol) using photocatalyst eosin Y (2 mol%) by irradiation with a 34 W blue LED lamp in toluene has been examined. The reaction was continued under ambient air for 24 h using PIDA (**31**) (Table 2.38, entry 1). The desired product 3-phenyl-2*H*-azirin-2-yl acetate (**32a**) has been isolated in 40% yield. There was no improvement of the yield after 36 h. Only 13% of the desired product was obtained in the absence of photocatalyst (Table 2.38, entry 2). No considerable improvement of the reaction was observed by increase of reaction time for 24-36 h. The reaction by variation of different parameters has been summarized in Table 2.38.

Table 2.38. Optimization of the reaction conditions.[a]



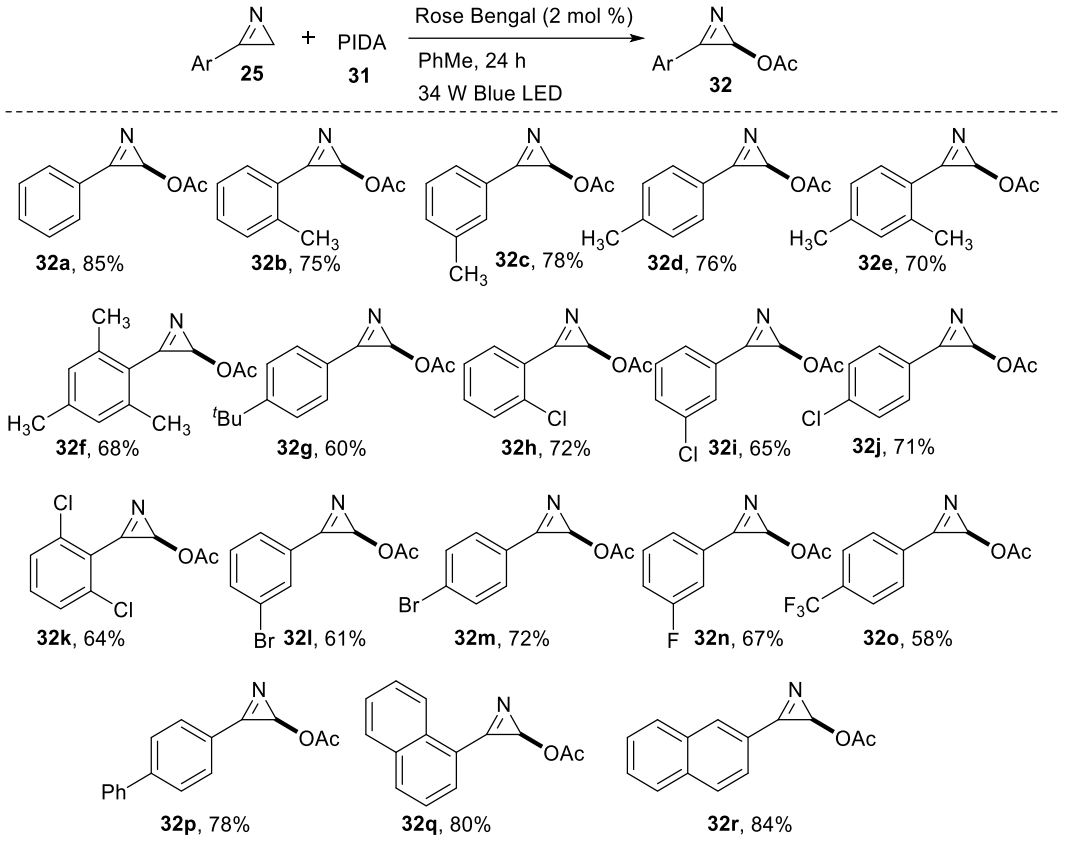
Entry	Photocatalyst (2 mol %)	Solvent	Yields (%)[b]
1	Eosin Y	toluene	40
2	--	toluene	13

3	$Ru(bpy)_3Cl_2·6H_2O$	toluene	25
4	$Ir(ppy)_3$	toluene	30
5	Rose Bengal	toluene	85
6	Rose Bengal	MeCN	20
7	Rose Bengal	DCM	nd[b]
8	Rose Bengal	1,2-DCE	25
9	Rose Bengal	benzene	16
10	Rose Bengal	acetone	45
11	Rose Bengal	CCl_4	25
12	Rose Bengal	THF	38
13	Rose Bengal	DMF	nd[b]
14	Rose Bengal	DMSO	<10
15	Rose Bengal	1,4-dioxane	35
16	Rose Bengal	MeOH	nd[b]
17	Rose Bengal	EtOH	<10
18	Rose Bengal	H_2O	nd[b]
19	Rose Bengal	toluene	55[c], 86[d]
20[e]	Rose Bengal	toluene	Trace

[a]***Reaction conditions:*** **25a** (1.0 mmol), PIDA (**31**, 1.0 mmol), photocatalyst (2 mol %), 34 W blue LED at room temperature using different solvents (3 mL) for 24 h. [b]nd = not detected in TLC. [c]1 mol % RB was used. [d]3 mol % RB was used. [e]The reaction was carried out in dark condition.

For this process several photocatalysts, like $Ru(bpy)_3Cl_2·6H_2O$, $Ir(ppy)_3$ and Rose Bengal (RB), were studied. Among these, RB was found to be the best and afforded 85% yield of our desired product (Table 2.38, entry 5). A variety of aprotic polar solvents like acetonitrile, DCM, 1,2-DCE, benzene, acetone, CCl_4, THF, DMF, DMSO, 1,4-dioxane, as well as few protic polar solvent like MeOH, EtOH and H_2O (Table 2.38, entries 6-18) have been tested for this reaction. No solvents were found effective like toluene, which gives 85% acyloxylated product (**32a**) (Table 2.38, entry 5). Increase of the amount of rose bengal from 2 mol% to 3 mol% found no considerable change but from 2 mol% to 1 mol% decreased the yield (Table 2.38, entry 19). Furthermore, the desired coupling product was not observed in dark condition (Table 2.38, entry 20). So, the reaction using 2 mol% of RB as photoredox catalyst, PIDA, toluene as solvent on irradiation with 34 Watt blue LED under aerobic condition is the optimized reaction conditions (Table 2.38, entry 5).

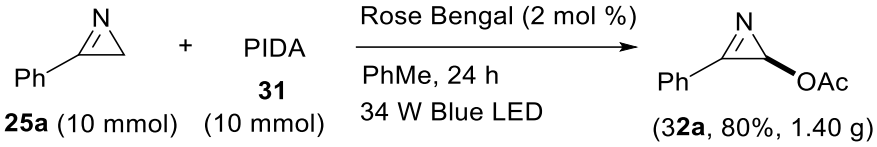
Table 2.39. Substrates scope for the C(sp^3)-H acyloxylation of aryl-2*H*-azirines.



Reaction conditions: 3-aryl-2*H*-azirine (**25**, 1 mmol), PIDA (**31**, 1 mmol), Rose Bengal (2 mol %), toluene (3.0 mL) under 34 W Blue LED irradiation for 24 h, ambient air, room temperature.

Then this reaction for acyloxilation of C(sp^3)-H of various substituted aryl 2*H*-azirines has been explored (Table 2.39). A series of acyloxylated azirine were obtained (**32a-32r**) using this protocol. It has been observed that simple 3-phenyl-2*H*-azirine (**25a**) produced the desired 3-phenyl-2*H*-azirin-2-yl acetate (**32a**) in 85% yield. 3-Aryl-2*H*-azirines bearing electron-donating group (like -methyl) in -*ortho*, -*meta* and -*para* positions of the phenyl ring efficiently reacted with PIDA to provide good yields (**32b,** 75%; **32c,** 78%; **32d,** 76%). As well as, reactions with disubstituted and trisubstituted electron-donating methyl group proceeded efficiently (**32e,** 70%; **32f**, 68%). It has ben found that strong electron-donating substituent (like *tert*-butyl) underwent smooth reaction under optimal reaction conditions (**32g,** 60%). Similarly, 2*H*-azirines with electron withdrawing groups like chloro-, bromo-, fluoro- underwent smooth reaction and afforded the products (**32h,** 72%; **32i,** 65%; **32j,** 71%; **32k,** 64%; **32l,** 61%; **32m,** 72%; **32n,** 67%). Furthermore, the acyloxylation reaction proceeded smoothly in case of strong electron-withdrawing group (–CF_3) containing aryl-2*H*-azirine which afforded moderate yield (**32o,** 58%). Aryl-2H-azirine with 4-biphenyl, 1- and 2-naphthyl moieties produced the desired products **32p** (78%), **32q** (80%), **32r** (84%).

It is worthy to mention that, though this protocol is applicable for a wide range of aryl-2*H*-azirine it was not possible to apply it for 2*H*-azirine with alkyl- and heteroaryl- moieties. Attempts were taken to prepare many heteroaryl- and alkyl- substituted 2*H*-azirines with the alkenes such as 3-vinyl pyridine and 3-vinylthiophene, *n*-octene, allyl bromide, cyclohexene, cyclooctene etc. The reactions have been carried out under aerobic conditions. Inert atmosphere is not required and no other external additives or oxidants are needed for this reaction. Under the present reaction conditions no decomposition or polymerization has been observed. No by-products have been isolated in any reaction. The reactions are regioselective and high yielding. Characterizations of the synthesized known compounds were made by comparison of spectral data. For newly synthesized compounds IR, analytical and HRMS data has been given.

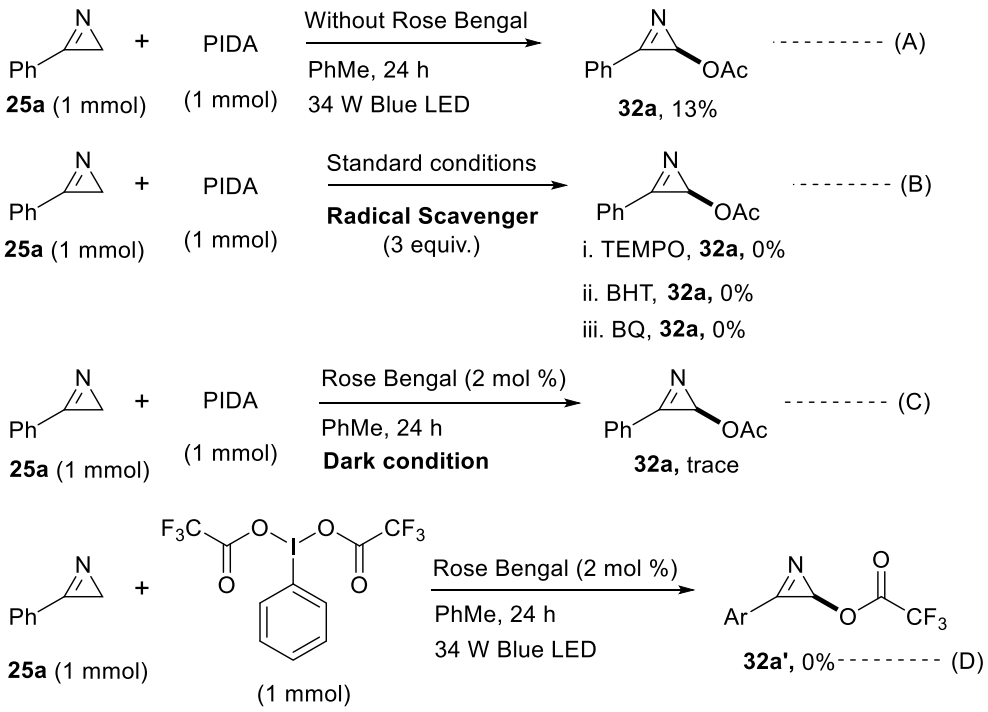


Scheme 2.48

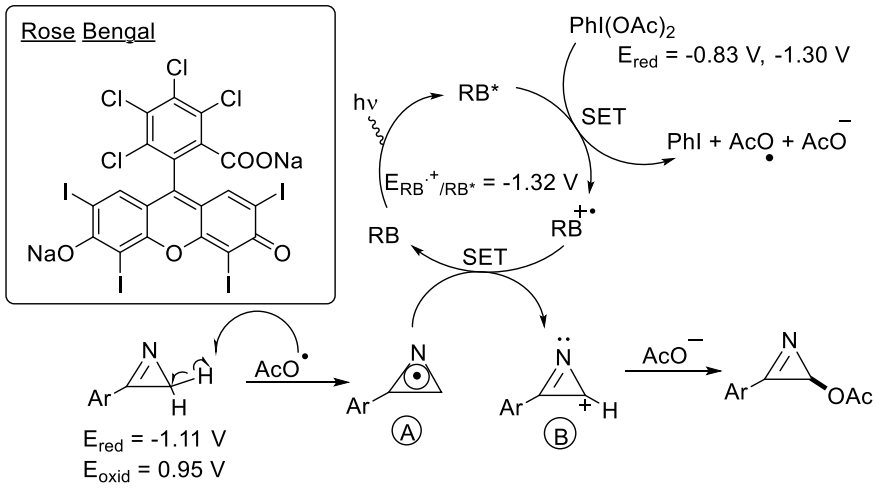
The reaction of 3-phenyl-2*H*-azirine (**25a**) has been carried out in large scale (10 mmol). The reaction is very much effective and 80% (1.40 gm) yield of the desired product has been isolated (Scheme 2.48).

To predict the probable mechanism, few additional experiments have been carried out (Scheme 2.49). In the absence of a photocatalyst a less amount of product was obtained (Scheme 2.49, eq A). Use of radical scavengers like 2,6-di-*tert*-butyl-4-methyl phenol (BHT), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and *p*-benzoquinone (BQ) the reaction did not proceed (Scheme 2.49**,** eq B). Moreover, in the dark condition a trace amount of desired product was obtained (Scheme 2.49, eq C). So, the reaction involved a radical pathway which requires light irradiation. In addition, by using other hypervalent iodine(III) reagents such as [bis(trifluoroacetoxy)iodo]benzene (Scheme 2.49, eq D) and 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole-4-carboxylic acid 1-oxide (*m*IBX) no reaction proceed and it remains ineffectual under the optimized reaction conditions.

By comparing excited-state oxidation potential (−1.32 V vs Fc+/Fc) and reduction potential (+0.49 V vs Fc+/Fc) values of the photocatalyst (RB*) with redox potentials of PIDA (Ered = −1.30 V, −0.83 V vs Fc+/Fc) and azirine (**25a)** (Eoxid = +0.95 V; Ered = −1.11 V vs Fc+/Fc), it is reasonable to suggest that the excitedstate of rose bengal (RB*) has been oxidized by PIDA. On the basis of the control experiments (Scheme 2.49), and cyclic voltammetry, a probable mechanism of the reaction has been proposed, as shown in Scheme 2.50.



Scheme 2.49

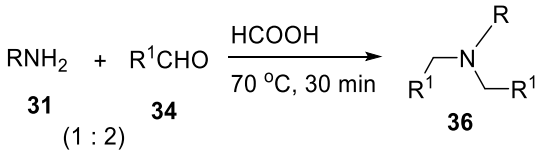


Scheme 2.50

The excited rosebengal (RB^{*}) takes an electron (SET) from PIDA and transforms it to acetoxy radical ($CH_3COO^{\cdot}$), PhI (detected from the reaction mixture by GC–MS), and acetate anion (CH_3COO^{-}), whereas RB became a cation radical ($RB^{+\cdot}$). The hydrogen atom abstraction by acetoxy radical could lead to the formation of 2*H*-azirine radical [**A**]. The 2*H*-azirine radical [**A**] could then transfer one electron to the cation radical ($RB^{+\cdot}$), leading to the formation of intermediate carbocation B and ground state of photocatalyst (RB) and completes the photocatalytic cycle. Finally, carbocation B in the subsequent reaction with the acetate anion affords the desired product.

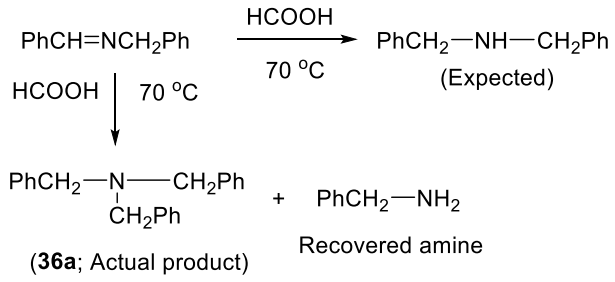
2.13. CHEMOSELECTIVE SYNTHESIS OF TERTIARY AMINES FROM ALDEHYDES BY REDUCTIVE AMINATION

It is known that aziri(di)ne can be transformed into azomethine derivatives. On the other hand, azomethines themselves are capable of cyclizing into these azaheterocycles. *i.e*., azomethines can be considered both as products of the transformation of aziri(di)nes and as their synthetic precursors. Therefore, within the framework of our work, we investigated the synthetic methods and the reactivity of azomethines in some key transformations. A typical method for the synthesis of azomethines is the interaction of the carbonyl and amino components in a solvent. It is also known that azomethines are capable of being reduced in the presence of various types of reducing agents, including in the presence of formic acid/formates, giving secondary amines. We found that during the direct interaction of amines and aldehydes in formic acid, tertiary amines were formed with yields up to 30% under heating conditions. In this work a variety of tertiary amines are prepared by changing both the amines as well as aldehydes (Scheme 2.51).



Scheme 2.51

Initially, reduction of ready-made imine isolated from the benzylamine and benzaldehyde in presence of formic acid has been done. Gratifyingly, only the tertiary amine (**36a**) with fewer yields has been acquired and recovered some unreacted amine within 30 min. Any corresponding secondary amine was not observed in this reaction (Scheme 2.52). To make confirm the total structural analysis of the compound (**36a**) by ^{1}H NMR, ^{13}C NMR and X-ray analysis has been done.



Scheme 2.52

To prove the possible pathway and to get an optimized reaction conditions some experiments by taking a mixture of benzaldehyde (**34a**) and benzylamine (**31a**) instead of prepared imines followed by reduction assuming that the formic acid may catalyze the imine formation as well as the reduction has been carried out (Table 2.40). Study commenced taking readily available

benzyl amine (**31a**) and benzaldehyde (**34a**) as the model substrates in the presence of equivalent amount of formic acid at 70 °C for 30 min under neat conditions (Table 2.40, entry 1). The desired tribenzylamine (**36a**) was obtained in 40% yield after 30 min and no further improvement was noticed by increasing reaction time; in addition 40% benzyl amine was recovered. Best result was obtained by using 1 equiv of amine (**31a**) and 2 equiv of aldehyde (**34a**) in presence of 1 equiv of formic acid at 70 °C where 75% yield was isolated (Table 2.40, entry 3).

Table 2.40. Optimization of the reaction conditions.[a]

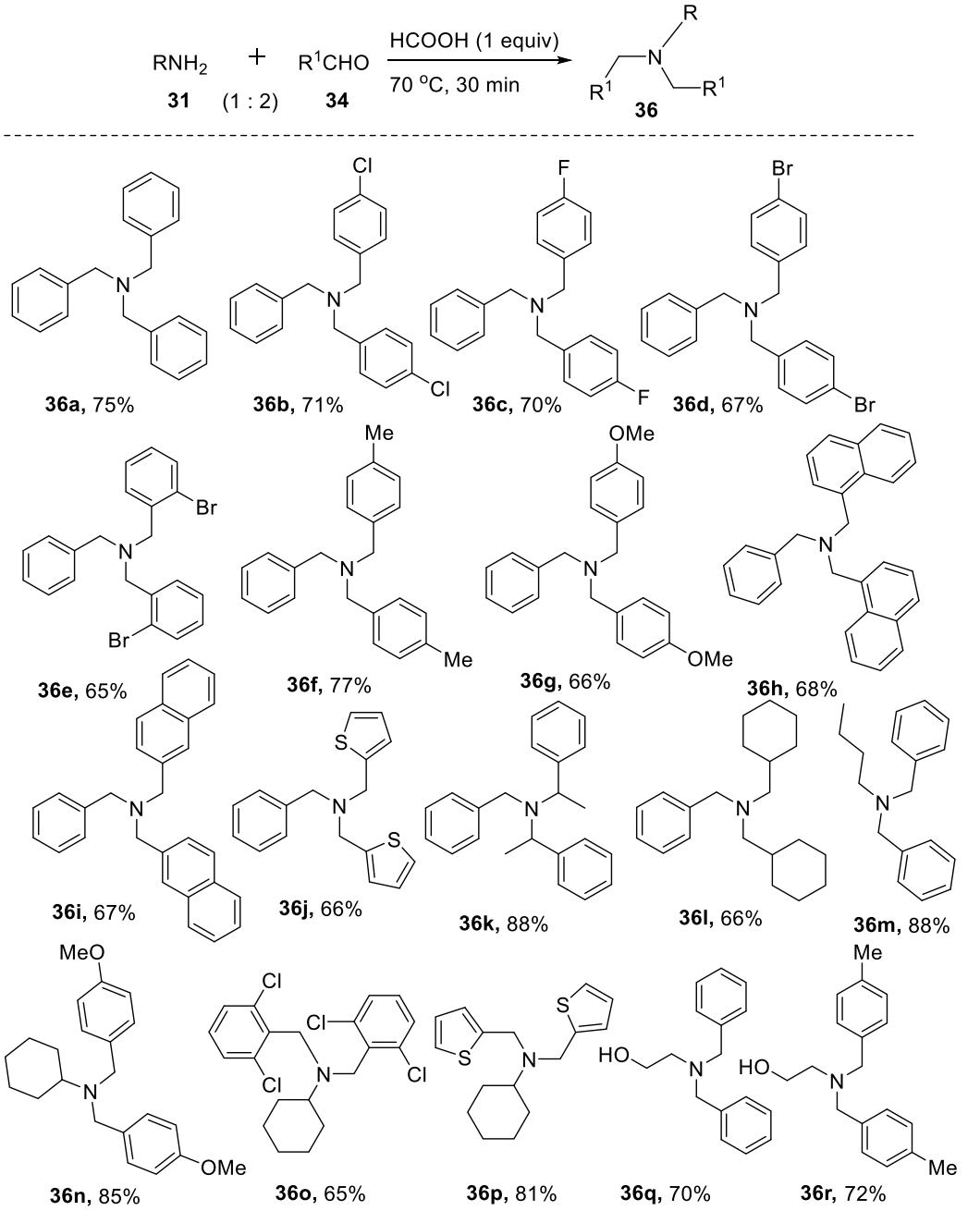
$PhCH_2NH_2$ **(31a)**	PhCHO **(34a)**	$(PhCH_2N)_3N$ **(36a)** (% yield)	$PhCH_2NH_2$ **(31a)** (% recovered)
1	1	40	40
1	1.5	60	20
1	2	75	trace
1	2.5	45	0[b]

[a]***Reaction conditions*****:** A mixture of **31a** and **34a** was stirred at 70 °C for 30 min in presence of formic acid (1 equiv. amount with respect to benzyl amine). All are isolated yields. [b]Recovered benzaldehyde (**34a**) was 20%.

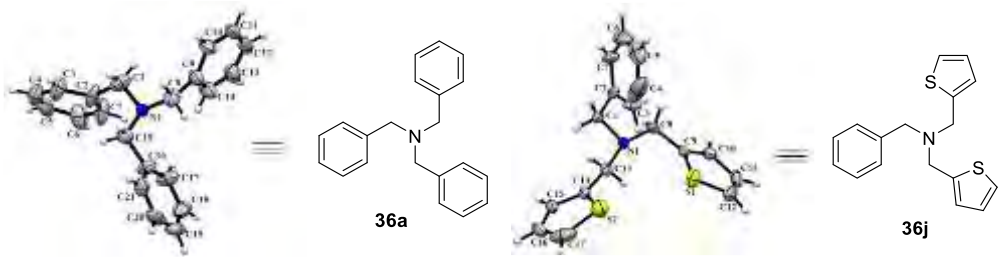
A variety of combinations of aldehydes and amines has been tested to generalize this observation as described in Table 2.41. Initially we started our work by treating a mixture of benzylamine (**31a**) and benzaldehyde (**34a**) at 70°C for 30 min and successfully isolated the desired product tribenzylamine (**36a**) in 75% yield. It was observed that benzaldehyde substituted with electron withdrawing such as chloro-, fluoro- and bromo-groups as well as electron donating groups like Me, OMe reacted easily with benzylamine (**31a**) to get the desired products (**36b-36g**) in good yields. 1-Naphthaldehyde and 2-naphthaldehyde reacted smoothly with benzylamine (**31a**) to get the products *N,N*-bis(naphthalen-1-ylmethyl)(phenyl)methanamine (**36h**) and *N*-benzyl(naphthalen-2-yl)-*N*-(naphthalen-2-ylmethyl)methanamine (**36i**) in 68% and 67% yields respectively. Similarly hetero-aldehyde like thiophene-2-carbaldehyde, aliphatic aldehyde such as 2-phenylpropanal and cyclohexanecarbaldehyde reacted smoothly with benzylamine (**31a**) to offer the desired products (**36j, 36k** and **36l**) in satisfactory yields. Aliphatic amine butan-1-amine underwent smooth reaction with benzaldehyde (**34a**) under present conditions yielding the corresponding product (**36m**) in 88% yield. Another aliphatic amine cyclohexanamine reacts smoothly with substituted benzaldehydes yielding the corresponding products (**36n** and **36o**) in 85% and 65% yields, respectively. Also the cyclohexanamine readily reacted with thiophene-2-carbaldehyde yielding the related product (**36p**) in 81% yield. Another aliphatic amine 2-aminoethan-1-ol also reacted easily with benzaldehyde and tolyl aldehydes to affird the desired

products (**36q** and **36r**) in 70% and 72% yields respectively. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data and X-ray crystallographic analysis of tribenzylamine (**36a**) and *N*-benzyl-1-(thiophen-2-yl)-*N*-(thiophen-2-ylmethyl)methanamine (**36j**) was performed to confirm the structure of the product as shown in Figure 2.8.

Table 2.41. Substrate scope for the synthesis of sterically hindered tertiary amines (**36**).



Reaction conditions: amine (**31**, 1.0 mmol), aldehyde (**34**, 2.0 mmol) and formic acid (1.0 mmol, 46 mg) at 70°C for 30 min.



CCDC 1578549 **CCDC 1575142**

A) B)

Figure 2.8. X-Ray crystallographic data for the structure of compounds **36a** (A) and **36j** (B)

To make a firm conclusion the following crossed experiments by taking two different carbonyl compounds along with the amine has been carried out and observed the expected mixture of products. The results are summarized in Table 2.42. Here it was observed that for each case except the 1st case two different aldehydes reacted with the amine yielding three types of product. These three products obtained from the reaction of amine and aldehyde R^1CHO (product 1), the reaction of amine and aldehyde R^2CHO (product 3) and the reaction of amine with both the aldehydes (product 2).

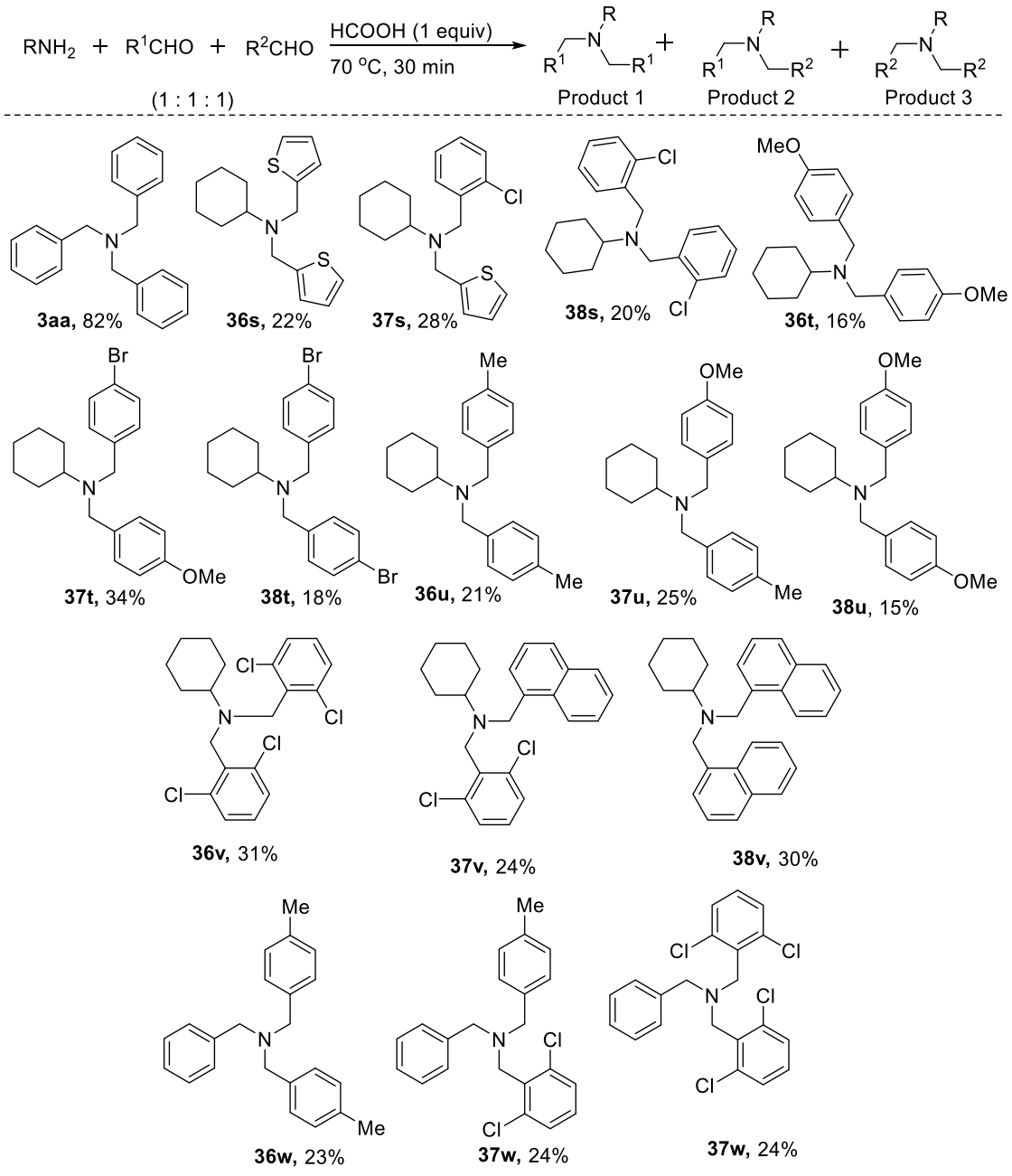
Finally, some secondary amines using the same reaction conditions were observed (Table 2.43). Pyridin-2-amine reacted with benzaldehyde affording the secondary amine (**36′a**) in 85% yield. So, some reactions with some aniline derivatives containing electron withdrawing group as well as containing both the electron withdrawing and electron donating group were carried out. Surprisingly, they reacted smoothly with benzaldehyde to give the secondary amines (**36′b-36′e**) predominantly over the tertiary amines. The yield of the compounds is in the range of 70–87%. Possibly this is due to the steric factor of the amines; the secondary amine is reluctant towards the formation of the immium ion followed by reduction and consequently secondary amine is the final product.

However, this procedure did not work when a mixture (2:1) of ketones and various amines have been taken (Scheme 2.53). Accordingly some experiments were performed by taking the mixture (2:2:1) of ketones and aldehydes with amine to examine the chemoselectivity of our method. It was observed that selectively the tertiary amines from aldehyde only and the unreacted ketones have been recovered from the reaction mixture. The results are described in Scheme 2.54.

From the results it can be concluded that HCOOH initially at lower temperature breaks (hydrolysis) certain imines to produce the carbonyl compounds and amines but at higher temperature the undissociated imines may reduce to the corresponding secondary amine. After hydrolysis the corresponding carbonyl compounds combine with reduced secondary amine to yield

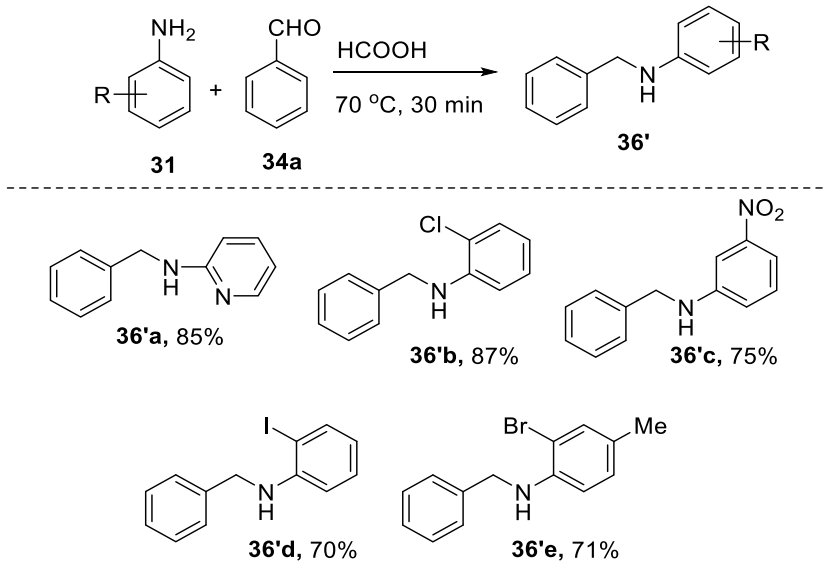
the iminium ions which get reduced by $HCOO^-$ to furnish the corresponding tertiary amine. There were no unreacted amines when two equivalents of aldehydes have been used in this reaction. So, the reaction is going by one equivalent of formic acid which reduces the half of the imine (**I**) and half as iminium ion [**II**] as shown Scheme 2.55.

Table 2.42. Crossed experiments to synthesize tertiary amines.

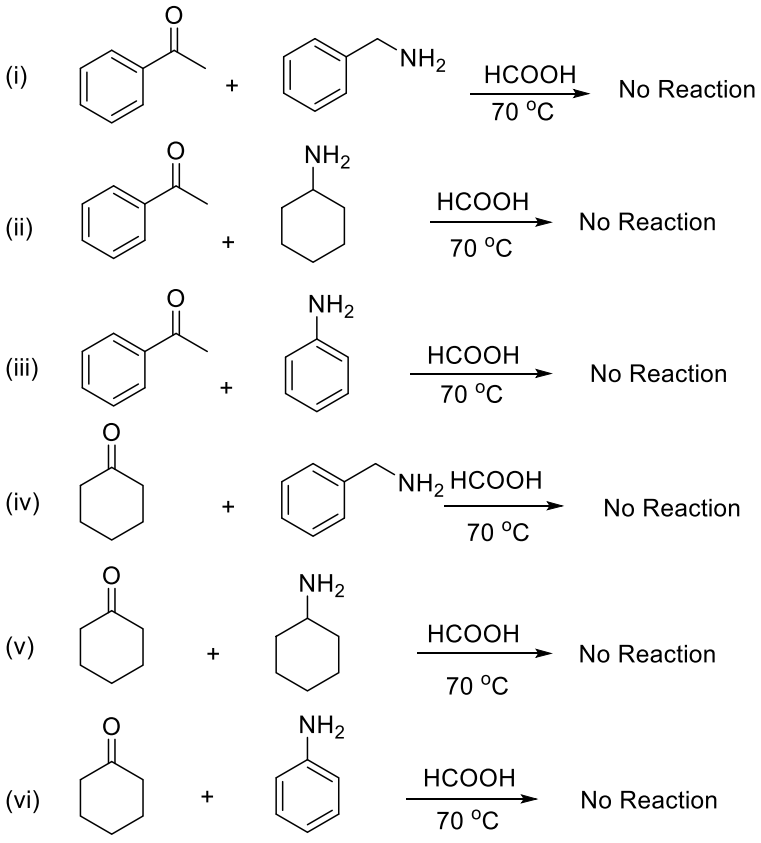


Reaction conditions: amine (**31**, 1.0 mmol), aldehyde (**34**, 1.0 mmol), aldehyde (**35**, 1.0 mmol) and formic acid (1.0 mmol, 46 mg) at 70 °C for 30 min.

Table 2.43. Formation of secondary amines.

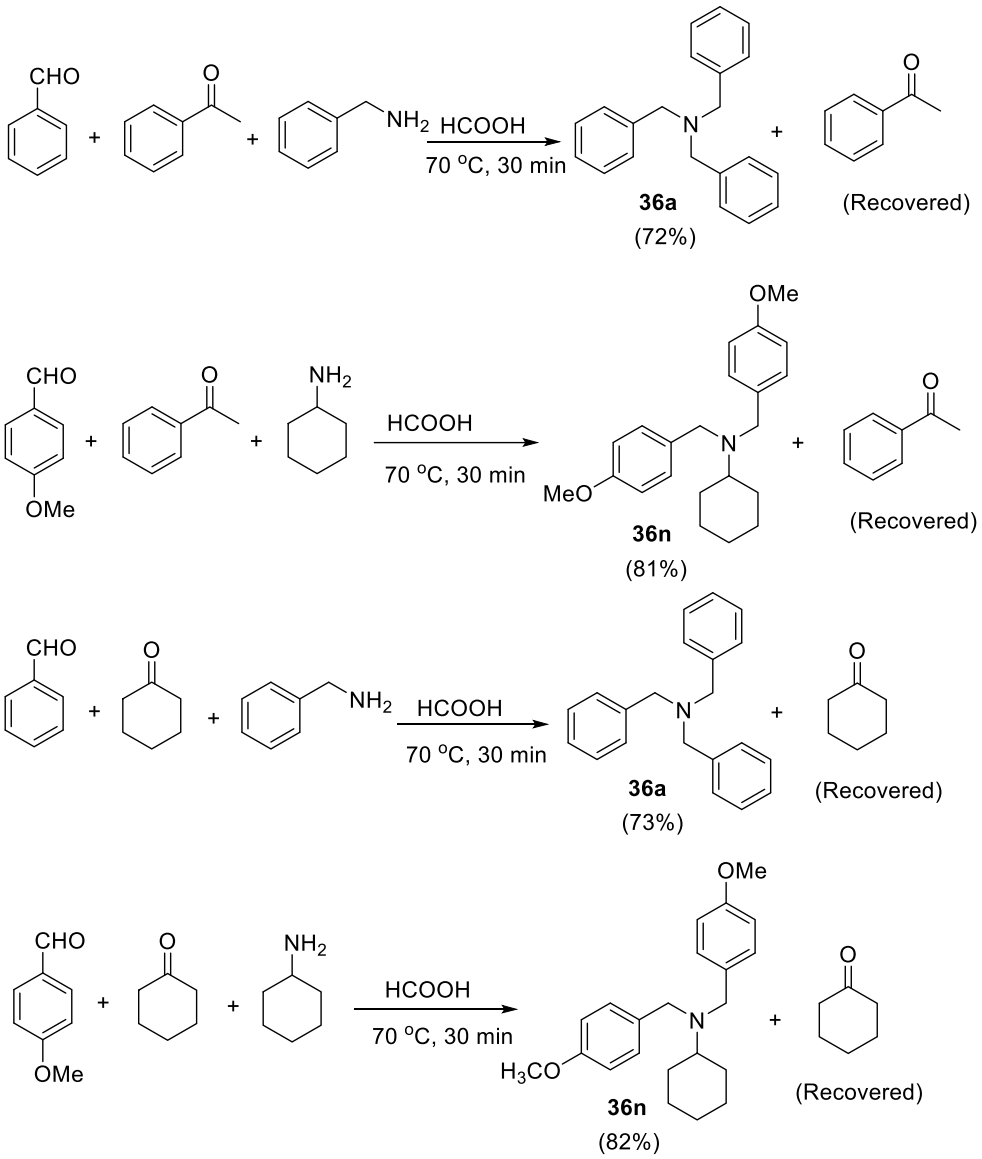


Reaction conditions: amine (**31**, 1.0 mmol), aldehyde (**34a**, 1.0 mmol) and formic acid (1.0 mmol, 46 mg) at 70°C for 30 min.

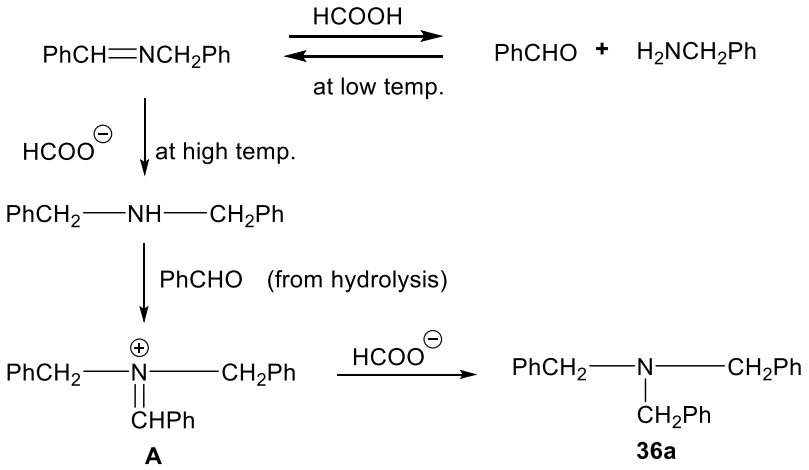


Reaction conditions: amine (1.0 mmol), ketones (2.0 mmol) and formic acid (1.0 mmol, 46 mg) at 70 °C for 30 min.

Scheme 2.53



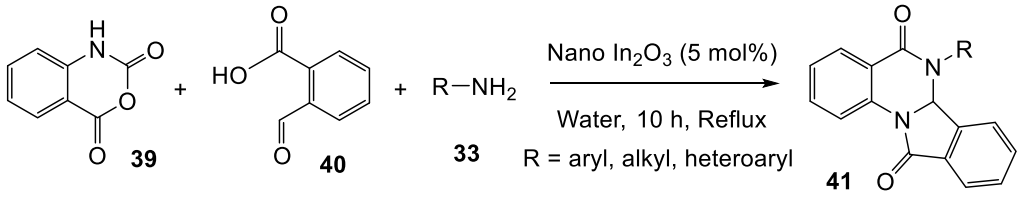
Scheme 2.54



Scheme 2.55

2.14. SYNTHESIS OF ISOINDOLO[2,1-*a*]QUINAZOLINES

In the development of our research, we investigated the interaction of primary amines with some carbonyl compounds under the conditions of using "green" synthesis methods. For example, we have developed a convenient method for the indium oxide nanoparticle catalyzed synthesis of isoindolo[2,1-*a*]quinazoline derivatives *via* a water mediated three-component coupling of 2-carboxybenzaldehyde, isatoic anhydride and various amines (Scheme 2.56).



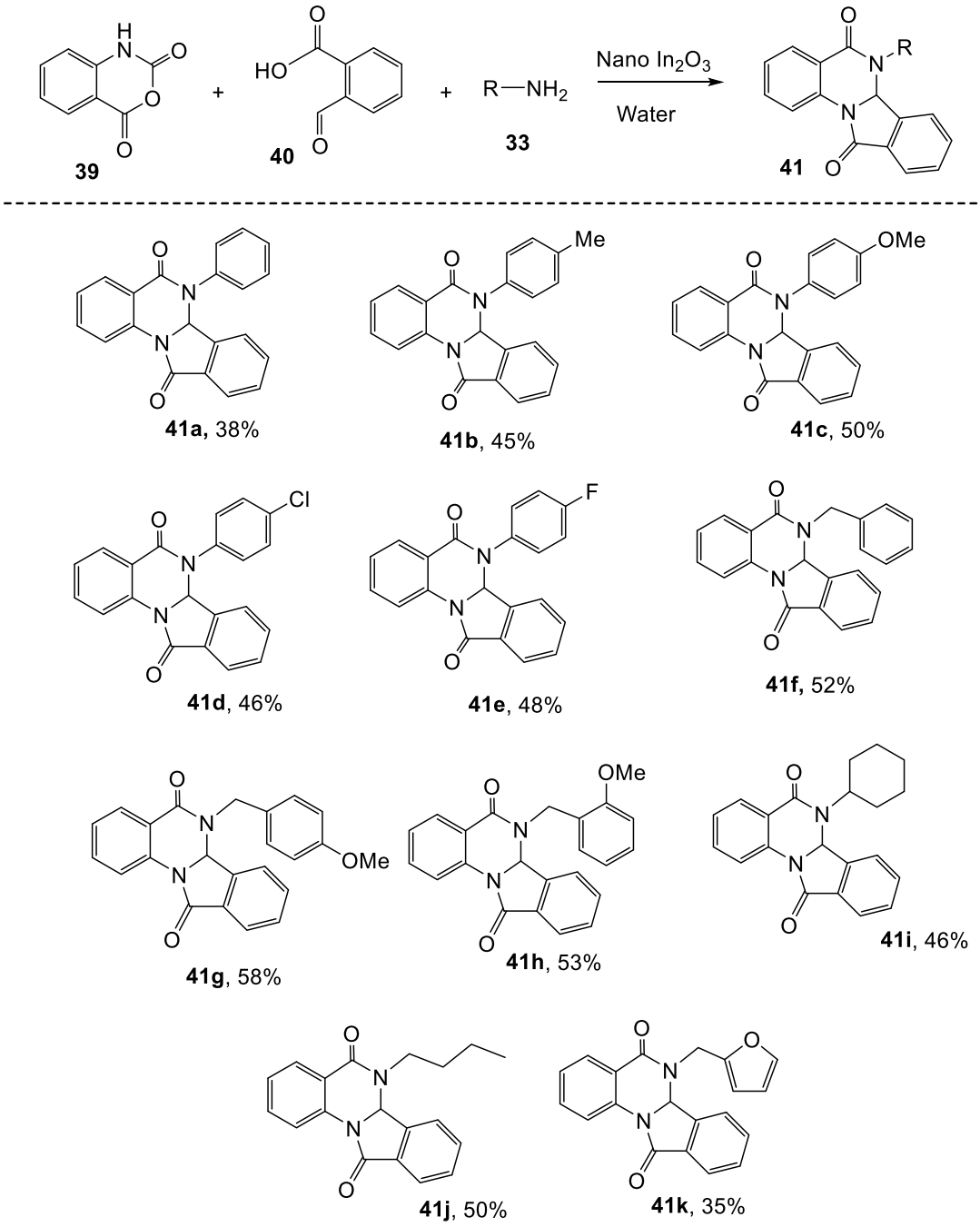
Scheme 2.56

The scope of this 'on-water' reaction was investigated with a variety of amines. As shown in Table 2.44, a wide range of aromatic, aliphatic and heteroaryl amines afforded the corresponding isoindolo[2,1-*a*]quinazoline derivatives with excellent yields. Several sensitive functionalities such as, –OMe (**41c**, **41g**, **41h**), halogens –Cl, –F (**41d**, **41e**) were unaffected under the present reaction conditions. In addition, aliphatic amines such as cyclohexyl amine, and *n*-butyl amine were also produced the desired products with high yields (**41i**, **41j**). It is also notable that heteroaryl amine produced the afforded product without polymerization (**41k**). Benzyl amine as well as substituted benzyl amines generated the isoindolo[2,1-*a*]quinazoline derivatives with satisfactory yields (**41f**, **41g**, **41h**). The substrate scope of the present method has proven to be broad. In addition, we have developed a greener reaction condition bearing lower *E*-factor [336] of 0.45 and 0.47 in the cases of synthesizing products (**41a)** and (**41b**) respectively.

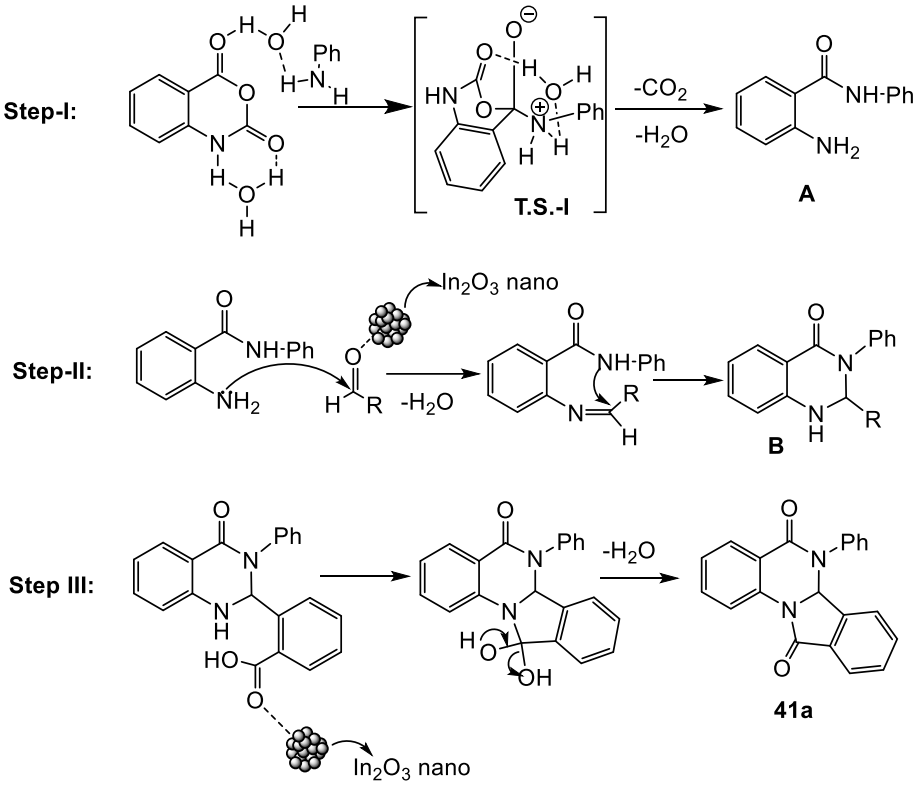
The probable mechanism of this multicomponent reaction is outlined in Scheme 2.57. Water plays an important role in this transformation. Probably, water molecules accelerate the first step of the reaction. Electrophilicity of the carbonyl group of the isatoic anhydride is increased by many folds through hydrogen bonding between water molecule and oxygen atom of the carbonyl group. Due to the hydrogen bond between oxygen atom of the water molecule and hydrogen atom of amine, nucleophilicity of the amine is increased. As a consequence of this dual activation, T.S.-I get more stability which intern lead to the formation of intermediate [**A**] by elimination of CO_2 and H_2O. After that intermediate [**A**] reacts with the aldehydes in presence of In_2O_3 nano to form the quinazolinone intermediate [**B**] (Step II), which upon intramolecular cyclization afforded the product (Step III). Nano CuO might activate the aldehyde and carboxylic acid through the co-

ordination with the oxygen of the corresponding carbonyl group which facilitate the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon.

Table 2.44. Scope of amines in nano In_2O_3 catalyzed 'on-water' synthesis of isoindolo[2,1-*a*]quinazolines.



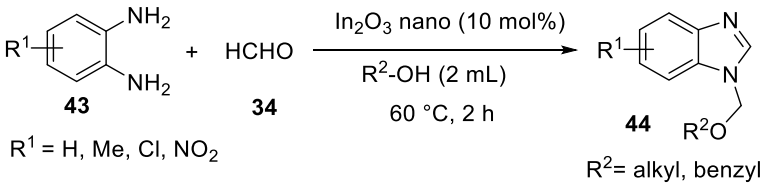
Reactions conditions: 1 mmol of **39**, 1 mmol of **40** and 1 mmol of **33** in the presence of In_2O_3 nano (5 mol%) in 3 mL of water under refluxed conditions for 12 h. Isolated yields.


Step-I:
T.S.-I
A
Step-II:
In2O3 nano
-H2O
B
Step III:
-H2O
41a
In2O3 nano

Scheme 2.57

2.15. SYNTHESIS OF *N*-ALKOXYLATED BENZIMIDAZOLES IN PRESENCE OF NANO INDIUM OXIDE

In addition to aromatic and aliphatic monoamines the reactions of some diamines with carbonyl compounds in the presence of various catalytic systems were studied. Thus, we have developed a convenient method for the synthesis of *N*-substituted benzimidazole derivatives (*N*-alkoxylated benzimidazoles) by means of multicomponent reaction (MCR) between *o*-phenylenediamines (OPDs), formaldehyde and alcohols in a one pot domino fashion by using indium oxide nano particles (nano In_2O_3) (Scheme 2.58). To the best of our knowledge, this is the first time report for the synthesis of *N*-alkoxylated benzimidazoles by means of MCR in the presence of metal NPs.



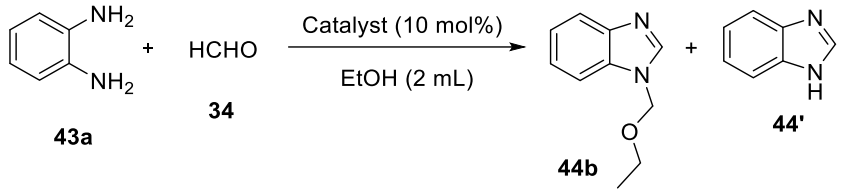
Scheme 2.58

We initiated our observation by using *o*-phenylenediamine (**43a**, 0.5 equiv.) and 37% formaldehyde (**34**, 2 equiv.) in presence of In_2O_3 nano (5 mol%) in ethanol solvent (2 mL) at 60 °C under the open air. To our delight, the reaction underwent smoothly and 50% of 1-(ethoxymethyl)-1*H*-benzo[*d*]imidazole (**44b**) and 15% of 1*H*-benzo[d]imidazole (**5**) were isolated within 2 h (Table 2.45, entry 1). Inspired by this result when we increased the amount of In_2O_3 nano to 10 mol% the yield of the reaction increased significantly with 76% of product (**44b**) and 20% of product (**44′**) (Table 2.45, entry 2). Further increase of catalyst loading did not improve the yield of the reaction (Table 2.45, entry 3). Again, the yield of the reaction did not improve appreciably by increasing the reaction time but with reducing the reaction time the yield of both products (**44b**) and (**44′**) decreased considerably (Table 2.45, entry 6 & 7). Increasing temperature from 60 °C to 80 °C no considerable improvement has been noticed whereas, decreasing the temperature decreased the yield of both products (**44b**) and (**44′**) (Table 2.45, entry 4 & 5). We examined other indium catalysts like $InCl_3$, $In(OTf)_3$, $Zn(OTf)_2$ as well as CuO NPs, but the target products were isolated in lower yields (Table 2.45, entry 8-11). And in the absence of any catalyst, the reaction did not proceed at all (Table 2.45, entry 12).

Next, for enrichment of our present methodology and to get a better knowledge of the solvent effects, we have screened a series of mix-solvent as summarized in Table 2.46. For polar aprotic solvents like DCE, THF, 1,4-dioxane and DCM in the presence of ethanol the targeted

product (**44b**) was found in 20-35% yields (Table 2.46, entry 1-4). When we used nonpolar aprotic solvent like toluene, DCB and also polar aprotic solvent like DMSO with ethanol we got lower and a trace amount of yield of the products (Table 2.46, entry 5-7). We acquired the best result affording 76% yield of our desired product (**44b**) when we used only ethanol as a solvent (Table 2.46, entry 8). So, the optimized condition was considered by using 10 mol% of In_2O_3 nano and ethanol as solvent as well as reactant (2 mL) at 60 °C for 2 h.

Table 2.45. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield of **44b** (%)[b]	Yield of **44′** (%)[b]
1	In_2O_3 nano (5)	60	2	50	15
2	In_2O_3 nano (10)	60	2	76	20
3	In_2O_3 nano (20)	60	2	76	20
4	In_2O_3 nano (10)	80	2	70	20
5	In_2O_3 nano (10)	40	2	45	10
6	In_2O_3 nano (10)	60	4	72	20
7	In_2O_3 nano (10)	60	1	60	15
8	$InCl_3$ (10)	60	2	58	21
9	$In(OTf)_3$ (10)	60	2	55	20
10	$Zn(OTf)_2$ (10)	60	2	<10	NR[c]
11	CuO nano (10)	60	2	55	20
12	-	60	2	NR[c]	NR[c]

[a]***Reaction conditions:*** All the reactions were carried out on 1 mmol scale, **43a** (1 equiv.), 37% HCHO (**34**, 2 equiv.) in presence of catalyst and ethanol (2 mL). [b]Isolated yield. [c]NR = no reaction.

Table 2.46. Screening of the solvent effects.[a]

Entry	Solvents (2 mL)	Yield of **44b** (%)[b]	Yield of **44′** (%)[b]
1	DCM	25	<10
2	DCE	35	15
3	THF	20	<5

4	1,4- dioxane	20	<8
5	DMSO	trace	ND[c]
6	Toluene	15	<8
7	DCB	20	<8
8	EtOH	76	20

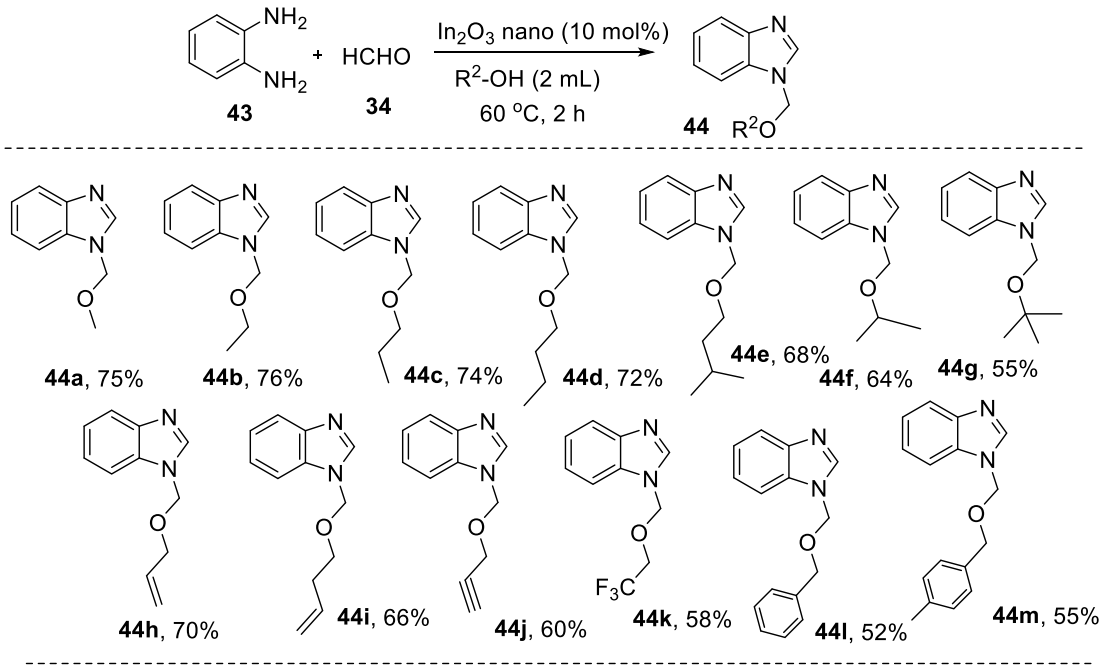
[a]***Reaction conditions:*** All the reactions were carried out on 1 mmol scale, **43a** (1 equiv.), 37% HCHO (**34**, 2 equiv.) in presence of different solvent (2 mL). [b]Isolated yield. [c]ND = not detected in TLC.

After optimization, we explored the substrate scope of this methodology and the results are summarized in Table 2.47 & 2.48. A library of *N*-alkoxylated benzimidazole derivatives was synthesized by varying different alcohols. At first, we used different primary as well as saturated alcohols like methanol, propanol, butanol and isobutanol which were subjected to react with 1,2-phenylenediamine (**43**) and it was observed that the corresponding desired products were obtained in 68-76% yields (**44a**-**44e**). Next, in case of secondary and tertiary alcohols, the corresponding desired products were obtained in moderate yields (**44f** & **44g**). Remarkably, unsaturated alcohols like prop-2-en-1-ol, but-3-en-1-ol and propargyl alcohol were also examined and the reactions underwent without any difficulty to produce the products (60-70% yields) (**44h**-**44j**). Even, trifluoroethanol responded for this present protocol affording moderate yield (**44k**). Moreover, benzyl alcohol and 4-methyl benzyl alcohol also gave the alkoxylated products in 52% and 55% yields (**44l, 44m**). For all these reactions no additional solvent was needed but the alcohols themselves acted as solvent and reactant.

Next, our attention was turned to the use of substituted phenylenediamine to expand the general applicability of the present procedure (Table 2.48). Surprisingly, 4-chlorobenzene-1,2-diamine reacted well with ethanol but produced the *N*-alkoxylated product (86%) with 1:1 mixture of isomers (**44o**). We have also changed alcoholic part like methanol, propanol but we get the same mixture of the product (**44n**, **44p**) with good yields (85% and 84% respectively).

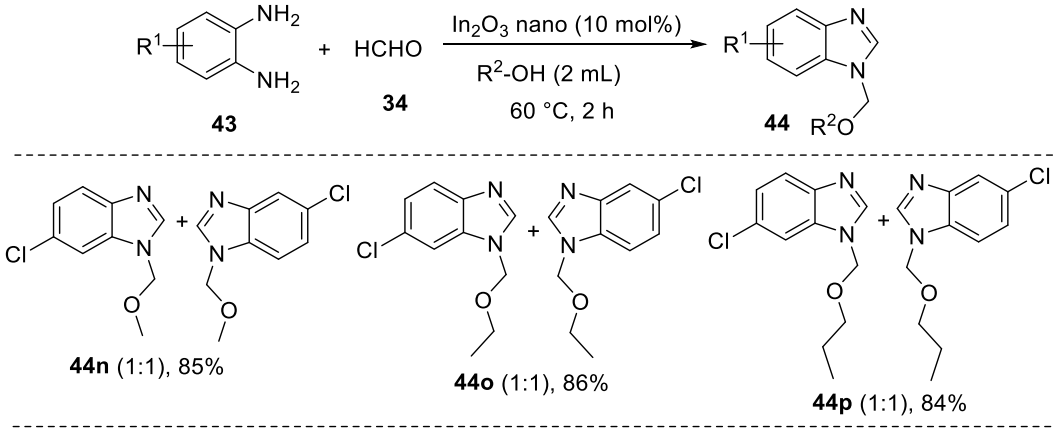
Moreover, the synthetic applicability of this protocol was investigated on the gram scale using the model reaction in our laboratory setup. As shown in Scheme 2.59, the reaction could afford 1.27 g of product (**44b**) in 72% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of *N*-alkoxylated benzimidazole derivatives.

Table 2.47. Substrates scope using different alcohols.

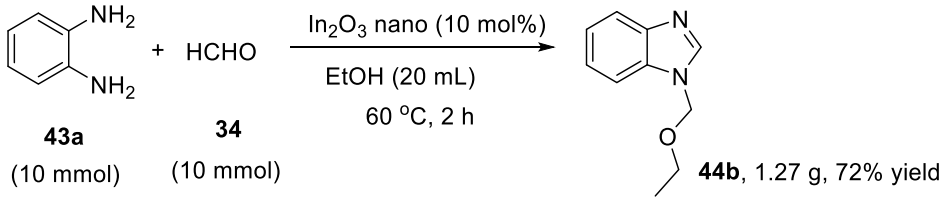


Reaction conditions: All reactions were carried out on 1 mmol scale, **43** (1 equiv.), 37% HCHO (**34**, 2 equiv.) in presence of In_2O_3 nano (10 mol%) and alcohol (2 mL).

Table 2.48. Substrates scope using substituted *o*-phenylenediamines.



Reaction conditions: All the reactions were carried out on 1 mmol scale, **43** (1 equiv.), 37% HCHO (**34**, 2 equiv.) in presence of In_2O_3 nano and alcohol (2 mL).



Scheme 2.59

To check the recyclability of the catalyst, it was separated from the reaction mixture by ultra centrifugation, washed with water, dried under vacuum followed by drying at 110 °C and reused for further reactions. The catalyst maintained its high level of activity even after being recycled five times for synthesizing product (**44b**) as shown in Table 2.49. The morphology of nano-In_2O_3 was determined by HRTEM. A comparative study of the HRTEM of the fresh catalyst and the recovered catalyst after five cycles shows that the catalyst does not undergo agglomeration during the recycling process (Figure 2.9).

Table 2.49. Recycling of In_2O_3 nanoparticles for synthesizing product (**44b**)[a]

No. of cycle	Yields (%)[b]	Catalyst recovery (%)
1	76	97
2	75	95
3	75	93
4	72	90
5	71	87

[a]***Reaction conditions:*** Carried out with 1 mmol of **43a** and 1 mmol of **34** in the presence of catalyst in ethanol (2 mL) at 60 °C for 2 h. [b]Isolated yields.

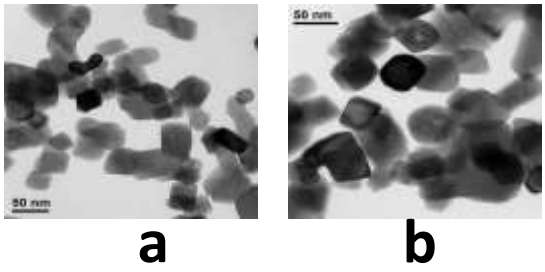
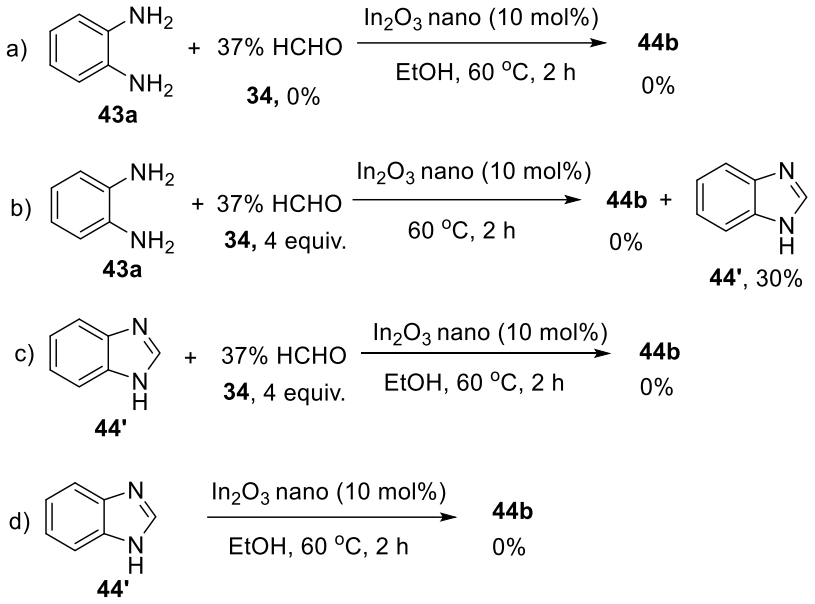


Figure 2.9. HRTEM images of (a) fresh In_2O_3 nanoparticles and (b) In_2O_3 nanoparticles after the fifth cycle.

For the mechanistic investigation of our present protocol, we performed some control experiments (Scheme 2.60). When the reaction was carried out in absence of formaldehyde no desired product was obtained (Scheme 2.60a). Again, the targeted product was not formed in the absence of ethanol but we got only benzimidazole product (**44′**) in 30% yield (Scheme 2.60b). Next, by taking only synthesized benzimidazole (**44′**) instead of 1,2-phenylenediamine (**43a**) and formaldehyde, no desired product was obtained under the optimized reaction conditions (Scheme 2.60c). Similarly, the present reaction did not proceed when benzimidazole (**44′**) reacted with ethanol in the absence of formaldehyde under the same reaction conditions (Scheme 2.60d). So,

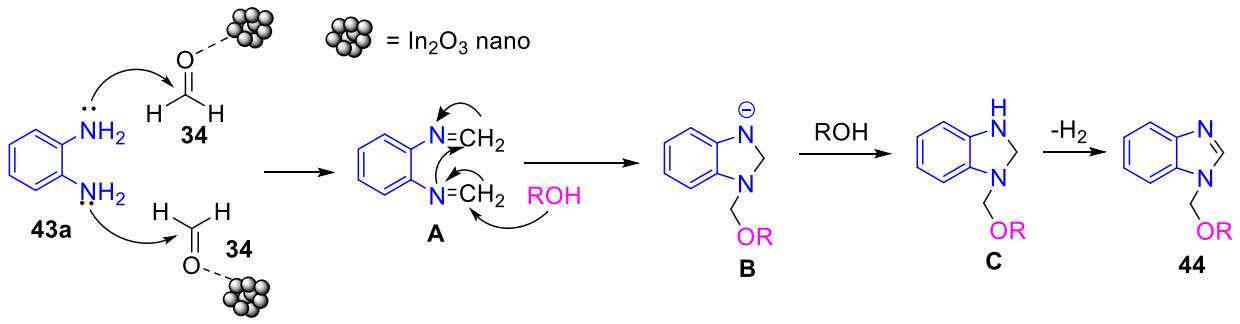
from the above observations, it is clear that the reaction does not proceed *via* the formation of benzimidazole as intermediate.



All reactions were carried out on a 1 mmol scale.

Scheme 2.60

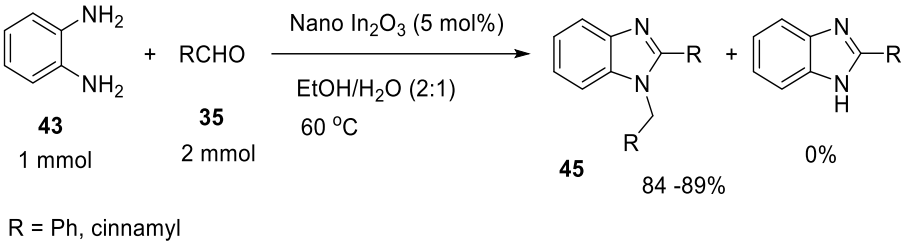
On the basis of these experimental observations, A probable mechanistic pathway has been proposed for the synthesis of *N*-alkoxylated benzimidazole derivatives as shown in Scheme 2.61. Initially, *o*-phenylenediamine (**43a**) reacts with formaldehyde (**34**) to form 1,2-diimine intermediate [**A**]. In_2O_3 nano might activate the formaldehyde through the co-ordination with the oxygen of the corresponding carbonyl group which facilitates the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon. The addition of alcohol with one imine produces the nucleophilic nitrogen which by intra-molecular imine cyclization furnish the intermediate [**B**]. The intermediate [**B**] after protonation gives intermediate [**C**] which on aromatization by dehydrogenation produce the final product.



Scheme 2.61

2.16. SYNTHESIS OF 1,2-DISUBSTITUTED BENZIMIDAZOLES IN PRESENCE OF NANO INDIUM OXIDE

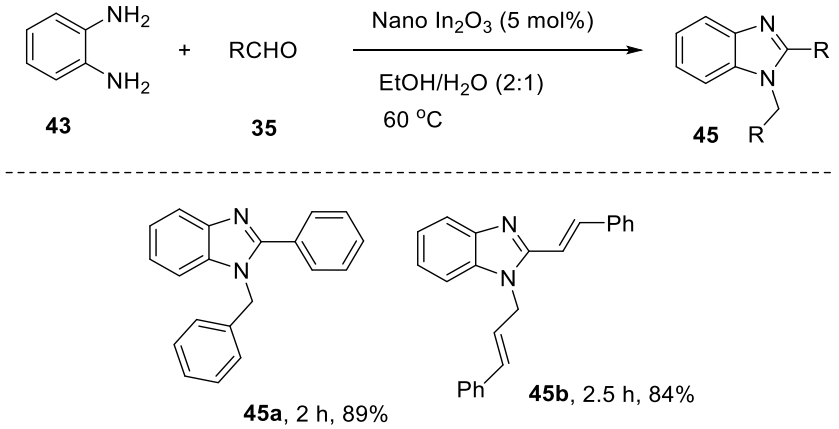
Inspired by the above-mentioned results and using the the same reaction conditions we have developed a synthetic approach to 1,2-disubstituted 1*H*-benzo[*d*]imidazole (**45**) using other aldehydes such as benzaldehyde and cinnamaldehyde. We have observed that a mixture of aldehyde, *o*-phenylenediamine in the presence of nano In_2O_3 (5 mol %) in an EtOH/H_2O (2:1) mixture at 60 ºC furnished 1,2-disubstituted benzimidazoles in good yields (Scheme 2.62).



Scheme 2.62

It was found that simple benzaldehyde as well as *α,β*-unsaturated aldehyde such as cinnamaldehyde reacted well under these conditions (**45a** & **45b**) (Table 2.50). In general, the reactions are fast, and clean. No detectable side products have been traced. 1,2-Disubstituted benzimidazole derivatives were formed in all the cases. However, the synthesis of unsymmetrical 1,2-disubstituted benzimidazole was unsuccessful under the present reaction conditions.

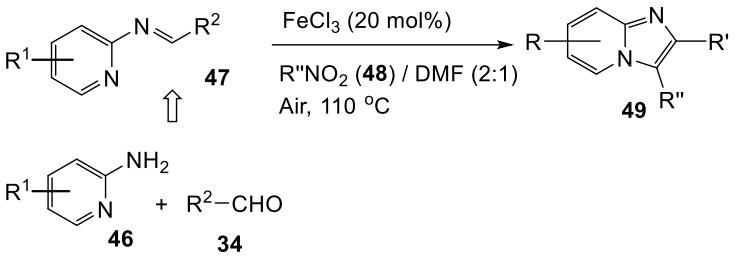
Table 2.50. Synthesis of 1,2-disubstitured benzimidazole derivatives.



Reaction conditions: 1 mmol of **43**, 2 mmol of **35** in presence of 5 mol% nano In_2O_3 at 60 °C in EtOH and H_2O (2:1) mixture.

2.17. SYNTHESIS OF IMIDAZO[1,2-*a*]PYRIDINES BY IRON(III)-CATALYZED THREE-COMPONENT DOMINO STRATEGY

In order to develop efficient approached toward some other fused imidazoles in the presence of other metal catalysts by means of MCRs. To do that by azomethines (**47**) obtained from 2-aminopyridine (**46**) were reacted with nitroalkanes in the presence of iron(III) chloride to afford imidazolo[1,2-*a*]pyridines (**49**) (Scheme 2.63). In addition, we found that this reaction can be done in one-pot without isolation of azomethines. Thus, an efficient, one-pot, three-component domino strategy has been developed for the synthesis of imidazo[1,2-*a*]pyridines using catalytic amount of Fe(III) chloride under ambient air in high yields by the reaction between easily available aldehydes and 2-aminopyridines in a mixture of nitroalkane and DMF (2:1) (Scheme 2.63).

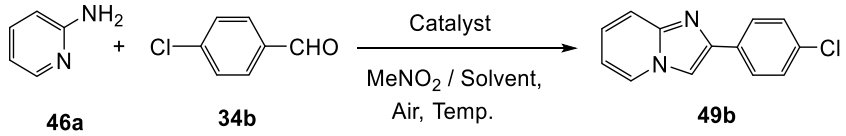


Scheme 2.63

The study was initiated by using 2-aminopyridine **46a** and 4-chlorobenzaldehyde **34b** as the model substrates for this reaction using 20 mol% $FeCl_3$ as the catalyst in nitromethane as solvent for 5 hours at 110 °C. Gratifyingly, the expected product was obtained in 36% yield (entry 1, Table 2.51). Inspired by this result, we tested various iron salts in different solvents as well as varying the temperature (Table 2.51). The use of a mixture of nitromethane and DMF (2:1) as a binary solvent yielded product (**49b**) in 72% (entry 2, Table 2.51). It indicated that the binary solvent system might play an important role for this conversion.[8] So, we examined the model reaction with various binary solvent systems such as nitromethane with DMSO, toluene, CH_3CN etc. It was found that the use of a mixture of nitromethane and DMF (2:1) afforded the product product (**49b**) in maximal yield (entry 6, Table 2.51). Increasing the temperature did not improve the yield whereas decreasing the temperature lowered the yield to 64%. $FeCl_3$ was found to be more effective catalyst compared to other iron salts like $FeBr_3$ and $Fe(OTf)_3$. In this case $FeBr_3$ and $Fe(OTf)_3$ make strong complexes with 2-aminopyridine which probably suppressed the formation of product. 20 mol% $FeCl_3$ was proved to be optimal. By increasing the amount of catalyst (30 mol%) did not improve the yield noticeably (entry 13, Table 2.51) whereas decreasing the amount of catalyst (10 mol%) decreased the yield (entry 14, Table 2.51). In the absence of catalyst no product was observed. Use of any additive like piperidine or acetic acid did not improve

the yield of this transformation (entries 7 & 8, Table 2.51). Thus, optimal reaction conditions were obtained using 2-aminopyridine (**46a**, 1 mmol), 4-chlorobenzaldehyde (**34b**, 1.1 mmol) in presence of 20 mol% of $FeCl_3$ in a mixture of nitromethane and DMF (2:1) at 110 °C (entry 6, Table 2.51) under ambient air.

Table 2.51. Optimization of the reaction conditions.[a]



46a **34b** **49b**

Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Yield (%)[b]
1[c]	$FeCl_3$ (20 mol%)	$MeNO_2$ (3 mL)	110	36
2	$FeCl_3$ (20 mol%)	$MeNO_2$/DMF (1.5/1.5 mL)	110	72
3	$FeCl_3$ (20 mol%)	$MeNO_2$/Toluene (1.5/1.5 mL)	110	28
4	$FeCl_3$ (20 mol%)	$MeNO_2$/DMSO (1.5/1.5 mL)	110	33
5	$FeCl_3$ (20 mol%)	$MeNO_2$/MeCN (1.5/1.5 mL)	110	26
6	**$FeCl_3$ (20 mol%)**	**$MeNO_2$/DMF (2/1 mL)**	**110**	**78**
7[d]	$FeCl_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	110	76
8[e]	$FeCl_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	110	74
9	$FeCl_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	90	64
10	$FeCl_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	130	72
11	$FeBr_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	110	42
12	$Fe(OTf)_3$ (20 mol%)	$MeNO_2$/DMF (2/1 mL)	110	37
13	$FeCl_3$ (30 mol%)	$MeNO_2$/DMF (2/1 mL)	110	79
14	$FeCl_3$ (10 mol%)	$MeNO_2$/DMF (2/1 mL)	110	64
15	--	$MeNO_2$/DMF (2/1 mL)	110	ND[f]

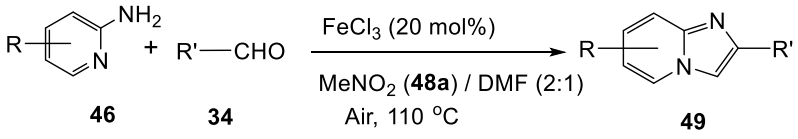
[a] ***Reaction conditions:*** Carried out with 1 mmol of **46a** and 1.1 mmol of **34b** in solvent (3 mL) for 5 h.
[b] Isolated yields.
[c] Reaction carried out under refluxed condition.
[d] 20 mol% piperidine was used as an additive.
[e] 20 mol% AcOH was used as an additive.
[f] Not determined in TLC.

With the optimized reaction conditions in hand, we explored the scope of this reaction (Table 2.52). Our attention was focused on the use of substituted aldehydes and 2-aminopyridines to prove the general applicability of the reaction conditions (**49a**–**49p**). It can be seen that electron-rich and electron-deficient aldehydes reacted efficiently with various 2-aminopyridines to afford the desired products with good yields under the optimized reaction conditions. The chloro- and iodo-substituted benzaldehydes gave the corresponding products (**49b**) and (**49l**) in 78% and 76% yields

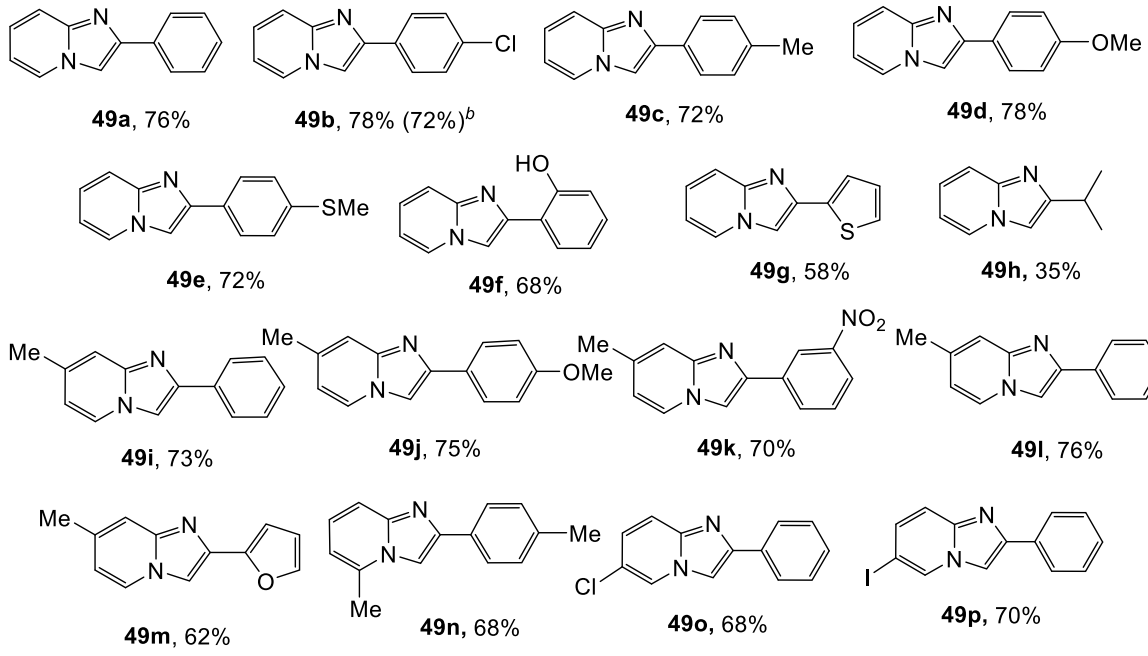
respectively. We were pleased to notice that under the stated conditions, aminopyridines substituted with halogens such as –Cl, and –I (**49o** and **49p**) smoothly reacted with benzaldehyde without forming any dehalogenated products. The aldehyde containing an electron donating OMe group on the aromatic ring also showed good efficiency (**49d** and **49j**).

2-Hydroxybenzaldehyde afforded the corresponding product (**49f**) which is very useful for photophysical studies and displays excited-state intramolecular proton transfer (ESIPT) [185]. In addition, heteroaryl aldehydes such as furfural and thiophene-2-carboxaldehyde could also participate in the multicomponent reaction to produce the desired products in moderate yields without affecting the heterocyclic moieties (**49g** and **4m**). We were delighted to find that the –SMe substituted benzaldehyde was also tolerated under our catalytic conditions with 72% isolated yield (**49e**). Aliphatic aldehyde isobutyraldehyde also afforded the desired product with moderate yield (**49h**). This methodology is also applicable on a gram-scale synthesis. We have successfully prepared the imidazopyridine (**49b**) in 72% yield by the reaction of 2-aminopyridine (20 mmol) with 4-chlorobenzaldehyde (22 mmol).

Table 2.52. Scope of the iron(III)-catalyzed three-component reaction.



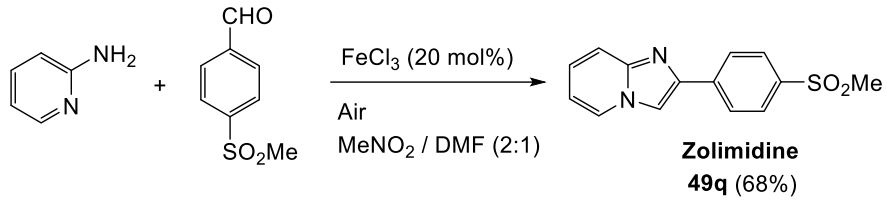
46 **34** **49**



Reaction conditions: **46** (1.0 mmol), **34** (1.1 mmol), $FeCl_3$ (20 mol%), nitroalkane (2.0 mL), DMF (1.0 mL) at 110 ºC for 5 h. All are isolated yields.

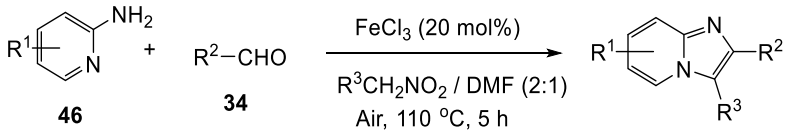
[b] **46** (20.0 mmol), **34** (22.0 mmol), $FeCl_3$ (20 mol%), $MeNO_2$ (40.0 mL), DMF (20.0 mL) at 110 ºC for 5 h.

Thus synthesized compound (**49e**) can be utilized for the synthesis of the marketed drug zolimidine by oxidation employing the reported method [355]. We have also successfully synthesized this drug under our present reaction conditions with good yield (Scheme 2.64).



Scheme 2.64

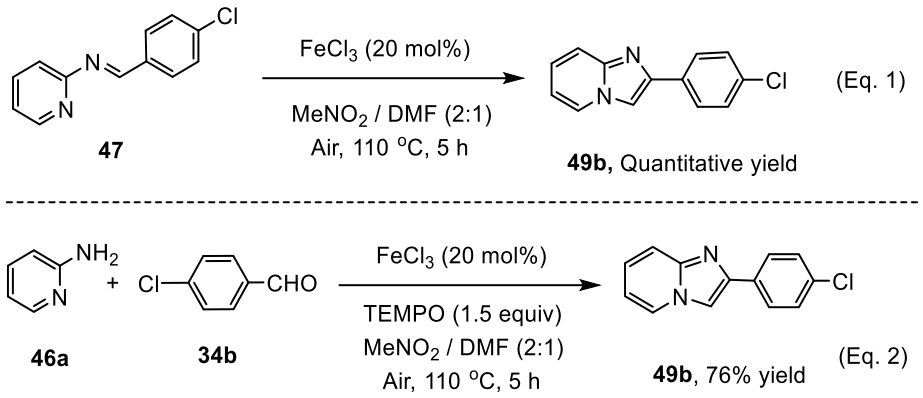
By virtue of our method, we are able to synthesize substituted imidazo[1,2-*a*]pyridines at the C-3 position. The synthesis of 3-substituted imidazo[1,2-*a*]pyridines is possible by changing nitromethane to other nitroalkanes (Scheme 2.65). Both nitroethane and nitropropane worked well under the present reaction conditions. The desired 3-substituted imidazo[1,2-*a*]pyridines were obtained in good yields (**49r**–**49v**). An aliphatic aldehyde also reacted under the optimized reaction conditions (**49t**).



R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = Me, **49r**, 76%
R^1 = H, R^2 = C_6H_5, R^3 = Me, **49s**, 78%
R^1 = 4-Me, R^2 = $(CH_3)_2CH$, R^3 = Me, **49t**, 38%
R^1 = H, R^2 = C_6H_5, R^3 = Et, **49u**, 75%
R^1 = 4-Me, R^2 = C_6H_5, R^3 = Et, **49v**, 74%

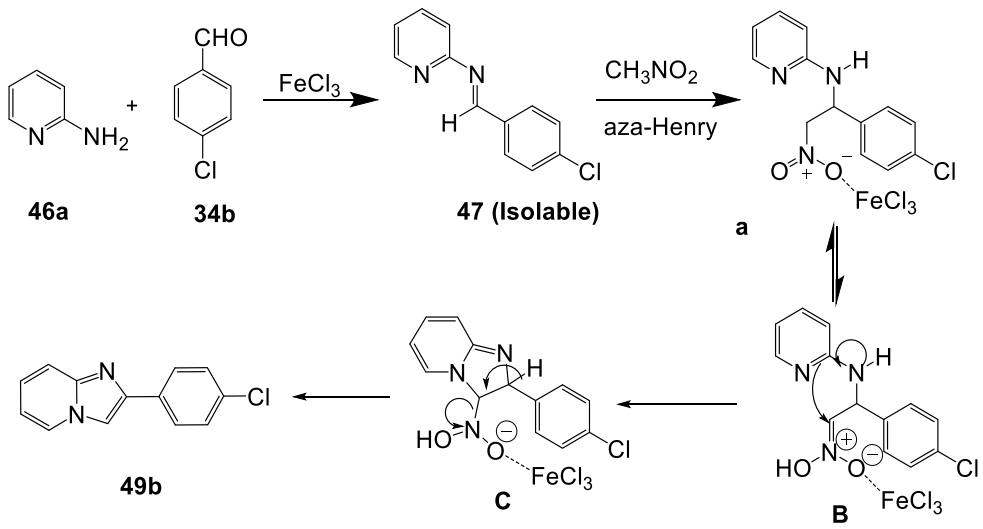
Scheme 2.65

To understand the reaction mechanism, a few experiments were performed which are represented in Scheme 2.66. First of all, we have synthesized the corresponding imine **47** by reacting with 2-aminopyridine (**46a**) and 4-chlorobenzaldehyde (**34b**) in ethanol. When the imine (**47**) was subjected under the optimized reaction conditions, the corresponding imidazo[1,2-*a*]pyridine (**49b**) was obtained in quantitative yield (Eq. 1). Furthermore, the imine (**47**) has been isolated from the reaction mixture by quenching the reaction after 30 minutes. Moreover, the formation of nitrostyrene was not observed in the reaction. This suggests that the imine (**47**) is the key intermediate for this reaction. No significant decrease in yield was observed when the reaction was carried out in presence of a radical scavenger, TEMPO (1.2 equiv.) (Eq. 2) which favours the formation of imidazo[1,2-*a*]pyridines through the nonradical mechanistic pathway.



Scheme 2.66

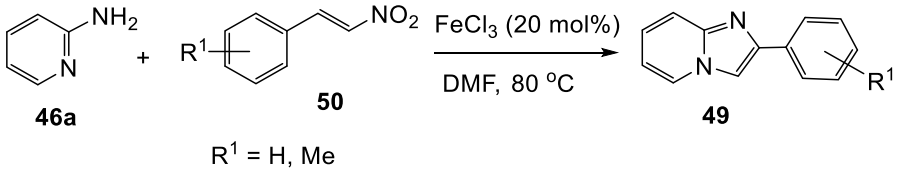
From the results of the above experiments, a probable mechanism of the reaction is represented in Scheme 2.67. Initially, an imine (**47**) is formed by the condensation between 2-aminopyridine and aldehyde. The next step is the formation of the intermediate [**A**] through the addition of nitromethane to the imine *via* aza-Henry reaction [334]. Probably $FeCl_3$ assisted these two steps by increasing the electrophilicity of both the aldehyde and the imine. Intermediate [**A**] tautomerizes to intermediate [**B**], which undergoes an intramolecular cyclization affording intermediate [**C**]. The final product then results from a subsequent elimination of both water and nitroxyl (HNO) [356, 357]. Perhaps Fe(III) chloride acts as an Lewis acid which facilitates the intramolecular cyclization.



Scheme 2.67

2.18. SYNTHESIS OF IMIDAZO[1,2-*a*]PYRIDINES BY IRON(III)-CATALYZED CASCADE REACTION BETWEEN NITROOLEFINS AND 2-AMINOPYRIDINES

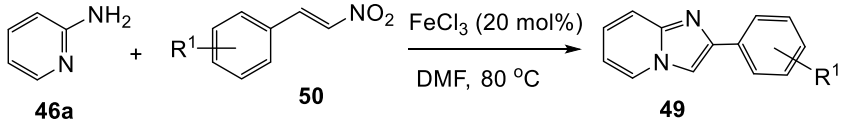
In continuation of our studies it was found that similar imidazo[1,2-*a*]pyridines can be formed by means of the reaction between 2-aminopyridines with *β*-nitrostyrenes by using a similar cheapp and affordable catalytic system. This approach can be considered as a more rational method for obtaining imidazo[1,2-*a*]pyridines, since the reaction is carried out in a shorter time, with the participation of available reagents and a catalyst ($FeCl_3$), and the yield reaches 84% (Scheme 2.68). The reaction proceeds through Michael addition followed by intra-molecular cyclization and *in situ* denitration.

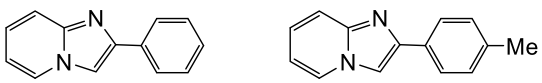


Scheme 2.68

We have also checked the substrates scope of this reaction and we have seen simple nitrostyrene as well as substituted nitrostyene gave the desired products (**49**) with good yields as shown in Table 2.53.

Table 2.53. Substrate scope for the reaction of nitroolefins and 2-aminopyridines.

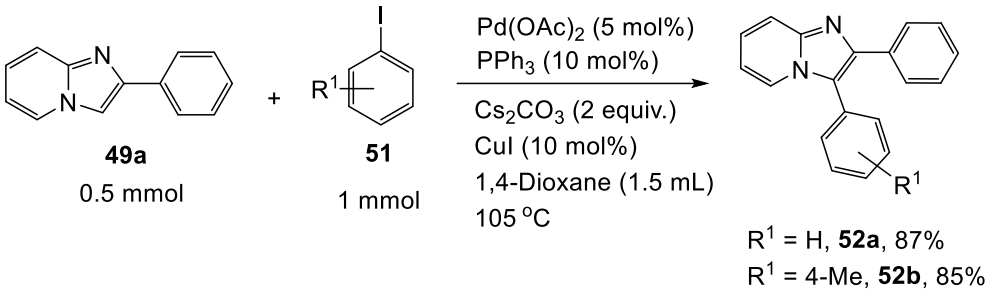




49a, 84% **49c, 80%**

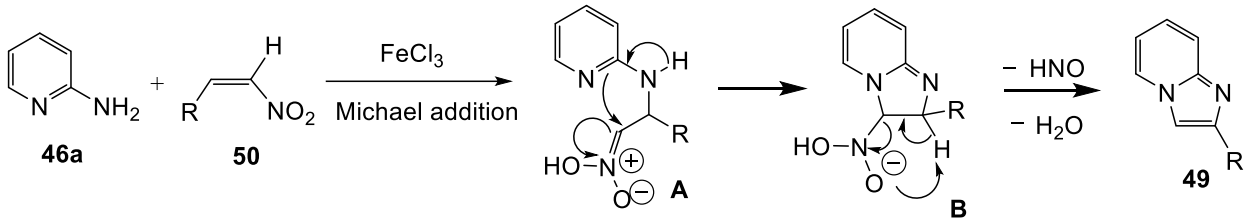
Reactions conditions: 1.2 mmol of **46a** and 1.0 mmol of **50** in the presence of $FeCl_3$ (20 mol%) in 2 mL of DMF at 80 °C for 2 h.

In addition, further functionalization of 3-unsubstituted imidazo[1,2-*a*]pyridines (**49a,c**) was carried out by using a modified method by using iodobenzene *via* direct C-H arylation catalyzed by $Pd(OAc)_2$ in the presence of CuI and $CaCO_3$ in refluxing 1,4-dioxane (Scheme 2.69) [358]. 3-Aryl substituted imidazo[1,2-*a*]pyridines (**52**) were obtained in high yields.



Scheme 2.69

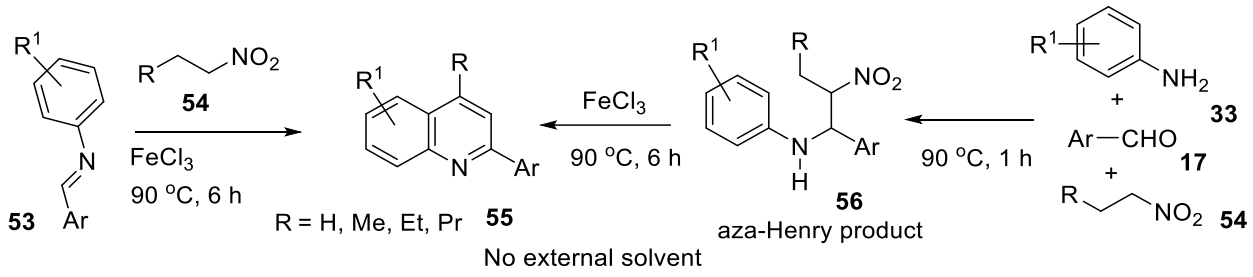
A plausible mechanism for this iron(III) catalyzed cascade reaction is outlined in Scheme 2.70. The first step of the reaction is the Michael addition of 2-aminopyridine (**46a**) with nitroolefin (**50**) to form the intermediate [**A**]. Probably Fe(III)-chloride accelerated the reaction by increasing the electrophilicity of the nitroolefin through coordination. The second step is the intramolecular cyclization of the intermediate [**A**] leading, *via* intermediate [**B**], to the final product by subsequent removal of water and nitroxyl (HNO).[81]



Scheme 2.70

2.19. FACILE SYNTHESIS OF SUBSTITUTED QUINOLINES BY IRON(III)-CATALYZED CASCADE REACTION BETWEEN ANILINES, ALDEHYDES AND NITROALKANES

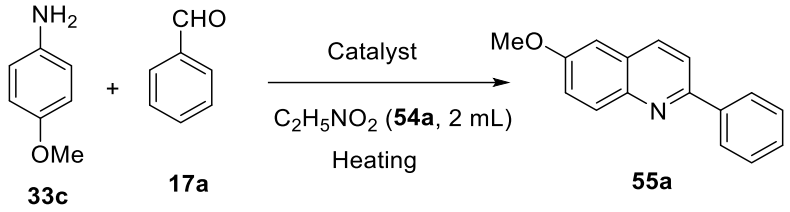
As part of our work, we also demonstrated the possibility of effective one-pot synthesis of substituted quinolines using a similar catalytic system by reacting aromatic azomethines (**53**) with nitroethane and its homologues (Scheme 2.71). Similarly, we have developed a $FeCl_3$-catalyzed one-pot simple protocol for the synthesis of 2-arylquinolines by a three-component coupling of simple anilines, aldehydes, and nitroalkanes without synthesizing the azomethine, but the reaction went through the formation of azomethine (Scheme 2.71).



Scheme 2.71

For the initial study, we started by choosing 4-methoxyaniline (**33c,** 0.5 mmol) and benzaldehyde (**17a,** 0.5 mmol) as the model substrates for this reaction using 20 mol% $FeCl_3$ as the catalyst in nitroethane (**54a**) as a solvent for 6 h at 60 °C under ambient air. Gratifyingly, the expected product 6-methoxy-2-phenylquinoline (**55a**) was obtained in 32% yield (entry 1, Table 2.54). Inspired by this result, we increased the temperature to 90 °C and 88% yield was obtained (entry 2, Table 2.54). $FeCl_3$ was found to be the most effective one among various iron salts such as $FeCl_2$, $FeBr_3$, $FeBr_2$, $Fe(acac)_3$, $Fe(OTf)_3$, $FeSO_4$ (entries 3-8, Table 2.54). We have also tested with $CuCl_2$ and CuI as catalysts but not effective for this conversion (entries 9-10, Table 2.54). By increasing temperature, the reaction did not improve whereas, decreasing the temperature lowered the yield to 32% (entry 11 & entry 12, Table 2.54). In addition, increasing the amount of catalyst (30 mol%) no considerable improvement was observed (entry 13, Table 2.54) whereas decreasing the amount of catalyst (10 mol%) decreased the yield (entry 14, Table 2.54). As well, by increasing the time no further improvement of yield was observed but in 3 h 54% yield was obtained (entries 15-16, Table 2.54). In the absence of any catalyst, no product formation was observed (entry 17, Table 2.54). Other common Lewis acids like $AlCl_3$ and $ZnCl_2$ were not effective for this reaction (entries 18 and 19, Table 2.54). Thus, optimal reaction conditions were obtained using 4-methoxyaniline (**33c**, 0.5 mmol), benzaldehyde (**17a**, 0.5 mmol) in presence of 20 mol% of $FeCl_3$ in 2 mL of nitroethane (**54a**) at 90 °C for 6 h (entry 2, Table 2.54) under ambient air.

Table 2.54. Optimization of the reaction conditions.[a]



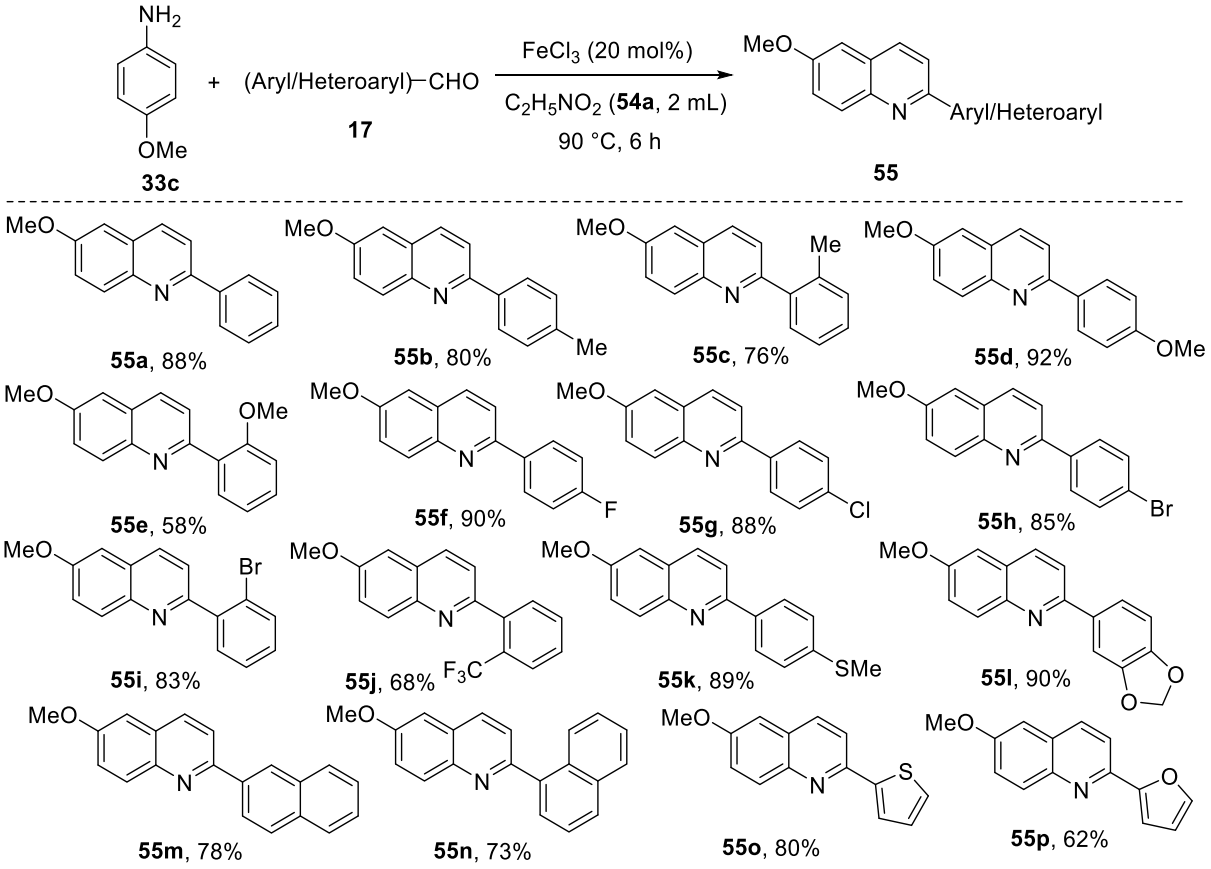
Entry	Catalysts (mol%)	Temp.	Time (h)	Yields[b] (%)
1	$FeCl_3$ (20)	60 °C	6	32
2	**$FeCl_3$ (20)**	**90 °C**	**6**	**88**
3	$FeCl_2$ (20)	90 °C	6	30
4	$FeBr_3$ (20)	90 °C	6	60
5	$FeBr_2$ (20)	90 °C	6	50
6	$Fe(acac)_3$ (20)	90 °C	6	ND
7	$Fe(OTf)_3$ (20)	90 °C	6	ND
8	$FeSO_4$ (20)	90 °C	6	ND
9	$CuCl_2$ (20)	90 °C	6	trace
10	CuI (20)	90 °C	6	<20
11	$FeCl_3$ (20)	110 °C	6	78
12	$FeCl_3$ (20)	40 °C	6	32
13	$FeCl_3$ (10)	90 °C	6	64
14	$FeCl_3$ (30)	90 °C	6	87
15	$FeCl_3$ (20)	90 °C	10	88
16	$FeCl_3$ (20)	90 °C	3	54
17	----	90 °C	6	ND
18	$AlCl_3$ (20)	90 °C	6	ND[c]
19	$ZnCl_2$ (20)	90 °C	6	trace

[a]***Reaction conditions:*** Carried out with 0.5 mmol of **33c** and 0.5 mmol of **17a** in the presence of catalyst in presence of 2 mL of nitroethane (**54a**), [b]Isolated yields, [c]Not detected in TLC.

After having the optimized reaction conditions in hand, various aldehydes (**17**) were introduced to react with 4-methoxyaniline (**33c**) as well as other substituted anilines to prove the general applicability of this methodology. First, the effect of substituents of aryl aldehydes was tested. The results are summarized in Scheme 2.72. In most cases, the desired products were obtained in good to excellent yields (**55a**-**55p**). We have mentioned in the optimization that simple benzaldehyde (**17a**) gave the desired product **55a** in 88% yield. Other benzaldehydes bearing electron-donating substituents such as Me, OMe (**4b**, **4c**, **4d** and **4e**) and electron-withdrawing substituents such as F, Cl, Br reacted well to afford the corresponding 2-arylquinoline derivatives (**55f**-**55i**). Strong electron-withdrawing group like CF_3 in the benzaldehyde moiety also successfully gave the desired product without any difficulty (**55j**). The SMe group was also well tolerated under this reaction conditions and the desired compound (**55k)** has been synthesized with excellent yield (89%). Aldehyde contains the acid-sensitive group was unaffected under the

present reaction conditions which signify the mildness of the reaction conditions (**55l**). We have also tested 2-naphthaldehyde and 1-naphthaldehyde which also reacted smoothly under the optimized conditions obtaining 78% and 73% yields respectively (**55m** and **55n**). In addition, heteroaryl aldehydes reacted well without accompanying self-condensation or ring cleavage (**55o** and **55p**).

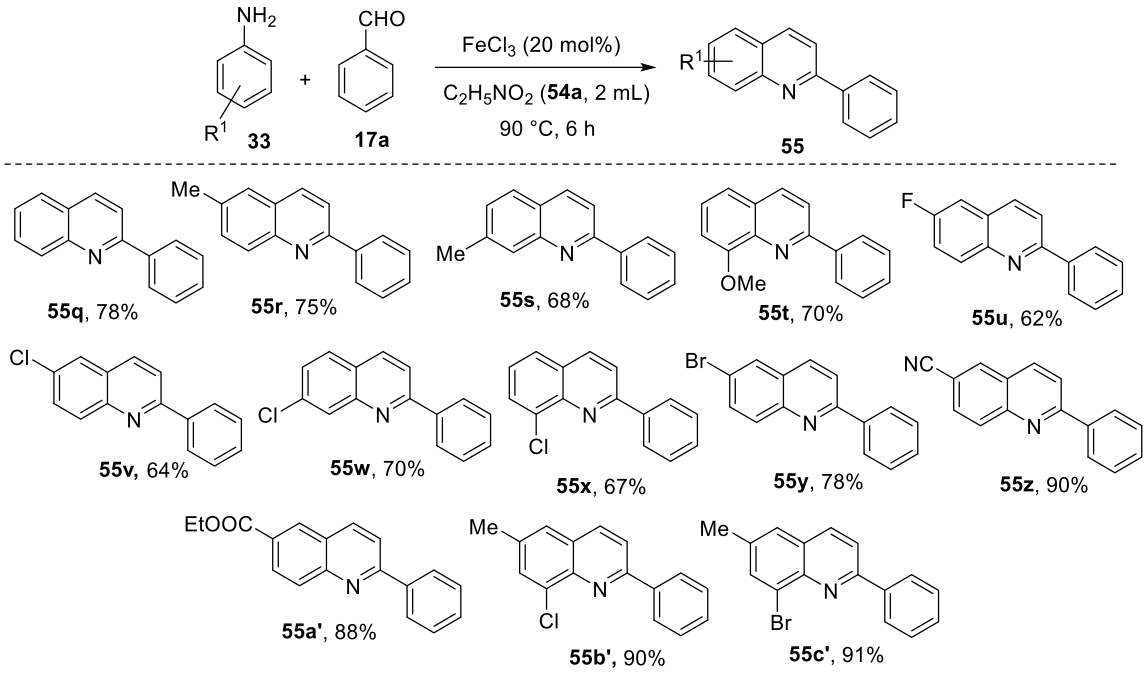
Then our attention was turned to the use of substituted anilines to extend the general applicability of the reaction conditions as summarized in Scheme 2.73. Simple aniline produced the desired product **55q** in 78% yield. Other anilines bearing electron-donating substituents such as Me, OMe (**554**, **55s** and **55t**) and electron-withdrawing substituents such as F, Cl, Br reacted well to afford the corresponding 2-arylquinoline derivatives (**55u**-**55y**). The nitrile and carbonyl functionalities were also well tolerated under the present reaction conditions and gave 90% and 88% yields respectively (**55z** and **55a′**). We have also observed that the presence of both electron-withdrawing and electron-donating substituents in same aniline moiety afforded the corresponding quinoline derivatives in excellent yields (**55b′** and **55c′**).



Reaction conditions: 0.5 mmol of **33c** and 0.5 mmol of **17** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroethane (**54a**) at 90 °C for 6 h.

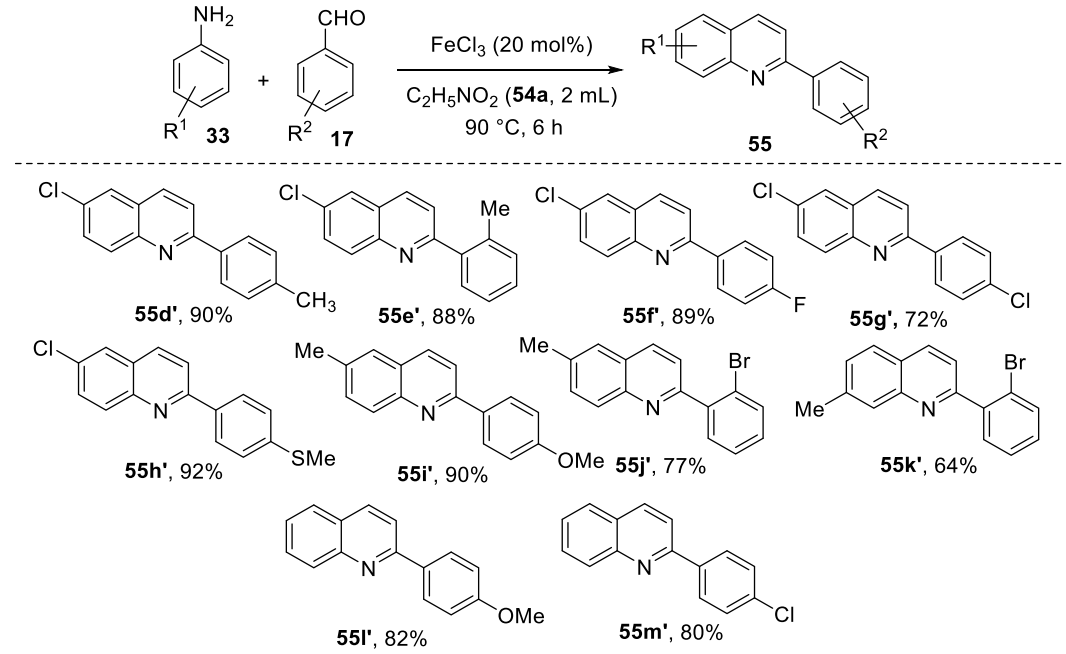
Scheme 2.72

In addition, a wide range of both substituted anilines and benzaldehydes were employed to prove the wide applications of our present procedure (**55d′-55m′**) (Scheme 2.74). Several sensitive functionalities such as, halogens F, Cl, Br (**55d′-55k′** and **55m′**), OMe (**55i′** and **55l′**), SMe (**55h′**) were unaffected under the present reaction conditions and the desired products were obtained in 64-92% yields.



Reaction conditions: 0.5 mmol of **33** and 0.5 mmol of **17a** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroethane (**54a**) at 90 °C for 6 h.

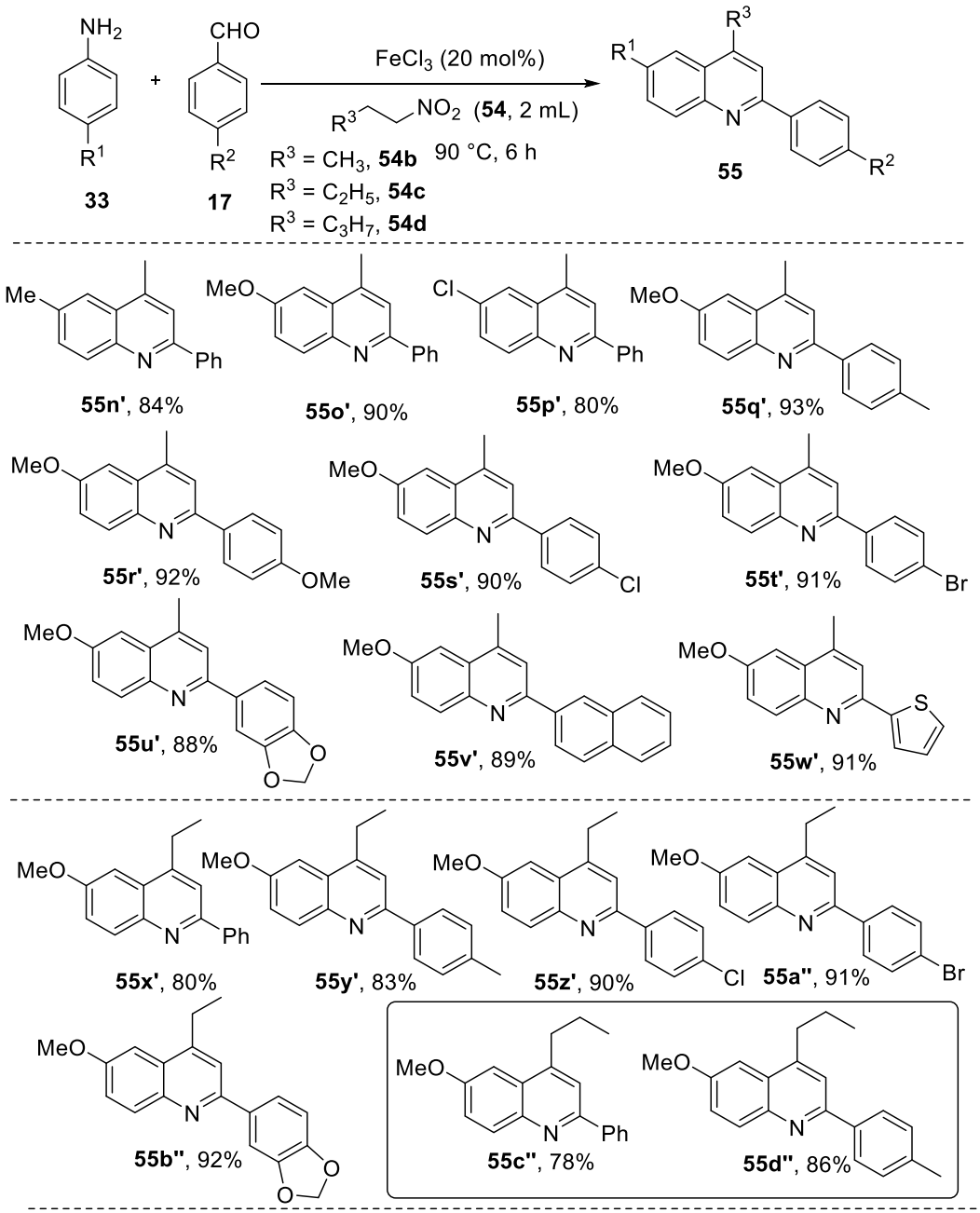
Scheme 2.73



Reaction conditions: 0.5 mmol of **33** and 0.5 mmol of **17** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroethane (**54a**) at 90 °C for 6 h.

Scheme 2.74

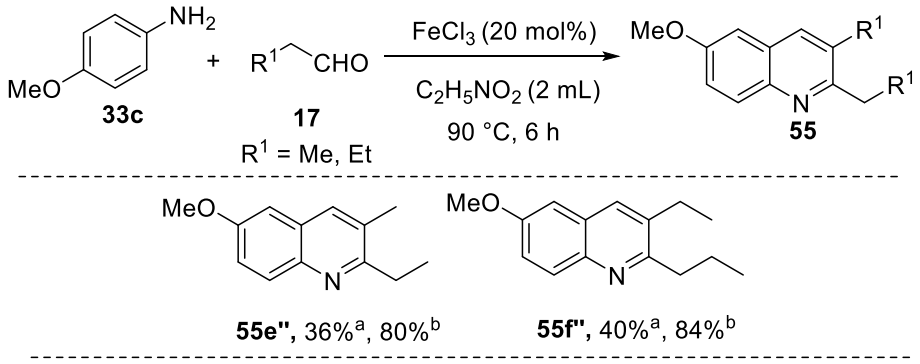
Finally, we have examined different nitroalkanes (**54**) such as nitropropane, nitrobutane and nitropentane to prove the general applicability of our methodology (Scheme 2.75). When we used nitropropane (**54b**) the reaction proceeded smoothly and afforded the desired products in good to excellent yields (**55n′-55w′**) for all cases. We are delighted to mention that under the same reaction conditions nitrobutane (**54c**) gave the corresponding quinolines (**55x′-55b′′**) in good yields. Finally, the nitropentane (**54d**) has also been tested and we were able to synthesize 2,4,6-disubstituted quinolines (**55c′′, 55d′′**) in satisfactory yields.



Reaction conditions: 0.5 mmol of **33** and 0.5 mmol of **17** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroalkane (**54**) at 90 °C for 6 h.

Scheme 2.75

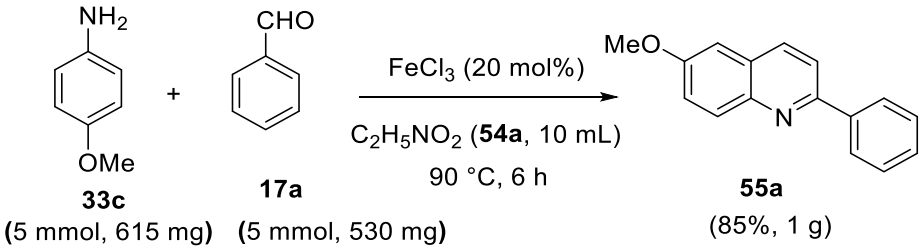
To extend the scope of the present methodology, we examined aliphatic aldehydes also (Scheme 2.76, **55e″**, **55f″**). After careful evaluation of the ^{1}H and ^{13}C NMR spectra, we came to the point that the obtained products were 2,3-dialkyl-substituted quinolines. Here, the nitroethane did not take part in the reaction, only acted as a solvent. This phenomenon was previously reported by Shimizu *et al.* [359].



[a]***Reaction conditions:*** 0.5 mmol of **33c** and 0.5 mmol of **17** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroethane at 90 °C for 6 h; [b]***Reaction conditions:*** 0.5 mmol of **33c** and 2.5 mmol of **17** in the presence of 20 mol% $FeCl_3$ in 2 mL of nitroethane at 90 °C for 6 h.

Scheme 2.76

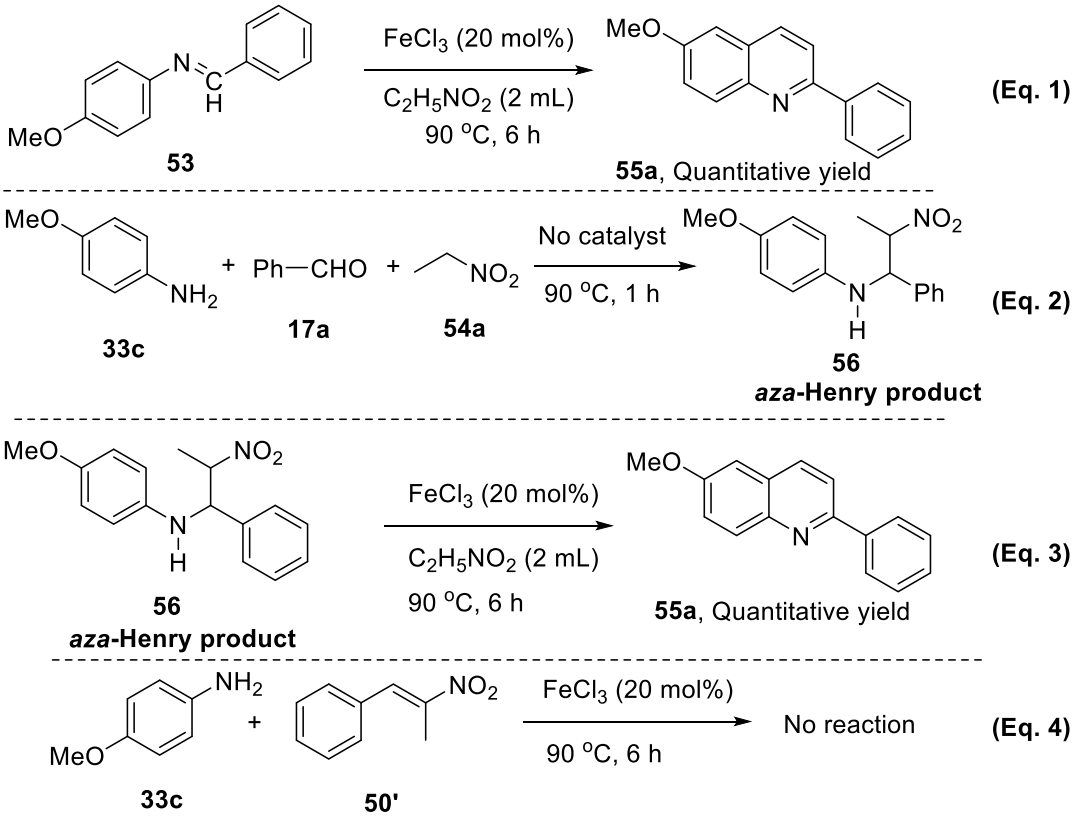
Moreover, the impending synthetic applicability of this protocol was investigated on the gram scale using the model reaction in our laboratory setup. As shown in Scheme 2.77, the reaction could afford 1 g of product (**55a**) in 85% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of quinolines derivatives.



Scheme 2.77

It is worthy to mention that all these reactions were performed under an open atmosphere and are not sensitive to air and moisture. All the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. The reaction conditions were mild enough and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all the reaction combinations giving rise to high yields of desired products and regioselectivity of the protocol.

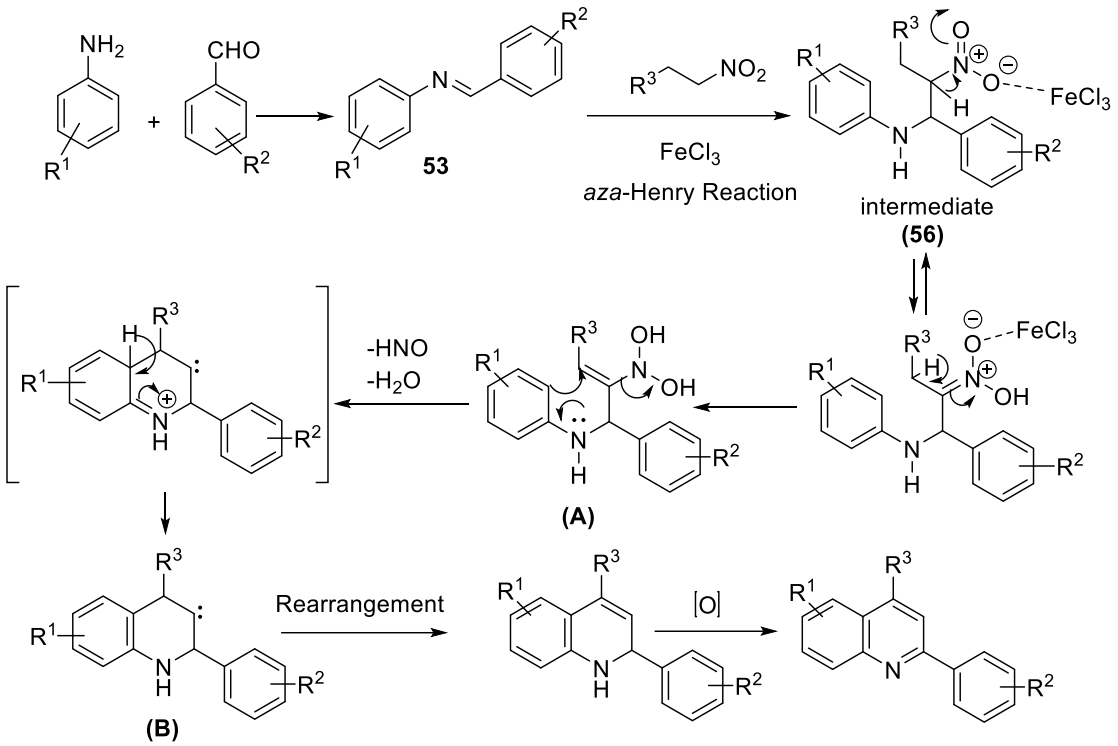
Based on the literature [356, 357, 359] and some additional experiments performed (Scheme 2.78) we predict the possible reaction pathway. First of all, we synthesized the corresponding imine [**A**] by reacting with 4-methoxyaniline (**33c**) and benzaldehyde (**17a**) in ethanol. When the imine (**53**) was subjected to the optimized reaction conditions, the corresponding 2-arylquinoline (**55a)** was obtained in quantitative yield (**Eq. 1**). Furthermore, the imine A has been isolated from the reaction mixture by quenching the reaction after 30 min. After another 1 h, we have also isolated the aza-Henry adduct as intermediate [**56**]. This aza-Henry adduct has also been isolated by the additional experiment (**Eq. 2**). When aza-Henry adduct (**56**) was subjected to the optimized reaction conditions, the corresponding 2-arylquinoline (**55a**) was obtained in quantitative yield (**Eq. 3**). This experiment also proves that **56** was the key intermediate in our reaction. Moreover, the formation of nitrostyrene (**50′**) was not observed in the reaction. Even we also performed a reaction between 4-methoxyaniline (**33c**) and *β*-methyl-*β*-nitrostyrene (**50′**) under the same reaction conditions but the reaction did not proceed at all (**Eq. 4**).



Scheme 2.78

The above observations suggest that the reaction proceeds through the initial formation of imine (**53**) which on reaction with nitro alkane produces the aza-Henry adduct (**56**). By rearrangement of nitro group aza-Henry intermediate (**56**) produces another intermediate [**A**] with gem hydroxyl group on nitrogen. Elimination of HNO and H_2O [356, 357] and ortho cyclisation of intermediate [**A**] produce a new carbon-carbon bond with adjacent carbene [**B**] (Scheme 2.79).

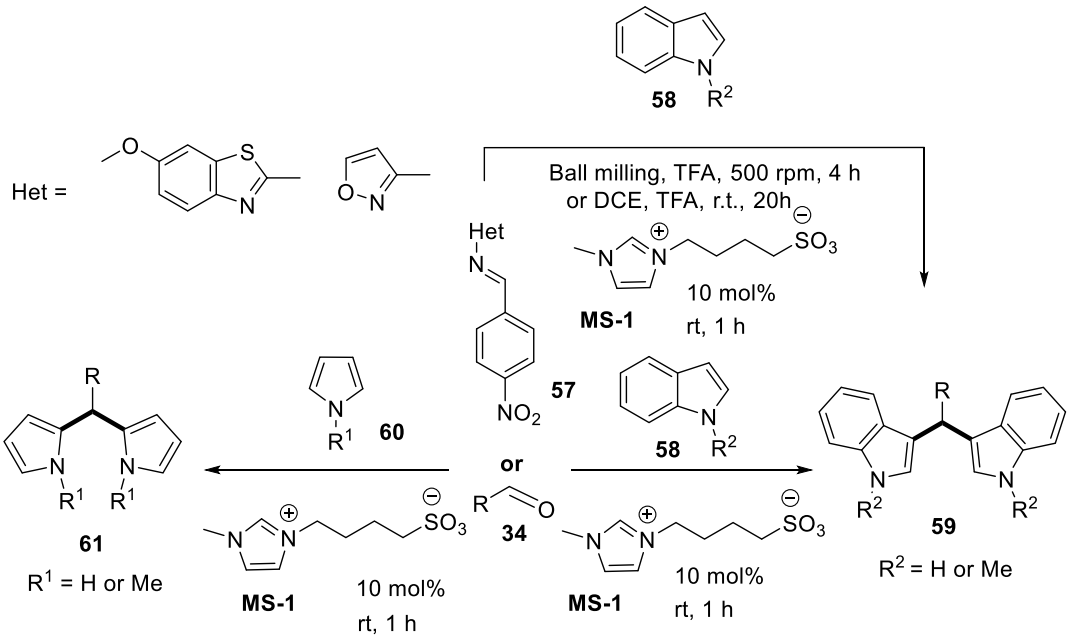
Finally, rearrangement of carbene dihydroquinoline, on oxidation, converted to the corresponding quinoline.



Scheme 2.79

2.20. SYNTHESIS OF DIPYRROMETHANES AS WELL AS BIS(INDOLYL)METHANES CATALYZED BY IMIDAZOLIUM ZWITTERIONIC MOLTEN SALT

In order to explore the applicapability of racional/green approaches for the functionalization of azomethines and their precursors the possibility of functionalization of some heterocyclic azomethines/Schiff bases (**57**) under the action of *C*-nucleophiles, namely such common ones as indoles, was investigated. Thus, azomethines were reacted with inoles in the presence of catalytic amounts of CF_3CO_2H (TFA) in dichlorethane at room temperature for 20 hours or under ball milling conditions at 500 rpm for 4 hours, as well as in the media of anionic ionic liquid/zwitterionic salt, namely, 4-(3-methylimidazolium)butanesulfonate (**MS-1**) (Scheme 2.80). It was observed that along with the formation of the products of nucleophilic addition along the C=N bond of azomethine, namely, *α,α*-disubstituted azolyl amines (up to 47% yields), the formation of bispyrromethanes (**59**) was also observed in yields up to 35%. Most likely a partial hydrolysis of the Schiff base takes place followed by the reaction of the resulting aldehyde with indole. This suggestion was confirmed by the following: the reaction between the precursor of azomethines (**57**), 4-nitrobenzaldehyde, and indole in the presence of TFA in solution or under ball milling at 500 rpm for 4 h, led to the formation of bispyrromethane (**59o**) in 95% yield.



Scheme 2.80

Regarding the aldehyde, there are examples in literature where 2,5-dihydro-1*H*-pyrroles and 2*H*-isoindoles gave *N*-substituted (benzo)pyrroles by the reaction with aldehydes in presence of TM catalysts. On the other hand, transition metal/ionic liquid-catalyzed examples of *N*-acylation and *N*-alkylation of (benzo)pyrroles by various carbonyl-containing components are widely

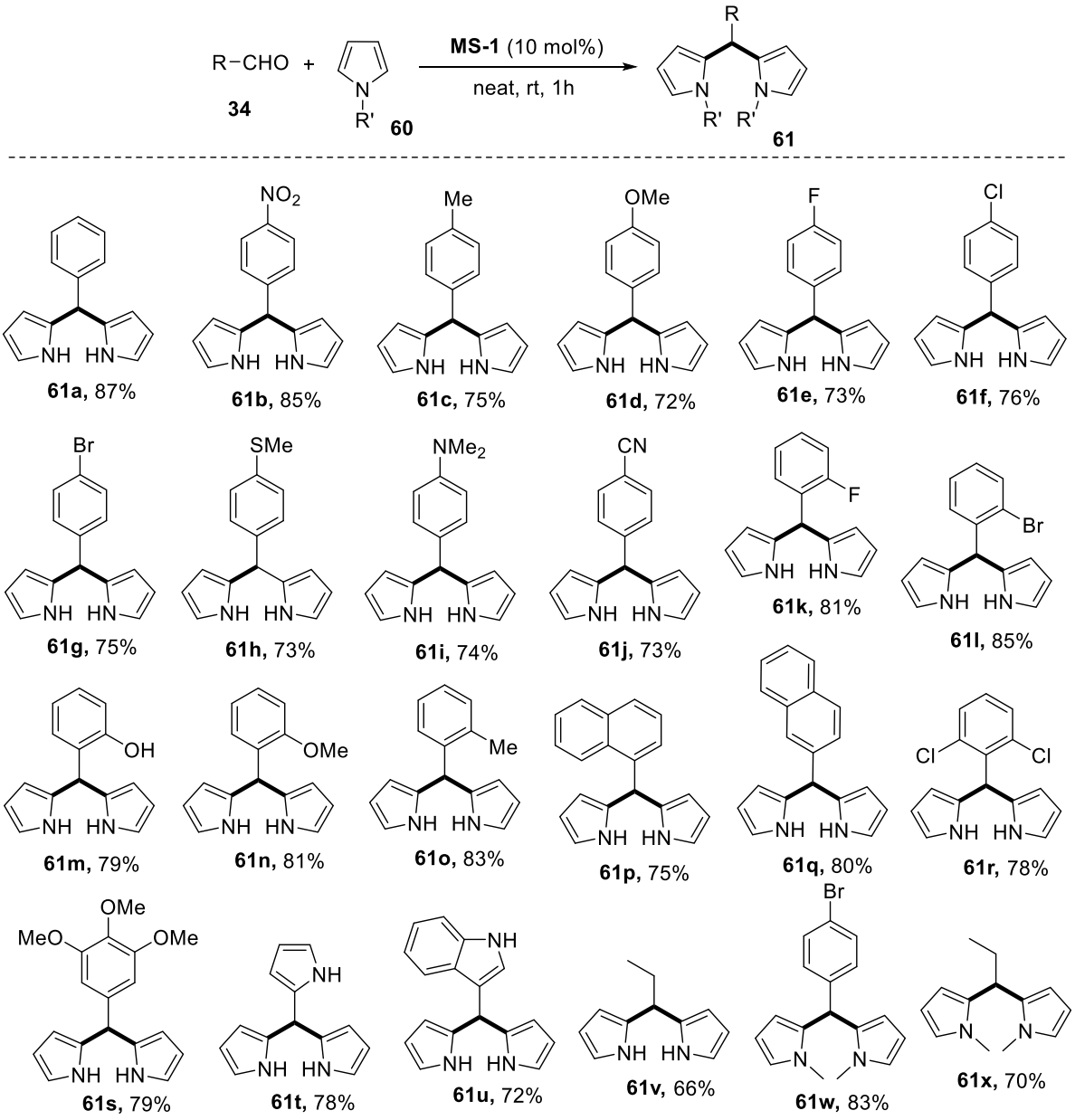
represented. Finally, examples of the preparation of bispyrromethanes by the reaction of pyrroles with aldehydes are widely known.

Therefore, further in our work we studied the interaction of pyrroles and indoles (as possible amino and/or C-components) in reactions with aldehydes (**34**). Anionic ionic liquid/zwitterionic salt, namely, 4-(3-methylimidazolium)butanesulfonate (**MS-1**) was used both as catalyst and as a reaction media (Scheme 2.80).

We have initialized our experiment by taking a mixture of benzaldehyde (**34a**) (1 mmol), pyrrole (**60a**) (2 mmol) and molten salt (10 mol%) and stirred at room temperature for 1 h to synthesize 2,2'-(phenylmethylene)bis(1*H*-pyrrole) (**61a**). Gratifyingly we got 87% yield. With this result, we have further explored our methodology towards the scope and limitations of this procedure. A wide range of aromatic, aliphatic, and heteroaryl aldehydes was subjected to prove the general applicability of our present procedure which is summarized in Table 2.55. We have observed that various 4-substituted and 2-substituted aromatic aldehydes gave the desired products in good yields (**61b**-**61o**). Several sensitive functionalities such as –OH, OMe, NO_2, halogen (F, Cl, Br) are unaffected under the present reaction conditions. In addition, the reaction with di and tri substituted aldehydes resulted in the desired products (**61r**) and (**61s**) in 78% and 79% yields respectively. So, the aromatic aldehydes substituted with electron-withdrawing or donating groups can easily be used as different substrates for this reaction. 1- and 2-naphthaldehyde are also able to react with pyrrole to give the respective products (**61p)** and (**61q**). Furthermore, aliphatic aldehyde gave good response reacting with pyrrole and the desired product 2,2'-(propane-1,1-diyl)bis(1*H*-pyrrole) (**61v**) is obtained in 66% yield. We have further extended this reaction with heterocyclic aldehydes. Heteroaryl aldehydes such as 1*H*-pyrrole-2-carbaldehyde and 1*H*-indole-3-carbaldehyde also afforded desired products (**61t**) and (**61u**) in good yields. In addition, satisfying yields were obtained by the reaction of *N*-methylpyrrole with aromatic aldehydes as well as aliphatic aldehydes (**61w**) and (**61x**).

Next, with these results, we have elongated our method taking indole for the synthesis of bis(indolyl)methanes using the same reaction conditions. Indole (**58a)** (2 mmol) reacted smoothly with benzaldehyde (**34a**) (1 mmol) to afford the desired product (**59a**) in 86% yield and the reaction has occurred at similar conditions as performed in case of pyrrole.

Table 2.55. Molten salt-catalyzed synthesis of various dipyrromethanes.

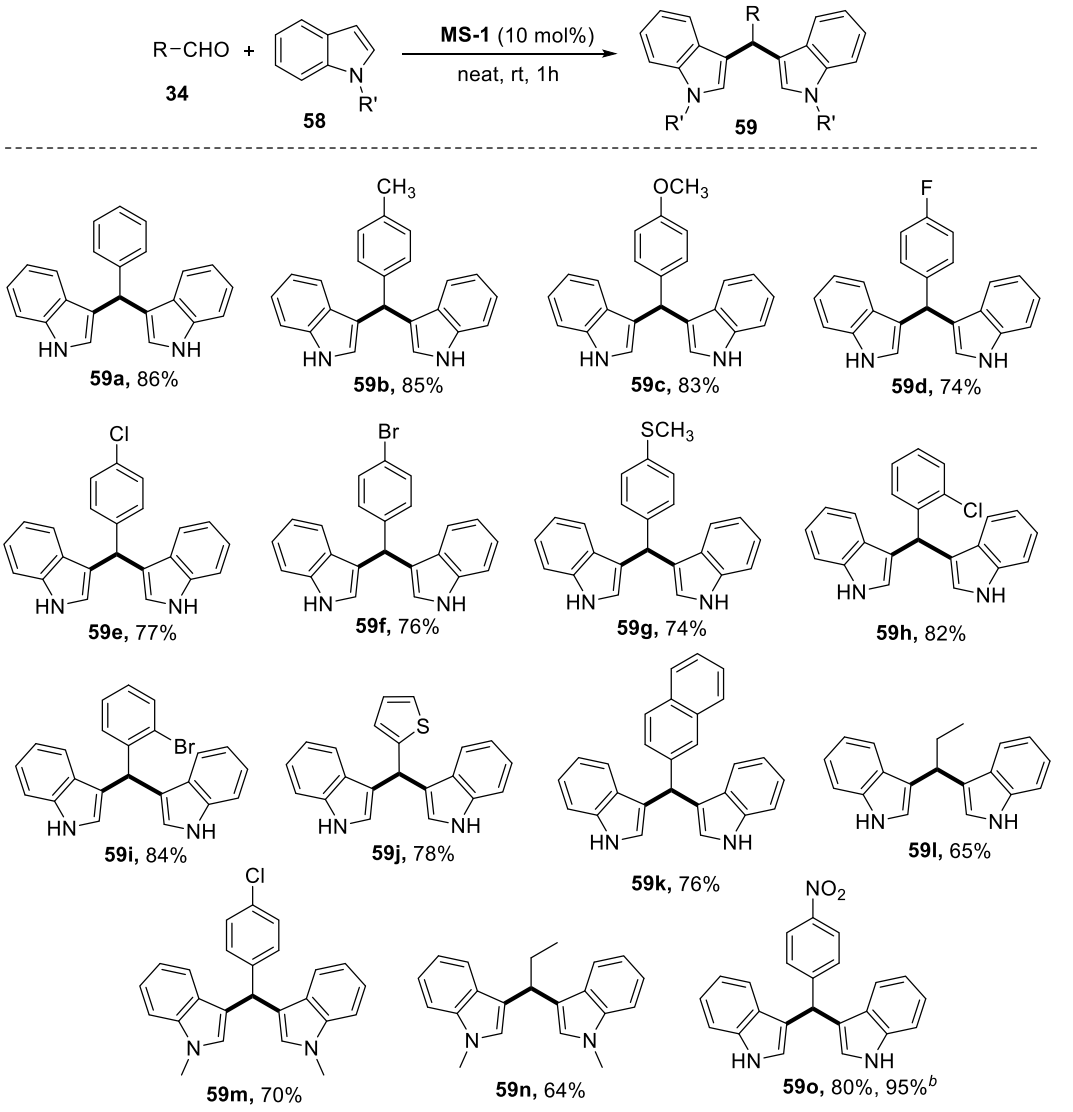


Reaction conditions: aldehyde (**34**, 1 mmol), pyrrole (**60**, 1.2 mmol), **MS-1** (22 mg, 10 mol%), rt, 1 h.

We further carried out the reaction taking some other aromatic aldehydes where good yields of products (**59b-59i**) and (**59k**) were observed. Here the *ortho*- or *para*-substituted (with both electron-withdrawing and donating groups) aldehydes are also effective for carrying out the reaction and the results are summarized in Table 2.56. The reaction also responded with aliphatic aldehyde and leads to product (**59l**) with a moderate yield. When a heterocyclic aldehyde (*e.g.* thiophene-2-carbaldehyde) was treated with indole, the corresponding desired product (**59j**) was obtained in 78% yield. We have also performed the reaction varying the indole part. Here, we have taken *N*-methylindole reacting with an aromatic aldehyde and an aliphatic aldehyde and the desired products (**59m** and **59n**) were formed in moderate yields. In addition, as we discussed earlier, we

have also used 4-nitrobenzaldehyde to obtain the desired product (**59o**) in presence of molten salt (**MS-1**) as well as under ball milling conditions where we got 80% and 95% yields respectively.

Table 2.56 Molten salt-catalyzed synthesis of various bis(indolyl)methanes.[a]



[a]***Reaction conditions:*** aldehyde (**34**, 1 mmol), indole (**58**, 2 mmol), **MS-1** (22 mg, 10 mol%), rt, 1 h;
[b]***Reaction conditions***: 4-nitrobenzaldehyde (1 mmol) and indole (2 mmol) in the presence of TFA (2-3 drops) under ball milling at 500 rpm for 4 h.

All these reactions were performed in an open atmosphere and are not sensitive to air and moisture. All of the known synthesized compounds have been characterized by spectral data and X-ray crystallographic analysis of 2,2'-((3,4,5-trimethoxyphenyl)methylene)bis(1*H*-pyrrole) (**61s**, CCDC 1574761) was performed to confirm the structure of the product as shown in Figure 2.10.

We have also checked the selectivity of our procedure (Scheme 2.81). It was interesting when 1 mmol of benzaldehyde (**34a**) reacted with a mixture of 1 mmol of pyrrole (**60a**) and 1

mmol of indole (**58a**) only pyrrole part reacted with benzaldehyde to form product (**61a)**. The indole part remained unreacted.

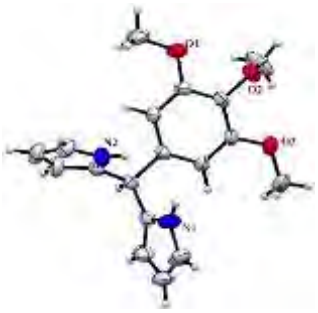
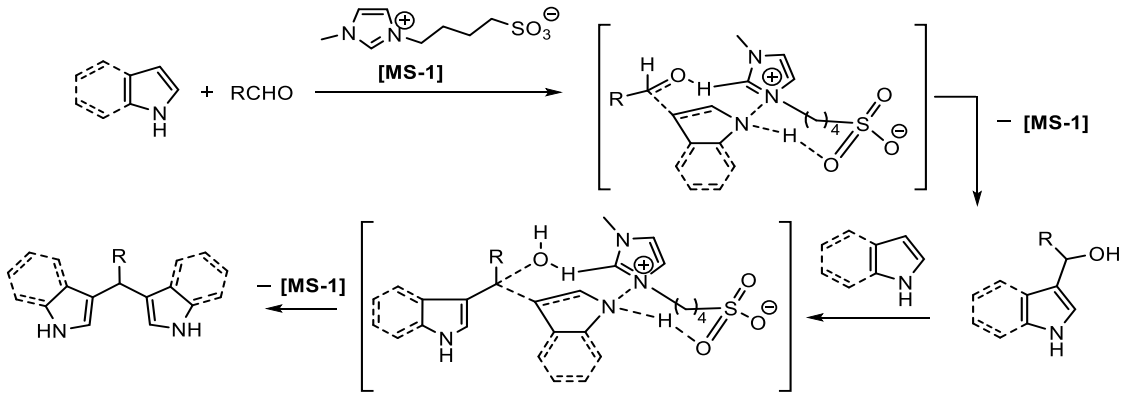


Figure 2.10. X-Ray crystallographic data for the structure of compound (**61s)**

Scheme 2.81

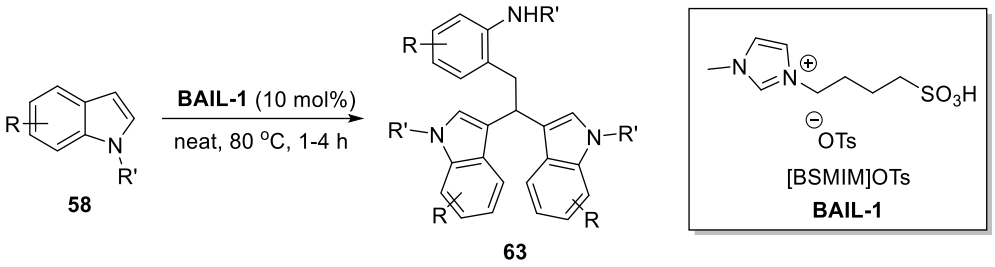
Based on the literature [360] we have proposed the conventional mechanism for both the reactions (Scheme 2.82). Imidazolium ion-based zwitterionic molten salt contains an unconventional C–H bond which plays a crucial role in catalyzing the reaction *via* electrophilic activation of the aldehydes. Chakraborti *et al*. proposed the role of the imidazolium-based ILs as an "electrophile nucleophile dual activation by a relay of cooperative hydrogen bond and charge-charge interactions" [371, 372]. According to this mechanism of catalysis highlighted the importance of imidazolium-based cationic moiety for "electrophilic activation" of the aldehyde through hydrogen bond formation with the C-2 hydrogen.



Scheme 2.82

2.21. TANDEM TRIMERIZATION OF INDOLES CATALYZED BY BRØNSTED ACIDIC IONIC LIQUID

Upon a more detailed study of the reaction described above, we found that even in the absence of aldehydes, indoles were capable of forming products of formal trimerization, namely 2-(2,2-di(1-*R*-indole-3-yl)ethyl)anilines (**63**) in presence of ionic liquid, namely (**BAIL-1**). It is worthy to mention that a very few methods are available for the synthesis of indole 3,3′-trimers. We have observed, a very selective synthesis of indole 3,3′-trimers in good to excellent yields without any side products in the presence of 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs (**BAIL-1**) (10 mo%) at 80 °C (Scheme 2.83). This present reaction proceeded under neat conditions, the desired 3,3′-trimers with various *N*-protected indoles obtained in major suppressing the formation of other polymers and there is no need to perform column chromatography for purification.

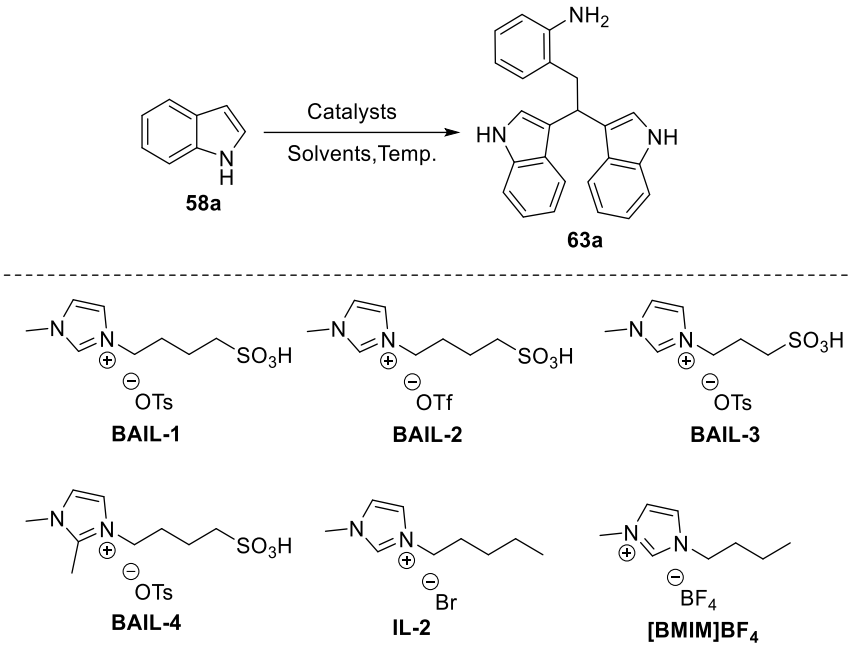


Scheme 2.83

Initially, we have taken simple indole (**58a**) in presence of 10 mol% 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs (**BAIL-1**) as the catalyst in the reaction at 80 °C for 1 hour under neat condition (Table 2.57, entry 1). We are delighted to note that the desired 3,3′-trimer product, namely, 2-(2,2-di(1*H*-indol-3-yl)ethyl)aniline (**63a**) was obtained in 85%. Immediately, we extended the reaction time under the same reaction condition from 1 h to 3 h but the yield was not improved. Secondly, the role of various ionic liquids such as **BAIL-2, BAIL-3,** and **BAIL-4** have been checked (Table 2.57, entry 2-4) but **BAIL-1** was found to be the best for the formation of indole trimer product. No desired products have been found using other ionic liquids like IL-2 and [BMIM]BF_4 (Table 2.57, entry 5 & 6). The role of various solvent has been examined to realize the solvent effects. Some protic solvents such as water, ethanol, *n*-propanol, *n*-butanol and polyethylene glycol (PEG) (Table 2.57, entry 7-11) produced very less product and some aprotic solvents like 1,2-DCE, CH_3CN afforded very poor yields (Table 2.57, entry 12 & 13). We observed that our expected product in maximum yield (84%) was obtained under solvent-free conditions at 80 °C for 1 h (Table 2.57, entry 1) which indicates the detrimental effect of the solvents on this transformation. The high temperature was not beneficial for this reaction (Table

2.57, entry 14) while decreasing the reaction temperature decreased the yield (Table 2.57, entry 15). Finally, we have observed that 10 mol% of **BAIL-1** afforded better yield (85%) compared to 5 mol% (67% yield) (Table 2.57, entry 16). Increasing the catalyst loading to 20 mol% no improvement of the yield was observed (Table 2.57, entry 17). It is worthy to mention that no conversion has been detected without catalyst (Table 2.57, entry 18). So, the optimized reaction conditions have been considered by employing 10 mol% **BAIL-1** at 80 °C under solvent-free conditions for 1 h the optimal yield (85%) was obtained (Table 2.57, entry 16).

Table 2.57. Optimization of the reaction conditions.[a]



Entry	Catalysts (10 mol%)	Solvents	Temp. (°C)	Yields[b] (%)
1	BAIL-1	neat	80 °C	85, 82[c]
2	BAIL-2	neat	80 °C	74
3	BAIL-3	neat	80 °C	70
4	BAIL-4	neat	80 °C	75
5	IL-2	neat	80 °C	trace
6	[BMIM]BF_4	neat	80 °C	nr
7	BAIL-1	H_2O	80 °C	61
8	BAIL-1	EtOH	80 °C	40
9	BAIL-1	^{n}PrOH	80 °C	28
10	BAIL-1	^{n}BuOH	80 °C	22
11	BAIL-1	PEG	80 °C	19
12	BAIL-1	1,2-DCE	80 °C	30

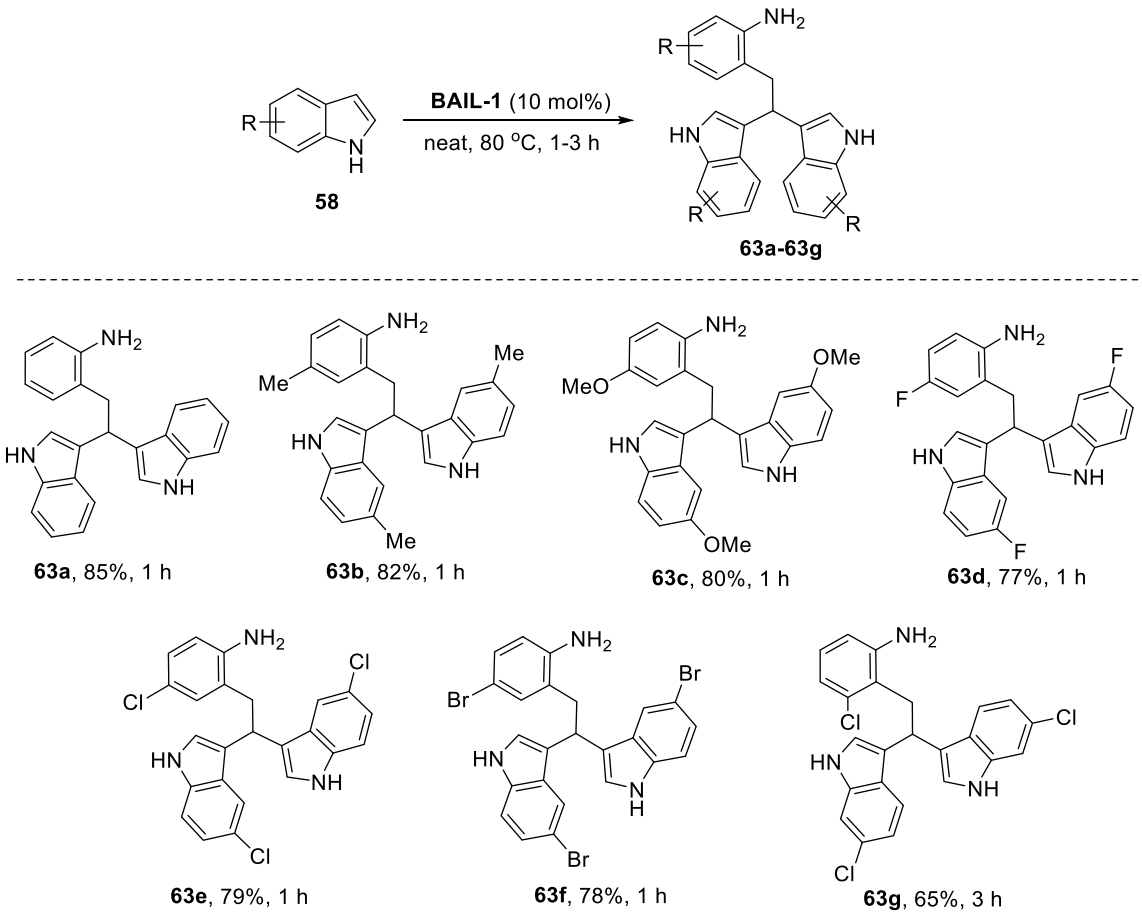
13	BAIL-1	CH_3CN	80 °C	33
14	BAIL-1	neat	100 °C	83
15	BAIL-1	neat	60 °C	71
16	BAIL-1	neat	80 °C	67[d]
17	BAIL-1	neat	80 °C	85[e]
18	--	neat	80 °C	ND[f]

[a]***Reaction conditions:*** indole (1.0 mmol), **BAIL-1** (10 mol%), stirred for 1 h. [b]Isolated yields. [c]Reaction time 3 h. [d]5 mol% **BAIL-1** was used. [e]20 mol% **BAIL-1** was used. [f]Not detected in TLC.

Various indoles (**58**) were examined for the trimerization reaction to prove the general applicability of this methodology. During optimization, we have already seen that simple indole (**58a**) gave the trimer product in 85% yield which is an MDM2-p53 inhibitor. The reaction underwent smoothly with Indole derivatives substituted with electron-donating substituents (5-Me, 5-OMe) to give the corresponding 3,3′-trimer products (**63b**, **63c**) in excellent yields. Similarly under the same reaction conditions Indoles with different electron-withdrawing groups such as -fluoro, -chloro and -bromo groups at C-5 position reacted to provide the respective 3,3′-trimer products (**63d-63f**) in good yields. 6-Chloro-substituted indole also underwent the reaction to provide the desired product (**63g**) in moderate yield (Table 2.58).

Then the substrates scope with the *N*-protected indoles under similar reaction conditions has been explored as summarized in Table 2.59. *N*-methylindole and *N*-ethylindole reacted very smoothly to give the products (**63h**) in 81% yield and (**63i**) in 79% yield respectively. Indoles protected with *n*-propyl and *iso*-propyl groups also supportive of the reaction conditions and reacted to form their corresponding 3,3-′trimer products (**63j**, **63k**) in good yields. In addition, *iso*-butyl protected indole derivative provided the respective product (**63l)** with 70% yield. Similarly, long-chain alkyl groups like *n*-butyl and *n*-pentyl protected indoles nicely underwent the reaction under the optimized conditions and afforded the corresponding products (**63m**, **63n**) in satisfactory yields. Next, *N*-allyl and propargyl substituted indoles were also introduced to react where the corresponding trimers (**63o**, **63p**) were formed in good yields keeping the unsaturated group unaffected. *N*-benzylindole afforded the corresponding product (**63q**) in 74% yield. Other substituted indoles like 5-Methyl, 5-methoxy and 5-chloro substituted *N*-methyl indoles reacted smoothly and the desired products (**63r**), (**63s**), and (**63t**) were formed with good yields. In addition, 5-methoxy and 5-chloro substituted *N*-ethyl indoles also gave the corresponding products (**63u**) and (**63v**) in satisfactory yields (Table 2.59).

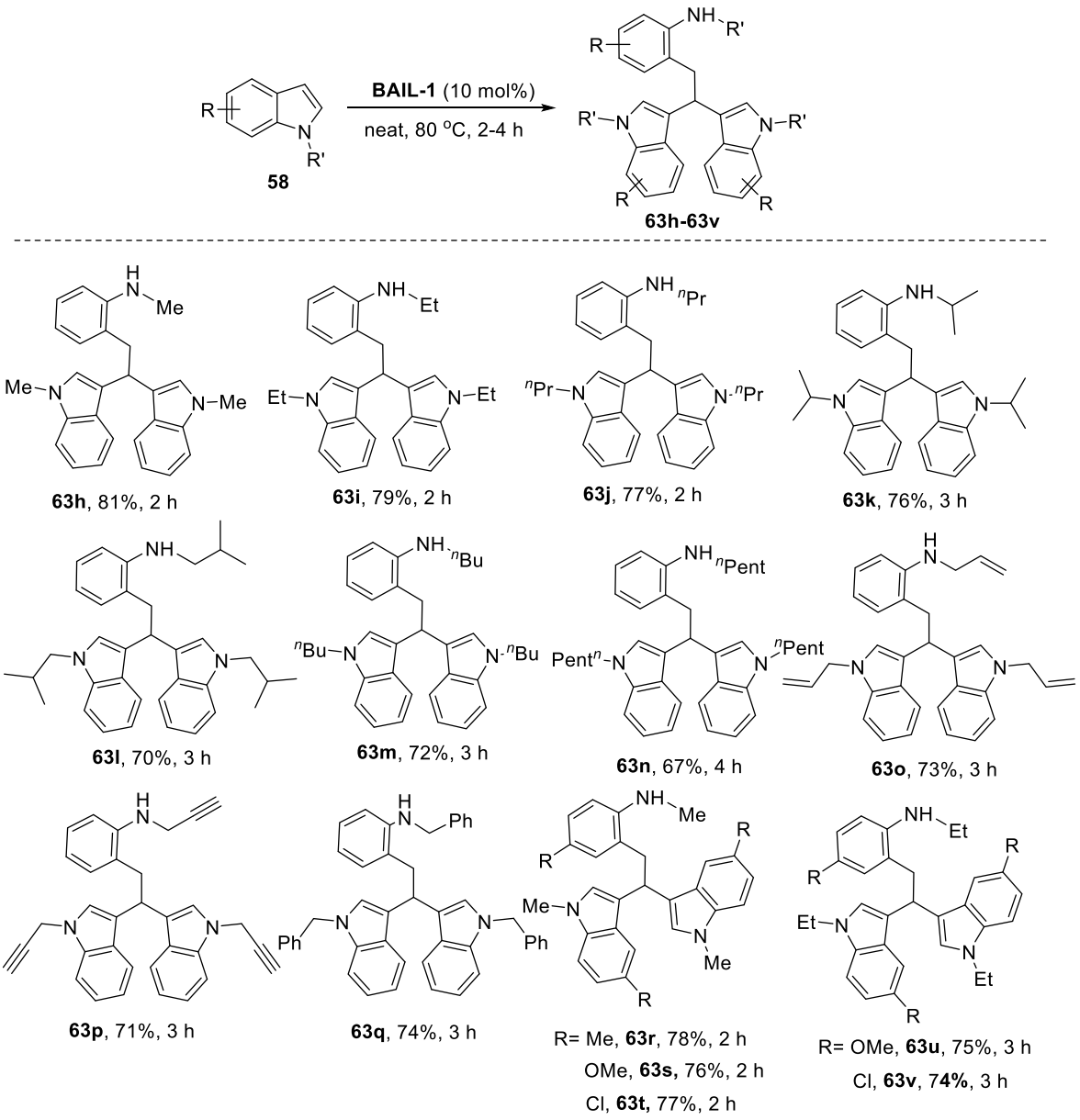
Table 2.58 Synthesis of 3,3′-trimer derivatives of various indole in the presence of **BAIL-1**.



[a]***Reaction conditions:*** 1 mmol of **58** in presence of **BAIL-1** (10 mol%) at 80 °C.

The reaction under present reaction conditions are not sensitive to air and moisture and need no inert medium and was performed under an open atmosphere. No column chromatography has been performed for purification. After completion of the reaction, water was added to the reaction mixture and the reaction mixture was then filtered off to get the crude residue which was then washed with ethanol to get the pure product. In our method, no other polymers of indole, 2,3′-trimers, and dimers were not observed. Even, we have not observed any by-products for all reaction combinations which are supported by good yields of the protocol. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. X-ray crystallographic analysis of 2-(2,2-bis(5-chloro-1-ethyl-1*H*-indol-3-yl)ethyl)-4-chloro-*N*-ethylaniline (**63v**, CCDC 1854580) have also been provided to confirm the structure of the product as shown in Figure 2.11.

Table 2.59 Synthesis of 3,3′-trimer derivatives of various *N*-protected indoles.



All reactions were performed on 1 mmol scale in presence of **BAIL-1** (10 mol%) at 80 °C.

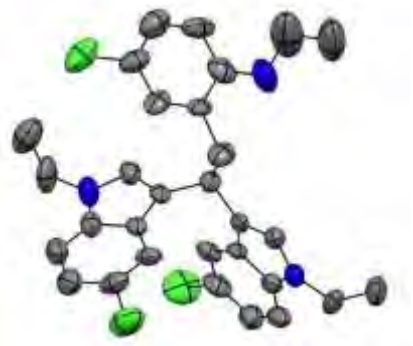
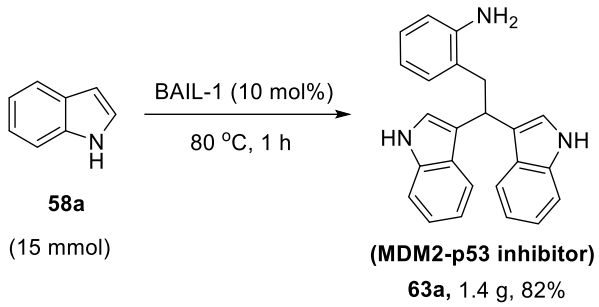


Figure 2.11. X-Ray crystallographic data for the structure of compound (**63v**).

Furthermore, the potential synthetic applicability of this method was investigated on the gram scale using the model reaction. As shown in Scheme 2.84, the reaction could afford 1.4 g of product **(63a)** (an MDM2-p53 inhibitor) in 82% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for large-scale synthesis of indole 3,3′-trimer derivatives.



Scheme 2.84

After successful preparation of bis(indolyl)methane compounds (3,3′-trimer), we turned our attention towards the recovery and reusability of the catalyst and for that, we have performed the reaction of 1*H*-indole (**58a**) in presence of 10 mol% acidic ionic liquid (**BAIL-1**) at 80 °C under neat condition. The reaction mixture was allowed to cool to room temperature after completion and then water was added to it. The reaction mixture was then filtered off and the ionic liquid was recovered by evaporating the water. The catalyst showed its high level of activity for synthesizing the target product (**63a**) even after being recycled five times as shown in Table 2.60 and in Figure 2.12.

Table 2.60. Recycling of **BAIL-1** for synthesizing compound (**63a**).[a]

No. of cycle	Yields (%)[b]	Catalyst recovery (%)
1	85	95
2	84	92
3	80	88
4	80	85
5	77	82

[a]Carried out with 1 mmol of **58a** and 10 mol% of catalyst (**BAIL-1**) under the neat condition at 80 °C for 1 h. [b]Isolated yields.

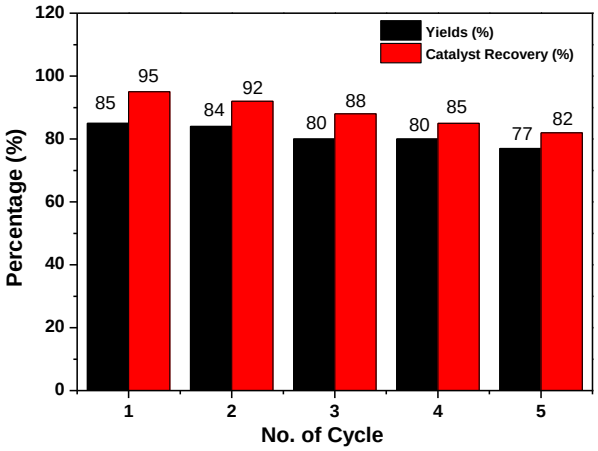
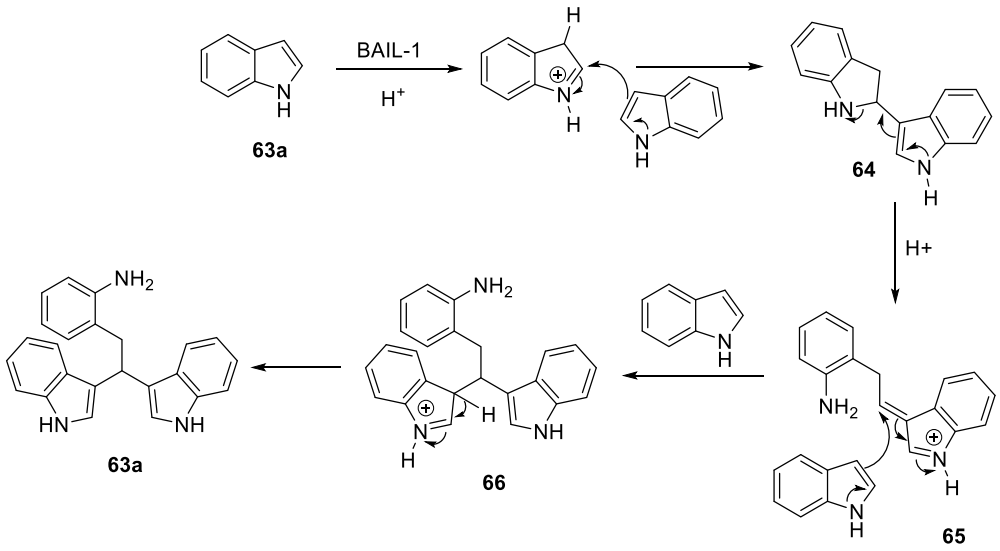


Figure 2.12. Representation of catalyst recycling and recovery

A plausible mechanistic pathway for the trimerization of indole has been suggested as shown in Scheme 2.85. Indole 3,3′-trimers transformation occurs possibly through the generation of indolinium cation by taking a proton from **BAIL-1**. After that, another indole moiety attacks the indolinium cation from C-3 position to form intermediate [**64**]. The intermediate [**64**] gets broken and converted to the specie [**65**] which then involves the addition of the third indole to produce the indole trimer (**63a)** through the formation of intermediate [**66**].



Scheme 2.85

2.22. MOLECULAR IODINE-FREE REGIOSELECTIVE 1,2-DIFUNCTIONALIZATION OF OLEFINS AND FORMATION OF TERMINAL ACETALS IN PRESENCE OF $NH_2OH{\cdot}HCl$ AND $NaIO_4$

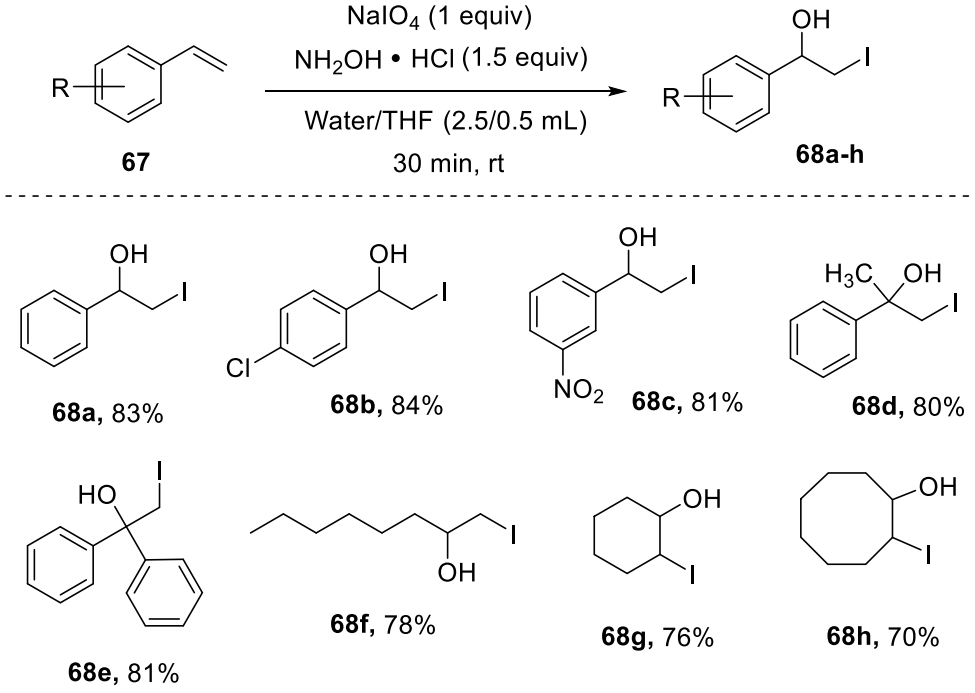
In continuation of our reaserches we have studied the transformations of compounds with unsaturated CC bonds, such as alkenes (styrenes) or acetylenes in some key reactions. Like azomethines, styrenes can be considered as precursors of aziridines, as well as products of their transformations. Therefore, in the framework of our work, we considered the reactivity of styroles, including those activated by electron acceptor groups, in some key transformations for aziridines, as well as in new transformations that are not available in a number of aziridines. Thus, the reactivity of inactive styrenes (**67**) was studied when interacting with the above-described (Chapter 2.4) for aziridines of the $NaIO_4/NH_2OH{\cdot}HCl$ system. Thus, when interacting with this styrene system in THF or CH_3CN at room temperature in air, *β*-iodohydrins (*β*-halo alcohols) (**68**) were unexpectedly obtained (Scheme 2.86).

As a reflection of our keen interest in research field, we are eager to find out a general and efficient methodology for the synthesis of *β*-iodo-*β′*-hydroxy ethers, *β*-iodoethers, iodohydrins, and *β*-iodoacetoxy compounds in terms of using basic chemicals as starting materials, increasing efficiency, operational simplicity, mild reaction conditions, and economic practicability is highly desirable.

We have reported an efficient approach for the regioselective synthesis of various iodohydrins, *β*-iodoethers, *β*-iodo-*β′*-hydroxy ethers, and *β*-iodo acetoxy compounds from alkenes using the combination of $NaIO_4$ and $NH_2OH{\cdot}HCl$ at room temperature within a short reaction time, as a effect of continuation of our research in organic synthesis. Recently, we have reported the combination of $NaIO_4$ and $NH_2OH{\cdot}HCl$ as a good, selective and mild oxidizing agent for the oxidation of alcohols to the corresponding carbonyl compounds at room temperature.[64] Based on this report we can suspect that the iodine generated in an *in situ* condition may undergo addition reaction to the double bond to form the iodonium ion which in presence of different reaction media or nucleophilic solvents like alcohols, water, carboxylic acids etc. might afford the corresponding iodohydrins, *β*-iodoethers, *β*-iodo-*β′*-hydroxy ethers, and *β*-iodoacetoxy compounds.

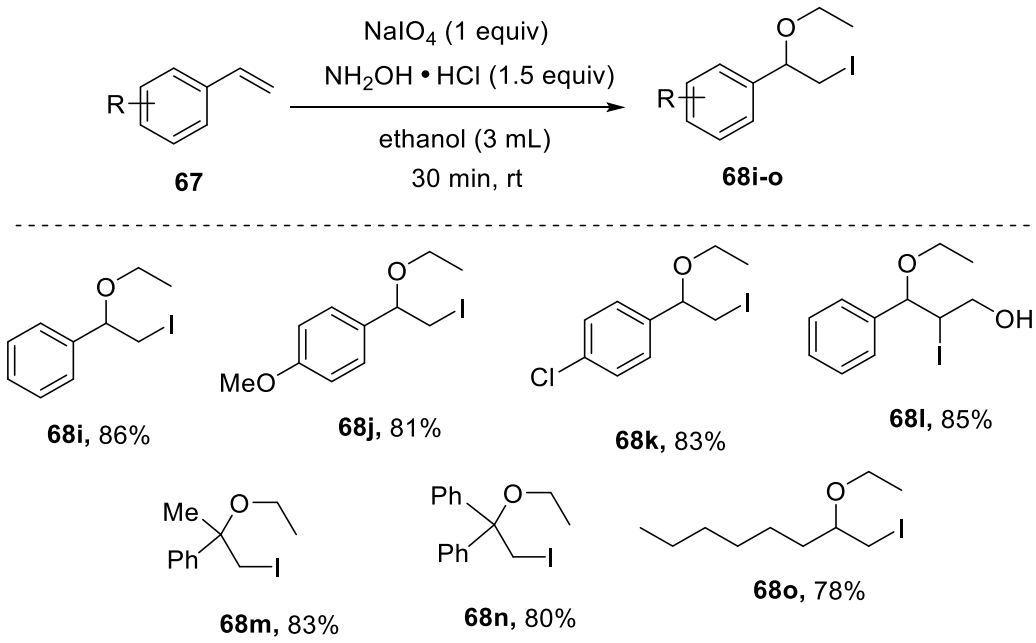
To establish the general applicability of the methodology first we have used solvent (nucleophile) like water for the synthesis of iodohydrin compounds (Scheme 2.86). We have successfully synthesized iodohydrin (**68a-h**) with satisfactory yields. It is worth mentioning that a little amount of THF was added to water as solvent to synthesize the iodohydrins. The simple styrene reacted very well with water/THF to give the corresponding product (**68a**). Also the chloro-

and nitro- substituted styrenes smoothly affored the desired products (**68b**, **68c**). It worth to mention that *α*-methyl styrene and 1,1-diphenylethylene both reacted well to give the corresponding iodohydrins (**68d**, **68e**). Also the aliphatic olefins like 1-octene, cyclohexene and cyclooctene can succesfully afford the desired iodohydrins (**68f-68h**) with good yields. However, *β*-methyl-*β*-nitrostyrene did not response under this present reaction conditions to give the corresponding iodohydrin.



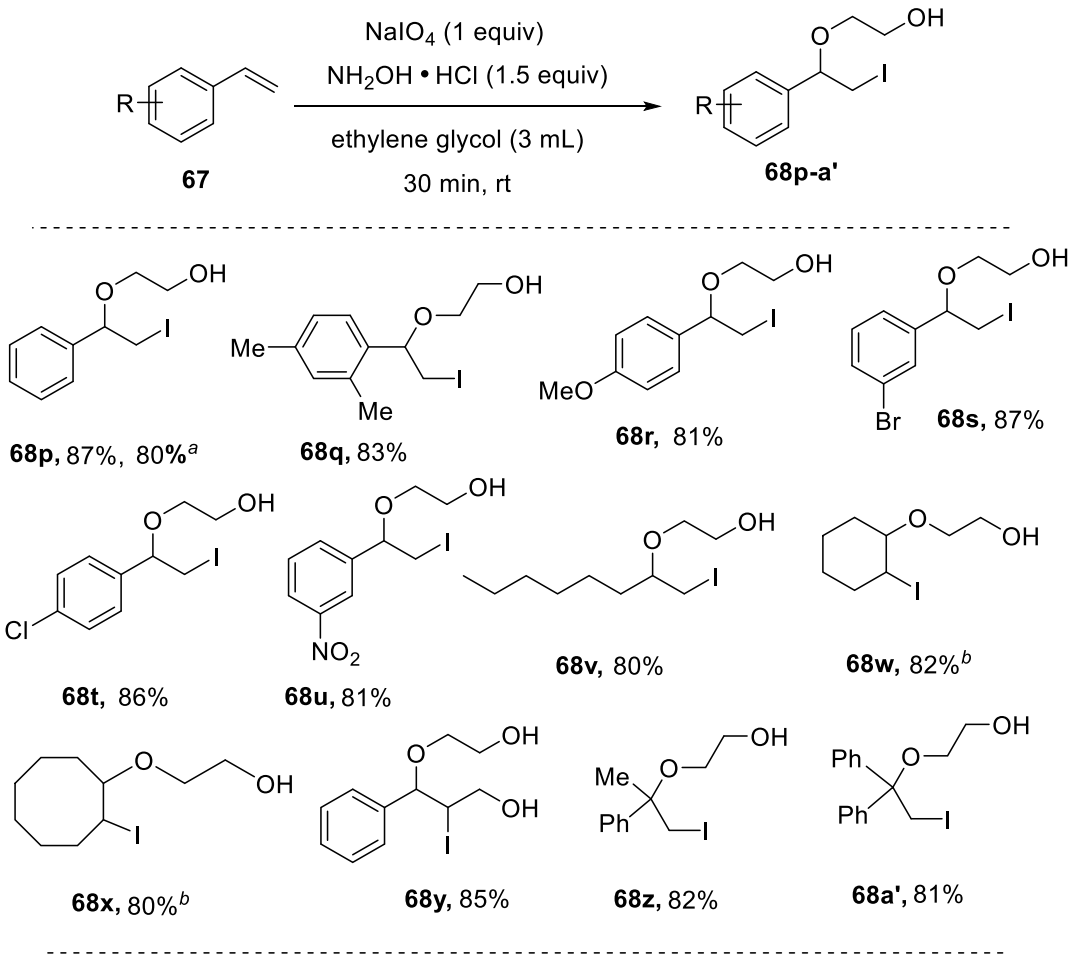
Scheme 2.86

Next step is the exploration of our present methodology using ethanol as a nucleophilic solvent. Ethanol efficiently reacted with olefinic systems to afford various *β*-iodoethers. To our delight the corresponding *β*-iodoethers (**68i-o**) were obtained regioselectively in good yields and the results are summarized in Scheme 2.87. Simple styrene reacted very smoothly with ethanol to produce the desired *β*-iodoether (**68i**) with high yield. Further we have investigated the wide scope of this reaction. Styrenes substituted by different groups like electron donating OMe group as well as electron withdrawing halogen group underwent smooth reactions to give the final products, (**68j**) and (**68k**), respectively. Cinnamyl alcohol also subjected to the same reaction condition to check the effect of alcoholic group in the olefinic system but as usual it can also afford the desired product with excellent yield (**68l**). *α*-Methylstyrene and 1,1-diphenylethylene also give the corresponding products (**68m**) and (**68n**) in 83% and 80% yields respectively by positive participation in the reaction course. Above all, aliphatic alkene such as 1-octene also afforded the desired product (**68o**) with good yield which is another important addition to prove the general applicability of this present protocol.



Scheme 2.87

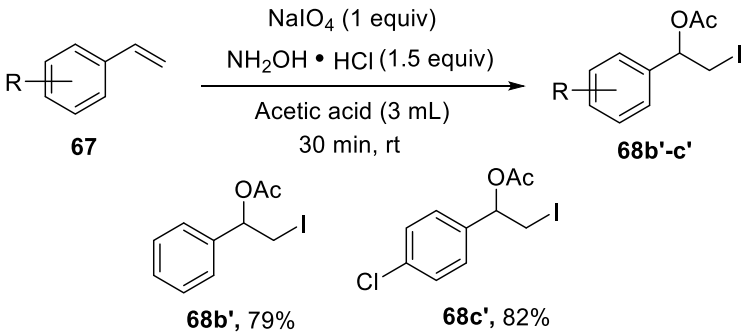
Further, we have investigated the scope and limitations of this reaction using ethylene glycol as nucleophilic solvent **(**Scheme 2.88**)**. We have given our attention to the use of different olefinic systems as substrate to prove the general applicability of the reaction conditions. It was observed that electron-rich and electron-deficient styrenes both were reacted efficiently with ethylene glycol to afford the desired products with good yields under the present reaction conditions. Also the styrene containing an electron donating Me & OMe group on the aromatic ring showed good efficiency to form products (**68q**) and (**68r**). The bromo- and chloro-substituted styrenes were also efficient as a substrate and gave the corresponding products (**68s**) and (**68t**) in 87% and 86% yields respectively without forming any dehalogenated products. Other electron withdrawing substituent NO_2 group on styrene moiety successfully afforded the desired product with satisfactory yield (**68u**). Similarly the aliphatic olefinic systems were also found to afford the desired products (**68v**-**68x**) with good yields. Our present protocol is also effective to produce the corresponding *β*-iodo-*β′*-hydroxyether (**68y**) from cinnamyl alcohol. Again under the same reaction conditions *α*-methylstyrene and 1,1-diphenylethylene both can produce the final desired products (**68z**, **68a′**) with good yields. However, sodium 4-vinyl benzenesulfonate, *β*-methyl-*β*-nitrostyrene, and cholesterol did not give the corresponding iodoethers under the present reaction conditions. This protocol is also applicable on a gram-scale synthesis and styrene (10 mmol) successfully reacted with ethylene glycol to synthesize the iodo-ether (**68p**) in 80% yield. It was worth mentioning that all the reactions were occurred very smoothly and *β*-iodo-*β′*-hydroxy ethers were found to be furnished regioselectively in all cases.



[a]styrene **1a** (10 mmol), $NaIO_4$ (10 mmol), $NH_2OH.HCl$ (15 mmol) in 30 mL of ethylene glycol at room temperature for 30 min. [b]*cis* product.

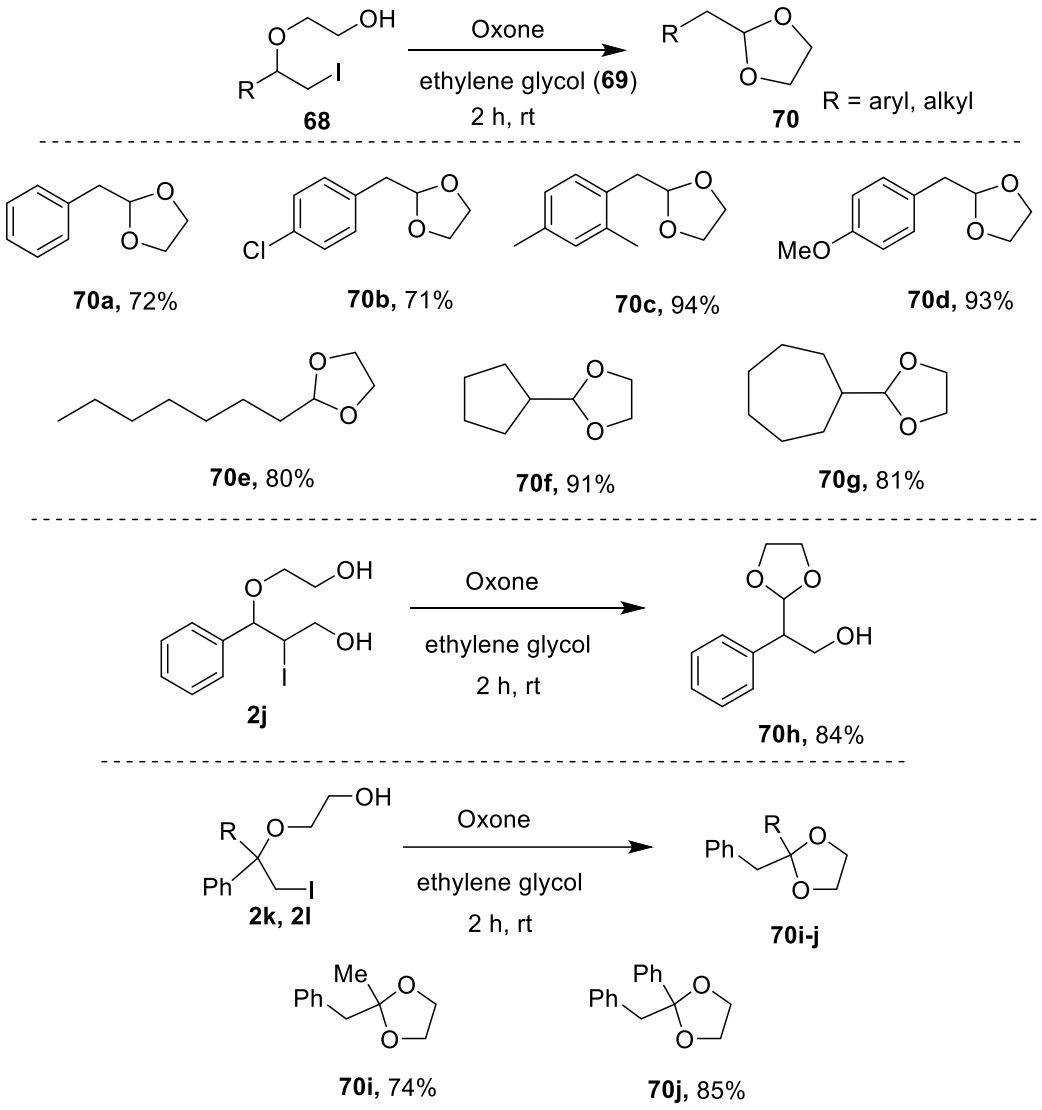
Scheme 2.88

To establish the general applicability of the methodology we have used other solvent (nucleophile) like acetic acid for the synthesis of *β*-iodoacetoxy compounds (Scheme 2.89). We have successfully synthesized *β*-iodoacetoxy compounds with satisfactory yields which further accelerates the scope of this transformation. The simple styrene reacted very well with acetic acid to give the corresponding product (**68b′**). Also the chloro- substituted styrene smoothly affored the desired product (**68c′**).



Scheme 2.89

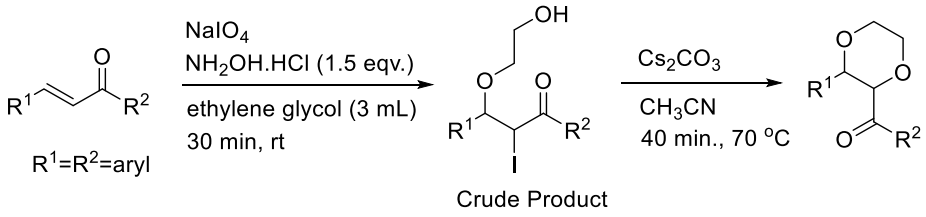
Acetal formation at the terminal position of alkenes instead of aldehydes as substrate is always a demanding task. Narender *et al.* reported a metal-free approach for the synthesis of terminal acetals by tandem oxidative rearrangement of olefins using oxone as an oxidant in the presence of iodine [276]. Significantly we must have to mention that our synthesized compounds (**68p-a′**) are the key intermediate for synthesizing the terminal acetals. By employing this reported method [276] we have successfully synthesized a number of terminal acetals (**70a-j**) from the previously synthesized *β*-iodo-*β′*-hydroxy ethers (**68p-a′**) using oxone as oxidant (Scheme 2.90).



Scheme 2.90

2.23. SYNTHESIS OF 2,3-DISUBSTITUTED 1,4-DIOXANES BEARING A CARBONYL FUNCTIONALITY FROM *α,β*-UNSATURATED KETONES

In the continuation of the research, styrene activated by the presence of acyl fragments, namely chalcones, were studied in the above-mentioned reaction. Based on the practical value of the process described above (Scheme 2.88), ethylene glycol was also studied as a nucleophilic agent. As a result, it was shown that the reaction leads to the formation of 3-(2-hydroxyethyloxy)-2-iodo-1,3-diaryl-1-ones (**72**), released with yields up to 94% (Scheme 2.91 & 2.92). So, here reagent combinations of $NaIO_4$ and $NH_2OH{\cdot}HCl$ have been used where an *α,β*-unsaturated ketone can be converted into *β*-iodo-*β′*-hydroxy ethers using ethylene glycol as nucleophile as well as reaction medium. This *β*-iodo-*β′*-hydroxy ether under Williamson ether synthesis conditions can be easily converted to 2,3-di-substituted 1,4-dioxane using cesium carbonate as a base. It is worthy to mention that product of the first step has not been isolated and the next step was carried out just by adding base and solvent (Scheme 2.91). The carbonyl group of chalcone did not interfere under this reaction condition. Substituted 1,4-dioxane with carbonyl group in adjacent to the 1,4-dioxane ring has been synthesized as the sole product.

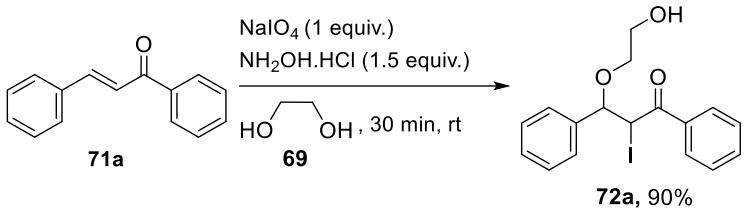


Scheme 2.91

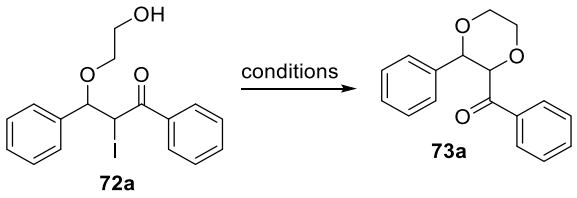
The synthetic procedure involved two steps. In the first step, the reaction of a freshly prepared simple chalcone (**71a**) with 1 equiv $NaIO_4$ and 1.5 equiv $NH_2OH{\cdot}HCl$ as an oxidant in ethylene glycol solvent at room temperature produces product (**72a**) in 90% yield within 30 min at room temperature (Scheme 2.92). At the second step, 3-(2-hydroxyethoxy)-2-iodo-1,3-diphenylpropan-1-one (**72a**) was subjected to a base Cs_2CO_3 in CH_3CN solvent at 70 °C and the desired product (**73a**) was isolated in 94% yield within 40 min (Scheme 2.93). Encouraged by this initial result, the reaction has carried out under different temperatures in different solvents to optimize the reaction conditions and the results are shown in Table 2.61 and Table 2.62. Here it is worthy to mention that for optimization of the reaction conditions, we have performed the second steps with the crude product of the initial step.

At first, we have tested the temperature effects of this reaction. It was found that at 70°C temperature the reaction gave the best result (94% yield) after 40 min in acetonitrile solvent. To examine the solvent effect, various common solvents like acetonitrile, toluene, DCM, 1,2-DCE,

acetone, DMF, DMSO, THF, 1,4-dioxane and methanol were tested (entries 1-10**,** Table 2.62). To our delight, 94% yield of the desired product was obtained in acetonitrile (entry 1, Table 2.62). Then, a series of other bases like K_2CO_3, Na_2CO_3, Ag_2CO_3, Li_2CO_3, NaOH, KOH was also investigated (entries 11-16, Table 2.62). The results indicated that other bases were not so effective in promoting the reaction, while Cs_2CO_3 gave a satisfactory yield of the product (entry 1, Table 2.62) and finally, this has been accepted as optimized reaction conditions by using 1 equiv. Cs_2CO_3 in acetonitrile at 70°C for 40 min (Table 2.62, entry 1). By increasing the amount of the base also could not increase the yield even after the prolonged time (entry 17, Table 2.62).

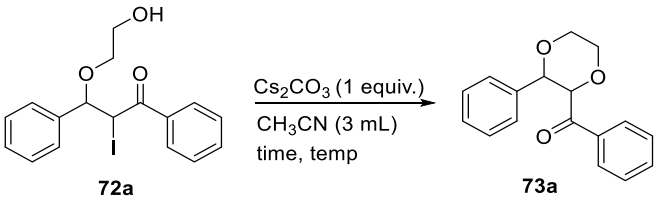


Scheme 2.92



Scheme 2.93

Table 2.61. Optimization of the reaction temperature and time



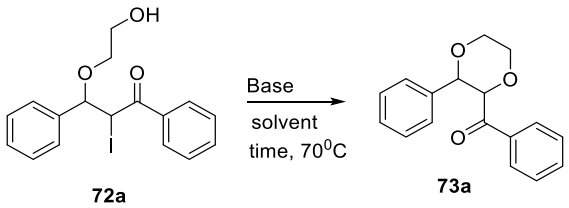
Entry	Temperature (°C)	Time	Yield (%)
1	rt	12 h	nd[b]
2	40	6 h	<10
3	55	1 h	70
4	70	40 min	94
5	100	40 min	90

[a]***Reaction conditions:*** 1 mmol of **72a** was reacted with Cs_2CO_3 (1 equiv.) in acetonitrile solvent (3 mL) at various temperatures varying different reaction times. [b]Not detected in TLC.

After obtaining the optimized reaction conditions in hand, we became interested in exploring the substrate scope of this methodology and the results are represented in Table 2.63. A

series of substituted 1,4-dioxanes (**73a–r**) were synthesized under the optimized reaction conditions in good to excellent yields. It was observed that the *α,β*–unsaturated ketones substituted with electron-donating substituents like -Me, -OMe as well as electron-withdrawing groups such as -chloro and -fluoro reacted easily to get the desired products (**73b-73e**) in good yields.

Table 2.62. Optimization of the reaction conditions.[a]



72a **73a**

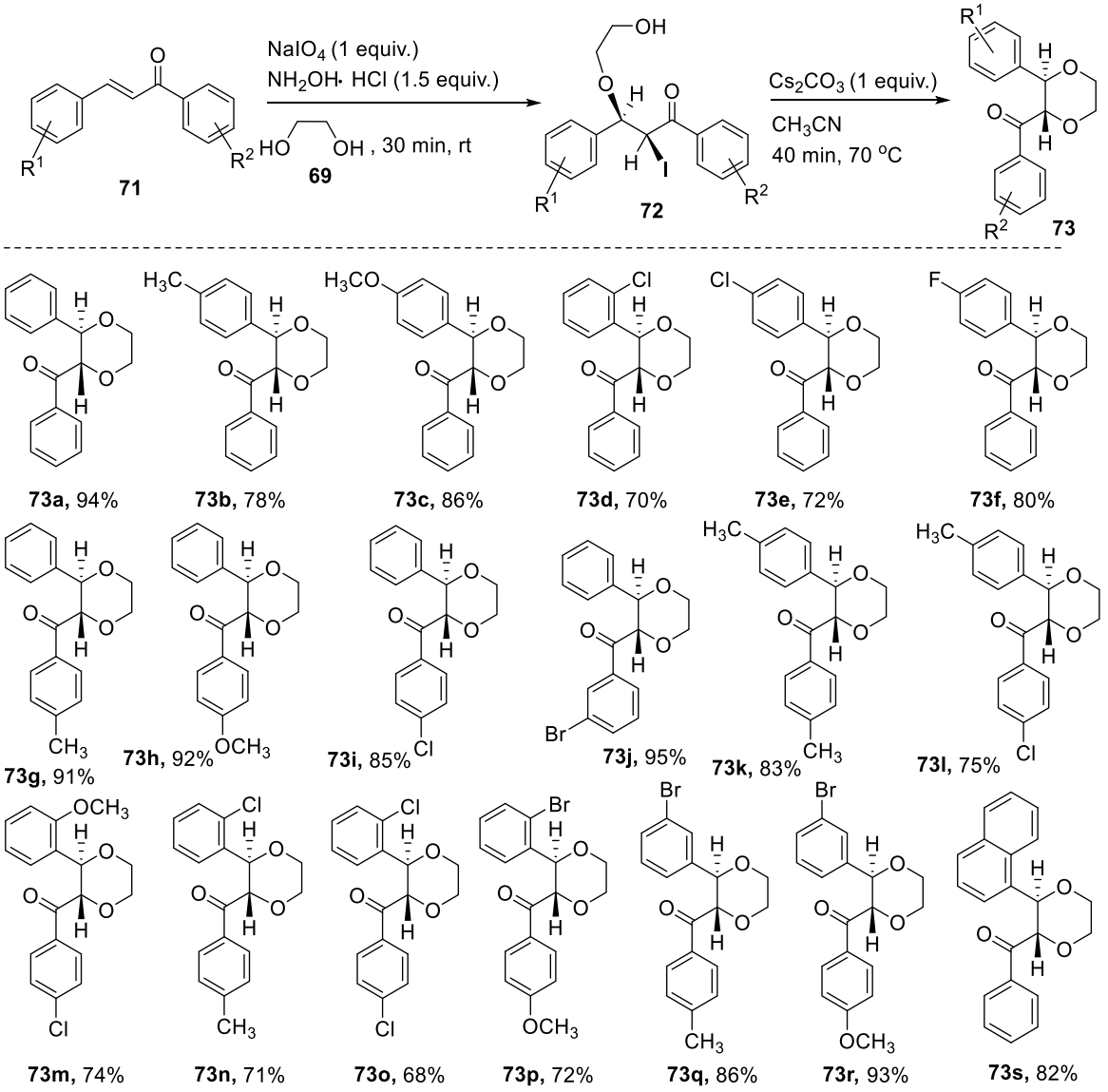
Entry	Base (equiv.)	Solvent	Time (min)	Yield (%)
1	Cs_2CO_3 (1)	CH_3CN	40	94
2	Cs_2CO_3 (1)	toluene	40	55
3	Cs_2CO_3 (1)	DCM	40	nd[c]
4	Cs_2CO_3 (1)	1,2-DCE	40	35
5	Cs_2CO_3 (1)	acetone	40	73
6	Cs_2CO_3 (1)	DMF	40	88
7	Cs_2CO_3 (1)	DMSO	40	trace
8	Cs_2CO_3 (1)	THF	40	47
9	Cs_2CO_3 (1)	1,4-dioxane	40	30
10	Cs_2CO_3 (1)	MeOH	40	32
11	K_2CO_3 (1)	CH_3CN	40	nd[b]
12	Na_2CO_3 (1)	CH_3CN	40	nd[b]
13	Ag_2CO_3 (1)	CH_3CN	40	nd[b]
14	Li_2CO_3 (1)	CH_3CN	40	nd[b]
15	NaOH (1)	CH_3CN	40	nd[b]
16	KOH (1)	CH_3CN	40	nd[b]
17	Cs_2CO_3 (1.5)	CH_3CN	60	85

[a]***Reaction conditions:*** 1 mmol of **72a** was reacted at 70 °C with various bases in various solvents. [b]Not detected in TLC.

α,β–Unsaturated ketones in which ketone part substituted with electron-donating substituents like -Me and -OMe provided the corresponding products (**73g**) and (**73h**) in 91% and 92% yields respectively while the reactions with electron-withdrawing groups, such as –Cl and –Br, afforded products (**73i**) and (**73j**) in 85% and 95% yields respectively. Substitution in the

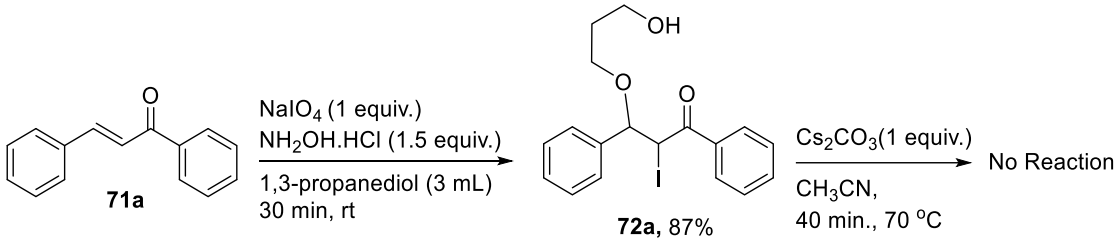
phenyl rings from both sides of the *α,β*–unsaturated ketones have been tested and observed the similar reaction to afford the desired products. Moderate to high yields were observed (68-93%) for all the cases in case of products (**73k-r**), for precursors, bearing both electron-withdrawing and electron-donating functional groups. In addition, 1-naphthaldehyde substituted *α,β*-unsaturated ketone, namely, 3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one also reacted smoothly under this conditions to get the product (3-(naphthalen-1-yl)-1,4-dioxan-2-yl)(phenyl)methanone (**73s**) in 82% yield. However, we were unable to synthesize large ring dioxane. For an attempt, we carried out a reaction taking 1,3-propanediol instead of ethylene glycol in the initial step and obtained 3-(3-hydroxypropoxy)-2-iodo-1,3-diphenylpropan-1-one (**72a)** in 87% yield in the 1st step (Scheme 2.94). However, compound (**72a**) remained unreacted with cesium carbonate.

Table 2.63. Substrate scope of the present method[a]

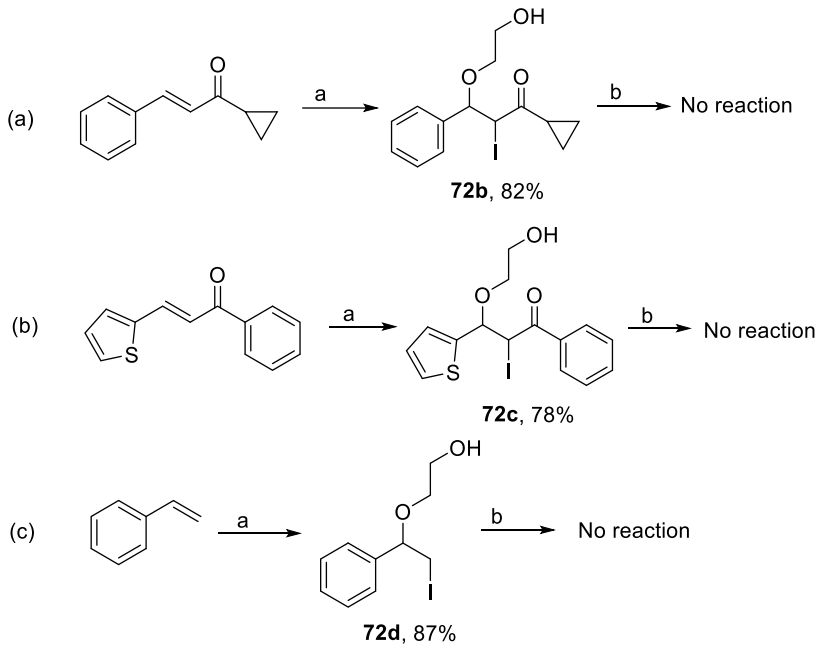


Reaction conditions: All reactions were performed on a 1 mmol scale in presence of $NaIO_4$ (1 mmol) and $NH_2OH.HCl$ (1.5 mmol) in 3 mL of ethylene glycol at room temperature for 30 min. 1 mmol of **72** was reacted at 70 °C with various bases (1 equiv.) in various solvents or neat conditions. After the workup the reaction mixture was reacted with Cs_2CO_3 (1 equiv.) in acetonitrile solvent at 70 °C for 40 min.

Again, it is worthy to mention that chalocones having aliphatic as well as heterocyclic moities did not respond to afford the desired products. After the reaction under similar conditions we isolated only the *β*-iodo-*β′*-hydroxy ethers (**72b)** and (**72c**), which are products before cyclization, in 82% and 78% yields, respectively. Similarly, simple styrene also underwent the 1st step but not the desired cyclization step (Scheme 2.95).



Scheme 2.94



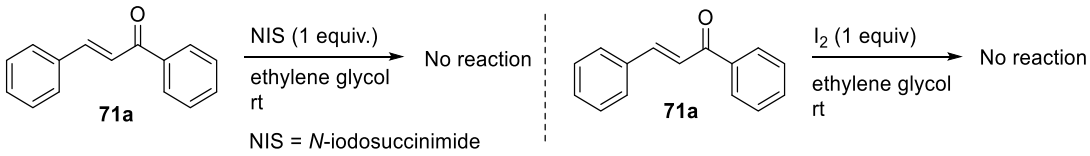
Reagents and conditions:

a: $NaIO_4$ (1 equiv.), NH_2OH· HCl (1.5 equiv.), ethylene glycol, rt

b: Cs_2CO_3 (1 equiv.), CH_3CN, 40 min, 70 °C

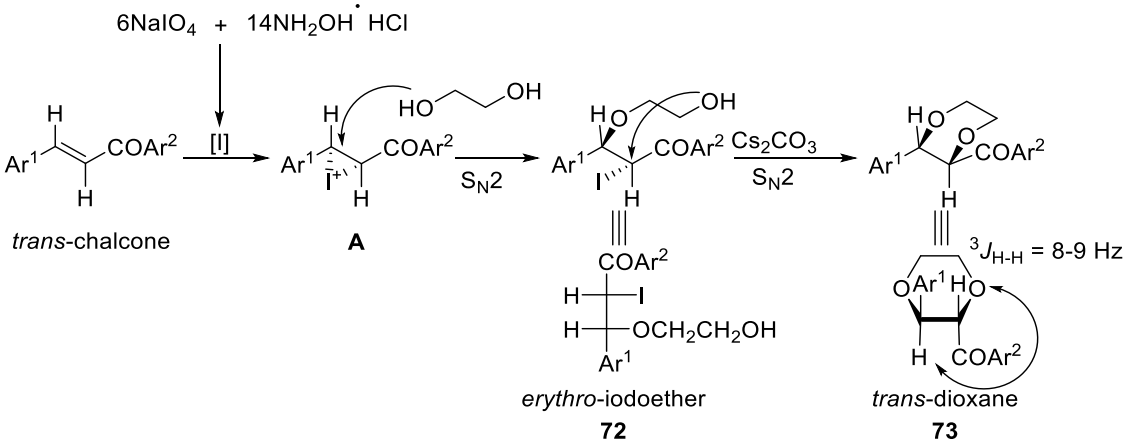
Scheme 2.95

Finally, we carried out two control experiments to understand the the mechanistic path of the reaction. When the reaction was carried out in the presence of *N*-iodosuccinimide (NIS) as well as simple molecular iodine under similar reaction conditions no product was obtained even in the 1st step (Scheme 2.96).



Scheme 2.96

A probable mechanism has been proposed for this two-step conversion (Scheme 2.97). Based on the present experiments, literature [361] and our previous works on the preparation of iodohydrine compounds it can be suggested that an in situ generated electrophilic iodine reagent undergoes simple addition to the chalcone giving the intermediate [**A**]. In the presence of excess ethylene glycol which acts as nucleophile reacts with the intermediate [**A**] giving the compound (**72**). Then in presence of a base, the intramolecular Williamson ether synthesis, probably *via* S_N2 mechanistic pathway, produces the desired product (**73**).

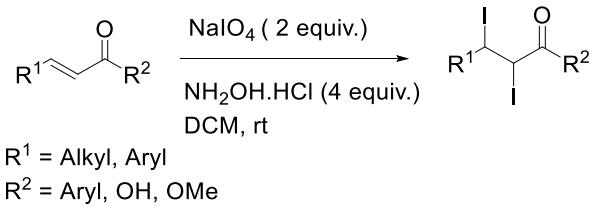


Scheme 2.97

The intriguing stereoselectivity of the proposed method should be mentioned. Dioxanes (**73**) are formed as a single trans-stereoisomer as established by the spin-spin coupling constant (SSCC) between protons at C2 and C3 of the dioxane ring. The structural assignment is based on the fact that trans-substituted dioxanes typically exhibit a SSCC of 9 Hz, while *cis*-substituted counterparts exhibit 4 Hz SSCC [362]. The observed value of 8-9 Hz is consistent with the *trans* configuration of substituents at positions C2 and C3. Thus, in the ^{1}H NMR spectrum of dioxanes (**73**), the characteristic signals of protons at C2 and C3 are registered as doublets with *vicinal* SSCC 8-9 Hz at 4.8-4.9 ppm. Remaining dioxane ring protons (at C5 and C6 carbon atoms) and aromatic protons registered as multiplet at 4.0 and 6.7-7.7 ppm, respectively. In ^{13}C NMR spectrum, all expected signals are observed as: atoms C2 and C3 at 80 ppm and atoms C5 and C6 at 66 ppm; carbonyl atom at 195 ppm and aryl carbons in the range 127 to 160 ppm. The high stereoselectivity of the proposed method was attributed to the *trans*-configuration of the starting chalcone and selectivity of the following transformations: iodination of the trans-chalcone gives *trans*-iodonium cyclic cation [**A**], ring opening of this cyclic iodonium intermediate with ethyleneglycol yielding *erythro*-iodoether (**72**) and followed by the configuration inversion during the S_N2 substitution of iodine forming the dioxane ring (Scheme 2.97).

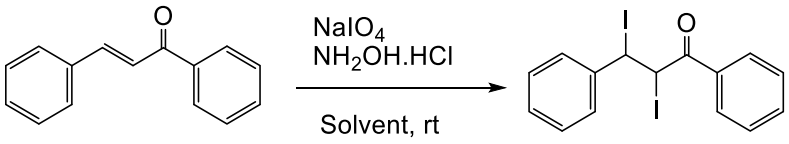
2.24. SYNTHESIS OF *VICINAL* DIIODO COMPOUNDS

Interestingly, in the absence of *O*-nucleophiles, the use of the $NaIO_4/NH_2OH{\cdot}HCl$ reagent system in reactions with chalcones or cinnamic acid led to the formation of diiodosubstituted derivatives with yields up to 84% (Scheme 2.98).



Scheme 2.98

Table 2.64. Optimization of the reaction conditions.



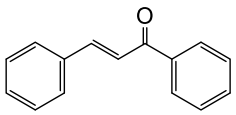
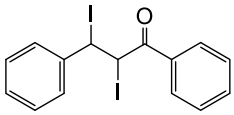
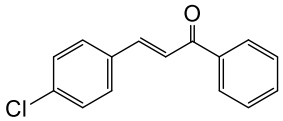
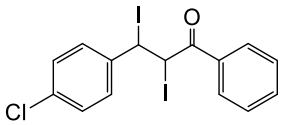
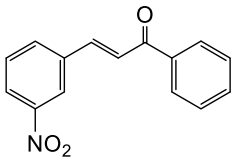
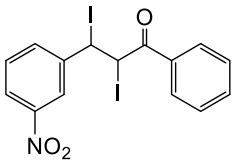
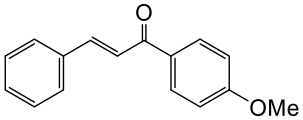
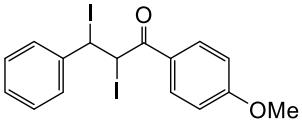
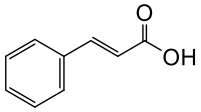
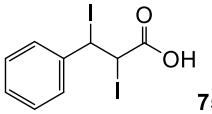
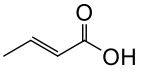
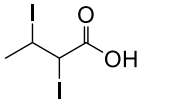
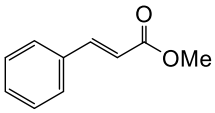
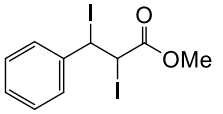
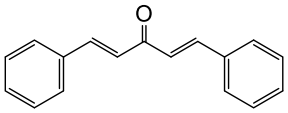
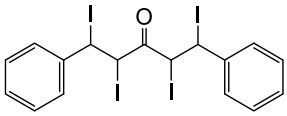
Entry	C=C : $NaIO_4$: $NH_2OH.HCl$	Solvent (2 mL)	Yield (%)
1	1 : 1 : 1	DCM	20
2	1 : 1 : 1.5	DCM	30
3	1 : 1 : 2	DCM	34
4	1 : 2 : 3	DCM	40
5	1 : 2 : 4	DCM	84
6	1 : 2 : 5	DCM	84
7	1 : 2.5 : 5	DCM	82
8	1 : 2 : 4	MeCN	14
9	1 : 2 : 4	THF	12
10	1 : 2 : 4	1,4-Dioxane	<10
11	1 : 2 : 4	1,2-DCE	75

Reaction conditions: 1 mmol of chalcone with various proportions of $NaIO_4$ and $NH_2OH.HCl$ in solvent (2 mL).

For optimization of the reagents combination we chose different ratios of $NaIO_4$ and $NH_2OH.HCl$ as shown in Table 2.64 with simple chalcone as model substrate. First of all we used

1:1 proportion of $NaIO_4$ and $NH_2OH.HCl$ and very lower amount (20%) of desired product was observed (entry 1, Table 2.64). By increasing the proportion of $NH_2OH.HCl$ from 1 to 1.5 the desired product was increased to 40% (entries 2-4, Table 2.64).

Table 2.65. Diiodination of the *α,β*-unsaturated carbonyl compounds.[a]

Entry	Substrates	Products	Yields (%)
1		 **75a**	84
2		 **75b**	81
3		 **75c**	82
4		 **75d**	80
5		 **75e**	83
7		 **75f**	81
8		 **75g**	84
8[b]		 **75h**	82

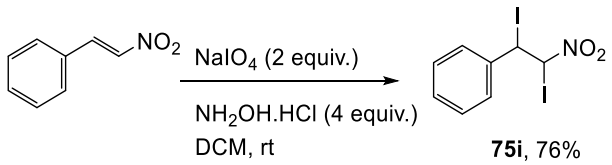
[a] ***Reaction conditions:*** 1 mmol of olefin, 2 equiv. of $NaIO_4$, 4 equiv. of $NH_2OH.HCl$ in DCM (2 mL).
[b] 4 Equiv. of $NaIO_4$ and 8 equiv. of $NH_2OH.HCl$ were used.

The maximum amount of yield was obtained by using 2:4 ratios of $NaIO_4^-$ and $NH_2OH.HCl$ respectively (entry 5, Table 2.64). Further increasing the amount of both the reagents in different ratios the yield of the diiodo product did not improve significantly (entries 6-7, Table 2.64). We have also examined the role of solvent for this reaction and found that solvent plays a vital role in the reaction. Only DCM and 1,2-DCE act as a good solvent for these particular

reactions. In presence of other solvents such as acetonitrile, THF, 1,4-dioxane etc. the reaction did not work well (yields are less than 15%, entries 8-10, Table 2.64). 1.2-Dichloethane as solvent afforded good yield (75%, entry 11, Table 2.64) but not as good as dichloromethane. Finally, optimized reaction conditions were obtained using 2 equiv. of $NaIO_4$ and 4 equiv. of $NH_2OH.HCl$ with respect to the 1 equiv. of *α,β*-unsaturated carbonyl compounds in DCM (2 mL) at room temperature.

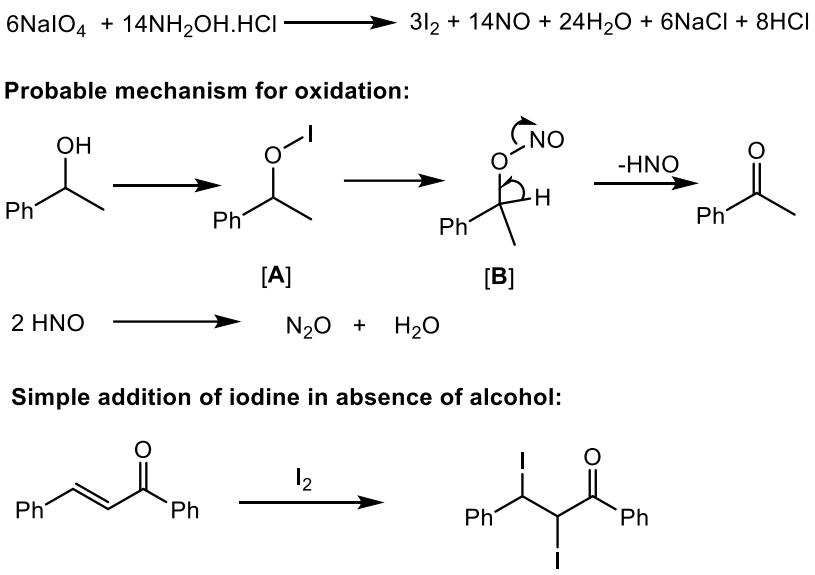
With optimized reaction conditions in hand, the scope and limitations of this reaction were investigated (Table 2.65). Different *α,β*-unsaturated carbonyl compounds were subjected to give the corresponding diiodo compounds. The reaction proceeded well with chalcones and unsaturated acids afforded the *vicinal* diiodo derivatives with satisfactory yields (**75a-f**). *α,β*-Unsaturated ester underwent this reaction without any hydrolyzed product (**75g**). Functional groups like –Cl, $-NO_2$ in chalcone were also unaffected under the present reaction conditions (**75b,c**). When dibenzylidine acetone was subjected under these conditions using 4 equiv. of $NaIO_4$, 8 equiv. of $NH_2OH.HCl$, the expected tetraiodo product was obtained with high yield (**75h**).

Another important observation is the reaction of nitrostyrene under these present reaction conditions to give 1,2-diiodo nitro derivative (**75i)** in 76% yield (Scheme 2.99). This compound is synthetically very useful as it contains a nitro group and two excellent leaving groups which can readily be replaced by a heteroatom and can be applied in C-C coupling reaction.



Scheme 2.99

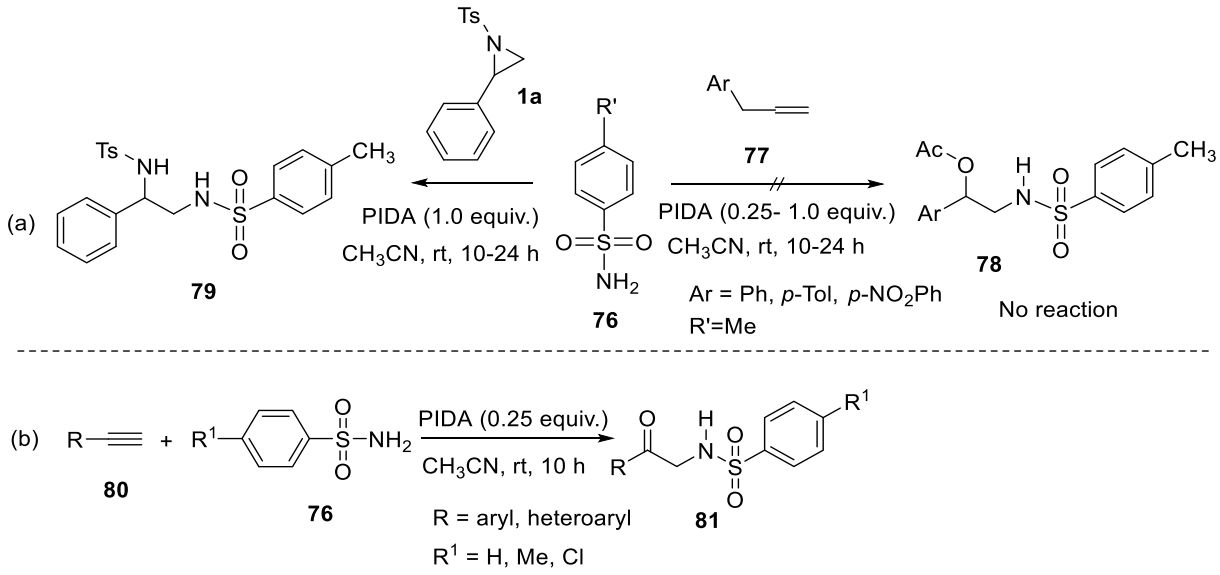
It is worthy to mention that mechanism of this reaction has not been well investigated. We have proposed a mechanism where iodine is generated *in situ* and undergoes the addition to the double bond giving the diiodo compound under mild reaction conditions (Scheme 2.100).


6NaIO4 + 14NH2OH.HCl
3I2 + 14NO + 24H2O + 6NaCl + 8HCl
Probable mechanism for oxidation:
OH
Ph
O
I
Ph
[A]
O
NO
H
Ph
[B]
-HNO
O
Ph
2 HNO
N2O + H2O
Simple addition of iodine in absence of alcohol:
O
Ph
Ph
I2
I
O
Ph
Ph
I

Scheme 2.100

2.25. AMIDATION REACTIONS OF TERMINAL ALKYNES WITH BENZENESULFONAMIDE

Interaction of vinyl(het)arenes with *N*-nucleophiles is a promising way to produce amino/amido-substituted styrenes or alkanes. Above, in the framework of our work, we demonstrated the opening of the aziridine cycle (under the action of nucleophiles, leading to the formation of a wide range of *β*-functionalized amines (Chapter 2.1-2.6). Also, the possibility of obtaining *α*-aminoketones was demonstrated using the example of azirines (Chapter 2.10). To assess the possibility of obtaining products similar to those obtained by nucleophilic attack on 2-aryl-1-tosylazyridines, we evaluated the C-H functionalization of styrene (**77**) (allyl benzene), 2-phenyl-1-tosylazyridine (**1a)** (Scheme 2.101a), as well as aryl acetylenes (**80**) (Scheme 2.101b) under the action of sulfamides (**76**) in the presence of (diacetoxy)iodobenzene (PIDA) in acetonitrile at room temperature. Thus, allyl benzene (**77**), regardless of the nature of the reaction holding substituent, did not produce the expected amination products (**78**) under these conditions. Aziridine (**1a)** gave ethylenediamine-bistosylate (**79**). When arylacetylenes (**80)** were involved in a similar reaction *α*-sulfonylaminoketones (**81)** were obtained in 72-87% yields. So, we have developed a reaction of terminal alkynes with benzenesulfonamide affording *α*-aminoketones (*α*-sulfonylaminoketones) in good to excellent yields in the presence of PIDA as oxidant (Scheme 2.101b).

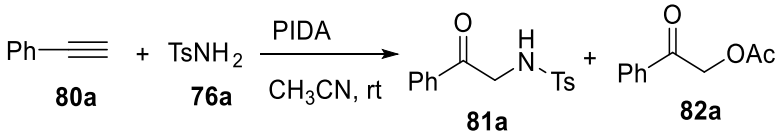


Scheme 2.101

We started our study by mixing phenylacetylene (**80a**) (0.5 mmol) and 4-methylbenzenesulfonamide (**76a**) (0.5 mmol) using PIDA (1 equiv.) as oxidant, at room temperature in acetonitrile solvent. Gratifyingly, benzenesulfonamide (*α*-sulfonylaminoketone) (**81a**) was obtained in 65% yield along with 12% of *α*-acetoxyacetophenone (**82a)** after 10 h (Table

2.66, entry 1). Encouraged by this result, we carried out the reaction in different conditions to optimize the reaction, and the results are summarized in Table 2.66. At first, we investigated the loading effect of the oxidant (PIDA) and sulfonamide ($TsNH_2$) (**76a**) in different ratios. Using 0.5 equiv. of PIDA and 1 equiv. of $TsNH_2$ (**76a**), the yields of products (**81a**) and (**82a**) were 74% and <5% respectively (Table 2.66, entry 2). When the amount of PIDA was decreased to 0.25 equiv. the desired product (**81a**) was obtained in 80% yield along with trace amount of compound (**82a**) (Table 2.66, entry 3). Again, increasing the amount of $TsNH_2$ (**76a**) from 1 to 2 equiv. no enhancement of the yield was noticed (Table 2.66, entry 4). The yield of the reaction did not improve significantly by increasing the reaction time, but upon reducing the reaction time, the yield of product (**81a)** was lowered considerably (Table 2.66, entry 6). Based on these observations we concluded that using 0.25 equiv. of PIDA and 1 equiv. of the $TsNH_2$ (**76a**) in acetonitrile solvent gave the best result after 10 h (Table 2.66, entry 3).

Table 2.66. Optimization of the PIDA driven amidation.[a]



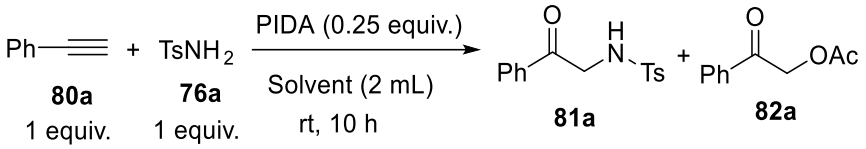
Entry	PIDA (equiv.)	$TsNH_2$ (equiv.)	Time (h)	Conversion (%)	Yield of 3a (%)[b]	Yield of 4a (%)[b]
1	1	1	10	77	65	12
2	0.5	1	10	78	74	<5
3	**0.25**	**1**	**10**	**82**	**80**	**trace**
4	0.25	2	10	83	81	trace
5	0.25	1	20	84	81	trace
6	0.25	1	6	48	45	trace

[a]***Reaction conditions:*** All reaction are carried out in 0.5 mmol scales, **80a** (0.5 mmol), **76a** (as stated amount) and oxidant (PIDA), at room temperature in MeCN, [b] Isolated yield.

Next, a series of experiments have been carried out to examine the role of solvents which are summarized in Table 2.67. Considering the green concept, we have tried the reaction in water (Table 2.67, entry 1) and isolated only product (**82a**) in a 36% yield with a trace amount of product (**81a**). Whereas in methanol, the desired product (**81a**) was obtained in 25% yield along with 20% of product (**82a**) (Table 2.67, entry 2). Next, nonpolar aprotic solvent like toluene showed moderate conversion (52%) with 22% of product (**81a**) and 30% of product (**82a**) (Table 2.67, entry 3), but surprisingly in other aprotic polar solvents like 1,2-DCE and 1,4-dioxane, product (**81a**) was obtained in lower amounts, but the yields were 30-32% for product (**82a**) (Table 2.67,

entries 4 & 5). In the case of acetonitrile, we got the best result (80% yield) of product (**81a**) and trace amount of product (**82a**) with 82% conversion (Table 2.67, entry 6). Thus, the optimized reaction condition was achieved using 0.25 equiv. of PIDA and 1 equiv. of the $TsNH_2$ (**76a**) with respect to phenylacetylene (**80a**) at room temperature in MeCN for 10 h (Table 2.67, entry 6).

Table 2.67. Screening of the solvent effects of the amidation reactions.[a]



Entry	Solvent	Conversion (%)	Yield of 81a (%)[b]	Yield of 82a (%)[b]
1	H_2O	39	Trace	36
2	MeOH	45	25	20
3	Toluene	52	22	30
4	1,2-DCE	42	10	32
5	1,4-Dioxane	33	Trace	30
6	**CH_3CN**	**82**	**80**	**Trace**

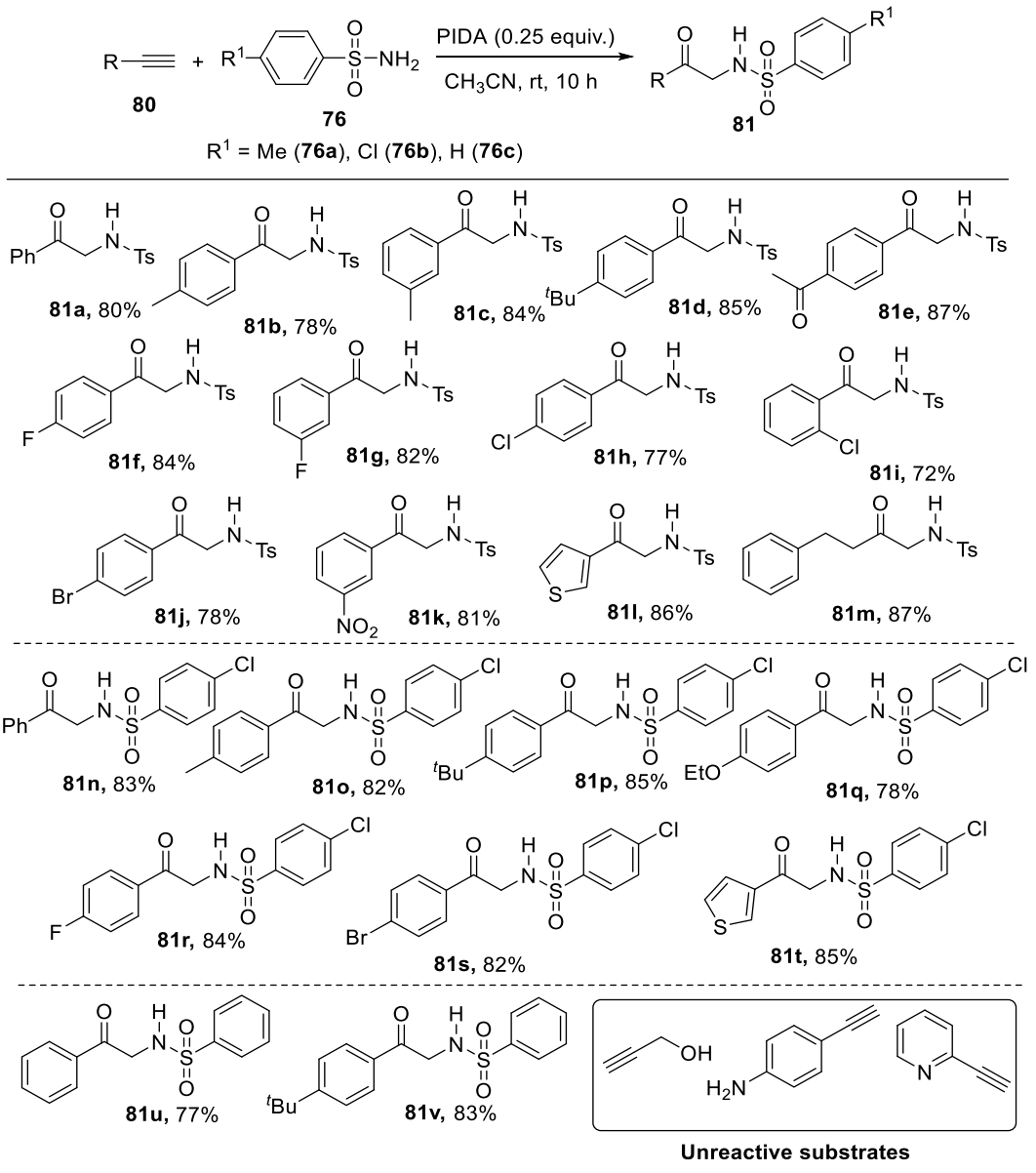
[a] ***Reaction conditions:*** All reaction are carried out in 0.5 mmol scale; **80a** (0.5 mmol), **76a** (1 equiv.) and oxidant (PIDA, 0.25 equiv.), at room temperature in different solvents (2 mL) for 10 h. [b] Isolated yield.

After optimizing the reaction conditions, we explored the substrate scope employing different terminal alkynes to react with 4-methylbenzenesulfonamide, and the results are summarized in Scheme 2.102. Phenylacetylene afforded the desired product (**81a**) in good yield. The regioselectivity is very important for this reaction, and we found no effect on the regioselectivity of the reaction when phenylacetylene was used substituted with electron-donating or electron-withdrawing groups in the phenyl moiety. The presence of various electron-donating substituents such as methyl (**81b, 81c**) and *tert*-butyl (**81d**) produced the desired products in good to excellent yields (78-85%). Similarly, a variety of electron-withdrawing groups like ketones, halogens (F, Cl, Br) and nitro at different positions of the phenylacetylene substrate (**81e-81k**) also reacted efficiently with good to excellent yields. The heterocyclic moiety, thiophene, afforded the corresponding product with excellent yield (**81l**). It is worthy to mention that an aliphatic alkyne also gave the desired product (**81m**) in excellent yield.

Next, we have explored our present methodology with another sulfonamide to react with terminal alkynes under the same reaction condition. 4-Chlorobenzenesulfonamide (**76b**) reacted with different terminal alkynes. Phenylacetylene, substituted phenylacetylene with electron donating substituents like $-CH_3$, $-C(CH_3)_3$, -OEt, furnished the desired products with good to excellent yields (**81n-81q**). Additionally, phenylacetylene substituted with electron-withdrawing

groups like -F, -Br afforded the desired products in good yields (**81r**, **81s**). The thiophene-containing substrate was found to be equally effective to afford the desired product (**81t**) with good yield. Simple benzenesulfonamide (**76c**) also successfully reacted with phenylacetylene and 4-tert-butyl phenylacetylene to produce the desired products (**81u**, **81v**) in good yields. However, the present methodology is not applicable for the propargyl alcohol, 4-ethynylaniline and 2-ethynylpyridine.

All these reactions were carried out in an open atmosphere and are not sensitive to air and moisture. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials.



Reaction conditions: All reaction are carried out in 0.5 mmol scale, **80** (0.5 mmol), **76** (0.5 mmol) and PIDA (0.25 equiv.), at room temperature in MeCN (2 mL) for 10 h. All are isolated yields.

Scheme 2.102

All of the known synthesized compounds have been characterized by NMR and the new compounds by NMR and the X-ray crystallographic analysis of 4-methyl-*N*-(2-oxo-2-(thiophen-3-yl)ethyl)benzenesulfonamide (**81l**) was performed to confirm the structure of the product as shown in Figure 2.13.

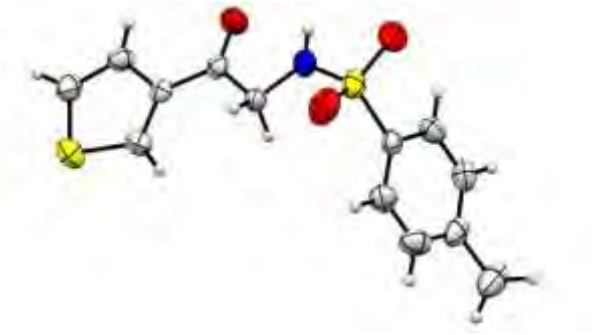
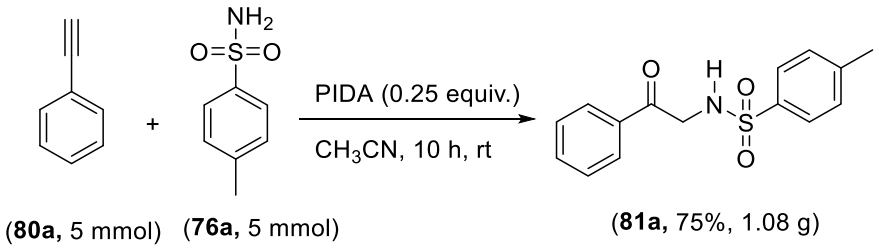


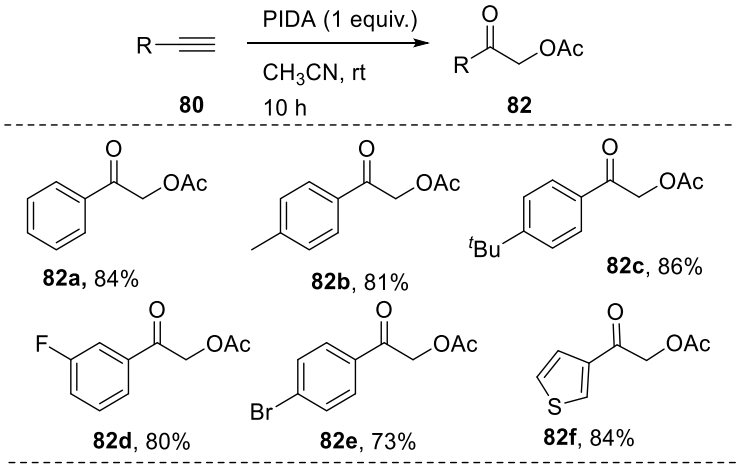
Figure 2.13. X-Ray crystallographic data for the structure of compound **(81l)**.

Furthermore, the potential synthetic applicability of this method was investigated on the gram scale using the model reaction in our laboratory setup. As shown in Scheme 2.103, the reaction could afford 1.08 g of product (**81a**) in 75% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large scale synthesis of α-sulfonylaminoketone derivatives.



Scheme 2.103

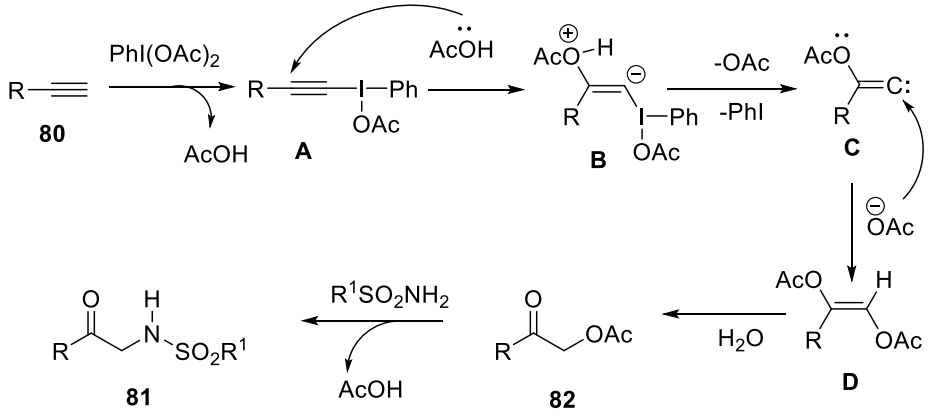
Finally, we checked the reaction in absence of sulfonamide, and we isolated exclusively 84% of *α*-acetoxy ketone (**82a**) when the reaction was performed between phenylacetylene and 1 equiv. of PIDA at room temperature [363, 364]. Different *α*-acetoxy ketone derivatives have been synthesized by varying different phenylacetylenes (Scheme 2.104). Phenylacetylenes containing electron-donating substituents such as methyl and *tert*-butyl afforded the products (**82b)** and (**82c**) in 81% and 86% yields respectively. Arylacetylenes bearing electron-withdrawing groups, like fluoro- or bromo-, resulted in *α*-acetoxy ketone derivatives (**82d)** and (**82e**) in good to excellent yields. Acetylene bearing heterocyclic moiety like 3-ethynylthiophene reacted well to afford corresponding product (**82f**) in 84% yield.



Reaction conditions: All reactions are carried out in 0.5 mmol scales, **80** (0.5 mmol) and PIDA (1 equiv.), at room temperature in MeCN (2 mL) for 10 h. All are isolated yields.

Scheme 2.104

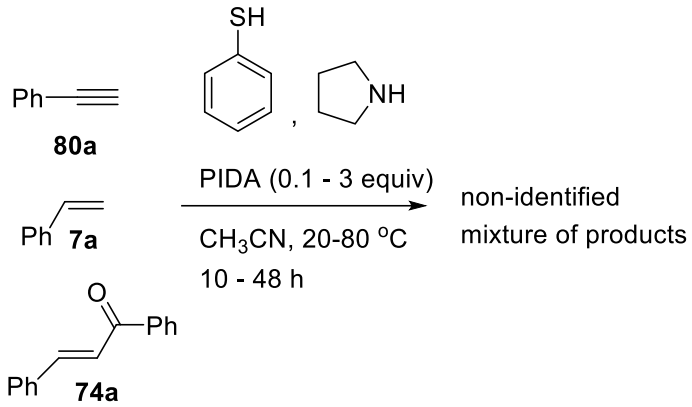
Based on the literature data [363, 365] and our observation in the absence of sulfonamide we propose the reaction pathway shown in Scheme 2.105. Reaction of alkyne (**80**) with $PhI(OAc)_2$ affordes the phenylalkynyl iodanyl acetate intermediate [**A**] which on Michael type addition of AcOH provides intermediate [**B**]. On removal of acetate the intermediate carbene [**C**] is formed which would then react with an acetoxy nucleophile or acidic acid leading to a diacetoxy alkene intermediate [**D**]. This one would then evolve to an α-acetoxy ketone (**82**) by reacting with the residual water, which could then lead to the α-sulfonylaminoketone (**81**) when sulphonamides are present. When α-acetoxy ketone (**82a**) was subjected to react with sulphonamide (**76a**), it afforded the desired product (**81a**) which supports our mechanistic path.



Scheme 2.105

Based on the successful experience of obtaining α-sulfonylaminoketones and in the development of further research, the possibility of using (diacetoxy)iodobenzene (PIDA) for activation during thioamidation reactions, *i.e.* simultaneous administration of a fragment of amines

and thiols by a multiple CC bond in alkenes/alkynes, was studied. For this purpose, the interaction of activated alkene, styrene (**7a**), chalcone (**74a**), and phenylacetylene (**80a**) with pyrrolidine and thiophenol was studied in the presence of (diacetoxy) iodobenzene (PIDA) under the above conditions (Schemes 2.102, 2.104). However, in control experiments, the interaction did not lead to the formation of the expected thioamination products, and in all cases an unidentified mixture of several products was fixed in the reaction mass (Scheme 2.106). This indicates the need for a more detailed study of these processes.



Scheme 2.106

2.26. SYNTHESIS OF SELENOESTERS FROM *α*-AMINO CARBONYL DERIVATIVES

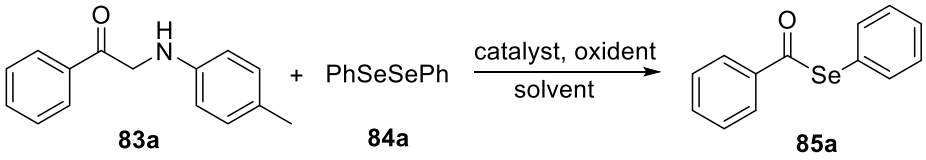
Further, we found that the obtained *α*-sulfonylaminoketones (**81**), as well as the *N*-acyl-*α*-aminoketones (**27**) described in Chapter 2.10, can be considered as convenient synthons for obtaining *N*-substituted *α*-aminoketones (**83)**. The latter were first used by us to obtain selenoesters (**85)** with yields up to 84% by reacting with diselenides in the presence of iron(III) chloride and benzoyl peroxide in dichloromethane at room temperature (Scheme 2.107) and that are inaccessible by other methods. As a result of the reaction, we have developed a convenient method for achieving selenoesters avoiding the conventional procedure which involves breaking of C-C bond of *α*-aminocarbonyl compounds which is quite interesting. We have observed that the reaction of *α*-aminocarbonyl compounds with diselenides affords selenoesters (benzoselenoate derivatives) in good yields in the presence of $FeCl_3$ as catalyst and benzoyl peroxide (BPO) as oxidant (Scheme 2.107).

Scheme 2.107

The study was initiated by investigating the reaction of 1-phenyl-2-(*p*-tolylamino)ethan-1-one (**83a**) (1 mmol) and diphenyl diselenide (**84a**) (0.5 mmol) employing 10 mol% of $FeCl_3$ and 1 equiv. of TBHP (*tert*-butyl hydroperoxide) as an oxidant in dichlomethane (DCM) at room temperature under ambient air (the reaction was monitored by checking TLC). Gratifyingly, the coupling product, Se-phenyl benzoselenoate (**85a**), was obtained in 40% yield after 3 h (Table 2.68, entry 1). Encouraged by this result, we carried out the reaction in different conditions to optimize the reaction, and the results are summarized in Table 2.68. First, we changed the oxidant by DTBP (di-*tert*-butyl peroxide) but no considerable increase of the yield (48%) has been observed (Table 1, entry 2). TBPB (*tert*-butyl peroxybenzoate) was also not an efficient oxidant for this conversion; where 35% yield was observed (Table 2.68, entry 3). To get a better result, we introduced another oxidant BPO (benzoyl peroxide) which gave 84% yield of the desired product (Table 2.68, entry 4). Other common oxidants like *m*-CPBA (*m*-chloroperoxybenzoic acid) and H_2O_2 were also introduced, but in both cases only trace amounts of yield were found (Table 2.68, entry 5 and 6). We also carried out the reaction under the O_2 atmosphere, but trace amount of yield was observed (Table 2.68, entry 7). But in the presence of both O_2 and BPO the yield decreased to 72% which proved that O_2 was not needed as co-oxidant with BPO to improve the yield (Table 2.68, entry 7c). Instead of peroxo compounds, per sulphate reagents such as $K_2S_2O_8$ and

$(NH_4)_2S_2O_8$ (Table 2.68, entry 8 and 9) were not suitable oxidants for this reaction and only 15% and a trace amount of products were formed respectively. So, to make a conclusion BPO was the suitable and best choice of oxidant to give the maximum amount of yield. Various iron salts such as $FeCl_2$, $FeBr_3$, $FeSO_4$ and $Fe(NO_2)_3$ were also investigated. These were found to be less effective for this transformation (Table 2.68, entries 10−13). Other metal salts like $CuCl_2$ and $Cu(OTf)_2$ have been tested as a catalyst but the reaction did not proceed at all (Table 2.68, entry 14 and 15). Similarly, $InCl_3$, $ZnCl_2$, and $AlCl_3$ were not found as a suitable catalyst for this reaction (Table 2.68, entry 16-18). Brønsted acid such as trifluoroacetic acid (TFA) was also examined but the reaction did not proceed (Table 2.68, entry 19). Hence, $FeCl_3$ was found to be the best catalyst to obtain the highest amount of yield. To interpret the solvent effects, the reaction was examined in various solvents (Table 2.68, entries 20-26). To our delight, the desired product was obtained in high yield (84%) in DCM. Other common solvents such as 1,2-DCE, acetonitrile, THF, 1,4-dioxane, ethanol, toluene, and DMSO were not so effective. A higher amount of catalyst loading (20 mol%) did not improve the yield further (Table 2.68, entry 27), but on decreasing the amount of catalyst (5 mol%), the yield was decreased significantly (Table 2.68, entry 28). When the reaction was performed under argon atmosphere the desired product was obtained in 62% yield (Table 2.68, entry 29). In the absence of any catalyst, the reaction did not occur (Table 2.68, entry 30). Thus, the optimized reaction condition was achieved using 1 mmol of α-aminocarbonyl compounds and 0.5 mmol of diselenides in presence of 10 mol% $FeCl_3$ and 1 equiv. of BPO with respect to α-aminocarbonyl compounds at room temperature in DCM (2 mL) for 3 h (Table 2.68, entry 4).

Table 2.68. Optimization of the reaction conditions.[a]



83a **84a** **85a**

Entry	Catalyst (10 mol%)	Oxidant (1 equiv)	Solvent (2 mL)	Yield[b] (%)
1	$FeCl_3$	TBHP	DCM	40
2	$FeCl_3$	DTBP	DCM	48
3	$FeCl_3$	TBPB	DCM	35
4	**$FeCl_3$**	**BPO**	**DCM**	**84**
5	$FeCl_3$	m-CPBA	DCM	trace
6	$FeCl_3$	H_2O_2	DCM	trace
7	$FeCl_3$	O_2	DCM	trace, 72[c]

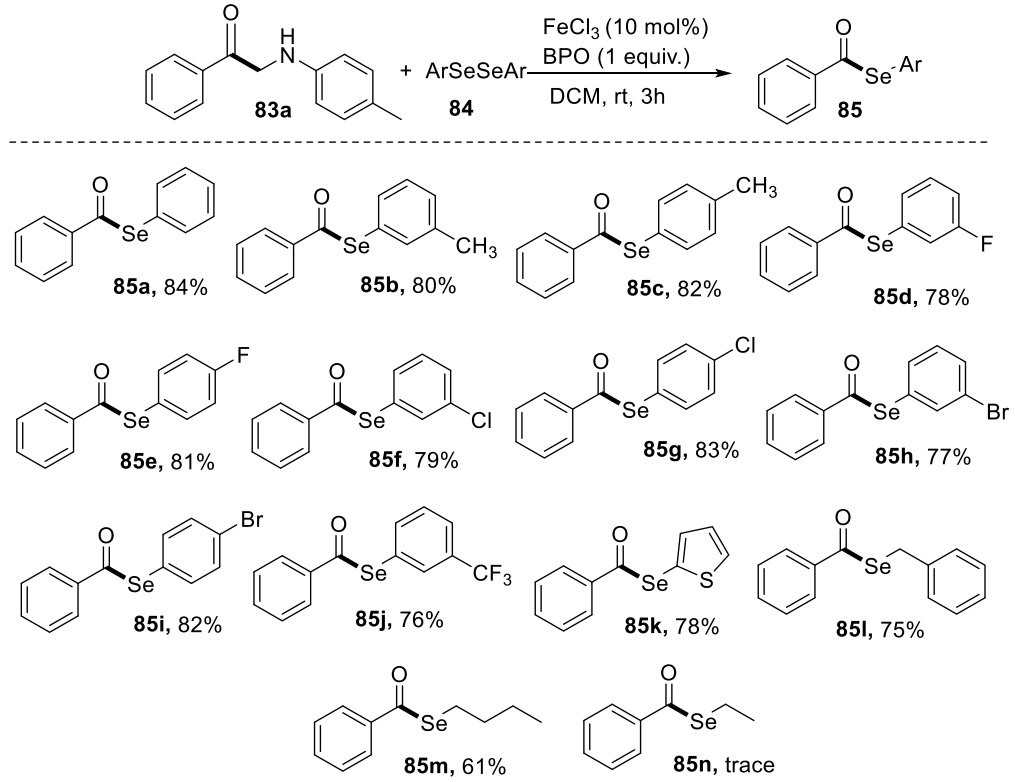
8	$FeCl_3$	$K_2S_2O_8$	DCM	15
9	$FeCl_3$	$(NH_4)_2S_2O_8$	DCM	trace
10	$FeCl_2$	BPO	DCM	44
11	$FeBr_3$	BPO	DCM	59
12	$FeSO_4$	BPO	DCM	33
13	$Fe(NO_2)_3$	BPO	DCM	26
14	$CuCl_2$	BPO	DCM	NR
15	$Cu(OTf)_2$	BPO	DCM	NR
16	$InCl_3$	BPO	DCM	NR
17	$ZnCl_2$	BPO	DCM	NR
18	$AlCl_3$	BPO	DCM	NR
19	TFA	BPO	DCM	NR
20	$FeCl_3$	BPO	1,2-DCE	54
21	$FeCl_3$	BPO	MeCN	22
22	$FeCl_3$	BPO	THF	15
23	$FeCl_3$	BPO	1,4-dioxane	NR
24	$FeCl_3$	BPO	EtOH	trace
25	$FeCl_3$	BPO	Toluene	30
26	$FeCl_3$	BPO	DMSO	NR
27	$FeCl_3$	BPO	DCM	84[d]
28	$FeCl_3$	BPO	DCM	45[e]
29	$FeCl_3$	BPO	DCM	62[f]
30	-	BPO	DCM	NR

[a]***Reaction conditions:*** **83a** (1.0 mmol), **84a** (0.5 mmol), oxidant (1 equiv.), catalyst (10 mol%), solvent (2 mL), at room temperature. [b] Isolated yields. [c]O_2 and BPO both were used as the oxidant. [d]$FeCl_3$ (20 mol%) was used. [e]5 mol% $FeCl_3$ was used. [f] The reaction was carried out under argon atmosphere.

After optimizing the reaction conditions, we explored the substrate scope employing different diaryl and dialkyl diselenides to react with α-aminocarbonyl (**83a**), and the results are summarized in Table 2.69. 3-Methyl substituted diphenyl diselenide (**84b**) and 4-methyl substituted diphenyl diselenide (**84c**) reacted smoothly to afford the desired products (**85b**) and (**85c**) in excellent yields (80% and 82% respectively). Next, some halogen-substituted diphenyl diselenide compounds were used and it was observed that both 3- and 4-fluoro substituted diphenyl diselenide (**84d**, **84e**) underwent the reaction to give the products (**85d)** and (**85e)** in 78% and 81% yields respectively. The reactions are equally effective for 3- and 4-chloro diphenyl diselenide

(**85f**, **85g**). 3-Bromo and 4-bromo containing diphenyl diselenides were also able to react with compound (**83a**) to provide the seleno ester products (**85h**) and (**85i**) in good yields (77% and 82%). Trifluoromethyl substituted diaryl diselenides were also examined and it smoothly reacted to give the product (**85j)** in 76% yield. Hence, it is notable that diaryl diselenides containing both electron-donating and electron-withdrawing groups successfully reacted with compound (**83a**). The heterocyclic moiety, thiophene-substituted diselenide (**84k**) afforded the corresponding product with good yield (**85k**). It is worthy to mention that the aliphatic diselenide also gave the desired products (**85l, 85m**) in moderate to good yield. While 1,2-diethyldiselane did not respond very well and produced a trace amount of product (**85n**).

Table 2.69. Substrate scopes for the present method using different diselenides.

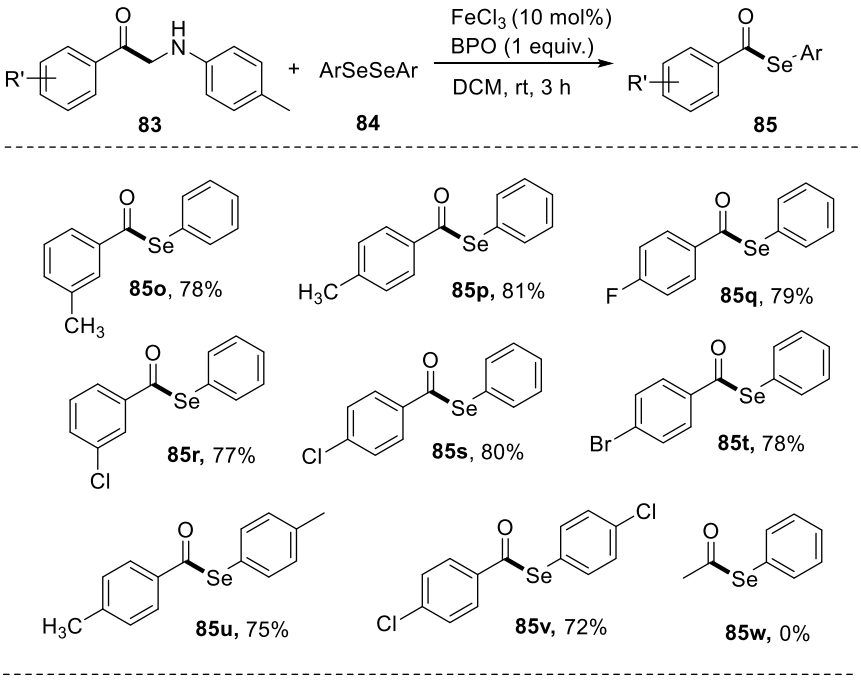


Reaction conditions: α-aminocarbonyl compounds (**83a**, 1.0 mmol), diaryl diselenides (**84**, 0.5 mmol), benzoyl peroxide (1 equiv), $FeCl_3$ (10 mol %), DCM (2 mL) at room temperature for 3 h.

Then our attention was turned to the use of substituted α-aminocarbonyl derivatives to prove the general applicability of the reaction conditions as summarized in Table 2.70. Under the same reaction conditions, we have synthesized the selenolesters from various α-aminocarbonyl derivatives. Gratifyingly, substrates with electron-donating groups at 3- and 4- position easily underwent the reaction to afford the desired products (**85o**) and (**85p**) in 78% and 81% yields. Similarly, the desired products were also obtained when halo substituents (F, Cl, or Br) were introduced in starting compounds. For example, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4 containing α-aminocarbonyl derivatives smoothly underwent the reaction with $(PhSe)_2$ to give the

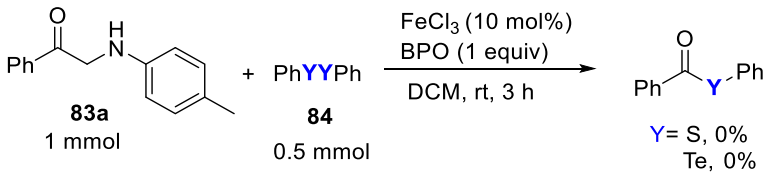
corresponding products (**85q**, **85r**, **85s, 85t**) with very good yields. 4-Methyl and 4-chloro substituted phenyl compounds reacted smoothly with 1,2-bis(4-chlorophenyl)diselane to give the desired products (**85u**) and (**85v**) respectively with good yields. Whereas, an aliphatic α-aminocarbonyl compound was not able to afford the desired product (**85w**).

Table 2.70. Synthesis of phenyl selenoesters from different α-aminocarbonyl derivatives.



Reaction conditions: α-aminocarbonyl compounds (**83**, 1.0 mmol), diaryl diselenides (**84**, 0.5 mmol), benzoyl peroxide (1 equiv), $FeCl_3$ (10 mol%), DCM (2 mL) at room temperature for 3 h.

To explore a reaction scope other organochalcogenides such as disulfides and ditellurides were introduced, but no desired products were obtained under the present reaction conditions (Scheme 2.108).



Scheme 2.108

It is worthy to mention that all these reactions were performed under ambient temperature and are not sensitive to air and moisture. All the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. The reaction conditions were mild enough and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all the reaction combinations giving rise to high yields of desired products. X-ray crystallographic analysis of Se-(3-bromophenyl)

benzoselenoate (**85h**, CCDC 1913495) was performed to confirm the structure of the product as shown in Figure 2.14.

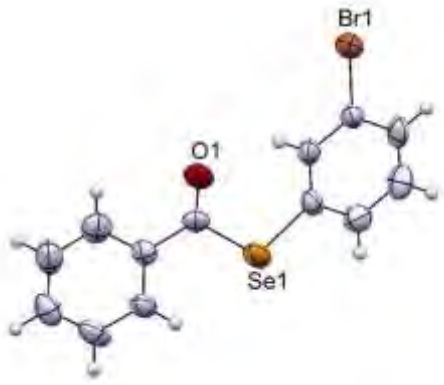
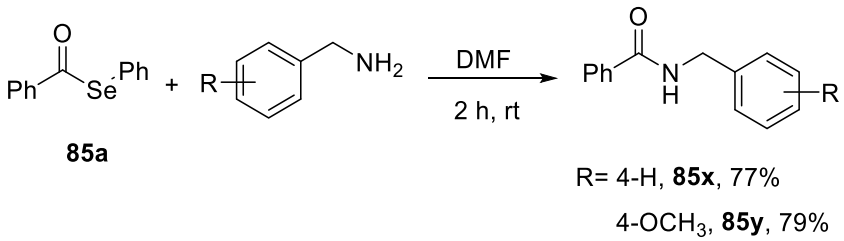


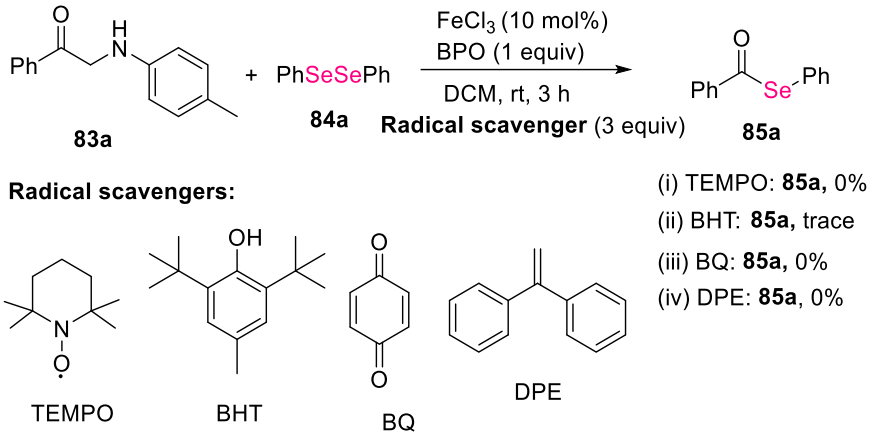
Figure 2.14. X-Ray crystallographic data for the structure of compound (**85h**)

Amide bond formation is one of the most important strategies in synthetic transformations. In biological sciences, peptide ligation methodologies have altered the path by which large polypeptides and proteins are produced by various chemical synthesis. A native peptide bond generation is very much acceptable by years. However, with several numbers of reported methods of forming a peptide bond, selenoesters were also found to be useful reactants for amide bond formation. With the help of our method of synthesizing selenoesters, we were also able to produce amide bonds. Following the previous method [366] we carried out the reaction of synthesized selenoester (**85a**) with benzylamine and 4-methoxybenzylamine led the formation of amide products (**85x**) and (**85y)** respectively (Scheme 2.109). The reactions were carried out under room temperature in DMF solution.



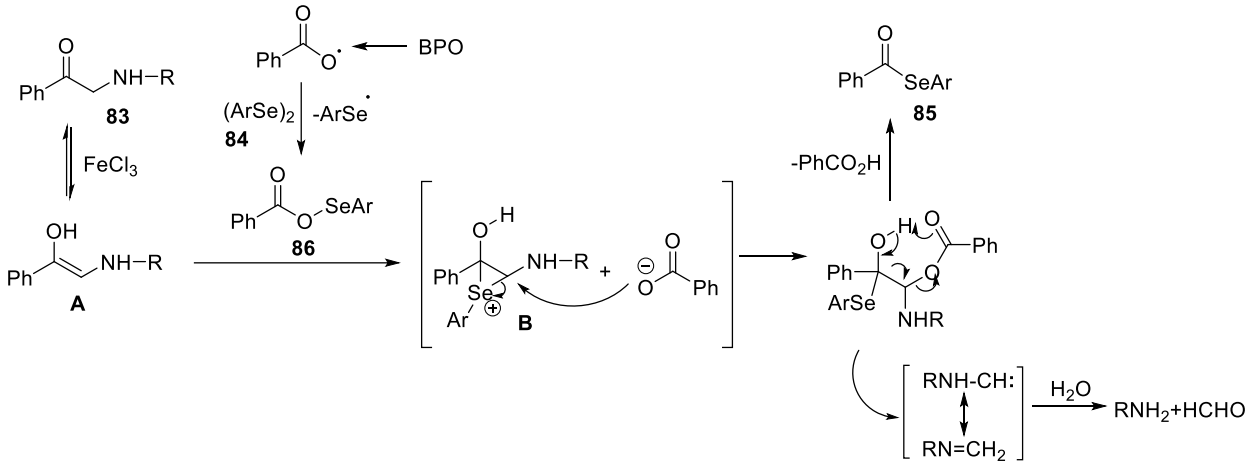
Scheme 2.109

A few control experiments were carried out taking the model substrates to get a better understanding of the mechanistic pathway of the reaction (Scheme 2.110). No product was obtained in the presence of radical scavengers like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), benzoquinone (BQ) and 1,1-diphenylethylene (DPE) whereas only a trace amount of product was obtained in the presence of butylated hydroxytoluene (BHT). These results suggest that the reaction probably proceeds through a radical pathway.



Scheme 2.110

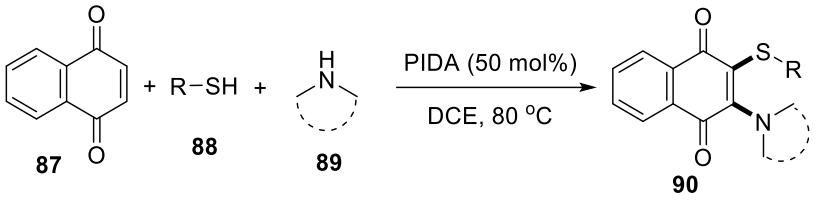
Based on our above observations and on the basis of the previous literature report [367] a plausible mechanism is proposed in Scheme 2.111. Initially, the decomposition of BPO produces benzoyloxy radical, which reacts with $(ArSe)_2$ to form benzoyloxyselenide (**83**). Then the reaction of benzoylxyselenide with the *α*-aminocarbonyl compound may proceed *via* an ionic mechanism where the phenylselenenyl ion ($PhSe^+$) adds to the enolate form [**A**] of *α*-aminocarbonyl**,** generating the seleniranium ion intermediate [**B**]**.** Elimination of benzoic acid and the carbene (final products as aniline and formaldehyde) from this intermediate [**B**] produces the desired product (**85**).



Scheme 2.111

2.27. SYNTHESIS OF THIOAMINATED NAPHTHOQUINONES

We have mentioned above our unsucsessful attempts to carry out tioamidation reactions along C=C bond in styrenes under oxidative conditions (in the presence of PIDA) (Sceme 2.106). On the other hand, *para*-quinones can be considered formally as *α,β*-unsaturated carbonyl compounds. Therefor, in a farme of our work we have stude the reactivity on 1,4-naphthoquinone (**87**), as representative of *para*-quinones in thioamination reaction. As a result of a three-component one-pot reaction between 1,4-naphthoquinone (**87**), cycloalkylamines and thiophenols in dichloroethane in the presence of PIDA affored the desired thioamonation products (**90)** in up to 88% yields (Scheme 2.112).



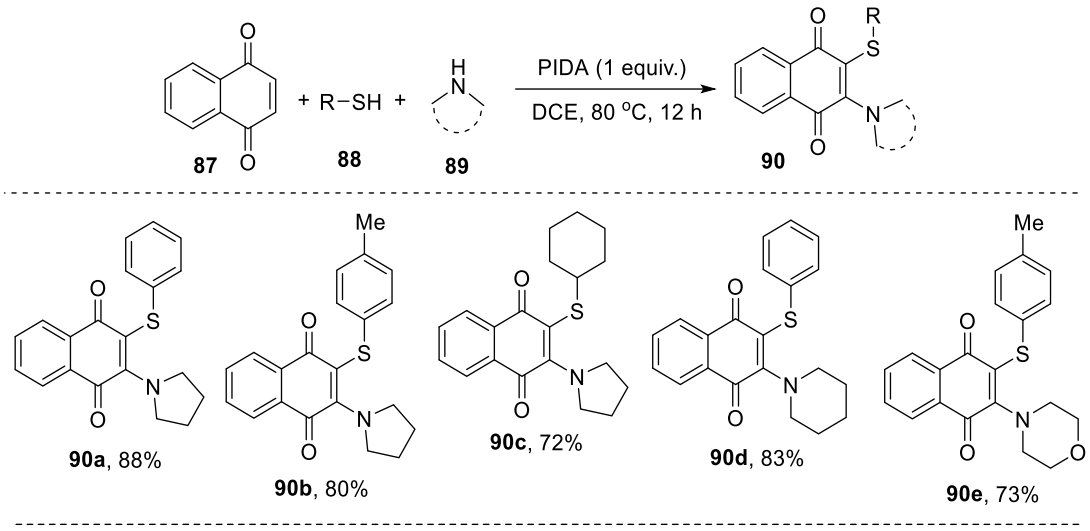
Scheme 2.112

We have explored the generality and efficiency of the present protocol taking 1,4-naphthoquinone reacting with various aliphatic and aromatic thiol and amine compounds (Table 2.71). Thus, the treatment of 1,4-naphthoquinone (**87**) with benzenethiol and pyrrolidine successfully led to the desired thioaminated product (**90a)** in 88% yield *via* simultaneous C-N and C-S bond formation. The reaction was carried out with *para*-substituted (-Me) aromatic thiols and the corresponding product resulted in good yield (80%). Moreover, aliphatic thiol such as cyclohexanethiol also effectively underwent the reaction to provide the thioaminated product. Delightfully, we examined the reaction taking another cyclic secondary amine, piperidine which smoothly reacted with thiophenol to afford the corresponding product in good yield. In addition, morpholine was found to be equally productive for this oxidative coupling reaction and provided the corresponding compound reacting with substituted thiophenol.

To understand the mechanistic pathway, we have carried out few control experiments (Scheme 2.113). We directed individual reaction of 1,4-naphthoquinone (**87**) initially with benzenethiol (**88a**) (Scheme 2.113a) and in another experiment (Scheme 2.113b) a secondary amine *i.e.* pyrrolidine (**89a**) under the same optimized condition. We observed that the reaction with benzenethiol (**88a**) did not produce the targeted product (**90f**), while upon reacting with pyrrolidine 1,4-naphthoquinone (**87**) afforded the aminated product (**90g**) in 90% yield. With these convincing results, we were interested to perform another reaction by taking the aminated product (**90g**) reacting with benzenethiol (**88a**) under the standard condition and interestingly, the desired

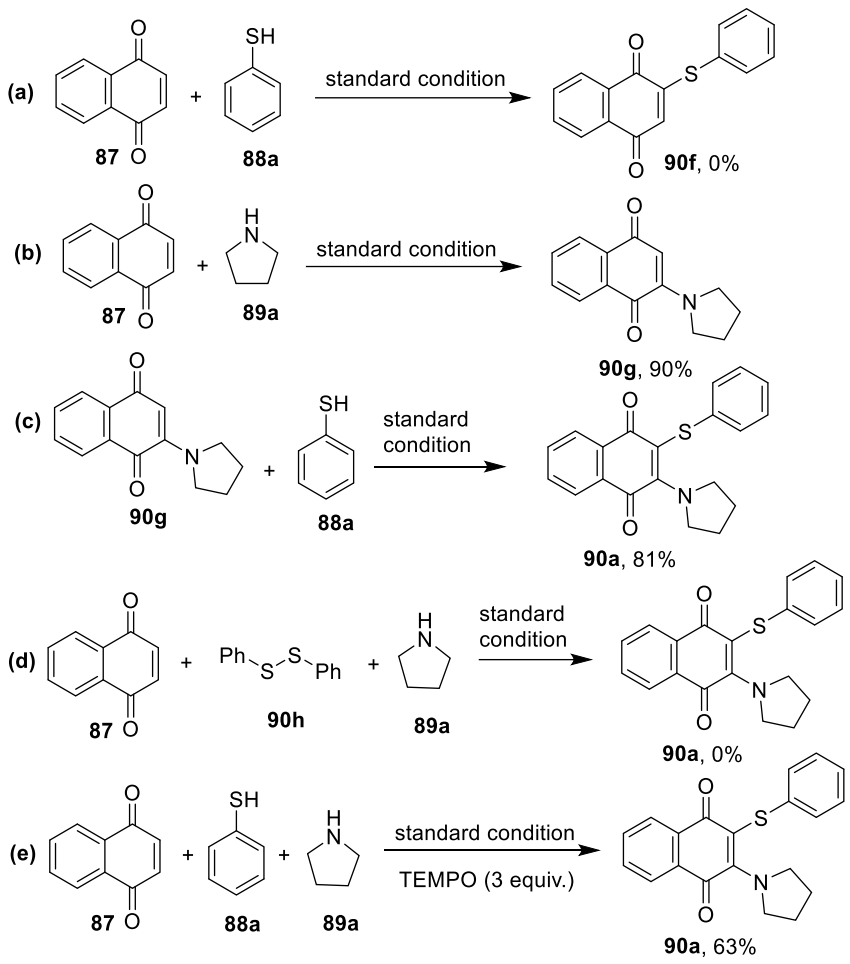
thioaminated product (**90a**) was obtained in 81% yield (Scheme 2.113c). However, the reaction with diphenyl disulfide (**90h**) under the same reaction condition produced no desired product (**90a**) (Scheme 2.113d). Moreover, a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was also introduced for this reaction to check the possibility of being a radical pathway and the expected product (**90a**) was generated with promising quantity (Scheme 2.113e). Considering these results, the possibility of a radical pathway has been ruled out for the reaction.

Table 2.71. Scope of thioamination of 1,4-naphthoquinone.

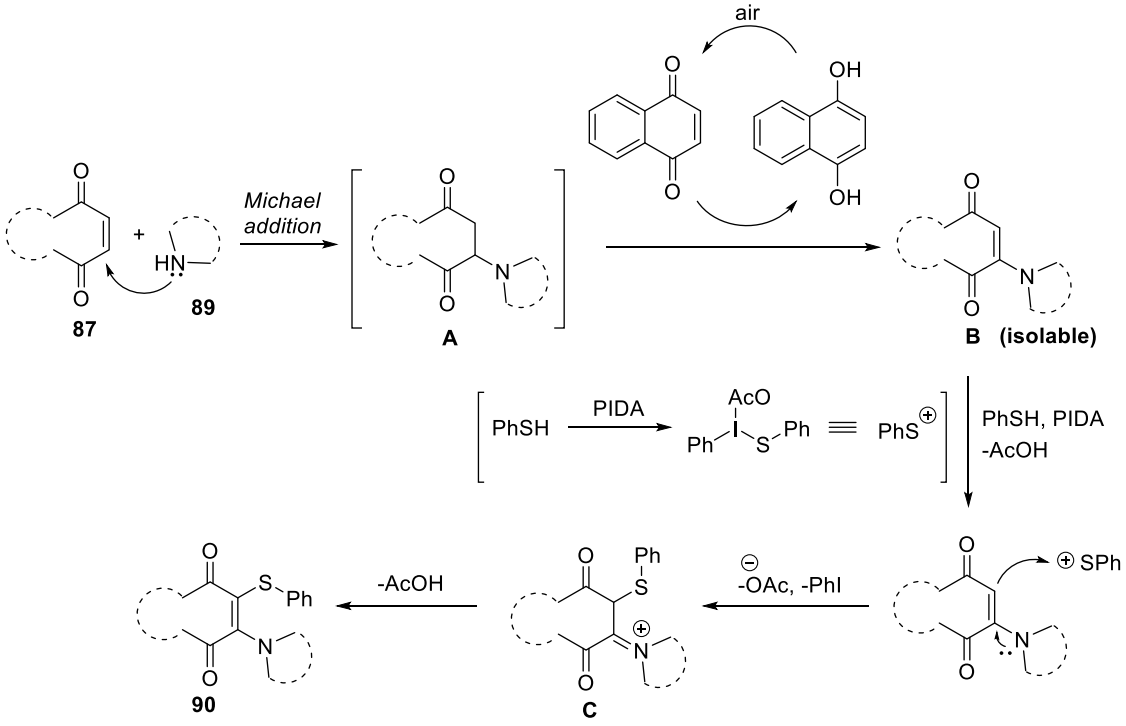


Reaction conditions: **87** (1 mmol), **88** (1 mmol), **89** (3 mmol), PIDA (1 equiv.), 1,2-DCE (2 mL), 80 °C, 12 h.

Based on the above result a probable mechanism has been described in Scheme 2.114. Initially, amine (**89**) is attached directly to 1,4-naphthoquinone (**87**) through Michael addition and an intermediate [**A**] is formed which is readily oxidized by 1,4-napthoquinone to give [**B**] along with the formation of hydroquinone. After that 1,4-naphthoquinone regenerates by the aerobic oxidation of hydroquinone [368, 369]. In this context, we were able to separate an intermediate [**90g**] which was mentioned in the control experiment section. On the other hand, recently it has been shown that in the presence of hypervalent iodine(III) PIDA, thiophenol can generate sulfenium ion [370]. Meanwhile, after *in situ* generations of this sulfenium ion, the nucleophilic attack of [**B**] may occur to form another intermediate [**C**]. Subsequently, this intermediate was encouraged for an oxidative elimination to afford the desired thioaminated product (**90**).



Scheme 2.113



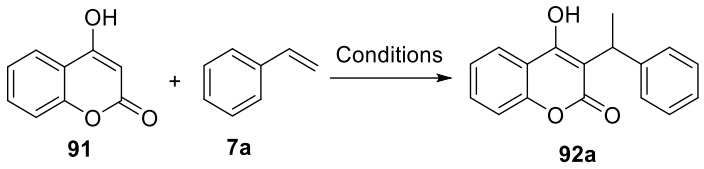
Scheme 2.114

2.28. C3-ALKYLATION OF 4-HYDROXYCOUMARIN

As part of the development of the topic, we investigated the interaction of the above-described compounds with a multiple bond with such a typical *C*-nucleophile as 4-hydroxycoumarin (**91a**) (based on the fact that coumarins are potential pharmacophores and fluorophores). Thus, the interaction of styrene (**7**) with 4-hydroxycoumarin (**91a**) led to the formation of *C*-benzylation products at the C3 position of the coumarin backbone, namely (**92**). So, herein, we have described TsOH (*p*-toluenesulfonic acid)-catalyzed mild and efficient methodology for C3-alkylation of 4-hydroxycoumarin by the reaction with styrenes under neat conditions (Scheme 2.115).

We have initiated the investigation for the C3-alkylation of 4-hydroxycoumarin taking 4-hydroxycoumarin (**91**) (1 mmol) and styrene (**7a**) (1.5 mmol) in presence of 20 mol% of TsOH and the reaction mixture was stirred under aqueous medium at 80 ºC temperature for 4 h (Table 2.72, entry 1). After getting 61% of moderate yield, we further performed the reaction under ethanolic medium and lower yield was found (Table 2.72, entry 2). After that, some other organic solvents like 1,2-dichloroethane, 1,4-dioxane, toluene and acetonitrile were introduced to check the activity of the reaction but those resulted in poor product formation (Table 2.72, entries 3-6). At that point, we were interested to perform the reaction under neat condition, which produced a satisfactory yield (78%) of the desired product (Table 2.72, entry 7). Then, we investigated the reaction by applying other available Brønsted acids such as trifluoroacetic acid (TFA), HCl, formic acid, acetic acid and benzoic acid but those catalysts were unable to proceed the reaction (Table 2.72, entry 8-12). Heating plays an important role in this reaction. The yield was not enhanced noticeably by increasing the temperature while a lower yield was obtained after decreasing the temperature (Table 2.72, entry 13-14). By increasing or decreasing the reaction time the yield was not improved (Table 2.72, 15-16). We have observed that 20 mol% of TsOH as the catalyst afforded better yield (78%) compared to that of 10 mol% where only 45% yield was obtained (Table 2.72, entry 17). Even by increasing the catalyst loading the yield did not increase (Table 2.72, entry 18). After considering above all experiments, the optimized reaction conditions were achieved by taking 4-hydroxycoumarin (**91**) (1 mmol) and styrene (**7a**) (1.5 mmol) in presence of 20 mol% of TsOH at 80 ºC for 4 h under neat conditions.

Table 2.72. Optimization of the reaction conditions on model reaction between 4-hydroxycoumarin (**91**) and styrene (**7a**) in presence of different catalysts.[a]

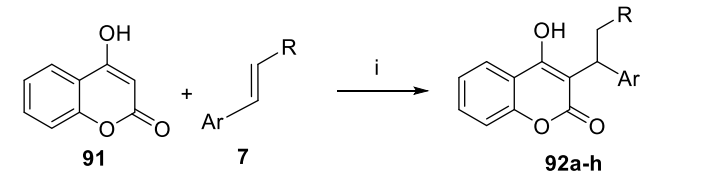


Entry	Catalysts (mol%)	Solvent (2 mL)	Temp. (ºC)	Time (h)	Yields (%)[b]
1	TsOH (20)	H_2O	80 ºC	4	61
2	TsOH (20)	EtOH	80 ºC	4	49
3	TsOH (20)	DCE	80 ºC	4	28
4	TsOH (20)	1,4-dioxane	80 ºC	4	33
5	TsOH (20)	Toluene	80 ºC	4	16
6	TsOH (20)	MeCN	80 ºC	4	21
7	TsOH (20)	neat	80 ºC	4	78
8	TFA (20)	neat	80 ºC	4	trace
9	HCl (20)	neat	80 ºC	4	nr
10	HCO_2H (20)	neat	80 ºC	4	trace
11	AcOH (20)	neat	80 ºC	4	trace
12	$PhCO_2H$ (20)	neat	80 ºC	4	trace
13	TsOH (20)	neat	120 ºC	4	79
14	TsOH (20)	neat	50 ºC	4	37
15	TsOH (20)	neat	80 ºC	5	76
16	TsOH (20)	neat	80 ºC	3	68
17	TsOH (10)	neat	80 ºC	4	45
18	TsOH (30)	neat	80 ºC	4	78

[a]***Reaction conditions:*** **91** (1 mmol), **7a** (1.5 mmol), catalysts (20 mol%), heating. [b]Isolated yield.

Based on the optimized reaction condition, we checked the scope and limitations of our reaction protocol. For this purpose, we have introduced some substituted styrenes reacting with 4-hydroxycoumarin under the similar conditions as summarized in Scheme 2.115. As we observed that simple styrene smoothly reacted with 4-hydroxycoumarin and produced 78% of desired product (**92a**). Then, 2-methylstyrene was introduced for the reaction which afforded the compound (**92b**) with in 70% yield. After getting this result, the reaction was carried out using 4-methylstyrene and we obtained the desired product (**92c**) in 75% yield. We had a choice to check

the activity of 4-methoxystyrene which gave corresponding product (**92d**) smoothly (77% yield). Therefore, it was notable that the styrene bearing electron-donating group easily underwent the reaction without any obstacles. After getting these satisfying results, we investigated the effect of other substituted styrenes. Performing the reaction with 4-chlorostyrene the desired product (**92e**) was obtained in a good yield (74%). Next, 3-bromostyrene was tested and 72% yield was formed as a desired product (**92f**). In addition, another electron-withdrawing styrene derivative like 4-flourostyrene also gave the desired product (**92g**) in 73% yield by the reaction with 4-hydroxycoumarin. With our delight, we have successfully synthesized phenprocoumon (**92h**) in 68% yield by treating *β*-methylstyrene with 4-hydroxycoumarin. Although, 1-nitro-3-vinylbenzene and methyl 4-vinylbenzoate did not afford the desired products (**92i**, **92j**) under the optimaized reaction conditions.



91 **7** **92a-h**

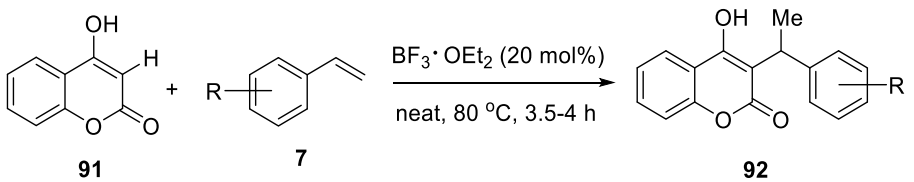
92a Ar = Ph, R= H, 78%
92b Ar = 2-MeC_6H_4, R= H, 70%
92c Ar = 4-MeC_6H_4, R= H, 75%
92d Ar = 4-$MeOC_6H_4$, R= H, 77%
92e Ar = 4-ClC_6H_4, R= H, 74%
92f Ar = 3-BrC_6H_4, R= H, 72%
92g Ar = 4-FC_6H_4, R= H, 73%
92h Ar = C_6H_5, R= Me, 68%
92i Ar = 3-$NO_2C_6H_4$, R= H, 0%
92j Ar = 4-$CO_2EtC_6H_4$, R= H, 0%

Reagents and optimal conditions: i, **91**/**7** = 1:1.5 (mol/mol), TsOH (20 mol%), neat, 80 °C, 4 h (6 h for **92f**).

Scheme 2.115

Next, we were interested to produce anticoagulant drug phenprocoumon (**92h**) in gram scale range and for that purpose, the reaction between 4-hydroxycoumarin (10 mmol) and *β*-methylstyrene (**91h**) (15 mmol) was performed in the presence of TsOH (20 mol%) under the optimized reaction conditions. As a result, 1.7 g (61%) of the desired product (**92h**) has been isolated successfully.

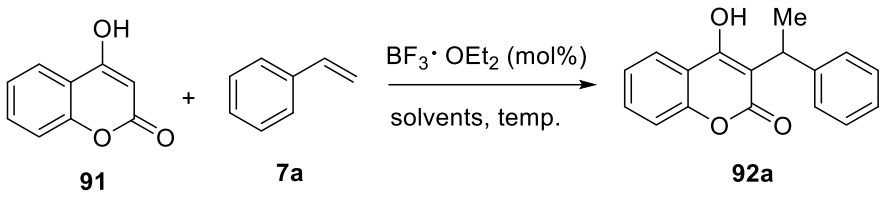
We have developed another similar catalytic method for direct C3-alkylation of 4-hydroxycoumarins using styrene the presence of $BF_3{\cdot}Et_2O$ without any solvent and under 80 °C temperature (Scheme 2.116).



91 **7** **92**

Scheme 2.116

Table 2.73. Optimization of the reaction conditions.[a]



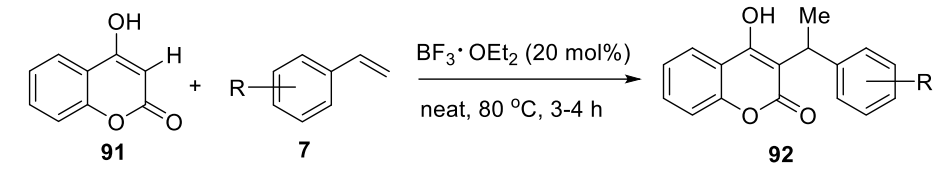
91 **7a** **92a**

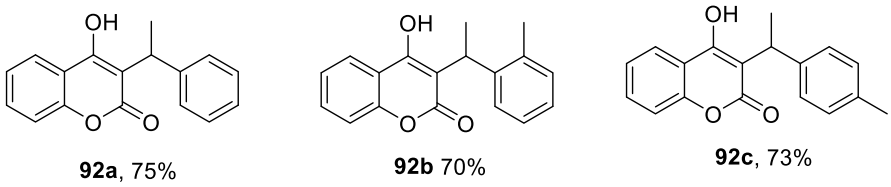
Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Yield (%)[b]
1	BF_3 .OEt_2 (20)	1,2-DCE	80 °C	54
2	BF_3 .OEt_2 (20)	MeCN	80 °C	30
3	BF_3 .OEt_2 (20)	toluene	80 °C	22
4	BF_3 .OEt_2 (20)	THF	80 °C	15
5	BF_3 .OEt_2 (20)	H_2O	80 °C	traces
6	BF_3 .OEt_2 (20)	neat	80 °C	75
7	BF_3 .OEt_2 (20)	neat	100 °C	75
8	BF_3 .OEt_2 (10)	neat	80 °C	41
9	BF_3 .OEt_2 (40)	neat	80 °C	76

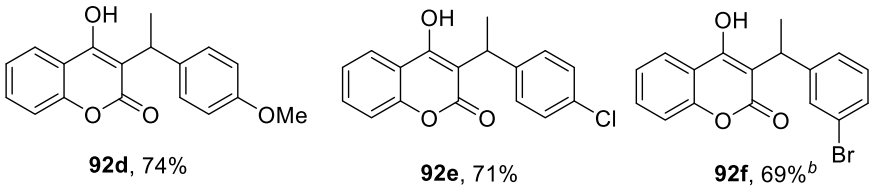
[a]***Reaction conditions:*** 4-hydroxycoumarin (**91**, 1 mmol) and styrene (**7a**, 1 mmol), BF_3.Et_2O (20 mol%), stirred for 4 h. [b]Isolated yields.

Under the optimized reaction condition, 4-hydroxycoumarin (**91)** reacted with styrene (**7a)** to give 4-hydroxy-3-(1-phenylethyl)-2*H*-chromen-2-one (**92a**) with 75% yield (Table 2.74). Coumarin (**91**) reacted well styrene containing either electron-donating or withdrawing groups. *Para*- and *ortho*-substituted vinylbenzenes (4-Me, 2-Me) gave the corresponding products (**92c**) and (**92b**) in 73% and 70% yields respectively. Upon reaction with 4-methoxysytrene 4-hydroxycoumarin was converted to the desired product (**92d**) in 74% yield. When 4-Cl and 3-Br substituted styrenes were subjected to react with coumatin (**91**) the target products (**92e)** and (**92f**) were obtained in 71% and 69% yield respectively.

Table 2.74. Synthesis of C3-alkylation derivatives of 4-hydroxycoumarins

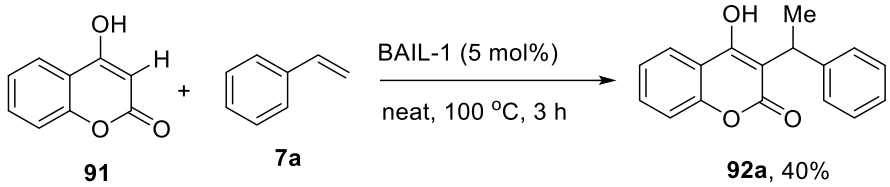






Reaction conditions: 4-hydroxycoumarin (**91**, 1 mmol) and styrenes (**7**, 1 mmol), $BF_3.Et_2O$ (20 mol%), [b]stirred for 4 h.

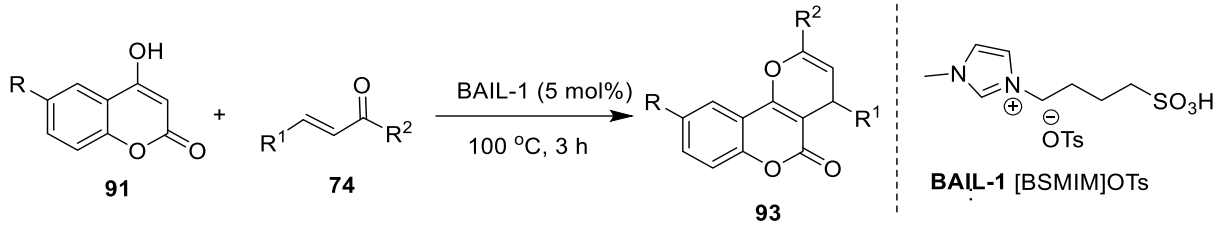
In addition, we have also carried the model reaction in presence of ionic liquid **BAIL-1** and 40% yield was obtained (Scheme 2.117).



Scheme 2.117

2.29. TANDEM REGIOSELECTIVE SYNTHESIS OF PYRANO[3,2-*c*]COUMARINS

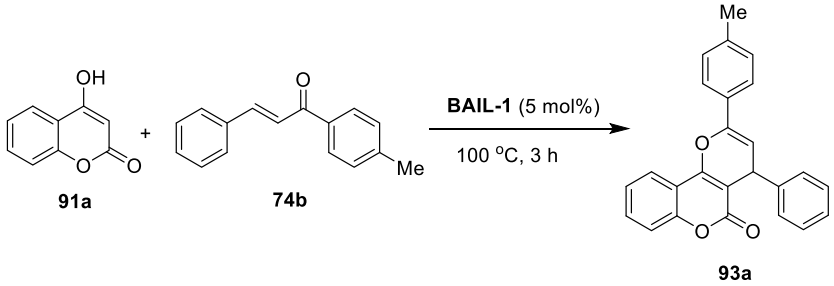
We fond further, that in the case of activated alkenes, chalcones (**74**), the interaction with 4-hydroxycoumarins (**91**) proceeded in a different way to afford pyrano[3,2-*c*]coumarins (**93**) as a results of tandem cyclization after the addition of chalcone (Scheme 2.118). The reactions proceeded in the presence of Brønsted acidic ionic liquid, 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs (**BAIL-1**) under neat conditions and no need to perform column chromatography for purification.



Scheme 2.118

For the initial study, 4-hydroxycoumarin (**91a**) and 3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (**74b**) was taken as the model substrates to optimize the reaction conditions employing 5 mol% 1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]OTs (**BAIL-1**) as the catalyst. Initially, the reaction was carried out in various organic solvents such as DMF, DMSO, methanol, ethanol, toluene, polyethylene glycol (PEG), 1,4-dioxane, DCE, etc. as well as in aqueous medium. The results are summarized in Table 2.75. Either no formation or trace amount of the desired product was observed in DMF, DMSO, water and DCE (Table 2.75, entries 1-3, 9). In the case of ethanol, methanol, toluene, PEG and dioxane the desired product was obtained in 18-44% yields (Table 2.75, entries 4-8). The targeted product was obtained with maximum yield (84%) under solvent-free conditions at 100 °C for 3 h (Table 2.75, entry 10). These results indicate the detrimental effect of the solvents for this transformation.

Table 2.75. Screening of the solvent effects.[a]



Entry	Solvents (2 mL)	Yields[b] (%)
1	DMF	<5
2	DMSO	<5

3[c]	Water	<5
4[c]	EtOH	18
5[c]	MeOH	23
6	Toluene	44
7	PEG	24
8[c]	Dioxane	30
9[c]	DCE	<5
10	**Neat**	**84**

[a]***Reaction conditions:*** A mixture of **91a** (1 mmol) and **74b** (1 mmol) was heated at 100 °C for 3 h, [b]Isolated yield. [c]Under reflux.

Table 2.76. Temperature effect on the tandem cyclization reaction.[a]

Entry	Temp. (°C)	Time (h)	Yields (%)[b]
1	RT	24	<10
2	60	3	48
3	80	3	67
4	**100**	**3**	**84**
5	100	6	84
6	120	3	81

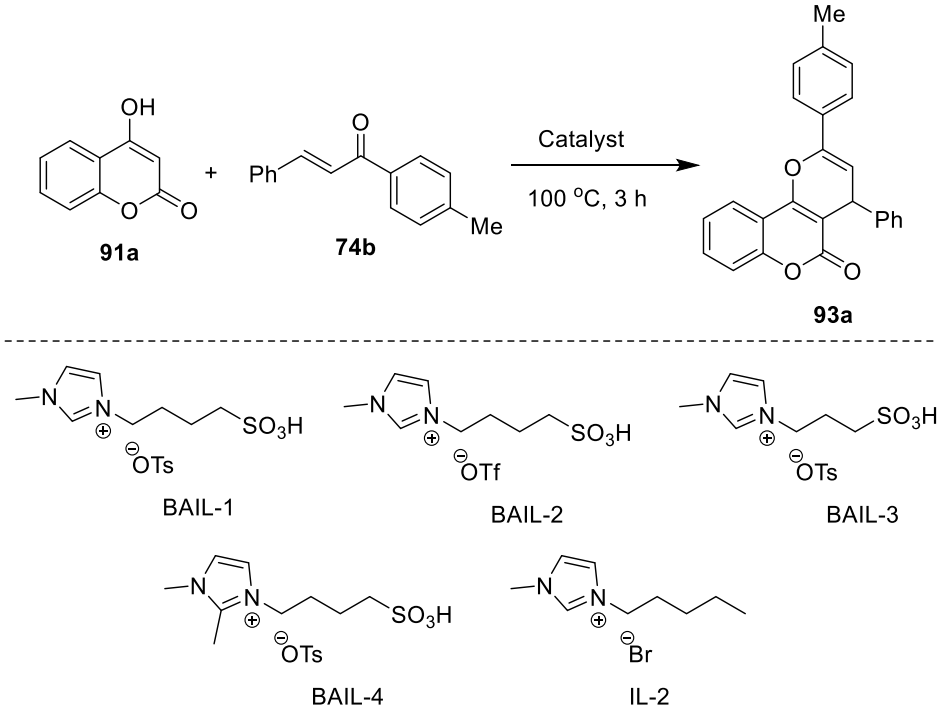
[a]***Reaction conditions:*** A mixture of **91a** (1 mmol), **74b** (1 mmol) and **BAIL-1** (5 mol%), [b]Isolated yields.

Next, the effects of reaction time and temperature on the reaction were also investigated. No significant amount of the desired product was formed when the reaction was carried out at room temperature (Table 2.76, entry 1). The best effective reaction temperature was found to be 100 °C (Table 2.76, entry 4) and the yield of the reaction did not improve by increasing the reaction time from 3 h to 6 h (Table 2.76, entry 5). Increasing the temperature was not beneficial (Table 2.76, entry 6) while decreasing the reaction temperature decreased the yield of the reaction (Table 2.76, entries 2 & 3).

We have examined a few other ionic liquids (ILs) synthesized in our laboratory as shown in Table 2.77. It has been observed that other ILs (**BAIL-2, BAIL-3, BAIL-4 and IL-2**) are not effective like **BAIL-1** for this tandem cyclization process. When 5 mol% of catalyst (**BAIL-2**) is used (Table 2.77, entry 2) the yield is considerably lower (72%) than **BAIL-1** (84%). Similarly, **BAIL-3** and **BAIL-4** were also less effective and afforded the desired product with 76% and 65% yields respectively (Table 2.77, entries 3 & 4). The yields of the reaction decreased when the chain length of the ionic liquid (**BAIL-3**) was reduced (Table 2.77, entry 3). No significant amount of product was obtained using IL-2 (Table 2.77, entry 5). Accordingly, we chose **BAIL-1** as a catalyst for this tandem cyclization. Finally, the catalyst loading was checked under these reaction conditions using **BAIL-1** as the catalyst for the same reaction. We have observed that 5 mol% of **BAIL-1** afforded better yield (84%) compared to that of 2 mol% (72% yield) (Table 2.77, entry

6). Similarly on using 10 mol% of the catalyst no improvement of the yield was observed (Table 2.77, entry 7). Other acid catalysts such as Brønsted once like PTSA and H_2SO_4 were not effective for this reaction and gave 52% and 43% yields respectively (Table 2.77, entries 8 & 9). In the absence of any catalyst no conversion has been detected (Table 2.77, entry 10). Thus the optimal yield (84%) was obtained when the reaction was carried out employing 5 mol% **BAIL-1** at 100 °C under solvent-free conditions for 3 h.

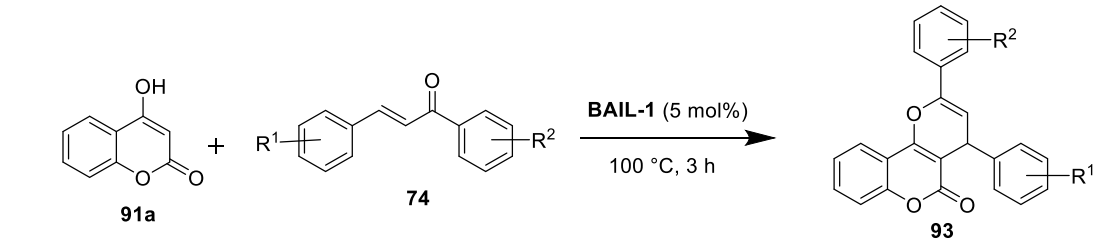
Table 2.77. Effect of various ionic liquids and catalyst loading.[a]

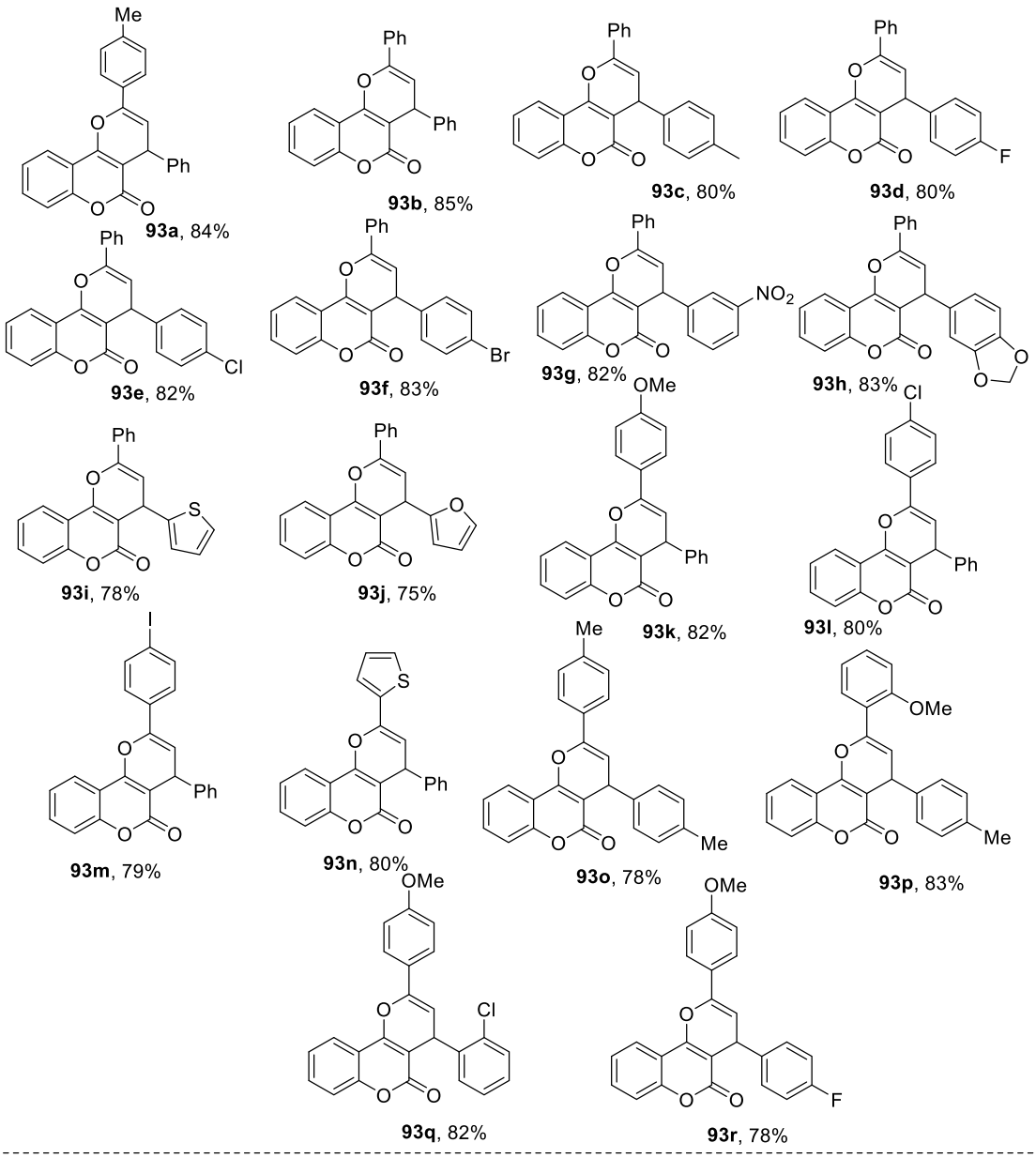


Entry	Catalyst	Catalyst loading(mol%)	Yields (%)[b]
1	**BAIL-1**	**5**	**84**
2	BAIL-2	5	72
3	BAIL-3	5	76
4	BAIL-4	5	65
5	IL-2	5	<10
6	BAIL-1	2	72
7	BAIL-1	10	84
8	PTSA[c]	10	52
9	H_2SO_4	10	43
10	No Catalyst	--	ND[d]

[a] *Reaction conditions:* Carried out with 0.5 mmol of **91a** and 0.5 mmol of **74b** in the presence of various catalysts under neat conditions, [b] Isolated yields, [c] PTSA = *p*-toluenesulfonic acid, [d]ND = not detected in TLC.

Table 2.78. Synthesis of various pyrano[3,2-*c*]coumarin derivatives.



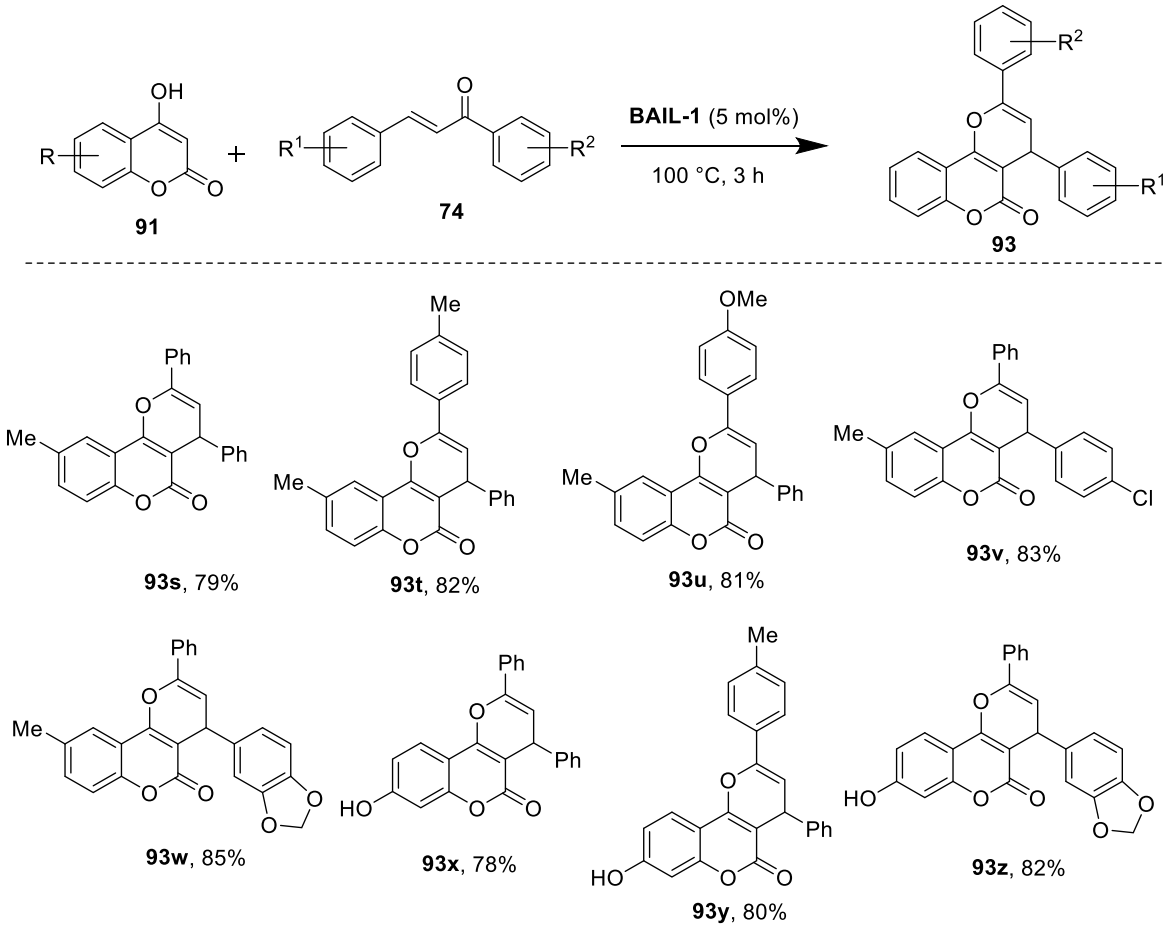


Reaction conditions: 1 mmol of **91a** and 1 mmol of **74** in presence of **BAIL-1** (5 mol%) at 100 °C for 3 h.

After getting the optimized reaction conditions in hand, various chalcones (**74**) were introduced to react with 4-hydroxycoumarin (**91a**) as well as substituted 4-hydroxycoumarin to prove the general applicability of this methodology. First, the effect of substituents on the both phenyl moieties of chalcone was tested. The results are summarized in Table 2.78. In the most cases, the desired products were obtained with good yields (**93a**-**93r**). The chalcones bearing electron donating substituents like -Me, -OMe afforded products (**93a**, **93c**, **93k**, **93o**, **93p**, **93q**,

93r), and chalcones bearing electron withdrawing substituents such as -I, -Cl, -F, -Br, -NO_2 reacted well to afford the corresponding pyrano[3,2-*c*]coumarin derivatives (**93d**, **93e**, **93f**, **93g**, **93l**, **93m**, **93q**, **93r**). The acid sensitive group containing chalcone was unaffected under the present reaction conditions which signify the mildness of the reaction conditions (**93h**). In addition, heteroaryl chalcones reacted well without accompanying self condensation or ring cleavage to afford products (**93i**, **93j**, **93n**). Then our attention was turned to the use of substituted 4-hydroxycoumarins to prove the general applicability of the reaction conditions as summarized in Table 2.79. 4-hydroxycoumarin bearing methyl and hydroxyl groups afforded the corresponding pyranocoumarins with high to excellent yields. Chalcones bearing functional groups like Me (for the products (**93t**, **93y**)), OMe (product (**93u**)) as well as acid sensitive functionalities were unaffected under the reaction conditions and the desired products were obtained in 79-85% yields.

Table 2.79. Substrate scopes of 4-hydroxycoumarins.



Reaction conditions: 1 mmol of **91** and 1 mmol of **74** in presence of **BAIL-1** (5 mol%) at 100 °C for 3 h.

All these reactions were carried out in an open atmosphere and are not sensitive to air and moisture. In addition, the reaction is highly regio selective. No other *regio*-isomer was isolated under the present reaction conditions. For purification no need to perform column

chromatography. After completion of the reaction, water was added to the reaction mixture and filtered it off. The pure product was obtained by recrystallizing the residue from hot ethanol. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any byproducts for all reaction combinations which are supported with high yields and regio selectivity of the protocol. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data and the X-ray crystallographic analysis of 4-phenyl-2-(thiophen-2-yl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (**93n**, CCDC 1539031) was performed to confirm the structure of the product as shown in Figure 2.15.

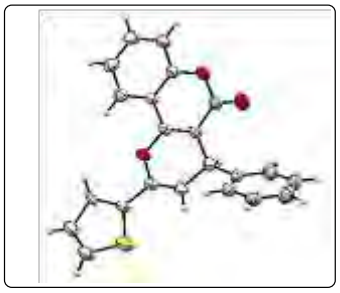
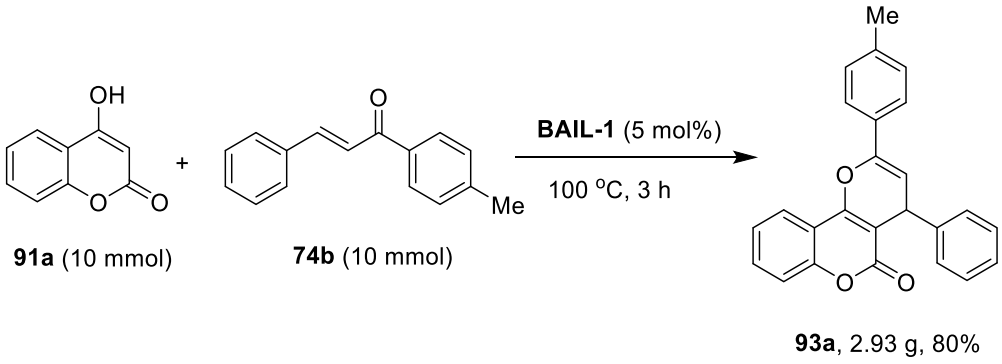


Figure 2.15. X-Ray crystallographic data for the structure of compound (**93n**).

Furthermore, the potential synthetic applicability of this method was investigated on a gram scale using the model reaction. As shown in Scheme 2.119, the reaction could afford 2.93 g of product (**93a**) in 80% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large scale synthesis of pyrano[3,2-*c*]coumarin derivatives.



Scheme 2.119

Next, we turn our attention towards the recovery and reusability of the catalyst. For this purpose, we have chosen the reaction of 4-hydroxycoumarin (**91a**) with 3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (**74b**) in presence of 5 mol% acidic ionic liquid (**BAIL-1**) at 100 °C as the model reaction. After completion of the reaction, water was added to the reaction mixture. The reaction mixture was then filtered off and the ionic liquid was recovered by evaporating the water. The pure

product was obtained by recrystallizing the residue from hot ethanol. The catalyst maintained its high level of activity even after being recycled five times for synthesizing of product (**93a**) as shown in Table 2.80.

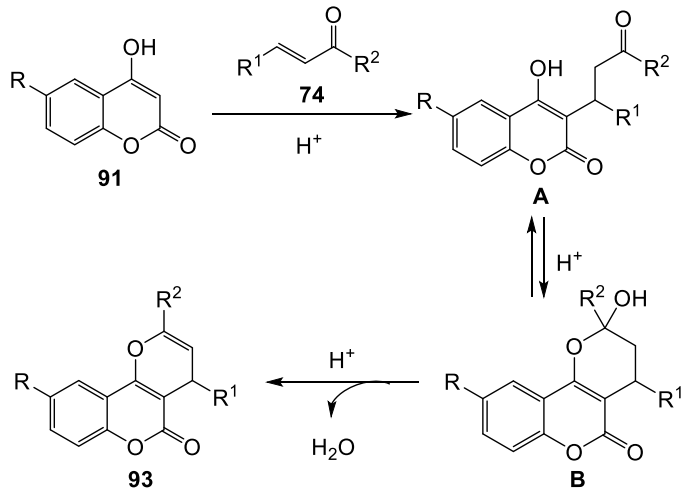
Table 2.80. Recycling of **BAIL-1** for synthesizing of product (**93a**).[a]

No. of cycle	Yields (%)	Catalyst recovery (%)
1	84	96
2	82	92
3	80	89
4	80	85
5	78	82

[a] Carried out with 1 mmol of **91a** and 1 mmol of **74a** in presence of **BAIL-1** at 100 °C for 3 h.

In addition, we have developed a greener reaction condition bearing lower *E*-factors [336] in cases of synthesizing the desired products (**93**) which is consistent with the principles of the atom economy.

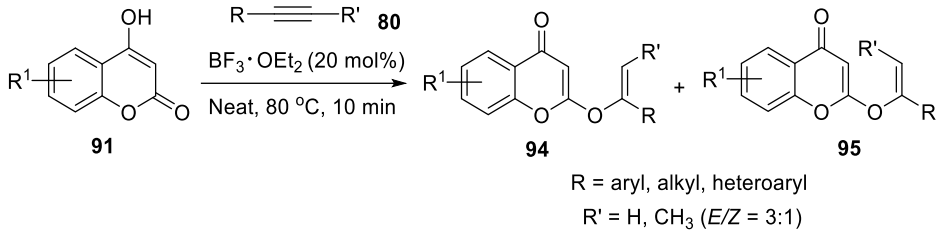
A plausible mechanistic pathway for this tandem reaction is outlined in Scheme 2.120. Probably the first step is the Michael addition of 4-hydroxycoumarin (**91**) to the *α,β*-unsaturated ketone (**74**) which gave the intermediate [**A**]. The intermediate [**A**] on intramolecular cyclization afforded the intermediate [**B**] which finally afforded the pyranocoumarin (**93**) on subsequent removal of water. The acidic ionic liquid activates the unsaturated ketone through protonation of the carbonyl group and increased the electrophilic character at the *β*-carbon which promote the Michael adduct formation. In addition, the acidic ionic liquid also helps to facilitate the intramolecular cyclization step by the protonation of the carbonyl group of intermediate [**A**].



Scheme 2.120

2.30. *O*-VINYLATION OF CARBONYL OXYGEN IN 4-HYDROXYCOUMARIN

Unlike chalcones and styrenes, acetylenes or alkynes reacted with 4-hydroxycoumarins (**91**) under the above-mentioned conditions to afford different products. Thus, we discovered a convenient and new observation towards *O*-vinylation of 4-hydroxycoumarin by the reaction with alkynes for the synthesis of 2-(vinyloxy)-4*H*-chromen-4-one derivatives (Scheme 2.121). To the best of our knowledge, this is the first report where the carbonyl oxygen of 4-hydroxycoumarin reacts with an electrophile to give an *O*-vinylated product.

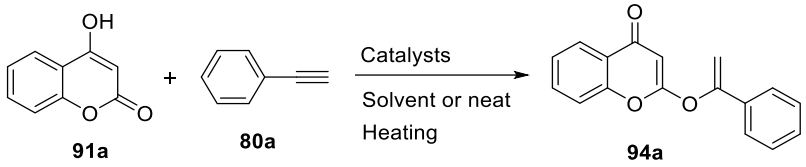


Scheme 2.121

The study was initiated by investigating the reaction of 4-hydroxycoumarin (**91a**) and phenylacetylene (**80a**) in the presence of different catalysts in different solvents. The reaction was carried out by employing 20 mol% of $BF_3.OEt_2$ in DCE at 80 °C under ambient air. Gratifyingly the product, 2-((1-phenylvinyl)oxy)-4*H*-chromen-4-one (**94a**) was obtained in moderate yield (56%) after a very short reaction time (10 min) (Table 2.81, entry 1). Encouraged by this result we carried out various reactions to optimize the reaction conditions and the results are summarized in Table 2.81. At first, the reaction was then carried out using some common solvents such as CH_3CN, toluene, DMSO, and DMF to make better product formation but yields get reduced to 34% for CH_3CN and 40% for toluene (Table 2.81, entries 2 & 3). The only trace amount of product was formed when DMSO and DMF were used (Table 2.81, entries 4 & 5). But surprisingly, the yield was increased to 86% in the absence of any solvent, under neat conditions (Table 2.81, entry 6). So it was finalized that the reaction could be done without a solvent. By increasing the reaction time the yield was not improved (82%). The reaction was further investigated using other Lewis acid catalysts under neat conditions. Copper-salts such as $CuBr_2$ and $Cu(OAc)_2$ are not efficient for this coupling reaction (Table 2.81, entries 8 & 9). The use of metal triflates such as $Cu(OTf)_2$, $In(OTf)_2$ and $Zn(OTf)_2$ could not enhance the product formation (Table 2.81, entries 10-12). $FeCl_3$ and $SnCl_4$ were not also so efficient to improve the yield of the reaction (Table 2.81, entries 13 & 14). The reaction did not proceed at all in presence of other Lewis acids such as $ZnCl_2$ and $AlCl_3$ (Table 2.81, entries 15 & 16). Two Brønsted acid catalysts such as TFA and PTSA were also introduced but no improvement of product yield was observed. The yields were found 42% and only 16% for TFA and PTSA respectively (Table 2.81, entries 17 & 18). Hence $BF_3.OEt_2$ (20

mol%) was considered as the best Lewis acid catalyst to obtain the maximum yield of the desired product. We also examined the reaction by increasing the amount of $BF_3.OEt_2$ from 20 mol% to 40 mol% but the yield was not enhanced and a lower yield was obtained when 10 mol % $BF_3.OEt_2$ was used (Table 2.81, entries 19 & 20). Finally, the optimized reaction condition was achieved using 20 mol % of $BF_3.OEt_2$ at 80 °C for 10 min under neat conditions (Table 2.81, entry 6) and under ambient air.

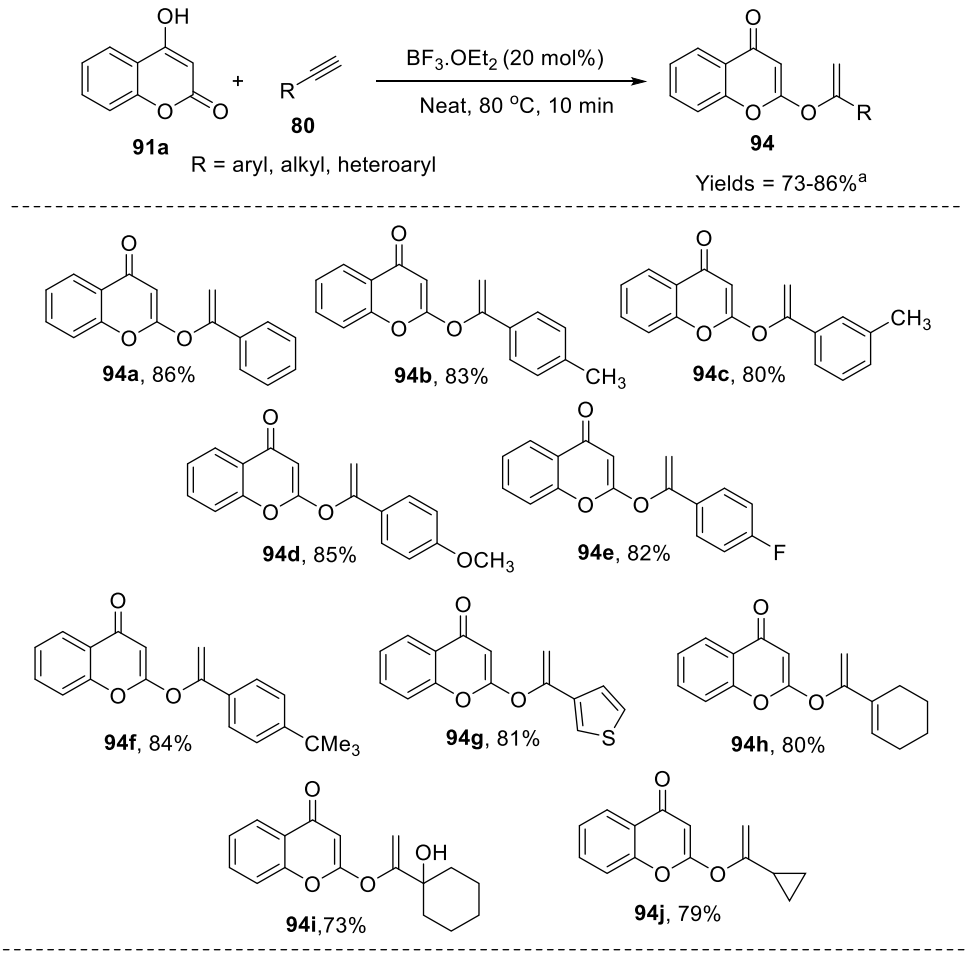
Table 2.81. Optimization of the reaction conditions for the synthesis of 2-(vinyloxy)-4*H*-chromen-4-ones.[a]



Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yields (%)
1	$BF_3{\cdot}OEt_2$ (20)	DCE	80	56
2	$BF_3{\cdot}OEt_2$ (20)	CH_3CN	80	34
3	$BF_3{\cdot}OEt_2$ (20)	Toluene	80	40
4	$BF_3{\cdot}OEt_2$ (20)	DMSO	80	trace
5	$BF_3{\cdot}OEt_2$ (20)	DMF	80	trace
6	$BF_3{\cdot}OEt_2$ (20)	neat	80	86, 82[b]
7	$BF_3{\cdot}OEt_2$ (20)	neat	60	67
8	$CuBr_2$ (10)	neat	80	NR
9	$Cu(OAc)_2$ (10)	neat	80	NR
10	$Cu(OTf)_2$ (10)	neat	80	13
11	$In(OTf)_2$ (10)	neat	80	30
12	$Zn(OTf)_2$ (10)	neat	80	trace
13	$FeCl_3$ (10)	neat	80	38
14	$SnCl_4$ (10)	neat	80	trace
15	$ZnCl_2$ (10)	neat	80	NR
16	$AlCl_3$ (10)	neat	80	NR
17	PTSA (10)	neat	80	42
18	TFA (10)	neat	80	16
19	$BF_3{\cdot}OEt_2$ (10)	neat	80	55
20	$BF_3{\cdot}OEt_2$ (40)	neat	80	86

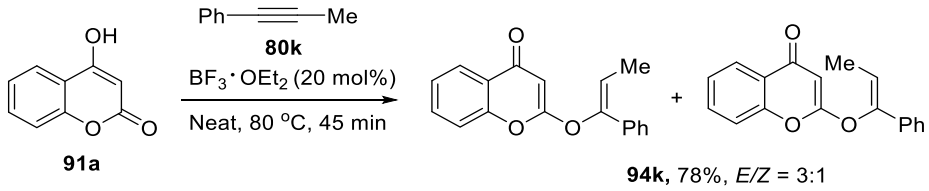
[a]***Reaction conditions:*** 1 mmol of **91a** and 1 mmol of **80a** were stirred for 10 min under heating in presence of different catalysts in different solvents or under neat conditions. [b]Reaction time 30 min.

Table 2.82. substrates scope of the reaction between 4-hydroxycoumarin and different alkynes.



Reaction conditions: 1 mmol of **91a** and 1 mmol of alkyne (**80**) were stirred for 10 min at 80 °C in presence of 20 mol% of BF_3·OEt_2 under neat conditions.

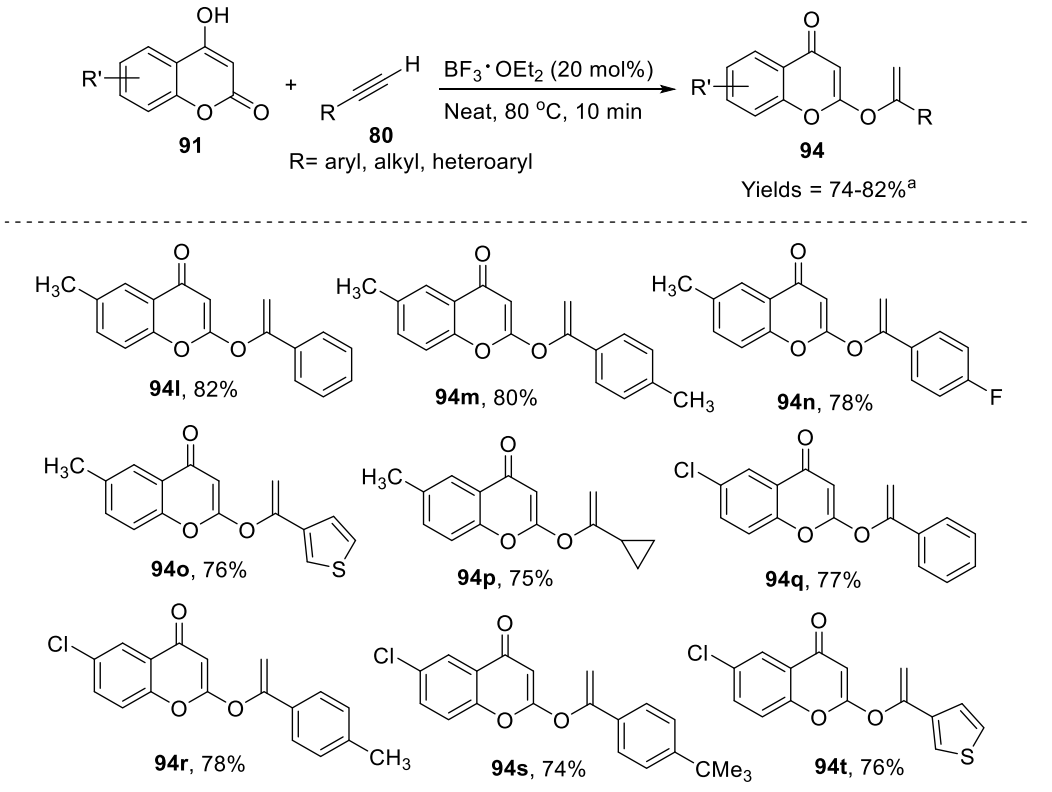
With this optimized reaction conditions, the substrate's scope of this protocol was investigated. We focused on the reaction of 4-hydroxycoumarin (**91a**) with various terminal alkynes (Table 2.82). The phenyl acetylenes substituted with various electron-donating groups (-CH_3, -OCH_3) at 3 or 4 positions of the phenyl ring afforded the desired products (**94b-d**) in excellent yields (80-85%). Phenyl acetylene with electron-withdrawing substituent produced the desired product (**94e**) also in high yield 82%. Highly electron-donating and bulky groups like (-CMe_3) reacted smoothly to afford the product (**94f**) in very good yield (84%). In addition, terminal alkyne substituted with heterocyclic moiety (3-ethynylthiophene) also worked well under the optimized reaction conditions (**94g**). It is worthy to mention that aliphatic alkynes also efficiently reacted with compound (**91a**) to give respective products (**94h-j**) in good yields (73-80%). In addition, we have also tested one example of the internal alkyne (prop-1-yn-1-ylbenzene, **80k**) which on reaction with compound (**91a**) led to the product (**94k**) with 78% yield in *E/Z* as 3:1 (Scheme 2.122).



Scheme 2.122

Then our attention was turned to the use of substituted 4-hydroxycoumarins to prove the general applicability of the reaction conditions as summarized in Table 2.83. This *O*-vinylation reaction was carried out with other substituted 4-hydroxycoumarin such as 6-methyl-4-hydroxycoumarin (**91b**) reacted very smoothly with phenylacetylene (**80a**) to afford the desired product (**94l**) in excellent yield 82%. Similarly, other substituted phenylacetylene bearing substituents at *para*- position (4-CH_3, 4-F) easily afforded the respective products (**94m**) and (**94n**) in 80% and 78% yields respectively.

Table 2.83. Substrates scope of the reaction between various 4-hydroxycoumarin and different alkynes.



Reaction conditions: 1 mmol of 4-hydroxycoumarin (**91b-c**) and 1 mmol of alkyne (**80**) were stirred for 10 min at 80 °C in the presence of 20 mol% of BF_3·OEt_2 under neat conditions.

Heteroaryl terminal alkyne also reacted smoothly with compound (**91b**) resulting the product (**94o**) in 76% yield. There was no exception for an aliphatic alkyne when it was treated with compound (**191b**) to give the product **(94p**) in 75% yield. The reaction of 6-Cl-4-

hydroxycoumarin (**91c**) afforded the desired product (**94q**) in 77% yield by reacting with phenylacetylene. Similarly, compound (**91c**) easily reacted with *para*-substituted phenylacetylene (4-Me, 4-CMe_3) to give the target products (**94r**) and (**94s**) with 78% and 74% yields respectively. Heteroarylated terminal alkyne furnished the desired product (**94t)** with 76% yield when reacted with compound (**91c**). All these reactions were carried out in an open atmosphere and are not sensitive to air and moisture. The reaction conditions are mild and give no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all reaction combinations which are supported with high yields and regio-selectivity of the protocol. All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data and the X-ray crystallographic analysis of 6-chloro-2-((1-(thiophen-3-yl)vinyl)oxy)-4*H*-chromen-4-one (**94t**, CCDC 1854580) was performed to confirm the structure of the product as shown in Figure 2.16.

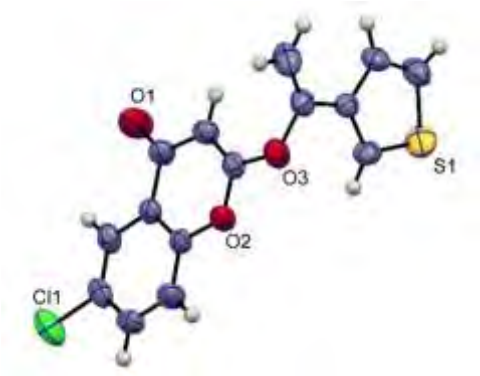


Figure 2.16. X-Ray crystallographic data for the compound (**94t**)

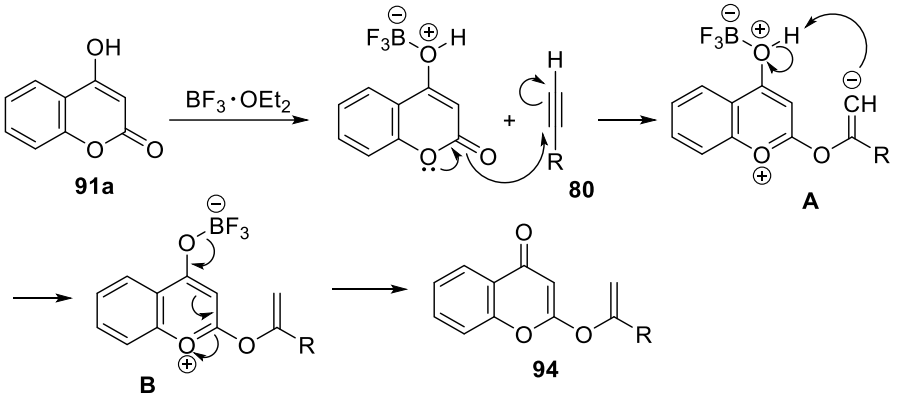
Very recently, a gold-catalyzed hydrofluorination of electron-deficient alkynes with triethylamine trihydrogen fluoride ($Et_3N{\cdot}3HF$) has been reported by the Toste group.[12] To correlate the mechanistic path with our observation we performed few control experiments. Initially to check the role of HF we carried out the reaction of 4-hydroxycoumarine (**91a**) with phenylacetylene (**80a**) using 20 mol% of HF in addition to 20 mol% of $BF_3{\cdot}OEt_2$ but no improvement of the reaction yield has been observed as well as the reaction time was also same. Then, we carried out a series of experiments as summarized in Table 2.84. Initially, we have taken a mixture of the alkyne (**80a**), $BF_3{\cdot}OEt_2$ (20 mol%) and HF (20 mol%) but no hydrofluorinated product of alkyne has been detected (Table 2.84, entry 1). Finally, taking only $BF_3{\cdot}OEt_2$ in different proportions no hydrofluorinated product of alkyne was also observed (Table 2.84, entries 2-3).

Table 2.84. Reaction of alkyne (**80a**) in the presence of $BF_3 \cdot OEt_2$ and/or HF.[a]

Entry	**80a**	$BF_3 \cdot OEt_2$	HF	Result[b]
1	1 mmol	20 mol%	20 (mol%)	NR
2	1 mmol	20 mol%	-	NR
3	1 mmol	1 equiv.	-	NR

[a]***Reaction conditions:*** 1 mmol of **80a** was stirred for 10 min under 80 °C temperature in the presence of different catalysts under neat conditions. [b]NR= No result.

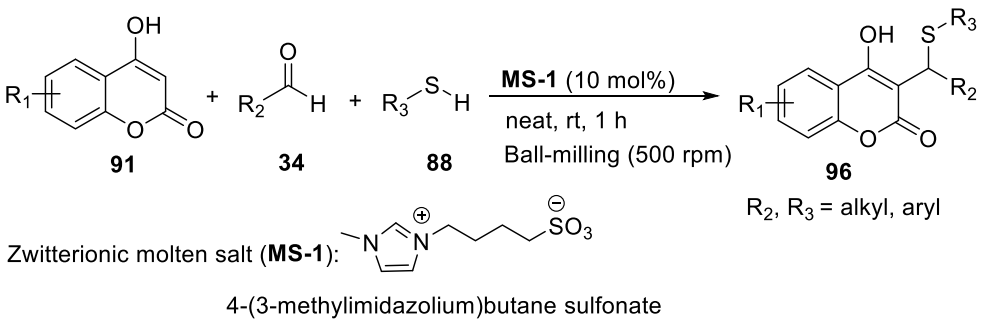
So, we have assumed that the possible reaction pathway may be explained according to Scheme 2.123. We know the oxygen atoms of lactone moiety are week nucleophiles so that the $BF_3 \cdot OEt_2$ initially coordinated with the hydroxyl oxygen. In the next step, the only possible nucleophilic addition of the carbonyl oxygen of the lactone with the alkyne (**80**) gave the intermediate [**A**] in the Markownikoff's way which was accelerated by the lone pair of the adjacent oxygen atom. The vinylic carbanion immediately on protonation produced another intermediate [**B**] which finally gave the desired product (**94)**.



Scheme 2.123

2.31. MECHANOCHEMICAL SYNTHESIS OF 4-HYDROXY-3-THIOMETHYLCOUMARINS USING IMIDAZOLIUM ZWITTERIONIC MOLTEN SALT

Numerous examples have been described in the literature for the synthesis of bis-coumarins by the reaction between 4-hydroxycoumarins with aldehydes, as well as cases of the introduction of thiols into coumarins, while the reactions took place in solutions under heating. As part of the work, we have developed a mechanochemical fast and convenient synthesis of 4-hydroxy-3-thiomethylcoumarins in the presence of imidazolium zwitterionic molten salt (**MS-1**) under ball-milling conditions by the reaction between 4-hydroxycoumarins, aldehydes and thiols (Scheme 2.124). To the best of our knowledge there is no other process available in literature to explore this one-pot synthesis by mechanochemical activation within short reaction time.

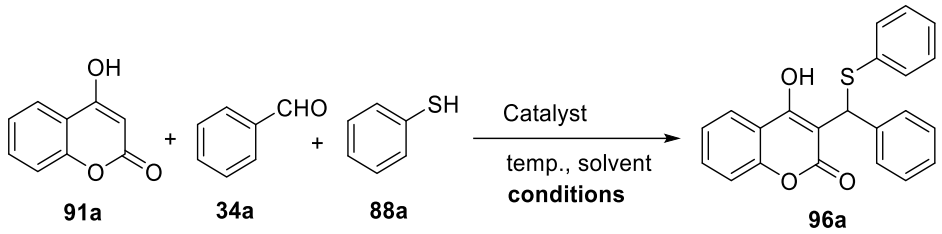


Scheme 2.124

Initially, a mixture of 4-hydroxycoumarin (**91a**) (1 mmol), benzaldehyde (**34a**) (1 mmol) and thiophenol (**88a**) (1.2 mmol) was reacted at room temperature for 3 h in presence of imidazolium zwitterionic molten salt (**MS-1**, 10 mol%) in ethanolic medium (Table 2.85, entry 1). To our delight, a pure solid product of 4-hydroxy-3-thiomethylcoumarin derivative (**96a)** was obtained in a moderate yield of 68%. An aqueous medium for the same reaction resulted in a lower amount of yield (60%) (Table 2.85, entry 2). For further evaluation, some aprotic solvents such as acetonitrile, dichloromethane and tetrahydrofuran (Table 2.85, entry 3-5) were employed which led to very poor appearance of the desired compound. After that we examined the effect of temperature; we refluxed the reaction under the same catalytic conditions, but no considerable improvement of the desired product was observed (Table 2.85, entries 6 & 7). So, we turned our attention to the concept of 'no solvent is the best solvent' and carried out the reaction under solvent-free conditions initially heating at 80 ^{o}C and then at room temperature (Table 2.85, entries 8 & 9). These observations showed that the yield formation was increased but not very encouraging. So, again we carried out the reaction by another switching from stirring to grinding in a mortar pastle for 1 h and 52% of the desired 4-hydroxycoumarin derivative was generated

(Table 2.85, entry 10). Next, we turned to carry out the reaction under ball-milling conditions. We have observed that using four balls (10 mm) with 500 rpm for 1 h gave the best result (91%) (Table 2.85, entry 11).

Table 2.85. Optimization of reaction conditions.[a]



entry	catalyst	solvents	conditions	temp. (ºC)	yields[b] (%)
1	MS-1	EtOH	stirring	rt	68
2	MS-1	H_2O	stirring	rt	60
3	MS-1	MeCN	stirring	rt	21
4	MS-1	DCM	stirring	rt	28
5	MS-1	THF	stirring	rt	39
6	MS-1	H_2O	stirring	reflux	66
7	MS-1	EtOH	stirring	reflux	70
8	MS-1	neat	stirring	80ºC	79
9	MS-1	neat	stirring	rt	75
10	MS-1	neat	grinding[c]	rt	52
11	MS-1	neat	ball-milling[d]	rt	91
12	MS-1	neat	ball-milling[e]	rt	60
13	MS-1	neat	ball-milling	rt	91[f]
14	MS-1	neat	ball-milling	rt	53[g]
15	PTSA	neat	ball-milling	rt	65
16	SSA	neat	ball-milling	rt	72

[a]***Reaction conditions:*** **91a** (1 mmol), **34a** (1 mmol), **88a** (1.2 mmol), molten salt (**MS-1**, 10 mol %). Conventional stirring was carried out for 3 h. [b]Isolated yields. [c]Grinding for 1 h. [d] Planetary Ball-milling apparatus Retsch™ PM 100 using 4 balls (size 10 mm), 500 rpm, 1 h. [e]Milling time 30 min. [f]20 mol% molten salt was used. [g]5 mol% molten salt was used.

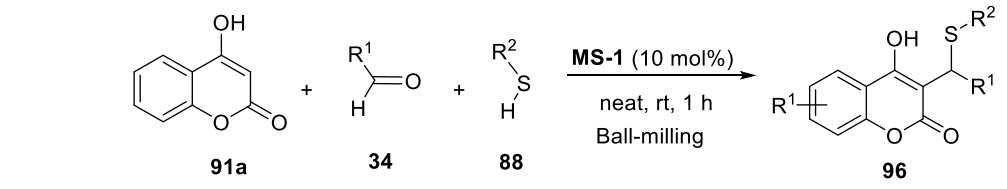
By decreasing the time (30 min) 60% of yield was obtained (Table 2.85, entry 12). Furthermore, we have observed that 20 mol% of molten salt did not alter the yield formation while it was reduced on using 5 mol% of the catalyst (Table 2.85, entries 13 & 14). The reaction was

also tested in presence of Brønsted acids like PTSA and SSA (silica sulfuric acid) but the reactions were not promising, and lesser amount of product formation was found in both cases (Table 2.85, entries 15 & 16). Thus, optimal reaction conditions were obtained using 4-hydroxycoumarin (**91a**) 1 mmol), benzaldehyde (**34a**) (1 mmol) and thiophenol (**88a**) (1.2 mmol) in the presence of 10 mol% of imidazolium zwitterionic molten salt (**MS-1**) under ball-milling conditions (4 balls with 500 rpm) for 1 h (Table 2.85, entry 11).

After having the optimized reaction conditions, a series of aromatic, aliphatic as well as heteroaryl aldehydes and thiols were reacted with 4-hydroxycoumarin (Scheme 2.125). The reactions were on great progress when the 4-hydroxycoumarin and thiophenol reacted with various para-substituted benzaldehydes. Both electron-donating and electron-withdrawing group substituted aromatic aldehydes produced the corresponding 4-hydroxycoumarin derivatives (**96b-96e**) in excellent amount of yields. On the other hand, 4-methylbenzenethiol and other *ortho*- and *para*-substituted benzaldehydes provided the desired products without any difficulties (**96f-96n**). As we noticed the endurance of various electronically and sterically diverse benzaldehydes, instantly the reaction was performed with 1- & 2-napthaldehyde which afforded the products (**96o**, **96p**) in 84% and 81% yields respectively. 6-Bromobenzo[*d*][1,3]dioxole-5-carbaldehyde and furan-3-carbaldehyde underwent the reaction greatly and products (**96q**) and (**96r**) were obtained in good yields. Few aliphatic aldehydes like cyclohexanecarbaldehyde and butyraldehyde reacted with similar efficiency with different thiophenols to form the corresponding products (**96s**, **96t**). After getting these comprehensive results, we were interested to check different types of aromatic and aliphatic thiols. On the introduction of *para*-substituted (-OMe, -Cl) thiophenols the reactions easily produced the respective 4-hydroxycoumarin compounds (**96u**, **96v**) in an excellent amount of yields. Likewise, naphthalene-2-thiol was able to produce the desired product **96w**. Additionally, several aliphatic thiols efficiently responsive reacting with different aromatic aldehyde to afford the desired compounds (**96x-96b'**) with very good to excellent amount of yields. However, it is worthy to mention that ketones do not react under the present reaction conditions. Simple ketones like acetone and acetophenone were tested where no reaction was observed.

Subsequently, substituted 4-hydroxycoumarins were also examined under the same optimal reaction condition using ball-milling technique (Scheme 2.126). It is needless to say that 6-methyl substituted 4-hydroxycoumarin effortlessly produced its derivatives (**96c'-96e'**) on reacting with various aromatic aldehydes and thiophenol. Besides, the products (**96f')** were obtained when 6-chloro-4-hydroxy-2*H*-chromen-2-one was introduced under similar reactions condition.In addition, 7-(diethylamino)-4-hydroxy-2*H*-chromen-2-one nicely gets converted to the desired product (**96i')** with 85% yield. Eventually, it was observed that 4-hydroxycoumarin

bearing either the electron-donating or electron-withdrawing group efficiently afforded the corresponding products with satisfying amount of yield formation.



91a **34** **88** **96**

R= H, **96a** (3h), 91%
p-CH_3, **96b** (4h), 87%
o-OCH_3, **96c** (5h), 84%
p-OCH_3, **96d** (5h), 88%
p-Cl, **96e** (3h), 86%

R= H, **96f** (3h), 89%
p-CH_3, **96g** (4h), 88%
p-OCH_3, **96h** (4h), 82%
p-OH, **96i** (5h), 67%
p-F, **96j** (7h), 83%
p-Cl, **96k** (3h), 90%
o-Br, **96l** (3h), 80%
p-Br, **96m** (3h), 87%
p-SCH_3, **96n** (6h), 76%

96o (3h), 84%

96p (4h), 81%

96q (4h), 89%

96r (7h), 64%

96s (3h), 68%

96t (3h), 82%

R= *p*-OCH_3, **96u** (4h), 87%
p-Cl, **96v** (4h), 90%

96w (3h), 92%

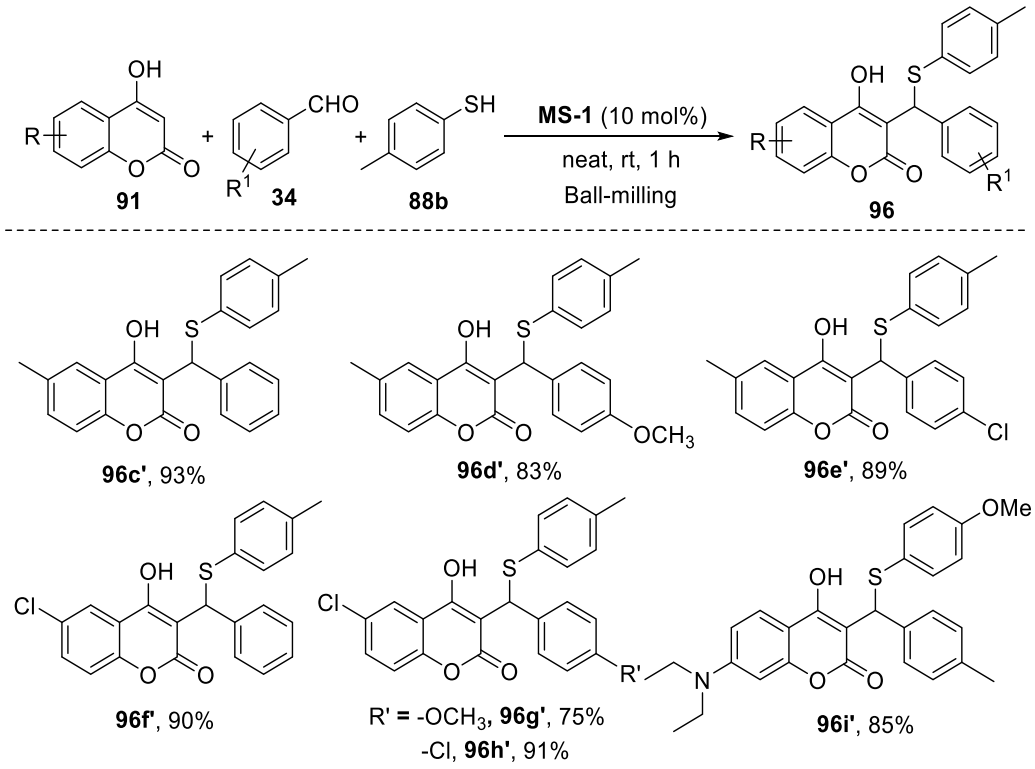
R= H, **96x** (7h), 79%
p-OCH_3, **96y** (6h), 88%
p-Cl, **96z** (5h), 89%

96a' (3h), 70%

96b' (3h), 74%

Reaction conditions: 4-hydroxycoumarin (**91a**, 1 mmol), aldehyde (**34**, 1 mmol), and thiol (**88**, 1.2 mmol) using 10 mol% of **MS-1** under ball milling; ball-milling apparatus Retsch PM 100 using four balls (size 10 mm), 500 rpm, 1 h. The time in the parenthesis indicates conventional stirring to get the comparable yields.

Scheme 2.125



Reaction conditions: substituted 4-hydroxycoumarin (1 mmol), benzaldehyde (1 mmol), 4-methylbenzenethiol (1.2 mmol), using 10 mol% of **MS-1** under Ball milling; Ball milling apparatus Retsch™ PM 100 using 4 balls (size 10 mm), 500 rpm, 1 h.

Scheme 2.126

We are delighted to narrate that the reactions were not air and moisture sensitive and no conventional column chromatographic technique was needed to purify the compounds. After completion of the reaction, the crude products were filtered off and thoroughly washed with the mixture of ethanol and hexane followed by the recrystallization got the pure desired products. The known synthesized compounds compared with earlier spectral data and the characterization of a new compounds have been explained by their spectral and analytical data. The X-ray crystallographic analysis 4-hydroxy-3-((4-methoxyphenyl)(*p*-tolylthio)methyl)-2*H*-chromen-2-one (**96h**, CCDC 2031503) finally confirmed the structure as shown in Figure 2.17.

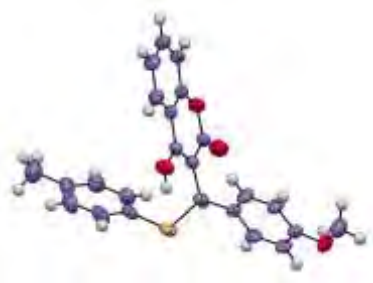
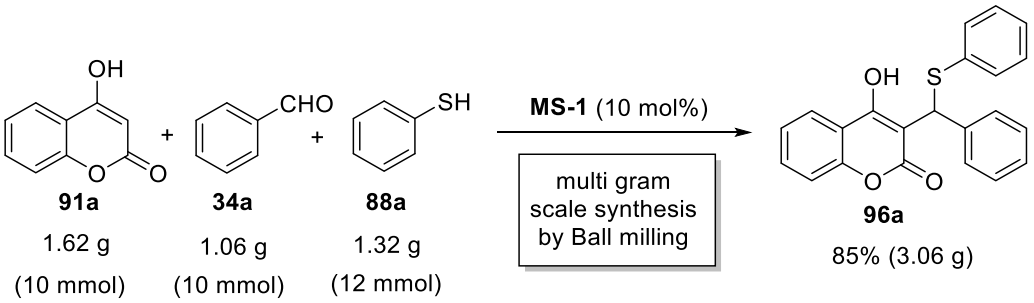


Figure 2.17. X-Ray crystallographic data for compound (**96h**).

We also investigated the efficiency of our method on a large scale and for this, we have employed 1.62 g of 4-hydroxycoumarin (**91a**), 1.06 g of benzaldehyde (**34a**), 1.32 g of thiophenol (**88aa**) and 10 mol% of zwitterionic molten salt as shown in Scheme 2.127. Thereafter, performing the reaction by ball-milling technique, we obtained 3.06 g of the desired product 4-hydroxy-3-(phenyl(phenylthio)methyl)-2*H*-chromen-2-one (**96a**).



Scheme 2.127

To check the reusability of our catalyst (MBS), the reaction mixture was carefully washed with water (10x3 mL) and filtered after completion of the reaction. Then the filtrate (aqueous part) was evaporated and the molten salt was recovered, dried and reused. By repeating the process, the catalyst has been reused for four times after proper drying. Here, we have displayed a comparison chart of the reusability of our catalyst with a comparable efficiency (Figure 2.18).

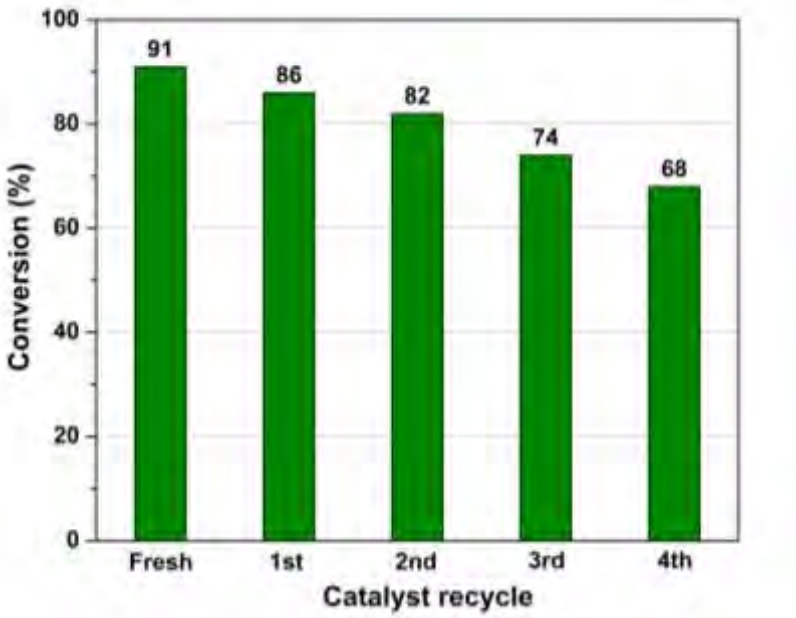
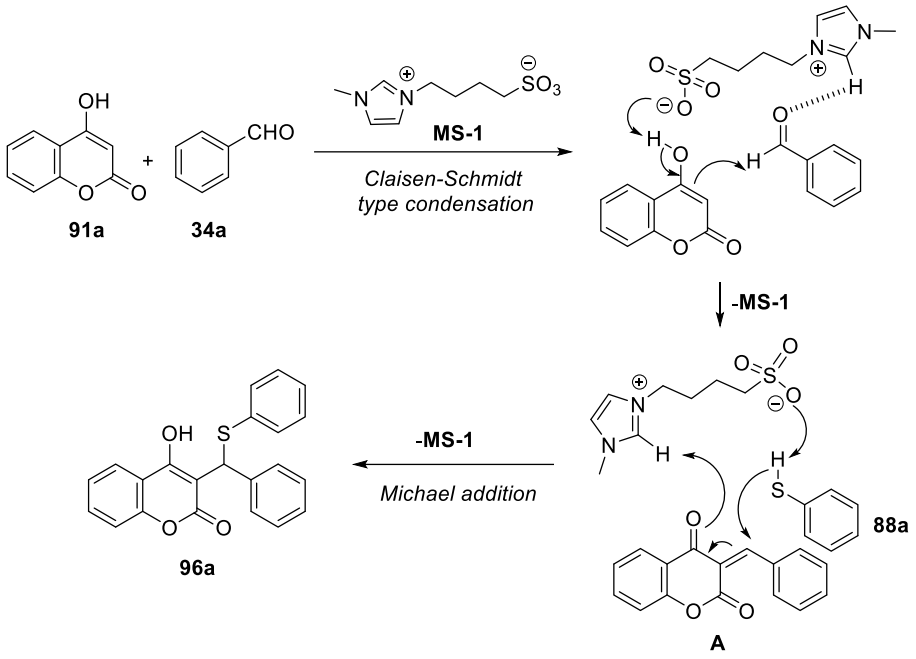


Figure 2.18. Recycling of the Zwitterionic molten salt (**MS-1**).

In 1992, the *E*-factor, or environmental impact factor, was introduced by Roger Sheldon [336]. This metric helps to quantify the amount of waste generated per kilogram of product. In this

present work, we have developed greener reaction conditions bearing lower *E*-factors for synthesizing the desired products (**96**), which is consistent with the principles of atom economy.

According to the literature [360], a plausible mechanism has been proposed in which imidazolium ion-based zwitterionic molten salt significantly controls the overall reaction steps (Scheme 2.128). The imidazolium-based zwitterionic molten salt can activate electrophile-nucleophile centre by the unconventional hydrogen bonding and charge-charge interactions [371, 372]. Here, electrophilicity of the aldehyde gets enhanced through the hydrogen bonding with C2–H bond of the imidazolium-based cationic part which leads to the Claisen-Schmidt type condensation reaction producing the *α,β*-unsaturated ketone (**A**) which acts as Michael acceptor. Finally, the Michael addition product of thiophenol (donor) gives the corresponding product (**96a**) where again the molten salt was released out playing the same role.



Scheme 2.128

2.32. QUANTUM CHEMICAL CALCULATIONS AND EVALUATION OF THE REACTIVITY OF KEY COMPOUNDS

To summarize and analyze the obatained results, the reactivity of key representatives of aziridines, azirines, and epoxides was evaluated in comparison with aldehydes and substituted styroles in multiple bond substitution reactions under the action of electrophilic and nucleophilic reagents. The DFT method was used to calculate the reactivity of compounds: ionization potential I, electron affinity A, electron-chemical potential μ, electrophilicity index ω, nucleophilicity index N, nucleophilicity index N', as well as the Fukui function f^- and the double descriptor Δf, taking into account the peculiarities of the electron density distribution.

Table 2.86. Global reactivity descriptors for the structures of the optimized equilibrium model, all values are indicated in eV. Tetracyanoethylene (TCE) was used as a comparison compound.

Compounds	E_{HOMO}	E_{LUMO}	I	A	μ	ω	N	N'
1a	-6.554	-1.026	6.55	1.03	-3.79	2.60	2.57	2.57
14	-6.500	-0.202	6.50	0.20	-3.35	1.78	2.62	2.98
18a	-6.498	-1.729	6.50	1.73	-4.11	3.55	2.62	2.26
25a	-6.788	-1.449	6.79	1.45	-4.12	3.18	2.33	2.32
25r	-6.716	-1.404	6.72	1.40	-4.06	3.10	2.40	2.36
25s	-6.038	-1.537	6.04	1.54	-3.79	3.19	3.08	2.47
7a	-6.031	-0.832	6.03	0.83	-3.43	2.26	3.09	2.86
50a	-6.946	-2.632	6.95	2.63	-4.79	5.32	2.18	1.79
74g	-6.339	-1.695	6.34	1.70	-4.02	3.48	2.78	2.31
74a	-6.312	-2.094	6.31	2.09	-4.20	4.19	2.81	2.12
47a	-6.094	-1.775	6.09	1.77	-3.93	3.58	3.03	2.33
53a	-5.903	-1.553	5.90	1.55	-3.73	3.20	3.22	2.50
34a	-6.943	-1.712	6.94	1.71	-4.33	3.58	2.18	2.17
87	-7.174	-3.171	7.17	3.17	-5.17	6.68	1.95	1.56
91a	-6.397	-1.590	6.40	1.59	-3.99	3.32	2.72	2.35
TCE	-9.121	-4.959	9.12	4.96	-7.04	11.91	0.00	1.00

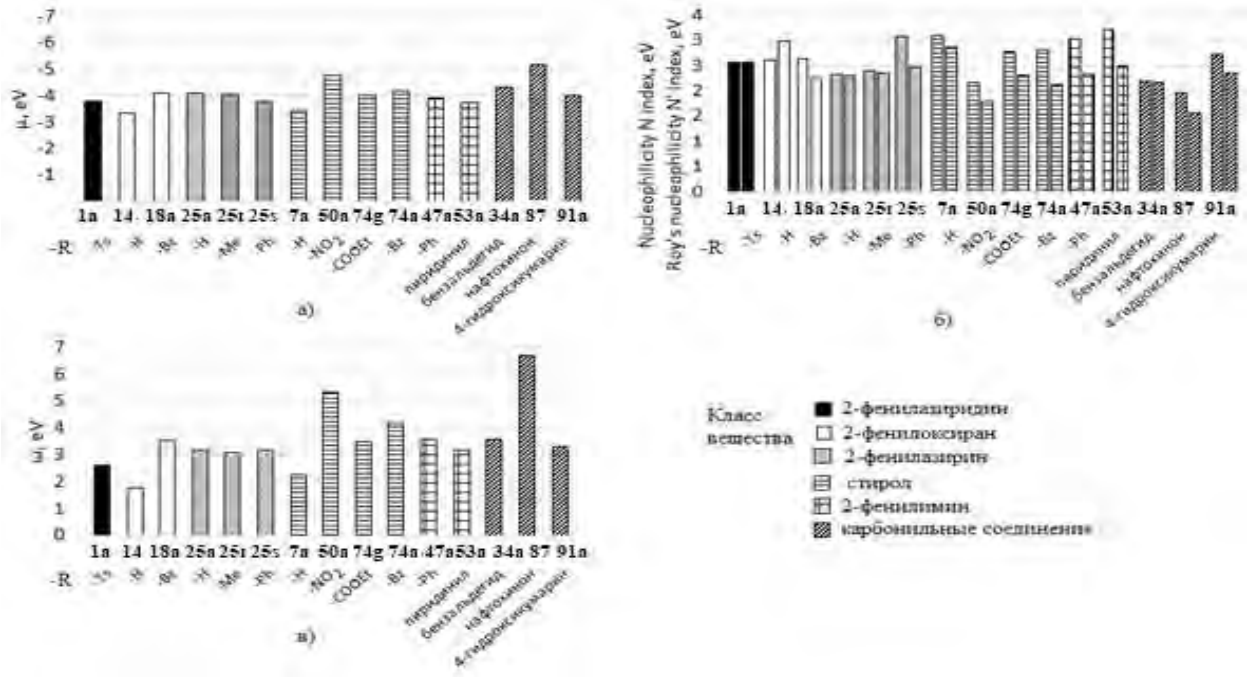


Figure 2.19. Values for the studied structures: a) the electronic chemical potential μ; b) the nucleophilicity indices N and N'; c) the electrophilicity indices ω.

According to the literature data, compounds with the electrophilicity index ω can be distributed as strong ($\omega > 1.5$ eV), medium ($0.8 < \omega < 1.5$ eV) and weak electrophiles ($\omega < 0.8$ eV).Similarly, according to the nucleophilicity index N, nucleophiles are divided into strong ($N >$ 3.0 eV), with moderate nucleophilicity ($2.0 < N < 3.0$ eV) and weak nucleophiles ($N < 2.0$ eV). The Fukui f^- function and the double Δf descriptor also make it possible to evaluate the nucleophilic and electrophilic regions of molecules during primary attack.

The global reactivity descriptors for the structures of the optimized equilibrium model for compounds (**1a**, **14**, **18a**, **25a**, **25r**, **25s**, **7a**, **50a**, **74g**, **74a**, **47a**, **53a**, **34a**, **87**) and (**91a**) are shown in Table 3. Thus, according to the values of the electron chemical potential μ among the three-membered cycles, it can be seen that 2-benzoyl-3-phenylepoxide (**18a**) is more reactive than 2-phenylepoxide (**14**), and among the azirines, 2-phenylazyrine (**25a**) is the most reactive. Naphthoquinone (**87**) and benzaldehyde (**34a**) have the highest values of μ (Figure 2.19a), and in 4-hydroxycoumarin (**91a**) μ is significantly lower.Ethylenes also show fairly high values of μ, the most reactive being nitrostyrene (**50a**). When replacing a substituent with a multiple bond with a benzoyl and ester group, the value of μ decreases. Styrene **7** is the least reactive.

To compare the reactivity of compounds (**1a**, **14**, **18a**, **25a**, **25r**, **25s**, **7a**, **50a**, **74g**, **74a**, **47a**, **53a**, **34a**, **87**) and (**91a**) with electrophilic reagents, their nucleophilicity index N and the nucleophilicity index N' were evaluated (Figure 2.19b). According to the data (Table 2.86), most substrates exhibit the properties of medium-strength nucleophiles.

According to the literature, for a high probability of electrophilic attack, the reaction centers must have a high value of the Fukui function f^-. The most positive part of the f^- function, shown in Figure 2.20, in compounds (**1a**, **14**, **18a**, **25a**, **25r**, **25s**) with three-membered cycles is localized on heteroatoms, and in 2,3-diphenylazirine (**25s**) it is localized and on the carbon atoms of the azirine ring. At the same time, all heterocycles, except for aziridine (**1a**), are characterized by a different f value on the two carbon atoms of the cycle. This shows their nonequivalence in reactions with electrophilic reagents. In compounds of other classes, increased values of f^- are observed on the double bond atoms C=C, C=N and C=O, since these sites are favorable for electrophilic attack.

The double descriptor shows a favorable center for primary electrophilic attack if $\Delta f < 0$. These centers (Figure 2.21) in three-membered cycles are located on heteroatoms and, in addition, on carbon atoms in epoxides and azirines. At the same time, in epoxide (**14**), the unsaturated carbon atom is more nucleophilic, and in epoxide (**18a**), the carbon in the electron acceptor benzoyl group is more electrophilic. The same is observed for azirines. Reduced values of the function are characteristic only in 2,3-diphenylazyrine (**6**) for the carbon atom replaced by an electron acceptor group. In structures with double bonds, the reduced values of Δf are localized at the C=C position, on the nitrogen atoms of the C=N bond and the oxygen atom of the carbonyl group.

For the electrophilicity of compounds (**1a**, **14**, **18a**, **25a**, **25r**, **25s**, **7a**, **50a**, **74g**, **74a**, **47a**, **53a**, **34a**, **87**) and (**91a**) in addition reactions with nucleophilic reagents, as well as in the reactions of aza-Henry and Michael, the value of the electrophilicity index ω is important (Figure 2.19b). For all studied compounds, this parameter exceeds 1.5. This means that on the electrophilicity scale, all compounds exhibit the properties of strong electrophiles. Moreover, the values of the electrophilicity index for different classes of substances (azirines, epoxides, imines, alkenes, carbonyl compounds) lie in approximately the same range, and within each class the values of ω depend on the nature of the substituents. Thus, according to calculations, 1,4-naphthoquinone is the best electrophile among carbonyl compounds, nitrostirol (**50a**) and chalcon (**74a**) have the most pronounced electrophilicity among ethylenes, and 3-benzoyl-2-phenylepoxide (**18a**) has the most pronounced electrophilicity among three-membered cycles. The trend of change in this descriptor is largely similar to estimates of global reactivity calculated from the chemical potential of electrons μ (Figure 2.19a). This suggests that in most transformations, all the studied compounds exhibit predominantly the properties of electrophiles.

The double descriptor $\Delta f > 0$ usually indicates a favorable site for a nucleophilic attack.These positions, shown in Figure 2.21, among the three-membered cycles within the cycle are characteristic only for azirines and are located on the carbon atom by the C=N bond. Also, in naphthoquinone **87**, carbonyl carbon atoms of the quinone ring are most favorable for attack, in

compounds (**50a**, **74g**, **74a**) carbon atoms with a phenyl substituent are most favorable for attack when bound with C=C.

Table 2.87. Comparison of calculated and experimental data*

Structures	Electrophilic center for nucleophilic attack (exp.)	The center with the highest possible positive Δf	
1a	N(Ts)-**C**(Ar)	**N**(Ts)-C(Ar); both atoms are susceptible to nucleophilic attack	
14	O-**C**(R)	**O**-**C**(R); both atoms are susceptible to nucleophilic attack	
7a	**C**(Ar)=C	**C**(Ar)=C	
50a	**C**(Ar)-C(=O)	**C**(Ph)-C(=O)	
	C=C(NO_2)	**C**=C(NO_2)	
74g	**C**(Ar)=C-C(=O)	**C**(Ph)=C-C(=O)	
74a	**C**(Ar)=C-C(=O)	**C**(Ph)=C-C(=O)	
	C(Ar)-**C**-C(=O) intermediate	**C**(Ar)=C-C(=O)	
	C(Ar)-C(=O)		
47a	N=**C**	N=**C**	
34a	**C**=O	**C**=O	
87	**C**=**C**	**C**=**C**	
Structures	Nucleophilic center for electrophilic attack (exp.)	The center with the highest positive f^-	The center with the maximum negative value of Δf
25a	**N**=C(Ar)	**N**=C(Ar)	**N**=C(Ar)
25r	**N**=C(Ar)	**N**=C(Ar)	**N**=C(Ar)
25s	**N**=C(Ar)	**N**=C(Ar)	**N**=C(Ar)
74a	**C**(Ar)=**C**-C(=O) with the formation of a triatomic cycle	C(Ar)=**C**-C(=O)	C(Ar)=**C**-C(=O)

*The gray color indicates that the double descriptor is not being played or is not being played completely.

In reactions in which hydrogen atom separation occurs, compounds with low bond polarity and low electron affinity will have the best reactivity. According to the corresponding descriptor A (Table. 2.87) The studied ones include epoxides, aziridines and azirines.

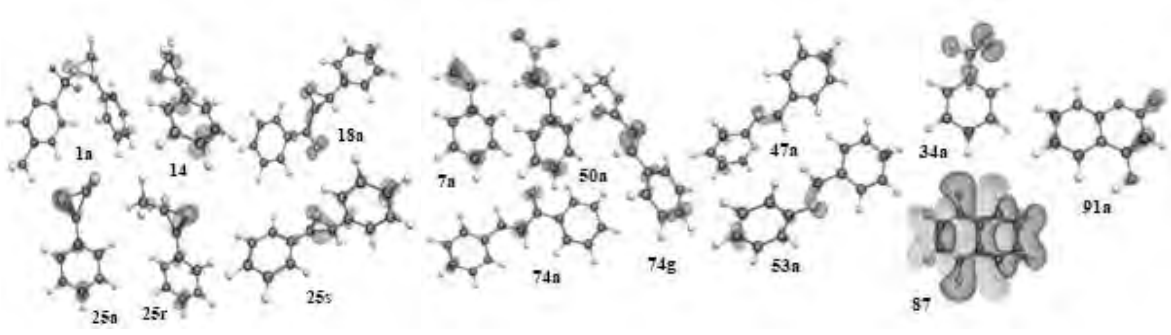


Figure 2.20. The Fukui function f^- with a contour of 0.007 au. Dark lines and a light surface correspond to the positive and negative areas of the f^- function, respectively.

According to the experimental data described above, in addition reactions, a nucleophile or an electrophile often attacks the same atom with a double bond. A comparison of the experimental data for each compound with the values of Δf (Table 2.87) shows that in most cases the theoretically calculated value of Δf coincides with the experimentally obtained data regarding the site of attack by nucleophilic and electrophilic reagents, with the exception of 2-phenyl-*N*-tosylazyrine (**1a**) and 2-phenylepoxide (**14**). Also for chalcon (**74a**) for each with an atom with a C= C bond may undergo a reaction with the formation of a triatomic cycle first, and then with a nucleophilic attack. However, the calculated data of Δf show that these carbon atoms differ significantly in electrophilicity and nucleophilicity.

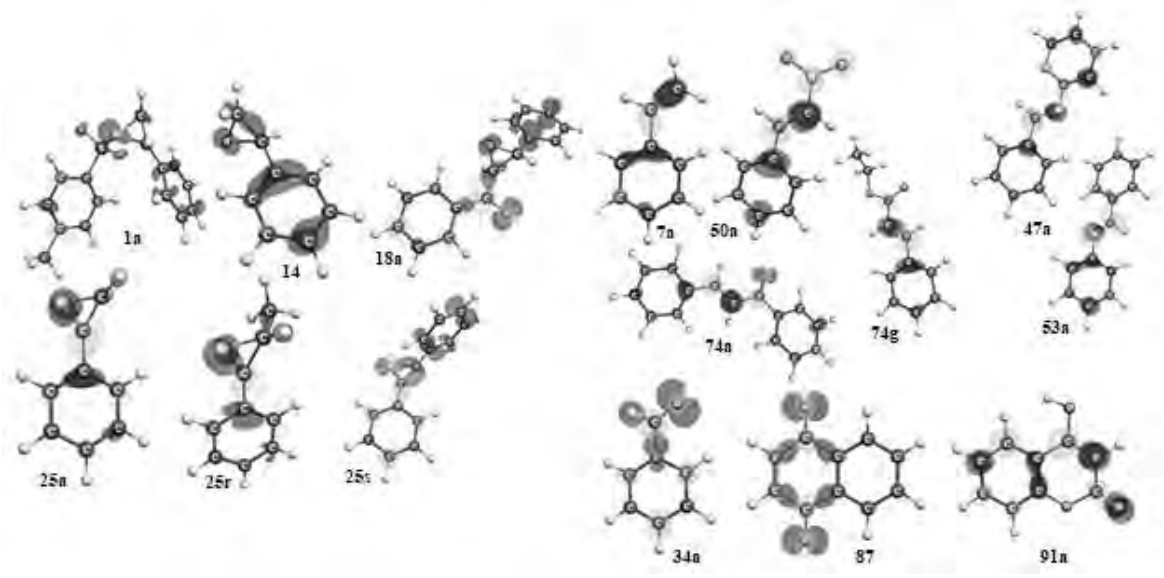


Figure 2.21. A double Δf descriptor with a contour of 0.007 au. On the maps, the light and dark surfaces correspond to the positive and negative regions of the Δf function, respectively.

Thus, based on theoretical calculations, including those confirmed by experimental data, it can be argued that azirines, aziridines and epoxides in reactions with electrophiles and nucleophiles exhibit a reactivity similar to aldehydes and styroles, which follows from the values of the nucleophilicity and electrophilicity indices. At the same time, according to calculations of the nucleophilicity index N and the Fukui function f^- among the three-membered heterocycles, epoxides have the best nucleophilic properties. All the considered compounds exhibit mainly the properties of electrophiles. In all classes of compounds under consideration, structures with aryl substituents have the best electrophilic properties.

2.33. EVALUATION OF THE BIOLOGICAL ACTIVITY OF THE OBTAINED COMPOUNDS USING MOLECULAR DOCKING AND *IN-SILICO* MODELING METHODS

At the final stage, the biological activity of the obtained compounds was evaluated, namely antitumor and antiviral (in relation to SARS-COV-2). For this purpose, the ability of pre-selected compounds (Figure 2.22) to inhibit cyclin-dependent kinases (CDK) in the **CDK2**/cyclin complex was evaluated in comparison with the well-known antitumor drug Dinaciclib (SCH-727965) (Figure 2.23a), as well as the ability to inhibit the main protease SARS-COV-2 in comparison with the experimental drug **X77** (Figure 2.23b).

The results of molecular docking are shown in Table 2.88. Thus, the leader compound in antitumor activity is disubstituted benzimidazole (**44l**) (free binding energy -13.58 kcal/mol), whereas the melatonin (**3g**) analog was the most promising antiviral candidate (-10.25 kcal/mol).

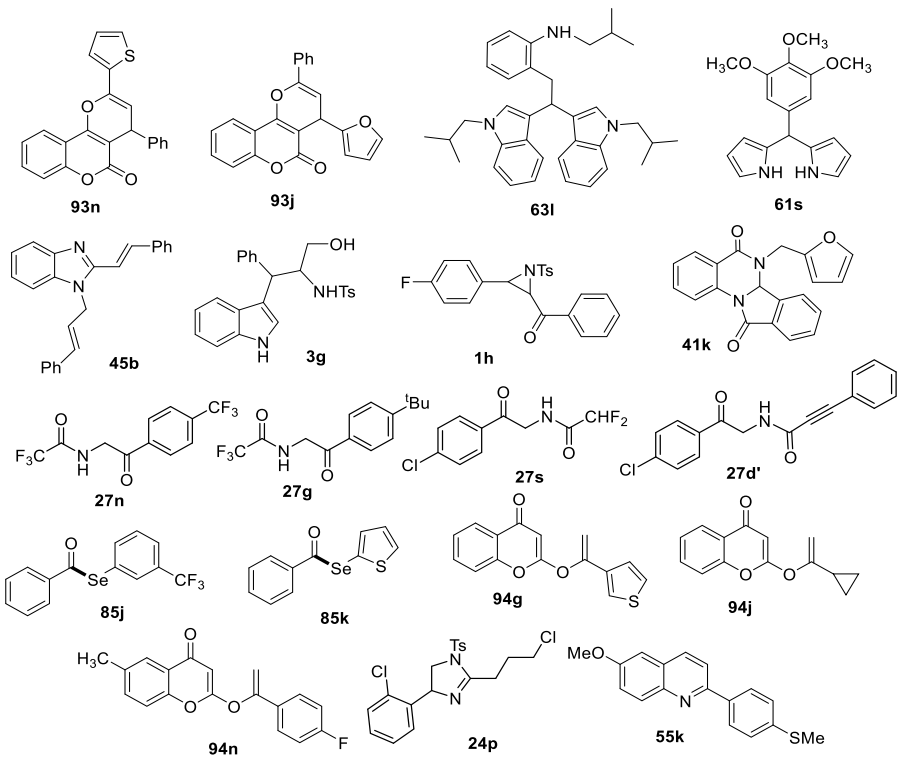
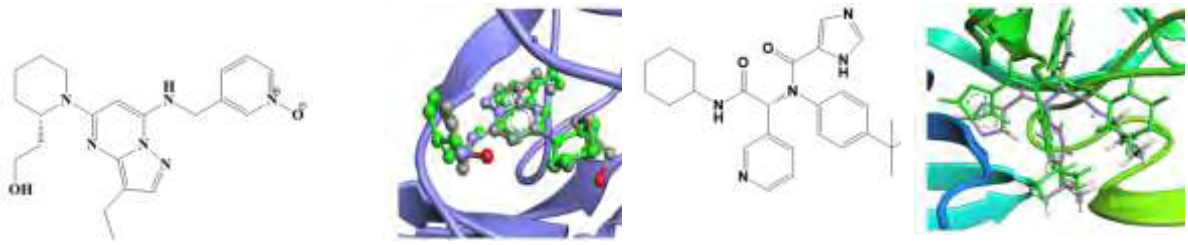


Figure 2.22. Structures of selected compounds



a) b)

Figure 2.23. Studies of docking of native ligands: a) Dinaciclib (SCH-727965) is an experimental drug that inhibits cyclin-dependent kinases (CDK)) in the **CDK2**/cyclin E complex; b) **X77** is an inhibitor of the main protease SARS-COV-2.

Figure 2.24 shows the complex of compound (**44l**) with the target protein **CDK2** in comparison with Dinacyclib, and Figure 2.25 shows the complex of compound (**3g**) with the main protease ***SARS-COV-2*** in comparison with the inhibitor X77.

Table 2.88. Charging modes CDK2 (512 W) and M pro SARS-COV-2 (6 W 63)

Compounds	Free binding energy, ΔG, kcal/mol		Compounds	Free binding energy, ΔG, kcal/mol	
	5l2w	**6w63**		**5l2w**	**6w63**
Dinacyclib (Ki=1 nm)	**-10,88**	-	Dinacyclib (Ki=1 nm)	**-10,88**	-
X77 (IC50=2.3 microns)	-	**-9,18**	**27n**	-9,06	-7,35
93n	**-12,81**	-7,98	**27g**	-9,00	-7,42
93j	**-12,24**	**-9,16**	**27s**	-8,21	-7,04
63l	**-11,99**	-9,01	**27d′**	**-11,99**	-8,56
61s	-8,03	-8,01	**85k**	**-10,05**	-8,32
44l	**-13,58**	**-9,12**	**94j**	-9,73	-7,43
3g	**-12,67**	**-10,25**	**94n**	**-11,59**	-8,01
1h	**-13,34**	**-9,20**	**24p**	**-12,51**	-8,39
41k	-10,69	-7,65	**55k**	**-11,32**	-7,95

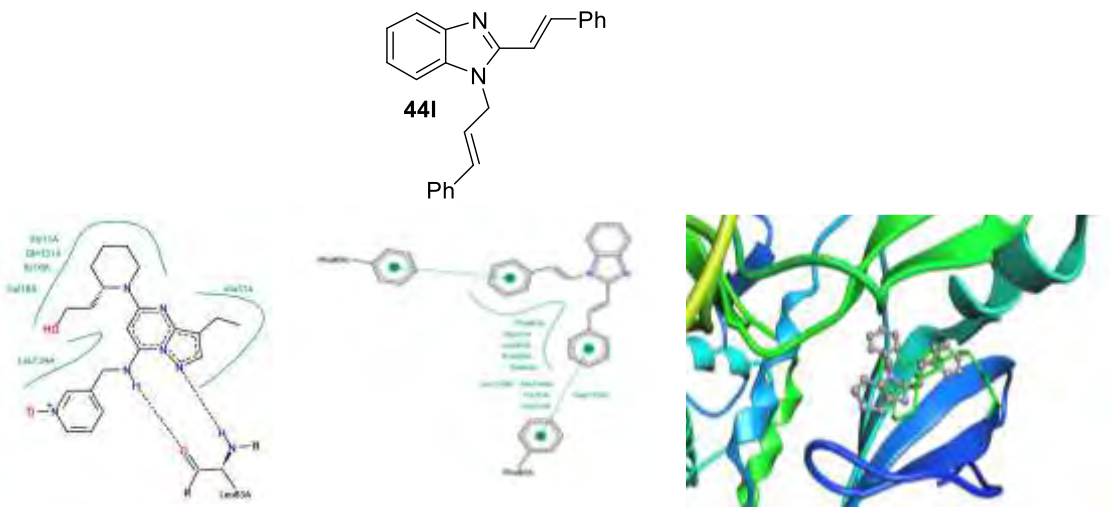


Figure 2.24. The complex of compound (**44l**) with the target protein **CDK2** in comparison with Dinacyclib (green)

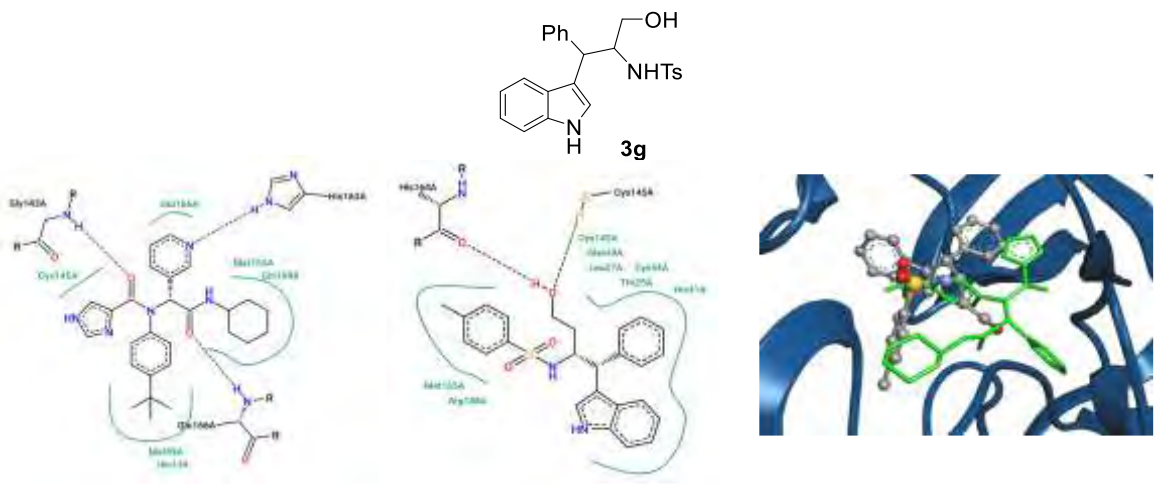


Figure 2.25. Complex of compound **(3g)** with the main protease *SARS-COV-2* in comparison with the inhibitor X77 (highlighted in green)

According to Table 2.88, compounds (**93n**, **93j**, **63l**, **44l**, **3g**, **1h**, **27d'**, **85j**, **94g**, **94n**, **24p**, **55k**) can also potentially have antitumor activity and their ability to bind to **CDK2** is higher than that of Dinacyclib. The leader compound (**44l**) has a slightly different profile of non-covalent interactions in the protein.

Similarly, antiviral activity can also be expected for compounds (**44l**, **3g)** and, possibly, compound (**93j**), which is higher compared to **X77**. However, these compounds had a different interaction profile with the main protease *SARS-COV-2*, which may negatively affect the actual biological activity.

CHAPTER 3. EXPERIMENTAL PART

General information

All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were determined on 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet) and coupling constants (J) were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ solution. Chemical shifts as internal standard are referenced to $CDCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.16$ for ^{13}C NMR) as internal standard. TLC was done on silica gel coated glass slide. X-ray single crystal data were collected using Mo Kα ($\lambda = 0.71073$ Å) radiation with a CCD area detector. Melting points were determined on a glass disk with an electrical bath and are uncorrected. TLC was monitored with aluminium backed silica gel 60 (HF254) plates (0.25 mm) using solvent with different polarity (petroleum ether (60-80 ºC) and ethyl acetate mixtures). Silica gel (60-120 mesh, SRL, India) and petroleum ether (boiling range 60-80 ºC) was used for column chromatography and was distilled before use. All solvents were dried and distilled before use. The aziridines were prepared by the reported method [19]. All the 2*H*-azirines were prepared according to the reported method [103]. For light induced reactions, Borosilicate glass tube was used as a reaction tube. The reaction tube was positioned 7 cm away from the exposed of Kessil 34 W blue LED (450-530 nm). Regular fan was used to maintain the temperature 28 to 30 °C during the reaction. In_2O_3 and CuO nano were purchased from Sigma-Aldrich. Imidazolium zwitterionic molten salt (**MS-1**) was prepared according to the previously reported methods [373, 374] Brønsted acidic ionic liquids (BAIL) were prepared according to the previously reported method [375]. For the reactions under ball milling conditions, a planetary Ball-milling apparatus Retsch PM100 was employed using four balls (stainless steel, size 10 mm). The reactions were performed in a 50 mL grinding jar.

3.1. Ring opening of aziridines in presence of imidazolium zwitterionic molten salt

3.1.1. Typical procedure for the synthesis of compounds (3):

A mixture of tosylaziridine **1** (0.50 mmol), nucleophile **2** (0.50 mmol) and **MS-1** (10 mg, 10 mol%) was taken in a sealed tube and the reaction mixture was stirred for 3 h at 85 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product using ethyl acetate-petroleum ether as eluent.

***N*-(2-(1*H*-Indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3a) [376]:** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), indole **2a** (0.50 mmol, 59 mg). Yield: 163 mg, 84%; Pale brown solid; mp 109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8 Hz, 1H), 7.18-7.03 (m, 9H), 6.92-6.86 (m, 2H), 4.43 (s, 1H), 4.22 (t, *J* = 7.6 Hz, 1H), 3.59-3.41 (m, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 141.1, 136.8, 136.6, 129.9, 128.9, 128.1, 127.2, 127.1, 126.6, 122.5, 122.2, 119.7, 119.2, 115.6, 111.4, 47.6, 42.7, 21.7.

4-Methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)-2-phenylethyl)benzenesulphonamide (3b): The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), *N*-methyl indole **2b** (0.50 mmol, 66 mg). Yield: 163 mg, 81%; Brown solid; mp 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.18-7.08 (m, 10H), 6.91-6.88 (m, 1H), 6.68 (s, 1H), 4.47 (s, 1H), 4.21 (t, *J* = 7.6 Hz, 1H), 3.60 (s, 3H), 3.56-3.51 (m, 1H), 3.46-3.42 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.3, 137.3, 136.9, 129.8, 128.8, 128.0, 127.2, 127.0, 126.97, 126.8, 122.0, 119.3, 119.2, 114.0, 109.5, 47.6, 42.7, 32.8, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93%; Found: C, 71.29; H, 5.95; N, 6.96%.

***N*-(2-(5-Methoxy-1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3c):** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), 5-methoxy indole **2c** (0.50 mmol, 74 mg). Yield: 168 mg, 80%; Brown solid; mp 78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.55 (d, *J* = 8 Hz, 2H), 7.17-7.09 (m, 8H), 6.82 (s, 1H), 6.74-6.61 (m, 1H), 6.60 (s, 1H), 4.47 (s, 1H), 4.20 (t, *J* = 7.6 Hz, 1H), 3.63 (s, 3H), 3.59-3.52 (m, 1H), 3.46-3.39 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.0, 143.6, 141.1, 136.8, 131.7, 129.8, 128.8, 128.1, 127.2, 127.1, 127.0, 122.9, 115.3, 112.6, 112.1, 101.1, 55.8, 47.5, 42.8, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.52; H, 5.78; N, 6.66%.

***N*-(2-(5-Bromo-1*H*-indol-3-yl)-2-phenylethyl)-4-methylbenzenesulphonamide (3d):** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), 5-bromo indole **2d** (0.50 mmol, 98 mg). Yield: 190 mg, 81%; Brown solid; mp 57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.21-7.12 (m, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.94 (s, 1H), 4.44 (s, 1H), 4.12 (t, *J* = 7.6 Hz, 1H), 3.53-3.41 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 140.7, 136.7, 135.2, 130.0, 129.0, 128.3, 128.0, 127.3, 127.2, 125.4, 123.4, 121.7, 115.3, 113.0, 112.9, 47.5, 42.4, 21.7; Anal. calcd for $C_{23}H_{21}BrN_2O_2S$: C, 58.85; H, 4.51; N, 5.97%; Found: C, 58.86; H, 4.50; N, 5.99%.

4-Methyl-*N*-(2-(2-methyl-1*H*-indol-3-yl)-2-phenylethyl)benzenesulphonamide (3e): The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), 2-methyl

indole **2e** (0.50 mmol, 65 mg). Yield: 162 mg, 80%; Red coloured gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.50 (d, *J* = 8 Hz, 2H), 7.17-7.06 (m, 8H), 7.01-6.97 (m, 2H), 6.78 (t, *J* = 7.6 Hz, 1H), 4.30-4.26 (m, 2H), 3.74-3.68 (m, 1H), 3.52-3.47 (m, 1H), 2.33 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 141.5, 136.5, 135.6, 133.7, 129.8, 128.6, 127.7, 127.2, 127.0, 126.7, 121.2, 119.7, 118.7, 110.8, 109.0, 46.4, 42.1, 21.6, 12.1; Anal. calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93 %; Found: C, 71.28; H, 5.96; N, 6.97%.

***N*-(2-(4-Chlorophenyl)-(1*H*-indol-3-yl)ethyl)-4-methylbenzenesulphonamide (3f):** The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine **1b** (0.50 mmol, 154 mg), indole **2a** (0.50 mmol, 59 mg). Yield: 168 mg, 79%; Pale brown solid; mp 83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.24 - 6.86 (m, 11H), 4.58 (t, *J* = 6 Hz, 1H), 4.19 (t, *J* = 7.6 Hz, 1H), 3.54-3.48 (m, 1H), 3.42-3.35 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 139.8, 136.7, 136.6, 132.7, 129.9, 129.4, 128.9, 127.1, 126.4, 122.6, 122.2, 119.8, 119.1, 115.1, 111.5, 47.4, 42.2, 21.6; Anal. calcd for $C_{23}H_{21}ClN_2O_2S$: C, 65.01; H, 4.98; N, 6.59%; Found: C, 65.04; H, 4.97; N, 6.55%.

***N*-(3-Hydroxy-1-(1*H*-indol-3-yl)-1-phenylpropan-2-yl)-4-methylbenzenesulphonamide (3g):** The typical procedure was applied to (3-phenyl-1-tosylaziridine-2-yl)methanol **1c** (0.50 mmol, 152 mg), indole **2a** (0.50 mmol, 59 mg). Yield: 172 mg, 82%; Red gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8 Hz, 1H), 7.20-6.89 (m, 11H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.33 (d, *J* = 9.2 Hz, 1H), 3.94 (s, 1H), 3.70-3.66 (m, 1H), 3.55-3.51 (m, 1H), 2.32 (s, 3H), 1.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 140.5, 136.7, 136.3, 129.7, 128.8, 128.5, 127.2, 126.9, 126.8, 122.3, 122.2, 119.7, 119.0, 115.4, 111.4, 63.6, 58.9, 43.9, 21.6; Anal. calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.57; H, 5.76; N, 6.67%.

***N*-(3-Hydroxy-1-(-1-methyl-1*H*-indol-3-yl)-1-phenylpropan-2-yl)-4-methylbenzenesulphonamide (3h):** The typical procedure was applied to (3-phenyl-1-tosylaziridine-2-yl)methanol **1c** (0.50 mmol, 152 mg), *N*-methyl indole **2b** (0.50 mmol, 66 mg). Yield: 167 mg, 77%; Red gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8 Hz, 1H), 7.16-7.03 (m, 9H), 6.94-6.90 (m, 1H), 6.82 (s, 1H), 4.81 (s, 1H), 4.32 (d, *J* = 9.2 Hz, 1H), 3.92 (s, 1H), 3.71-3.67 (m, 1H), 3.59 (s, 3H), 3.57-3.54 (m, 1H), 2.34 (s, 3H), 1.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 140.7, 137.0, 136.7, 129.7, 128.8, 128.4, 127.2, 127.1, 126.84, 126.81, 122.0, 119.3, 119.2, 114.0, 109.4, 63.6, 59.0, 43.9, 32.8, 21.7; Anal. calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.45%; Found: C, 69.11; H, 6.02; N, 6.41%.

***N*-(3-(1*H*-Indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulphonamide (3i):** The typical procedure was applied to phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone **1d** (0.50

mmol, 152 mg), indole **2a** (0.50 mmol, 59 mg). Yield: 186 mg, 75%; Red gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 8.02 (d, *J* = 1.6 Hz,1H), 7.63-6.78 (m, 18H), 5.72-5.69 (m, 1H), 5.19 (d, *J* = 11.2 Hz,1H), 4.59 (d, *J* = 2.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 143.7, 137.2, 136.2, 134.3, 134.0, 129.8, 129.6, 129.58, 129.0, 128.3, 127.6, 127.5, 126.9, 123.3, 122.2, 119.4, 118.9, 115.3, 111.3, 60.6, 45.0, 21.5; Anal. calcd for $C_{30}H_{26}N_2O_3S$: C, 72.85; H, 5.30; N, 5.66%; Found: C, 72.81; H, 5.34; N, 5.63%.

***N*-(3-(5-Bromo-1*H*-indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulphonamide (3j):** The typical procedure was applied to phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone **1d** (0.50 mmol, 152 mg), 5-bromo indole **2d** (0.50 mmol, 98 mg). Yield: 217 mg, 76%; Orange gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H), 8.06 (d, *J* = 2.4 Hz, 1H), 7.63-6.86 (m, 17H), 5.66-5.63 (m, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.51 (d, *J* = 2.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.7, 143.9, 136.7, 136.1, 134.7, 136.2, 129.8, 129.6, 129.5, 129.1, 128.5, 128.2, 127.8, 127.5, 126.6, 125.1, 124.6, 121.4, 115.1, 112.8, 60.7, 44.7, 21.5; Anal. calcd for $C_{30}H_{25}N_2O_3SBr$: C, 62.83; H, 4.39; N, 4.88%; Found: C, 62.81; H, 4.37; N, 4.89%.

***N*-(2-Methoxy-2-phenylethyl)-4-methylbenzenesulphonamide (3k) [5]:** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), methanol **2f** (1 mL). Yield: 125 mg, 82%; Pale yellow solid; mp 46 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8 Hz, 2H), 7.30-7.11 (m, 7H), 5.07 (s, 1H), 4.13-4.09 (m, 1H), 3.15-3.08 (m, 4H), 2.90-2.87 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.4, 137.0, 129.8, 128.8, 128.5, 127.2, 126.7, 82.1, 56.9, 49.4, 21.6.

***N*-(2-(4-Chlorophenyl)-2-methoxyethyl)-4-methylbenzenesulphonamide (3l):** The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine **1b** (0.50 mmol, 154 mg), methanol **2f** (1 mL). Yield: 134 mg, 79%; Colourless gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 4H), 7.17-7.15 (m, 2H), 5.01-4.99 (m, 1H), 4.22-4.19 (m, 1H), 3.23-3.18 (m, 4H), 2.97-2.91 (m, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.02, 136.96, 134.3, 129.9, 129.0, 128.1, 127.2, 81.5, 57.0, 49.3, 21.7; Anal. calcd for $C_{16}H_{18}ClNO_3S$: C, 56.55; H, 5.34; N, 4.12%; Found: C, 56.58; H, 5.38; N, 4.15%.

***N*-(2-Ethoxy-2-phenylethyl)-4-methylbenzenesulphonamide (3m) [5]:** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), ethanol **2g** (1 mL). Yield: 129 mg, 81%; Pale yellow solid; mp 49 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8 Hz, 2H), 7.30-7.11 (m, 7H), 5.03-5.01 (m, 1H), 4.23-4.20 (m, 1H), 3.29-3.08 (m, 3H), 2.90-2.84 (m, 1H),

2.33 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 139.1, 137.1, 129.8, 128.7, 128.3, 127.1, 126.6, 80.2, 64.5, 49.4, 21.6, 15.2.

***N*-(2-(4-Chlorophenyl)-2-ethoxyethyl)-4-methylbenzenesulphonamide (3n):** The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine **1b** (0.50 mmol, 154 mg), ethanol **2g** (1 mL). Yield: 138 mg, 78%; White solid; mp 56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, J = 8.4 Hz, 2H), 7.25-7.19 (m, 4H), 7.07 (d, J = 8.4 Hz, 2H), 4.98-4.96 (m, 1H), 4.23-4.20 (m, 1H), 3.28-3.07 (m, 3H), 2.88-2.81 (m, 1H), 2.34 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.7, 137.0, 134.1, 129.8, 128.9, 128.0, 127.1, 79.7, 64.7, 49.3, 21.6, 15.2; Anal. calcd for $C_{17}H_{20}ClNO_3S$: C, 57.70; H, 5.70; N, 3.96%; Found: C, 57.67; H, 5.73; N, 3.92%.

2-(4-Methylphenylsulfonamido)-1-phenylethyl acetate (3o): The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), acetic acid **2h** (1 mL). Yield: 133 mg, 80%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, J = 8 Hz, 2H), 7.23-7.13 (m, 7H), 5.63 (t, J = 6.4 Hz, 1H), 5.18 (s, 1H), 3.23 (t, J = 6.4 Hz, 2H), 2.34 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 143.7, 137.2, 137.0, 129.9, 128.8, 128.7, 127.1, 126.5, 74.3, 47.8, 21.6, 21.1; Anal. calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20%; Found: C, 61.27; H, 5.73; N, 4.21%.

1-(4-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethyl acetate (3p): The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine **1b** (0.50 mmol, 154 mg), acetic acid **2h** (1 mL). Yield: 151 mg, 82%; Yellowish green gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 8 Hz, 2H), 7.22-7.17 (m, 4H), 7.08 (d, J = 8.4 Hz, 2H), 5.61 (t, J = 6 Hz, 1H), 5.17 (s, 1H), 3.21 (t, J = 5.2 Hz, 2H), 2.35 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 143.8, 136.9, 135.7, 134.5, 129.9, 129.0, 128.0, 127.1, 73.6, 47.6, 21.6, 21.1; Anal. calcd for $C_{17}H_{18}ClNO_4S$: C, 55.51; H, 4.93; N, 3.81%; Found: C, 55.55; H, 4.90; N, 3.79%.

***N*-(2-(Diisopropylamino)-2-phenylethyl)-4-methylbenzenesulfonamide (3q):** The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), diisopropylamine **2i** (1 mL). Yield: 154 mg, 82%; Pale yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, J = 8 Hz, 2H), 7.16-7.05 (m, 7H), 4.00 (s, 1H), 2.81 (brs, 2H), 2.56-2.53 (m, 1H), 2.32-2.23 (m, 4H), 0.96 (d, J = 5.6 Hz, 6H), 0.82 (d, J = 5.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 136.9, 129.8, 129.2, 128.3, 127.6, 127.5, 127.3, 55.4, 51.4, 47.4, 22.7, 21.5, 18.9; Anal. calcd for $C_{21}H_{30}N_2O_2S$: C, 67.34; H, 8.07; N, 7.48%; Found: C, 67.33; H, 8.02; N, 7.49%.

***N*-(2-(4-Chlorophenyl)-2-(diisopropylamino)ethyl)-4-methylbenzenesulfonamide (3r):** The typical procedure was applied to 2-(4-chlorophenyl)-1-tosylaziridine **1b** (0.50 mmol, 154 mg), diisopropylamine **2i** (1 mL). Yield: 164 mg, 80%; Pale Yellow gummy mass; ^{1}H NMR ($CDCl_3$,

400 MHz): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.12-7.04 (m, 6H), 3.96 (s, 1H), 2.80 (brs, 2H), 2.54-2.47 (m, 1H), 2.31 (s, 3H), 2.25-2.15 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 6H), 0.83 (d, *J* = 4.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 136.8, 129.8, 129.3, 128.7, 128.5, 127.5, 127.3, 54.9, 51.3, 47.4, 22.7, 21.6, 19.0; Anal. calcd for $C_{21}H_{29}ClN_2O_2S$: C, 61.67; H, 7.15; N, 6.85%; Found: C, 61.69; H, 7.12; N, 6.81%.

4-Methyl-*N*-(2-phenyl-2-(1*H*-pyrrol-2-yl)ethyl)benzenesulfonamide (3s) [376]: The typical procedure was applied to 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), pyrrole **2j** (0.50 mmol, 35 µL). Yield: 137 mg, 81%; Deep brown gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.24-7.17 (m, 5H), 7.02-7.00 (m, 2H), 6.59-6.57 (m, 1H), 6.07-6.05 (m, 1H), 5.87 (s, 1H), 4.43 (s, 1H), 4.03 (t, *J* = 7.6 Hz, 1H), 3.46-3.32 (m, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 140.0, 136.8, 130.8, 129.9, 129.1, 128.1, 127.7, 127.3, 117.8, 108.6, 105.8, 47.6, 44.7, 21.7.

Typical procedure for the synthesis of melatonin derivative *N*-(2-(5-methoxy-1*H*-indol-3-yl)-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide (3t) including gram-scale synthesis: A mixture of phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone **1d** (1 mmol, 377 mg), 5-methoxy indole **2c** (1 mmol, 147 mg) and MBS (10 mol%, 20 mg) [for gram scale a mixture of phenyl(3-phenyl-1-tosylaziridine-2-yl)methanone **1d** (10 mmol, 3.77 g), 5-methoxy indole **2c** (10 mmol, 1.47 g) and MBS (10 mol%, 200 mg)] was taken in a sealed tube and the reaction mixture was stirred for 3 h at 85 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (20 mL; for gram scale 250 mL) and washed with brine solution (2x10 mL; for gram scale 2x50 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as red gummy mass (Yield: 420 mg, 80%; 3.88 g, 74% yield for gram scale synthesis) using ethyl acetate-petroleum ether (1:5) as eluent. Red gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (s, 1H), 8.05 (d, *J* = 2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.72 - 7.57 (m, 3H), 7.41(t, *J* = 8 Hz, 2H), 7.25-7.19 (m, 4H), 7.05-7.00 (m, 4H), 5.33 (d, *J* = 8.2 Hz, 1H), 4.64 (d, *J* = 2.8 Hz,1H), 3.46 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 153.8, 143.7, 137.3, 136.2, 134.4, 134.0, 131.3, 129.6, 129.5, 128.9, 128.3, 128.2, 127.6, 127.5, 127.4, 124.1, 114.9, 112.0, 111.9, 101.1, 60.5, 55.8, 45.1, 21.4; Anal. calcd for $C_{31}H_{28}N_2O_4S$: C, 70.97; H, 5.38; N, 5.34%; Found: C, 70.94; H, 5.37; N, 5.30%.

***N*-(2-(1*H*-indol-3-yl)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (3u):** The typical procedure was applied to 2,3-diphenyl-1-tosylaziridine **1e** (0.50 mmol, 175 mg), indole **2a** (0.50 mmol, 58 mg). Yield: 182 mg, 78%; White solid; mp 61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-

6.62 (m, 40H), 5.25 (d, *J* = 14Hz, 1H), 4.93 (d, *J* = 14 Hz, 1H), 4.78 (d, *J* = 6 Hz, 1H), 4.40 (d, *J* = 6 Hz, 1H), 2.24 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 142.9, 139.4, 138.7, 137.3, 136.2, 136.0, 129.6, 129.5 129.1, 129.0, 128.7, 128.5, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0 (2C), 125.8, 122.9, 122.8, 122.6, 122.1, 121.5, 119.8, 119.6, 119.5, 119.4, 119.1, 118.9, 118.4, 115.9, 111.4, 111.1, 110.9, 60.6, 56.3, 50.0, 39.0, 21.6, 21.5.

3.2. Ring opening of aziridines in presence of CuO nano particles

3.2.1. General procedure for the synthesis of compounds (3): A mixture of phenyl aziridine (**1**, 1 mmol) and nucleophile (2 mmol) was stirred in presence of CuO-nano (5-6 mg, 5 mol%) at 70 °C (oil bath) for 10 h in a seal tube as monitored by TLC for a complete reaction. After completion, the reaction mixture was cooled to room temperature and diluted with water (10 mL) and extracted with ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5% to 6%) as eluent.

***N*-(2-Ethoxy-2-phenylethyl)-4-methylbenzenesulfonamide (3n) [350]:** Pale Yellow Solid (255 mg, Yield: 80%), mp. 46-48 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.73-7.71 (m, 2H), 7.34-7.28 (m, 5H), 7.22-7.18 (m, 2H), 5.00-4.97 (m, 1H), 4.32-4.29 (m, 1H), 3.40-3.33 (m, 1H), 3.29-3.17 (m, 2H), 2.98-2.92 (m, 1H), 2.42 (s, 3H), 1.14 (t, *J* = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 143.6, 139.1, 137.1, 129.8, 128.7, 128.4, 127.2, 126.6, 80.3, 64.5, 49.5, 21.6, 15.3.

***N*-(2-Methoxy-2-phenylethyl)-4-methylbenzenesulfonamide (3l) [350]:** Pale Yellow Solid (229 mg, Yield: 75%), mp. 45-47 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.73-7.71 (m, 2H),7.35-7.28 (m, 5H), 7.21-7.19 (m, 2H), 5.00-4.97 (m, 1H), 4.21-4.18 (m, 1H), 3.23-3.19 (m, 1H), 3.17 (s, 3H), 2.98-2.92 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 143.6, 138.4, 137.1, 129.9, 128.8, 128.5, 127.2, 126.7, 82.1, 56.9, 49.4, 21.6.

4-Methyl-*N*-(1-phenyl-2-propoxyethyl)benzenesulfonamide (3u). White Solid (280 mg, Yield: 84%), mp. 47-50 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.74-7.71 (m, 2H), 7.34-7.28 (m, 5H), 7.21-7.19 (m, 2H), 5.00-4.97 (m, 1H), 4.30-4.26 (m, 1H), 3.28-3.11 (m, 3H), 3.00-2.93 (m, 1H), 2.42 (s, 3H), 1.56-1.50 (m, 2H), 0.87 (t, *J* = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 143.5, 139.1, 137.1, 129.8, 128.7, 128.4, 127.2, 126.7, 80.4, 70.8, 49.5, 23.0, 21.6, 10.7. HRMS (ESI, m/z) calcd for $C_{18}H_{23}NO_3S$ [M + Na^+] 356.1291, found 356.1294.

***N*-(2-Butoxy-1-phenylethyl)-4-methylbenzenesulfonamide (3v).** White Solid (333 mg, Yield: 96%), mp. 48-51 °C; ^{1}HNMR ($CDCl_3$, 400 MHz): *δ* 7.73-7.71 (m, 2H), 7.34-7.28 (m, 5H), 7.21-7.19 (m, 2H), 5.03-5.00 (m, 1H), 4.28-4.25 (m, 1H), 3.31-3.26 (m, 1H), 3.23-3.14 (m, 2H), 2.99-

2.93 (m, 1H), 2.42 (s, 3H), 1.53-1.45 (m, 2H), 1.34-1.26 (m, 2H), 0.87 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 143.5, 139.1, 137.1, 129.8, 128.7, 128.3, 127.2, 126.6, 80.4, 69.0, 49.5, 31.9, 21.6, 19.4, 14.0. HRMS (ESI, m/z) calcd for $C_{19}H_{25}NO_3S$ $[M + H]^+$ 348.1628; found 348.1645.

***N*-(2-(Allyloxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3w) [377].** White Solid (258 mg, Yield: 78%), mp. 54-58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 2H), 7.35-7.28 (m, 5H), 7.22-7.20 (m, 2H), 5.87-5.78 (m, 1H), 5.21-5.13 (m, 2H), 5.01-4.98 (m, 1H), 4.39-4.36 (m, 1H), 3.90-3.85 (m, 1H), 3.73-3.67 (m, 1H), 3.25-3.19 (m, 1H), 3.03-2.97 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.6, 137.1, 134.2, 129.8, 128.8, 128.5, 127.2, 126.8, 117.7, 79.8, 69.8, 49.4, 21.6.

***N*-(2-(But-2-en-1-yloxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3x).** White Solid (255 mg, Yield: 74%), mp. 58-60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 2H), 7.35-7.28 (m, 5H), 7.21-7.19 (m, 2H), 5.64-5.57 (m, 1H), 5.54-5.46 (m, 1H), 4.98-4.95 (m, 1H), 4.38-4.34 (m, 1H), 3.82-3.78 (m, 1H), 3.65-3.61 (m, 1H), 3.24-3.17 (m, 1H), 3.00-2.94 (m, 1H), 2.42 (s, 3H), 1.70-1.68 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 138.8, 137.1, 130.5, 129.8, 128.8, 128.5, 127.2, 127.0, 126.8, 79.5, 69.6, 49.4, 21.6, 17.9. Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05%; Found: C, 66.12; H, 6.79; N, 4.01%.

4-Methyl-*N*-(1-phenyl-2-(prop-2-yn-1-yloxy)ethyl)benzenesulfonamide (3y) [377]. White Gummy Mass (276 mg, Yield: 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.36-7.29 (m, 5H), 7.24-7.20 (m, 2H), 4.99-4.96 (m, 1H), 4.57-4.54 (m, 1H), 4.10-4.05 (m, 1H), 3.84-3.80 (m, 1H), 3.27-3.20 (m, 1H), 3.10-3.02 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.4, 137.1, 129.9, 128.9(2C), 127.2, 127.0, 79.5, 79.2, 75.1, 56.0, 49.1, 21.6.

***N*-(2-(2-Hydroxyethoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3z).** White Solid (289 mg, Yield: 86%), mp. 78-81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.30-7.23 (m, 5H), 7.20-7.17 (m, 2H), 6.36-6.33 (m, 1H), 4.34-4.31 (m, 1H), 3.70 (t, J = 8.8 Hz, 2H), 3.45-3.40 (m, 1H), 3.32-3.27 (m, 1H), 3.22-3.16 (m, 1H), 3.03-2.96 (m, 1H), 2.65 (s, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 138.7, 137.2, 129.8, 128.7, 128.4, 127.1, 126.6, 80.9, 70.3, 61.8, 49.6, 21.5. HRMS (ESI, m/z) calcd for $C_{17}H_{21}NO_4S$ $[M + H]^+$ 336.1264; found 336.1272.

***N*-(2-(2-Bromoethoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3a').** White Solid (294 mg, Yield: 74%), mp. 68-70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.74 (m, 2H), 7.33-7.30 (m, 5H), 7.23-7.20 (m, 2H), 5.17-5.15 (m, 1H), 4.35-4.32 (m, 1H), 3.68-3.63 (m, 1H), 3.51-3.46 (m, 1H), 3.40 (t, J = 11.6 Hz, 2H), 3.27-3.21 (m, 1H), 3.06-2.99 (m, 1H), 2.43 (s, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ 143.6, 138.1, 137.2, 129.9, 128.9, 128.7, 127.2, 126.7, 81.0, 68.8, 49.5, 31.0, 21.6. Anal. Calcd for $C_{17}H_{20}BrNO_3S$: C, 51.26; H, 5.06; N, 3.52%; Found: C, 51.21; H, 5.12; N, 3.59%.

4-Methyl-*N*-(1-phenyl-2-(*p*-tolyloxy)ethyl)benzenesulfonamide (3b'). Pale Yellow Gummy Mass (259 mg, Yield: 68%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 2H), 7.28-7.25 (m, 6H), 7.12-7.06 (m, 1H), 6.95-6.91 (m, 2H), 6.61-6.59 (m, 2H), 5.09-5.06 (m, 1H), 4.99-4.96 (m, 1H), 3.41-3.38 (m, 1H), 3.26-3.23 (m, 1H), 2.41 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.2, 142.7, 130.6, 129.5 129.0, 128.9, 128.0, 127.5, 126.2, 125.2, 115.6, 114.8, 77.8, 48.7, 20.6, 19.6. Anal. Calcd for $C_{22}H_{23}NO_3S$: C, 69.27; H, 6.08; N, 3.67%; Found: C, 69.35; H, 6.02; N, 3.76%.

***N*-(2-(4-Methoxyphenoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3c') [377].** White Solid (274 mg, Yield: 69%), mp. 95-98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.71 (m, 2H), 7.31-7.24 (m, 7H), 6.70-6.63 (m, 4H), 5.04-5.01 (m, 2H), 3.70 (s, 3H), 3.43-3.37 (m, 1H), 3.26-3.19 (m, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.4, 151.4, 143.7, 138.3, 137.2, 129.9, 128.9, 128.5, 127.2, 126.3, 117.1, 114.6, 79.6, 55.7, 49.6, 21.6.

***N*-(2-(2-Methoxyphenoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3d').** Pale Yellow Gummy Mass (266 mg, Yield: 67%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 2H), 7.35-7.29 (m, 5H), 7.23 (d, J = 8.4 Hz, 2H), 6.97-6.90 (m, 2H), 6.70-6.66 (m, 1H), 6.55-6.53 (m, 1H), 6.00-5.96 (m, 1H), 4.85-4.81 (m, 1H), 3.96 (s, 3H), 3.41-3.34 (m, 1H), 3.27-3.21 (m, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 137.7, 128.8, 127.8, 127.6, 126.1, 125.3, 122.5, 121.7, 120.0, 118.8, 118.0, 111.0, 108.5, 82.2, 54.9, 48.8, 20.6. Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52%; Found: C, 66.56; H, 5.75; N, 3.59%.

***N*-(2-(4-Bromophenoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3e').** Pale Brown Gummy Mass (294 mg, Yield: 66%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.71 (m, 2H), 7.31-7.28 (m, 5H), 7.25-7.22 (m, 4H), 6.60-6.57 (m, 2H), 5.18-5.15 (m, 1H), 5.07-5.04 (m, 1H), 3.45-3.38 (m, 1H), 3.28-3.22 (m, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 143.7, 137.5, 132.3, 130.0, 129.9, 129.1, 128.7, 127.1, 126.1, 117.7, 113.7, 79.1, 49.5, 21.6. Anal. Calcd for $C_{21}H_{20}BrNO_3S$: C, 56.51; H, 4.52; N, 3.14%; Found: C, 56.58; H, 4.59; N, 3.08%.

***N*-(2-(4-Iodophenoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3f').** White Solid (315 mg, Yield: 64%), mp. 74-78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 2H), 7.42-7.39 (m, 2H), 7.29-7.23 (m, 7H), 6.48-6.46 (m, 2H), 5.08-5.05 (m, 1H), 4.92-4.88 (m, 1H), 3.45-3.38 (m, 1H), 3.28-3.22 (m, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 143.8, 138.3, 137.5,

130.0, 129.9, 129.1(2C), 127.7, 127.1, 126.1, 118.3, 78.9, 52.7, 21.7. Anal. Calcd for $C_{21}H_{20}INO_3S$: C, 51.13; H, 4.09; N, 2.84%; Found: C, 51.07; H, 4.02; N, 2.77%.

***N*-(2-(2-Iodophenoxy)-1-phenylethyl)-4-methylbenzenesulfonamide (3g').** White Solid (310 mg, Yield: 63%), mp. 72-75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.34-7.31 (m, 6H), 7.29-7.24 (m, 5H), 4.92-4.88 (m, 1H), 4.79 (t, J = 13.6 Hz, 1H), 3.60-3.54 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 139.4, 138.3, 130.0, 129.3, 129.2, 129.1, 128.8, 127.8, 127.4, 127.2, 126.1, 123.4, 114.0, 80.3, 50.3, 21.7. Anal. Calcd for $C_{21}H_{20}INO_3S$: C, 51.13; H, 4.09; N, 2.84%; Found: C, 51.17; H, 4.03; N, 2.76%.

***N*-(2-(Butylthio)-1-phenylethyl)-4-methylbenzenesulfonamide (3m').** White Solid (298 mg, Yield: 82%), mp. 55-57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.33-7.27 (m, 4H), 7.21-7.17 (m, 3H), 4.88 (t, J = 12 Hz, 1H), 3.80 (t, J = 14.8 Hz, 1H), 3.34-3.30 (m, 2H), 2.45 (s, 3H), 2.32 (t, J = 14.8 Hz, 2H), 1.45-1.39 (m, 2H), 1.33-1.27 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 143.6, 139.4, 137.0, 129.8, 128.9, 127.9, 127.8, 127.2, 49.5, 47.7, 31.4, 30.9, 21.9, 21.6, 13.6. HRMS (ESI, m/z) calcd for $C_{19}H_{25}NO_2S_2$ $[M + Na]^+$ 386.1219; found 386.1227.

4-Methyl-*N*-(1-phenyl-2-(*p*-tolylthio)ethyl)benzenesulfonamide (3h'). White Solid (330 mg, Yield: 83%), mp. 82-85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56-7.53 (m, 2H), 7.18-7.15(m, 5H), 7.02-7.00 (m, 4H), 6.93 (d, J = 8 Hz, 2H), 4.77-4.75 (m, 1H), 3.98-3.95 (m, 1H), 3.28-3.24 (m, 2H), 2.34 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.5, 138.2, 137.0, 133.4, 129.9, 129.8, 129.2, 128.8, 128.0, 127.9, 127.2, 52.9, 47.0, 21.6, 21.2. Anal. Calcd for $C_{22}H_{23}NO_2S_2$: C, 66.47; H, 5.83; N, 3.52%; Found: C, 66.54; H, 5.88; N, 3.59%.

***N*-(2-((4-Methoxyphenyl)thio)-1-phenylethyl)-4-methylbenzenesulfonamide (3i') [378].** White Solid (335 mg, Yield: 81%), mp. 101-104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 2H), 7.42-7.37 (m, 4H), 7.34-7.31 (m, 1H), 7.27-7.24 (m, 2H), 7.19-7.16 (m, 2H), 6.89-6.86 (m, 2H), 4.92 (t, J = 12.4 Hz, 1H), 4.09 (t, J = 14.8 Hz, 1H), 3.92 (s, 3H), 3.50-3.47 (m, 2H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 143.6, 138.5, 136.2, 134.1, 129.9, 128.8, 128.0, 127.9, 127.2, 122.8, 114.6, 55.4, 53.5, 46.8, 21.6.

***N*-(2-((4-Chlorophenyl)thio)-1-phenylethyl)-4-methylbenzenesulfonamide (3j') [378].** White Solid (329 mg, Yield: 79%), mp. 104-106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.73 (m, 2H), 7.40-7.34 (m, 5H), 7.30-7.28 (m, 2H), 7.23-7.20 (m, 4H), 4.94 (t, J = 12.4 Hz, 1H), 4.22 (t, J =

14.8 Hz, 1H), 3.46-3.43 (m, 2H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 138.1, 136.9, 134.1, 131.7, 129.9, 129.2, 129.0, 128.3, 128.0, 127.3, 127.2, 53.0, 47.1, 21.6.

***N*-(2-((2-Fluorophenyl)thio)-1-phenylethyl)-4-methylbenzenesulfonamide (3k').** White Solid (341 mg, Yield: 85%), mp. 105-108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 2H), 7.30-7.26 (m, 6H), 7.22-7.20 (m, 1H), 7.15-7.13 (m, 2H), 7.07-6.99 (m, 2H), 4.89 (t, J = 12.8 Hz, 1H), 4.22 (t, J = 14.8 Hz, 1H), 3.43-3.39 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5 (d, $^1J_{C\text{-}F}$ = 245 Hz), 143.6, 137.9, 136.9, 135.6, 130.4 (d, $^4J_{C\text{-}F}$ = 7 Hz), 129.8, 128.9, 128.6, 128.2, 127.9, 127.2, 127.1, 126.8, 124.6 (d, $^3J_{C\text{-}F}$ = 3 Hz), 120.0, 119.8, 115.9 (d, $^2J_{C\text{-}F}$ = 22 Hz), 51.7, 47.2, 21.6. HRMS (ESI, m/z) calcd for $C_{21}H_{20}FNO_2S_2$ $[M + H]^+$ 402.0992; found 402.1016.

4-Methyl-*N*-(1-phenyl-2-(phenylthio)ethyl)benzenesulfonamide (3l') [378]. White Solid (333 mg, Yield: 87%), mp. 84-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55-7.53 (m, 2H), 7.16-7.11 (m, 10H), 7.04-7.02 (m, 2H), 4.82 (s, 1H), 4.05 (t, J = 14.8 Hz, 1H), 3.29-3.25 (m, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.3, 136.9 133.1, 132.6, 129.8, 129.0, 128.9, 128.1, 127.9, 127.8, 127.1, 52.5, 47.2, 21.6.

***N*-(2-(1*H*-Indol-3-yl)-1-phenylethyl)-4-methylbenzenesulfonamide (3a) [350].** Pale Brown Solid (296 mg, Yield: 76%), mp. 108-110 °C; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.67-7.65 (m, 2H), 7.35 (d, J = 1.2 Hz, 1H), 7.33-7.14 (m, 9H), 7.02-6.96 (m, 2H), 4.45 (t, J = 12.4 Hz, 1H), 4.32 (t, J = 14.8 Hz, 1H), 3.70-3.64 (m, 1H), 3.57-3.51 (m, 1H), 2.43 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 141.1, 136.9, 136.6, 129.9, 128.9, 128.1, 127.3, 127.2, 126.6, 122.5, 122.1, 119.8, 119.3, 115.7, 111.4, 47.5, 42.8, 21.7.

***N*-(2-(4-Chlorophenyl)-2-ethoxyethyl)-4-methylbenzenesulfonamide (3o).** White Solid (265 mg, Yield: 75%), mp. 55-57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.30-7.27 (m, 4H), 7.16-7.13 (m, 2H), 4.99-4.96 (m, 1H), 4.31-4.28 (m, 1H), 3.36-3.32 (m, 1H), 3.27-3.15 (m, 2H), 2.95-2.89 (m, 1H), 2.42 (s, 3H), 1.13 (t, J = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.7, 137.1 134.2, 129.9, 128.9, 128.0, 127.2, 79.7, 64.7, 49.3, 21.6, 15.3. Anal. Calcd for $C_{17}H_{20}ClNO_3S$: C, 57.70; H, 5.70; N, 3.96%; Found: C, 57.76; H, 5.77; N, 3.91%.

***N*-(2-(4-Chlorophenyl)-2-methoxyethyl)-4-methylbenzenesulfonamide (3m) [350].** Gummy mass (241 mg, Yield: 71%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.30-7.28 (m, 4H), 7.15-7.12 (m, 2H), 5.02 (s, 1H), 4.20-4.17 (m, 1H), 3.21-3.17 (m, 1H), 3.16 (s, 3H), 2.95-2.89 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.0, 136.9, 134.3, 129.9, 129.0, 128.1, 127.1, 81.5, 57.0, 49.3, 21.6.

***N*-(2-(Allyloxy)-1-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (3n').** White Solid (303 mg, Yield: 83%), mp. 63-65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.30-7.27 (m, 4H), 7.16-7.13 (m, 2H), 5.86-5.76 (m, 1H), 5.20-5.13 (m, 2H), 5.01-4.98 (m, 1H), 4.38-4.35 (m, 1H), 3.88-3.83 (m, 1H), 3.72-3.67 (m, 1H), 3.23-3.16 (m, 1H), 3.00-2.94 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.2, 137.0, 134.3, 134.0, 129.9, 129.0, 128.1, 127.1, 117.9, 79.1, 69.9, 49.3, 21.6. HRMS (ESI, m/z) calcd for $C_{18}H_{20}ClNO_3S$ $[M + Na]^+$ 388.0745; found 388.0785.

***N*-(2-(But-2-en-1-yloxy)-1-(4-chlorophenyl)ethyl)-4 methylbenzenesulfonamide (3o').** White Solid (296 mg, Yield: 78%), mp. 87-90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.68 (m, 2H), 7.29-7.27 (m, 4H), 7.15-7.13 (m, 2H), 5.64-5.44 (m, 2H), 5.02-4.99 (m, 1H), 4.36-4.33 (m, 1H), 3.80-3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.21-3.15 (m, 1H), 2.97-2.91 (m, 1H), 2.42 (s, 3H), 1.69-1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.3, 137.0, 134.2, 130.6, 129.8, 128.9, 128.1, 127.1, 126.8, 78.8, 69.7, 49.3, 21.6, 17.9. HRMS (ESI, m/z) calcd for $C_{19}H_{22}ClNO_3S$ $[M + H]^+$ 380.1082; found 380.1109.

***N*-(1-(4-Chlorophenyl)-2-(prop-2-yn-1-yloxy)ethyl)-4-methylbenzenesulfonamide (3p').** White Solid (305 mg, Yield: 84%), mp. 64-66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.69 (m, 2H), 7.31-7.28 (m, 4H), 7.17-7.15 (m, 2H), 4.98 (s, 1H), 4.58-4.54 (m, 1H), 4.09-4.05 (m, 1H), 3.84-3.79 (m, 1H), 3.25-3.18 (m, 1H), 3.05-2.99 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.0, 136.0, 134.7, 129.9, 129.1, 128.4, 127.2, 78.9, 78.8, 75.4, 56.2, 49.0, 21.6. HRMS (ESI, m/z) calcd for $C_{18}H_{18}ClNO_3S$ $[M + Na]^+$ 386.0588; found 386.0609.

***N*-(1-(4-Chlorophenyl)-2-(2-hydroxyethoxy)ethyl)-4-methylbenzenesulfonamide (3q'):** White Solid (292 mg, Yield: 79%), mp. 84-86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 2H), 7.21-7.18 (m, 4H), 7.09-7.07 (m, 2H), 6.18-6.15 (m, 1H), 4.29-4.26 (m, 1H), 3.66-3.63 (m, 2H), 3.38-3.35 (m, 1H), 3.28-3.23 (m, 1H), 3.15-3.09 (m, 1H), 2.94-2.88 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.2, 137.1, 134.2, 129.8, 128.9, 128.0, 127.1, 80.3, 70.5, 61.8, 49.4, 21.6. HRMS (ESI, m/z) calcd for $C_{17}H_{20}ClNO_4S$ $[M + Na]^+$ 392.0694; found 392.0696.

***N*-(1-(4-Bromophenyl)-2-butoxyethyl)-4-methylbenzenesulfonamide (3r').** White Solid (340 mg, Yield: 80%), mp. 88-90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.68 (m, 2H), 7.44-7.42 (m, 2H), 7.30-7.27 (m, 2H), 7.08-7.06 (m, 2H), 4.97 (d, J = 9.2 Hz, 1H), 4.26-4.23 (m, 1H), 3.27-3.14 (m, 3H), 2.95-2.88 (m, 1H), 2.42 (s, 3H), 1.52-1.44 (m, 2H), 1.33-1.26 (m, 2H), 0.86 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 138.2, 137.0, 131.8, 129.8, 128.3, 127.1, 122.2,

79.8, 69.1, 49.3, 31.8, 21.6, 19.4, 14.0. Anal. Calcd for $C_{19}H_{24}BrNO_3S$: C, 53.52; H, 5.67; N, 3.29%; Found: C, 53.59; H, 5.76; N, 3.37%.

***N*-(2-(1*H*-Indol-3-yl)cyclohexyl)-4-methylbenzenesulfonamide (3s') [376].** Brown Gummy Mass (210 mg, Yield: 57%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (s, 1H), 7.31-7.27 (m, 2H), 7.20-7.13 (m, 3H), 6.94-6.90 (m, 3H), 6.79 (d, J = 2.4 Hz, 1H), 4.38 (d, J = 3.6 Hz, 1H), 3.21-3.14 (m, 1H), 2.69-2.63 (m, 1H), 2.33 (s, 3H), 1.82-1.68 (m, 3H), 1.42-1.35 (m, 3H), 0.90-0.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 136.5, 133.9, 130.5, 129.2, 126.8, 122.2, 121.7, 119.6, 119.2, 116.7, 111.4, 57.3, 41.8, 34.8, 33.6, 26.2, 25.1, 21.6.

***N*-(2-Butoxy-3-oxo-1,3-diphenylpropyl)-4-methylbenzenesulfonamide (3t').** White Solid (271 mg, Yield: 60%), mp. 92-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.95 (m, 2H), 7.94-7.88 (m, 1H), 7.77-7.75 (m, 2H), 7.64-7.59 (m, 1H), 7.51-7.45 (m, 3H), 7.36-7.33 (m, 1H), 7.26-7.23 (m, 4H), 6.26 (d, J = 8 Hz, 1H), 5.88 (d, J = 8 Hz, 1H), 3.46-3.40 (m, 2H), 2.37 (s, 3H), 1.36-1.31 (m, 2H), 1.18-1.13 (m, 2H), 0.76 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.8, 143.8, 138.2, 135.1, 134.6, 133.2, 131.5, 129.8, 129.6, 129.3, 128.9, 128.2, 127.0, 82.0, 66.5, 46.2, 31.3, 21.6, 19.2, 13.8. Anal. Calcd for $C_{26}H_{29}NO_4S$: C, 69.15; H, 6.47; N, 3.10%; Found: C, 69.22; H, 6.58; N, 3.02%.

3.3. Ring opening of aziridines using formic acid

3.3.1. General procedure for the synthesis of compounds (6): A mixture of tosylaziridine **1** (0.50 mmol) and HCOOH (**5**, 0.5 mmol, 23 µL) was taken in a sealed tube. The reaction mixture was then stirred for 3 h at 100 °C. After completion (TLC) the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

2-((4-Methylphenyl)sulfonamido)-1-phenylethyl formate (6a): Yield: 138 mg, 86%; Cream-white solid; mp 75-77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.25-7.15 (m, 7H), 5.77-5.74 (m, 1H), 5.29-5.26 (m, 1H), 3.27-3.23 (m, 2H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 143.8, 136.9, 136.5, 129.9, 128.9, 128.8, 127.1, 126.5, 74.3, 47.7, 21.6. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{17}NNaO_4S$ 342.0776, Found 342.0779.

1-(4-Chlorophenyl)-2-((4-methylphenyl)sulfonamido)ethyl formate (6b): Yield: 151 mg, 85%; Cream-white solid; mp 80-82°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H), 7.62-7.60 (m, 2H), 7.20-7.15 (m, 4H), 7.10-7.08 (m, 2H), 5.75-5.72 (m, 1H), 5.47-5.44 (m, 1H), 3.22 (t, J = 6.4 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 143.8, 136.8, 135.0, 134.7, 129.9, 129.0, 128.0, 127.0, 73.5, 47.4, 21.6. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}ClNNaO_4S$ 376.0386, Found 376.0391.

1-(2-Chlorophenyl)-2-((4-methylphenyl)sulfonamido)ethyl formate (6c): Yield: 149 mg, 84%; Pale yellow gummy liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.25-7.12 (m, 6H), 6.12-6.10 (m, 1H), 5.46-5.44 (m, 1H), 3.40-3.33 (m, 1H), 3.23-3.16 (m, 1H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 143.7, 137.0, 134.2, 132.0, 129.84, 129.81, 129.78, 127.4, 127.3, 127.1, 71.1, 46.1, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}ClNNaO_4S$ 376.0386, Found 376.0384.

1-(4-Bromophenyl)-2-((4-methylphenyl)sulfonamido)ethyl formate (6d): Yield: 179 mg, 90%; Pale orange gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.69-7.67 (m, 2H), 7.44-7.40 (m, 2H), 7.29-7.26 (m, 2H), 7.13-7.10 (m, 2H), 5.81-5.78 (m, 1H), 5.33 (t, J = 6.4 Hz, 1H), 3.30 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 143.9, 136.8, 135.5, 132.0, 129.9, 128.3, 127.0, 123.0, 73.6, 47.4, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}BrNNaO_4S$ 419.9881, Found 419.9882.

1-(3-Fluorophenyl)-2-((4-methylphenyl)sulfonamido)ethyl formate (6e): Yield: 144 mg, 85%; Pale orange solid; mp 101-103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.23-7.18 (m, 3H), 6.97-6.84 (m, 3H), 5.76-5.73 (m, 1H), 5.29 (bs, 1H), 3.26-3.23 (m, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (d, $^1J_{C\text{-}F}$ = 245 Hz), 159.9, 143.9, 139.0, 138.9, 136.8, 130.5 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.9, 127.1, 122.2 (d, $^3J_{C\text{-}F}$ = 3 Hz), 116.0, 115.7, 113.6 (d, $^2J_{C\text{-}F}$ = 23 Hz), 73.5, 47.5, 21.6. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}FNNaO_4S$ 360.0682, Found 360.0685.

2-((4-Methylphenyl)sulfonamido)-1-(3-nitrophenyl)ethyl formate (6f): Yield: 146 mg, 80%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08-8.05 (m, 1H), 8.02-8.01 (m, 1H), 7.95 (s, 1H), 7.62-7.55 (m, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 5.87 (t, J = 6.0 Hz, 1H), 5.35-5.34 (m, 1H), 3.32 (t, J = 6.4 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 148.5, 144.1, 138.7, 136.8, 132.9, 130.0, 129.7, 127.0, 123.8, 121.6, 73.1, 47.4, 21.6. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}N_2NaO_6S$ 387.0627, Found 387.0619.

2-((4-Methylphenyl)sulfonamido)-1-(*p*-tolyl)ethyl formate (6g): Yield: 132 mg, 79%; Yellow gummy liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.73-7.70 (m, 2H), 7.31-7.26 (m, 2H),

7.13 (s, 4H), 5.80-5.77 (m, 1H), 5.01 (bs, 1H), 3.36-3.31 (m, 2H), 2.43 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 143.8, 139.0, 137.0, 133.4, 129.9, 129.6, 127.2, 126.6, 74.2, 47.6, 21.6, 21.3. HRMS (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{17}H_{19}KNO_4S$ 372.0672, Found 372.0674.

2-((4-Methylphenyl)sulfonamido)-1-(*m*-tolyl)ethyl formate (6h): Yield: 129 mg, 77%; Cream-white gummy liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.26-7.19 (m, 1H), 7.13-7.11 (m, 1H), 7.04-7.03 (m, 2H), 5.80-5.77 (m, 1H), 4.96 (t, *J* = 6.4 Hz, 1H), 3.37-3.33 (m, 2H), 2.43 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 143.8, 138.7, 137.1, 136.4, 129.9, 129.8, 128.9, 127.3, 127.2, 123.6, 74.3, 47.7, 21.6, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}NNaO_4S$ 356.0932, Found 356.0937.

1-(4-(Chloromethyl)phenyl)-2-((4-methylphenyl)sulfonamido)ethyl formate (6i): Yield: 153 mg, 83%; White solid; mp 76-78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.27-7.16 (m, 6H), 5.78-5.75 (m, 1H), 5.26-5.25 (m, 1H), 4.46 (s, 2H), 3.26-3.22 (m, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 143.8, 138.2, 136.9, 136.7, 129.9, 129.0, 127.1, 127.0, 73.9, 47.6, 45.6, 21.6. HRMS (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{17}H_{18}ClKNO_4S$ 406.0282, Found 406.0290.

2-((4-Methylphenyl)sulfonamido)-3-oxo-1,3-diphenylpropyl formate (6j): Yield: 140 mg, 66%; Pale yellow solid; mp 127-129°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H), 7.88-7.85 (m, 2H), 7.55-7.53 (m, 2H), 7.44-7.40 (m, 2H), 7.20-7.15 (m, 4H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.98-6.96 (m, 2H), 6.04 (d, *J* = 3.6 Hz, 1H), 5.55-5.53 (m, 1H), 5.48-5.45 (m, 1H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 160.6, 143.8, 136.7, 134.7, 134.1, 132.8, 129.9, 129.7, 129.3, 128.8, 128.4, 127.4, 127.1, 74.8, 60.2, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_5S$ 446.1038, Found 446.1039.

1-(4-Chlorophenyl)-2-((4-methylphenyl)sulfonamido)-3-oxo-3-phenylpropyl formate (6k): Yield: 137 mg, 60%; Pale orange solid; mp 134-136°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), 7.88-7.86 (m, 2H), 7.60-7.56 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.46-7.42 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.08-7.04 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.99 (d, *J* = 4.0 Hz, 1H), 5.58-5.56 (m, 1H), 5.45-5.42 (m, 1H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 160.4, 143.9, 136.6, 135.3, 134.9, 134.0, 129.9, 129.8, 129.4, 129.1, 128.9, 128.6, 127.1, 74.3, 60.0, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{23}H_{20}ClKNO_5S$ 496.0388, Found 496.0386.

1-(4-Fluorophenyl)-2-((4-methylphenyl)sulfonamido)-3-oxo-3-phenylpropyl formate (6l): Yield: 138 mg, 62%; Pale yellow solid; mp 143-145°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s,

1H), 7.88-7.86 (m, 2H), 7.60-7.56 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.46-7.42 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.99-6.96 (m, 2H), 6.87-6.83 (m, 2H), 6.02 (d, J = 4.0 Hz, 1H), 5.58-5.55 (m, 1H), 5.45-5.42 (m, 1H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 163.1 (d, $^{1}J_{C\text{-}F}$ = 247 Hz), 160.5, 143.9, 136.6, 134.9, 134.0, 129.9, 129.8, 129.41 (d, $^{4}J_{C\text{-}F}$ = 6 Hz), 129.36 (d, $^{3}J_{C\text{-}F}$ = 4 Hz), 129.1, 128.9, 127.1, 115.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 74.2, 60.1, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{23}H_{20}FKNO_5S$ 480.0683, Found 480.0696.

4-Hydroxy-3-((4-methylphenyl)sulfonamido)butan-2-yl formate (6m): Mixture of diastereomers [Syn(A):Anti(B) = 1:2]; Yield: 121 mg, 84%; Orange gummy liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 0.3H, 1A), 7.77-7.74 (m, 2.9H, 2A+2B), 7.70 (s, 0.8H, 1B), 7.29-7.26 (m, 2.9H, 2A+2B), 5.72 (d, J = 8.4 Hz, 0.4H, 1A), 5.66 (d, J = 8.4 Hz, 0.8H, 1B), 4.99-4.96 (m, 0.4H, 1A), 4.26-4.22 (m, 0.8H, 1B), 4.10-4.06 (m, 0.9H, 1B), 3.85-3.82 (m, 1H, 2A), 3.60-3.57 (m, 0.4H, 1A), 3.44-3.35 (m, 2H, 2B), 2.82 (bs, 1H, 1B), 2.40 (s, 4.5H, 3A+3B), 2.20 (bs, 0.5H, 1A), 1.22 (d, J = 6.4 Hz, 1.4H, 3A), 1.17 (d, J = 6.8 Hz, 2.7H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9, 143.8, 137.6, 129.8, 127.1, 68.9, 61.3, 57.8, 21.6, 18.1. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{17}NNaO_5S$ 310.0725, Found 310.0715.

2-((4-Methylphenyl)sulfonamido)cyclohexyl formate (6n): Yield: 122 mg, 82%; White solid; mp 111-113°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, J = 8.4 Hz, 2H), 7.52 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 5.33 (d, J = 8.4 Hz, 1H), 4.63-4.59 (m, 1H), 3.18-3.15 (m, 1H), 2.33 (s, 3H), 1.88-1.84 (m, 2H), 1.61-1.54 (m, 2H), 1.29-1.19 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8, 143.1, 138.5, 129.5, 127.0, 74.1, 56.3, 32.7, 30.8, 24.1, 23.4, 21.5. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{19}NNaO_4S$ 320.0932, Found 320.0927.

Typical procedure for the synthesis of *N*-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide: We have taken a mixture of 2-((4-methylphenyl)sulfinamido)-1-phenylethyl formate **3a** (0.5 mmol, 160 mg), AgOTf (0.7 mmol, 180 mg) and H_2O (0.5 mL) in a sealed tube and stirred at 60 °C for 3 h. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/EtOAc (10 mL) and washed with brine solution (1 x 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent the obtained crude product was subjected to column chromatography using petroleum ether/EtOAc (3:1) as eluent to obtain the analytically pure product as a white solid (Yield: 121 mg, 83%). White solid; mp 103-105°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, J = 8.0 Hz, 2H), 7.23-7.15 (m, 7H), 5.44 (bs, 1H), 4.71-4.68 (m, 1H), 3.14-3.08 (m, 1H), 2.95-2.90 (m, 1H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 140.9, 136.7, 129.9, 128.7, 128.2, 127.2, 126.0, 72.8, 50.3, 21.6.

3.4. Syntheses and ring opening of aziridines in presence of $NH_2OH{\cdot}HCl$ and $NaIO_4$

Typical procedure for the synthesis of 2-phenyl-1-tosylaziridine (1a): A mixture of styrene **1a** (1 mmol, 104 mg), $NaIO_4$ (1 mmol, 213 mg) and Chloramine-T (1 mmol, 228 mg) in 2.5 mL of DCM was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg) was added by portion for 5 min. The reaction mixture was stirred for 1 h at room temperature. After 1 h K_2CO_3 (1 mmol, 138 mg) and 2.5 mL acetonitrile was added to it and stirred for another 12 h. After completion (TLC), the reaction mixture was diluted with a 1 : 1 mixture of water/ethyl acetate (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3 x 5 mL) followed by brine solution (1 x 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether (1:15) as eluent to obtain the analytically pure product as a yellowish-white solid (Yield: 208 mg, 76%). Yellowish-white solid; mp 86-88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.25-7.11 (m, 7H), 3.70-3.67 (m, 1H), 2.89 (d, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 2.30 (d, *J* = 4.4 Hz, 1H).

2-(4-Chlorophenyl)-1-tosylaziridine (1b) [21]: Yield: 215 mg, 70%; White solid; mp 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 3.74-3.71 (m, 1H), 2.96 (d, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 2.33 (d, *J* = 4.4 Hz, 1H).

2-(4-Bromophenyl)-1-tosylaziridine (1c) [21]: Yield: 254 mg, 72%; White solid; mp 123-125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 3.63-3.60 (m, 1H), 2.87 (d, *J* = 7.2 Hz, 1H), 2.32 (s, 3H), 2.24 d, *J* = 4.4 Hz, 1H).

2-(2-Chlorophenyl)-1-tosylaziridine (1d): Yield: 219 mg, 71%; Gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.35-7.16 (m, 6H), 4.06-4.03 (m, 1H), 3.02 (d, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 2.29 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 134.5, 133. 7, 133.0, 129.8, 129.3, 129.1, 128.0, 127.4, 127.0, 38.8, 35.5, 21.6; Anal. calcd for $C_{15}H_{14}ClNO_2S$: C, 58.53; H, 4.58; N, 4.55%; Found: C, 58.56; H, 4.62; N, 4.59%.

2-(3-Fluorophenyl)-1-tosylaziridine (1e): Yield: 216 mg, 74%; Yellowish-white solid; mp 82-84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.27-7.15 (m, 3H), 6.96-6.81 (m, 3H), 3.69-3.66 (m, 1H), 2.90 (d, *J* = 7.2 Hz, 1H), 2.36 (s, 3H), 2.27 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (d, $^1J_{C\text{-}F}$ = 245 Hz), 145.0, 137.9, 137.8, 134.9, 130.3 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.9, 128.1, 122.6 (d, $^3J_{C\text{-}F}$ = 3 Hz), 115.5, 115.3, 113.5(d, $^2J_{C\text{-}F}$ = 22 Hz), 40.4, 36.3, 21.8; Anal. calcd for $C_{15}H_{14}FNO_2S$: C, 61.84; H, 4.84; N, 4.81%; Found: C, 61.80; H, 4.89; N, 4.87%.

Phenyl(3-phenyl-1-tosylaziridin-2-yl)methanone (1f) [19]: Yield: 272 mg, 72%; White solid; mp 139-141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.64-7.60 (m, 1H), 7.50-7.46 (m, 2H), 7.34 (s, 5H), 7.26-7.21 (m, 2H), 4.52 (d, *J* = 4.0 Hz, 1H), 4.29 (d, *J* = 4.0 Hz, 1H), 2.39 (s, 3H).

(3-(4-Chlorophenyl)-1-tosylaziridin-2-yl)(phenyl) methanone (1g) [19]: Yield: 284 mg, 69%; White solid; mp 148-150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.64-7.60 (m, 1H), 7.50-7.46 (m, 3H), 7.30-7.22 (m, 5H), 4.48 (d, *J* = 4.0 Hz, 1H), 4.24 (d, *J* = 4.0 Hz, 1H), 2.40 (s, 3H).

(3-(4-Fluorophenyl)-1-tosylaziridin-2-yl)(phenyl) methanone (1h): Yield: 261 mg, 66%; Grey solid; mp 105-107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.02 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.64-7.60 (m, 1H), 7.50-7.46 (m, 2H), 7.35-7.31 (m, 2H), 7.26-7.22 (m, 2H), 7.04-7.00 (m, 2H), 4.49 (d, *J* = 4.0 Hz, 1H), 4.28 (d, *J* = 4.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.3, 163.1 (d, $^1J_{C\text{-}F}$ = 246 Hz), 144.6, 136.6, 136.0, 134.3, 129.7, 129.6 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 9 Hz), 128.8, 128.7, 127.8, 115.8 (d, $^2J_{C\text{-}F}$ = 21 Hz), 50.1, 46.9, 21.7; Anal. calcd for $C_{22}H_{18}FNO_3S$: C, 66.82; H, 4.59; N, 3.54%; Found: C, 66.86; H, 4.65; N, 3.49%.

(4-Chlorophenyl)(3-phenyl-1-tosylaziridin-2-yl)methanone (1i): Yield: 280 mg, 68%; White solid; mp 144-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.35-7.33 (m, 4H), 7.26-7.23 (m, 2H), 7.17 (s, 1H), 4.53 (d, *J* = 4.4 Hz, 1H), 4.18 (d, *J* = 4.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.6, 144.9, 141.1, 136.7, 134.7, 133.2, 130.7, 129.9, 129.5, 129.3, 129.0, 128.0, 127.7, 50.6, 47.5, 21.9; Anal. calcd for $C_{22}H_{18}ClNO_3S$: C, 64.15; H, 4.40; N, 3.40%; Found: C, 64.19; H, 4.43; N, 3.35%.

(4-Chlorophenyl)(3-(4-fluorophenyl)-1-tosylaziridin-2-yl)methanone (1j): Yield: 279 mg, 65%; Yellowish-white solid; mp 143-145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.46-7.44 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.23 (m, 2H), 7.04-7.00 (m, 2H), 4.49 (d, *J* = 4.0 Hz, 1H), 4.17 (d, *J* = 4.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.2, 163.1 (d, $^1J_{C\text{-}F}$ = 247 Hz), 144.8, 140.9, 136.4, 134.4, 130.5, 129.7, 129.5 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.3, 128.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 127.8, 115.8 (d, $^2J_{C\text{-}F}$ = 22 Hz), 50.2, 46.6, 21.7; Anal. calcd for $C_{22}H_{17}ClFNO_3S$: C, 61.47; H, 3.99; N, 3.26%; Found: C, 61.54; H, 4.04; N, 3.21%.

Typical procedure for the synthesis of *N*-(2-iodo-2-phenylethyl)-4-methylbenzenesulfonamide (8a): A mixture of 2-Phenyl-1-tosylaziridine **1a** (1 mmol, 273 mg), $NaIO_4$ (1 mmol, 213 mg) in 5 mL of acetonitrile was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg) was added by portion for 5 min. The reaction mixture was stirred for 9 h at room temperature. After completion (TLC), the reaction

mixture was diluted with a 1 : 1 mixture of water/ethyl acetate (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3 x 5 mL) followed by brine solution (1 x 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether (1:15) as eluent to obtain the analytically pure product as a yellowish-white solid (Yield: 360 mg, 90%). Yellowish-white solid; mp 79-81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.30-7.17 (m, 7H), 4.98 (bs, 1H), 4.80-4.77 (m, 1H), 3.42-3.29 (m, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 137.9, 137.0, 130.0, 129.2, 129.0, 127.3, 127.1, 61.7, 50.4, 21.6; Anal. calcd for $C_{15}H_{16}INO_2S$: C, 44.90; H, 4.02; N, 3.49%; Found: C, 44.86; H, 4.03; N, 3.38%.

***N*-(2-(4-Chlorophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (8b):** Yield: 357 mg, 82%; Grey solid; mp 100-102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.62 (m, 2H), 7.25-7.14 (m, 6H), 4.87 (bs, 1H), 4.81-4.78 (m, 1H), 3.37-3.32 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 137.0, 136.5, 135.1, 130.0, 129.2, 128.8, 127.1, 60.9, 50.4, 21.7; Anal. calcd for $C_{15}H_{15}ClINO_2S$: C, 41.35; H, 3.47; N, 3.21%; Found: C, 41.28; H, 3.40; N, 3.25%.

***N*-(2-(4-Bromophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (8c):** Yield: 408 mg, 85%; White solid; mp 109-111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.29-5.26 (m, 1H), 4.83-4.80 (m, 1H), 3.39-3.35 (m, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 137.2, 137.0, 132.2, 130.1, 129.2, 127.2, 123.2, 60.9, 50.4, 21.8; Anal. Calcd For $C_{15}H_{15}BrINO_2S$: C, 37.52; H, 3.15; N, 2.92%; Found: C, 37.48; H, 3.09; N, 2.87%.

***N*-(2-(2-Chlorophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (8d):** Yield: 340 mg, 78%; Yellowish-white solid; mp 84-86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68-7.66 (m, 2H), 7.43-7.40 (m, 1H), 7.28-7.18 (m, 5H), 5.31-5.28 (m, 1H), 4.94-4.90 (m, 1H), 3.55-3.49 (m, 1H), 3.33-3.26 (m, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 137.1, 135.3, 132.9, 130.2, 130.00, 129.98, 128.8, 127.6, 127.2, 58.1, 49.3, 21.7; Anal. calcd for $C_{15}H_{15}ClINO_2S$: C, 41.35; H, 3.47; N, 3.21%; Found: C, 41.41; H, 3.41; N, 3.26%.

***N*-(2-(3-Fluorophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (8e):** Yield: 336 mg, 80%; Yellowish-white solid; mp 74-76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 2H), 7.33-7.26 (m, 3H), 7.08-6.98 (m, 3H), 4.97 (bs, 1H), 4.88-4.84 (m, 1H), 3.46-3.39 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (d, $^1J_{C-F}$ = 245 Hz), 144.1, 140.4, 140.3, 137.0, 130.6 (d, $^4J_{C-F}$ = 9 Hz), 130.0, 127.1, 123.1 (d, $^3J_{C-F}$ = 3 Hz), 116.3, 116.1, 114.5 (d, $^2J_{C-F}$ = 24 Hz), 60.9, 50.4, 21.7; Anal. calcd for $C_{15}H_{15}FINO_2S$: C, 42.97; H, 3.61; N, 3.34%; Found: C, 42.92; H, 3.54; N, 3.29%.

***N*-(3-Iodo-1-oxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide (8f):** Mixture of diastereomers [Syn(A):Anti(B) = 1:4]; Yield: 421 mg, 83%; Yellowish-white solid; mp 114-116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.63 (m, 2.5H, 2A+2B), 7.51-7.47 (m, 1.2H, 1A+1B), 7.45-7.42 (m, 2H, 2B), 7.38-7.36 (m, 0.5H, 2A), 7.34-7.30 (m, 2.4H, 2A+2B), 7.20-7.17 (m, 2.4H, 2A+2B), 7.16-7.13 (m, 3.7H, 3A+3B), 7.00-6.94 (m, 2.5H, 2A+2B), 5.81-5.79 (m, 0.2H, 1A), 5.60-5.57 (m, 1H, 1B), 5.35-5.31 (m, 1H, 1B), 5.24-5.21 (m, 0.2H, 1A), 5.10 (d, *J* = 4.0 Hz, 0.2H, 1A), 5.05 (d, *J* = 6.4 Hz, 1H, 1B), 2.20 (s, 0.7H, 3A), 2.18 (s, 3H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2**,** 143.7, 136.8, 136.6, 136.1, 135.3, 134.3, 129.6, 129.1, 129.0, 128.8, 128.6, 128.0, 127.2, 62.7, 61.8, 21.5; Anal. calcd for $C_{22}H_{20}INO_3S$: C, 52.29; H, 3.99; N, 2.77%; Found: C, 52.35; H, 4.06; N, 2.82%.

***N*-(3-(4-Chlorophenyl)-3-iodo-1-oxo-1-phenylpropan-2-yl)-4-methylbenzenesulfonamide (8g):** Mixture of diastereomers [Syn(A):Anti(B) = 1:5]; Yield: 442 mg, 82%; Grey solid; mp 130-132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.77 (m, 2.4H, 2A+2B), 7.62-7.59 (m, 1.2H, 1A+1B), 7.51-7.42 (m, 4.8H, 4A+4B), 7.30 (d, *J* = 8.4 Hz, 0.4H, 2A), 7.20-7.13 (m, 4.5H, 2A+4B), 7.09 (d, *J* = 8.0 Hz, 0.4H, 2A), 7.04 (d, *J* = 8.0 Hz, 2H, 2B), 5.91 (d, *J* = 9.2 Hz, 0.2H, 1A), 5.69 (d, *J* = 9.6 Hz, 1H, 1B), 5.39-5.34 (m, 1H, 1B), 5.28-5.25 (m, 0.2H, 1A), 5.16 (d, *J* = 3.2 Hz, 0.2H, 1A), 5.04 (d, *J* = 7.2 Hz, 1H, 1B), 2.32 (s, 0.6H, 3A), 2.29 (s, 3H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7**,** 144.1, 136.9, 135.4, 135.3, 135.1, 134.6, 134.4, 129.8, 129.7, 129.4, 129.1, 128.9, 128.8, 127.3, 62.5, 61.3, 21.8; Anal. Calcd for $C_{22}H_{19}ClINO_3S$: C, 48.95; H, 3.55; N, 2.59%; Found: C, 48.98; H, 3.52; N, 2.65%.

***N*-(3-(4-Fluorophenyl)-3-iodo-1-oxo-1-phenylpropan-2-yl)-4 methylbenzenesulfonamide (8h):** Mixture of diastereomers [Syn(A):Anti(B) = 1:3]; Yield: 387 mg, 74%; Gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.74 (m, 2.7H, 2A+2B), 7.60-7.57 (m, 1.3H, 1A+1B), 7.55-7.53 (m, 0.6H, 2A), 7.49-7.47 (m, 2.3H, 1A+2B), 7.45-7.40 (m, 2.3H, 1A+2B), 7.38-7.34 (m, 0.6H, 2A), 7.23-7.19 (m, 2H, 2B), 7.07 (d, *J* = 8.0 Hz, 0.6H, 2A), 7.01 (d, *J* = 8.0 Hz, 2H, 2B), 6.94-6.86 (m, 2.6H, 2A+2B), 5.99-5.97 (m, 0.3H, 1A), 5.83-5.81 (m, 1H, 1B), 5.40-5.36 (m, 1H, 1B), 5.29-5.26 (m, 0.3H, 1A), 5.17 (d, *J* = 4.0 Hz, 0.3H, 1A), 5.09 (d, *J* = 7.2 Hz, 1H, 1B), 2.28 (s, 0.9H, 3A), 2.26 (s, 3H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 163.0 (d, $^1J_{C\text{-}F}$ = 246 Hz), 143.8, 136.8, 135.3, 134.3, 132.5, 132.2, 129.9 (d, $^4J_{C\text{-}F}$ = 9 Hz), 129.6, 129.1, 128.9 (d, $^3J_{C\text{-}F}$ = 7 Hz), 127.1, 115.5 (d, $^2J_{C\text{-}F}$ = 21 Hz), 62.3, 61.2, 21.4; Anal. Calcd for $C_{22}H_{19}FINO_3S$: C, 50.49; H, 3.66; N, 2.68%; Found: C, 50.43; H, 3.69; N, 2.62%.

***N*-(1-(4-Chlorophenyl)-3-iodo-1-oxo-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (8i):** Mixture of diastereomers [Syn(A):Anti(B) = 1:3]; Yield: 416 mg, 77%; Gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.63 (m, 2.6H, 2A+2B), 7.54 (d, *J* = 8.4 Hz, 0.6H, 2A), 7.46 (d,

J = 8.4 Hz, 2H, 2B), 7.43-7.32 (m, 4H, 3A+3B), 7.26-7.24 (m, 5.2H, 4A+4B), 7.07 (d, *J* = 8.0 Hz, 0.6H, 2A), 7.02 (d, *J* = 8.0 Hz, 2H, 2B), 5.88 (d, *J* = 9.2 Hz, 0.3H, 1A), 5.74 (d, *J* = 9.6 Hz, 1H, 1B), 5.35-5.29 (m, 1H, 1B), 5.27-5.23 (m, 0.3H, 1A), 5.12 (d, *J* = 4.8 Hz, 0.3H, 1A), 5.09 (d, *J* = 7.2 Hz, 1H,1B), 2.29 (s,0.9H, 3A), 2.28 (s, 3H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.8**,** 144.0, 141.0, 136.9, 136.4, 133.5, 130.3, 129.8, 129.4, 129.3, 128.9, 128.2, 127.3, 62.8, 61.7, 21.7; Anal. Calcd for $C_{22}H_{19}ClINO_3S$: C, 48.95; H, 3.55; N, 2.59%; Found: C, 48.98; H, 3.59; N, 2.63%.

***N*-(1-(4-Chlorophenyl)-3-(4-fluorophenyl)-3-iodo-1-oxopropan-2-yl)-4-methylbenzenesulfonamide (8j):** Mixture of diastereomers [Syn(A):Anti(B) = 1:3]; Yield: 435 mg, 78%; Gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 8.4 Hz, 2H, 2B), 7.68 (d, *J* = 8.4 Hz, 0.6H, 2A), 7.53 (d, *J* = 8.0 Hz, 0.6H, 2A), 7.44-7.39 (m, 4.6H, 2A+4B), 7.34-7.31 (m, 0.6H, 2A), 7.26-7.20 (m, 2H, 2B), 7.09 (d, *J* = 8.0 Hz, 0.6H, 2A), 7.03 (d, *J* = 8.0 Hz, 2H, 2B), 6.93-6.87 (m, 2.6H, 2A+2B), 5.91 (d, *J* = 9.6 Hz, 0.3H, 1A), 5.78 (d, *J* = 9.6 Hz, 1H, 1B), 5.31-5.27 (m, 1H, 1B), 5.24-5.20 (m, 0.3H, 1A), 5.13 (d, *J* = 4.4 Hz,0.3H,1A), 5.02 (d, *J* = 7.6 Hz, 1H, 1B), 2.30 (s, 0.9H, 3A), 2.29 (s, 3H, 3B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 163.0 (d, $^1J_{C\text{-}F}$ = 247 Hz), 143.9, 141.0, 136.7, 133.8, 132.7, 132.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 130.3, 129.9 (d, $^3J_{C\text{-}F}$ = 8 Hz), 129.6, 127.1, 115.6 (d, $^2J_{C\text{-}F}$ = 22 Hz), 62.2, 60.9, 21.5; Anal. Calcd for $C_{22}H_{18}ClFINO_3S$: C, 47.37; H, 3.25; N, 2.51%; Found: C, 47.41; H, 3.32; N, 2.55%.

3.5. Differential addition of nucleophiles to aziridines and aldehydes under similar reaction conditions by using allylzinc halide

Experimental procedure for synthesis of compound (10a): A mixture of aziridine **1a** (1 mmol), allylic bromide **9a** (3 mmol), Zn dust (1 mmol) and $Cu(OAc)_2$ (10 mol%) was taken in a sealed tube. 2 mL of THF added to the mixture and the resulting mixture was stirred at 60 °C for 6 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and diluted with water (10-15 mL) and extracted with suitable amount of ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum and the resulting residue was purified by column chromatography on silica gel using hexane and ethyl acetate as eluent to afford the desired product **3a**. The identity and purity of the product were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

***N*-(2-Bromo-2-phenylethyl)-4-methylbenzenesulfonamide (10a):** 297 mg, Yield: 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.71-7.69 (m, 2H), 7.33-7.23 (m, 7H), 4.96 (t, *J* = 13.2 Hz, 1H), 4.88 (t, *J* = 14.8 Hz, 2H), 3.62-3.47 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 144.0, 138.3, 137.1, 130.0, 129.3, 129.1, 127.7, 127.2, 52.7, 50.2, 21.7. Anal. Calcd. for $C_{15}H_{16}BrNO_2S$: C, 50.86; H, 4.55; N, 3.95%; Found: C, 50.80; H, 4.47; N, 3.90%.

***N*-(2-Bromo-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (10b)**: 333 mg, Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.61 (m, 2H), 7.24-7.18 (m, 4H), 7.15-7.13 (m, 2H), 4.96 (t, J = 12.8 Hz, 1H), 4.82 (t, J = 14.4 Hz, 1H), 3.52-3.43 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 136.9(2C), 135.0, 130.0, 129.3, 129.2, 127.1, 51.5, 50.1, 21.7. Anal. Calcd. for $C_{15}H_{15}BrClNO_2S$: C, 46.35; H, 3.89; N, 3.60%; Found: C, 46.41; H, 3.81; N, 3.52%.

***N*-(2-Bromo-2-(2-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (10c):** 306 mg, Yield: 79%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.74 (m, 2H), 7.47-7.45 (m, 1H), 7.36-7.32 (m, 3H), 7.27-7.24 (m, 2H), 5.41-5.37 (m, 1H), 4.99 (t, J = 13.6 Hz, 1H), 3.66-3.59 (m, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 137.1, 135.7, 133.3, 130.3, 130.2, 130.0, 129.1, 127.7, 127.2, 49.1, 48.3, 21.7. Anal. Calcd. for $C_{15}H_{15}BrClNO_2S$: C, 46.35; H, 3.89; N, 3.60%; Found: C, 46.44; H, 3.80; N, 3.53%.

***N*-(2-Bromo-2-(4-bromophenyl)ethyl)-4-methylbenzenesulfonamide (10d):** 355 mg, Yield: 82%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.68 (m, 2H), 7.45-7.42 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.17-7.14 (m, 2H), 4.95 (t, J = 12.8 Hz, 1H), 4.88 (t, J = 14.8 Hz, 1H), 3.59-3.50 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 137.4, 136.9, 132.2, 130.0, 129.4, 127.1, 123.3, 51.6, 50.1, 21.7. Anal. Calcd. for $C_{15}H_{15}Br_2NO_2S$: C, 41.59; H, 3.49; N, 3.23%; Found: C, 41.50; H, 3.42; N, 3.29%.

***N*-(2-Bromo-2-(3-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (10e):** 297 mg, Yield: 80%; mp 63-65 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 2H), 7.32-7.27 (m, 3H), 7.08-7.05 (m, 1H), 7.02-6.96 (m, 2H), 5.00 (t, J = 13.2 Hz, 1H), 4.88 (t, J = 15.2 Hz, 1H), 3.56-3.49 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8 (d, $^{1}J_{C\text{-}F}$ = 246 Hz), 144.1, 140.7(2C), 136.9, 130.7 (d, $^{4}J_{C\text{-}F}$ = 8 Hz), 130.0, 127.1, 123.5 (d, $^{3}J_{C\text{-}F}$ = 3 Hz), 116.4, 116.2, 114.9 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 51.4, 50.1, 21.7. Anal. Calcd. for $C_{15}H_{15}BrFNO_2S$: C, 48.40; H, 4.06; N, 3.76%; Found: C, 48.30; H, 4.14; N, 3.86%.

***N*-(2-Bromocyclohexyl)-4-methylbenzenesulfonamide (10f):** 242 mg, Yield: 73%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.31 (d, J = 8 Hz, 2H), 4.83 (d, J = 1.2 Hz, 1H), 3.87-3.81 (m, 1H), 3.19-3.12 (m, 1H), 2.43 (s, 3H), 2.33-2.26 (m, 2H), 1.81-1.65 (m, 3H), 1.32-1.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.1, 129.7, 127.5, 59.0, 55.3, 36.3, 33.2, 25.7, 23.7, 21.7. Anal. Calcd. for $C_{13}H_{18}BrNO_2S$: C, 46.99; H, 5.46; N, 4.22%; Found: C, 46.91; H, 5.35; N, 4.29%.

***N*-(2,3-Dibromopropyl)-4-methylbenzenesulfonamide (10g):** Yellowish gummy mass, 259 mg, Yield: 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.75 (m, 2H), 7.33 (d, J = 8.4 Hz, 2H), 5.07 (s, 1H), 4.21-4.16 (m, 1H), 3.79-3.76 (m, 1H), 3.66-3.61 (m, 1H), 3.60-3.54 (m, 1H), 3.40-3.33 (m,

1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 136.7, 130.1, 127.2, 50.1, 47.3, 32.8, 21.7. Anal. Calcd. for $C_{11}H_{15}Br_2NO_2S$: C, 34.31; H, 3.93; N, 3.64%; Found: : C, 34.23; H, 3.84; N, 3.54%.

***N*-(2-Chloro-2-phenylethyl)-4-methylbenzenesulfonamide (10h):** 244 mg, Yield: 79%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.35-7.27(m, 7H), 4.89-4.85 (m, 2H), 3.51-3.38 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 137.9, 137.1, 130.0, 129.2, 129.1, 127.3, 127.2, 61.8, 50.5, 21.7. Anal. Calcd. for $C_{15}H_{16}ClNO_2S$: C, 58.15; H, 5.21; N, 4.52%; Found: C, 58.09; H, 5.28; N, 4.64%.

***N*-(2-Chloro-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (10i):** 275 mg, Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.32-7.29 (m, 4H), 7.24-7.21 (m, 2H), 4.94 (s, 1H), 4.88-4.85 (m, 1H), 3.48-3.35 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 136.9, 136.4, 135.1, 130.0, 129.2, 128.7, 127.1, 60.9, 50.4, 21.7. Anal. Calcd. for $C_{15}H_{15}Cl_2NO_2S$: C, 52.34; H, 4.39; N, 4.07%; Found: C, 52.25; H, 4.48; N, 4.01%.

***N*-(2-Chloro-2-(2-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (10j):** 258 mg, Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.74 (m, 2H), 7.50-7.48 (m, 1H), 7.35-7.29 (m, 3H), 7.28-7.24 (m, 2H), 5.39-5.36 (m, 1H), 5.20-5.16 (m, 1H), 3.62-3.55 (m, 1H), 3.40-3.33 (m, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 137.0, 135.2, 132.9, 130.1, 129.9 (2C), 128.8, 127.6, 127.2, 58.0, 49.2, 21.6. Anal. Calcd. for $C_{15}H_{15}Cl_2NO_2S$: C, 52.34; H, 4.39; N, 4.07%; Found: C, 52.25; H, 4.30; N, 4.17%.

***N*-(2-(4-Bromophenyl)-2-chloroethyl)-4-methylbenzenesulfonamide (10k):** 298 mg, Yield: 77%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.68 (m, 2H), 7.45-7.43 (m, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.17-7.15 (m, 2H), 5.07 (t, J = 13.2 Hz, 1H), 4.87-4.83 (m, 1H), 3.47-3.35 (m, 2H), 2.44 (s, 3H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 144.0, 137.0, 136.9, 132.1, 130.0, 129.0, 127.1, 123.2, 60.9, 50.3, 21.7. Anal. Calcd. for $C_{15}H_{15}BrClNO_2S$: C, 46.35; H, 3.89; N, 3.60%; Found: C, 46.25; H, 3.80; N, 3.67%.

***N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfonamide (10l):** 203 mg, Yield: 71%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 2H), 7.28 (d, J = 8 Hz, 2H), 5.32 (d, J = 4.4 Hz, 1H), 3.74-3.68 (m, 1H), 3.14-3.07 (m, 1H), 2.41 (s, 3H), 2.17-2.12 (m, 2H), 1.68-1.58 (m, 3H), 1.29-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 137.4, 129.7, 127.3, 62.1, 58.7, 34.9, 32.5, 24.3, 23.4, 21.6. Anal. Calcd. for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; N, 4.87%; Found: C, 54.17; H, 6.41; N, 4.78%.

***N*-(2-Iodo-2-phenylethyl)-4-methylbenzenesulfonamide (10m):** 344 mg, Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.28-7.24 (m, 5H), 5.01 (t, J = 15.6 Hz, 1H), 4.90 (t, J = 12.4 Hz, 1H), 3.72-3.65 (m, 1H), 3.54-3.49 (m, 1H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 140.0, 137.1, 130.0, 129.2, 128.8, 127.7, 127.1, 51.4, 30.0, 21.7. Anal. Calcd. for $C_{15}H_{16}INO_2S$: C, 44.90; H, 4.02; N, 3.49%; Found: C, 44.81; H, 4.11; N, 3.56%.

***N*-(2-(4-Chlorophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (10n):** 378 mg, Yield: 87%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.68 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.25-7.18 (m, 4H), 5.00 (t, J = 15.6 Hz, 1H), 4.81 (t, J = 13.2 Hz, 1H), 3.70-3.63 (m, 1H), 3.52-3.45 (m, 1H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 138.7, 137.0, 134.6, 130.0, 129.4, 129.1, 127.1, 51.4, 28.7, 21.7. Anal. Calcd. for $C_{15}H_{15}ClINO_2S$: C, 41.35; H, 3.47; N, 3.21%; Found: C, 41.43; H, 3.54; N, 3.14%.

***N*-(2-(2-Chlorophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (10o):** 356 mg, Yield: 82%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.69 (m, 2H), 7.39-7.37 (m, 1H), 7.29-7.25 (m, 3H), 7.20-7.14 (m, 2H), 5.42 (t, J = 15.2 Hz, 1H), 5.14 (t, J = 13.2 Hz, 1H), 3.74-3.67 (m, 1H), 3.64-3.57 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 137.4, 137.0, 133.0, 130.4, 130.0, 129.7, 128.5, 127.8, 127.1, 50.0, 24.9, 21.7. Anal. Calcd. for $C_{15}H_{15}ClINO_2S$: C, 41.35; H, 3.47; N, 3.21%; Found: C, 41.44; H, 3.40; N, 3.32%.

***N*-(2-(4-Bromophenyl)-2-iodoethyl)-4-methylbenzenesulfonamide (10p):** 403 mg, Yield: 84%; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.14-7.12 (m, 2H), 5.00-4.95 (m, 2H), 3.68-3.61 (m, 1H), 3.52-3.45 (m, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 144.0, 139.2, 137.0, 132.3, 130.0, 129.4, 127.1, 122.6, 51.3, 28.6, 21.7. Anal. Calcd. for $C_{15}H_{15}BrINO_2S$: C, 37.52; H, 3.15; N, 2.92%; Found: C, 37.59; H, 3.22; N, 2.85%.

***N*-(2-Iodocyclohexyl)-4-methylbenzenesulfonamide (10q):** 288 mg, Yield: 76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.29 (d, J = 8 Hz, 2H), 5.36 (d, J = 6.4 Hz, 1H), 4.02-3.96 (m, 1H), 3.31-3.23 (m, 1H), 2.40 (s, 3H), 2.34-2.30 (m, 1H), 2.15-2.11 (m, 1H), 1.98-1.87 (m, 1H), 1.69-1.64 (m, 1H), 1.52-1.46 (m, 1H), 1.35-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 137.5, 129.7, 127.4, 59.2, 37.9, 35.1, 32.9, 26.6, 23.6, 21.6. Anal. Calcd. for $C_{13}H_{18}INO_2S$: C, 41.17; H, 4.78; N, 3.69%; Found: C, 41.29; H, 4.65; N, 3.60%.

1-Phenylbut-3-en-1-ol (13a): 130 mg, Yield: 88%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (d, J = 4 Hz, 4H), 7.28-7.24 (m, 1H), 5.82-5.75 (m, 1H), 5.16-5.10 (m, 2H), 4.72-4.68 (m, 1H), 2.51-2.47

(m, 2H), 2.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 134.6, 128.5, 127.6, 125.9, 118.4, 73.4, 43.9. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16%; Found: C, 81.12; H, 8.23%.

1-(*p*-Tolyl)but-3-en-1-ol (13b): 137 mg, Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14-7.12 (m, 2H), 7.04 (d, J = 8 Hz, 2H), 5.74-5.64 (m, 1H), 5.06-5.00 (m, 2H), 4.58-4.55 (m, 1H), 2.41-2.37 (m, 2H), 2.44 (s, 3H), 2.18-2.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.0, 137.2, 134.7, 129.1, 125.9, 118.1, 73.3, 43.8, 21.2. Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70%; Found: C, 81.53; H, 8.83%.

1-(4-Methoxyphenyl)but-3-en-1-ol (13c): 153 mg, Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.16 (m, 2H), 6.80-6.77 (m, 2H), 5.75-5.65 (m, 1H), 5.07-5.01 (m, 2H), 4.59-4.55 (m, 1H), 3.70 (s, 3H), 2.42-2.38 (m, 2H), 2.14-2.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 136.2, 134.7, 127.2, 118.2, 113.8, 73.1, 55.3, 43.8. Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%; Found: C, 74.04; H, 7.84%.

1-(4-Fluorophenyl)but-3-en-1-ol (13d): 136 mg, Yield: 82%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.22 (m, 2H), 6.97-6.92 (m, 2H), 5.75-5.64 (m, 1H), 5.09-5.04 (m, 2H), 4.65-4.62 (m, 1H), 2.70 (s, 1H), 2.42-2.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3 (d, $^1J_{C\text{-}F}$ = 244 Hz), 139.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 134.3, 127.6 (d, $^4J_{C\text{-}F}$ = 8 Hz), 118.7, 115.3 (d, $^2J_{C\text{-}F}$ = 21 Hz), 72.8, 44.0. Anal. Calcd. for $C_{10}H_{11}FO$: C, 72.27; H, 6.67%; Found: C, 72.37; H, 6.78%.

1-(4-Chlorophenyl)but-3-en-1-ol (13e): 154 mg, Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.22 (m, 4H), 5.78-5.68 (m, 1H), 5.13-5.09 (m, 2H), 4.67-4.64 (m, 1H), 2.45-2.40 (m, 2H), 2.21-2.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 134.1, 133.3, 128.6, 127.3, 118.9, 72.7, 43.9. Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07%; Found: C, 65.69; H, 6.02%.

2-Phenylpent-4-en-2-ol (13f): 139 mg, Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.33 (m, 2H), 7.26-7.22 (m, 2H), 7.15-7.11 (m, 1H), 5.59-5.48 (m, 1H), 5.05-4.99 (m, 2H), 2.60-2.55 (m, 1H), 2.43-2.38 (m, 1H), 2.17 (s, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.7, 133.8, 128.2, 126.6, 124.8, 119.3, 73.7, 48.5, 29.8. Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70%; Found: C, 81.37; H, 8.61%.

2-(*p*-Tolyl)pent-4-en-2-ol (13g): 146 mg, Yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.22 (m, 2H), 7.05 (d, J = 8 Hz, 2H), 5.59-5.48 (m, 1H), 5.04-4.99 (m, 2H), 2.59-2.54 (m, 1H), 2.42-2.36 (m, 1H), 2.24 (s, 3H), 2.12 (s, 1H),1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 136.1, 133.9, 128.9, 124.8, 119.2, 73.6, 48.5, 29.9, 21.0. Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15%; Found: C, 81.70; H, 9.25%.

2-(4-Chlorophenyl)pent-4-en-2-ol (13h): 164 mg, Yield: 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.26 (m, 2H), 7.22-7.19 (m, 2H), 5.57-5.68 (m, 1H), 5.04-5.00 (m, 2H), 2.56-2.51 (m, 1H), 2.41-2.35 (m, 1H), 2.18 (s, 1H), 1.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.3, 133.3, 132.4, 128.3, 126.4, 119.7, 73.5, 48.5, 29.9. Anal. Calcd. for $C_{11}H_{13}ClO$: C, 67.18; H, 6.66%; Found: C, 67.11; H, 6.56%.

2-Bromo-2-phenylethan-1-ol (15a): 154 mg, Yield: 77%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.31 (m, 5H), 5.07-5.04 (m, 1H), 4.09-4.04 (m, 1H), 3.97-3.93 (m, 1H), 2.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 129.1, 129.0, 128.0, 67.6, 57.0. Anal. Calcd. for C_8H_9BrO: C, 47.79; H, 4.51%; Found: C, 47.88; H, 4.43%.

2-Chloro-2-phenylethan-1-ol (15b): 107 mg, Yield: 69%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.35 (m, 5H), 5.01-4.98 (m, 1H), 3.95-3.91 (m, 2H), 2.23-2.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 129.0, 128.9, 127.6, 68.0, 65.0. Anal. Calcd. for C_8H_9ClO: C, 61.36; H, 5.79%; Found: C, 61.28; H, 5.70%.

2-Iodo-2-phenylethan-1-ol (15c): 198 mg, Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.35 (m, 2H), 7.28-7.21 (m, 3H), 5.12 (t, J = 14.4 Hz, 1H), 4.04-3.99 (m, 1H), 3.84-3.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.1, 129.1, 128.7, 128.0, 68.7, 35.8. Anal. Calcd. for C_8H_9IO: C, 38.74; H, 3.66%; Found: C, 38.67; H, 3.59%.

3.6. Synthesis of *β*-(nitrooxy)-substituted amines by regioselective ring opening of aziridines

General procedure for the synthesis of *β*-(nitrooxy)-substituted amine derivatives (11):

Respective aziridine (**1**, 1 mmol) was taken in a preheated sealed tube in presence of $Zn(NO_3)_2{\cdot}6H_2O$ (1 equiv) was stirred at 80 °C under neat condition for 1-6 h. After completion of the reaction (TLC) the mixture was cooled to room temperature and quenched by adding water (2 mL) and extracted with ethyl acetate (5 mL x 2). The organic layer was collected and dried over anhydrous Na_2SO_4. The crude residue was obtained after evaporating the solvent in vacuum and was purified by column chromatography on silica gel (60–120 mesh) using a mixture petroleum ether and ethyl acetate as an eluting solvent to afford the pure product.

2-(4-Methylphenylsulfonamido)-1-phenylethyl nitrate (11a) [379]. Yellow solid (302 mg, 90%), mp: 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.37-7.36 (m, 3H), 7.32-7.26 (m, 4H), 5.83-5.80 (m, 1H), 5.13 (s, 1H), 3.38-3.32 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 136.8, 134.8, 130.1, 129.8, 129.2, 127.1, 126.6, 83.6, 46.0, 21.7.

2-(4-Methylphenylsulfonamido)-1-(*p*-tolyl)ethyl nitrate (11b) [379]. Pale yellow gummy mass, (304 mg, 87%); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.73 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.16 (s, 4H), 5.79-5.75 (m, 1H), 4.97 (t, J = 6.4 Hz, 1H), 3.37-3.20 (m, 2H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 139.9, 136.9, 131.7, 130.0, 129.9, 127.1, 126.6, 83.6, 45.9, 21.7, 21.3.

2-(4-Methylphenylsulfonamido)-1-(*m*-tolyl)ethyl nitrate (11c). White Solid, (322 mg, 92%), mp: 89-91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.30-7.27 (m, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.11-7.09 (m, 2H), 5.84-5.80 (m, 1H), 5.24 (s, 1H), 3.45-3.33 (m, 2H), 2.46 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 139.0, 136.9, 134.7, 130.5, 130.0, 129.0, 127.2, 127.1, 123.6, 83.7, 46.0, 21.6, 21.4. Anal. Calcd For $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; N, 8.00%; Found: C, 54.78; H, 5.12; N, 8.05%.

1-(4-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (11d). Light yellow gummy mass (289 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, J = 8.0 Hz, 2H), 7.35-7.30 (m, 4H), 7.23-7.21 (m, 2H), 5.81-5.78 (m, 1H), 4.90 (s, 1H), 3.37-3.30 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.3, 136.8, 135.9, 133.3, 130.1, 129.5, 128.0, 127.1, 82.9, 45.9, 21.7. Anal. Calcd For $C_{15}H_{15}ClN_2O_5S$: C, 48.59; H, 4.08; N, 7.55%; Found: C, 48.51; H, 4.01; N, 7.46%.

1-(2-Chlorophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (11e) [380]. Pale yellow oil (322 mg, 87%) ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, J = 8.4 Hz, 2H), 7.38-7.36 (m, 1H), 7.32-7.27 (m, 5H), 6.23-6.20 (m, 1H), 5.27-5.23 (m, 1H), 3.57-3.50 (m, 1H), 3.31-3.23 (m, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 137.0, 132.9, 132.5, 130.5, 130.2, 130.0, 127.7, 127.1, 126.7, 79.9, 44.7, 21.6.

1-(3-Fluorophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (11f). Colourless oil (290 mg, 82%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 8.0 Hz, 2H), 7.37-7.30 (m, 3H), 7.09-6.95 (m, 3H), 5.82-5.79 (m, 1H), 5.21 (s, 1H), 3.38-3.28 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (d, $^{1}J_{C\text{-}F}$ = 246 Hz), 144.3, 137.3 (2C), 136.7, 131.0 (d, $^{4}J_{C\text{-}F}$ = 8 Hz), 130.1, 127.1, 122.3 (d, $^{3}J_{C\text{-}F}$ = 3 Hz), 116.8, 116.6, 113.6 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 82.7, 45.9, 21.7. Anal. Calcd For $C_{15}H_{15}FN_2O_5S$: C, 50.84; H, 4.27; N, 7.91%; Found: C, 50.92; H, 4.20; N, 7.98%.

1-(4-Bromophenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (11g). Pale yellow oil (348 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, J = 8.0 Hz, 2H), 7.49-7.47 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 5.80-5.77 (m, 1H), 5.16 (s, 1H), 3.36-3.30 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 136.7, 133.8, 132.4, 130.1, 128.3, 127.0, 123.9,

82.9, 45.8, 21.7. Anal. Calcd For $C_{15}H_{15}BrN_2O_5S$: C, 43.39; H, 3.64; N, 6.75%; Found: C, 43.29; H, 3.70; N, 6.68%.

2-(4-Methylphenylsulfonamido)-1-(3-nitrophenyl)ethyl nitrate (11h). White gummy mass (324 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22-8.19 (m, 1H), 8.13-8.12 (m, 1H), 7.72-7.66 (m, 3H), 7.57 (t, J = 8.0 Hz ,1H), 7.30 (d, J = 8.0 Hz , 2H), 5.95-5.92 (m, 1H), 5.37 (t, J = 6.4 Hz, 1H), 3.43-3.38 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.6, 144.4, 137.1, 136.6, 132.8, 130.4, 130.1, 127.0, 124.6, 121.7, 82.1, 45.8, 21.6. Anal. Calcd For $C_{15}H_{15}N_3O_7S$: C, 47.24; H, 3.96; N, 11.02%; Found: C, 47.15; H, 3.82; N, 10.94%.

1-(4-(Chloromethyl)phenyl)-2-(4-methylphenylsulfonamido)ethyl nitrate (11i). Light yellow gummy mass (338 mg, 88%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 8.0 Hz, 2H), 7.40-7.38 (m, 2H), 7.32-7.27 (m, 4H), 5.85-5.81 (m, 1H), 5.23-5.20 (m, 1H), 4.55 (s, 2H), 3.36-3.31 (m, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 139.1, 136.7, 135.0, 130.1, 129.3, 127.1, 127.0, 83.2, 45.9, 45.5, 21.6. Anal. Calcd For C16H17ClN2O5S: C, 49.94; H, 4.45; N, 7.28%; Found: C, 49.84; H, 4.36; N, 7.37%.

2-(4-Methylphenylsulfonamido)cyclohexyl nitrate (11j) [382]. Colourless solid (282 mg, 90%), mp: 116-117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.37 (s, 1H), 4.81-4.75 (m, 1H), 3.29-3.21 (m, 1H), 2.42 (s, 3H), 2.04-1.98 (m, 2H), 1.70-1.61 (m, 2H), 1.42-1.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.6, 129.8, 127.0, 82.9, 54.0, 32.4, 29.0, 23.4, 23.1, 21.6.

2-(4-Methylphenylsulfonamido)-3-oxo-1,3-diphenylpropyl nitrate (11k). White gummy mass (317 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.78 (m, 2H), 7.67-7.63 (m, 3H), 7.59-7.57 (m, 1H), 7.51-7.47 (m, 2H), 7.25-7.24 (m, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.03-7.00 (m, 2H), 6.06-6.03 (m, 1H), 5.62 (d, J = 8.4 Hz, 1H), 5.57-5.54 (m, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 144.0, 134.8, 129.9, 129.8, 129.3 (2C), 128.9, 128.8, 128.6, 127.7, 127.3, 127.2, 83.1, 59.2, 21.6. Anal. Calcd For $C_{22}H_{20}N_2O_6S$: C, 59.99; H, 4.58; N, 6.36%; Found: C, 59.90; H, 4.47; N, 6.30%.

1-(4-Fluorophenyl)-2-(4-methylphenylsulfonamido)-3-oxo-3-phenylpropyl nitrate (11l). Yellow gummy mass (343 mg, 75%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.80 (m, 2H), 7.70-7.61 (m, 3H), 7.52-7.48 (m, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05-7.01 (m, 2H), 6.95-6.90 (m, 2H), 6.03 (d, J = 4.8 Hz, 1H), 5.73 (d, J = 8.8 Hz, 1H), 5.54-5.51 (m, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.0, 163.5 (d, $^1J_{C\text{-}F}$ = 248 Hz), 144.1, 136.7, 135.0, 134.2, 129.8 (d, $^3J_{C\text{-}F}$ = 4Hz), 129.4 (d, $^4J_{C\text{-}F}$ = 9 Hz), 128.8, 128.6, 128.5, 127.1, 115.9 (d, $^2J_{C\text{-}F}$ = 22 Hz), 82.5, 58.9,

21.6. Anal. Calcd For $C_{22}H_{19}FN_2O_6S$: C, 57.64; H, 4.18; N, 6.11%; Found: C, 57.54; H, 4.06; N, 6.03%.

4-Hydroxy-3-(4-methylphenylsulfonamido)butan-2-yl nitrate (11m). Brown gummy mass (234 mg, 77%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.22 (d, J = 9.2 Hz, 1H), 5.15-5.08 (m, 1H), 4.48-4.38 (m, 2H), 3.83-3.79 (m, 1H), 2.44 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 136.7, 130.2, 127.1, 78.9, 69.8, 53.4, 21.7, 15.3. Anal. Calcd For $C_{11}H_{16}N_2O_6S$: C, 43.42; H, 5.30; N, 9.21%; Found: C, 43.31; H, 5.22; N, 9.26%.

4-Bromo-3-(4-methylphenylsulfonamido)butan-2-yl nitrate (11n). Light yellow oil (308 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.31-5.25 (m, 2H), 4.14-4.10 (m, 1H), 3.42-3.28 (m, 2H), 2.43 (s, 3H), 1.46 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.3, 136.5, 130.1, 127.1, 78.8, 52.4, 45.9, 21.7, 16.0. Anal. Calcd For $C_{11}H_{15}BrN_2O_5S$: C, 35.98; H, 4.12; N, 7.63%; Found: C, 35.87; H, 4.04; N, 7.56%.

Typical procedure for the synthesis of *N*-(2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (11o) [382].

A mixture of 11j (0.25 mmol), Zn dust (6 equiv) and NH_4Cl (10 equiv) in acetic acid (2 mL) were taken in a dry sealed tube and heated at 80 ˚C for 1 h. After that the reaction mixture was neutralized by the saturated solution of $NaHCO_3$. Then it was extracted with dichloromethane (5 mL) and the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the crude product was subjected to column chromatography to obtain the pure product.

***N*-(2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (11o) [382].** White solid (50.50 mg, 75%), mp: 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.96 (d, J = 6.8 Hz, 1H), 3.31-3.26 (m, 1H), 2.89-2.81 (m, 1H), 2.66 (s,1H), 2.43 (s, 3H), 2.03-1.99 (m, 1H), 1.74-1.58 (m, 3H), 1.25-1.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 137.5, 129.9, 127.3, 73.5, 59.8, 33.5, 32.0, 24.8, 24.0, 21.7.

3.7. A domino approach for the synthesis of *α,β*-epoxyketones from carbonyl compounds

General procedure for the synthesis of compounds (18):

A mixture of acetophenone (**16a**, 1 mmol) and the corresponding aldehyde (1 mmol) was taken in a sealed tube. Then *tert*-butyl hydrogen peroxide (TBHP, 180 mg, 2 equiv., 5.0-6.0 M in decane), cesium carbonate (Cs_2CO_3, 325 mg, 1 equiv.) are added to the reaction mixture. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (TLC), the

reaction mixture was diluted with ethylacetate (10 mL) and water (10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4% to 5%) as eluent to get the analytically pure product.

Typical procedure for the synthesis of phenyl(3-phenyloxiran-2-yl)methanone (18a) on gram scale: A mixture of acetophenone (**16a**, 10 mmol) and benzaldehyde (**17a**, 10 mmol) was taken in a seal tube. Then *tert*-butyl hydrogen peroxide (TBHP, 2 equiv.), Cesium carbonate (Cs_2CO_3, 1 equiv.) are added to the reaction mixture. The reaction mixture was stirred at room temperature for 3 h (TLC). After completion of the reaction, the reaction mixture was diluted with ethylacetate (30 mL) and water (30 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4% to 5%) as eluent to get the analytically pure product as white solid (**18a**, 2.01 g, 90%).

Phenyl(3-phenyloxiran-2-yl)methanone (18a) [57]: White solid (215 mg, 96%), mp: 90-91 °C (lit.[57] mp: 89-91 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (m, 2H), 7.64-7.59 (m, 1H), 7.50-7.46 (m, 2H), 7.40-7.36 (m, 5H), 4.31 (d, J = 1.6 Hz, 1H), 4.07 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 193.1, 135.5(2C), 134.1, 129.1, 128.9, 128.8, 128.4, 125.8, 61.0, 59.4.

Phenyl(3-(*p*-tolyl)oxiran-2-yl)methanone (18b) [52]: Pale yellow oil(224 mg, 94%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.80 (m, 2H), 7.31-7.25 (m, 5H), 7.18-7.16 (m, 2H), 4.18 (d, J = 2.0 Hz, 1H), 3.96 (d, J = 2.0 Hz, 1H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.7, 145.2, 135.8, 133.2, 129.7, 129.1, 128.9, 128.6, 125.9, 61.0, 59.4, 21.9.

(3-(4-Methoxyphenyl)oxiran-2-yl)(phenyl)methanone (18c) [57]: White solid (218 mg, 86%), mp: 76-78 °C (lit.[57] mp: 77-78 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.46 (m, 2H), 7.30-7.28 (m, 2H), 6.93-6.91 (m, 2H), 4.30 (d, J = 2.0 Hz, 1H), 4.02 (d, J = 1.6 Hz, 1H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 193.3, 160.4, 135.6, 134.0, 128.9, 128.4, 127.4, 127.3, 114.3, 61.1, 59.5, 55.4.

(3-(2-Methoxyphenyl)oxiran-2-yl)(phenyl)methanone (18d) [51]: White powder (223 mg, 88%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.47 (m, 2H), 7.33-7.29 (m, 2H), 6.99 (t, J = 6.8 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.39 (d, J = 2.0 Hz, 1H), 4.19 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 193.7, 158.2, 135.6, 133.9, 129.8, 128.8, 128.4, 125.5, 124.2, 120.8, 110.4, 60.5, 55.8, 55.4.

(3-(4-Fluorophenyl)oxiran-2-yl)(phenyl)methanone (18e) [52]: Pale yellow oil(220 mg, 91%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.46 (m, 2H), 7.36-7.32 (m, 2H), 7.10-7.05 (m, 2H), 4.26 (d, J = 2.0 Hz, 1H), 4.06 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.9, 164.5, 162.0, 135.5, 134.1, 131.4, 131.3, 129.0, 128.4, 127.7, 127.6, 116.0, 115.8, 61.0, 58.8.

(3-(2-Fluorophenyl)oxiran-2-yl)(phenyl)methanone (18f) [52]: Pale yellow oil(210 mg, 87%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.20-7.16 (m, 1H), 7.11-7.06 (m, 1H), 4.33 (d, J = 1.6 Hz, 1H), 4.30 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.9, 162.8, 160.3, 135.4, 134.1, 130.5, 130.4, 128.9, 128.8, 128.4, 128.1, 126.5, 126.4, 124.7, 124.7, 124.6, 123.1, 123.0, 115.7, 115.5, 60.0, 54.2(2C).

(3-(4-Chlorophenyl)oxiran-2-yl)(phenyl)methanone (18g) [57]: White solid (233 mg, 90%), mp: 110-112 °C (lit.[57] mp: 110 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 2H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 2H), 7.38-7.35 (m, 2H), 7.32-7.28 (m, 2H), 4.25 (d, J = 2.0 Hz, 1H), 4.05 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.8, 135.4, 135.0, 134.2, 134.1, 129.1, 129.0, 128.4, 127.2, 61.0, 58.8.

(3-(2-Chlorophenyl)oxiran-2-yl)(phenyl)methanone (18h) [52]: Pale yellow oil (241 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.33-7.31 (m, 2H), 4.41 (d, J = 1.6 Hz, 1H), 4.17 (d, J = 2.0 Hz, 1H), ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.9, 135.5, 134.2, 133.9, 133.4, 129.9, 129.5, 129.0, 128.5, 127.4, 126.3, 60.2, 57.3, 57.2.

(3-(2,6-Dichlorophenyl)oxiran-2-yl)(phenyl)methanone (18i) [46]: White solid (270 mg, 92%), mp: 101-102 °C (lit.[46] mp: 99-100 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19-8.16 (m, 2H), 7.68-7.64 (m, 1H), 7.56-7.53 (m, 2H), 7.36-7.34 (m, 2H), 7.28-7.24 (m, 1H), 4.53 (d, J = 2.0 Hz, 1H), 4.29 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 193.5, 135.8, 134.2, 131.6, 130.4, 129.0, 128.8, 128.6, 57.4, 57.3.

(3-(4-Bromophenyl)oxiran-2-yl)(phenyl)methanone (18j) [52]: Pale yellow oil(270 mg, 89%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 7.41-7.36 (m, 5H), 4.22 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.7, 138.3, 135.3, 134.7, 129.7, 129.2, 128.9, 125.9, 102.4, 61.1, 59.5.

(3-(3-Nitrophenyl)oxiran-2-yl)(phenyl)methanone (18k) [46]: (226 mg, 84%), mp: 120-122 °C (lit.[46] mp: 118-119 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.21 (m, 2H), 8.02-7.99 (m, 2H),

7.73-7.71 (m, 1H), 7.66-7.58 (m, 2H), 7.52-7.48 (m, 2H), 4.32 (d, J = 2.0 Hz, 1H), 4.21 (d, J = 1.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.3, 148.7, 138.0, 135.3, 134.4, 131.9, 130.0, 129.1, 128.5, 124.0, 120.9, 60.8, 58.1.

(3-(4-Nitrophenyl)oxiran-2-yl)(phenyl)methanone (18l) [46]: Yellow crystals (229 mg, 85%), mp: 126-127 °C (lit.[46] mp: 124 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27-8.23 (m, 2H), 8.01-7.99 (m, 2H), 7.66- 7.62 (m, 1H), 7.56-7.48 (m, 4H), 4.29 (d, J = 1.6 Hz, 1H), 4.20 (d, J = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.3, 148.5, 143.0, 135.4, 134.5, 129.2, 128.6, 126.8, 124.3, 61.0, 58.2.

(3-(Naphthalen-2-yl)oxiran-2-yl)(phenyl)methanone (18m) [52]: Pale yellow oil, (244 mg, 89%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 2H), 7.90-7.84 (m, 4H), 7.64-7.60 (m, 1H), 7.53-7.41 (m, 5H), 4.41 (d, J = 2.0 Hz, 1H), 4.25 (d, J = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 193.1, 135.5, 134.1, 133.7, 133.1, 133.0, 129.0, 128.9, 128.4, 128.0, 127.9, 126.8, 126.0, 122.5, 61.2, 59.7.

(3-(Benzo[*d*][1,3]dioxol-5-yl)oxiran-2-yl)(phenyl)methanone (18n): Yellowish liquid (244 mg, 91%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 2H), 7.62-7.58 (m, 1H), 7.48-7.45 (m, 2H), 6.87-6.85 (m, 1H), 6.80-6.77 (m, 2H), 5.96 (s, 2H), 4.24 (d, J = 2.0 Hz, 1H), 3.97 (d, J = 1.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 193.1, 148.4, 148.3, 135.5, 134.0, 129.3, 128.9, 128.3, 120.3, 108.5, 105.5, 101.4, 61.0, 59.5. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51%; Found: C, 71.58; H, 4.42%.

(3-Phenyloxiran-2-yl)(*p*-tolyl)methanone (18o) [57]: White solid (231 mg, 97%), mp: 60-62 °C (lit.[57] mp: 58-60 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.26-7.21 (m, 5H), 7.14-7.12 (m, 2H), 4.14 (d, J = 2.0 Hz, 1H), 3.92 (d, J = 2.0 Hz, 1H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.5, 145.0, 135.6, 133.0, 129.5, 128.9, 128.7, 128.4, 125.7, 60.8, 59.2, 21.7.

(4-Methoxyphenyl)(3-phenyloxiran-2-yl)methanone (18p) [57]: White solid (244 mg, 96%), mp: 61-63 °C (lit.[57] mp: 60-62 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89-7.87 (m, 2H), 7.28-7.23 (m, 5H), 6.83-6.81 (m, 2H), 4.14 (d, J = 2.0 Hz, 1H), 3.94 (d, J = 2.0 Hz, 1H), 3.74 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 191.3, 164.2, 135.7, 130.7, 128.9, 128.7, 128.5, 125.8, 114.1, 60.8, 59.1, 55.5.

(4-Chlorophenyl)(3-phenyloxiran-2-yl)methanone (18q) [51]: White powder (241 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.95 (m, 2H), 7.47-7.34 (m, 7H), 4.23 (d, J = 1.6 Hz, 1H),

4.07 (d, J = 1.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.2, 140.7, 135.4, 133.8, 129.9, 129.3, 129.2, 128.9, 125.9, 61.2, 59.5.

(3-Bromophenyl)(3-phenyloxiran-2-yl)methanone (18r): White solid (276 mg, 91%), mp: 60-62 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (t, J = 3.6 Hz, 1H), 7.86-7.84 (m, 1H), 7.66-7.64 (m, 1H), 7.33-7.26 (m, 6H), 4.15 (d, J = 2.0 Hz, 1H), 3.99 (d, J = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.1, 137.1, 136.9, 135.2, 131.4, 130.5, 129.3, 128.9, 127.0, 125.9, 123.3, 61.0, 59.6. Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66%; Found: C, 59.48; H, 3.72%.

(4-Iodophenyl)(3-phenyloxiran-2-yl)methanone (18s): Light yellow solid (297 mg, 85%), mp: 120-122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 7.41-7.34 (m, 5H), 4.22 (d, J = 2.0 Hz, 1H), 4.06 (d, J = 1.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.7, 138.3, 135.3, 134.7, 129.7, 129.3, 128.9, 125.9, 102.4, 61.1, 59.5. Anal. Calcd for $C_{15}H_{11}IO_2$: C, 51.45; H, 3.17%; Found: C, 51.40; H, 3.11%

(3-Nitrophenyl)(3-phenyloxiran-2-yl)methanone (18t) [46]: (234 mg, 87%), mp: 190-192 °C (lit.[46] mp: 189-191 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.83 (t, J = 3.6 Hz, 1H), 8.45-8.43 (m, 1H), 8.36-8.33 (m, 1H), 7.71 (t, J = 16 Hz, 1H), 7.40-7.34 (m, 5H), 4.29 (d, J = 1.6 Hz, 1H), 4.20 (d, J = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 191.7, 148.6, 136.5, 134.8, 134.1, 130.3, 129.4, 128.9, 128.1, 125.9, 123.4, 61.3, 59.6.

(4-(Methylsulfonyl)phenyl)(3-phenyloxiran-2-yl)methanone (18u): White solid (269 mg, 89%), mp: 112-114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19-8.16 (m, 2H), 8.06-8.03 (m, 2H), 7.40-7.32 (m, 5H), 4.26 (d, J = 2.0 Hz, 1H), 4.07 (d, J = 2.0 Hz, 1H), 3.07 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.6, 144.9, 139.2, 134.9, 129.4, 128.9, 128.0, 125.7, 61.4, 59.7, 44.3. Anal.Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67%; Found: C, 63.61; H, 4.61%.

***p*-Tolyl(3-(*p*-tolyl)oxiran-2-yl)methanone (18v) [54]:** White crystals (237 mg, 94%), mp: 97-99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.79 (m, 2H), 7.16-7.08 (m, 6H), 4.16 (d, J = 1.6 Hz, 1H), 3.91 (d, J = 1.6 Hz, 1H), 2.30 (s, 3H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 192.7, 145.0, 139.0, 133.1, 132.6, 129.5, 129.4. 128.5, 125.8, 60.9, 59.4, 21.9, 21.3.

(2-Methoxyphenyl)(3-(*p*-tolyl)oxiran-2-yl)methanone (18w): White solid (236 mg, 88%), mp: 143-145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85-7.83 (m, 1H), 7.56-7.51 (m, 1H), 7.30-7.28 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.08-7.04 (m, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.33 (d, J = 2.0 Hz, 1H), 3.99 (d, J = 1.6 Hz, 1H), 3.63 (s, 3H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):δ 195.1,

159.6, 138.6, 134.9, 133.5, 130.7, 129.3, 126.0, 125.8, 121.0, 111.6, 64.5, 59.9, 55.7, 21.3. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%; Found: C, 76.03; H, 5.97%.

(3-(4-Chlorophenyl)oxiran-2-yl)(*p*-tolyl)methanone (18x) [52]: White solid (254 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 1H), 7.26-7.24 (m, 2H), 7.21-7.16 (m, 4H), 4.13 (d, J = 2.0 Hz, 1H), 3.94 (d, J = 1.6 Hz, 1H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 192.3, 145.2, 134.9, 134.2, 133.0, 129.6, 129.0, 128.5, 127.2, 60.8, 58.6, 21.8.

(3-(4-Chlorophenyl)oxiran-2-yl)(4-methoxyphenyl)methanone (18y) [52]: White gummy mass (277 mg, 96%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.96 (m, 2H), 7.34-7.26 (m, 4H), 6.92 (d, J = 8.8 Hz, 1H) 4.19 (d, J = 1.6 Hz, 1H), 4.02 (d, J = 1.6 Hz, 1H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 191.0, 164.3, 134.8, 134.3, 130.8, 129.0, 128.5, 127.2, 114.2, 60.8, 58.5, 55.6.

(3-(2-Chlorophenyl)oxiran-2-yl)(4-methoxyphenyl)methanone (18z): White solid (263 mg, 91%), mp: 94-96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 8.8 Hz, 2H), 7.38-7.35 (m, 2H), 7.30-7.28 (m, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.36 (d, J = 1.2 Hz, 1H), 4.11 (d, J = 2.0 Hz, 1H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 191.0, 164.3, 134.0, 133.3, 130.8, 129.7, 129.3, 128.5, 127.3, 126.2, 114.1, 59.9, 56.9, 55.6. Anal. Calcd for $C_{16}H_{13}ClO_3$: C, 66.56; H, 4.54%; Found: C, 66.46; H, 4.62%.

(4-Chlorophenyl)(3-(4-chlorophenyl)oxiran-2-yl)methanone (18a′) [52]: Pale yellow oil (270 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.82 (m, 2H), 7.36-7.33 (m, 2H), 7.27-7.24 (m, 2H), 7.20-7.17 (m, 2H), 4.10 (d, J = 2.0 Hz, 1H), 3.95 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 191.7, 140.7, 135.0, 133.9, 133.6, 129.8, 129.3, 129.1, 127.2, 61.0, 58.7.

(3-Bromophenyl)(3-(4-bromophenyl)oxiran-2-yl)methanone (18b′): White solid (334 mg, 90%), mp: 120-122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (t, J = 3.6 Hz, 1H), 7.92-7.90 (m, 1H), 7.75-7.72 (m, 1H), 7.54-7.51 (m, 2H), 7.36 (d, J = 16 Hz, 1H), 7.24-7.21 (m, 2H), 4.17 (d, J = 1.6 Hz, 1H), 4.04 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 191.8, 137.0, 134.3, 132.1, 131.4, 130.6, 127.5, 127.0, 123.4, 123.3, 60.9, 58.9. Anal. Calcd for $C_{15}H_{10}Br_2O_2$: C, 47.16; H, 2.64%; Found: C, 47.10; H, 2.54%.

(3-Phenyloxiran-2-yl)(thiophen-2-yl)methanone (18c′) [48]: (205 mg, 89%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.99 (m, 1H), 7.74-7.73 (m, 1H), 7.39-7.32 (m, 5H), 7.18-7.16 (m, 1H), 4.16 (d, J = 1.6 Hz, 1H), 4.07 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.4, 141.0, 135.3, 135.2, 133.6, 129.1, 128.7, 128.5, 125.8, 62.0, 59.5.

(3-(2-Methoxyphenyl)oxiran-2-yl)(thiophen-2-yl)methanone (18d′): White solid (244 mg, 94%), mp: 93-95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.89 (m, 1H), 7.62-7.61 (m, 1H), 7.23-7.19 (m, 1H), 7.14-7.12 (m, 1H), 7.07-7.04 (m, 1H), 6.87 (t, J = 14.8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 4.39 (d, J = 2.0 Hz, 1H), 3.89 (d, J = 1.6 Hz, 1H), 3.70 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.9, 158.3, 141.1, 135.0, 133.6, 129.8, 128.4, 125.3, 123.8, 120.7, 110.4, 61.4, 55.7, 55.4. Anal. Calcd for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65%; Found: C, 64.65; H, 4.69%.

(3-(4-Fluorophenyl)oxiran-2-yl)(thiophen-2-yl)methanone (18e′): Light yellow oil (231 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89-7.88 (m, 1H), 7.64-7.63 (m, 1H), 7.22-7.19 (m, 2H), 7.07-7.05 (m, 1H), 6.95 (t, J = 16.8 Hz, 1H), 4.04 (d, J = 1.6 Hz, 1H), 3.95 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.2, 164.3, 161.8, 140.9, 135.4, 133.7, 131.1, 131.0, 128.5, 127.6, 127.5, 115.9, 115.7, 61.8, 58.8. Anal. Calcd for $C_{13}H_9FO_2S$: C, 62.89; H, 3.65%; Found: C, 62.98; H, 3.60%.

(3-(4-Chlorophenyl)oxiran-2-yl)(thiophen-2-yl)methanone (18f′): Brown solid (215 mg, 81%), mp: 75-77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.99 (m, 1H), 7.76-7.75 (m, 1H), 7.38-7.35 (m, 2H), 7.29-7.26 (m, 2H), 7.19-7.17 (m, 1H), 4.15 (d, J = 1.6 Hz, 1H), 4.03 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.2, 141.0, 135.6, 135.1, 133.8, 129.1, 128.7, 128.4, 127.2, 62.0, 58.9. Anal. Calcd for $C_{13}H_9ClO_2S$: C, 58.98; H, 3.43%; Found: C, 58.91; H, 3.37%.

(3-(2,6-Dichlorophenyl)oxiran-2-yl)(thiophen-2-yl)methanone (18g′): White solid (260 mg, 87%), mp: 142-144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02-8.01 (m, 1H), 7.71-7.69 (m, 1H), 7.27-7.25 (m, 2H), 7.20-7.13 (m, 2H), 4.23 (d, J = 2.0 Hz, 1H), 4.22 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.4, 141.6, 135.9, 135.5, 134.0, 131.4, 130.5, 128.7, 128.6, 58.9, 57.2. Anal. Calcd for $C_{13}H_8Cl_2O_2S$: C, 52.19; H, 2.70%; Found: C, 52.24; H, 2.75%.

(3-(4-Nitrophenyl)oxiran-2-yl)(thiophen-2-yl)methanone (18h′): White solid (228 mg, 83%), mp: 160-162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27-8.24 (m, 2H), 8.01-8.00 (m, 1H), 7.79-7.77 (m, 1H), 7.54-7.51 (m, 2H), 7.21-7.18 (m, 1H), 4.28 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):δ 186.5, 148.4, 142.7, 140.8, 135.9, 134.0, 128.8, 126.8, 124.2, 61.9, 58.2. Anal.Calcd for $C_{13}H_9NO_4S$: C, 56.72; H, 3.30; N, 5.09%; Found: C, 56.66; H, 3.34; N, 5.01%.

(3-(4-Chlorophenyl)oxiran-2-yl)(furan-2-yl)methanone (18i′): Brown oil (212 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.60 (m, 1H), 7.39-7.38 (m, 1H), 7.30-7.28 (m, 2H), 7.22-7.19 (m, 2H), 6.54-6.53 (m, 1H), 4.06 (d, J = 1.6 Hz, 1H), 4.03 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR

($CDCl_3$, 100 MHz): δ 181.8, 151.3, 147.9, 135.1, 134.0, 129.1, 127.3, 119.7, 112.9, 60.6, 59.0.Anal. Calcd for $C_{13}H_9ClO_3$: C, 62.79; H, 3.65%; Found: C, 62.88; H, 3.60%.

Cyclopropyl(3-phenyloxiran-2-yl)methanone (18j′) [48]: Colorless oil (177 mg, 94%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.17 (m, 5H), 3.97 (d, J = 2.4 Hz, 1H), 3.47 (d, J = 1.6 Hz, 1H), 2.09-2.03 (m, 1H), 1.07-1.01 (m, 2H), 0.89-0.86 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):δ 205.7, 135.2, 128.8, 128.6, 125.7, 63.3, 57.6, 15.6, 12.3, 11.7.

Cyclopropyl(3-(*p*-tolyl)oxiran-2-yl)methanone (18k′): Yellow oil (186 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.21 (m, 2H), 6.90-6.88 (m, 2H), 4.03 (d, J = 1.6 Hz, 1H), 3.80 (s, 3H), 3.58 (d, J = 1.6 Hz, 1H), 2.19-2.15 (m, 1H), 1.16-1.12 (m, 2H), 1.01-0.98 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):δ 206.2, 160.3, 127.3, 127.2, 114.2, 63.5, 57.8, 55.4, 15.7, 12.4, 11.9. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%; Found: C, 77.12; H, 6.91%.

3-Hydroxy-1-phenylhexan-1-one (18m'): Colourless oil (161 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.92 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.43 (m, 2H), 4.23-4.20 (m, 1H), 3.32 (d, J = 3.2 Hz, 1H), 3.17-3.12 (m, 1H), 3.06-2.99 (m, 1H), 1.60-1.45 (m, 4H), 0.94-0.92 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):δ 201.1, 136.8, 133.6, 128.7, 128.1, 67.5, 45.1, 38.7, 18.8, 14.1. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%; Found: C, 74.91; H, 8.30%.

3-Hydroxy-4-methyl-1-phenylpentan-1-one (18o'): Colourless oil (165 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.94 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.44 (m, 2H), 4.00-3.97 (m, 1H), 3.24 (d, J = 3.2 Hz, 1H), 3.18-3.13 (m, 1H), 3.06-2.99 (m, 1H), 1.82-1.77 (m, 1H), 1.01-0.97 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):δ 201.4, 137.0, 133.5, 128.7, 128.2, 72.4, 42.1, 33.2, 18.6, 18.0. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%; Found: C, 74.90; H, 8.32%.

3.8. Conversion of aziridines to oxazolidines

Typical procedure for the synthesis of 2-benzyl-5-phenyl-3-tosyloxazolidine (21a) [349] using styrene (7a) in presence of AgOTf and NBS: A mixture of 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), AgOTf (0.7 mmol, 180 mg), H_2O (0.5 mmol, 9 μL) and 0.5 mL of DCM was taken in a sealed tube and stirred at room temperature for 1 h. Then NBS (0.6 mmol, 105 mg) and styrene **7a** (0.6 mmol, 62 mg) were added to the reaction mixture and stirred for another 4 h. After completion (TLC), the reaction mixture was diluted with 1:1 mixture of water/ethyl acetate (10 mL) and washed with saturated solution of $Na_2S_2O_3$ (3x5 mL) and saturated solution of aq. $NaHCO_3$ (1x10 mL) respectively followed by brine solution. Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was

subjected to column chromatography using ethyl acetate-petroleum ether (1:19) as eluent to obtain the analytically pure product as a brown gummy mass (Yield: 139 mg, 71%). The isolated product was a mixture of two diastereomers (A:B = 1:9). Brown gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.4 Hz, 1.8 H, 2*B*), 7.65 (d, *J* = 8.0 Hz, 0.2 H, 2*A*), 7.37-7.24 (m, 10H, 10*A*+10*B*), 7.02-7.00 (m, 1.8 H, 2*B*), 6.85 (d, *J* = 6.4 Hz, 0.2 H, 2*A*), 5.52-5.42 (m, 1H, 1*A*+1*B*), 4.95-4.92 (m, 0.1H, 1*A*), 4.09-4.05 (m, 0.9H, 1*B*), 3.81-3.77 (m, 0.9H, 1*B*), 3.71-3.67(m, 0.1H, 1*A*), 3.29-3.16 (m, 2H, 2*A*+2*B*), 3.12-3.06(m, 0.1H, 1*A*), 2.86-2.81 (m, 0.9H, 1*B*), 2.45-2.41 (3.1H, 3*A*+3*B*+1*B*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 144.2, 140.5, 138.0, 136.5, 136.2, 135.7, 135.0, 133.3, 130.7, 130.3, 130.2, 129.9, 129.84, 129.78, 128.8, 128.65, 128.58, 128.55, 128.47, 128.25, 128.19, 128.0, 127.9, 127.2, 126.9, 126.4, 126.1, 125.8, 92.4, 91.7, 79.0, 78.0, 53.9, 53.8, 42.51, 42.47, 21.7, 21.6.

2-(4-Chlorobenzyl)-5-phenyl-3-tosyloxazolidine (21b): Mixture of two diastereomers (A:B = 2:3); Yield: 141 mg, 66%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.4 Hz, 1.2 H, 2*B*), 7.57 (d, *J* = 8.4 Hz, 0.8 H, 2*A*), 7.31-7.08 (m, 11 H, 11*A*+11*B*), 6.95-6.92 (m, 1.2 H, 2*B*), 6.79 (d, *J* = 6.8 Hz, 0.8 H, 2*A*), 5.38-5.30 (m, 1.0 H, 1*A*+1*B*), 4.87-4.83 (m, 0.4 H, 1*A*), 4.02-3.98 (m, 0.6 H, 1*B*), 3.74-3.70 (m, 0.6 H, 1*B*), 3.63-3.59 (m, 0.5 H, 1*A*), 3.18-3.08 (m, 2.1 H, 2*A*+2*B*), 3.04-3.00 (m, 0.4 H, 1*A*), 2.78-2.72 (m, 0.6 H, 1*B*), 2.40-2.35 (m, 3.4 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 14 4.3, 137.9, 136.3, 134.8, 134.6, 134.1, 133.1, 132.9, 132.2, 131.8, 130.8, 130.4, 130.3, 130.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.9, 126.5, 126.4, 125.8, 125.7, 92.0, 91.4, 79.1, 78.1, 54.0, 53.8, 41.8, 41.7, 21.8, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{22}ClNO_3NaS$ 450.0907, Found 450.0873.

2-(4-Bromobenzyl)-5-phenyl-3-tosyloxazolidine (21c): Mixture of two diastereomers (A:B = 2:3); Yield: 151 mg, 64%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.0 Hz, 1.2 H, 2*B*), 7.64 (d, *J* = 8.0 Hz, 0.9 H, 2*A*), 7.45-7.22 (m, 11 H, 11*A*+11*B*), 7.02-7.00 (m, 1.2 H, 2*B*), 6.87 (d, *J* = 7.2 Hz, 0.8 H, 2*A*), 5.45-5.38 (m, 1.0 H, 1*A*+1*B*), 4.95-4.91 (m, 0.4 H, 1*A*), 4.10-4.06 (m, 0.7 H, 1*B*), 3.82-3.78 (m, 0.6 H, 1*B*), 3.71-3.67 (m, 0.4 H, 1*A*), 3.21-3.17 (m, 2.0 H, 2*A*+2*B*), 3.12-3.08 (m, 0.4 H, 1*A*), 2.86-2.80 (m, 0.6 H, 1B), 2.47-2.43 (m, 3.4 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 144.4, 137.9, 136.3, 135.1, 134.8, 134.6, 133.1, 132.5, 132.2, 131.8, 131.7, 131.6, 131.3, 130.3, 130.0, 128.8, 128.7, 128.6, 128.3, 128.0, 127.9, 126.4, 125.7, 121.1, 121.0, 91.9, 91.4, 79.1, 78.1, 54.0, 53.8, 41.8, 41.7, 21.8, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{22}BrNO_3NaS$ 496.0381, Found 496.0357.

2-Benzyl-5-(4-bromophenyl)-3-tosyloxazolidine (21d): Mixture of two diastereomers (A:B = 2:3); Yield: 149 mg, 63%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.68 (m, 1.2 H, 2*B*), 7.53-7.50 (m, 0.8 H, 2*A*), 7.37-7.11 (m, 10 H, 10*A*+10*B*), 6.80-6.77 (m, 1.2 H, 2*B*), 6.65-

6.61 (m, 0.8 H, 2*A*), 5.45-5.35 (m, 1.0 H, 1*A*+1*B*), 4.84-4.81 (m, 0.4 H, 1*A*), 3.99-3.94 (m, 0.6 H, 1*B*), 3.74-3.68 (m, 0.6 H, 1*B*), 3.57-3.53 (m, 0.4 H, 1*A*), 3.16-3.08 (m, 2.3 H, 2*A*+2*B*), 3.05-3.03 (m, 0.4 H, 1*A*), 2.71-2.65 (m, 0.6 H, 1*B*), 2.39-2.36 (m, 3.4 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 144.4, 137.7, 136.0, 135.6, 135.5, 134.9, 134.5, 133.5, 132.5, 132.2, 131.9, 131.61, 131.58, 131.4, 130.8, 130.4, 130.3, 129.9, 128.5, 128.3, 128.1, 127.9, 127.2, 127.0, 122.6, 122.0, 121.1, 92.3, 91.8, 91.7, 91.4, 78.4, 78.0, 53.81, 53.76, 53.7, 42.5, 42.4, 41.8, 41.6, 21.9, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{22}BrNO_3NaS$ m/z = 496.0381, Found 496.0366.

2-(4-Bromobenzyl)-5-(4-bromophenyl)-3-tosyloxazolidine (21e): Mixture of two diastereomers (A:B = 1:1); Yield: 170 mg, 62%; Orange gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 8.4 Hz, 1.0 H, 2*B*), 7.57 (d, *J* = 8.0 Hz, 1.0 H, 2*A*), 7.51-7.19 (m, 11 H, 11*A*+11*B*), 6.87 (d, *J* = 8.4 Hz, 1.0 H, 2*B*), 6.71 (d, *J* = 8.4 Hz, 1.0 H, 2*A*), 5.46-5.37 (m, 1H, 1*A*+1*B*), 4.91-4.88 (m, 0.5 H, 1*A*), 4.08-4.04 (m, 0.5 H, 1*B*), 3.81-3.77 (m, 0.5 H, 1*B*), 3.62-3.58 (m, 0.5 H, 1*A*), 3.18-3.13 (m, 2.0 H, 2*A*+2*B*), 2.78-2.73 (m, 0.5 H, 1*B*), 2.47-2.44 (m, 3.5 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.6, 137.6, 135.4, 134.5, 133.3, 132.5, 132.2, 131.8, 131.65, 131.58, 131.4, 130.3, 129.9, 128.9, 128.3, 128.0, 127.84, 127.82, 127.7, 127.1, 122.8, 122.0, 121.1, 91.8, 91.4, 78.4, 53.8, 53.7, 41.8, 41.6, 21.8. HRMS (ESI/TOF-Q) m/z: $[M + K]^+$ Calcd for $C_{23}H_{21}Br_2KNO_3S$ m/z = 587.9246, Found 587.9269.

2-(4-Chlorobenzyl)-5-(4-bromophenyl)-3-tosyloxazolidine (21f): Mixture of two diastereomers (A:B = 1:1); Yield: 154 mg, 61%; Orange gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.0 Hz, 1.0 H, 2*B*), 7.49 (d, *J* = 8.4 Hz, 1.0 H, 2*A*), 7.42-7.11 (m, 12 H, 12*A*+12*B*), 6.80 (d, *J* = 8.0 Hz, 1.0 H, 2*B*), 6.64 (d, *J* = 8.4 Hz, 1.0 H, 2*A*), 5.39-5.30 (m, 1H, 1*A*+1*B*), 4.83-4.80 (m, 0.5 H, 1*A*), 4.00-3.96 (m, 0.5 H, 1*B*), 3.74-3.69 (m, 0.5 H, 1*B*), 3.55-3.50 (m, 0.5 H, 1*A*), 3.12-3.07 (m, 2.2 H, 2*A*+2*B*), 2.71-2.65 (m, 0.5 H, 1*B*), 2.39-2.37 (m, 3.5 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.6, 137.6, 135.4, 134.8, 133.9, 133.0, 132.5, 132.2, 132.1, 131.8, 131.6, 131.4, 130.9, 130.3, 129.9, 129.3, 128.6, 128.4, 128.0, 127.8, 127.1, 122.7, 122.0, 91.9, 91.8, 91.44, 91.36, 78.4, 53.8, 53.7, 41.83, 41.77, 41.64, 41.57, 21.8. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}BrClNO_3NaS$ m/z = 529.9991, Found 529.9977.

2-Benzyl-5-(4-chlorophenyl)-3-tosyloxazolidine (21g): Mixture of two diastereomers (A:B = 2:3); Yield: 143 mg, 67%; Gummy yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.68 (m, 1.3 H, 2*B*), 7.53-7.49 (m, 0.8 H, 2*A*), 7.31-7.01 (m, 11 H, 11*A*+11*B*), 6.86-6.83 (m, 1.2 H, 2*B*), 6.70-6.67 (m, 0.8 H, 2*A*), 5.39-5.30 (m, 1.0 H, 1*A*+1*B*), 4.85-4.81 (m, 0.4 H, 1*A*), 4.01-3.95 (m, 0.6 H, 1*B*), 3.73-3.68 (m, 0.6 H, 1*B*), 3.57-3.51 (m, 0.5 H, 1*A*), 3.16-3.04 (m, 2.5 H, 2*A*+2*B*+1*A*), 2.70-2.65 (m, 0.6 H, 1*B*), 2.39-2.36 (m, 3.5 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7,

144.6, 137.0, 135.5, 134.7, 134.6, 133.9, 133.0, 132.1, 131.8, 130.8, 130.4, 130.30, 130.27, 129.9, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 127.85, 127.76, 127.0, 126.9, 126.8, 92.3, 91.9, 91.7, 91.4, 78.4, 53.9, 53.8, 53.7, 42.5, 42.4, 41.8, 41.6, 21.8, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{22}ClNO_3NaS$ m/z = 450.0907, Found 450.0874.

2-(4-Chlorobenzyl)-5-(4-chlorophenyl)-3-tosyloxazolidine (21h): Mixture of two diastereomers (A:B = 1:1); Yield: 145 mg, 63%; Yellow gummy mass; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.4 Hz, 1.0 H, 2*B*), 7.50 (d, *J* = 8.0 Hz, 1.0 H, 2*A*), 7.31-7.01 (m, 10 H, 10*A*+10*B*), 6.86 (d, *J* = 8.4 Hz, 1.0 H, 2*B*), 6.69 (d, *J* = 8.4 Hz, 1.0 H, 2*A*), 5.39-5.30 (m, 1H, 1*A*+1*B*), 4.85-4.82 (m, 0.5 H, 1*A*), 4.02-3.98 (m, 0.5 H, 1*B*), 3.73-3.69 (m, 0.5 H, 1*B*), 3.55-3.51 (m, 0.5 H, 1*A*), 3.12-3.05 (m, 2.2 H, 2*A*+2*B*), 2.71-2.65 (m, 0.5 H, 1*B*), 2.39-2.36 (m, 3.5 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.5, 137.0, 134.9, 134.8, 134.6, 134.4, 134.0, 133.4, 133.0, 132.1, 131.8, 130.3, 129.9, 129.3, 129.0, 128.9, 128.7, 128.6, 128.4, 127.8, 127.7, 127.5, 126.8, 91.9, 91.4, 78.4, 53.9, 53.7, 41.8, 41.6, 21.75, 21.69. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}Cl_2NO_3NaS$ m/z = 484.0517, Found 484.0541.

2-(4-Bromobenzyl)-5-(4-chlorophenyl)-3-tosyloxazolidine (21i): Mixture of two diastereomers (A:B = 2:3); Yield: 156 mg, 62%; Cream-white gummy mass; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.0 Hz, 1.2 H, 2*B*), 7.50 (d, *J* = 8.4 Hz, 0.8 H, 2*A*), 7.37-7.12 (m, 8 H, 8*A*+8*B*), 7.03 (d, *J* = 8.8 Hz, 0.9 H, 2*A*), 6.85 (d, *J* = 8.4 Hz, 1.2 H, 2*B*), 6.70 (d, *J* = 8.4 Hz, 0.8 H, 2*A*), 5.39-5.30 (m, 1H, 1*A*+1*B*), 4.85-4.82 (m, 0.4 H, 1*A*), 4.02-3.98 (m, 0.6 H, 1*B*), 3.74-3.69 (m, 0.6 H, 1*B*), 3.55-3.51 (m, 0.4 H, 1*A*), 3.11-3.05 (m, 2.1 H, 2*A*+2*B*), 2.71-2.65 (m, 0.6 H, 1*B*), 2.39-2.36 (m, 3.4 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.5, 137.0, 134.9, 134.8, 134.6, 134.5, 134.0, 133.3, 132.5, 132.2, 132.1, 131.8, 131.6, 131.4, 130.3, 129.9, 128.9, 128.7, 128.6, 128.4, 127.8, 127.7, 126.8, 121.1, 91.9, 91.8, 91.4, 91.3, 78.4, 53.9, 53.7, 41.83, 41.77, 41.65, 41.58, 21.8, 21.7. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}BrClNO_3NaS$ m/z = 529.9991, Found 530.0024.

Typical procedure for the synthesis of 2-benzyl-5-phenyl-3-tosyloxazolidine (21a) [349] using AgOTf in absence styrene and NBS: A mixture of 2-phenyl-1-tosylaziridine **1a** (0.50 mmol, 137 mg), AgOTf (0.7 mmol, 180 mg) and H_2O (0.5 mmol, 9 μL) was taken in a sealed tube followed by addition of 0.5 mL of DCM and the reaction mixture was stirred at room temperature for 2 h. After completion (TLC), the reaction mixture was diluted with 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution. Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether (1:19) as eluent to obtain the analytically pure product as a yellow gummy mass (Yield: 148 mg, 75%). The isolated product

was a mixture of two diastereomers (A:B = 2:3). Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.0 Hz, 1.2 H, 2*B*), 7.58 (d, *J* = 8.4 Hz, 0.8 H, 2*A*), 7.30-7.06 (m, 10 H, 10*A*+10*B*), 6.95-6.92 (m, 1.2 H, 2*B*), 6.78 (d, *J* = 6.8 Hz, 0.8 H, 2*A*), 5.44-5.34 (m, 1H, 1*A*+1*B*), 4.88-4.84 (m, 0.4 H, 1*A*), 4.01-3.97 (m, 0.6 H, 1*B*), 3.74-3.70 (m, 0.6 H, 1*B*), 3.64-3.60 (m, 0.4 H, 1*A*), 3.22-3.09 (m, 2H, 2*A*+2*B*), 3.03-2.98 (m, 0.4 H, 1*A*), 2.79-2.73 (m, 0.6 H, 1*B*), 2.38-2.34 (m, 3.1 H, 3*A*+3*B*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.5, 144.2, 138.0, 136.5, 136.2, 135.7, 135.0, 133.3, 130.7, 130.4, 130.2, 129.9, 128.7, 128.6, 128.55, 128.47, 128.3, 128.2, 128.0, 127.9, 126.91, 126.89, 126.4, 125.8, 92.4, 91.7, 79.1, 78.0, 54.0, 53.8, 42.51, 42.49, 21.72, 21.66.

2-(4-Bromobenzyl)-5-(4-bromophenyl)-3-tosyloxazolidine (21e): Mixture of two diastereomers (A:B = 1:9); Yield: 191 mg, 69%; Cream white solid; mp 115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.4 Hz, 1.8 H, 2*B*), 7.49 (d, *J* = 8.4 Hz, 0.2 H, 2*A*), 7.38-7.13 (m, 8 H, 8*A*+8*B*), 6.79 (d, *J* = 8.4 Hz, 1.8 H, 2*B*), 6.64 (d, *J* = 7.2 Hz, 0.2 H, 2*A*), 5.39-5.30 (m, 1H, 1*A*+1*B*), 4.84-4.81 (m, 0.1 H, 1*A*), 4.00-3.97 (m, 0.9 H, 1*B*), 3.74-3.69 (m, 0.9 H, 1*B*), 3.55-3.51 (m, 0.1 H, 1*A*), 3.14-3.05 (m, 2.1 H, 2*A*+2*B*+1*A*), 2.71-2.65 (m, 0.9 H, 1*B*), 2.40-2.37 (m, 3.1 H, 3*A*+3*B*+1*A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.6, 135.4, 134.9, 134.8, 134.5, 132.5, 132.2, 131.9, 131.7, 131.6, 131.4, 130.3, 129.9, 129.2, 128.2, 128.1, 127.8, 127.1, 126.6, 122.8, 122.3, 122.0, 121.1, 91.8, 91.4, 78.4, 78.3, 53.8, 53.7, 41.8, 41.6, 21.8, 21.6.

2-(4-Chlorobenzyl)-5-(4-chlorophenyl)-3-tosyloxazolidine (21h): Mixture of two diastereomers (A:B = 1:1); Yield: 163 mg, 71%; White solid; mp 105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 8.4 Hz, 1H, 2*B*), 7.60 (d, *J* = 8.4 Hz, 1H, 2*A*), 7.40 (d, *J* = 8.0 Hz, 1H, 2*B*), 7.31-7.22 (m, 6.4 H, 6*A*+6*B*), 7.12 (d, *J* = 8.4 Hz, 1H, 2*A*), 6.95 (d, *J* = 8.4 Hz, 1H, 2*B*), 6.79 (d, *J* = 8.8 Hz, 1H, 2*A*), 5.49-5.40 (m, 1H, 1*A*+1*B*), 4.95-4.91 (m, 0.5 H, 1*A*), 4.11-4.07 (m, 0.5 H, 1*B*), 3.83-3.79 (m, 0.5 H, 1*B*), 3.65-3.61 (m, 0.5 H, 1*A*), 3.22-3.15 (m, 2.5 H, 2*A*+2*B*+1*A*), 2.80-2.75 (m, 0.5H, 1*B*), 2.49-2.46 (m, 3.1 H, 3*A*+3*B*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 144.6, 137.0, 134.9, 134.8, 134.6, 134.4, 134.0, 133.4, 133.0, 132.1, 131.8, 130.3, 129.9, 128.9, 128.7, 128.6, 128.4, 127.9, 127.8, 126.8, 91.9, 91.4, 78.4, 53.9, 53.7, 41.8, 41.6, 21.8, 21.7.

3.9. Mechanochemical synthesis of 2-imidazolines

General procedure for the synthesis of compound (24).

A mixture of aziridine **1** (0.25 mmol), nitrile (**23**, 0.25 mmol) and perchloric acid (0.25 mmol) was taken in a mortar. The reaction mixture was thoroughly ground at room temperature for 5 min. After completion (TLC) the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with sodium bicarbonate (1x10 mL) and followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent

furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

2,4-Diphenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24a) [77]. White liquid, 357 mg, yield 95%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.53-7.51 (m, 1H), 7.46-7.44 (m, 1H), 7.41-7.39 (m, 2H), 7.23-7.19 (m, 6H), 6.98-6.96 (m, 2H), 5.01-4.97 (m, 1H), 4.46-4.41 (m, 1H), 3.88-3.83 (m, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.0, 138.8, 135.7, 128.6, 125.3, 124.3, 124.0, 123.9, 122.7, 121.9, 121.7, 121.5, 120.5, 62.0, 51.0, 15.8.

4-Phenyl-2-(*p*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24b). White solid, 328 mg, yield 84%, mp 186-188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 8.4 Hz, 2H), 7.34-7.32 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.13-7.10 (m, 5H), 6.88-6.86 (m, 2H), 4.88-4.84 (m, 1H), 4.36-4.31 (m, 1H), 3.78-3.73 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 144.7, 141.8, 141.7, 134.6, 130.0, 129.9, 128.7, 128.6, 127.7, 127.5, 127.4, 126.5, 67.9, 57.0, 21.8, 21.7. Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17%; Found: C, 70.78; H, 5.78; N, 7.09%.

2-(3-Methoxyphenyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24c). Yellow liquid, 301 mg, yield 74%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.42 (m, 2H), 7.34-7.33 (m, 2H), 7.283-7.276 (m, 1H), 7.23-7.19 (m, 5H), 7.08-7.05(m, 1H), 7.00-6.98 (m, 2H), 5.01-4.96 (m, 1H), 4.47-4.41 (m, 1H), 3.89-3.84 (m, 4H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 159.0, 144.8, 141.6, 134.7, 131.5, 129.9, 129.0, 128.7, 127.8, 127.6, 126.5, 122.4, 117.6, 115.0, 68.1, 57.1, 55.6, 21.7. Anal. Calcd. for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89%; Found: C, 67.89; H, 5.38; N, 6.80%.

2-(2-Chlorophenyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24d) [76]. Colourless liquid, 259 mg, yield 63%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.46 (m, 3H), 7.41-7.40 (m, 2H), 7.35-7.31 (m, 1H), 7.28-7.22 (m, 5H), 7.17-7.15(m, 2H), 5.27-5.23 (m, 1H), 4.42-4.37 (m, 1H), 3.87-3.82 (m, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 144.8, 141.6, 134.8, 133.7, 131.42, 131.40, 130.0, 129.8, 129.7, 128.8, 127.82, 127.76, 126.7, 126.2, 68.3, 55.7, 21.7.

2-(3-Chlorophenyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24e). Yellowish brown gum, 218 mg, yield 53%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.67 (m, 2H), 7.50-7.47 (m, 1H), 7.44-7.38 (m, 3H), 7.24-7.22 (m, 5H), 7.00-6.97 (m, 2H), 5.03-4.99 (m, 1H), 4.46-4.41 (m, 1H), 3.89-3.84 (m, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 145.1, 141.3, 134.6, 133.9, 132.1, 131.3, 130.0, 129.74, 129.68, 129.2, 128.8, 128.2, 127.7, 126.4, 68.2, 56.9, 21.7. Anal. Calcd. for $C_{22}H_{19}ClN_2O_2S$: C, 64.30; H, 4.66; N, 6.82%; Found: C, 64.39; H, 4.60; N, 6.92%.

2-(4-Chlorophenyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24f). Yellow solid, 267 mg, yield 65%, mp 175-177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.72 (m, 2H), 7.43-7.39 (m, 4H), 7.22-7.20 (m, 5H), 6.95-6.93(m, 2H), 4.99-4.95 (m, 1H), 4.45-4.40 (m, 1H), 3.87-3.83 (m, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 145.0, 141.4, 137.6, 134.4, 131.4, 130.0, 128.8, 128.7, 128.3, 127.71, 127.67, 126.4, 68.0, 57.0, 21.8. Anal. Calcd. for $C_{22}H_{19}ClN_2O_2S$: C, 64.30; H, 4.66; N, 6.82%; Found: C, 64.40; H, 4.58; N, 6.75%.

2-(2-Fluorophenyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24g). Yellow solid, 241 mg, yield 61%, mp 106-108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.45 (m, 1H), 7.42-7.38 (m, 3H), 7.18-7.14 (m, 6H), 7.08-7.04 (m, 1H), 6.98-6.95(m, 2H), 5.12-5.08 (m, 1H), 4.32-4.26 (m, 1H), 3.77-3.72 (m, 1H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8 (d, $^1J_{C\text{-}F}$ = 251 Hz), 154.6, 144.9, 141.7, 134.7, 132.6 (d, $^6J_{C\text{-}F}$ = 9 Hz), 131.4, 130.0, 128.84, 127.8 (d, $^5J_{C\text{-}F}$ = 4 Hz), 126.5, 123.7(d, $^4J_{C\text{-}F}$ = 3 Hz), 119.2 (d, $^3J_{C\text{-}F}$ = 14 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 22 Hz), 68.3, 55.9, 21.8. Anal. Calcd. for $C_{22}H_{19}FN_2O_2S$: C, 66.99; H, 4.85; N, 7.10%; Found: C, 66.90; H, 4.76; N, 7.04%.

2-(3-Methoxyphenyl)-4-(*o*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24h). Brown semi-solid, 311 mg, yield 74%, mp 106-108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.34 (m, 4H), 7.31-7.30 (m, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.12-7.04(m, 3H), 7.00-6.96 (m,1H), 6.78 (d, J = 7.6 Hz, 1H), 5.14-5.09 (m, 1H), 4.50-4.45 (m, 1H), 3.86 (s, 3H), 3.74-3.69 (m, 1H), 2.41 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 159.0, 144.8, 140.0, 134.8, 134.4, 131.6, 130.4, 129.9, 129.0, 127.7, 127.3, 126.4, 125.8, 122.4, 117.6, 115.0, 65.1, 56.5, 55.6, 21.7, 19.5. Anal. Calcd. for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.49; H, 5.68; N, 6.76%.

2-(3-Methoxyphenyl)-4-(*m*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24i). Colourless liquid, 212 mg, yield 68%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.43 (m, 2H), 7.34-7.33 (m, 2H), 7.283-7.278 (m, 1H), 7.22-7.20 (m, 2H), 7.12-7.04 (m,3H), 6.80 (d, J = 8.0 Hz, 2H), 4.96-4.92 (m, 1H), 4.45-4.40 (m, 1H), 3.87-3.82 (m, 4H), 2.42 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 159.0, 144.8, 141.5, 138.4, 134.8, 131.5, 129.9, 129.0, 128.6, 128.4, 127.8, 127.2, 123.7, 122.5, 117.6, 115.0, 68.1, 57.0, 55.6, 21.8, 21.5. Anal. Calcd. for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66%; Found: C, 68.67; H, 5.82; N, 6.73%.

2-(2-Fluorophenyl)-4-(*m*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24j). Yellow gum, 225 mg, yield 55%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.46 (m, 4H), 7.26-7.21 (m, 3H), 7.17-7.12 (m, 2H), 7.05 (d, J = 7.6 Hz, 1H), 6.85-6.84 (m,2H), 5.16-5.12 (m, 1H), 4.38-4.33 (m, 1H), 3.84-3.79 (m, 1H), 2.43 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8 (d, $^1J_{C\text{-}F}$ = 251 Hz), 154.4, 144.8, 141.5, 138.5, 134.6, 132.6 (d, $^6J_{C\text{-}F}$ = 9 Hz), 131.4, 129.9, 128.6 (d, $^5J_{C\text{-}F}$ = 20 Hz), 127.8, 127.2, 123.7 (d, $^4J_{C\text{-}F}$ = 7 Hz), 119.2 (d, $^3J_{C\text{-}F}$ = 14 Hz), 115.9 (d, $^2J_{C\text{-}F}$ = 22 Hz), 68.3, 55.9,

21.8, 21.5. Anal. Calcd. for $C_{23}H_{21}FN_2O_2S$: C, 67.63; H, 5.18; N, 6.86%; Found: C, 67.54; H, 5.12; N, 6.95%.

4-(2-Chlorophenyl)-2-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24k) [76]. Yellow liquid, 378 mg, yield 92%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.80 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.44 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.33-7.31 (m, 1H), 7.18-7.13 (m, 3H), 7.05-7.01 (m, 1H), 6.92-6.90 (m, 1H), 5.26-5.22 (m, 1H), 4.61-4.55 (m, 1H), 3.80-3.75 (m, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 138.8, 133.7, 128.6, 126.1, 125.5, 124.3, 124.0, 123.9, 123.3, 122.5, 121.9, 121.6, 121.4, 121.0, 59.3, 50.2, 15.7.

4-(2-Chlorophenyl)-2-(*m*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24l). Yellowish white solid, 331 mg, yield 78%, mp 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.58 (m, 2H), 7.40-7.31 (m, 5H), 7.18-7.14 (m, 3H), 7.07-7.03 (m, 1H), 6.96-6.93 (m,1H), 5.25-5.21 (m, 1H), 4.60-4.55 (m, 1H), 3.80-3.75 (m, 1H), 2.42 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 144.7, 139.7, 137.6, 134.7, 132.2, 132.1, 130.35, 130.26, 129.8, 129.3, 128.5, 127.8, 127.6, 127.5, 127.1, 127.0, 65.3, 56.2, 21.7, 21.5. Anal. Calcd. for $C_{23}H_{21}ClN_2O_2S$: C, 65.01; H, 4.98; N, 6.59%; Found: C, 65.11; H, 4.90; N, 6.52%.

4-(2-Chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24m). Off-white gummy mass, 419 mg, yield 95%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.31 (m, 6H), 7.18-7.14 (m, 3H), 7.10-7.02 (m, 2H), 6.94-6.91 (m, 1H), 5.26-5.21 (m,1H), 4.61-4.56 (m, 1H), 3.87 (s, 3H), 3.80-3.75 (m, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.0, 159.0, 144.8, 139.7, 134.6, 132.1, 129.9, 129.3, 129.0, 128.5, 127.6, 127.5, 127.0, 122.4, 117.7, 115.1, 65.3, 56.3, 55.6, 21.7. Anal. Calcd. for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35%; Found: C, 62.72; H, 4.89; N, 6.42%.

4-(2-Chlorophenyl)-2-(3-chlorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24n). Off-white solid, 387 mg, yield 87%, mp 116-118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 2H), 7.53-7.50 (m, 1H), 7.43-7.38 (m, 3H), 7.34-7.32 (m,1H), 7.19-7.16 (m, 3H), 7.08-7.04 (m, 1H), 6.92-6.90 (m, 1H), 5.27-5.23 (m, 1H), 4.61-4.55 (m, 1H), 3.80-3.75 (m, 1H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 145.1, 139.4, 134.6, 134.0, 132.2, 132.1, 131.5, 130.0, 129.7, 129.4, 129.3, 128.7, 128.3, 127.6, 127.4, 127.1, 65.6, 56.2, 21.7. Anal. Calcd. for $C_{22}H_{18}Cl_2N_2O_2S$: C, 59.33; H, 4.07; N, 6.29%; Found: C, 59.38; H, 4.14; N, 6.38%.

4-(2-Chlorophenyl)-2-(4-chlorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24o). Yellow liquid, 405 mg, yield 91%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 2H), 7.45-7.43 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.33-7.31 (m, 1H), 7.18-7.14 (m,3H), 7.05-7.01 (m, 1H), 6.87-6.85 (m, 1H), 5.23-5.19 (m, 1H), 4.59-4.54 (m, 1H), 3.79-3.74 (m, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$,

100 MHz): δ 160.3, 145.0, 139.5, 137.8, 134.5, 132.1, 131.4, 130.0, 129.4, 128.8, 128.6, 128.3, 127.6, 127.4, 127.1, 65.5, 56.3, 21.7. Anal. Calcd. for $C_{22}H_{18}Cl_2N_2O_2S$: C, 59.33; H, 4.07; N, 6.29%; Found: C, 59.27; H, 4.01; N, 6.20%.

4-(2-Chlorophenyl)-2-(2-fluorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24p). Colourless liquid, 382 mg, yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62-7.58 (m, 1H), 7.52-7.50 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.34-7.32 (m, 1H), 7.27-7.25 (m,1H), 7.19-7.14 (m, 4H), 7.11-7.07 (m, 1H), 7.04-7.02 (m, 1H), 5.50-5.45 (m, 1H), 4.54-4.48 (m, 1H), 3.77-3.72 (m, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7(d, $^1J_{C\text{-}F}$ = 241 Hz), 155.7, 144.9, 139.7, 134.6, 132.7 (d, $^6J_{C\text{-}F}$ = 9 Hz), 131.5, 129.9, 129.4, 128.7, 127.7 (d, $^5J_{C\text{-}F}$ = 9 Hz), 127.4 (d, $^4J_{C\text{-}F}$ = 45 Hz), 123.8 (d, $^3J_{C\text{-}F}$ = 3 Hz), 116.0(d, $^2J_{C\text{-}F}$ = 21 Hz), 65.5, 55.2, 21.7. Anal. Calcd. for $C_{22}H_{18}ClFN_2O_2S$: C, 61.61; H, 4.23; N, 6.53%; Found: C, 61.53; H, 4.14; N, 6.43%.

4-(2-Chlorophenyl)-2-(4-fluorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24q). Yellow gum, 382 mg, yield 89%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.82 (m, 2H), 7.37-7.30 (m, 3H), 7.18-7.13 (m, 5H), 7.05-7.01 (m,1H), 6.89-6.86 (m, 1H), 5.23-5.18 (m, 1H), 4.60-4.55 (m, 1H), 3.79-3.75 (m, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8 (d, $^1J_{C\text{-}F}$ = 250 Hz), 160.2, 144.9, 139.6, 134.5, 132.3, 132.2 (d, $^4J_{C\text{-}F}$ = 9 Hz), 129.9, 129.4, 128.6, 127.5 (d, $^3J_{C\text{-}F}$ = 18 Hz), 127.0, 126.4, 115.2 (d, $^2J_{C\text{-}F}$ = 22 Hz), 65.3, 56.3, 21.7. Anal. Calcd. for $C_{22}H_{18}ClFN_2O_2S$: C, 61.61; H, 4.23; N, 6.53%; Found: C, 61.70; H, 4.32; N, 6.62%.

4-(3-Chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24r). Off-white solid, 375 mg, yield 85%, mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, J = 8.4 Hz, 2H), 7.36-7.29 (m, 3H), 7.20-7.16 (m, 4H), 7.09-7.07 (m,1H), 6.93-6.89 (m, 2H), 5.01-4.97 (m, 1H), 4.47-4.42 (m, 1H), 3.86-3.82 (m, 4H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5, 159.1, 145.1, 143.8, 134.7, 134.4, 131.3, 130.8, 130.0, 129.9, 129.0, 127.7, 126.6, 124.7, 122.5, 117.7, 115.1, 67.3, 56.8, 55.6, 21.8. Anal. Calcd. for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35%. Found: C, 62.60; H, 4.84; N, 6.45%.

4-(4-Chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24s). Off-white solid, 357 mg, yield 81%, mp 104-106°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, J = 8.4 Hz, 2H), 7.35-7.33 (m, 2H), 7.284-7.277 (m, 1H), 7.18 (d, J = 8.0 Hz, 4H), 7.09-7.06 (m, 1H), 6.92 (d, J = 8.4 Hz, 2H), 5.00-4.96 (m, 1H), 4.56-4.40 (m, 1H), 3.85-3.81 (m, 4H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 159.1, 145.0, 140.4, 134.6, 133.4, 131.3, 129.9, 129.0, 128.8, 127.8, 127.7, 122.4, 117.7, 115.1, 67.2, 56.9, 55.6, 21.7. Anal. Calcd. for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35%; Found: C, 62.60; H, 4.85; N, 6.28%.

4-(3-Bromophenyl)-2-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24t). Colourless liquid, 346 mg, yield 76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.43 (m, 2H), 7.38-7.33 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12-7.06 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.00-4.96 (m, 1H), 4.46-4.41 (m, 1H), 3.86-3.81 (m, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.6, 139.0, 138.1, 128.3, 125.5, 124.6, 124.2, 124.0, 123.9, 123.5, 121.9, 121.7, 121.1, 119.2, 116.9, 61.2, 50.8, 15.9. Anal. Calcd. for $C_{22}H_{19}BrN_2O_2S$: C, 58.03; H, 4.21; N, 6.15%; Found: C, 58.09; H, 4.27; N, 6.22%.

4-(3-Bromophenyl)-2-(*p*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24u). Yellow liquid, 404 mg, yield 86%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34-7.32 (m, 2H), 6.95-6.84 (m, 1H), 7.27-7.23 (m. 2H),7.18 (d, *J* = 8.0 Hz, 2H), 7.10-7.05 (m, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.95-4.91(m, 1H), 4.44-4.39 (m, 1H), 3.84-3.79 (m, 1H), 2.44 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 145.0, 144.2, 142.0, 134.3, 130.5, 130.2, 130.0, 129.9, 129.5, 128.6, 127.7, 127.2, 125.2, 122.9, 67.1, 56.8, 21.85, 21.78. Anal. Calcd. For $C_{23}H_{21}BrN_2O_2S$: C, 58.85; H, 4.51; N, 5.97%; Found: C, 58.76; H, 4.46; N, 5.89%.

4-(3-Bromophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24v). Light yellow gum, 408 mg, yield 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.35-7.34 (m, 3H), 7.294-7.287 (m, 1H), 7.25-7.18 (m, 2H), 7.12-7.05 (m, 3H), 6.96(d, *J* = 8.0 Hz, 1H), 5.00-4.95 (m, 1H), 4.47-4.41 (m, 1H), 3.86-3.81 (m, 4H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5, 159.0, 145.1, 144.1, 134.4, 131.3, 130.7, 130.3, 130.0, 129.5, 129.1, 127.7, 125.2, 122.9, 122.5, 117.7, 115.1, 67.2, 56.8, 55.6, 21.9. Anal. Calcd. For $C_{23}H_{21}BrN_2O_3S$: C, 56.91; H, 4.36; N, 5.77%; Found: C, 56.84; H, 4.30; N, 5.84%.

4-(4-Bromophenyl)-2-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24w) [76]. Colourless liquid, 364 mg, yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.56-7.52 (m, 1H), 7.46-7.43 (m, 2H), 7.37-7.31 (m, 5H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.86-6.83 (m, 2H), 4.99-4.95 (m, 1H), 4.45-4.40 (m, 1H), 3.85-3.81 (m, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5, 139.0, 134.9, 128.5, 125.8, 125.5, 124.0, 123.9, 122.4, 122.0, 121.9, 121.7, 115.4, 61.1, 50.9, 15.7.

4-(4-Bromophenyl)-2-(*m*-tolyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24x). White gummy mass, 375 mg, yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.51 (m, 1H), 7.39-7.31 (m, 7H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.87-6.84 (m, 2H), 4.98-4.94(m, 1H), 4.45-4.39 (m, 1H), 3.85-3.80 (m, 1H), 2.43 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 145.0, 141.0, 137.7, 134.6, 132.3, 131.8, 130.4, 129.9, 128.4, 128.1, 127.8, 127.7, 127.2, 121.4, 67.2, 56.8, 21.8, 21.5. Anal. Calcd. For $C_{23}H_{21}BrN_2O_2S$: C, 58.85; H, 4.51; N, 5.97%; Found: C, 58.92; H, 4.56; N, 5.90%.

4-(4-Bromophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24y). Off-white solid, 398 mg, yield 82%, mp 130-132°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.28 (m, 7H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.09-7.06 (m, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.99-4.95(m, 1H), 4.46-4.40 (m, 1H), 3.86-3.81 (m, 4H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 159.1, 145.0, 140.9, 134.6, 131.8, 131.3, 129.9, 129.0, 128.1, 127.7, 122.4, 121.4, 117.7, 115.1, 67.2, 56.9, 55.6, 21.8. Anal. Calcd. For $C_{23}H_{21}BrN_2O_3S$: C, 56.91; H, 4.36; N, 5.77%; Found: C, 56.84; H, 4.30; N, 5.68%.

4-(4-Bromophenyl)-2-(2-fluorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24z). Colourless liquid, 360 mg, yield 76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50-7.42 (m, 2H), 7.37-7.35 (m, 2H), 7.30-7.28 (m, 2H), 7.19-7.13 (m, 3H), 7.11-7.06 (m, 1H), 6.85-6.83 (m, 2H), 5.10-5.05(m, 1H), 4.32-4.27 (m, 1H), 3.73-3.69 (m, 1H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8 (d, $^1J_{C\text{-}F}$ = 245 Hz), 155.1, 145.1, 140.8, 134.5, 132.8 (d, $^6J_{C\text{-}F}$ = 7 Hz), 131.9, 131.4 (d, $^5J_{C\text{-}F}$ = 2 Hz), 129.9, 127.9 (d, $^4J_{C\text{-}F}$ = 43 Hz), 123.8 (d, $^3J_{C\text{-}F}$ = 2 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 20 Hz), 67.5, 55.7, 21.8. Anal. Calcd. For $C_{22}H_{18}BrFN_2O_2S$: C, 55.82; H, 3.83; N, 5.92%; Found: C, 55.88; H, 3.87; N, 5.98%.

4-(4-Bromophenyl)-2-(4-fluorophenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24a'). Off-white solid, 359 mg, yield 74%, mp 205-207 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.79 (m, 2H), 7.36-7.31 (m, 4H), 7.18-7.11 (m, 4H), 6.83-6.81 (m, 2H), 4.96-4.92 (m, 1H), 4.44-4.39 (m, 1H), 3.85-3.80 (m, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8 (d, $^1J_{C\text{-}F}$ = 250 Hz), 159.5, 145.2, 140.8, 134.4, 132.3 (d, $^4J_{C\text{-}F}$ = 8 Hz), 131.7, 129.9, 128.2 (d, $^3J_{C\text{-}F}$ = 40 Hz), 127.6, 121.4, 115.1 (d, $^2J_{C\text{-}F}$ = 22 Hz), 67.1, 56.9, 21.7. Anal. Calcd. For $C_{22}H_{18}BrFN_2O_2S$: C, 55.82; H, 3.83; N, 5.92%; Found: C, 55.74; H, 3.88; N, 5.84%.

2-Methyl-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24b') [76].

White solid, 179 mg, yield 57%, mp 100-102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.17-7.15 (m, 3H), 6.96-6.94(m, 2H), 4.91-4.87 (m, 1H), 4.11-4.06 (m, 1H), 3.56-3.51 (m, 1H), 2.36 (s, 3H), 2. 30 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6, 144.9, 141.6, 135.3, 130.2, 128.7, 127.7, 127.3, 126.4, 66.6, 55.6, 21.6, 16.8.

4-(2-Chlorophenyl)-2-methyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24c') [76]. White solid, 293 mg, yield 84%, mp 156-158°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (d, *J* = 8.0 Hz, 2H), 7.34-7.30 (m, 3H), 7.19-7.16 (m, 2H), 7.10-7.08 (m,1H), 5.34-5.29 (m, 1H), 4.33-4.28 (m, 1H), 3.55-3.50 (m, 1H), 2.44-2.42 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6, 144.9, 139.8, 135.5, 132.4, 130.2, 129.5, 128.8, 127.6, 127.3, 127.2, 63.9, 54.9, 29.8, 21.7, 17.1.

2-(3-Chloropropyl)-4-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (24d'). Yellow liquid, 222 mg, yield 59%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.67 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.19-7.16 (m, 3H), 6.95-6.92(m, 2H), 4.94-4.90 (m, 1H), 4.12-4.07 (m, 1H), 3.62-3.59 (m, 2H), 3.54-3.50 (m, 1H), 2.87-2.85 (m, 2H), 2.39 (s, 3H), 2.19-2.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 145.0, 141.8, 135.2, 130.3, 128.9, 127.8, 127.4, 126.5, 67.0, 55.8, 44.5, 29.2, 27.1, 21.8. Anal. Calcd. for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43%; Found: C, 60.64; H, 5.74; N, 7.50%.

4-(2-Chlorophenyl)-2-(3-chloropropyl)-1-tosyl-4,5-dihydro-1*H*-imidazole (24e'). Brown liquid, 329 mg, yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.35-7.31 (m, 3H), 7.20-7.16 (m, 2H), 7.04-7.02 (m,1H), 5.36-5.32 (m, 1H), 4.36-4.30 (m, 1H), 3.74-3.70 (m, 2H), 3.56-3.51 (m, 1H), 3.01-2.98 (m, 2H), 2.44 (s, 3H), 2.33-2.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132.3, 130.7, 130.4, 130.0, 129.9, 129.6, 129.1, 127.6, 127.4, 127.3, 127.2, 63.5, 55.0, 44.4, 29.3, 27.0, 21.8. Anal. Calcd. for $C_{19}H_{20}Cl_2N_2O_2S$: C, 55.48; H, 4.90; N, 6.81%; Found: C, 55.40; H, 4.82; N, 6.76%.

4-(2-Chlorophenyl)-2-styryl-1-tosyl-4,5-dihydro-1*H*-imidazole (24f'). Off-white solid, 358 mg, yield 82%, mp 128-130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.75 (m, 1H), 7.67-7.62 (m, 4H), 7.48-7.39 (m, 4H), 7.34-7.32 (m,1H), 7.23-7.15 (m, 3H), 7.10-7.06 (m, 1H), 6.95-6.93 (m, 1H), 5.42-5.37 (m, 1H), 4.37-4.32 (m, 1H), 3.61-3.56 (m, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.2, 144.8, 141.0, 140.1, 135.5, 134.7, 132.3, 130.1, 129.9, 129.4, 129.1, 128.7, 128.0, 127.7, 127.5, 127.1, 115.3, 64.1, 55.1, 21.7. Anal. Calcd. for $C_{24}H_{21}ClN_2O_2S$: C, 65.97; H, 4.84; N, 6.41%; Found: C, 65.89; H, 4.76; N, 6.37%.

4-(4-Chlorophenyl)-2-styryl-1-tosyl-4,5-dihydro-1*H*-imidazole (24g'). Colourless liquid, 341 mg, yield 78%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.59 (m, 3H), 7.54-7.52 (m, 2H), 7.40-7.32 (m, 4H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.13-7.10 (m, 2H), 6.83-6.81 (m, 2H), 4.99-4.94 (m, 1H), 4.17-4.12 (m, 1H), 3.55-3.51 (m, 1H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 145.0, 141.1, 140.7, 135.4, 134.5, 133.5, 130.2, 130.0, 129.1, 128.9, 128.0, 127.9, 127.6, 115.1, 66.4, 55.8, 21.7. Anal. Calcd. for $C_{24}H_{21}ClN_2O_2S$: C, 65.97; H, 4.84; N, 6.41%; Found: C, 65.90; H, 4.74; N, 6.35%.

4-(4-Bromophenyl)-2-styryl-1-tosyl-4,5-dihydro-1*H*-imidazole (24h'). Yellow liquid, 337 mg, yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.58 (m, 3H), 7.54-7.51 (m, 2H), 7.39-7.31 (m, 4H), 7.28-7.24 (m, 2H), 7.19-7.17 (m, 2H), 6.77-6.75 (m, 2H), 4.97-4.92 (m, 1H), 4.16-4.11 (m, 1H), 3.55-3.50 (m, 1H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 145.0, 141.23, 141.17, 135.4, 134.5, 131.8, 130.1, 130.0, 129.0, 128.2, 128.0, 127.5, 121.6, 115.1, 66.4, 55.7, 21.7. Anal. Calcd. For $C_{24}H_{21}BrN_2O_2S$: C, 59.88; H, 4.40; N, 5.82%; Found: C, 59.80; H, 4.33; N, 5.76%.

3.10. Synthesis of *N*-acyl-/*N*-formyl-*α*-aminoketones

Typical procedure for the synthesis of 2-substituted 3-phenyl-2*H*-azirines (25)

To a suspension of NaN_3 (.715 g, 11 mmol) in acetonitrile (3 mL) was added dropwise a solution of iodine monochloride (.807 g, 4.97 mmol) in CH_2Cl_2 (6 mL) at −20 °C, and the mixture was stirred at the same temperature. After 30 min, a solution of styrene (.5 mL, 4.36 mmol) in CH_2Cl_2 (2 mL) was added slowly, and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the organic materials were extracted two times with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation of solvents, the resulting crude materials were used immediately for the next step without any furthur purification.

To a solution of the obtained compounds above in Et_2O (10 mL) was added ^{t}BuOK (.592 g, 5.23 mmol) at 0°C, and the mixture was stirred for 1.5 h. The reaction mixture was filtered through Whatman filter paper and the solvent was removed in vacuo. The resulting crude materials were purified by column chromatography (silica gel; hexane) to give vinyl azide. Then, vinyl azide was refluxed with toluene for 4 h. After the removal of the solvent azirine was obtained and used for the next step.

Synthesis of 3-phenyl-2*H*-azirine (25a).

In a round bottom flask, 10 mmol of styrene (1.041 g) was taken in CH_2Cl_2 (8 mL) and stirred at room temperature. Bromine (1.600 g, 10 mmol) in CH_2Cl_2 (6 mL) was added slowly into it and was stirred for 2 h. Then, the CH_2Cl_2 was removed in vacuum to get the 1-(1,2-dibromoethyl)benzene residue as a crystalline solid (2.481 g, 94%). 1-(1,2-Dibromoethyl)benzene (2.481 g, 9.4 mmol) was dissolved in 14 mL of dimethyl sulfoxide. After a slow stream of N_2 was passed through the apparatus, sodium azide (0.975 g, 15 mmol) was slowly added into the solution and for 45 min afterward. The mixture became thick with precipitated azido bromide and was stirred for a further 13 h at room temperature. The reaction mixture after treatment with 0.4 g (10 mmol) of sodium hydroxide in 0.4 mL of deionized water was stirred at room temperature for 24 h. Then, the mixture was poured into 40 mL of 2% sodium bicarbonate aqueous solution and extracted with dichloromethane. The extract was washed with deionized water. Dichloromethane was removed in vacuum and evaporated to yield crude 1-azidostyrene as red oil. The oil was passed through a column of silica gel using petroleum ether as eluent. The eluent was removed in vacuum, and the residual pale yellow oil was dissolved in 20 mL of toluene. Then, the solution was refluxed for 4 h. After the removal of the solvent and distillation of the crude product, 0.820 g of 3-phenyl-2*H*-azirine (70% yield) was obtained and used for the next experiment without further purification.

General procedure for the synthesis of compounds (27a-27q).

A mixture of 3-aryl-2*H*-azirine (**25**) (1.0 mmol) and trifluoromethylacetic acid in freshly distilled toluene (3 mL) was taken in a reaction vessel (oven-dried) equipped with a magnetic stirrer bar. The reaction vessel was stirred at room temperature under open atmosphere for 10 min. After completion (TLC) the reaction mixture was diluted with a mixture of 10 mL water/ethyl acetate (1:1). Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60−120 mesh) using ethyl acetate/petroleum ether as eluent.

General procedure for the synthesis of compounds (27r-27e').

A mixture of 3-aryl-2*H*-azirine **25** (1.0 mmol), different acids (1.0 mmol) and freshly distilled toluene (3 mL) was taken in a reaction vessel (oven-dried) equipped with a magnetic stirrer bar. The reaction vessel was stirred at room temperature under open atmosphere for 10 min. The reaction mixture was diluted with a mixture of 10 mL water/ethyl acetate (1:1) after completion of the reaction (TLC). Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60−120 mesh) using ethyl acetate/petroleum ether as eluent.

General procedure for the synthesis of compounds (27f'-27t').

A mixture of 3-aryl-2*H*-azirine **25** (1.0 mmol) and formic acid (1.0 mmol) was taken in a reaction vessel (oven-dried) equipped with a magnetic stirrer bar. The reaction vessel was stirred at room temperature under open atmosphere for 10 min. No extra solvent (toluene) was taken here. The reaction mixture was diluted with a mixture of 10 mL water/ethyl acetate (1:1) after completion (TLC). Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60−120 mesh) using ethyl acetate/petroleum ether as eluent.

General procedure for the synthesis of compounds (29).

A mixture of 3-aryl-2*H*-azirine **25** (1.0 mmol), formic acid (1.0 mmol), formaldehyde (1.0 mmol) was taken in a reaction vessel (oven-dried) equipped with a magnetic stirrer bar. The reaction vessel was stirred at room temperature under open atmosphere for 10 min in neat conditions. The reaction mixture was diluted with a mixture of 10 mL water/ethyl acetate (1:1) after completion of the reaction (TLC). Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation

of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60−120 mesh) using ethyl acetate/petroleum ether as eluent.

Typical procedure for the synthesis of 1,2,4-triazine (27aa).

A mixture of 2,2,2-trifluoro-*N*-(2-oxo-2-phenylethyl)acetamide (**27a,** 0.5 mmol), hydrazine hydrate (1.0 mmol) and freshly distilled acetic acid (1 mL) was taken in a reaction vessel (oven-dried) equipped with a magnetic stirrer bar. The reaction vessel was stirred at 70 °C temperature under open atmosphere for 5 h. The reaction mixture was diluted with a mixture of 10 mL water/ethyl acetate (1:1) after completion of the reaction (TLC) and washed with sodium bicarbonate. Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60−120 mesh) using ethyl acetate/petroleum ether as eluent.

2,2,2-Trifluoro-*N*-(2-oxo-2-phenylethyl)acetamide (27a) [383]. Off white solid (217 mg, yield 94%) mp 105-107 °C; R_f = 0.80 (petroleum ether/EtOAc = 88/12); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 3H), 4.82 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.2, 157.3 (q, J_{C-F} = 38.0 Hz), 134.9, 133.8, 129.3, 128.2, 115.8 (q, J_{C-F} = 286.0 Hz), 46.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7.

2,2,2-Trifluoro-*N*-(2-oxo-2-(*o*-tolyl)ethyl)acetamide (27b). Brown gummy (196 mg, yield 80%); R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.56 (bs, 1H), 7.50-7.46 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 4.73 (d, *J* = 4.4 Hz, 2H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 157.3 (q, J_{C-F} = 38.0 Hz), 140.4, 133.4, 133.2, 132.8, 129.0, 126.4, 115.9 (q, J_{C-F} = 286.0 Hz), 47.6, 22.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7, -75.8; Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.80; H, 4.02; N, 5.63.

2,2,2-Trifluoro-*N*-(2-oxo-2-(*m*-tolyl)ethyl)acetamide (27c). Red gummy (221 mg, yield 90%) R_f = 0.70 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77-7.75 (m, 2H), 7.56 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 4.79 (d, *J* = 4.4 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 157.3 (q, J_{C-F} = 38.0 Hz), 139.2, 135.6, 133.8, 129.1, 128.6, 125.3, 120.1, 115.8 (q, J_{C-F} = 286.0 Hz), 46.3, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7; Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.94; H, 4.18; N, 5.80.

2,2,2-Trifluoro-*N*-(2-oxo-2-(*p*-tolyl)ethyl)acetamide (27d) [383]. Pale yellow solid (225 mg, yield 92%) mp 108-110 °C; R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J = 8.0 Hz, 2H), 7.57 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.76 (d, J = 4.4 Hz, 2H),

2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 157.3 (q, J_{C-F} = 38.0 Hz), 146.0, 131.3, 129.9, 128.2, 115.8 (q, J_{C-F} = 286.0 Hz), 46.1, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7.

***N*-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27e).** Brown solid (228 mg, yield 88%) mp 102-104 °C; R_f = 0.80 (petroleum ether/EtOAc = 88/12); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 4.69 (d, *J* = 4.0 Hz, 2H), 2.54 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.6, 157.2 (q, J_{C-F} = 38.0 Hz), 144.5, 140.7, 133.6, 130.3, 129.4, 126.9, 115.9 (q, J_{C-F} = 286.0 Hz), 47.3, 22.1, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.8; Anal. Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.50; H, 4.78; N, 5.32.

***2*,2,2-Trifluoro-*N*-(2-mesityl-2-oxoethyl)acetamide (27f).** Brown gummy (213 mg, yield 78%); Rf = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (s, 1H), 6.88 (s, 2H), 4.43 (d, *J* = 4.8 Hz, 2H), 2.30 (s, 3H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.7, 157.6 (q, J_{C-F} = 38.0 Hz), 140.1, 135.4, 133.4, 128.9, 118.6 (q, J_{C-F} = 288.0 Hz), 50.7, 21.2, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6; Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.08; H, 5.03; N, 5.07.

***N*-(2-(4-(*Tert*-butyl)phenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27g).** Pale yellow solid (250 mg, yield 87%) mp 93-95 °C; R_f = 0.80 (petroleum ether/EtOAc = 87/13); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.60 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 4.79 (d, *J* = 4.4 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.8, 158.9, 157.30 (q, J_{C-F} = 38.0 Hz), 131.2, 128.1, 126.2, 115.8 (q, J_{C-F} = 286.0 Hz), 46.2, 35.4, 31.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7; Anal. Calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.62; H, 5.70; N, 4.95.

***N*-(2-(3-Chlorophenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27h).** Yellowish Brown gummy (226 mg, yield 85%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.95 (m, 1H), 7.86-7.84 (m, 1H), 7.65-7.62 (m, 1H), 7.50-7.45 (m, 2H), 4.80 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.2, 157.4 (q, J_{C-F} = 38.0 Hz), 135.8, 135.3, 134.8, 130.6, 128.3, 126.2, 115.8 (q, J_{C-F} = 286.0 Hz), 46.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.8; Anal. Calcd for $C_{10}H_7ClF_3NO_2$: C, 45.22; H, 2.66; N, 5.27. Found: C, 45.29; H, 2.73; N, 5.37.

***N*-(2-(4-Chlorophenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (2i) [383].** Brown solid (218 mg, yield 82%) mp 94-96 °C; R_f = 0.60 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.52-7.49 (m, 3H), 4.79 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.1, 157.3 (q, J_{C-F} = 39.0 Hz), 141.6, 132.1, 129.7, 129.5, 115.8 (q, J_{C-F} = 286.0 Hz), 46.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7.

***N*-(2-(3-Bromophenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27j).** Brownish white solid (229 mg, yield 74%) mp 108-110 °C; R_f = 0.65 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.09 (m, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.43-7.38 (m, 1H), 4.79 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.1, 157.4 (q, J_{C-F} = 39.0 Hz), 137.7, 135.5 131.2, 130.8, 126.6, 123.6, 115.8 (q, J_{C-F} = 286.0 Hz), 46.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7; Anal. Calcd for $C_{10}H_7BrF_3NO_2$: C, 38.74; H, 2.28; N, 4.52. Found: C, 38.62; H, 2.20; N, 4.21.

***N*-(2-(4-Bromophenyl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27k).** White solid (267 mg, yield 86%) mp 112-114 °C; R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.53 (bs, 1H), 4.78 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.4, 157.3 (q, J_{C-F} = 38.0 Hz), 132.6, 132.5, 130.2, 129.5, 115.8 (q, J_{C-F} = 286.0 Hz), 46.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7; Anal. Calcd for $C_{10}H_7BrF_3NO_2$: C, 38.74; H, 2.28; N, 4.52. Found: C, 38.63; H, 2.20; N, 4.47.

2,2,2-Trifluoro-*N*-(2-(3-fluorophenyl)-2-oxoethyl)acetamide (27l). Brown gummy (224 mg, yield 90%); R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77-7.75 (m, 1H), 7.68-7.65 (m, 1H), 7.55-7.49 (m, 2H), 7.39-7.34 (m, 1H), 4.81 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.2, 163.1(d, $^1J_{C-F}$ = 249 Hz), 157.4 (q, J_{C-F} = 38.0 Hz), 135.7, 131.1 (d, $^5J_{C-F}$ = 6 Hz), 123.9 (d, $^4J_{C-F}$ = 3 Hz), 122.0 (d, $^3J_{C-F}$ = 22 Hz), 114.9 (d, $^2J_{C-F}$ = 23 Hz), 115.8 (q, J_{C-F} = 285.0 Hz), 46.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7, -75.9; Anal. Calcd for $C_{10}H_7F_4NO_2$: C, 48.21; H, 2.83; N, 5.62. Found: C, 48.16; H, 2.78; N, 5.54.

2,2,2-Trifluoro-*N*-(2-(4-fluorophenyl)-2-oxoethyl)acetamide (27m) [384]. Pale yellow gummy (212 mg, yield 85%) mp 108-110 °C; R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-7.99 (m, 2H), 7.54 (bs, 1H), 7.22-7.17 (m, 2H), 4.79 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.7, 168.03, 165.5, 166.7 (d, $^1J_{C-F}$ = 257 Hz), 157.4 (q, J_{C-F} = 38.0 Hz), 130.9 (d, $^4J_{C-F}$ = 9 Hz), 130.3 (d, $^3J_{C-F}$ = 3 Hz), 116.6 (d, $^2J_{C-F}$ = 22 Hz), 115.8 (q, J_{C-F} = 286.0 Hz), 46.2.

2,2,2-Trifluoro-*N*-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)acetamide (27n) [384]. Yellowish white solid (260 mg, yield 87%) mp 108-110 °C; R_f = 0.80 (petroleum ether/EtOAc = 89/11); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.44 (s, 1H), 4.86 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.5, 157.4 (q, J_{C-F} = 38.0 Hz), 156.6, 136.6, 136.5, 136.3, 136.0, 128.6, 126.4 (q, J_{C-F} = 4.0 Hz), 123.4 (q, J_{C-F} = 272.0 Hz), 115.8 (q, J_{C-F} = 286.0 Hz), 46.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4, -75.7.

***N*-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-2,2,2-trifluoroacetamide (27o).** Off white solid (230 mg, yield 75%) mp 130-132 °C; R_f = 0.65 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 2H), 7.76-7.73 (m, 2H), 7.65-7.62 (m, 2H), 7.55 (bs, 1H), 7.51-7.42 (m, 3H), 4.85 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.7, 157.3 (q, J_{C-F} = 38.0 Hz), 147.7, 139.4, 132.4, 129.2, 128.85, 128.78, 127.9, 127.4, 115.9 (q, J_{C-F} = 286.0 Hz), 46.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7; Anal. Calcd for $C_{16}H_{12}F_3NO_2$: C, 62.54; H, 3.94; N, 4.56. Found: C, 62.48; H, 3.87; N, 4.46.

2,2,2-Trifluoro-*N*-(2-(naphthalen-1-yl)-2-oxoethyl)acetamide (27p) [384]. Pale yellow solid (225 mg, yield 80%) mp 100-102 °C; R_f = 0.75 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.00-7.98 (m, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.68-7.52 (m, 4H), 4.88 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.8, 157.3 (q, J_{C-F} = 38.0 Hz), 135.3, 134.2, 130.9, 130.5, 129.3, 129.2, 128.9, 127.1, 125.6, 124.5, 115.9 (q, J_{C-F} = 286.0 Hz), 47.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.7.

2,2,2-Trifluoro-*N*-(2-(naphthalen-2-yl)-2-oxoethyl)acetamide (27q). Yellowish brown solid (214 mg, yield 76%) mp 116-118 °C; R_f = 0.70 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 8.02-7.89 (m, 4H), 7.66-7.59 (m, 3H), 4.94 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.0, 157.3 (q, J_{C-F} = 38.0 Hz), 136.4, 132.5, 131.0, 130.4, 129.8, 129.6, 129.3, 128.1, 127.5, 123.1, 115.8 (q, J_{C-F} = 286.0 Hz), 46.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6; Anal. Calcd for $C_{14}H_{10}F_3NO_2$: C, 59.79; H, 3.58; N, 4.98. Found: C, 59.70; H, 3.51; N, 4.91.

2,2-Difluoro-*N*-(2-oxo-2-phenylethyl)acetamide (27r). Brown gummy mass (170 mg, yield 80%); R_f = 0.60 (petroleum ether/EtOAc = 75/25); ^{1}H NMR (CDCl3, 400 MHz): δ 7.99-7.96 (m, 2H), 7.67-7.63 (m, 1H), 7.54-7.50 (m, 2H), 7.46 (bs, 1H), 5.98 (t, *J* = 54.0 Hz, 1H), 4.80 (d, *J* = 4.4 Hz, 2H). 13C NMR ($CDCl_3$, 100 MHz): δ 192.7, 162.8 (t, $^2J_{C-F}$ = 26 Hz), 134.7, 134.1, 129.2, 128.1, 108.4 (t, $^1J_{C-F}$ = 250 Hz), 46.0. 19F NMR (376 MHz, $CDCl_3$) δ -126.4 (d, $^2J_{F-H}$ = 56.0 Hz). Anal. Calcd for $C_{10}H_9F_2NO_2$: C, 56.34; H, 4.26; N, 6.57. Found: C, 56.39; H, 4.31; N, 6.51.

***N*-(2-(4-Chlorophenyl)-2-oxoethyl)-2,2-difluoroacetamide (27s).** Brown gummy mass (203 mg, yield 82%); R_f = 0.50 (petroleum ether/EtOAc = 75/25); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92-7.90 (m, 2H), 7.50-7.48 (m, 2H), 7.43 (bs, 1H), 5.98 (t, *J* = 54.0 Hz, 1H), 4.77 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 162.8 (t, $^2J_{C-F}$ = 25 Hz), 141.3, 132.4, 129.6, 129.5, 108.4 (t, $^1J_{C-F}$ = 251 Hz), 45.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.4 (d, $^2J_{F-H}$ = 52.6 Hz). Anal. Calcd for $C_{10}H_8ClF_2NO_2$: C, 48.50; H, 3.26; N, 5.66. Found: C, 48.56; H, 3.21; N, 5.60.

2,2,2-Trichloro-*N*-(2-oxo-2-(*p*-tolyl)ethyl)acetamide (27t). Brown gummy mass (250 mg, yield 85%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (bs, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.75 (d, J = 4.4 Hz, 2H), 2.41 (s, 3H). 13C NMR ($CDCl_3$, 100 MHz): δ 192.1, 161.9, 145.8, 131.4, 129.8, 128.1, 92.2, 47.6, 21.8. Anal. Calcd for $C_{11}H_{10}Cl_3NO_2$: C, 44.85; H, 3.42; N, 4.76. Found: C, 44.80; H, 3.36; N, 4.70.

2,2,2-Trichloro-*N*-(2-(4-chlorophenyl)-2-oxoethyl)acetamide (27u). Brown gummy mass (252 mg, yield 80%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.91 (m, 2H), 7.85 (bs, 1H), 7.51-7.49 (m, 2H), 4.79 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.5, 162.1, 141.4, 132.3, 129.6, 129.5, 92.1, 47.8. Anal. Calcd for $C_{10}H_7C_{l4}NO_2$: C, 38.13; H, 2.24; N, 4.45. Found: C, 38.08; H, 2.30; N, 4.40.

2-Bromo-*N*-(2-oxo-2-phenylethyl)acetamide (27v). Brown gummy mass (205 mg, yield 80%); R_f = 0.60 (petroleum ether/EtOAc = 60/40); ^{1}H NMR (CDCl3, 400 MHz): δ 7.99-7.97 (m, 2H), 7.65-7.62 (m, 1H), 7.56 (bs, 1H), 7.53-7.49 (m, 2H), 4.78 (d, *J* = 4.4 Hz, 2H), 3.96 (s, 2H). 13C NMR ($CDCl_3$, 100 MHz): δ 193.4, 165.9, 134.5 134.2, 129.1, 128.1, 47.0, 28.8. Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 46.88; H, 3.89; N, 5.40.

2-Bromo-*N*-(2-oxo-2-(*m*-tolyl)ethyl)acetamide (27w). Orange gummy mass (243 mg, yield 90%); R_f = 0.55 (petroleum ether/EtOAc = 60/40); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.58 (bs, 1H), 7.42-7.34 (m, 2H), 4.74 (d, *J* = 4.4 Hz, 2H), 3.94 (s, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.5, 165.9, 138.9, 135.1, 134.2, 128.9, 128.5, 125.2, 46.9, 28.7, 21.3. Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.85; H, 4.55; N, 5.12.

2-Bromo-*N*-(2-(4-chlorophenyl)-2-oxoethyl)acetamide (27x). White gummy mass (255 mg, yield 88%); R_f = 0.60 (petroleum ether/EtOAc = 60/40); ^{1}H NMR (CDCl3, 400 MHz): δ 7.92-7.90 (m, 2H), 7.51-7.47 (m, 3H), 4.74 (d, *J* = 4.4 Hz, 2H), 3.95 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 166.0, 141.0, 132.6, 129.5, 129.4, 46.9, 28.7. Anal. Calcd for $C_{10}H_9BrClNO_2$: C, 41.34; H, 3.12; N, 4.82. Found: C, 41.29; H, 3.07; N, 4.75.

2-Bromo-*N*-(1-oxo-1-phenylpropan-2-yl)acetamide (27y). Brown liquid (194 mg, yield 72%); R_f = 0.55 (petroleum ether/EtOAc = 60/40); ^{1}H NMR (CDCl3, 400 MHz): δ 7.99-7.97 (m, 2H), 7.64-7.60 (m, 2H), 7.52-7.48 (m, 2H), 5.55-5.48 (m, 1H), 3.91 (d, *J* = 2.8 Hz, 2H), 1.46 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 165.2, 134.3, 133.6, 129.1, 128.9, 50.9, 29.0, 19.6. Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.96; H, 4.35; N, 5.13.

***N*-(2-Oxo-2-phenylethyl)propiolamide (27z).** Yellow gummy mass (161 mg, yield 86%); R_f = 0.55 (petroleum ether/EtOAc = 60/40); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.96 (m, 2H), 7.66-7.63 (m, 1H), 7.53-7.49 (m, 2H), 7.05 (bs, 1H), 4.81 (d, *J* = 4.4 Hz, 2H), 2.89 (s, 1H). 13C NMR (CDCl3, 100 MHz): δ 192.9, 152.1, 134.6, 134.1, 129.2, 128.1, 77.0, 74.1, 46.6. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.52; H, 4.79; N, 7.53.

***N*-(2-(4-Chlorophenyl)-2-oxoethyl)propiolamide (27a').** Brownish white gummy mass (199 mg, yield 90%); R_f = 0.55 (petroleum ether/EtOAc = 60/40); 1H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.89 (m, 2H), 7.49-7.47 (m, 2H), 7.00 (bs, 1H), 4.77 (d, *J* = 4.4 Hz, 2H), 2.88 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9, 152.1, 141.2, 132.5, 129.54, 129.47, 76.9, 74.3, 46.6. Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.55; H, 3.60; N, 6.27.

***N*-(2-Oxo-1,2-diphenylethyl)propiolamide (27b').** Off-white gummy mass (195 mg, yield 74%); R_f = 0.55 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.91 (m, 2H), 7.50-7.47 (m, 3H), 7.42-7.36 (m, 6H), 6.93 (s, 1H), 2.98 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.2, 152.0, 134.2, 133.8, 132.6, 129.8, 129.4, 129.0, 128.9, 128.8, 79.3, 76.4, 74.2. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.49; H, 4.92; N, 5.26.

***N*-(2-Oxo-2-phenylethyl)-3-phenylpropiolamide (27c').** Brownish yellow semi-solid (229 mg, yield 87%); R_f = 0.55 (petroleum ether/EtOAc = 80/20); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.96 (m, 2H), 7.64-7.60 (m, 1H), 7.56-7.54 (m, 2H), 7.51-7.47 (m, 2H),7.43-7.39 (m, 1H), 7.37-7.33 (m, 2H), 7.13 (bs, 1H), 4.86 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 153.4, 134.4, 134.2, 132.7, 130.3, 129.1, 128.6, 128.1, 120.1, 85.6, 82.7, 46.7. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.50; H, 4.93; N, 5.26.

***N*-(2-(4-Chlorophenyl)-2-oxoethyl)-3-phenylpropiolamide (27d').** Brown gummy mass (253 mg, yield 85%); R_f = 0.50 (petroleum ether/EtOAc = 65/35); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.55-7.52 (m, 2H), 7.47-7.39 (m, 3H), 7.36-7.32 (m, 2H), 7.09 (bs, 1H), 4.82 (d, *J* = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.2, 153.4, 141.0, 132.7, 132.5, 130.3, 129.4, 128.6, 120.0, 85.8, 82.6, 46.7. Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.58; H, 4.06; N, 4.70. Found: C, 68.52; H, 4.02, N, 4.77.

***N*-(2-Oxo-1,2-diphenylethyl)-3-phenylpropiolamide (27e').** Off-white gummy mass (302 mg, yield 89%); R_f = 0.50 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97-7.95 (m, 2H), 7.60-7.58 (m, 2H), 7.55-7.51 (m, 3H), 7.47-7.35 (m, 9H), 6.99 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.7, 153.4, 134.4, 133.8, 133.2, 133.0, 130.9, 129.8, 129.4, 129.05, 128.99, 128.8,

128.7, 119.5, 88.0, 80.3, 79.0. Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.36; H, 5.11; N, 4.07.

***N*-(2-Oxo-2-phenylethyl)formamide (27f').** Brown liquid (147 mg, yield 90%); R_f = 0.55 (petroleum ether/EtOAc = 50/50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, *1*H), 7.99-7.96 (m, 2H), 7.66-7.61 (m, 1H), 7.53-7.49 (m, 2H), 6.79 (bs, 1H), 4.82-4.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.6, 161.2, 134.5, 134.3, 129.1, 128.1, 45.1. Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.18; H, 5.62; N, 8.67.

***N*-(2-Oxo-2-(o-tolyl)ethyl)formamide (27g').** Brown liquid (156 mg, yield 88%); R_f = 0.60 (petroleum ether/EtOAc = 48/52); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, *1*H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.39-7.35 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 2H), 6.87 (bs, 1H), 4.64-4.63 (m, 2H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.4, 161.3, 139.7, 134.0, 132.8, 132.5, 128.9, 126.2, 46.5, 21.8. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.83; H, 6.35; N, 7.97.

***N*-(2-Oxo-2-(*m*-tolyl)ethyl)formamide (27h').** Brown liquid (150 mg, yield 85%); R_f = 0.55 (petroleum ether/EtOAc = 45/55); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, *1*H), 7.78-7.75 (m, 2H), 7.44-7.36 (m, 2H), 6.84 (bs, 1H), 4.79-4.78 (m, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 161.3, 139.0, 135.2, 134.3, 129.0, 128.6, 125.2, 45.1, 21.4. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.22; N, 7.82.

***N*-(2-Oxo-2-(*p*-tolyl)ethyl)formamide (27i').** Brown liquid (161 mg, yield 91%); R_f = 0.50 (petroleum ether/EtOAc = 50/50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 1H), 7.89-7.86 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.81 (bs, 1H), 4.78-4.76 (m, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.2, 161.2, 145.5, 131.8, 129.8, 128.2, 44.9, 21.9. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.86; H, 6.35; N, 7.97.

***N*-(2-(2,4-Dimethylphenyl)-2-oxoethyl)formamide (27j').** Brown solid (155 mg, yield 81%) mp 85-87 °C; R_f = 0.65 (petroleum ether/EtOAc = 50/50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (s, *1*H), 7.64-7.62 (m, 1H), 7.06-7.04 (m, 3H), 4.66-4.65 (m, 2H), 2.49 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 161.4, 143.7, 140.1, 133.3, 131.1, 129.2, 126.7, 46.1, 21.9, 21.4. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.02; H, 6.78; N, 7.17.

***N*-(2-Mesityl-2-oxoethyl)formamide (27k').** Yellow solid (160 mg, yield 78%) mp 82-84 °C; R_f = 0.60 (petroleum ether/EtOAc = 48/52); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (s, *1*H), 6.84 (s, 2H), 6.76 (bs, 1H), 4.38 (d, *J* = 4.8 Hz, 2H), 2.27 (s, 3H), 2.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 100

MHz): δ 204.6, 161.3, 139.5, 136.1, 133.3, 128.7, 49.5, 21.1, 19.0. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.14; H, 7.30; N, 6.73.

***N*-(2-(2-Chlorophenyl)-2-oxoethyl)formamide (27l').** Brown liquid (158 mg, yield 80%); R_f = 0.65 (petroleum ether/EtOAc = 46/54); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (s, *1*H), 7.67-7.64 (m, 1H), 7.46-7.45 (m, 2H), 7.38-7.34 (m, 1H), 6.72 (bs, 1H), 4.74-4.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 161.2, 135.5, 133.3, 132.1, 131.2, 130.0, 127.3, 48.1. Anal. Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.79; H, 4.17; N, 7.02.

***N*-(2-(3-Bromophenyl)-2-oxoethyl)formamide (27m').** Brown gummy (184 mg, yield 76%); R_f = 0.55 (petroleum ether/EtOAc = 40/60); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (s, *1*H), 8.06-8.05 (m, 1H), 7.86-7.83 (m, 1H), 7.71-7.69 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H) 7.01 (bs, 1H), 4.75-4.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.7, 161.5, 137.1, 135.9, 131.0, 130.6, 126.5, 123.3, 45.1. Anal. Calcd for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.58; H, 3.27; N, 5.70.

***N*-(2-(4-Bromophenyl)-2-oxoethyl)formamide (27n').** Brown liquid (211 mg, yield 87%); R_f = 0.70 (petroleum ether/EtOAc = 48/52); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 1H), 7.85-7.81 (m, 2H), 7.66-7.64 (m, 2H), 6.76 (bs, 1H), 4.77-4.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.8, 161.2, 133.0, 132.5, 129.8, 129.5, 45.0. Anal. Calcd for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; N, 5.79. Found: C, 44.61; H, 3.39; N, 5.70.

***N*-(2-(4-Fluorophenyl)-2-oxoethyl)formamide (27o').** Brown liquid (152 mg, yield 84%); R_f = 0.60 (petroleum ether/EtOAc = 45/55); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (s, 1H), 8.02-7.97 (m, 2H), 7.18-7.14 (m, 2H), 6.90 (bs, 1H), 4.77 (d, *J* = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.2, 166.5 (d, $^3J_{C\text{-}F}$ = 255 Hz), 161.4, 130.8(d, $^1J_{C\text{-}F}$ = 9 Hz), 116.3(d, $^2J_{C\text{-}F}$ = 21 Hz), 44.9. Anal. Calcd for $C_9H_8FNO_2$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.62; H, 4.40; N, 7.64.

***N*-(2-(3-Nitrophenyl)-2-oxoethyl)formamide (27p').** Yellow solid (173 mg, yield 83%); mp 122-124 °C; R_f = 0.80 (petroleum ether/EtOAc = 20/80); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77-8.76 (m, *1*H), 8.46-8.43 (m, 1H), 8.34 (s, 1H), 8.31-8.28 (m, 1H), 7.76-7.71 (m, 1H), 6.95 (bs, 1H), 4.88-4.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1, 161.5, 148.6, 135.6, 133.6, 130.5, 128.4, 123.0, 45.3. Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.87; H, 3.81; N, 13.51.

***N*-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)formamide (27q').** Brown solid (208 mg, yield 87%) mp 118-120 °C; R_f = 0.50 (petroleum ether/EtOAc = 40/60); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 8.06-8.04 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.64-7.62 (m, 2H), 7.50-7.46 (m, 2H), 7.44-7.40

(m, 1H), 6.82 (bs, 1H), 4.84 (d, J = 4.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.2, 161.2, 147.2, 139.5, 132.9, 129.2, 128.7, 127.7, 127.4, 45.1. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.21; H, 5.39; N, 5.80.

***N*-(2-(Naphthalen-1-yl)-2-oxoethyl)formamide (27r').** Brown liquid (158 mg, yield 74%); R_f = 0.55 (petroleum ether/EtOAc = 50/50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 6.8 Hz, 1H) 7.90 (d, J = 7.6 Hz, 1H), 7.66-7.63 (m, 1H), 7.59-7.53 (m, 2H), 6.86 (bs, 1H), 4.87 (d, J = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.6, 161.3, 134.7, 134.1, 131.7, 130.4, 128.92, 128.87, 128.8, 127.0, 125.6, 124.5, 46.7. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.16; H, 5.12; N, 6.47.

***N*-(1-Oxo-1-phenylpropan-2-yl)formamide (27s').** Yellowish white gummy mass (156 mg, yield 88%); R_f = 0.55 (petroleum ether/EtOAc = 50/50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 7.99-7.97 (m, 2H), 7.64-7.60 (m, 1H), 7.52-7.48 (m, 2H), 6.86 (bs, 1H), 5.68-5.61 (m, 1H), 1.46 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.5, 160.5, 134.3, 133.7, 129.1, 128.9, 49.0, 19.9. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.21; N, 7.85.

***N*-(2-Oxo-1,2-diphenylethyl)formamide (27t').** Off-white gummy mass (179 mg, yield 75%); R_f = 0.50 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (s, 1H), 7.95-7.93 (m, 2H), 7.55-7.51 (m, 1H), 7.49-7.46 (m, 2H), 7.43-7.36 (m, 5H), 7.00 (s, 1H). ^{13}C NMR (CDCl3, 100 MHz): δ 192.9, 160.1, 134.4, 134.1, 133.8, 133.2, 129.7, 129.4, 129.0, 128.9, 77.2. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.25; H, 5.41; N, 5.80.

***N*-(Hydroxymethyl)-*N*-(2-oxo-2-phenylethyl)formamide (29a).** Brown liquid (151 mg, yield 78%); R_f = 0.60 (petroleum ether/EtOAc = 25/75); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H), 7.99-7.96 (m, 2H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 2H), 4.93 (s, 2H), 4.90 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.2, 163.7, 134.7, 134.4, 129.0, 128.3, 73.8, 49.3. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.07; H, 5.66; N, 7.17.

***N*-(Hydroxymethyl)-*N*-(2-oxo-2-(*o*-tolyl)ethyl)formamide (29b).** Yellowish brown liquid (149 mg, yield 72%); R_f = 0.55 (petroleum ether/EtOAc = 30/70); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.44-7.40 (m, 1H), 7.31-7.28 (m, 2H), 4.88 (s, 2H), 4.76 (s, 2H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 163.7, 139.2, 135.0, 132.5, 132.4, 128.8, 126.0, 73.7, 51.1, 21.4. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.70; H, 6.40; N, 6.68.

***N*-(Hydroxymethyl)-*N*-(2-oxo-2-(*m*-tolyl)ethyl)formamide (29c).** Brown liquid (153 mg, yield 74%); R_f = 0.50 (petroleum ether/EtOAc = 30/70); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 7.77-7.74 (m, 2H), 7.43-7.34 (m, 2H), 4.89 (s, 2H), 4.87 (s, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 163.8, 138.9, 135.0, 134.7 128.9, 128.8, 125.5, 73.6, 49.1, 21.4. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.71; H, 6.38; N, 6.82.

***N*-(Hydroxymethyl)-*N*-(2-mesityl-2-oxoethyl)formamide (29d).** Brown liquid (160 mg, yield 68%); R_f = 0.60 (petroleum ether/EtOAc = 20/80); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H), 6.86 (s, 2H), 4.89 (s, 2H), 4.51 (s, 2H), 2.29 (s, 3H), 2.26 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.6, 163.5, 139.5, 136.0, 133.6, 128.8, 73.7, 53.8, 21.2, 19.1. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.44; H, 7.36; N, 5.90.

***N*-(2-(4-Fluorophenyl)-2-oxoethyl)-*N*-(hydroxymethyl)formamide (29e).** Brown liquid (148 mg, yield 70%); R_f = 0.60 (petroleum ether/EtOAc = 20/80); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H), 8.03-7.99 (m, 2H), 7.18-7.14 (m, 2H), 4.90 (s, 2H), 4.88 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.5, 166.5 (d, $^3J_{C\text{-}F}$ = 255 Hz), 131.1, (d, $^1J_{C\text{-}F}$ =10 Hz), 116.3 (d, $^2J_{C\text{-}F}$ = 22 Hz), 73.7, 49.1. Anal. Calcd for $C_{10}H_{10}FNO_3$: C, 56.87; H, 4.77; N, 6.63. Found: C, 56.80; H, 4.69; N, 6.55.

***N*-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-*N*-(hydroxymethyl)formamide (29f).** Yellow liquid (167 mg, yield 62%); R_f = 0.55 (petroleum ether/EtOAc = 30/70); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (s, 1H), 8.05-8.03 (m, 2H), 7.71-7.69 (m, 2H), 7.63-7.61 (m, 2H),7.49-7.41 (m, 3H), 4.96 (s, 2H), 4.92 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.7, 163.8, 147.0, 139.6, 133.3, 129.1, 128.9, 128.6, 127.6, 127.4, 73.8, 49.3. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.30; H, 5.55; N, 5.28.

***N*-(Hydroxymethyl)-*N*-(2-(naphthalen-1-yl)-2-oxoethyl)formamide (29g).** Brown liquid (158 mg, yield 65%); R_f = 0.60 (petroleum ether/EtOAc = 25/75); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (s, 1H), 8.05-8.03 (m, 2H), 7.71-7.69 (m, 2H), 7.63-7.61 (m, 2H),7.49-7.41 (m, 3H), 4.96 (s, 2H), 4.92 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.7, 163.8, 147.0, 139.6, 133.3, 129.1, 128.9, 128.6, 127.6, 127.4, 73.8, 49.3. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.30; N, 5.69.

6-Phenyl-3-(trifluoromethyl)-1,2,4-triazine (27aa) [385]. Yellow semi-solid (191 mg, yield 85%); R_f = 0.50 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 8.18-8.16 (m, 2H), 7.65-7.60 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 155.8 (q, $J_{C\text{-}F}$ = 38.0 Hz), 147.1,132.4, 131.9, 129.8, 119.9(q, $J_{C\text{-}F}$ = 278 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.4. Anal. Calcd for $C_{10}H_6F_3N_3$: C, 53.34; H, 2.69; N, 18.66. Found: C, 53.28; H, 2.62; N, 18.60.

3.11. Synthesis of bis(β,β′-dialkoxy carbonyl) compounds by oxidative cleavage of aziridines

General procedure for the synthesis of compounds (3)

1 mmol of aziridine (**1**) and 2 mL of DMSO was taken in a dry sealed tube then the resulting mixture was stirred and heated at 100 ºC for 45 min. After that the resulting mixture was cooled to room temperature and dimethyl malonoate or diethyl malonoate (2 equiv.) and ^{t}BuOK (1 equiv.) were added to the same reaction vessel. The final mixture was stirred at room temperature for 45 min. (monitored by TLC). The reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). Then organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent the crude product was collected and purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent.

Tetramethyl 2-benzoylpropane-1,1,3,3-tetracarboxylate (30a) [386]. Pale Yellow Oil (334mg, 88%) ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (m, 2H), 7.59-7.55 (m, 1H), 7.55-7.45 (m, 2H), 4.87 (t, J = 8.0 HZ, 1H), 4.11 (d, J = 8.0 HZ, 2H), 3.72(s, 6H), 3.53(s, 6H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.9, 168.3, 168.1, 136.4, 133.6, 129.0, 128.7, 53.1, 52.9, 52.4, 44.1.

Tetramethyl 2-(2-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30b) [386]. Pale Yellow Oil (315 mg, 80%) ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.85 (m, 1H), 7.39-7.35 (m, 1H), 7.30-7.28 (m, 1H), 7.24-7.22 (m, 1H), 4.77 (t, J = 8.0 Hz, 1H), 4.05 (d, J = 8.0 Hz, 2H), 3.65(s, 6H), 3.60(s, 6H), 2.44(s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.9, 168.0, 167.9, 139.4, 136.5, 131.8, 131.7, 129.5, 125.6, 52.8, 52.8, 51.5, 47.2, 20.6.

Tetramethyl 2-(3-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30c) [386]. Light yellow oil (276 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.80 (m, 2H), 7.39-7.34 (m, 2H), 4.86 (t, J = 8.0 Hz, 1H), 4.11 (d, J = 8.0 Hz, 2H), 3.72(s, 6H), 3.54(s, 6H), 2.41 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.8, 168.1, 168.0 138.4, 136.2, 134.3, 129.3, 128.4, 126.2, 52.9, 52.8, 52.2, 44.1, 21.3.

Tetramethyl 2-(4-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30d) [386]. Pale yellow Oil (335 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92-7.90 (m, 2H), 7.28-7.26 (m, 2H), 4.85 (t, J = 8.4 Hz, 1H), 4.10 (d, J = 8.0 Hz, 2H), 3.72(s, 6H), 3.53(s, 6H), 2.40 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.4, 168.3, 168.1, 144.6, 133.8, 129.4, 129.2, 53.0, 52.9, 52.4, 44.0, 21.8.

Tetramethyl 2-(3-bromobenzoyl)propane-1,1,3,3-tetracarboxylate (30e). Pale yellow Oil (326 mg, 71%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (t, J = 1.6 Hz, 1H), 7.96-7.94 (m, 1H), 7.71-7.68 (m, 1H), 7.36 (t, J = 8.0 Hz, 1H), 4.78 (t, J = 8.0 Hz, 1H), 4.09 (d, J = 8.0 Hz, 2H), 3.73 (s,

6H), 3.57 (s, 6H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 168.1, 167.9, 138.4, 136.3, 131.9, 130.2, 127.7, 123.0, 53.1, 53.0, 52.5, 44.1. Anal. Calcd. For $C_{18}H_{19}BrO_9$: C, 47.08; H, 4.17; Found C, 47.15; H, 4.25.

Tetramethyl 2-(4-bromobenzoyl)propane-1,1,3,3-tetracarboxylate (30f) [386]. Pale yellow oil (339 mg, 74%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89-7.87 (m, 2H), 7.63-7.61 (m, 2H), 4.80 (t, J = 8.0 Hz, 1H), 4.09 (d, J = 8.0 HZ, 2H), 3.73 (s, 6H), 3.56 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.2, 168.2, 168.1, 132.5, 132.0, 130.6, 128.5, 53.1, 53.0, 52.6, 43.9.

Tetramethyl 2-(2-chlorobenzoyl)propane-1,1,3,3-tetracarboxylate (30g). Light Yellow oil (311 mg, 75%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 1H), 7.41-7.34 (m, 3H), 4.85 (t, J = 7.6 Hz, 1H), 4.06 (d, J = 7.2 Hz, 2H), 3.69 (s, 6H), 3.65 (s, 6H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 168.0, 167.9, 137.1, 132.4, 130.8, 130.8, 126.9, 120.5, 53.1, 53.0, 51.3, 48.6. Anal. Calcd. For $C_{18}H_{19}ClO_9$: C, 52.12; H, 4.62; Found: C, 52.05; H, 4.68.

Tetramethyl 2-(4-chlorobenzoyl)propane-1,1,3,3-tetracarboxylate (30h) [386]. Pale Yellow Oil (331 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97-7.95 (m, 2H), 7.46-7.44 (m, 2H), 4.80 (t, J = 8.4 Hz, 1H), 4.09 (d, J = 8.0 Hz, 2H), 3.73(s, 6H), 3.56(s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 168.2, 168.0, 140.1, 134.9, 130.5, 129.0, 53.2, 53.0, 52.5, 43.9.

Tetraethyl 2-benzoylpropane-1,1,3,3-tetracarboxylate (30i) [386]. Pale yellow Oil (375 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 2H), 7.57-7.53 (m, 1H), 7.47-7.43 (m, 2H), 4.86 (t, J = 8.0 Hz, 1H), 4.19-4.13 (m, 4H), 4.07 (d, J = 8.0 Hz, 2H), 4.00-3.94 (m, 4H), 1.23 (t, J = 7.2 Hz, 6H), 1.11 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.0, 167.9, 167.7, 136.9, 133.4, 129.1, 128.6, 62.0, 52.9, 43.8, 14.0, 13.8.

Tetraethyl 2-(2-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30j). yellow oil (364 mg, 81%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86 (m, 1H), 7.37-7.35 (m, 1H), 7.24-7.20 (m, 2H), 4.75 (t, J = 7.6 Hz, 1H), 4.09-4.02 (m, 8H), 4.00 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.24-1.16 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.1, 167.7, 167.5, 139.3, 137.0, 131.6, 131.6, 129.5, 125.4, 61.9, 61.8, 52.0, 46.9, 20.7, 13.8, 13.8. Anal. Calcd. For $C_{23}H_{30}O_9$: C, 61.32; H, 6.71; Found: C, 61.41; H, 6.81.

Tetraethyl 2-(3-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30k). Pale yellow oil (315 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.81 (m, 2H), 7.36-7.34 (m, 2H), 4.84 (t, J = 8.4 Hz, 1H), 4.17-4.15 (m, 4H), 4.07 (d, J = *8.0* Hz, 2H), 3.99-3.96 (m, 4H), 2.40(s, 3H), 1.23 (t, J = 7.2 HZ, 6H), 1.12 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.6, 168.0, 167.8, 138.4,

134.3, 130.0, 129.5, 128.5, 126.4, 62.0, 52.8, 43.9, 14.0, 13.8. Anal. Calcd. For $C_{23}H_{30}O_9$: C, 61.32; H, 6.71; Found: $C_{23}H_{30}O_9$: C, 61.42; H, 6.65.

Tetraethyl 2-(4-methylbenzoyl)propane-1,1,3,3-tetracarboxylate (30l). Pale yellow oil (387 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.26-7.23 (m, 2H), 4.83 (t, J = 8.0 Hz, 1H), 4.19-4.13 (m, 4H), 4.06 (d, J = 8.0 Hz, 2H), 4.05-3.93 (m, 4H), 2.39 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H), 1.10 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.4, 168.0, 167.8, 144.3, 134.2, 129.3, 129.2, 62.0, 52.9, 43.6, 21.8, 14.0, 13.8. Anal. Calcd. For $C_{23}H_{30}O_9$: C, 61.32; H, 6.71; Found: C, 61.26; H, 6.64.

Tetraethyl 2-(3-bromobenzoyl)propane-1,1,3,3-tetracarboxylate (30m). Light yellow oil (371 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14-8.13 (m, 1H), 7.98-7.95 (m, 1H), 7.69-7.67 (m, 1H), 7.37-7.33 (m, 1H), 4.76 (t, J = 8.0 Hz, 1H), 4.18-4.16 (m, 4H), 4.06-4.00 (m, 6H), 1.24 (t, J = 7.2 Hz, 6H), 1.14 (t, J = *7.2* Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 167.8, 167.6, 138.8, 136.2, 131.9, 130.1, 127.8, 122.9, 62.2, 53.0, 43.8, 14.0, 13.9. Anal. Calcd. For $C_{22}H_{27}BrO_9$: C, 51.27; H, 5.28; Found: C, 51.32; H, 5.20.

Tetraethyl 2-(4-bromobenzoyl)propane-1,1,3,3-tetracarboxylate (30n) [386]. Pale yellow Oil (391 mg, 76%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.89 (m, 2H), 7.61-7.59 (m, 2H), 4.78 (t, J = 8.8 Hz, 1H), 4.21-4.14 (m, 4H), 4.05 (d, J = 8.4 Hz, 2H), 4.02-3.98 (m, 4H), 1.24 (t, J = 7.6 Hz, 6H), 1.13 (t, J = *7.2* Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 167.9, 167.6, 135.8, 135.2, 131.8, 130.6, 62.1, 61.8, 53.0, 43.5, 14.0, 13.9.

Tetraethyl 2-(2-chlorobenzoyl)propane-1,1,3,3-tetracarboxylate (30o). yellow oil (367 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 1H), 7.39-7.30 (m, 3H), 4.84 (t, J = 7.2 Hz, 1H), 4.17-4.11 (m, 4H), 4.08-4.02 (m, 4H), 4.00 (d, J = 7.2 Hz, 2H), 1.25-1.21 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.3, 167.6, 167.5, 137.5, 132.2, 130.9, 130.6, 129.6, 126.8, 62.1, 51.8, 48.3, 14.0, 14.0. Anal. Calcd. For $C_{22}H_{27}ClO_9$: C, 56.11; H, 5.78; Found: C, 56.18; H, 5.69.

Tetraethyl 2-(4-chlorobenzoyl)propane-1,1,3,3-tetracarboxylate (30p). Pale Yellow Oil (386 mg, 82%) ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 2H), 7.44-7.42 (m, 2H), 4.79 (t, J = *8.0* Hz, 1H), 4.20-4.16 (m, 4H), 4.05 (d, J = 8.0 Hz, 2H), 4.03-3.98 (m, 4H), 1.24 (t, J = 7.6 Hz, 6H), 1.13 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 167.9, 167.7, 139.9, 135.4, 130.5, 128.9, 62.2, 62.1, 53.1, 43.6, 14.0, 13.9. Anal. Calcd. For $C_{22}H_{27}ClO_9$: C, 56.11; H, 5.78; Found: C, 56.04; H, 5.70.

4-Methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (27u′) [352]. White Solid (248 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.83 (m, 2H), 7.79-7.77 (m, 2H), 7.63-7.59 (m, 1H), 7.48-7.45 (m, 2H), 7.30-7.28 (m, 2H), 5.66 (t, J = 4.8 Hz, 1H), 4.46 (d, J = 4.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6, 143.9, 136.2, 134.5, 133.9, 129.9, 129.1, 128.0, 127.3, 48.8, 21.6.

3.12. Visible-light-induced regioselective C(sp^3)-H acyloxylation of aryl-2*H*-azirines with (diacetoxy)iodobenzene

General procedure for the synthesis of compound 32.

A mixture of 3-Aryl-2*H*-azirine **1** (1.0 mmol), rose bengal (2.0 mol %, 20 mg) and freshly distilled toluene (3 mL) was taken in an reaction vessel (oven dried) equipped with a magnetic stirrer bar. Then (diacetoxyiodo)benzene (322 mg, 1 mmol) was added to the resultant mixture. The reaction vessel was irradiated using a blue LED (34 W, 450-530 nm) at room temperature under open atmosphere for 24 h. The reaction mixture was diluted with a mixture of 10 ml water/ethyl acetate (1:1) after completion of the reaction (TLC). Anhydrous Na_2SO_4 was used to dry the combined organic layer. Evaporation of solvent furnished the crude product. The pure product was obtained by column chromatography on silica gel (60-120 mesh) using ethyl acetate-petroleum ether as eluent.

General procedure for the synthesis of 3-phenyl-2*H*-azirin-2-yl acetate (32a) on the gram-scale.

In an oven dried reaction vessel, a mixture of 3-phenyl-2*H*-azirine **25a** (1.17 g, 10 mmol), rose bengal (2 mol %, 200 mg) and freshly distilled toluene (30 mL) was taken equipped with a magnetic stirrer bar. Then (diacetoxyiodo)benzene (3.22 g, 10 mmol) was added to the resultant mixture. The reaction vessel was irradiated using a blue LED (34 W, 450-530 nm) at room temperature under open atmosphere for 24 h. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (80 mL) and followed by brine solution (2 x 50 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent under vacuo furnished the crude product. The crude product was subjected to column chromatography on silica gel (60−120 mesh) using ethyl acetate-petroleum ether (60-80^{0}C) as eluent to obtain the analytically pure product as pale yellow liquid (1.40 g, yield 80%).

3-Phenyl-2*H*-azirin-2-yl acetate (32a) [387]. Pale yellow liquid (149 mg, yield 85%); R_f = 0.55 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 2H), 7.67-7.63 (m,

1H), 7.60-7.56 (m, 2H), 5.19 (s, 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 171.5, 134.2, 130.3, 129.4, 123.2, 58.6, 21.1.

3-(*o*-Tolyl)-2*H*-azirin-2-yl acetate (32b) [387]. Pale yellow liquid (132 mg, yield 75%); R_f = 0.50 (petroleum ether/EtOAc = 96/4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.88 (m, 1H), 7.55-7.51 (m, 1H), 7.41-7.37 (m, 2H), 5.20 (s, 1H), 2.71 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 170.4, 141.7, 133.8, 132.4, 131.2, 126.6, 121.8, 57.4, 21.2, 19.9.

3-(*m*-Tolyl)-2*H*-azirin-2-yl acetate (32c) [387]. Pale yellow liquid (147 mg, yield 78%); R_f = 0.55 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.79 (m, 2H), 7.47-7.46 (m, 2H), 5.19 (s, 1H), 2.45 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 171.4, 139.4 135.0, 130.7, 129.3, 127.5, 123.1, 58.7, 21.4, 21.2.

3-(*p*-Tolyl)-2*H*-azirin-2-yl acetate (32d) [387]. Pale yellow liquid (144 mg, yield 76%); R_f = 0.45 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 5.17 (s, 1H), 2.46 (s, 3H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 171.7, 170.9, 145.3, 130.3, 130.2, 120.4, 58.7, 22.1, 21.2.

3-(2,4-Dimethylphenyl)-2*H*-azirin-2-yl acetate (32e). Pale yellow liquid (142 mg, yield 70%); R_f = 0.55 (petroleum ether/EtOAc = 95/5); IR (KBr) 3131, 1751, 1400, 1222, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, J = 8.4 Hz, 1H), 7.20-7.18 (m, 2H), 5.17 (s, 1H), 2.66 (s, 3H), 2.41 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 169.8, 144.8, 141.6, 132.4, 132.0, 127.3, 119.0, 57.4, 21.9, 21.2, 19.8. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89%; Found: C, 70.86; H, 6.39; N, 6.83%. HRMS (ESI) ($[M + Na]^+$) Calcd. for $[C_{12}H_{13}NO_2]^+$: 240.1001; Found 240.0995.

3-Mesityl-2*H*-azirin-2-yl acetate (32f). Pale yellow liquid (148 mg, yield 68%); R_f = 0.60 (petroleum ether/EtOAc = 95/5); IR (KBr) 3132, 1748, 1399, 1226, 1034, 861 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.00 (s, 2H), 5.30 (s, 1H), 2.60 (s, 6H), 2.36 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 167.5, 144.6, 142.3, 129.7, 117.8, 57.6, 21.7, 21.3, 20.2. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45%; Found: C, 71.81; H, 6.89; N, 6.40%. HRMS (ESI) ($[M + Na]^+$) Calcd. for $[C_{13}H_{15}NO_2]^+$: 406.1127; Found 406.1117.

3-(4-(*Tert*-butyl)phenyl)-2*H*-azirin-2-yl acetate (32g) [387]. Pale yellow liquid (139 mg, yield 60%); R_f = 0.55 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.92 (m, 2H), 7.61-7.59 (m, 2H), 5.17 (s, 1H), 2.05 (s, 3H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.8, 171.0, 158.3, 130.3, 126.5, 120.5, 58.7, 31.8, 31.3, 21.2.

3-(2-Chlorophenyl)-2*H*-azirin-2-yl acetate (32h) [387]. Pale yellow liquid (151 mg, yield 72%); R_f = 0.65 (petroleum ether/EtOAc = 94/6);^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.58-7.57 (m, 2H), 7.51-7.48 (m, 1H), 5.30 (s, 1H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 170.1, 136.8, 134.9, 132.6, 130.9, 130.7, 127.5, 58.3, 21.2.

3-(3-Chlorophenyl)-2*H*-azirin-2-yl acetate (32i) [387]. Pale yellow liquid (136 mg, yield 65%); R_f = 0.50 (petroleum ether/EtOAc = 95/5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.98 (m, 1H), 7.91-7.89 (m, 1H), 7.64-7.61 (m, 1H), 7.55-7.51 (m, 1H), 5.17 (s, 1H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.3, 135.6, 134.1, 130.8, 130.0, 128.3, 125.0, 58.6, 21.1.

3-(4-Chlorophenyl)-2*H*-azirin-2-yl acetate (32j) [387]. Pale yellow liquid (149 mg, yield 71%); R_f = 0.65 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.93 (m, 2H), 7.57-7.55 (m, 2H), 5.14 (s, 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.0, 140.7, 131.5, 129.9, 121.7, 58.5, 21.1.

3-(2,6-Dichlorophenyl)-2*H*-azirin-2-yl acetate (32k). Pale yellow liquid (156 mg, yield 64%); R_f = 0.45 (petroleum ether/EtOAc = 95/5); IR (KBr) 3131, 1751, 1222, 1034, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, 3H), 5.39 (s, 1H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 168.7, 138.6, 134.6, 129.4, 120.7, 57.7, 21.2. Anal. Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.21; H, 2.89; N, 5.74%; Found: C, 49.13; H, 2.81; N, 5.82%. HRMS (ESI) ([M + Na]$^+$) Calcd. for $[C_{10}H_7Cl_2NO_2]^+$: 265.9752; Found 265.9748.

3-(3-Bromophenyl)-2*H*-azirin-2-yl acetate (32l) [387]. Pale yellow liquid (155 mg, yield 61%); R_f = 0.50 (petroleum ether/EtOAc = 96/4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.145-8.137 (m, 1H), 7.96-7.93 (m, 1H), 7.79-7.76 (m, 1H), 7.49-7.45 (m, 1H), 5.16 (s, 1H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.2, 137.0, 132.9, 131.0, 128.7, 125.2, 123.4, 58.6, 21.1.

3-(4-Bromophenyl)-2*H*-azirin-2-yl acetate (32m) [387]. Pale yellow liquid (183 mg, yield 72%); R_f = 0.55 (petroleum ether/EtOAc = 96/4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86 (m, 2H), 7.74-7.72 (m, 2H), 5.14 (s, 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 171.1, 132.8, 131.4, 129.2, 122.0, 58.4, 21.0.

3-(3-Fluorophenyl)-2*H*-azirin-2-yl acetate (32n). Pale yellow liquid (129.4 mg, yield 67%); R_f = 0.45 (petroleum ether/EtOAc = 95/5); IR (KBr) 3132, 1753, 1400, 1222, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.79 (m, 2H), 7.72-7.69 (m, 1H), 7.60-7.55 (m, 1H), 7.60-7.55 (m, 1H), 7.38-7.33 (m, 1H), 5.16 (s, 1H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.4, 163.0 (d, $^1J_{C\text{-}F}$ = 248 Hz), 131.2 (d, $^5J_{C\text{-}F}$ = 8 Hz), 129.0, 126.1 (d, $^4J_{C\text{-}F}$ = 2 Hz), 121.2 (d, $^3J_{C\text{-}F}$ = 21 Hz),

116.8 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 58.6, 21.1. Anal. Calcd for $C_{10}H_8FNO_2$: C, 62.18; H, 4.17; N, 7.25%; Found: C, 62.10; H, 4.24; N, 7.19%. HRMS (ESI) ($[M + H]^+$) Calcd. for $[C_{10}H_8FNO_2]^+$: 194.0617; Found 194.0610.

3-(4-(Trifluoromethyl)phenyl)-2*H*-azirin-2-yl acetate (32o) [387]. Pale yellow liquid (141 mg, yield 58%); R_f = 0.60 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 5.18 (s, 1H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 171.4, 130.7 (q, *J* = 33 Hz), 129.1, 126.5, 126. 4 (q, *J* = 5 Hz), 124.9 (q, *J* = 102 Hz), 58.5, 21.1.

3-([1,1'-Biphenyl]-4-yl)-2*H*-azirin-2-yl acetate (32p) [387]. Pale yellow solid (196 mg, yield 78%); R_f = 0.55 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09-8.07 (m, 2H), 7.82-7.80 (m, 2H), 7.67-7.64 (m, 2H), 7.51-7.43 (m, 3H), 5.21 (s, 1H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 171.1, 147.0, 139.7, 130.8, 129.2, 128.7, 128.1, 127.5, 121.9, 58.7, 21.2.

3-(Naphthalen-1-yl)-2*H*-azirin-2-yl acetate (32q) [387]. Pale yellow liquid (180 mg, yield 80%); R_f = 0.55 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.96 (d, *J* = 8.4 Hz, 1H), 8.18-8.13 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.76-7.72 (m, 1H), 7.67-7.63 (m, 2H), 5.29 (s, 1H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 170.4, 135.0, 133.6, 133.4, 131.8, 128.9, 128.7, 127.4, 125.4, 124.7, 118.9, 56.5, 21.2.

3-(Naphthalen-2-yl)-2*H*-azirin-2-yl acetate (32r) [387]. Pale yellow liquid (189 mg, yield 84%); R_f = 0.45 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 8.06-8.00 (m, 3H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.66-7.60 (m, 2H), 5.28 (s, 1H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.7, 171.5, 136.0, 132.9, 132.8, 129.50, 129.48, 129.2, 128.2, 127.4, 124.5, 120.5, 58.9, 21.2.

3.13. Chemoselective synthesis of tertiary amines from aldehydes by reductive amination

General procedure for the synthesis of compounds (36)

Procedure for synthesis of tertiary amine from an amine and an aldehyde:

A mixture of amine (1.0 mmol), aldehyde (2.0 mmol) and HCOOH (1.0 mmol, 46 mg) was stirred for 30 minutes on a heating bath at 70 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous

Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

Procedure for synthesis of tertiary amine from an amine and a mixture of two aldehydes:

A mixture of amine (1.0 mmol), two aldehydes (each 1.0 mmol) and HCOOH (1.0 mmol, 46 mg) was stirred for 30 minutes on a heating bath at 70 °C. The reaction was monitored by TLC. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

Tribenzylamine (36a). Off-white Solid, 215 mg, Yield 75%, mp 60-62°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, J = 7.6 Hz, 6H), 7.36-7.33 (m, 6H), 7.27-7.24 (m, 3H), 3.59 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.8, 128.9, 128.3, 127.0, 58.0.

***N*-Benzyl-*N*-(4-chlorobenzyl)-1-(4-chlorophenyl)methanamine (36b).** White Solid, 252 mg, Yield 71%, mp 54-56°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.15 (m, 13H), 3.43 (s, 2H), 3.40 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 138.0, 132.7, 130.1, 128.8, 128.55, 128.46, 127.2, 58.0, 57.3. Anal. Calcd for $C_{21}H_{19}Cl_2N$: C, 70.79; H, 5.38; N, 3.93% Found: C, 70.70; H, 5.32; N, 3.88%.

***N*-Benzyl-*N*-(4-fluorobenzyl)-1-(4-fluorophenyl)methanamine (36c).** Yellowish white oil, 226 mg, Yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.31 (m, 8H), 7.27-7.25 (m, 1H), 7.04-6.99 (m, 4H), 3.53 (s, 2H), 3.51 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0 (d, $^1J_{C\text{-}F}$= 244 Hz), 139.4, 135.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 130.3 (d, $^3J_{C\text{-}F}$ = 8 Hz), 128.8, 128.4, 127.1, 115.2 (d, $^2J_{C\text{-}F}$ = 20 Hz), 57.9, 57.2. Anal. Calcd for $C_{21}H_{19}F_2N$: C, 78.08; H, 5.98; N, 4.26%; Found: C, 78.00; H, 5.92; N, 4.33%.

***N*-Benzyl-*N*-(4-bromobenzyl)-1-(4-bromophenyl)methanamine (36d).** White Solid, 292 mg, Yield 67%, mp 74-76°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.35 (m, 4H), 7.29-7.22 (m, 4H), 7.17 (d, J = 8.4 Hz, 5H), 3.44 (s, 2H), 3.40 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.1, 138.5, 131.5, 130.5, 128.8, 128.5, 127.2, 120.9, 58.0, 57.3. Anal. Calcd for $C_{21}H_{19}Br_2N$: C, 56.66; H, 4.30; N, 3.15%; Found: C, 56.76; H, 4.36; N, 3.08%.

***N*-Benzyl-*N*-(2-bromobenzyl)-1-(2-bromophenyl)methanamine (36e).** Colourless oil, 289 mg, Yield 65%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.67 (m, 2H), 7.51-7.49 (m, 2H), 7.42- 7.40 (m, 2H), 7.33-7.23 (m, 5H), 7.10-7.06 (m, 2H), 3.73 (s, 4H), 3.68 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.1, 138.6, 132.8, 130.4, 128.9, 128.44, 128.40, 127.5, 127.2, 124.4, 58.7, 57.7. Anal. Calcd for $C_{21}H_{19}Br_2N$: C, 56.66; H, 4.30; N, 3.15%; Found: C, 56.60; H, 4.22; N, 3.12%.

***N*-Benzyl-*N*-(4-methylbenzyl)-1-(*p*-tolyl)methanamine (36f).** Yellow gummy solid, 236 mg, Yield 77%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J = 7.6 Hz, 2H), 7.39-7.35 (m, 6H), 7.30-7.26 (m, 1H), 7.19 (d, J = 7.6 Hz, 4H), 3.61 (s, 2H), 3.58 (s, 4H), 2.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.9, 136.7, 136.4, 129.0, 128.8, 128.3, 126.9, 57.8, 57.6, 21.2. Anal. Calcd for $C_{23}H_{25}N$: C, 87.57; H, 7.99; N, 4.44%; Found: C, 87.49; H, 7.91; N, 4.34%.

***N*-Benzyl-*N*-(4-methoxybenzyl)-1-(4-methoxyphenyl)methanamine (36g).** Creamy white solid, 231 mg, Yield 66%, mp 78-80°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, J = 7.2 Hz, 2H), 7.26-7.22 (m, 6H), 7.18-7.15 (m, 1H), 6.80-6.78 (m, 4H), 3.72 (s, 6H), 3.46 (s, 2H), 3.41 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 140.0, 131.8, 130.0, 128.8, 128.3, 126.9, 113.7, 57.7, 57.1, 55.4. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03%; Found: C, 79.56; H, 7.20; N, 4.08%.

***N*-Benzyl-1-(naphthalen-1-yl)-*N*-(naphthalen-1-ylmethyl)methanamine (36h).** White Solid, 263 mg, Yield 68%, mp 82-84°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 6.8 Hz, 2H), 7.45-7.37 (m, 4H), 7.30-7.19 (m, 7H), 3.99 (s, 4H), 3.60 (s, 2H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.4, 135.1, 133.9, 132.6, 129.8, 128.3, 128.2, 128.1, 127.2, 125.6, 125.5, 125.3, 125.2, 59.2, 57.6. Anal. Calcd for $C_{29}H_{25}N$: C, 89.88; H, 6.50; N, 3.61%; Found: C, 89.81; H, 6.45; N, 3.57%.

***N*-Benzyl-1-(naphthalen-2-yl)-*N*-(naphthalen-2-ylmethyl)methanamine (36i).** White Solid, 259 mg, Yield 67%, mp 60-62°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.82 (m, 8H), 7.63-7.60 (m, 2H), 7.49-7.42 (m, 6H), 7.36-7.23 (m, 3H), 3.76 (s, 4H), 3.65 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.7, 137.3, 133.5, 132.9, 129.0, 128.4, 128.1, 127.8, 127.5, 127.3, 127.1, 126.0, 125.6, 58.3, 58.1. Anal. Calcd for $C_{29}H_{25}N$: C, 89.88; H, 6.50; N, 3.61%; Found: C, 89.94; H, 6.43; N, 3.57%.

***N*-Benzyl-1-(thiophen-2-yl)-*N*-(thiophen-2-ylmethyl)methanamine (36j).** Pale yellow Solid, 244 mg, Yield 66%, mp 54-56°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50-7.46 (m, 2H), 7.38-7.35 (m, 2H), 7.29-7.26 (m, 3H), 6.99-6.96 (m, 4H), 3.86 (s, 4H), 3.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 100

MHz): δ 142.9, 139.1, 128.8, 128.4, 127.2, 126.5, 125.8, 125.0, 57.2, 52.0. Anal. Calcd for $C_{17}H_{17}NS_2$: C, 68.19; H, 5.72; N, 4.68%; Found: C, 68.15; H, 5.63; N, 4.58%.

***N*-Benzyl-2-phenyl-*N*-(2-phenylpropyl)propan-1-amine (36k).** Deep yellow oil, 301 mg, Yield 88%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.07 (m, 15H), 3.73 (d, J = 14.8 Hz, 1/2H), 3.56 (s, 1H), 3.42 (d, J = 14.0 Hz, 1/2H), 2.96-2.87 (m, 2H), 2.63-2.45 (m, 4H), 1.28 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 146.3, 140.03, 140.00, 129.1, 129.0, 128.9, 128.35, 128.28, 128.12, 128.06, 127.53, 127.48, 126.7, 126.1, 63.1, 62.7, 59.7, 59.6, 38.4, 38.3, 20.0, 19.9. Anal. Calcd for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08%; Found: C, 87.34; H, 8.43; N, 4.03%.

***N*-Benzyl-1-cyclohexyl-*N*-(cyclohexylmethyl)methanamine (36l).** Pale yellow oil, 197 mg, Yield 66%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.20 (m, 5H), 3.46 (s, 2H), 2.11 (d, J = 6.8 Hz, 4H), 1.84-1.81 (m, 4H), 1.69-1.66 (m, 6H), 1.49-1.45 (m, 2H), 1.23-1.16 (m, 6H), 0.78- 0.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.9, 128.9, 128.0, 126.5, 62.1, 60.0, 36.1, 31.9, 27.1, 26.4. Anal. Calcd for $C_{21}H_{33}N$: C, 84.22; H, 11.11; N, 4.68%; Found: C, 84.14; H, 11.04; N, 4.63%.

***N*,*N*-Dibenzylbutan-1-amine (36m).** Colourless oil, 222 mg, Yield 88%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.20 (m, 8H), 7.15-7.12 (m, 2H), 3.46 (S, 4H), 2.34-2.31 (m, 2H), 1.43- 1.38 (m, 2H), 1.24-1.18 (m, 2H), 0.77-0.73 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.2, 128.9, 128.2, 126.8, 58.4, 53.3, 29.4, 20.6, 14.2. Anal. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53%; Found: C, 85.25; H, 9.10; N, 5.61%.

***N*,*N*-Bis(4-methoxybenzyl)cyclohexanamine (36n).** Colourless oil, 288 mg, Yield 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.25 (m, 4H), 6.84-6.81 (m, 4H), 3.79 (s, 6H), 3.54 (s, 4H), 2.48-2.41 (m, 1H), 1.87-1.84 (m, 2H), 1.77-1.74 (m, 2H), 1.59-1.57 (m, 1H), 1.34-1.25 (m, 2H), 1.18-1.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 133.5, 129.6, 113.6, 57.5, 55.4, 53.1, 28.8, 26.7, 26.3. Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13%; Found: C, 77.75; H, 8.57; N, 4.04%.

***N*,*N*-Bis(2,6-dichlorobenzyl)cyclohexanamine (36o).** White Solid, 271 mg, Yield 65%, mp 95-97°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17-7.14 (m, 4H), 7.02-6.98 (m, 2H), 3.80 (s, 4H), 2.28-2.22 (m, 1H), 1.93-1.91 (m, 2H), 1.72-1.69 (m, 2H), 1.54-1.35 (m, 3H), 1.14-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.7, 135.3, 128.7, 128.3, 59.0, 48.1, 28.8, 26.6. Anal. Calcd for $C_{20}H_{21}Cl_4N$: C, 57.58; H, 5.07; N, 3.36%; Found: C, 57.64; H, 5.01; N, 3.46%.

***N,N*-Bis(thiophen-2-ylmethyl)cyclohexanamine (36p).** Off white Solid, 294 mg, Yield 81%, mp 50-52°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.10 (m, 2H), 6.84-6.83 (m, 4H), 3.79 (s, 4H), 2.55-2.49 (m, 1H), 1.83-1.79 (m, 2H), 1.72-1.67 (m, 2H), 1.22-1.19 (m, 4H), 1.12-1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.9, 126.4, 124.6, 124.5, 58.0, 48.7, 28.9, 26.5, 26.2. Anal. Calcd for $C_{16}H_{21}NS_2$: C, 65.93; H, 7.26; N, 4.81%; Found: C, 65.83; H, 7.18; N, 4.89%.

2-(Dibenzylamino)ethan-1-ol (36q). Colourless oil, 169 mg, Yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.24 (m, 10H), 3.63 (s, 4H), 3.59-3.57 (m, 2H), 2.68-2.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.9, 129.1, 128.6, 127.4, 58.7, 58.3. 54.9. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80%; Found: C, 79.56; H, 7.85; N, 5.72%.

2-(Bis(4-methylbenzyl)amino)ethan-1-ol (36r). Colourless oil, 194 mg, Yield 72%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, J = 8.0 Hz, 4H), 7.13 (d, J = 8.0 Hz, 4H), 3.57-3.54 (m, 6H), 2.65-2.62 (m, 2H), 2.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.9, 135.8, 129.2, 129.1, 58.6, 57.9, 54.6, 21.2. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20%; Found: C, 80.34; H, 8.72; N, 5.25%.

***N*-(2-Chlorobenzyl)-*N*-(thiophen-2-ylmethyl)cyclohexanamine (37s).** Deep yellow gummy liquid, 80 mg, Yield 28%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 8.8 Hz, 1H), 7.22-7.03 (m, 5H), 6.84-6.82 (m, 1H), 3.79 (s, 2H), 3.72 (s, 2H), 2.48-2.41 (m, 1H), 1.87-1.83 (m, 2H), 1.73-1.69 (m, 2H), 1.55-1.51 (m, 1H), 1.29-0.98 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 130.2, 129.3, 129.1, 127.7, 126.8, 126.7, 126.5, 124.5, 124.4, 58.7, 50.7, 49.3, 28.9, 26.5, 26.3. Anal. Calcd for $C_{18}H_{22}ClNS$: C, 67.58; H, 6.93; N, 4.38%; Found: C, 67.51; H, 6.86; N, 4.32%.

***N,N*-Bis(2-chlorobenzyl)cyclohexanamine (38s).** White oil, 69 mg, Yield 20%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.50 (m, 2H), 7.21-7.18 (m, 2H), 7.11-7.03 (m, 4H), 3.72 (s, 4H), 2.45-2.38 (m, 1H), 1.91-1.88 (m, 2H), 1.74-1.70 (m, 2H), 1.56-1.52 (m, 1H), 1.35-1.06 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 133.9, 130.2, 129.2, 127.7, 126.7, 59.7, 51.4, 29.0, 26.5, 26.4. Anal. Calcd for $C_{20}H_{23}Cl_2N$: C, 68.97; H, 6.66; N, 4.02%; Found: C, 68.90; H, 6.73; N, 4.05%.

***N*-(4-Bromobenzyl)-*N*-(4-methoxybenzyl)cyclohexanamine (37t).** Pale yellow gummy liquid, 132 mg, Yield 34%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.38 (m, 2H), 7.26-7.21 (m, 4H), 6.85-6.83 (m, 2H), 3.79 (s, 3H), 3.55 (s, 4H), 2.47-2.40 (m, 1H), 1.88-1.75 (m, 4H), 1.62-1.58 (m, 1H), 1.34-1.10 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5, 140.6, 131.3, 131.2, 130.2, 129.6, 120.2, 113.6, 57.8, 55.3, 53.3, 53.2, 28.8, 26.6, 26.3. Anal. Calcd for $C_{21}H_{26}BrNO$: C, 64.95; H, 6.75; N, 3.61%; Found: C, 64.90; H, 6.68; N, 3.54%.

***N,N*-Bis(4-bromobenzyl)cyclohexanamine (38t).** Pale yellow gummy Solid, 79 mg, Yield 18%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.37 (m, 4H), 7.21 (d, J = 8.4 Hz, 4H), 3.54 (s, 4H), 2.43-2.36 (m, 1H), 1.86-1.74 (m, 4H), 1.32-1.06 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.2, 131.4, 130.2, 120.5, 58.1, 53.4, 28.8, 26.5, 26.2. Anal. Calcd for $C_{20}H_{23}Br_2N$: C, 54.94; H, 5.30; N, 3.20%; Found: C, 54.84; H, 5.37; N, 3.28%.

***N*-(4-Methoxybenzyl)-*N*-(4-methylbenzyl)cyclohexanamine (37u).** Pale yellow gummy liquid, 81 mg, Yield 25%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 1H), 7.29-7.25 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 6.84-6.82 (m, 2H), 3.79 (s, 3H), 3.58 (s, 2H), 3.56 (s, 2H), 2.51-2.47 (m, 1H), 2.32 (s, 3H), 1.89-1.85 (m, 2H), 1.77-1.74 (m, 2H), 1.63-1.57 (m, 2H), 1.35-1.27 (m, 2H), 1.13-1.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 138.4, 130.0, 129.8, 129.6, 128.9, 128.5, 113.6, 57.6, 55.3, 53.4, 53.1, 28.8, 26.7, 26.3, 21.2. Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33%; Found: C, 81.76; H, 9.14; N, 4.35%.

***N,N*-Bis(4-methylbenzyl)cyclohexanamine (36u).** White Solid, 64 mg, Yield 21%, mp 52- 54°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, J = 9.2 Hz, 4H), 7.08 (d, J = 8.0 Hz, 4H), 3.57 (s, 4H), 2.50-2.42 (m, 1H), 2.31 (s, 6H), 1.89-1.85 (m, 2H), 1.76-1.73 (m, 2H), 1.34-1.08 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 136.0, 128.9, 128.5, 57.6, 53.5, 28.8, 26.7, 26.3, 21.2. Anal. Calcd for $C_{22}H_{29}N$: C, 85.94; H, 9.51; N, 4.56%; Found: C, 85.85; H, 9.45; N, 4.51%.

***N*-(2,6-Dichlorobenzyl)-*N*-(naphthalen-1-ylmethyl)cyclohexanamine (37v).** White Solid, 95 mg, Yield 24%, mp 70-72°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.44-7.33 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.07-7.03 (m, 1H), 4.11 (s, 2H), 4.05 (s, 2H), 2.58-2.52 (m, 1H), 2.05-2.02 (m, 2H), 1.80-1.78 (m, 2H), 1.61-1.59 (m, 1H), 1.55-1.45 (m, 2H), 1.14-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 136.1, 135.6, 133.7, 132.6, 128.7, 128.5, 128.2, 127.4, 127.2, 125.4, 125.22, 125.19, 125.0, 59.8, 52.1, 49.3, 28.3, 26.6, 26.4. Anal. Calcd for $C_{24}H_{25}Cl_2N$: C, 72.36; H, 6.33; N, 3.52%; Found: C, 72.31; H, 6.27; N, 3.45%.

***N,N*-Bis(naphthalen-1-ylmethyl)cyclohexanamine (38v).** White Solid, 114 mg, Yield 30%, mp 115-117°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, J = 9.6 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 6.8 Hz, 2H), 7.46-7.42 (m, 2H), 7.40-7.36 (m, 2H), 7.30-7.26 (m, 2H), 4.16 (s, 4H), 2.67-2.59 (m, 1H), 2.10-2.07 (m,2H), 1.84-1.82 (m, 2H), 1.64-1.58 (m, 3H), 1.18-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.0, 133.9, 132.6, 128.3, 127.65, 127.56, 125.5, 125.30, 125.26, 125.2, 58.6, 52.7, 28.1, 26.6, 26.4. Anal. Calcd for $C_{28}H_{29}N$: C, 88.61; H, 7.70; N, 3.69%; Found: C, 88.56; H, 7.64; N, 3.75%.

***N*-Benzyl-*N*-(2,6-dichlorobenzyl)-1-(*p*-tolyl)methanamine (37w).** Off white solid, 89 mg, Yield 24%, mp 69-71°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.25 (m, 2H), 7.20-7.09 (m, 7H), 7.01-6.94 (m, 3H), 3.77 (s, 2H), 3.47 (d, J = 6.0 Hz, 4H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.5, 137.3, 136.5, 136.2, 135.0, 129.2, 128.8, 128.4, 128.0, 126.9, 57.95, 57.90, 53.5, 21.3. Anal. Calcd for $C_{22}H_{21}Cl_2N$: C, 71.36; H, 5.72; N, 3.78%; Found: C, 71.31; H, 5.64; N, 3.85%.

***N,N*-Bis(2,6-dichlorobenzyl)(phenyl)methanamine (38w).** White Solid, 102 mg, Yield 24%, mp 86-88°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.28 (m, 2H), 7.26-7.14 (m, 7H), 7.10-7.06 (m, 2H), 3.88 (s, 4H), 3.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.3, 137.6, 134.5, 129.5, 129.0, 128.3, 127.6, 126.9, 59.1, 53.2. Anal. Calcd for $C_{21}H_{17}Cl_4N$: C, 59.32; H, 4.03; N, 3.29%; Found: C, 59.27; H, 4.01; N, 3.21%.

General procedure for the synthesis of compounds (36′)

A mixture of amine (1.0 mmol), aldehyde (2.0 mmol) and HCOOH (1.0 mmol, 46 mg) was stirred for 30 minutes on a heating bath at 70°C. After completion (monitored by TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

***N*-Benzylpyridin-2-amine (36′a).** Pale brown Solid, 156 mg, Yield 85%, mp 66-68°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.09 (m, 1H), 7.42-7.26 (m, 6H), 6.60-6.57 (m, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.00 (s, 1H), 4.50 (d, *J* = 6.0 Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.7, 148.3, 139.3, 137.6, 128.7, 127.5, 127.3, 113.2, 106.9, 46.4. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21%; Found: C, 78.16; H, 6.50; N, 15.16%.

***N*-Benzyl-2-chloroaniline (36′b).** Colourless oil, 177 mg, Yield 87%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.30 (m, 6H), 7.15-7.11 (m, 1H), 6.70-6.66 (m, 2H), 4.78 (s, 1H), 4.43 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 138.9, 129.2, 128.9, 127.9, 127.5, 127.4, 119.2, 117.6, 111.6, 48.0. Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.73; H, 5.56; N, 6.43%; Found: C, 71.64; H, 5.51; N, 6.37%.

***N*-Benzyl-3-nitroaniline (36′c).** Yellow Solid, 168 mg, Yield 75%, mp 75-77°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55-7.53 (m, 1H), 7.46-7.44 (m, 1H), 7.39-7.37 (m, 4H), 7.34-7.26 (m, 2H), 6.91-6.88 (m, 1H), 4.45 (s,1H), 4.44-4.39 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.5, 148.9,

138.2, 129.9, 129.0, 127.8, 127.6, 118.8, 112.3, 106.7, 48.2. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27%; Found: C, 68.34; H, 5.22; N, 12.20%.

***N*-Benzyl-2-iodoaniline (36′d).** Pale yellow gummy liquid, 216 mg, Yield 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.67 (m, 1H), 7.38-7.26 (m, 5H), 7.18-7.14 (m, 1H), 6.55-6.53 (m, 1H), 6.47-6.43 (m,1H), 4.64 (s, 1H), 4.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.2, 139.1, 138.8, 129.6, 128.9, 127.5, 127.3, 119.0, 111.1, 85.4, 48.5. Anal. Calcd for $C_{13}H_{12}IN$: C, 50.51; H, 3.91; N, 4.53%; Found: C, 50.56; H, 3.83; N, 4.59%.

***N*-Benzyl-2-bromo-4-methylbenzenamine (36′e).** Pale yellow oil, 196 mg, Yield 71%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50-7.47 (m, 1H), 7.38-7.34 (m, 4H), 7.29-7.26 (m, 1H), 6.95- 6.92 (m, 1H), 6.53-6.51 (m, 1H), 4.61 (s, 1H), 4.39-4.38 (m, 2H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7, 139.1, 132.9, 129.1, 128.9, 128.8, 127.4, 127.3, 111.8, 109.7, 48.4, 20.1. Anal. Calcd for $C_{14}H_{14}BrN$: C, 60.89; H, 5.11; N, 5.07%; Found: C, 60.95; H, 5.06; N, 5.02%.

3.14. Synthesis of isoindolo[2,1-*a*]quinazolines

Representative example for synthesis of 6-(2-methoxy-benzyl)-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41h): A mixture of isatoic anhydride (163 mg, 1 mmol), 2-carboxybenzaldehyde (150 mg, 1 mmol) and 2-methoxybenzyl amine (130 µL, 137 mg, 1 mmol) was stirred in presence of In_2O_3 nano (5 mol%) in water (3 mL) under refluxed conditions for 12 h (TLC). After completion of the reaction, ethylacetate (10 mL) was added to the reaction mixture. Then the insoluble In_2O_3 nanoparticles was filtered by Teflon membrane (PTFE, 0.2 µm pore size) and the filtrate was extracted with ethylacetate (5 mL) followed by washing with brine (5 mL) and dried over Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4:1 to 3:1) as eluent. The In_2O_3 nanoparticles was thoroughly washed with the ethanol, dried and reused for the next cycle. Yield: 53%; White solid, mp. 160-162 °C; IR (KBr)**:** 3024, 1959, 1716, 1656, 1476 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.67-7.51 (m, 3H), 7.42-7.36 (m, 2H), 7.23-7.21 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.92-6.88 (m, 2H), 6.38 (s, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 4.84 (d, *J* = 17.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.2, 156.5, 138.0, 137.0, 133.6, 132.6, 132.5, 130.5, 129.4, 128.3, 127.1, 125.4, 125.3, 124.8, 124.4, 120.9, 120.5, 120.2, 110.5, 70.9, 55.4, 42.4. Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56%; Found: C, 74.51; H, 4.82; N, 7.52%.

6-Phenyl-6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (41a) [152]: Yield: 38%; White solid, mp. 184-186 °C; IR (KBr)**:** 3029, 1963, 1721, 1658, 1468 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.09 (m, 2H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.63-7.55 (m, 2H), 7.53-7.29 (m, 5H), 7.26-

7.22 (m, 1H), 7.16-7.13 (m, 1H), 6.44 (s, 1H), 6.04 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 164.3, 138.8, 138.3, 137.2, 134.0, 132.3, 132.2, 130.4, 129.9, 129.5, 129.3, 125.5, 125.4, 124.6, 120.4, 120.3, 120.2, 72.1.

6-*p*-Tolyl-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41b) [153]: Yield: 45%; Gummy mass; IR (KBr)**:** 3015, 1718, 1655, 1472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 7.61-7.41 (m, 4H), 7.28-7.18 (m, 4H), 6.42 (s, 1H), 6.13 (d, J = 7.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 164.2, 139.0, 138.7, 137.0, 135.3, 134.3, 133.8, 132.1, 132.0, 130.3, 130.1, 129.6, 129.4, 125.4, 125.2, 124.3, 120.2, 72.2, 21.3.

6-(4-Methoxy-phenyl)-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41c): Yield: 50%; White solid, mp. 141-143 °C; IR (KBr)**:** 3033, 1967, 1717, 1661, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H), 7.80 (d, J = 7.2 Hz, 1H), 7.54-7.49 (m, 1H), 7.41-7.32 (m, 2H), 7.20-7.14 (m, 2H), 6.95-6.50 (m, 3H), 6.35 (s, 1H), 6.10 (d, J = 8 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.2, 159.6, 138.6, 136.9, 133.6, 132.0, 131.9, 130.6, 130.0, 129.2, 125.4, 125.0, 124.2, 120.2, 120.0, 114.9, 114.5, 72.2, 55.4. Anal. Calcd. for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.53; N, 7.86%; Found: C, 74.07; H, 4.42; N, 7.77%.

6-(4-Chloro-phenyl)-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41d) [153]: Yield: 46%; White solid, mp. 186-188 °C; IR (KBr)**:** 3021, 1954, 1718, 1656, 1479 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.15 (m, 2H), 7.97 (d, J = 7.6 Hz, 1H), 7.70-7.66 (m, 1H), 7.64-7.50 (m, 3H), 7.42-7.32 (m, 4H), 6.51 (s, 1H), 6.28 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 164.4, 138.5, 137.3, 136.8, 135.2, 134.3, 132.5, 132.3, 130.6, 130.1, 129.6, 129.5, 125.5, 124.8, 120.5, 120.2, 120.1, 72.3.

6-(4-Fluoro-phenyl)-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41e): Yield: 48%; Gummy mass; IR (KBr)**:** 3027, 1951, 1718, 1659, 1477 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.13 (m, 2H), 7.98 (d, J = 7.6 Hz, 1H), 7.72-7.68 (m, 1H), 7.59-7.53 (m, 2H), 7.39-7.32 (m, 3H), 7.08-6.74 (m, 2H), 6.51 (s, 1H), 6.24 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.2, 162.5 (d, $^1J_{C\text{-}F}$ = 247 Hz), 138.4, 137.0, 134.0, 133.9 (d, $^4J_{C\text{-}F}$ = 3 Hz), 132.2, 132.0, 130.3, 129.4, 125.2 (d, $^3J_{C\text{-}F}$ = 6 Hz), 124.6, 120.3, 120.0, 116.8, 116.5, 115.7 (d, $^2J_{C\text{-}F}$ = 21 Hz), 72.2; Anal. Calcd. for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.81; N, 8.14%; Found: C, 73.17; H, 3.76; N, 8.07%.

6-Benzyl-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41f) [152]: Yield: 52%; White solid, mp. 154-156 °C; IR (KBr)**:** 3024, 1956, 1715, 1660, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.88 (d, J = 6.8 Hz, 1H), 7.87-7.44 (m,

3H), 7.34-7.11 (m, 7H), 6.27 (s, 1H), 5.42 (d, *J* = 16.4 Hz, 1H), 4.54 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 164.1, 137.6, 136.8, 136.1, 133.7, 132.6, 132.5, 130.5, 129.4, 129.0, 127.2, 126.2, 125.4, 125.3, 124.9, 120.1, 120.0, 70.6, 46.6.

6-(4-Methoxy-benzyl)-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41g) [152]: Yield: 58%; White solid, mp. 143-145 °C; IR (KBr)**:** 3028, 1959, 1718, 1656 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.56-7.23 (m, 5H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 6.8 Hz, 2H), 6.21 (s, 1H), 5.30 (d, *J* = 16.4 Hz, 1H), 4.44 (d, *J* = 16.4 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 164.2, 158.7, 137.7, 136.8, 133.7, 132.6, 130.6, 129.8, 129.4, 128.0, 127.6, 125.5, 125.3, 125.0, 120.3, 120.2, 114.4, 70.7, 55.3, 46.1.

6-Cyclohexyl-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41i) [152]: Yield: 46%; White solid, mp. 150-152 °C; IR (KBr)**:** 3021, 1717, 1659, 1468 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.77-7.62 (m, 2H), 7.48-7.41 (m, 2H), 7.32-7.28 (m, 1H), 6.92-6.83 (m, 2H), 6.02 (d, *J* = 7.2 Hz, 1H), 3.89-3.82 (m, 1H), 1.99-1.38 (m, 5H), 1.26-1.16 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 168.2, 146.0, 145.4, 134.6, 132.8, 130.6, 127.8, 127.0, 125.6, 123.1, 118.9, 117.7, 114.1, 86.2, 48.5, 33.1, 25.5, 24.8.

6-Butyl-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41j): Yield: 50%; White solid, mp. 158-160 °C; IR (KBr)**:** 3022, 1965, 1714, 1660, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.02 (m, 3H), 7.74-7.65 (m, 3H), 7.63-7.59 (m, 1H), 7.34-7.28 (m, 1H), 6.23 (s, 1H), 3.92-3.86 (m, 1H), 3.73-3.67 (m, 1H), 1.59-1.31 (m, 4H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.5, 138.1, 136.5, 133.2, 132.8, 132.6, 130.5, 128.9, 125.2, 125.1, 125.0, 120.4, 120.0, 70.4, 42.7, 30.2, 20.0, 13.7; Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14%;. Found: C, 74.41; H, 5.84; N, 9.08%.

6-Furan-2-ylmethyl-6,6*a*-dihydro-isoindolo[2,1-*a*]quinazoline-5,11-dione (41k) [152]: Yield: 35%; Gummy mass; IR (KBr)**:** 3023, 1718, 1657, 1474 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-7.90 (m, 4H), 7.65-7.53 (m, 3H), 7.34 (d, *J* = 1.2 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.32-6.30 (m, 2H), 6.28 (s, 1H), 5.35 (d, *J* = 16.4 Hz, 1H), 4.37 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.8, 150.4, 142.1, 138.1, 136.8, 133.6, 132.8, 132.6, 130.6, 129.2, 126.0, 125.2, 125.0, 120.3, 120.1, 110.8, 108.6, 70.9, 39.6.

3.15. Synthesis of *N*-alkoxylated benzimidazoles in presence of nano indium oxide

General procedure for the synthesis of compounds (44)

A mixture of *ortho*-phenylenediamine (1 mmol, 108 mg), alcohol (2 mL) and indium oxide nano (10 mol%) was taken in a dry sealed tube and the resulting mixture was stirred at 60 ºC. Formaldehyde (37%, 2 mmol, 55 µl) was added drop wise to the resulting mixture and stirred for 2 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and nano In_2O_3 was recovered by centrifugation. After that the reaction mixture was extracted with ethyl acetate (10 mL) and washed with water (2 x 5 mL). Then organic layer was dried over anhydrous sodium sulphate. The crude product was collected after evaporation by rotary evaporator under reduced pressure. Analytically pure product was obtained by purification of crude product using column chromatography on silica gel (60-120 mesh) where petroleum ether and ethyl acetate were used as eluent.

1-(Methoxymethyl)-1*H*-benzo[*d*]imidazole (44a). Brown gummy (121 mg, 75%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (s, 1H), 7.83-7.81 (m, 1H), 7.55-7.52 (m, 1H), 7.36-7.30 (m, 2H), 5.50 (s, 2H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 143.2, 133.7, 123.7, 122.9, 120.6, 110.3, 76.2, 56.4. Anal. Calcd. For $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27%; Found: C, 66.81; H, 6.24; N, 17.34%.

1-(Ethoxymethyl)-1*H*-benzo[*d*]imidazole (44b). Brown gummy (133 mg, 76%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (s, 1H), 7.82-7.80 (m, 1H), 7.56-7.53 (m, 1H), 7.35-7.29 (m, 2H), 5.55 (s, 2H), 3.49-3.44 (m, 2H), 1.17 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 143.2, 133.8, 123.6, 122.8, 120.5, 110.3, 74.7, 64.6, 14.9. Anal. Calcd. For $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90 %; Found: C, 68.84; H, 6.81; N, 17.20%.

1-(Propoxymethyl)-1*H*-benzo[*d*]imidazole (44c). Brown oil (140 mg, 74%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.82-7.80 (m, 1H), 7.55-7.53 (m, 1H), 7.35-7.29 (m, 2H), 5.54 (s, 2H), 3.35 (t, J = 6.8 Hz, 2H), 1.57-1.51 (m, 2H), 0.84 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.1, 133.7, 123.6, 122.8, 120.5, 110.4, 74.9, 70.7, 22.6, 10.5. Anal. Calcd. For $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73%; Found: C, 69.25; H, 7.46; N, 14.33%.

1-(Butoxymethyl)-1*H*-benzo[*d*]imidazole (44d). Brown gummy (147 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.82-7.80 (m, 1H), 7.55-7.53 (m, 1H), 7.33-7.30 (m, 2H), 5.53 (s, 2H), 3.39 (t, J = 6.8 Hz, 2H), 1.52-1.48 (m, 2H), 1.31-1.26 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.1, 133.8, 123.6, 122.8, 120.5, 110.4, 74.9, 68.9, 31.4,

19.2, 13.8. Anal. Calcd. For $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71%; Found: C, 70.38; H, 7.86; N, 13.80%.

1-((*Iso*-pentyloxy)methyl)-1*H*-benzo[*d*]imidazole (44e). Yellow oil (148 mg, 68%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H), 7.82-7.80 (m, 1H), 7.55-7.53 (m, 1H), 7.34-7.30 (m, 2H), 5.53 (s, 2H), 3.42 (t, J = 6.8 Hz, 2H), 1.65-1.59 (m, 1H), 1.44-1.39 (m, 2H), 0.80 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 143.1, 133.7, 123.7, 122.9, 120.5, 110.4, 75.0, 67.5, 38.1, 25.0, 22.5. Anal. Calcd. For $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83%; Found: C, 71.32; H, 8.34; N, 12.91%.

1-(*Iso*-propoxymethyl)-1*H*-benzo[*d*]imidazole (44f). Brown gummy (121 mg, 64%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (s, 1H), 7.99-7.80 (m, 1H), 7.56-7.54 (m, 1H), 7.36-7.29 (m, 2H), 5.57 (s, 2H), 3.69-3.63 (m, 1H), 1.13 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.0, 123.6, 122.8, 120.5, 110.5, 72.6, 70.0, 22.1. Anal. Calcd. For $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73%; Found: C, 69.62; H, 7.36; N, 14.63%.

1-(*Tert*-butoxymethyl)-1*H*-benzo[*d*]imidazole (44g). Colourless solid (112 mg, 55%), mp: 207-210 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.81-7.79 (m, 1H), 7.53-7.51 (m, 1H), 7.35-7.29 (m, 2H), 5.56 (s, 2H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 142.8, 131.7, 123.4, 122.6, 120.5, 110.5, 75.3, 69.0, 28.0. Anal. Calcd. For $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71%; Found: C, 70.76; H, 7.85; N, 13.79%.

1-((Allyloxy)methyl)-1*H*-benzo[*d*]imidazole (44h).Yellow oil (131 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H), 7.82-7.80 (m, 1H), 7.55-7.52 (m, 1H), 7.36-7.29 (m, 2H), 5.88-5.79 (m, 1H), 5.56 (s, 2H), 5.29-5.22 (m, 2H), 3.95-3.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 143.1, 133.1, 123.7, 122.9, 120.5, 118.8, 110.4, 91.5, 73.6, 69.4. Anal. Calcd. For $C_{11}H_{12}N_2O$: C, 7.19; H, 6.43; N, 14.88%; Found: C, 7.35; H, 6.38; N, 14.96%.

1-((But-3-en-1-yloxy)methyl)-1*H*-benzo[*d*]imidazole (44i). Brown gummy (133 mg, 66%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.82-7.80 (m, 1H), 7.55-7.53 (m, 1H), 7.34-7.31 (m, 2H), 5.74-5.64 (m, 1H), 5.55 (s, 2H), 5.05-5.00 (m, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.30-2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.1, 134.4, 123.7, 122.9, 120.5, 117.1, 110.4, 92.4, 74.9, 68.3, 33.8. Anal. Calcd. For $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%; Found: C, 71.09; H, 6.83; N, 13.95%.

1-((Prop-2-yn-1-yloxy)methyl)-1*H*-benzo[*d*]imidazole (44j). Brown gummy (111 mg, 60%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.83-7.81 (m, 1H), 7.59-7.57 (m, 1H), 7.37-7.30 (m, 2H), 5.72 (s, 2H), 4.07 (d, J = 2.4 Hz, 2H), 2.57 (t, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ

144.1, 143.4, 123.9, 123.1, 120.6, 110.3, 77.8, 76.6, 72.0, 55.0. Anal. Calcd. For $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04%; Found: C, 71.14; H, 5.35; N, 15.13%.

1-((2,2,2-Trifluoroethoxy)methyl)-1*H*-benzo[*d*]imidazole (44k). Brown gummy (133mg, 58%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.84-7.82 (m, 1H), 7.54-7.52 (m, 1H), 7.38-7.33 (m, 2H), 5.68 (s, 2H), 3.93-3.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4(2C), 124.0, 123.2, 120.8, 110.0, 92.4, 70.4. Anal. Calcd. For $C_{10}H_9F_3N_2O$: C, 52.18; H, 3.94; N, 12.17%; Found: C, 52.02; H, 3.98; N, 12.09%.

1-((Benzyloxy)methyl)-1*H*-benzo[*d*]imidazole (44l). Brown gummy (123mg, 52%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H), 7.87-7.82 (m, 2H), 7.56-7.54 (m, 1H), 7.38-7.33 (m, 6H), 5.60 (s, 2H), 4.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.3, 143.1, 128.7, 128.6, 128.4, 128.1, 127.0, 123.7, 122.9, 120.5, 110.4, 73.4, 70.2. Anal. Calcd. For $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%; Found: C, 75.79; H, 5.87; N, 11.84%.

1-(((4-Methylbenzyl)oxy)methyl)-1*H*-benzo[*d*]imidazole (44m). Brown gummy (138mg, 55%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 1H), 7.84-7.82 (m, 1H), 7.55-7.53 (m, 1H), 7.36-7.31 (m, 2H), 7.18-7.16 (m, 4H), 5.56 (s, 2H), 4.14 (s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 143.2, 138.3, 133.7, 133.2, 129.5, 128.3, 123.7, 123.0, 120.5, 110.5, 73.3, 70.1, 21.3. Anal. Calcd. For $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10%; Found: C, 76.32; H, 6.33; N, 11.19%.

6-Chloro-1-(methoxymethyl)-1*H*-benzo[*d*]imidazole and **5-Chloro-1-(methoxymethyl)-1*H*-benzo[*d*]imidazole (44n)**. Reddish gum (169 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (s, 1H), 7.97 (s, 1H), 7.80-7.79 (m, 1H), 7.73-7.71 (m, 1H), 7.54-7.53 (m, 1H), 7.46-7.44 (m, 1H), 7.32-7.27 (m, 2H), 5.48 (s, 2H), 5.46 (s, 2H), 3.30 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 144.3, 143.8, 142.8, 134.2, 132.2, 129.6, 128.7, 124.2, 123.7, 121.4, 120.4, 111.2, 110.6, 76.3(2C), 56.5(2C). Anal. Calcd. For $C_9H_9ClN_2O$: C, 54.97; H, 4.61; N, 14.25%; Found: C, 55.84; H, 4.66; N, 14.15%.

6-Chloro-1-(ethoxymethyl)-1*H*-benzo[*d*]imidazole and **5-Chloro-1-(ethoxymethyl)-1*H*-benzo[*d*]imidazole (44o)**. Reddish gum (179 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (s, 1H), 7.96 (s, 1H), 7.80-7.79 (m, 1H), 7.72-7.70 (m, 1H), 7.55-7.54 (m, 1H), 7.47-7.45 (m, 1H), 7.31-7.26 (m, 2H), 5.52 (s, 2H), 5.50 (s, 2H), 3.49-3.43 (m, 4H), 1.20-1.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 144.2, 143.8, 142.8, 134.4, 132.4, 129.6, 128.6, 124.2, 123.7, 121.4, 120.4, 111.2, 110.6, 74.9, 74.8, 64.8, 64.7, 14.8. Anal. Calcd. For $C_{10}H_{11}ClN_2O$: C, 57.02; H, 5.26; N, 13.30%; Found: C, 56.82; H, 5.21; N, 13.37%.

6-Chloro-1-(propoxymethyl)-1*H*-benzo[*d*]imidazole and **5-Chloro-1-(propoxymethyl)-1*H*-benzo[*d*]imidazole (44p)**. Reddish gum (184 mg, 82%) ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (s, 1H), 7.96 (s, 1H), 7.80-7.79 (m, 1H), 7.73-7.70 (m, 1H), 7.55-7.54 (m, 1H), 7.48-7.45 (m, 1H), 7.31-7.27 (m, 2H), 5.52 (s, 2H), 5.50 (s, 2H), 3.37-3.32 (m, 4H), 1.58-1.51 (m, 4H), 0.91-0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 144.2, 143.8, 142.8, 134.3, 132.3, 129.5, 128.6, 124.2, 123.6, 121.4, 120.3, 111.3, 110.7, 75.2, 75.1, 70.9, 70.8, 22.6, 10.5. Anal. Calcd. For $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47%; Found: C, 58.97; H, 5.78; N, 12.56%.

1*H*-benzo[*d*]imidazole (44′). White Solid (24 mg, 20%), mp: 171-174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 7.68-7.66 (m, 2H), 7.31-7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 123.1.

3.16. Synthesis of 1,2-disubstituted benzimidazoles in presence of nano indium oxide

Typical procedure for synthesis of (45): A mixture of *o*-phenylenediamine (**1**, 1 mmol) and aldehyde (**35**, 2 mmol) was stirred in presence of nano In_2O_3 (5 mol%) in an EtOH/H_2O (2:1) mixture (5 mL) at 60 ºC for 2 h (TLC). After completion, the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and nano In_2O_3 was recovered by centrifugation. The reaction mixture was extracted with diethyl ether (2 x 10 mL) and dried over Na_2SO_4. Evaporation of solvent furnished the crude product which was recrystallized from methanol to afford the analytically pure product.

1-Benzyl-2-phenyl-1*H*-benzimidazole (45a): White solid; mp. 132-134 °C; IR (KBr): 3178, 2978, 1612, 1525, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8 Hz, 1H), 7.69-7.67 (m, 2H), 7.49-7.44 (m, 3H), 7.34-7.30 (m, 4H), 7.25-7.19 (m, 2H), 7.13-7.08 (m, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.4, 136.6, 136.2, 131.7, 129.7, 129.3, 129.0, 128.5, 128.1, 126.1, 123.1, 122.5, 120.5, 110.7, 48.9.

1-(3-Phenyl-allyl)-2-styryl-1*H*-benzoimidazole (45b): Brown oil; IR (KBr): 3445, 2924, 1467, 1265 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 16 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.60-7.03 (m, 14H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.36-6.30 (m, 1H), 5.04 (d, *J* = 4.5 Hz, 1H), 4.99 (d, *J* = 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.8, 142.3, 138.8, 135.9, 135.8, 135.1, 134.6, 132.8, 130.4, 129.4, 129.1, 129, 128.8, 128.3 (2C), 127.6, 126.7, 123.3, 123.2, 123.1, 119.2, 112.4, 109.8, 45.5; Anal. Cald. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33%. Found: C, 85.54; H, 5.89; N, 8.24%.

3.17. Synthesis of imidazo[1,2-*a*]pyridines by iron(III)-catalyzed three-component domino strategy

Representative example for synthesis of 2-(4-chloro-phenyl)-imidazo[1,2-*a*]pyridine (49b) [355]. A mixture of 2-aminopyridine **46a** (94 mg, 1 mmol) and 4-chlorobenzaldehyde **34b** (154 mg, 1.1 mmol) was heated in presence of anhydrous $FeCl_3$ (20 mol%) in nitromethane (2 mL) and DMF (1 mL) at 110 °C for 5h (TLC). After completion, the reaction mixture was cooled to room temperature and extracted with dichloromethane (10 mL) followed by washing with brine (5 mL) and dried over Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate (3:1 to 2:1) as eluent. Yield: 78%; Yellowish white solid; mp. 138-140 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 6.8 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.81 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.19-7.14 (m, 1H), 6.77 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 144.7, 133.8, 132.3, 129.0, 127.3, 125.7, 125.0, 117.6, 112.7, 108.3.

Typical procedure for the synthesis of the drug zolimidine (49q). A mixture of 2-aminopyridine **1a** (94 mg, 1 mmol) and 4-(methylsulfonyl)benzaldehyde (202 mg, 1.1 mmol) was heated in presence of anhydrous $FeCl_3$ (20 mol%) in nitromethane (2 mL) and DMF (1 mL) at 110 °C for 5 h (TLC). After completion, the reaction mixture was cooled to room temperature and extracted with dichloromethane (10 mL) followed by washing with brine (5 mL) and dried over Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate (1:2) as eluent. Yellowish white solid. mp. 240-242 ºC; Yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.03 (m, 3H), 7.90-7.88 (m, 3H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 6.75 (t, *J* = 6.4 Hz, 1H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 143.3, 139.3, 139.1, 127.9, 126.6, 126.0, 125.8, 117.7, 113.2, 109.8, 44.6.

2-Phenyl-imidazo[1,2-*a*]pyridine (49a) [355]. Yield: 76%; Yellowish white solid; mp. 108-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 6.8 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.81 (s, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.15-7.11 (m, 1H), 6.73 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.5, 133.5, 128.6, 127.9, 125.9, 125.5, 124.6, 117.3, 112.3, 108.0.

2-*p*-Tolyl-imidazo[1,2-*a*]pyridine (49c) [355]. Yield: 72%; White solid; mp. 116-118 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.71 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 6.4 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 145.5, 137.7, 130.8, 129.3, 125.8, 125.4, 124.4, 117.3, 112.2, 107.7, 21.2.

2-(4-Methoxy-phenyl)-imidazo[1,2-*a*]pyridine (49d) [355]. Yield: 78%; White gummy mass; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 6.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.58 (s, 1H),

7.49 (d, *J* = 8.8 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.58 (t, *J* = 6.8 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 145.3, 127.1, 126.2, 125.3, 124.4, 116.9, 114.0, 112.1, 107.1, 55.1.

2-(4-Methylsulfanyl-phenyl)-imidazo[1,2-*a*]pyridine (49e) [355]. Yield: 72%; Yellow solid; mp. 141-142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 6.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.65 (s, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.06-7.02 (m, 1H), 6.63 (t, *J* = 8.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 144.8, 138.1, 130.1, 126.4, 126.2, 125.4, 124.7, 117.0, 112.3, 107.8, 15.5.

2-Imidazo[1,2-*a*]pyridin-2-yl-phenol (49f) [194]. Yield: 68%; Yellowish white solid; mp. 142-143 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.66 (br, 1H), 8.00 (d, *J* = 6.8 Hz, 1H), 7.70 (s, 1H), 7.48-7.44 (m, 2H), 7.17-7.10 (m, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.1, 143.3, 129.5, 125.6, 125.3, 125.1, 118.9, 117.5, 116.5, 116.1, 113.0, 106.6.

2-Thiophen-2-yl-imidazo[1,2-*a*]pyridine (49g) [355]. Yield: 58%; Yellowish white solid; mp. 132-134 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 6.8 Hz, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 7.45-7.44 (m, 1H), 7.44-7.27 (m, 1H), 7.13-7.06 (m, 2H), 6.71 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 140.6, 137.3, 127.6, 125.3, 124.9, 124.7, 123.5, 117.0, 112.4, 107.3.

2-*iso*-Propyl*H*-imidazo[1,2-*a*]pyridine (49h). Yellow oil. Yield: 35%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 6.8 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.27 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 6.75 (t, *J* = 6.8 Hz, 1H), 3.12-3.05 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 144.1, 140.4, 125.7, 116.5, 112.9, 107.7, 27.9, 22.4. Anal. Calcd. For C10H12N2: C, 74.97; H, 7.55; N, 17.48%; Found: C, 74.92; H, 7.47; N, 17.41%.

7-Methyl-2-phenyl-imidazo[1,2-*a*]pyridine (49i) [355]. Yield: 73%; Yellowish white solid; mp. 148-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.8 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.74 (s, 1H), 7.43 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.32-7.30 (m, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 145.0, 135.9, 133.5, 128.6, 127.8, 125.9, 124.7, 115.6, 115.2, 107.5, 21.3.

2-(4-Methoxy-phenyl)-7-methyl-imidazo[1,2-*a*]pyridine (49j) [194]. Yield: 75%; White solid; mp. 142-144 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 6.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.40 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.58 (d, *J* = 6.0 Hz, 1H), 3.75 (s, 3H), 2.31 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 144.7, 143.3, 137.5, 127.4, 124.9, 124.5, 115.9, 114.8, 114.2, 106.7, 55.3, 21.3.

7-Methyl-2-(3-nitro-phenyl)-imidazo[1,2-*a*]pyridine (49k) [355]. Yield: 70%; Yellow solid; mp. 174-176 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.43 (s, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 6.70 (d, *J* = 6.8 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.3, 145.4, 141.7, 136.1, 135.9, 131.6, 130.2, 126.3, 121.9, 119.6, 115.2, 115.0, 109.9, 20.8.

2-(4-Iodo-phenyl)-7-methyl-imidazo[1,2-*a*]pyridine (49l) [194]. Yield: 76%; Yellowish white solid; mp. 207-208 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.2 Hz, 1H), 7.72-7.69 (m, 3H), 7.64-7.61 (m, 2H), 7.34 (s, 1H), 6.57 (d, *J* = 6.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 144.2, 137.6, 135.9, 133.3, 127.5, 124.7, 115.7, 115.2, 107.6, 93.1, 21.3.

2-Furan-2-yl-7-methyl-imidazo[1,2-*a*]pyridine (49m) [194]. Yield: 62%; Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 6.8 Hz, 1H), 7.40 (s, 1H), 7.24-7.24 (m, 1H), 7.10 (s, 1H), 6.68-6.67 (m, 1H), 6.30-6.27 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 145.5, 141.5, 136.9, 135.7, 124.5, 115.0, 114.7, 111.1, 106.9, 106.1, 20.9.

5-Methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine (49n) [194]. Yield: 68%; Gummy mass; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.80 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.25-7.21 (m, 1H), 6.70 (d, *J* = 6.4 Hz, 1H), 2.70 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 137.7, 134.2, 130.9, 129.4, 125.9, 124.8, 114.7, 111.5, 104.9, 21.2, 18.7.

6-Chloro-2-phenyl-imidazo[1,2-*a*]pyridine (49o) [355]. Yield: 68%; Yellowish white solid; mp. 144-146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.81 (s, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36-7.32 (m, 1H), 7.13 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 143.9, 133.1, 128.7, 128.3, 126.1, 126.0, 123.3, 120.5, 117.7, 108.4.

6-Iodo-2-phenyl-imidazo[1,2-*a*]pyridine (49p) [355]. Yield: 70%; Yellow solid; mp. 168-170 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.86-7.83 (m, 2H), 7.71 (s, 1H), 7.37-7.33 (m, 3H), 7.28-7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 144.1, 133.0, 132.6, 130.4, 128.7, 128.3, 126.0, 118.5, 107.7, 75.1.

2-(4-Chlorophenyl)-3-methylimidazo[1,2-*a*]pyridine (49r). Yield: 76%; White solid; mp. 122-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 6.8 Hz, 1H), 7.53-7.50 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.04-7.00 (m, 1H), 6.66 (d, *J* = 8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 143.9, 140.3, 133.2, 132.6, 129.4, 128.5, 124.2, 122.8, 116.8, 116.0, 112.3, 9.3. Anal. Calcd. for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; N, 11.54%; Found: C, 69.22; H, 4.52; N, 11.47%.

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (49s). Yield: 78%; White solid; mp. 147-148 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 6.8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.49-7.45 (m, 2H), 7.37-7.34 (m, 1H), 7.19-7.15 (m, 1H), 6.83 (t, *J* = 9.2 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 141.9, 134.4, 128.5, 128.4, 127.5, 123.9, 122.9, 117.2, 116.0, 112.2, 9.5; Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45%; Found: C, 80.66; H, 5.78; N, 13.41%.

2-*iso*Propyl-3,7-dimethyl*H*-imidazo[1,2-*a*]pyridine (49t). Yellow oil. Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 6 Hz, 1H), 7.49 (s, 1H), 6.39 (d, *J* = 6 Hz, 1H), 3.63-3.59 (m, 1H), 2.19 (s, 3H), 1.78 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 156.5, 152.8, 148.5, 141.7, 114.2, 108.1, 30.7, 22.0, 19.7, 19.6, 9.9. Anal. Calcd. For C12H16N2: C, 76.55; H, 8.57; N, 14.88%; Found: C, 76.47; H, 8.51; N, 14.82%.

3-Ethyl-2-phenylimidazo[1,2-*a*]pyridine (49u). Yield: 75%; Yellow gummy mass; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.28-7.24 (m, 1H), 7.13-7.09 (m, 1H), 6.77-6.74 (m, 1H), 2.94 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 140.6, 133.5, 128.6, 128.3, 127.8, 124.7, 122.9, 121.9, 117.1, 112.8, 16.8, 12.2; Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60%; Found: C, 81.01; H, 6.28; N, 12.54%.

3-Ethyl-7-methyl-2-phenyl-imidazo[1,2-*a*]pyridine (49v). Yield: 74%; Light yellow gummy mass; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8 Hz, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.53 (s, 1H), 7.40-7.32 (m, 2H), 6.62 (d, *J* = 6.8 Hz, 1H), 2.93 (q, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 141.4, 133.3, 132.3, 129.8, 128.6, 128.4, 122.3, 121.4, 115.7, 115.3, 21.3, 16.7, 12.3; Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85%; Found: C, 81.27; H, 6.78; N, 11.78%.

3.18. Synthesis of imidazo[1,2-*a*]pyridines by iron(III)-catalyzed cascade reaction between nitroolefins and 2-aminopyridines

Typical procedure for iron(III) catalyzed synthesis of 2-Phenyl-imidazo[1,2-*a*]pyridine (49a) [194]. A mixture of 2-aminopyridine **46a** (112 mg, 1.2 mmol), nitrostyrene **50a** (149 mg, 1 mmol), was stirred in presence of anhydrous $FeCl_3$ (20 mol%) in DMF (2 mL) at 80 ºC for 2 h (TLC). After completion, the reaction mixture was cooled to room temperature and extracted with dichloromethane (10 mL) followed by washing with brine (5 mL) and dried over Na_2SO_4. After

evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 2:1) as eluent. Yield: 84%; White solid; mp. 108-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 6.8 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.81 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.33-7.29 (m, 1H), 7.16-7.11 (m, 1H), 6.73 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.6, 133.6, 128.7, 127.9, 126.0, 125.5, 124.7, 117.4, 112.4, 108.1.

2-*p*-Tolyl-imidazo[1,2-*a*]pyridine (49c) [194]. Yield: 80%; Yellowish white solid; mp. 116-118 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 6.8 Hz, 1H), 7.78-7.75 (m, 3H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.19-7.12 (m, 3H), 6.72 (t, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.6, 138.0, 129.4, 126.0, 125.5, 125.0, 117.2, 112.6, 107.7, 21.2.

Typical procedure for functionalization of imidazo[1,2-*a*]pyridine: Imidazo[1,2-*a*]pyridine (87 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.0025 mmol), PPh_3 (13 mg, 0.05 mmol), Cs_2CO_3 (326 mg, 1 mmol) and CuI (9.5 mg, 0.05 mmol) were taken in sealed tube and iodobenzene (204 mg, 1 mmol), 1,4-dioxane (1.5 mL) were added to it. Then sealed tube was evacuated-backfilled with argon (3 cycles) and then it was heated at 105 ºC for 15 hour. After cooling the reaction mixture, it was extracted with ethyl acetate. The organic layer was evaporated and crude product was purified by column chromatography. Pure product **52a** obtained as a white solid. Yield: 87%; White solid; mp. 148-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.8 Hz, 1H), 7.73-7.67 (m, 3H), 7.57-7.54 (m, 3H), 7.53-7.46 (m, 2H), 7.32-7.20 (m, 4H), 6.76 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.7, 142.2, 134.0, 130.7, 129.8, 129.5, 128.9, 128.3,128.1, 127.5, 124.8, 123.3, 121.1, 117.5, 112.3; Anal. Cald. for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36%. Found: C, 84.35; H, 5.17; N, 10.31%.

2-Phenyl-3-*p*-tolyl-imidazo[1,2-*a*]pyridine (52b). Yield: 85%; White solid; mp. 184-186 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.2 Hz, 1H), 7.58-7.55 (m, 3H), 7.17-7.00 (m, 8H), 6.54 (t, *J* = 7.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.3, 141.6, 138.7, 133.7, 130.4, 130.3, 130.0, 129.3, 128.7, 128.0, 127.8, 127.3, 126.3, 124.6, 123.1, 120.9, 117.1, 117.0, 112.1, 21.2; Anal. Cald. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85%. Found: C, 84.41; H, 5.62; N, 9.79%.

3.19. Facile synthesis of substituted quinolines by iron(III)-catalyzed cascade reaction between anilines, aldehydes and nitroalkanes

Typical procedure for the synthesis of 6-methoxy-2-phenylquinoline (55a): A mixture of 4-methoxyaniline (**33c,** 0.5 mmol) and benzaldehyde (**17a,** 0.5 mmol) was taken in 2 mL of nitroethane (**54a**) in a sealed tube. Then ferric chloride ($FeCl_3$, 20 mol%) was added to the reaction mixture. Next, the reaction mixture was stirred at 90 °C for 6 h. After completion of the reaction

(TLC), the reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1% to 2%) as eluent as white solid (**55a**, 103 mg, 88%).

Typical procedure for the synthesis of 6-methoxy-2-phenylquinoline (55a) on gram scale: A mixture of 4-methoxyaniline (**33c,** 5 mmol) and benzaldehyde (**17a,** 5 mmol) in 10 mL of nitroethane (**54a**) was taken in a sealed tube. Then ferric chloride ($FeCl_3$, 20 mol%) was added to the reaction mixture. Next, the reaction mixture was stirred at 90 °C for 6 h. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (1% to 2%) as eluent as white solid (**54a**, 1 g, 85%).

6-Methoxy-2-phenylquinoline (55a) [218]: White solid (103 mg, 88%), mp: 127-129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.07 (m, 4H), 7.82 (d, J = 8.4 Hz, 1H), 7.54-7.50 (m, 2H), 7.47-7.45 (m, 1H), 7.41-7.38 (m, 1H), 7.07 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.7, 155.1, 144.4, 139.9, 135.6, 131.3, 129.0, 128.9, 128.2, 127.4, 122.4, 119.3, 105.1, 55.6.

6-Methoxy-2-(*p*-tolyl)quinoline (55b): White solid (100 mg, 80%), mp: 142-143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.02 (m, 4H), 7.81 (d, J = 8.4 Hz, 1H), 7.39-7.36 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.7, 155.2, 144.5, 139.1, 137.1, 135.6, 131.2, 129.7, 128.1, 127.3, 122.3, 119.2, 105.2, 55.7, 21.4. . Anal. Calcd. For $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%; Found: C, 81.82; H, 6.01; N, 5.53%.

6-Methoxy-2-(*o*-tolyl)quinoline (55c): Brown solid (89 mg, 76%), mp: 52-53 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.06 (m, 2H), 7.50-7.48 (m, 2H), 7.41-7.38 (m, 1H), 7.33-7.30 (m, 3H), 7.12 (d, J = 2.8 Hz, 1H), 3.96 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.9(2C), 144.1, 140.9, 136.1, 135.0, 131.1, 130.9, 129.8, 128.4, 127.8, 126.1, 122.7, 122.4, 105.1, 55.7, 20.5. Anal. Calcd. For $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%; Found: C, 81.98; H, 6.14; N, 5.53%.

6-Methoxy-2-(4-methoxyphenyl)quinoline (55d) [221]: White solid (121 mg, 92%), mp: 180-182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.03 (m, 4H), 7.77 (d, J = 8.8 Hz, 1H), 7.38-7.35 (m,

1H), 7.06-7.02 (m, 3H), 3.93 (s, 3H), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.6, 157.5, 154.8, 144.4, 135.5, 132.5, 131.1, 128.6, 127.9, 122.3, 118.9, 114.3, 105.2, 55.6, 55.5.

6-Methoxy-2-(2-methoxyphenyl)quinoline (55e): Yellow oil (79 mg, 58%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07-8.03 (m, 2H), 7.85-7.81 (m, 2H), 7.42-7.34 (m, 2H), 7.14-7.10 (m, 2H), 7.04-7.02 (m, 1H), 3.95 (s, 3H), 2.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.7, 157.3, 154.8, 144.5, 134.1, 131.5, 131.2, 130.1, 128.1, 123.8, 121.9, 121.4, 111.6, 105.1, 55.8, 55.7, 53.5. Anal. Calcd. For $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%; Found: C, 76.87; H, 5.62; N, 5.20%.

2-(4-Fluorophenyl)-6-methoxyquinoline (55f) [209]: White solid (114 mg, 90%), mp: 122-123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14-8.09 (m, 3H), 8.06-8.03 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.40-7.37 (m, 1H), 7.21-7.17 (m, 2H), 7.08 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 163.7 (d, $^{1}J_{C\text{-}F}$ = 247 Hz), 157.9, 154.1, 144.5, 136.1 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 135.7, 131.2, 129.2 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 128.2, 122.6, 119.0, 115.8 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 105.2, 55.7.

2-(4-Chlorophenyl)-6-methoxyquinoline (55g) [209]: White solid (103 mg, 88%), mp: 193-195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-8.03 (m, 4H), 7.79 (d, J = 8.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.40-7.37 (m, 1H), 7.09 (d, J = 2.8 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.0, 153.8, 144.5, 138.3, 135.8, 135.2, 131.3, 129.1, 128.7, 128.4, 122.7, 118.9, 105.2, 55.7.

2-(4-Bromophenyl)-6-methoxyquinoline (55h): White solid (133 mg, 85%), mp: 218-219 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-8.01 (m, 4H), 7.79 (d, J = 8.4 Hz, 1H), 7.64-7.62 (m, 2H), 7.40-7.37 (m, 1H), 7.08 (d, J = 2.8 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.0, 153.9, 144.5, 138.8, 135.8, 132.0, 131.3, 128.9, 128.4, 123.6, 122.7, 118.9, 105.1, 55.7. Anal. Calcd. For $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46%; Found: C, 61.26; H, 3.92; N, 4.38%.

2-(2-Bromophenyl)-6-methoxyquinoline (55i): Brown solid (130 mg, 83%), mp: 114-115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-8.06 (m, 2H), 7.70-7.61 (m, 3H), 7.44-7.39 (m, 2H), 7.30-7.26 (m, 1H), 7.13 (d, J = 2.8 Hz, 1H), 3.96 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.2, 156.4, 144.1, 141.8, 134.5, 133.4, 131.7, 131.2, 129.9, 128.3, 127.9, 123.1, 122.5, 122.1, 105.2, 55.7. Anal. Calcd. For $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46%; Found: C, 61.09; H, 3.88; N, 4.52%.

6-Methoxy-2-(2-(trifluoromethyl)phenyl)quinoline (55j): Yellow oil (117 mg, 77%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.66-7.52 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.42-7.39 (m, 1H), 7.13 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.2, 155.7, 143.9, 140.5, 134.8, 131.8 (2C), 128.7,

128.5, 128.3, 126.5 (q, J = 5 Hz), 125.7, 122.8, 122.3, 105.1, 55.7. Anal. Calcd. For $C_{17}H_{12}F_3NO$: C, 67.33; H, 3.99; N, 4.62%; Found: C, 67.23; H, 3.92; N, 4.57%.

6-Methoxy-2-(4-(methylthio)phenyl)quinoline (55k): Yellow solid (125 mg, 89%), mp: 148-149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09-8.03 (m, 4H), 7.80 (d, J = 8.8 Hz, 1H), 7.39-7.36 (m, 3H), 7.08 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.8, 154.5, 144.5, 139.9, 136.6, 135.6, 131.2, 128.2, 127.7, 126.7, 122.4, 119.0, 105.2, 55.7, 15.8. Anal. Calcd. For $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98%; Found: C, 72.50; H, 5.44; N, 4.91%.

2-(Benzo[*d*][1,3]dioxol-5-yl)-6-methoxyquinoline (55l): Yellow solid (126 mg, 90%), mp: 125-127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.01 (m, 2H), 7.74-7.69 (m, 2H), 7.62-7.60 (m, 1H), 7.38-7.35 (m, 1H), 7.06 (d, J = 2.8 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.03 (s, 2H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.6, 154.5, 148.6, 148.5, 144.3, 135.6, 134.4, 131.1, 128.0, 122.4, 121.4, 119.0, 108.6, 107.8, 105.1, 101.4, 55.6. Anal. Calcd. For $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02%; Found: C, 73.18; H, 4.60; N, 5.09%.

6-Methoxy-2-(naphthalen-2-yl)quinoline (55m) [206]: Brown solid (111 mg, 78%), mp: 116-117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.58 (s, 1H), 8.36-8.33 (m, 1H), 8.16-8.11 (m, 2H), 8.00-7.98 (m, 3H), 7.90-7.88 (m, 1H), 7.53-7.51 (m, 2H), 7.42-7.39 (m, 1H), 7.11 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.9, 155.0, 144.6, 137.2, 135.7, 133.8, 133.7, 131.3, 128.9, 128.6, 128.3, 127.8, 126.8, 126.6, 126.4, 125.1, 122.5, 119.5, 105.2, 55.7.

6-Methoxy-2-(naphthalen-1-yl)quinoline (55n): Yellow solid (104 mg, 73%), mp: 94-95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17-8.15 (m, 3H), 7.95-7.93 (m, 2H), 7.73-7.71 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.61-7.57 (m, 1H), 7.54-7.44 (m, 3H), 7.16 (d, J = 2.8 Hz, 1H), 3.97 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.0, 157.0, 144.3, 138.8, 135.1, 134.1, 131.4, 131.2, 129.0, 128.4, 128.1, 127.7, 126.5, 126.0, 125.8, 125.5, 125.3, 123.6, 122.5, 105.2, 55.7. Anal. Calcd. For $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91%; Found: C, 84.24; H, 5.21; N, 4.98%.

6-Methoxy-2-(thiophen-2-yl)quinoline (55o) [206]: White solid (96 mg, 80%), mp: 135-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-7.98 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.68-7.67 (m, 1H), 7.43-7.42 (m, 1H), 7.36-7.33 (m, 1H), 7.15-7.13 (m, 1H), 7.05 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.7, 150.4, 145.7, 144.2, 135.5, 130.9, 128.3, 128.1, 128.0, 125.2, 122.5, 118.1, 105.4, 55.7.

2-(Furan-2-yl)-6-methoxyquinoline (55p): Yellow oil (75 mg, 67%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.57-7.53 (m, 2H), 7.37-7.34 (m, 1H), 7.08-7.06 (m, 2H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.7, 149.6, 144.4, 144.0, 141.6, 135.4, 130.8, 128.1, 127.8, 122.3, 119.4, 109.2, 105.4, 55.7. Anal. Calcd. For $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%; Found: C, 74.72; H, 4.83; N, 6.29%.

2-Phenylquinoline (55q) [218]: Yellow solid (82 mg, 80%), mp: 88-89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, J = 8.8 Hz, 1H), 8.19-8.16 (m, 3H), 7.88 (d, J = 8.4 Hz, 1H), 7.84-7.82 (m, 1H), 7.76-7.71 (m, 1H), 7.55-7.44 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.5, 148.4, 139.8, 136.9, 129.9, 129.8, 129.4, 129.0, 127.7, 127.6, 127.3, 126.4, 119.2.

6-Methyl-2-phenylquinoline (55r) [218]: Yellow solid (93 mg, 85%), mp: 92-93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20-8.18 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58-7.53 (m, 4H), 7.50-7.46 (m, 1H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.5, 146.9, 139.8, 136.1(2C), 131.9, 129.4, 129.1, 128.8, 127.5, 127.2, 126.4, 119.0, 21.6.

7-Methyl-2-phenylquinoline (55s) [218]: Yellow solid (80 mg, 73%), mp: 96-97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18-8.14 (m, 3H), 7.96 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.54-7.51 (m, 2H), 7.47-7.44 (m, 1H), 7.38-7.35 (m, 1H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.5, 148.7, 140.1, 140.0, 136.6, 129.3, 128.9(2C), 128.7, 127.7, 127.2, 125.4, 118.3, 22.0.

8-Methoxy-2-phenylquinoline (55t) [218]: Yellow oil (82 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21-8.18 (m, 3H), 7.91 (d, J = 8.4 Hz, 1H), 7.53-7.49 (m, 2H), 7.47-7.39 (m, 3H), 7.09-7.06 (m, 1H), 4.11 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.4, 155.7, 140.3, 139.9, 136.9, 129.3, 128.9, 128.4, 127.8, 126.6, 119.6, 119.5, 108.2, 56.3.

6-Fluoro-2-phenylquinoline (55u) [218]: Yellow solid (72 mg, 65%), mp: 105-107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18-8.14 (m, 4H), 7.90 (d, J = 8.8 Hz, 1H), 7.55-7.43 (m, 5H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.5 (d, $^{1}J_{C\text{-}F}$ = 247 Hz), 156.9, 145.5, 139.5, 136.3 (d, $^{4}J_{C\text{-}F}$ = 5 Hz), 132.3 (d, $^{3}J_{C\text{-}F}$ = 10 Hz), 129.5, 129.0, 127.7 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 120.1, 119.9, 110.6 (d, $^{2}J_{C\text{-}F}$ = 22 Hz).

6-Chloro-2-phenylquinoline (55v) [218]: Yellow solid (81 mg, 68%), mp: 110-111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16-8.09 (m, 4H), 7.90 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.67-

7.64 (m, 1H), 7.55-7.46 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.7, 146.8, 139.4, 136.0, 132.1, 131.5, 130.7, 129.7, 129.0, 127.9, 127.7, 126.3, 119.9.

7-Chloro-2-phenylquinoline (55w) [223]: Yellow solid (87 mg, 73%), mp: 119-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21-8.15 (m, 4H), 7.88 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.56-7.46 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.4, 148.8, 139.2, 136.7, 135.6, 129.8, 129.0, 128.8(2C), 127.7, 127.4, 125.7, 119.3.

8-Chloro-2-phenylquinoline (55x) [219]: Yellow oil (84 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31-8.28 (m, 2H), 8.22 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.86-7.83 (m, 1H), 7.75-7.73 (m, 1H), 7.56-7.53 (m, 2H), 7.50-7.41 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.6, 144.5, 139.2, 137.3, 134.1, 129.9, 129.0, 128.6, 127.8, 127.4, 126.7, 126.2, 119.5.

6-Bromo-2-phenylquinoline (55y) [218]: Yellow solid (111 mg, 78%), mp: 122-123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16-8.09 (m, 3H), 8.03 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.80-7.77 (m, 1H), 7.55-7.46 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.8, 147.0, 139.3, 135.8, 133.2, 131.6, 129.7, 129.6, 129.0, 128.4, 127.6, 120.2, 119.9.

2-Phenylquinoline-6-carbonitrile (55z) [218]: Yellow solid (103 mg, 90%), mp: 136-138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.16 (m, 5H), 7.96 (d, J = 8.8 Hz, 1H), 7.84-7.81 (m, 1H), 7.57-7.49 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.0, 149.3, 138.6, 137.0, 133.8, 131.2, 130.4(2C), 129.1, 127.8, 126.5, 120.5, 118.8, 109.8.

Ethyl 2-phenylquinoline-6-carboxylate (55a′): White solid (122 mg, 88%), mp: 109-110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, J = 2.0 Hz, 1H), 8.32-7.26 (m, 2H), 8.19-8.16 (m, 3H), 7.90 (d, J = 8.8 Hz, 1H), 7.55-7.48 (m, 3H), 4.45 (q, J = 7.2 Hz, 2H) 1.45 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.3, 159.3, 150.2, 139.2, 138.0, 130.6, 130.0, 129.3, 129.0, 128.1, 127.8, 126.3, 119.7, 61.4, 14.5. Anal. Calcd. For $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05%; Found: C, 77.89; H, 5.37; N, 5.01%.

8-Chloro-6-methyl-2-phenylquinoline (55b′): Yellow solid (113 mg, 90%), mp: 88-90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28-8.26 (m, 2H), 8.09 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.55-7.52 (m, 2H), 7.49-7.46 (m, 2H), 2.50 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 156.6, 142.9, 139.2, 136.6, 136.4, 133.5, 131.9, 129.7, 129.0, 128.4, 127.6, 125.6, 119.4, 21.5. Anal. Calcd. For $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52%; Found: C, 75.78; H, 4.87; N, 5.46%.

8-Bromo-6-methyl-2-phenylquinoline (55c′): Yellow solid (135 mg, 91%), mp: 94-96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31-8.29 (m, 2H), 8.09 (d, J = 8.8 Hz, 1H), 7.92-7.90 (m, 2H), 7.55-7.52 (m, 3H), 7.49-7.45 (m, 1H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.8, 143.7, 139.1, 136.9, 136.7, 135.4, 129.7, 129.0, 128.4, 127.7, 126.4, 125.2, 119.3, 21.4. Anal. Calcd. For $C_{16}H_{12}BrN$: C, 64.45; H, 4.06; N, 4.70%; Found: C, 64.53; H, 4.12; N, 4.62%.

6-Chloro-2-(*p*-tolyl)quinoline (55d′) [221]: White solid (114 mg, 90%), mp: 113-114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.04 (m, 4H), 7.84 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.65-7.62 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.6, 146.8, 139.8, 136.5, 135.8, 131.8, 131.3, 130.5, 129.7, 127.7, 127.5, 126.2, 119.7, 21.4

6-Chloro-2-(*o*-tolyl)quinoline (55e′): Yellow solid (111 mg, 88%), mp: 93-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, J = 8.4 Hz, 2H), 7.82(d, J = 2.4 Hz, 1H), 7.68-7.65 (m, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51-7.49 (m, 1H), 7.36-7.32 (m, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.6, 146.3, 140.3, 136.1, 135.2, 132.1, 131.3, 131.0, 130.6, 129.7, 128.8, 127.4, 126.2, 126.1, 123.3, 20.4. Anal. Calcd. For $C_{16}H_{12}ClN$: C, 75.74; H, 13.97; N, 5.52%; Found: C, 75.80; H, 4.71; N, 5.43%.

6-Chloro-2-(4-fluorophenyl)quinoline (55f′): White solid (114 mg, 89%), mp: 145-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.05 (m, 4H), 7.82-7.77 (m, 2H), 7.66-7.63 (m, 1H), 7.22-7.18 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 166.5 (d, $^{1}J_{C\text{-}F}$ = 248 Hz), 156.5, 146.7, 136.0, 135.4 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 132.1, 131.3, 130.8, 129.5 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 127.7, 126.2, 119.5, 116.0 (d, $^{2}J_{C\text{-}F}$ = 21 Hz). Anal. Calcd. For $C_{15}H_9ClFN_2$: C, 69.91; H, 3.52; N, 5.44%; Found: C, 69.98; H, 3.60; N, 5.49%.

6-Chloro-2-(4-chlorophenyl)quinoline (55g′) [221]: White solid (99 mg, 72%), mp: 165-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.05 (m, 4H), 7.82 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.66-7.63 (m, 1H), 7.50-7.47 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.3, 146.7, 137.7, 136.1, 135.9, 132.3, 131.4, 130.9, 129.2, 128.8, 127.9, 126.3, 119.4.

6-Chloro-2-(4-(methylthio)phenyl)quinoline (55h′): Yellow solid (131 mg, 92%), mp: 108-109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09-8.05 (m, 4H), 7.84 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.65-7.62 (m, 1H), 7.38-7.36 (m, 2H), 2.54 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.9, 146.7, 140.9, 135.9, 135.8, 131.9, 131.3, 130.7, 127.8, 127.7, 126.4, 126.2, 119.4, 15.5. Anal. Calcd. For $C_{16}H_{12}ClNS$: C, 67.24; H, 4.23; N, 4.90%; Found: C, 67.17; H, 4.29; N, 4.98%.

2-(4-Methoxyphenyl)-6-methylquinoline (55i′) [206]: White solid (113 mg, 90%), mp: 136-137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13-8.02 (m, 4H), 7.79 (d, J = 8.4 Hz, 1H), 7.56-7.52 (m, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.54 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.8, 156.2, 147.0, 136.1, 135.8, 132.6, 132.0, 129.3, 128.9, 127.0, 126.5, 118.7, 114.3, 55.5, 21.7.

2-(2-Bromophenyl)-6-methylquinoline (55j′): Brown solid (115 mg, 77%), mp: 81-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.71-7.62 (m, 4H), 7.59-7.57 (m, 1H), 7.46-7.42 (m, 1H), 7.31-7.27 (m, 1H), 2.57 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.0, 146.6, 141.9, 136.8, 135.1, 133.3, 132.1, 131.7, 130.0, 129.5, 127.8, 127.3, 126.5, 122.8, 122.0, 21.8. Anal. Calcd. For $C_{16}H_{12}BrN$: C, 64.45; H, 4.06; N, 4.70%; Found: C, 64.37; H, 4.14; N, 4.78%.

2-(2-Bromophenyl)-7-methylquinoline (55k′): Yellow solid (95 mg, 64%), mp: 76-77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71-7.69 (m, 1H), 7.64-7.61 (m, 2H), 7.46-7.41 (m, 2H), 7.31-7.27 (m, 1H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.8, 148.3, 141.9, 140.2, 135.5, 133.3, 131.6, 130.1, 130.0, 129.2, 128.8, 127.8, 127.3, 125.3, 122.0, 22.1. Anal. Calcd. For $C_{16}H_{12}BrN$: C, 64.45; H, 4.06; N, 4.70%; Found: C, 64.53; H, 4.01; N, 4.63%.

2-(4-Methoxyphenyl)quinoline (55l′) [218]: Brown solid (96 mg, 82%), mp: 115-116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19-8.13 (m, 4H), 7.83 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.73- 7.69 (m, 1H), 7.52-7.50 (m, 1H), 7.06-7.04 (m, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.0, 157.1, 148.4, 136.7, 132.4, 129.7, 129.0, 127.6, 127.0, 126.0, 118.7, 114.4, 55.5.

2-(4-Chlorophenyl)quinoline (55m′) [223]: Yellow solid (96 mg, 80%), mp: 96-98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, J = 8.4 Hz, 1H), 8.17-8.11 (m, 3H), 7.85-7.82 (m, 2H), 7.76-7.72 (m, 1H), 7.56-7.49 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 156.2, 148.4, 138.2, 137.1, 135.7, 130.0, 129.8, 129.1, 129.0, 127.6, 127.4, 126.6, 118.7.

4,6-Dimethyl-2-phenylquinoline (55n′): Yellow oil (98 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.60-7.58 (m, 2H), 7.53-7.43 (m, 5H), 2.54 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 159.7, 145.3, 141.1, 136.3, 136.2, 131.2, 129.2, 129.1, 129.0, 128.4, 128.2, 127.7, 125.6, 21.7, 20.7. Anal. Calcd. For $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00%; Found: C, 87.57; H, 6.55; N, 6.07%.

6-Methoxy-4-methyl-2-phenylquinoline (55o′): Yellow solid (112 mg, 90%), mp: 69-71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 9.2 Hz, 1H), 7.90 (s, 1H), 7.59-7.57 (m, 2H), 7.50-7.46

(m, 2H), 7.44-7.42 (m, 1H), 7.33-7.30 (m, 1H), 7.03 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.1, 157.8, 142.8, 141.0, 135.7, 130.8, 129.5, 129.0, 128.6, 128.3, 128.1, 121.5, 104.3, 55.6, 20.7. Anal. Calcd. For $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%; Found: C, 81.84; H, 6.13; N, 5.71%.

6-Chloro-4-methyl-2-phenylquinoline (55p′): Brown oil (101 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.60-7.57 (m, 3H), 7.52-7.44 (m, 3H), 2.47 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.0, 145.1, 140.6, 135.9, 132.2, 131.1, 130.5, 129.8, 128.9, 128.5, 128.3, 125.5, 20.8. Anal. Calcd. For $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52%; Found: C, 75.66; H, 4.84; 5.61%.

6-Methoxy-4-methyl-2-(*p*-tolyl)quinoline (55q′): Light pink solid (122 mg, 93%), mp: 128-129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, J = 9.2 Hz, 1H), 7.88 (s, 1H), 7.49-7.47 (m, 2H), 7.32-7.27 (m, 3H), 7.03-7.02 (m, 1H), 3.93 (s, 3H), 2.45 (s, 3H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.2, 157.8, 142.9, 138.3, 137.8, 135.7, 130.9, 129.6, 129.0(2C), 128.6, 121.4, 104.4, 55.6, 21.4, 20.8. Anal. Calcd. For $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32%; Found: C, C, 82.16; H, 6.58; N, 5.41%.

6-Methoxy-2-(4-methoxyphenyl)-4-methylquinoline (55r′): White solid (128 mg, 92%), mp: 92-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 9.2 Hz, 1H), 7.88 (s, 1H), 7.55-7.53 (m, 2H), 7.32-7.29 (m, 1H), 7.03-7.00 (m, 3H), 3.93 (s, 3H), 3.87 (s, 3H), 2.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 159.6, 157.8(2C), 142.9, 135.7, 133.6, 130.8, 130.4, 129.6, 128.5, 121.4, 113.8, 104.4, 55.6, 55.5, 20.9. Anal. Calcd. For $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01%; Found: C, 77.32; H, 6.08; N, 5.09%.

2-(4-Chlorophenyl)-6-methoxy-4-methylquinoline (55s′): White solid (127 mg, 90%), mp: 137-138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.55-7.51 (m, 2H), 7.46-7.43 (m, 2H), 7.33-7.30 (m, 1H), 7.03 (d, J = 6.4 Hz, 1H) 3.93 (s, 3H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.1, 156.8, 142.9, 139.5, 136.0, 134.2, 130.8, 130.5, 129.3, 128.8, 128.6, 121.8, 104.3, 55.6, 20.6. Anal. Calcd. For $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94 %; Found: C, 71.87; H, 4.88; N, 4.83%.

2-(4-Bromophenyl)-6-methoxy-4-methylquinoline (55t′): White solid (149 mg, 91%), mp: 120-121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 1H), 7.91 (s, 1H), 7.62-7.59 (m, 2H), 7.48-7.45 (m, 2H), 7.33-7.30 (m, 1H), 7.04-7.03 (m, 1H), 3.94 (s, 3H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.0, 156.8, 142.8, 139.9, 136.0, 131.5, 130.8, 129.3(2C), 128.8, 122.5,

121.8, 104.3, 55.7, 20.6. Anal. Calcd. For $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27%; Found: C, 62.28; H, 4.39; N, 4.20%.

2-(Benzo[*d*][1,3]dioxol-5-yl)-6-methoxy-4-methylquinoline (55u′): Light yellow solid (129 mg, 88%), mp: 125-126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.31-7.28 (m, 1H), 7.08-7.03 (m, 2H), 7.01-7.00 (m, 1H), 6.91-6.89 (m, 1H), 3.91 (s, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.8, 157.5, 147.6(2C), 142.8, 135.8, 135.0, 130.7, 129.5, 128.5, 122.9, 121.5, 109.8, 108.2, 104.3, 101.2, 55.6, 20.7. Anal. Calcd. For $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%; Found: C, 73.80; H, 5.10; N, 4.68%.

6-Methoxy-4-methyl-2-(naphthalen-2-yl)quinoline (55v′): White solid (133 mg, 89%), mp: 132-134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 2H), 7.96-7.89 (m, 4H), 7.74-7.71 (m, 1H), 7.54-7.50 (m, 2H), 7.36-7.33 (m, 1H), 7.07 (d, J = 2.8 Hz, 1H), 3.95 (s, 3H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.1, 158.0, 143.0, 138.6, 135.8, 133.4, 133.1, 131.0, 129.8, 128.7, 128.5, 128.3, 128.0, 127.8, 127.0, 126.4, 126.3, 121.6, 104.5, 55.7, 20.8. Anal. Calcd. For $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68%; Found: C, 84.16; H, 5.79; N, 4.60%.

6-Methoxy-4-methyl-2-(thiophen-2-yl)quinoline (55w′): White solid (116 mg, 91%), mp: 98-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86 (m, 1H), 7.71 (s, 1H), 7.44-7.43 (m, 1H), 7.34-7.33 (m, 1H), 7.21-7.18 (m, 1H), 7.05-7.03 (m, 1H), 6.85-6.84 (m, 1H), 3.79 (s, 3H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.8, 150.3, 145.4, 142.7, 136.4, 130.6, 128.7, 128.2, 127.6(2C), 127.2, 121.7, 104.2, 55.5, 21.8. Anal. Calcd. For $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%; Found: C, 70.50; H, 5.21; N, 5.59%.

4-Ethyl-6-methoxy-2-phenylquinoline (55x′): Yellow gummy mass (105 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, J = 9.2 Hz, 1H), 7.95 (s, 1H), 7.54-7.52 (m, 2H), 7.49-7.42 (m, 3H), 7.33-7.30 (m, 1H), 7.08 (d, J = 2.8 Hz, 1H), 3.94 (s, 3H), 2.77 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.2, 157.9, 142.5, 141.0, 135.6, 134.0, 130.8, 128.9, 128.4, 128.0, 127.0, 121.6, 104.5, 55.6, 26.1, 14.9. Anal. Calcd. For $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32%; Found: C, 82.18; H, 6.46; N, 5.38%.

4-Ethyl-6-methoxy-2-(*p*-tolyl)quinoline (55y′): Yellow oil (115 mg, 83%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 9.2 Hz, 1H), 7.90 (s, 1H), 7.42-7.40 (m, 2H), 7.30-7.23 (m, 3H), 7.04 (d, J = 2.4 Hz, 1H), 3.91 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 2.40 (s, 3H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.3, 157.7, 142.5, 138.2, 137.7, 135.7, 133.8, 130.7, 129.0, 128.8, 128.7, 121.5, 104.5, 55.6, 26.1, 21.4, 14.9. Anal. Calcd. For $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%; Found: C, 82.18; H, 6.98; N, 5.13%.

2-(4-Chlorophenyl)-4-ethyl-6-methoxyquinoline (55z′): White solid (133 mg, 90%), mp: 90-92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 9.2 Hz, 1H), 7.95 (s, 1H), 7.50-7.43 (m, 4H), 7.34-7.31 (m, 1H), 7.08 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.0, 156.9, 142.6, 139.6, 135.5, 134.2(2C), 130.8, 130.4, 128.9, 128.6, 121.9, 104.5, 55.7, 26.1, 14.9. Anal. Calcd. For $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70%; Found: C, 72.68; H, 5.37; N, 4.67%.

2-(4-Bromophenyl)-4-ethyl-6-methoxyquinoline (55a′′): White solid (156 mg, 91%), mp: 99-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 9.2 Hz, 1H), 7.95 (s, 1H), 7.62-7.59 (m, 2H), 7.45-7.40 (m, 2H), 7.34-7.31 (m, 1H), 7.08-7.07 (m, 1H), 3.94 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.0, 156.9, 142.6, 140.0, 135.4, 134.2, 131.6, 130.8, 130.7, 128.9, 122.4, 121.9, 104.5, 55.7, 26.1, 14.9. Anal. Calcd. For $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09%; Found: C, 63.25; H, 4.80; N, 4.16%.

2-(Benzo[*d*][1,3]dioxol-5-yl)-4-ethyl-6-methoxyquinoline (55b′′): Yellow gummy (141 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 9.2 Hz, 1H), 7.92 (s, 1H), 7.32-7.29 (m, 1H), 7.06-6.99 (m, 3H), 6.90 (d, J = 8.0 Hz, 1H), 6.01 (s, 2H), 3.93 (s, 3H), 2.79 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.8, 157.6, 147.6, 147.5, 142.5, 135.7, 135.0, 134.0, 130.7, 128.7, 122.7, 121.6, 109.7, 108.3, 104.5, 101.2, 55.6, 26.1, 14.9. Anal. Calcd. For $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56%; Found: C, 74.20; H, 5.68; N, 4.51%.

6-Methoxy-2-phenyl-4-propylquinoline (55c′′): Yellow gummy (108 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, J = 9.2 Hz, 1H), 7.93 (s, 1H), 7.54-751 (m, 2H), 7.49-7.39 (m, 3H), 7.33-7.30 (m, 1H), 7.07 (d, J = 9.2 Hz, 1H), 3.95 (s, 3H), 2.73 (t, J = 8.0 Hz, 2H), 1.60-1.52 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.4, 157.9, 142.7, 141.3, 134.8, 134.2, 130.9, 129.0, 128.7, 128.4, 128.0, 121.6, 104.6, 55.7, 35.0, 23.9, 14.0. Anal. Calcd. For $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%; Found: C, 82.21; H, 6.84; N, 5.01%.

6-Methoxy-4-propyl-2-(*p*-tolyl)quinoline (55d′′): Yellow oil (125 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H), 7.35-7.33 (m, 2H), 7.24-7.18 (m, 3H), 6.99 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 2.66 (t, J = 8.0 Hz, 2H), 2.34 (s, 3H), 1.54-1.45 (m, 2H), 0.79 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.4, 157.8, 142.6, 138.3, 137.7, 134.6, 134.2, 130.8, 129.0, 128.8, 128.6, 121.5, 104.5, 55.6, 35.0, 23.8, 21.4, 14.0. Anal. Calcd. For $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81%; Found: C, 82.48; H, 7.33; N, 4.89%.

2-Ethyl-6-methoxy-3-methylquinoline (55e′′) [359]: Pale yellow oil (80 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 9.2 Hz, 1H), 7.74 (s, 1H), 7.28-7.25 (m, 1H), 6.97 (d, J = 2.8

Hz, 1H), 3.90 (s, 3H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 1.35 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.8, 157.3, 142.7, 135.0, 130.0, 129.8, 128.3, 120.8, 104.6, 55.6, 29.3, 19.2, 13.1.

***3*-Ethyl-6-methoxy-2-propylquinoline (55f′′) [359]:** Pale yellow oil (96 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* = 9.2 Hz, 1H), 7.75 (s, 1H), 7.26-7.23 (m, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 3.88 (s, 3H), 2.92-2.88 (m, 2H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.82-1.76 (m, 2H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.03 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 159.5, 157.3, 142.5, 135.8, 133.1, 130.0, 128.3, 120.9, 104.8, 55.6, 37.7, 25.3, 23.1, 14.6, 14.5.

4-Methoxy-*N*-(2-nitro-1-phenylpropyl)aniline (56): Yellow oil (132 mg, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.33 (m, 2H), 7.31-7.28 (m, 3H), 6.69-6.67 (m, 2H), 6.55-6.53 (m, 2H), 4.87-4.83 (m, 1H), 4.70 (d, *J* = 8.4 Hz, 1H), 4.16 (bs, 1H), 3.68 (s, 3H), 1.42 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.1, 139.9, 138.1, 129.2, 128.6, 127.1, 115.9, 114.8, 87.8, 63.1, 55.7, 17.2. Anal. Calcd. For $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78%; Found: C, 67.04; H, 6.28; N, 9.86%.

3.20. Synthesis of dipyrromethanes as well as bis(indolyl)methanes catalyzed by imidazolium zwitterionic molten salt

Typical procedure for synthesis of 2,2'-(phenylmethylene)bis(1*H*-pyrrole) (61a): A mixture of benzaldehyde (**34a**, 106 mg, 1 mmol) and pyrrole (**60a**, 134 mg, 2 mmol) was stirred in presence of zwitterionic-salt (**MS-1**, 22 mg, 10 mol%) at room temperature for 1 hour in a sealed tube as indicated by TLC for a complete reaction. After completion, the reaction mixture was cooled to room temperature and diluted with water (10 mL) and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (6% to 8%) as eluent. The identity and purity of the product were confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

2,2'-(Phenylmethylene)bis(1*H*-pyrrole) (61a) [240]: Yield: 87%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (s, 2H), 7.25-7.20 (m, 2H), 7.18-7.10 (m, 3H), 6.59-6.57 (m, 2H), 6.08-6.06 (m, 2H), 5.83-5.81 (m, 2H), 5.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 142.2, 132.6, 128.7, 128.5, 127.1, 117.3, 108.5, 107.3, 44.1.

2,2'-((4-Nitrophenyl)methylene)bis(1*H*-pyrrole) (61b) [240]: Yield: 85%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18-8.15 (m, 2H), 8.03 (s, 2H), 7.39-7.35 (m, 2H), 6.76-6.74 (m, 2H), 6.19-6.16

(m, 2H), 5.89-5.86 (m, 2H), 5.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 149.8, 147.1, 130.9, 129.4, 123.9, 118.1, 108.9, 108.0, 43.9.

2,2'-(*p*-Tolylmethylene)bis(1*H*-pyrrole) (61c) [239]: Yield: 75%, Pale Yellow Solid, mp. 110-112°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 2H), 7.15-7.10 (m, 4H), 6.69-6.68 (m, 2H), 6.17-6.15 (m, 2H), 5.93-5.92 (m, 2H), 5.44 (s, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 136.7, 132.8, 129.5, 128.4, 117.2, 108.5, 107.2, 43.7, 21.2.

2,2'-((4-Methoxyphenyl)methylene)bis(1*H*-pyrrole) (61d) [239]: Yield: 72%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (s, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.54-6.53 (m, 2H), 6.06-6.04 (m, 2H), 5.79 (s, 2H), 5.27 (s, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6, 134.3, 133.0, 129.5, 117.2, 114.0, 108.4, 107.1, 55.4, 43.2.

2,2'-((4-Fluorophenyl)methylene)bis(1*H*-pyrrole) (61e) [240]: Yield: 73%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 2H), 7.20-7.15 (m, 2H), 7.03-6.97 (m, 2H), 6.71-6.70 (m, 2H), 6.18-6.15 (m, 2H), 5.90-5.88 (m, 2H), 5.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9 (d, $^1J_{C\text{-}F}$ = 243 Hz), 138.0 (d, $^3J_{C\text{-}F}$ = 3 Hz), 132.4, 130.0 (d, $^4J_{C\text{-}F}$ = 7 Hz), 117.5, 115.5 (d, $^2J_{C\text{-}F}$ = 21 Hz), 108.6, 107.4, 43.3.

2,2'-((4-Chlorophenyl)methylene)bis(1*H*-pyrrole) (61f) [240]: Yield: 76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 2H), 7.30-7.27 (m, 2H), 7.16-7.13 (m, 2H), 6.72-6.70 (m, 2H), 6.17-6.15 (m, 2H), 5.90-5.88 (m, 2H), 5.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.8, 132.9, 132.1, 129.9, 128.9, 117.6, 108.7, 107.5, 43.5.

2,2'-((4-Bromophenyl)methylene)bis(1*H*-pyrrole) (61g) [239]: Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 2H), 7.45-7.42 (m, 2H), 7.10-7.07 (m, 2H), 6.72-6.70 (m, 2H), 6.17-6.15 (m, 2H), 5.90-5.88 (m, 2H), 5.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 132.0, 131.8, 130.2, 121.0, 117.6, 108.7, 107.5, 43.6.

2,2'-((4-(Methylthio)phenyl)methylene)bis(1*H*-pyrrole) (3h) [388]: Yield: 73%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 2H), 7.22-7.20 (m, 2H), 7.14-7.12 (m, 2H), 6.70-6.68 (m, 2H), 6.17-6.15 (m, 2H), 5.92-5.90 (m, 2H), 5.43 (s, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 137.1, 132.5, 129.0, 127.0, 117.4, 108.6, 107.3, 43.6, 16.1.

4-(Di(1*H*-pyrrol-2-yl)methyl)-*N*,*N*-dimethylaniline (61i) [240]: Yield: 74%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (s, 2H), 7.09-7.07 (m, 2H), 6.71-6.66 (m, 4H), 6.16-6.14 (m, 2H), 5.95-5.92 (m, 2H), 5.39 (s, 1H), 2.93 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.9, 133.4, 130.0, 129.2, 117.0, 113.0, 108.5, 107.0, 43.2, 40.8.

4-(Di(1*H*-pyrrol-2-yl)methyl)benzonitrile (61j) [237]: Yield: 73%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 2H), 7.60-7.58 (m, 2H), 7.32-7.30 (m, 2H), 6.73-6.72 (m, 2H), 6.18-6.16 (m, 2H), 5.87-5.85 (m, 2H), 5.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.8, 132.5, 131.1, 129.3, 118.9, 118.0, 110.9, 108.8, 107.9, 44.1.

2,2'-((2-Fluorophenyl)methylene)bis(1*H*-pyrrole) (61k) [393]: Yield: 81%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 2H), 7.18-7.13 (m, 1H), 7.07-6.95 (m, 3H), 6.61-6.60 (m, 2H), 6.08-6.06 (m, 2H), 5.83-5.82 (m, 2H), 5.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5 (d, $^{1}J_{C\text{-}F}$ = 245 Hz), 131.3, 130.8 (d, $^{3}J_{C\text{-}F}$ = 4 Hz), 129.6, 129.4, 128.8 (d, $^{4}J_{C\text{-}F}$ = 7 Hz), 124.5(2C), 117.5, 115.7 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 108.6, 107.3, 37.4.

2,2'-((2-Bromophenyl)methylene)bis(1*H*-pyrrole) (61l) [236]: Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (s, 2H), 7.48-7.46 (m, 1H), 7.16-7.12 (m, 1H), 7.03-6.98 (m, 2H), 6.59-6.58 (m, 2H), 6.08-6.06 (m, 2H), 5.79-5.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.8, 133.1, 131.4, 130.0, 128.6, 127.8, 124.5, 117.4, 108.6, 107.6, 43.4.

2-(Di(1*H*-pyrrol-2-yl)methyl)phenol (61m) [240]: Yield: 79%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 2H), 7.21-7.16 (m, 1H), 7.08-7.06 (m, 1H), 6.94-6.90 (m, 1H), 6.85-6.83 (m, 1H), 6.70-6.68 (m, 2H), 6.18-6.16 (m, 2H), 6.00-5.99 (m, 2H), 5.56 (s, 1H), 5.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 131.3, 130.2, 128.7, 128.6, 121.5, 118.0, 117.4, 108.6, 107.1, 40.0.

2,2'-((2-Methoxyphenyl)methylene)bis(1*H*-pyrrole) (61n) [390]: Yield: 81%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 2H), 7.15-7.09 (m, 1H), 6.98-6.96 (m, 1H), 6.81-6.78 (m, 2H), 6.51-6.49 (m, 2H), 6.03-6.01 (m, 2H), 5.79-5.77 (m, 2H), 5.68 (s, 1H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.8, 132.7, 131.0, 129.6, 128.2, 121.0, 116.8, 111.3, 108.2, 106.8, 55.8, 37.6.

2,2'-(*o*-Tolylmethylene)bis(1*H*-pyrrole) (61o) [391]: Yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (s, 2H), 7.07-6.99 (m, 3H), 6.84 (d, J = 6.8 Hz, 1H), 6.51-6.50 (m, 2H), 6.05-6.03 (m, 2H), 5.77-5.75 (m, 2H), 5.48 (s, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 136.4, 132.1, 130.6, 128.0, 127.0, 126.3, 117.2, 108.5, 107.4, 40.5, 19.4.

2,2'-(Naphthalen-1-ylmethylene)bis(1*H*-pyrrole) (61p) [392]: Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.02 (m, 1H), 7.93 (s, 2H), 7.88-7.85 (m, 1H), 7.79 (d, J = 8 Hz, 1H), 7.49-7.38 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 6.69-6.68 (m, 2H), 6.26 (s, 1H), 6.18-6.16 (m, 2H), 5.96-5.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.2, 134.1, 132.3, 131.7, 128.9, 128.0, 126.5, 126.2, 125.9, 125.7, 123.8, 117.2, 108.7, 107.6, 40.4.

2,2'-(Naphthalen-2-ylmethylene)bis(1*H*-pyrrole) (61q) [393]: Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 2H), 7.86-7.76 (m, 3H), 7.64 (s, 1H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 1H), 6.71-6.70 (m, 2H), 6.21-6.19 (m, 2H), 5.99-5.97 (m, 2H), 5.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.7, 133.6, 132.7, 132.4, 128.5, 128.0, 127.7, 127.0, 126.8, 126.3, 126.0, 117.4, 108.6, 107.5, 44.2.

2,2'-((2,6-Dichlorophenyl)methylene)bis(1*H*-pyrrole) (61r) [393]: Yield: 78%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (s, 2H), 7.33 (d, J = 8 Hz, 2H), 7.13 (t, J = 16 Hz, 1H), 6.73-6.72 (m, 2H), 6.49 (s, 1H), 6.21-6.18 (m, 2H), 6.08-6.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.2, 136.0, 129.8, 129.5, 128.7, 117.0, 108.8, 107.5, 40.1.

2,2'-((3,4,5-Trimethoxyphenyl)methylene)bis(1*H*-pyrrole) (61s) [393]: Yield: 79%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 2H), 6.73-6.71 (m, 2H), 6.45 (s, 2H), 6.20-6.18 (m, 2H), 5.99-5.97 (m, 2H), 5.43 (s, 1H), 3.85 (s, 3H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 137.9, 136.9, 132.4, 117.3, 108.5, 107.3, 105.6, 60.9, 56.1, 44.3.

Tri(1*H*-pyrrol-2-yl)methane (61t) [240]: Yield: 78%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (s, 3H), 6.65-6.63 (m, 3H), 6.21-6.19 (m, 3H), 6.05-6.04 (m, 3H), 5.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.3, 117.5, 108.5, 106.9, 37.3.

3-(Di(1*H*-pyrrol-2-yl)methyl)-1*H*-indole (61u) [393]: Yield: 72%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), 8.00 (s, 2H), 7.36 (t, J = 16.4 Hz, 2H), 7.22-7.18 (m, 1H), 7.07-7.03 (m, 1H), 6.9 (d, J = 2.8 Hz, 1H), 6.66-6.64 (m, 2H), 6.18-6.15 (m, 2H), 6.06-6.04 (m, 2H), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.7, 132.7, 126.7, 123.2, 122.5, 120.0, 119.7, 117.4, 116.8, 111.4, 108.5, 106.6, 35.5.

2,2'-(Propane-1,1-diyl)bis(1*H*-pyrrole) (61v) [237]: Yield: 66%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (s, 2H), 6.64-6.62 (m, 2H), 6.16-6.14 (m, 2H), 6.09-6.07 (m, 2H), 3.87 (t, J = 15.2 Hz, 1H), 2.01-1.94 (m, 2H), 0.93 (t, J = 14.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.6, 117.1, 108.2, 105.6, 39.6, 27.7, 12.4.

2,2'-((4-Bromophenyl)methylene)bis(1-methyl-1*H*-pyrrole) (61w) [237]: Yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.41 (m, 2H), 7.02-7.00 (m, 2H), 6.59 (t, J = 3.6 Hz, 2H), 6.02 (t, J = 6.4 Hz, 2H), 5.47-5.46 (m, 2H), 5.21 (s, 1H), 3.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.5, 133.0, 131.7, 130.6, 122.4, 120.7, 109.2, 106.7, 41.5, 34.0.

2,2'-(Propane-1,1-diyl)bis(1-methyl-1*H*-pyrrole) (61x) [394]: Yield: 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.41-6.40 (m, 2H), 5.96-5.94 (m, 2H), 5.81-5.79 (m, 2H), 3.73 (t, J = 14.8 Hz, 1H),

3.30 (s, 6H), 1.96-1.91 (m, 2H), 0.90 (t, J = 14.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.2, 121.7, 106.7, 106.3, 37.5, 33.9, 27.9, 12.7.

3,3'-(Phenylmethylene)bis(1*H*-indole) (59a) [250]: Yield: 86%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 2H), 7.41-7.34 (m, 6H), 7.30-7.26 (m, 2H), 7.24-7.15 (m, 3H), 7.03-6.99 (m, 2H), 6.65-6.44 (m, 2H), 5.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 136.8, 128.8, 128.3, 127.2, 126.3, 123.7, 122.1, 120.1, 119.9, 119.4, 111.1, 40.3.

3,3'-(*p*-Tolylmethylene)bis(1*H*-indole) (59b) [250]: Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (s, 2H), 7.48 (d, J = 8 Hz, 2H), 7.36-7.25 (m, 6H), 7.21-7.11 (m, 4H), 6.48 (s, 2H), 6.13 (s, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.2, 136.7, 136.1, 130.3, 128.5, 127.2, 124.0, 121.9, 119.8, 119.2, 119.0, 111.2, 36.2, 19.6.

3,3'-((4-Methoxyphenyl)methylene)bis(1*H*-indole) (59c) [250]: Yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (s, 2H), 7.26 (d, J = 8 Hz, 2H), 7.13-7.08 (m, 4H), 7.03 (t, J = 14.8 Hz, 2H), 6.88 (t, J = 14.8 Hz, 2H), 6.68-6.66 (m, 2H), 6.37 (d, J = 2 Hz, 2H), 5.69 (s, 1H), 3.62 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9, 136.7, 136.4, 129.7, 127.1, 123.7, 121.9, 120.0, 119.9, 119.2, 113.7, 111.2, 55.3, 39.4.

3,3'-((4-Fluorophenyl)methylene)bis(1*H*-indole) (59d) [395]: Yield: 74%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 2H), 7.24 (d, J = 8 Hz, 2H), 7.17-7.11 (m, 4H), 7.08-7.03 (m, 2H), 6.92-6.88 (m, 2H), 6.84-6.79 (m, 2H), 6.39 (d, J = 1.6 Hz, 2H), 5.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5 (d, $^1J_{C\text{-}F}$ = 242 Hz), 139.8 (d, $^3J_{C\text{-}F}$ = 3 Hz), 136.8, 130.2 (d, $^4J_{C\text{-}F}$ = 8 Hz), 127.0, 123.7, 122.1, 119.9, 119.6, 119.4, 115.0 (d, $^2J_{C\text{-}F}$ = 20 Hz), 111.3, 39.5.

3,3'-((4-Chlorophenyl)methylene)bis(1*H*-indole) (59e) [250]: Yield: 77%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 2H), 7.38-7.35 (m, 4H), 7.29-7.23 (m, 4H), 7.21-7.17 (m, 2H), 7.04-7.00 (m, 2H), 6.63-6.62 (m, 2H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7, 136.8, 131.9, 130.2, 128.5, 127.0, 123.7, 122.2, 119.9, 119.5, 119.3, 111.2, 39.7.

3,3'-((4-Bromophenyl)methylene)bis(1*H*-indole) (59f) [250]: Yield: 76%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (s, 2H), 7.42-7.33 (m, 6H), 7.23-7.18 (m, 4H), 7.05-7.01 (m, 2H), 6.60-6.59 (m, 2H), 5.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.2, 136.8, 131.4, 130.6, 127.0, 123.7, 122.2, 120.0, 119.9, 119.5, 119.1, 111.2, 39.8.

3,3'-((4-(Methylthio)phenyl)methylene)bis(1*H*-indole) (59g) [396]: Yield: 74%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (s, 2H), 7.47 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 7.35-7.33 (m, 2H), 7.27-7.23 (m, 4H), 7.11-7.07 (m, 2H), 6.70-6.69 (m, 2H), 5.92 (s, 1H), 2.53 (s, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ 141.3, 136.8, 135.6, 129.3, 127.1, 126.8, 123.7, 122.0, 120.0, 119.6, 119.3, 111.2, 39.8, 16.1.

3,3'-((2-Chlorophenyl)methylene)bis(1*H*-indole) (59h) [250]: Yield: 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (s, 2H), 7.55 (d, J = 8 Hz, 3H), 7.34-7.22 (m, 6H), 7.17-7.12 (m, 3H), 6.52-6.51 (m, 2H), 6.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4, 136.6, 133.9, 130.3, 129.5, 127.6, 126.9, 126.7, 124.0, 122.0, 119.7, 119.3, 118.0, 111.3, 36.6.

3,3'-((2-Bromophenyl)methylene)bis(1*H*-indole) (59i) [395]: Yield: 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.72 (m, 1H), 7.60 (s, 2H), 7.54 (d, J = 8 Hz, 2H), 7.33-7.27 (m, 5H), 7.20-7.13 (m, 4H), 6.49-6.48 (m, 2H), 6.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 136.6, 132.8, 130.5, 127.9, 127.3, 126.9, 124.8, 124.0, 122.0, 119.8, 119.3, 118.2, 111.3, 39.5.

3,3'-(Thiophen-2-ylmethylene)bis(1*H*-indole) (59j) [394]: Yield: 78%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (s, 2H), 7.32 (d, J = 8 Hz, 2H), 7.09-7.07 (m, 2H), 7.03-6.96 (m, 3H), 6.90-6.87 (m, 2H), 6.76-6.73 (m, 2H), 6.49 (d, J = 2 Hz, 2H), 6.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.8, 136.5, 126.7, 126.5, 125.2, 123.7, 123.3, 122.0, 119.8, 119.5, 119.4, 111.3, 35.3.

3,3'-(Naphthalen-2-ylmethylene)bis(1*H*-indole) (59k) [395]: Yield: 76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 2H), 7.83-7.80 (m, 1H), 7.78-7.76 (m, 2H), 7.72-7.70 (m, 1H), 7.54-7.51 (m, 1H), 7.44-7.41 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 7.19-7.16 (m, 2H), 7.02-6.98 (m, 2H), 6.65-6.64 (m, 2H), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.7, 136.8, 133.7, 132.5, 128.0, 127.9, 127.7, 127.2, 126.9, 125.8, 125.4, 123.9, 122.1, 120.8, 120.1, 119.6, 119.4, 111.2, 40.4.

3,3'-(Propane-1,1-diyl)bis(1*H*-indole) (59l) [250]: Yield: 65%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (s, 2H), 7.60 (d, J = 8 Hz, 2H), 7.33(d, J = 8 Hz, 2H), 7.17-7.13 (m, 2H), 7.06-7.6.99 (m, 4H), 4.39 (t, J = 14.8 Hz, 1H), 2.30-2.22 (m, 2H), 1.02 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.7, 127.4, 121.8, 121.5, 120.5, 119.8, 119.1, 111.1, 36.0, 28.8, 13.2.

3,3'-((4-Chlorophenyl)methylene)bis(1-methyl-1*H*-indole) (59m) [397]: Yield: 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.34 (m, 2H), 7.31-7.29 (m, 2H), 7.26-7.24 (m, 4H), 7.23-7.19 (m, 2H), 7.02-6.98 (m, 2H), 6.51 (s, 2H), 5.85 (s, 1H), 3.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.1, 137.5, 131.8, 130.2, 128.5, 128.4, 127.4, 121.7, 120.0, 118.9, 117.9, 109.3, 39.6, 32.8.

3,3'-(Propane-1,1-diyl)bis(1-methyl-1*H*-indole) (59n) [397]: Yield: 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J = 8 Hz, 2H), 7.28-7.26 (m, 2H), 7.20-7.16 (m, 2H), 7.05-7.01 (m, 2H), 6.85 (s, 2H), 4.37 (t, J = 14.4 Hz, 1H), 3.72 (s, 6H), 2.26-2.18 (m, 2H), 1.00 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 127.8, 126.4, 121.3, 119.9, 119.2, 118.5, 109.2, 35.9, 32.8, 29.4, 13.3.

3,3'-((4-Nitrophenyl)methylene)bis(1*H*-indole) (59o): Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 1H), 6.72 (s, 2H), 7.05 (m, 2H), 7.22 (m, 2H), 7.32–7.44 (m, 4H)), 7.53 (d, J = 8. Hz, 2H), 8.03 (s, 2H), 8.16 (d, J = 8 Hz, 2H). Mass spectrum, m/z: 367.0 $[M]^+$. Anal. Calcd. For $C_{23}H_{17}N_3O_2$: C 75.19, H 4.66, N 11.44%; Found, %: C 75.04, H 4.49, N 11.24%.

Reaction of indole with 4-nitrobenzaldehyde under ball milling: A 25 mL steel reactor equipped with four stainless steel grinding balls with a diameter of 10 mm was charged with indole (1 mmol), 4-nitrobenzaldehyde (1 mmol), and 2–3 drops of trifluoroacetic acid. The mixture was stirred at 500 rpm for 4 h. The resulting mass was dissolved in ethyl acetate (20 mL), washed with water (3×10 mL), the organic layer was dried with anhydrous Na_2SO_4, and the solvent was distilled off under reduced pressure. The products were isolated by column chromatography (silica gel, eluent: $CHCl_3$–AcOEt (95:5). Analytical samples of the products were obtained by recrystallization from ethanol.

3.21. Tandem trimerization of indoles catalyzed by brønsted acidic ionic liquid

Typical procedure for the synthesis of 2-(2,2-di(1*H*-indol-3-yl)ethyl)aniline (63a): **BAIL-1** (10 mol%) was added to indole (**58a**, 1 mmol) and the mixture was stirred at 80 °C for 1 h (TLC). After completion of the reaction, water was added to the reaction mixture. Then the crude product was filtered off and the ionic liquid was recovered by evaporating the water. The recovered ionic liquid was reused for a subsequent fresh batch of the reaction after reactivation. The crude product was washed with ethanol to afford the pure product as brown solid.

2-(2,2-Di(1*H*-indol-3-yl)ethyl)aniline (63a) [257]: Yield: 85%, 99 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.16-7.12 (m, 2H), 7.01-6.96 (m, 4H), 6.92 (d, J = 2.4 Hz, 2H), 6.66-6.62 (m, 1H), 6.56-6.54 (m, 1H), 4.86 (t, J = 14.8 Hz, 1H), 3.41 (d, J = 7.2 Hz, 2H), 3.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.8, 136.6, 130.4, 127.0 (2C), 126.1, 122.0, 121.9, 119.7, 119.6, 119.2, 118.8, 115.8, 111.2, 37.2, 34.5.

2-(2,2-Bis(5-methyl-1*H*-indol-3-yl)ethyl)-4-methylaniline (63b) [257]: Yield: 82%, 107 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (s, 2H), 7.28 (s, 2H), 7.19 (d, J = 8 Hz, 2H), 7.02-6.99 (m, 2H), 6.93-6.83 (m, 4H), 6.48 (d, J = 8 Hz, 2H), 4.83 (t, J = 14.4 Hz, 1H), 3.38 (d, J = 7.2 Hz, 2H), 3.09 (s, 2H), 2.40 (s, 6H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 134.9, 130.9, 128.2, 128.0, 127.3, 127.2, 126.5, 123.4, 122.2, 119.4, 119.3, 116.0, 110.7, 37.3, 34.6, 21.5, 20.6.

2-(2,2-Bis(5-methoxy-1*H*-indol-3-yl)ethyl)-4-methoxyaniline (63c) [257]: Yield: 80%, 117 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (s, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 6.99 (d, J = 2.4 Hz,

2H), 6.85 (d, J = 2.4 Hz, 2H), 6.79 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.58-6.54 (m, 2H), 6.47 (d, J = 8.4 Hz, 1H), 4.71 (t, J = 14.8 Hz, 1H), 3.69 (s, 6H), 3.55 (s, 3H), 3.38 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 152.9, 138.7, 131.9, 128.0, 127.5, 122.7, 119.5, 117.1, 116.3, 112.7, 112.1, 111.8, 101.8, 55.9, 55.7, 37.7, 35.0.

2-(2,2-Bis(5-fluoro-1*H*-indol-3-yl)ethyl)-4-fluoroaniline (63d) [257]: Yield: 77%, 103 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 2H), 7.25-7.22 (m, 2H), 7.09 (d, J = 2.4 Hz, 2H), 7.00-6.97 (m, 2H), 6.89-6.84 (m, 2H), 6.69-6.66 (m, 1H), 6.60-6.57 (m, 1H), 6.52-6.48 (m, 1H), 4.66 (t, J = 16 Hz, 1H), 3.34 (d, J = 7.6 Hz, 2H), 3.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6 (d, $J_{C\text{-}F}$ = 233 Hz), 140.8, 133.2, 127.2 (d, $J_{C\text{-}F}$ = 15 Hz), 123.5, 119.0 (d, $J_{C\text{-}F}$ = 7 Hz), 116.9, 116.7 (d, $J_{C\text{-}F}$ = 7 Hz), 113.7, 113.4, 111.9, 111.8, 110.7, 110.5, 104.5 (d, $J_{C\text{-}F}$ = 23 Hz), 36.9, 34.5.

2-(2,2-Bis(5-chloro-1*H*-indol-3-yl)ethyl)-4-chloroaniline (63e) [257]: Yield: 79%, 119 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 2H), 7.30 (d, J = 2 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.08-7.06 (m, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.95-6.92 (m, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 4.66 (t, J = 14.8 Hz, 1H), 3.28 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.4, 135.0, 133.7, 130.1, 127.8, 127.1, 125.1, 123.4, 123.2, 122.5, 119.0, 118.6, 117.0, 112.4, 36.9, 34.3.

2-(2,2-Bis(5-bromo-1*H*-indol-3-yl)ethyl)-4-bromoaniline (63f) [257]: Yield: 78%, 151 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 2H), 7.43 (d, J = 8 Hz, 2H), 7.22-7.16 (m, 4H), 7.09-7.06 (m, 1H), 6.98 (d, J = 2.4 Hz, 2H), 6.94 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.65 (t, J = 14.8 Hz, 1H), 3.27 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 135.3, 133.0, 130.1, 128.5, 127.5, 125.1, 123.0, 122.1, 118.5, 117.5, 112.8, 112.7, 110.6, 37.0, 34.3.

2-(2,2-Bis(6-chloro-1*H*-indol-3-yl)ethyl)-3-chloroaniline (63g) [257]: Yield: 65%, 98 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 2H), 7.29 (d, J = 1.6 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 1.6 Hz, 2H), 6.92-6.89 (m, 2H), 6.75-6.72 (m, 1H), 6.56-6.53 (m, 2H), 4.68 (t, J = 16 Hz, 1H), 3.35 (s, 2H), 3.30 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 136.9, 132.3, 131.5, 128.0, 125.3, 123.7, 122.3, 120.3, 120.0, 119.1, 118.5, 115.3, 111.1, 36.5, 34.3.

2-(2,2-Bis(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-methylaniline (63h) [257]: Yield: 81%, 106 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.21-7.17 (m, 2H), 7.13-7.08 (m, 1H), 7.02-6.98 (m, 3H), 6.86 (s, 2H), 6.63-6.59 (m, 1H), 6.48 (d, J = 7.6 Hz, 1H), 4.82 (t, J = 14.8 Hz, 1H), 3.71 (s, 6H), 3.36 (d, J = 7.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.8, 137.4, 129.9, 127.4, 127.2, 126.6, 125.8, 121.5, 119.8, 118.7, 118.4, 117.1, 109.7, 109.2, 37.7, 34.5, 32.8, 30.7.

2-(2,2-Bis(1-ethyl-1*H*-indol-3-yl)ethyl)-*N*-ethylaniline (63i): Yield: 79%, 114 mg; brown solid; mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.19-7.15 (m, 2H), 7.10-7.05 (m, 2H), 7.00-6.96 (m, 2H), 6.93 (s, 2H), 6.65-6.61 (m, 1H), 6.48 (d, J = 7.6 Hz, 1H), 4.77 (t, J = 14.4 Hz, 1H), 4.13-4.07 (m, 4H), 3.40 (d, J = 7.2 Hz, 2H), 2.72-2.67 (m, 2H), 1.40 (t, J = 14.8 Hz, 6H), 0.77 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.0, 136.4, 130.3, 127.5, 127.1, 126.2, 125.1, 121.3, 120.1, 118.6, 118.3, 117.0, 110.4, 109.3, 40.9, 38.4, 37.5, 35.6, 15.7, 14.2.

2-(2,2-Bis(1-propyl-1*H*-indol-3-yl)ethyl)-*N*-propylaniline (63j): Yield: 77%, 122 mg; white solid; mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, J = 8 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.23-7.19 (m, 2H), 7.15-7.08 (m, 2H), 7.05-7.01 (m, 2H), 6.97 (s, 2H), 6.65 (t, J = 14.8 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 4.85 (t, J = 14 Hz, 1H), 4.05 (t, J = 14.4 Hz, 4H), 3.45 (d, J = 6.8 Hz, 2H), 3.29 (s, 1H), 2.74 (t, J = 14.4 Hz, 2H), 1.90-1.81 (m, 4H), 1.23-1.16 (m, 2H), 0.94 (t, J = 14.8 Hz, 6H), 0.88 (t, J = 14.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.9, 136.7, 130.2, 127.4, 126.9, 126.4, 125.8, 121.2, 120.0, 118.4, 117.9, 116.7, 110.2, 109.3, 47.9, 45.8, 37.2, 35.3, 23.5, 22.3, 11.7, 11.5.

2-(2,2-Bis(1-isopropyl-1*H*-indol-3-yl)ethyl)-*N*-isopropylaniline (63k): Yield: 76%, 120 mg; brown solid; mp 112−114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.05-7.01 (m, 2H), 6.95-6.91 (m, 4H), 6.88-6.84 (m, 2H), 6.49-6.46 (m, 1H), 6.36 (d, J = 8 Hz, 1H), 4.62 (t, J = 14 Hz, 1H), 4.52-4.45 (m, 2H), 3.30 (d, J = 6.8 Hz, 2H), 3.30-3.22 (m, 1H), 2.98 (s, 1H), 1.36 (d, J = 6.4 Hz, 6H), 1.31 (d, J = 6.8 Hz, 6H), 0.63 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 136.4, 130.7, 127.5, 126.9, 126.4, 121.7, 121.1, 120.1, 118.6, 118.2, 116.5, 110.9, 109.5, 46.9, 43.4, 37.4, 36.4, 22.9, 22.8.

2-(2,2-Bis(1-isobutyl-1*H*-indol-3-yl)ethyl)-*N*-isobutylaniline (63l): Yield: 70%, 121 mg; white solid; mp 106−108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J = 8 Hz, 2H), 7.27-7.25 (m, 2H), 7.14-7.10 (m, 2H), 7.05-7.01 (m, 1H), 6.97-6.92 (m, 3H), 6.89 (s, 2H), 6.54-6.48 (m, 2H), 4.78 (t, J = 14.8 Hz, 1H), 3.83-3.80 (m, 4H), 3.40 (d, J = 7.2 Hz, 2H), 3.38 (s, 1H), 2.59 (d, J = 6.8 Hz, 2H), 2.18-2.09 (m, 2H), 0.88 (d, J = 6.4 Hz, 12H), 0.81 (d, J = 6.4 Hz, H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 137.0, 130.3, 127.4, 127.0, 126.4, 125.6, 121.2, 120.0, 118.5, 117.8, 116.6, 110.2, 109.6, 54.0, 52.0, 37.2, 35.1, 31.7, 29.6, 20.7, 20.4.

2-(2,2-Bis(1-butyl-1*H*-indol-3-yl)ethyl)-*N*-butylaniline (63m): Yield: 72%, 124 mg; brown gummy mass; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J = 8 Hz, 2H), 7.27 (d, J = 8Hz, 2H), 7.15-7.11 (m, 2H), 7.07-

7.00 (m, 2H), 6.97-93 (m, 2H), 6.89 (s, 2H), 6.60-6.56 (m, 1H), 6.46 (d, *J* = 8 Hz, 1H), 4.74 (t, *J* = 14 Hz, 1H), 4.05-4.00 (m, 4H), 3.38 (d, *J* = 7.2 Hz, 2H), 3.16 (s, 1H), 2.67 (t, *J* = 14.4 Hz, 2H), 1.78-1.70 (m, 4H), 1.30-1.21 (m, 6H), 1.08-1.02 (m, 2H), 0.91 (t, *J* = 14.8 Hz, 3H), 0.84 (t, *J* = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.2, 136.8, 131.1, 130.4, 129.0, 127.5, 127.1, 125.9, 121.3, 120.1, 118.5, 117.9, 110.4, 109.4, 46.0, 37.3, 35.6, 32.5, 31.2, 20.5, 20.3, 19.3, 14.0, 13.9.

2-(2,2-Bis(1-pentyl-1*H*-indol-3-yl)ethyl)-*N*-pentylaniline (63n): Yield: 67%, 125 mg; brown gummy mass; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.07-7.03 (m, 2H), 6.97-6.92 (m, 2H), 6.88-6.85 (m, 2H), 6.81 (s, 2H), 6.52-6.48 (m, 1H), 6.39 (d, *J* = 7.6 Hz, 1H), 4.66 (t, *J* = 8 Hz, 1H), 3.96-3.92 (m, 4H), 3.31 (t, *J* = 7.2 Hz, 2H), 3.09 (s, 1H), 2.58 (t, *J* = 15.2 Hz, 2H), 1.75-1.61 (m, 6H), 1.24-1.15 (m, 12H), 0.81-0.78 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 136.6, 130.2, 127.3, 126.9, 125.9, 125.7, 121.1, 119.9, 118.4, 117.8, 116.7, 110.1, 109.2, 53.4, 46.1, 37.1, 35.4, 29.9, 29.4, 29.0, 29.7, 22.4, 22.3, 14.0, 13.9.

***N*-Allyl-2-(2,2-bis(1-allyl-1*H*-indol-3-yl)ethyl)aniline (63o):** Yield: 73%, 114 mg; brown solid; mp 84−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 8 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.15-7.11 (m, 2H), 7.06-6.91 (m, 6H), 6.61-6.57 (m, 1H), 6.46 (d, *J* = 8 Hz, 1H), 5.98-5.89 (m, 2H), 5.60-5.52 (m, 1H), 5.16-5.13 (m, 2H), 5.06-4.98 (m, 4H), 4.80 (t, *J* = 14.4 Hz, 1H), 4.65-4.63 (m, 4H), 3.40 (d, *J* = 7.2 Hz, 2H), 3.36-3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 136.9, 135.5, 133.8, 130.3, 127.6, 127.1, 126.0, 125.8, 121.5, 120.0, 118.8, 118.7, 117.3, 117.0, 115.9, 110.7, 109.6, 48.8, 46.6, 37.5, 35.1.

2-(2,2-Bis(1-(prop-2-yn-1-yl)-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)aniline (63p): Yield: 71%, 110 mg; brown solid; mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.12-7.09 (m, 2H), 7.03-6.96 (m, 2H), 6.92-6.88 (m, 4H), 6.62-6.58 (m, 1H), 6.45 (d, *J* = 8 Hz, 1H), 4.70-4.67 (m, 5H), 3.37 (s, 1H), 3.31-3.27 (m, 4H), 2.27 (t, *J* = 4.8 Hz, 2H), 2.03 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.7, 136.5, 130.4, 127.9, 127.2, 126.6, 125.1, 122.0, 120.1, 119.4, 119.3, 118.5, 111.1, 109.4, 81.4, 78.2, 73.5, 71.0, 37.8, 35.9, 35.0, 31.7.

***N*-Benzyl-2-(2,2-bis(1-benzyl-1*H*-indol-3-yl)ethyl)aniline (63q):** Yield: 74%, 153 mg; white solid; mp 135−137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, *J* = 8 Hz, 2H), 7.33-7.24 (m, 11H), 7.19-7.05 (m, 12H), 6.66 (t, *J* = 14.8 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 5.27 (s, 4H), 4.94 (t, *J* = 14.8 Hz, 1H), 3.97 (s, 2H), 3.86 (s, 1H), 3.52 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5,

139.7, 138.0, 137.0, 130.4, 128.8, 128.6, 127.6, 127.5, 127.4, 127.1, 127.0, 126.6, 126.2, 125.7, 121.7, 120.0, 119.0, 118.7, 117.3, 110.8, 109.8, 49.9, 48.2, 37.3, 35.0.

2-(2,2-Bis(1,5-dimethyl-1*H*-indol-3-yl)ethyl)-N,4-dimethylaniline (63r): Yield: 76%, 122 mg; white solid; mp 154-156°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.28 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.98-6.94 (m, 2H), 6.84 (s, 2H), 6.42 (d, J = 8 Hz, 1H) 4.79 (t, J = 13.2 Hz, 1H), 3.71 (s, 6H), 3.33 (d, J = 5.6 Hz, 2H), 2.42 (s, 6H), 2.39 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.8, 135.9, 130.8, 127.7, 127.6, 126.8, 126.3, 126.1, 123.1, 119.7, 118.2, 110.0, 108.8, 38.0, 34.7, 32.8, 31.0, 21.6, 20.6.

2-(2,2-Bis(5-methoxy-1-methyl-1*H*-indol-3-yl)ethyl)-4-methoxy-*N*-methylaniline (63s): Yield: 76%, 122 mg; brown solid; mp 79-81°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.13 (m, 2H), 6.83-6.81 (m, 6H), 6.68-6.66 (m, 2H), 6.40-6.37 (m, 1H), 4.66 (t, J = 14.4 Hz, 1H), 3.71 (s, 6H), 3.68 (s, 6H), 3.59 (s, 3H), 3.31 (d, J = 7.2 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5, 151.9, 142.5, 132.9, 127.9, 127.7, 127.2, 118.0, 116.9, 112.2, 111.7, 111.0, 109.9, 101.9, 56.0, 38.2, 34.8, 33.0, 31.5.

2-(2,2-Bis(5-chloro-1-methyl-1*H*-indol-3-yl)ethyl)-4-chloro-*N*-methylaniline (63t): Yield: 76%, 122 mg; white solid; mp 188-190°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.28 (m, 2H), 7.19-7.17 (m, 2H), 7.12-7.04 (m, 3H), 6.86-6.82 (m, 3H), 6.40 (d, J = 8.8 Hz, 1H), 4.62 (t, J = 14.8 Hz, 1H), 3.71 (s, 6H), 3.27 (s, 1H), 3.22 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.3, 135.9, 129.7, 128.1, 127.8, 127.2, 126.8, 124.7, 122.1, 121.8, 119.1, 117.3, 111.0, 110.4, 37.3, 34.2, 33.1, 30.8.

2-(2,2-Bis(1-ethyl-5-methoxy-1*H*-indol-3-yl)ethyl)-*N*-ethyl-4-methoxyaniline (63u): Yield: 75%, 131 mg; white solid; mp 70-72°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.17 (m, 2H), 6.92 (s, 2H), 6.82-6.80 (m, 4H), 6.72 (d, J = 2.8 Hz, 1H), 6.67-6.64 (m, 1H), 6.38 (d, J = 8.8 Hz, 1H), 4.63 (t, J = 14.8 Hz, 1H), 4.09-4.04 (m, 4H), 3.69 (s, 6H), 3.64 (s, 3H), 3.37 (d, J = 7.2 Hz, 2H), 2.58-2.52 (m, 2H), 1.38 (t, J = 14.4 Hz, 6H), 0.73 (t, J = 14.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 151.8, 141.8, 131.8, 128.4, 127.8, 125.5, 117.7, 116.8, 112.1, 111.7(2C), 109.9, 101.9, 55.9, 55.8, 41.1, 39.1, 37.8, 36.0, 15.7, 14.3.

2-(2,2-Bis(5-chloro-1-ethyl-1*H*-indol-3-yl)ethyl)-4-chloro-*N*-ethylaniline (63v): Yield: 74%, 132 mg; brown solid; mp 145-47°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.27 (m, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.01-7.07 (m, 2H), 7.03-7.01 (m, 1H), 6.93 (s, 2H), 6.85 (d, J = 2.4 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 4.57 (t, J = 14.4 Hz, 1H), 4.13-4.06 (m, 4H), 3.26 (d, J = 7.6 Hz, 2H), 2.98 (s, 1H), 2.70-2.65 (m, 2H), 1.40 (t, J = 14.4 Hz, 6H), 0.80 (t, J = 14 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100

MHz): δ 145.6, 134.9, 130.1, 128.3, 127.2, 127.1, 126.2, 124.6, 121.9, 121.6, 119.3, 117.0, 111.5, 110.5, 41.2, 38.6, 36.9, 35.4, 15.7, 14.3.

3.22. Molecular iodine-free regioselective 1,2-difunctionalization of olefins and formation of terminal acetals in presence of $NH_2OH{\cdot}HCl$ and $NaIO_4$

Typical procedure for the synthesis of 2-Iodo-1-phenylethanol (68a) [271]: A mixture of styrene **67a** (1 mmol, 104 mg), $NaIO_4$ (1 mmol, 213 mg) in a mixture of 2.5 mL of water and 0.5 mL of THF was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg) was added by portion for 5 min. The reaction mixture was then stirred for 30 min at room temperature. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3x5 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as a pale-yellow liquid (Yield: 206 mg, 83%) using ethyl acetate-petroleum ether (1:15) as eluent. Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.26 (m, 5H), 4.85-4.82 (m, 1H), 3.51-3.48 (m, 1H), 3.43-3.38 (m, 1H), 2.52 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 128.8, 128.5, 125.9, 74.1, 15.4.

1-(4-Chlorophenyl)-2-iodoethanol (68b): Yield: 237 mg, 84%; Pale yellow solid; mp 67-69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.29 (m, 4H), 4.81-4.78 (m, 1H), 3.48-3.44 (m, 1H), 3.38-3.33 (m, 1H), 2.61 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.7, 134.2, 129.0, 127.3, 73.4, 15.1; Anal. calcd for C_8H_8ClIO: C, 34.01; H, 2.85%; Found: C, 33.94; H, 2.78%.

2-Iodo-1-(3-nitrophenyl)ethanol (68c): Yield: 237 mg, 81%; Pale orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28-8.22 (m, 2H), 7.73 (d, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz,1H), 5.15 (q, J = 5.2 Hz, 1H), 3.87-3.83 (m, 1H), 3.71 (t, J = 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.5, 141.3, 133.5, 130.0, 124.1, 122.5, 59.7, 8.9; Anal. calcd for $C_8H_8INO_3$: C, 32.79; H, 2.75; N, 4.78%; Found: C, 32.72; H, 2.67; N, 4.70%.

1-Iodo-2phenylpropan-2-ol (68d): Yield: 218 mg, 80%; Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.20 (m, 5H), 3.70 - 3.61 (m, 2H), 2.34 (br, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 128.6 (2C), 127.6 (2C), 124.9, 72.8, 29.1, 24.3; Anal. calcd for $C_9H_{11}IO$: C, 41.24; H, 4.34 %; Found: C, 41.26; H, 4.30%.

2-Iodo-1,1-diphenylethanol (68e): Yield: 270 mg, 81%; Deep yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.6 Hz, 4H), 7.42-7.33 (m, 6H), 4.07 (s, 2H), 2.98 (s, 1H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 143.5 (2C), 128.4 (4C), 127.7 (4C), 126.2 (2C), 76.7, 22.5; Anal. calcd for $C_{14}H_{13}IO$: C, 51.87; H, 4.04%; Found: C, 51.83; H, 4.08%.

1-Iodooctan-2-ol (68f): Yield: 208 mg, 78%; Pale yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 - 3.50 (m, 1H), 3.41- 3.38 (m, 1H), 3.25-3.22 (m, 1H), 1.57 - 1.25 (m, 11H), 0.88 (t, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.2, 36.8, 31.8, 29.3, 25.8, 22.7, 16.9, 14.2; Anal. calcd for $C_8H_{17}IO$: C, 37.51; H, 6.69%; Found: C, 37.49; H, 6.72%.

2-Iodocyclohexanol (68g): Yield: 180 mg, 76%; Orange gummy mass; ^1H NMR (400 MHz, $CDCl_3$): δ 4.05-4.00 (m, 1H) 3.70-3.60 (m, 1H), 2.11-1.20 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.0, 43.4, 38.6, 33.6, 28.0, 24.4; Anal. calcd for $C_6H_{11}IO$: C, 31.88; H,4.90%; Found: C, 31.82; H, 4.96%.

2-Iodocyclooctanol (68h): Yield: 184 mg, 70%; Gummy brown liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 4.42-4.38 (m, 1H), 4.03- 3.98 (m, 1H), 2.21-1.90 (m, 6H), 1.65-1.44 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.4, 50.5, 34.4, 32.5, 27.0, 26.0, 25.7, 25.5; Anal. calcd for $C_8H_{15}IO$: C, 37.81; H, 5.95%; Found: C, 37.83; H, 5.91%.

Typical procedure for the synthesis of 1-(1-ethoxy-2-iodoethyl)benzene (68i) [271]: A mixture of styrene **67a** (1 mmol, 104 mg), $NaIO_4$ (1 mmol, 213 mg) in 3 mL of ethanol was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg) was added by portion for 5 min. The reaction mixture was then stirred for 30 min at room temperature. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3x5 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as an orange liquid (Yield: 237 mg, 86%) using ethyl acetate-petroleum ether (1:15) as eluent. Orange liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.35 (m, 5H), 4.46-4.43 (m, 1H), 3.52-3.44 (m, 2H), 3.41-3.34 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 128.7, 128.3, 126.5, 81.9, 65.1, 15.2, 11.0.

1-(1-Ethoxy-2-iodoethyl)-4-methoxybenzene (68j): Yield: 248 mg, 81%; Yellowish orange liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.23 (m, 2H), 6.91-6.88 (m, 2H), 4.38-4.34 (m, 1H), 3.81 (s, 3H), 3.46-3.26 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 159.7, 132.7, 128.1, 127.8, 114.1, 81.5, 64.9, 64.8, 55.4, 15.3, 15.28, 11.4; Anal. calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94%; Found: C, 43.12; H, 4.91%.

1-Chloro-4-(1-ethoxy-2-iodoethyl)benzene (68k): Yield: 257 mg, 83%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.38-4.35 (m, 1H), 3.45-3.40 (m, 2H), 3.34-3.26 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 134.1, 128.9, 128.0, 81.2, 65.3, 15.3, 10.5; Anal. calcd for $C_{10}H_{12}ClIO$: C, 38.67; H, 3.89%; Found: C, 38.61; H, 3.82%.

3-Ethoxy-2-iodo-3-phenylpropan-1-ol (68l): Yield: 260 mg, 85%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.31 (m, 5H), 4.62 (d, *J* = 7.2 Hz, 1H), 4.35-4.31 (m, 1H), 3.99-3.95 (m, 1H), 3.84-3.80 (m, 1H), 3.43-3.38 (m, 2H), 3.11 (br, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.4, 128.6, 128.5, 127.5, 86.4, 66.5, 65.6, 39.1, 15.3; Anal. calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94%; Found: C, 43.13; H, 4.90%.

1-(2-Ethoxy-1-iodopropan-2-yl)benzene (68m) [264]: Yield: 241 mg, 83%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.25 (m, 5H), 3.53-3.45 (m, 2H), 3.36-3.32 (m, 1H), 3.24-3.18 (m, 1H), 1.70 (s, 1H), 1.23-1.19 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 128.5, 127.7, 126.3, 76.7, 58.9, 24.8, 20.0, 15.7.

1-Ethoxy-2-iodo-1,1-diphenylethane (68n): Yield: 262 mg, 80%; Pale orange solid; mp 67-68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.18 (m, 10H), 4.10 (s, 2H), 3.22 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 128.5, 128.1, 127.3, 127.1, 127.0, 126.2, 80.2, 57.9, 16.8, 15.4; Anal. calcd for $C_{16}H_{17}IO$: C, 54.56; H, 4.86%; Found: C, 54.51; H, 4.82%.

2-Ethoxy-1-iodooctane (68o): Yield: 221 mg, 78%; Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.59-3.36 (m, 2H), 3.20-3.18 (m, 2H), 3.12-3.07 (m, 1H), 1.56-1.46 (m, 3H), 1.27-1.13 (m, 10H), 0.83-0.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 78.5, 65.1, 34.8, 31.9, 29.3, 25.4, 22.7, 15.6, 14.2, 10.6; Anal. calcd for $C_{10}H_{21}IO$: C, 42.26; H, 7.45%; Found: C, 42.18; H, 7.36%.

Typical procedure for the synthesis of 2-(2-Iodo-1-phenylethoxy)ethanol (68p) including gram-scale synthesis:

A mixture of styrene **67a** (1 mmol, 104 mg), $NaIO_4$ (1 mmol, 213 mg) in 3 mL of ethylene glycol (for gram scale a mixture of styrene **67a** (10 mmol, 1.04 g), $NaIO_4$ (10 mmol, 2.13 g) in 30 mL of ethylene glycol) was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg; for gram scale 15 mmol, 1.04 g) was added by portion for 5-10 min. Then the reaction mixture was stirred for 30 min at room temperature. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL; for gram scale 50 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3x5 mL; for gram scale 3x20 mL) followed by brine solution (1x10 mL; for gram scale 1x30 mL). Then the combined organic layer was dried over anhydrous

Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as a yellow liquid (Yield: 254 mg, 87%; 2.34 g, 80% yield for gram scale synthesis) using ethyl acetate-petroleum ether (1:15) as eluent. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.22 (m, 5H), 4.39-4.36 (m, 1H), 3.66 (s, 2H), 3.48-3.24 (m, 4H), 2.47 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.7, 128.8, 128.6, 126.4, 82.3, 70.7, 61.7, 11.0; Anal. calcd for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.49%; Found: C, 41.08; H, 4.46%.

2-(1-(2,4-Dimethylphenyl)-2-iodoethoxy)ethanol (68q): Yield: 275 mg, 83%; Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 7.6 Hz,1H), 6.95 (d, *J* = 8 Hz, 1H), 6.89 (s, 1H), 4.58 (t, *J* = 6.4 Hz,1H), 3.66 - 3.64 (m, 2H), 3.47-3.43 (m, 1H), 3.33 - 3.28 (m, 1H), 3.20 (d, *J* = 6.8 Hz, 2H), 2.47 (br, 1H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 135.2, 134.7, 131.6, 127.3, 125.5, 79.1, 70.7, 61.8, 21.1, 19.0, 10.0; Anal. calcd for $C_{12}H_{17}IO_2$: C, 45.02; H, 5.35 %; Found: C, 44.98; H, 5.30%.

2-(2-Iodo-1-(4-methoxyphenyl)ethoxy)ethanol (68r): Yield: 261 mg, 81%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.36-4.33 (m, 1H), 3.74 (s, 3H), 3.71-3.66 (m, 2H), 3.49-3.44 (m, 1H), 3.37-3.21(m, 3H), 2.25 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 131.7, 127.7, 114.3, 82.0, 70.6, 61.9, 55.4, 11.3; Anal. calcd for $C_{11}H_{15}IO_3$: C, 41.01; H, 4.69%; Found: C, 40.95; H, 4.67%.

2-(1-(3-Bromophenyl)-2-iodoethoxy)ethanol (68s): Yield: 323 mg, 87%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.44 (m, 2H), 7.25-7.21 (m, 2H), 4.43-4.40 (m,1H), 3.76-3.74 (m, 2H), 3.57-3.52 (m, 1H), 3.47-3.42 (m, 1H), 3.37-3.29 (m, 2H), 2.59 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.1, 131.7, 130.4, 129.5, 125.1, 122.9, 81.6, 71.0, 61.7, 10.3; Anal. calcd for $C_{10}H_{12}BrIO_2$: C, 32.37; H, 3.26%; Found: C, 32.32; H, 3.21%.

2-(1-(4-Chlorophenyl)-2-iodoethoxy)ethanol (68t): Yield: 281 mg, 86%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.34 (m, 2H), 7.28-7.26 (m, 2H), 4.46-4.43 (m, 1H), 3.76 (t, *J* = 4.4 Hz, 2H), 3.57-3.53 (m, 1H), 3.48-3.43 (m, 1H), 3.39-3.30 (m, 2H), 2.43 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 134.4, 129.1, 127.9, 81.6, 70.9, 61.8, 10.4; Anal. calcd for $C_{10}H_{12}ClIO_2$: C, 36.78; H, 3.70%; Found: C, 36.73; H, 3.62%.

2-(2-Iodo-1-(3-nitrophenyl)ethoxy)ethanol (68u): Yield: 273 mg, 81%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.21 (m, 2H), 7.71 (d, *J* = 8 Hz, 1H), 7.62-7.57 (m, 1H), 4.60-4.57 (m, 1H), 3.81 (s, 2H), 3.62-3.51 (m, 2H), 3.44-3.37 (m, 2H), 2.32 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.7, 142.2, 132.6, 130.0, 123.7, 121.7, 81.2, 71.3, 61.9, 9.7; Anal. calcd for $C_{10}H_{12}INO_4$: C, 35.63; H, 3.59; N, 4.15%; Found: C, 35.56; H, 3.53; N, 4.11%.

2-(1-Iodooctan-2-yloxy)ethanol (68v): Yield: 240 mg, 80%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77-3.56 (m, 4H), 3.36-3.31 (m, 1H), 3.28-3.20 (m, 1H), 2.23 (br, 1H), 1.81-1.73 (m, 1H), 1.65-1.55 (m, 2H), 1.40-1.30 (m, 8H), 0.92-0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 78.9, 70.6, 62.1, 34.7, 31.8, 29.3, 25.3, 22.7, 14.2, 10.6; Anal. calcd for $C_{10}H_{21}IO_2$: C, 40.01; H, 7.05%; Found: C, 39.98; H, 7.01%.

2-(2-Iodocyclohexyloxy)ethanol (68w): Yield: 221 mg, 82%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.01-3.95 (m, 1H), 3.72-3.67 (m, 3H), 3.48-3.44 (m, 1H), 3.30-3.24 (m, 1H), 2.41-2.36 (m, 1H), 2.11-2.07 (m, 1H), 2.01-1.89 (m, 1H), 1.80-1.76 (m, 1H), 1.50-1.46 (m, 1H), 1.31-1.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 83.3, 70.5, 62.0, 38.7, 36.5, 31.8, 27.9, 24.1; Anal. calcd for $C_8H_{15}IO_2$: C, 35.57; H, 5.60%; Found C, 35.53; H, 5.56%.

2-(2-Iodocyclooctyloxy)ethanol (68x): Yield: 238 mg, 80%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.33-4.28 (m, 1H), 3.69-3.62 (m, 4H), 3.37-3.33 (m, 1H), 2.11-1.56 (m, 9H), 1.32-1.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 87.0, 70.5, 61.9, 42.8, 33.2, 30.6, 27.2, 26.7, 25.8, 25.3; Anal. calcd for $C_{10}H_{19}IO_2$: C, 40.28; H, 6.42%; Found: C, 40.22; H, 6.34%.

3-(2-Hydroxyethoxy)-2-iodo-3-phenylpropan-1-ol (68y): Yield: 274 mg, 85%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.31 (m, 5H), 4.69 (d, J = 7.6 Hz, 1H), 4.39-4.35 (m, 1H), 4.19-4.11 (m, 1H), 3.93-3.81 (m, 1H), 3.74 (s, 2H), 3.60-3.29 (m, 2H), 3.18 (br, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.9, 128.7, 128.6, 127.6, 85.1, 70.9, 65.8, 61.7, 39.7; Anal. calcd for $C_{11}H_{15}IO_3$: C, 41.01; H, 4.69%; Found: C, 40.97; H, 4.63%.

2-(1-Iodo-2-phenylpropan-2-yloxy)ethanol (68z): Yield: 251 mg, 82%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.32 (m, 5H), 3.80-3.74 (m, 2H), 3.57 (d, J = 10.8 Hz,1H), 3.49-3.40 (m, 2H), 3.33-3.29 (m, 1H), 2.37 (br, 1H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4, 128.7, 128.0, 126.2, 76.5, 64.3, 62.2, 24.5, 20.3; Anal. calcd for $C_{11}H_{15}IO_2$: C, 43.16; H, 4.94%; Found: C, 43.12; H, 4.91%.

2-(2-Iodo-1,1-diphenylethoxy)ethanol (68a′): Yield: 298 mg, 81%; Pale yellow solid; mp 70-72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.25 (m, 10H), 4.18 (s, 2H), 3.84 (t, J = 4.4 Hz, 2H), 3.32 (t, J = 4.4 Hz, 2H), 2.21 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.9, 128.3, 127.6, 127.1, 80.2, 64.0, 62.3, 16.8; Anal. calcd for $C_{16}H_{17}IO_2$: C, 52.19; H, 4.65%; Found: C, 52.13; H, 4.61%.

Typical procedure for the synthesis of 2-Iodo-1-phenylethyl acetate (68b′) [265]: A mixture of styrene **1a** (1 mmol, 104 mg), $NaIO_4$ (1 mmol, 213 mg) in 3 mL of acetic acid was taken in a round bottomed flask at room temperature and then $NH_2OH{\cdot}HCl$ (1.5 mmol, 104 mg) was added by portion for 5 min. The reaction mixture was then stirred for 30 min at room temperature. After

completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (3x5 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as a yellow liquid (Yield: 229 mg, 79%) using ethyl acetate-petroleum ether (1:15) as eluent. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.34 (m, 5H), 5.98-5.86 (m, 1H), 3.82-3.70 (m, 1H), 3.48-3.45 (m, 1H), 2.14-2.13 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 169.9, 138.6, 137.3, 129.0, 128.9, 128.8, 126.8, 126.6, 75.3, 75.2, 46.6, 21.2, 21.1, 7.9.

1-(4-Chlorophenyl)-2-iodoethyl acetate (68c′): Yield: 266 mg, 82%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 4H), 5.93-5.81 (m, 1H), 3.76-3.70 (m, 1H), 3.45-3.42 (m, 1H), 2.13-2.13 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 169.8, 137.0, 135.8, 134.9, 134.7, 129.0, 128.2, 128.0, 74.5, 74.4, 46.3, 21.1, 21.0, 7.4; Anal. calcd for $C_{10}H_{10}ClIO_2$: C, 37.01; H, 3.11%; Found: C, 36.97; H, 3.05%.

Typical procedure for the synthesis of 2-benzyl-1,3-dioxolane (70a) [276]: Oxone (0.75 mmol, 230 mg) was slowly added to compound **68p** (1 mmol, 292 mg) in 2 mL of ethylene glycol in a round bottomed flask and the reaction mixture was stirred at room temperature for 2 h. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/DCM (10 mL) and washed with 10% (w/v) $Na_2S_2O_3$ (2x5 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as a red liquid (Yield: 116 mg, 71%) using ethyl acetate-petroleum ether (1:15) as eluent. Red liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.21 (m, 5H), 5.07 (t, J = 4.8 Hz, 1H), 3.99-3.82 (m, 4H), 2.97 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.3, 129.8, 128.5, 126.7, 104.8, 65.1, 40.9.

2-(4-Chlorobenzyl)-1,3-dioxolane (70b) [276]: Yield: 158 mg, 80%; White solid; mp 38-40 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.18 (m, 4H), 5.04 (t, J = 4.8 Hz, 1H), 3.94-3.82 (m, 4H), 2.93 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.6, 132.6, 131.2, 128.5, 104.4, 65.2, 40.2.

2-(2,4-Dimethylbenzyl)-1,3-dioxolane (70c): Yield: 180 mg, 94%; Pale orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, J = 7.5 Hz, 1H), 7.24-7.22 (m, 2H), 5.30 (t, J = 5 Hz, 1H), 4.21(t, J = 6.5 Hz, 2H), 4.08 (t, J = 6.5 Hz, 2H), 3.22 (d, J = 5 Hz, 2H), 2.59 (s, 3H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 136.0, 131.3, 130.8, 130.1, 126.4, 104.3 (2C), 64.7, 37.3, 20.8, 19.6; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%; Found: C, 74.95; H, 8.41%.

2-(4-Methoxybenzyl)-1,3-dioxolane (70d):[47] Yield: 180 mg, 93%; Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.10 (m, 2H), 6.78 – 6.75 (m, 2H), 4.94 (t, *J* = 4.8 Hz, 1H) 3.87-3.73 (m, 4H), 3.70 (s, 3H) 2.83 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4, 130.7 (2C), 128.3, 113.9 (2C), 104.9 (2C), 65.0, 55.3, 39.9.

2-Heptyl-1,3-dioxolane (70e): Yield: 138 mg, 80%; Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.77 (t, *J* = 4.8 Hz, 1H), 3.93-3.75 (m, 4H), 1.57 ((t, *J* = 4.8 Hz, 2H), 1.35-1.20 (m, 10H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 104.8, 64.9 (2C), 34.0, 31.8, 29.6, 29.3, 24.2, 22.7, 14.2; Anal. calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.7%; Found: C, 69.69; H, 11.69%.

2-Cyclopentyl-1,3-dioxolane (70f):[47] Yield: 130 mg, 91%; Yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.63 (d, *J* = 5.6 Hz, 1H), 3.91- 3.76 (m, 4H), 2.07-1.99 (m, 1H), 1.71- 1.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.9. 65.1 (2C), 43.1, 27.7 (2C), 25.9 (2C).

2-Cycloheptyl-1,3-dioxolane (70g): Yield: 138 mg, 81%; Pale yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.60 (d, *J* = 4.4 Hz, 1H), 3.89-3.75 (m, 4H), 2.11-2.07 (m, 1H), 1.67-1.51 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.1, 65.1 (2C), 43.2, 28.8 (2C), 26.9 (2C), 26.4 (2C); Anal. calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%; Found: C, 70.60; H, 10.69%.

2-(1,3-Dioxolan-2-yl)-2-phenylethanol (70h):[47] Yield: 162 mg, 84%; Pale yellow gummy mass; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.21 (m. 5H), 5.11 (d, *J* = 5.2 Hz, 1H), 4.08-4.03(m, 2H), 3.95-3.75 (m, 4H), 3.10-3.06 (m, 1H), 2.56 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.7, 128.5 (2C), 127.2, 106.3, 64.6 (2C), 63.6, 51.4.

2-Benzyl-2-methyl-1,3-dioxolane (70i): Yield: 121 mg, 68%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.22 (m, 5H), 3.92-3.89 (m, 2H), 3.77-3.73 (m, 2H), 2.92 (s, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.0, 130.6, 128.1, 126.5, 109.9, 64.9, 45.5, 24.4; Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%; Found: C, 74.07; H, 7.86%.

2-Benzyl-2-phenyl-1,3-dioxolane (70j): Yield: 215 mg, 85%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.03 (m, 10 H), 3.76-3.63 (m, 4H), 3.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 136.0, 130.9 (2C), 128.0, 127.9, 127.7, 126.4 (2C), 125.9 (2C), 110.0 (2C), 64.8 (2C), 47.1; Anal. calcd for $C_{17}H_{18}O_2$: C, 79.97; H, 6.71%; Found: C, 79.91; H, 6.73%.

3.23. Synthesis of 2,3-disubstituted 1,4-dioxanes bearing a carbonyl functionality from *α,β*-unsaturated ketones

Typical experimental procedure for the synthesized compounds (73a-s)

The synthetic procedure involved two steps. In the first step, chalcone **71a** (1 mmol), sodium meta periodate (1 mmol) and hydroxylamine hydrochloride (1.5 mmol) was taken with ethylene glycol

solvent in a sealed tube. The reaction mixture was stirred for 30 min at room temperature. After completion (TLC) the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporate the solvent and furnished the crude product. This crude product was taken in a sealed tube and adds cesium carbonate and acetonitrile solvent. The reaction mixture was stirred for 40 min at 70 °C. After completion (TLC) the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) followed by brine solution (1x10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate-petroleum ether as eluent to obtain the analytically pure product.

Phenyl(3-phenyl-1,4-dioxan-2-yl)methanone (73a). Off-white gum (252 mg, yield 94%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.67 (m, 2H), 7.43-7.39 (m, 1H), 7.31-7.23 (m, 4H), 7.18-7.11 (m, 3H), 4.88 (d, *J* = 8.8 Hz, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 4.02-3.95 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 137.1, 135.9, 133.4, 128.8, 128.6, 128.4, 127.6, 81.1, 79.9, 66.75, 66.68. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%; Found: C, 76.06; H, 6.05%.

Phenyl(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (73b). Yellow liquid (220 mg, yield 78%); R_f = 0.60 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.47-7.43 (m, 1H), 7.32-7.28 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.89-4.79 (m, 2H), 4.04-3.98 (m, 4H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 138.3, 135.9, 134.1, 133.4, 129.1, 128.9, 128.4, 127.5, 81.2, 79.8, 66.8, 66.7, 21.2. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%; Found: C, 76.51; H, 6.38%.

(3-(4-Methoxyphenyl)-1,4-dioxan-2-yl)(phenyl)methanone (73c). Yellow liquid (256 mg, yield 86%); R_f = 0.50 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 2H), 7.40-7.36 (m, 1H), 7.25-7.15 (m, 4H), 6.66-6.63 (m, 2H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.71 (d, *J* = 9.2 Hz, 1H), 3.95-3.90 (m, 4H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.6, 159.7, 135.8, 133.4, 129.3, 128.9, 128.4, 113.8, 81.1, 79.4, 66.8, 66.7, 55.3. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%; Found: C, 72.40; H, 6.02%.

(3-(2-Chlorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (73d). Orange gum (212 mg, yield 70%); R_f = 0.55 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 2H), 7.58-7.56 (m, 1H), 7.42-7.38 (m, 1H), 7.26-7.21 (m, 3H), 7.08-7.04 (m, 2H), 5.22 (d, *J* = 8.8 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 1H), 4.09-4.02 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 135.7,

135.1, 133.4, 133.3, 129.7, 129.6, 128.94, 128.89, 128.1, 127.0, 82.2, 76.3, 66.9, 66.7. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.39; H, 5.04%.

(3-(4-Chlorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (73e). Yellow liquid, 218 mg (yield 72%); R_f = 0.60 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.73 (m, 2H), 7.51-7.47 (m, 1H), 7.35-7.31 (m, 2H), 7.28-7.26 (m, 2H), 7.20-7.15 (m, 2H), 4.85-4.80 (m, 2H), 4.02-3.97 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 135.8, 135.7, 134.4, 133.7, 129.1, 128.9, 128.6, 127.5, 81.0, 79.1, 66.8. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.41; H, 4.95%.

(3-(4-Fluorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (73f). Yellow liquid (229 mg, yield 80%); R_f = 0.45 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.72 (m, 2H), 7.49-7.46 (m, 1H), 7.34-7.29 (m, 4H), 6.91-6.86 (m, 2H), 4.87-4.81 (m, 2H), 4.05-3.99 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 162.7 (d, $^1J_{C\text{-}F}$ = 244 Hz), 135.7, 133.7, 133.1, 129.4 (d, $^4J_{C\text{-}F}$ = 8 Hz), 128.7 (d, $^3J_{C\text{-}F}$ = 30 Hz), 115.4 (d, $^2J_{C\text{-}F}$ = 22 Hz), 81.1, 79.2, 66.9, 66.7. Anal. Calcd for $C_{17}H_{15}FO_3$: C, 71.32; H, 5.28%; Found: C, 71.27; H, 5.25%.

(3-Phenyl-1,4-dioxan-2-yl)(*p*-tolyl)methanone (73g). Off-white gum (257 mg, yield 91%); R_f = 0.50 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.33-7.30 (m, 2H), 7.22-7.15 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.90-4.83 (m, 2H), 4.04-3.98 (m, 4H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 144.4, 137.2, 133.4, 129.2, 129.0, 128.5, 128.4, 127.6, 81.0, 80.0, 66.8, 66.7, 21.8. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%; Found: C, 76.51; H, 6.38%.

(4-Methoxyphenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (73h). Yellow gum (274 mg, yield 92%); R_f = 0.60 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.69 (m, 2H), 7.33-7.30 (m, 2H), 7.22-7.15 (m, 3H), 6.77-6.75 (m, 2H), 4.87-4.82 (m, 2H), 4.05-3.97 (m, 4H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.7, 163.8, 137.2, 131.2, 128.9, 128.5, 128.4, 127.6, 113.7, 81.0, 80.0, 66.8, 66.7, 55.5. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%; Found: C, 72.41; H, 6.02%.

(4-Chlorophenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (73i). Yellow liquid (257 mg, yield 85%); R_f = 0.45 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 2H), 7.31-7.25 (m, 4H), 7.23-7.16 (m, 3H), 4.86-4.78 (m, 2H), 4.05-3.97 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 140.0, 136.9, 134.1, 130.2, 128.8, 128.5, 127.6, 81.3, 80.0, 66.8, 66.7. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.40; H, 4.92%.

(3-Bromophenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (73j). Yellow liquid (330 mg, yield 95%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.69 (m, 1H), 7.55-7.53 (m, 1H), 7.48-7.45 (m, 1H), 7.23-7.21 (m, 2H), 7.14-7.05 (m, 4H), 4.76 (d, *J* = 8.8 Hz, 1H), 4.70 (d, *J* = 8.8 Hz, 1H), 3.96-3.92 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.2, 137.5, 136.8, 136.2, 131.7, 129.9, 128.8, 128.5, 127.5, 127.2, 122.7, 81.3, 79.9, 66.7, 66.6. Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.35%; Found: C, 58.75; H, 4.29%.

***p*-Tolyl(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (73k).** Yellow gum (246 mg, yield 83%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.86-4.80 (m, 2H), 4.02-3.97 (m, 4H), 2.33 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 144.3, 138.2, 134.2, 133.5, 129.12, 129.07, 129.0, 127.5, 81.1, 79.7, 66.8, 66.7, 21.7, 21.2. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.08%; Found: C, 76.95; H, 6.01%.

(4-Chlorophenyl)(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (73l). Yellow liquid (237 mg, yield 75%); R_f = 0.60 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.57 (m, 2H), 7.22-7.19 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 4.76-4.68 (m, 2H), 3.97-3.92 (m, 4H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.3, 139.8, 138.4, 134.1, 133.8, 130.2, 129.1, 128.6, 127.3, 81.3, 79.7, 66.7, 66.6, 21.1. Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41%; Found: C, 68.20; H, 5.35%.

(4-Chlorophenyl)(3-(2-methoxyphenyl)-1,4-dioxan-2-yl)methanone (73m). Yellow gum (246 mg, yield 74%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.59 (m, 2H), 7.55-7.52 (m, 1H), 7.20-7.18 (m, 2H), 7.12-7.10 (m, 1H), 6.96-6.93 (m, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.10 (d, *J* = 8.8 Hz, 1H), 4.78 (d, *J* = 8.4 Hz, 1H), 4.08-4.03 (m, 3H), 3.97-3.92 (m, 1H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 155.8, 139.3, 134.2, 130.0, 129.6, 128.2, 127.4, 125.6, 120.9, 109.9, 84.0, 74.5, 67.1, 66.7, 54.5. Anal. Calcd for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15%; Found: C, 65.02; H, 5.11%.

(3-(2-Chlorophenyl)-1,4-dioxan-2-yl)(*p*-tolyl)methanone (73n). Orange gum (225 mg, yield 71%); R_f = 0.50 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.62 (m, 2H), 7.59-7.56 (m, 1H), 7.23-7.21 (m, 1H), 7.08-7.04 (m, 4H), 5.23 (d, *J* = 8.8 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.09-3.98 (m, 4H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.6, 144.2, 135.2, 133.5, 133.2, 129.7, 129.6, 129.1, 129.0, 128.9, 127.0, 82.1, 76.4, 66.9, 66.7, 21.7. Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41%; Found: C, 68.20; H, 5.46%.

(4-Chlorophenyl)(3-(2-chlorophenyl)-1,4-dioxan-2-yl)methanone (73o). Yellow liquid (229 mg, yield 68%); R_f = 0.45 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69-

7.66 (m, 2H), 7.60-7.58 (m, 1H), 7.25-7.18 (m, 3H), 7.13-7.05 (m, 2H), 5.20 (d, *J* = 8.8 Hz, 1H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.10-3.99 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 139.8, 135.0, 133.9, 133.3, 130.3, 129.8, 129.6, 128.9, 128.5, 127.2, 82.7, 76.3, 66.9, 66.7. Anal. Calcd for $C_{17}H_{14}Cl_2O_3$: C, 60.55; H, 4.19%; Found: C, 60.60; H, 4.12 %.

(3-(2-Bromophenyl)-1,4-dioxan-2-yl)(4-methoxyphenyl)methanone (73p). Yellow liquid (272 mg, yield 72%); R_f = 0.50 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.72 (m, 2H), 7.58-7.55 (m, 1H), 7.29-7.26 (m, 2H), 7.03-6.99 (m, 1H), 6.74-6.71 (m, 2H), 5.22-5.20 (m, 1H), 4.96-4.94 (m, 1H), 4.09-3.98 (m, 4H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 163.6, 136.9, 133.0, 131.4, 129.9, 129.2, 128.7, 127.6, 123.8, 113.4, 82.1, 78.5, 66.9, 66.7, 55.5. Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.25; H, 4.59%.

(3-(3-Bromophenyl)-1,4-dioxan-2-yl)(*p*-tolyl)methanone (73q). Yellow liquid (311 mg, yield 86%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.72 (m, 1H), 7.66-7.64 (m, 1H), 7.57-7.54 (m, 1H), 7.19-7.15 (m, 3H), 7.02-7.00 (m, 2H), 4.81 (d, *J* = 8.8 Hz, 1H), 4.73 (d, *J* = 8.8 Hz, 1H), 4.01-3.99 (m, 4H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 138.6, 137.6, 136.1, 133.9, 131.8, 129.9, 129.2, 127.4, 127.3, 122.7, 81.6, 79.8, 66.8, 66.7, 21.2. Anal. Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74%; Found: C, 59.93; H, 4.69%.

(3-(3-Bromophenyl)-1,4-dioxan-2-yl)(4-methoxyphenyl)methanone (73r). Yellow liquid (351 mg, yield 93%); R_f = 0.60 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.74 (m, 1H), 7.65-7.62 (m, 1H), 7.55-7.52 (m, 1H), 7.21-7.13 (m, 3H), 6.73-6.71 (m, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 4.70 (d, *J* = 9.2 Hz, 1H), 3.98-3.97 (m, 4H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.3, 159.8, 137.5, 136.0, 131.7, 129.9, 129.0, 128.7, 127.2, 122.6, 113.8, 81.4, 79.4, 66.7, 66.6, 55.2. Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.25; H, 4.50%.

(3-(Naphthalen-1-yl)-1,4-dioxan-2-yl)(phenyl)methanone (73s). Yellow liquid (261 mg, yield 82%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, *J* = 8.8 Hz, 1H), 7.66-7.58 (m, 3H), 7.50-7.45 (m, 1H), 7.42-7.36 (m, 3H), 7.33-7.29 (m, 1H), 7.25-7.21 (m, 1H), 7.04-7.00 (m, 2H), 5.48 (d, *J* = 8.4 Hz, 1H) 5.33 (d, *J* = 8.4 Hz, 1H), 4.18-4.09 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.0, 135.6, 133.7, 133.1, 131.0, 129.3, 128.7, 128.2, 127.8, 126.4, 125.9, 125.6, 125.1, 123.7, 81.1, 67.2, 66.8. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70%; Found: C, 79.15; H, 5.76%.

3.24. Synthesis of *vicinal* diiodo compounds

General procedure for the synthesis of *vicinal*-diiodo compounds: In a general experimental procedure a mixture of alkene (1 mmol), $NaIO_4$ (2 mmol, 426 mg) in 2 mL of DCM was taken in

an open round bottomed flask at room temperature and then $NH_2OH.HCl$ (4 mmol, 276 mg) was added by portion for 10 min. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/DCM (15 mL) and the DCM layer was collected and dried over anhydrous Na_2SO_4. Crude product was obtained by evaporation of solvent, which was purified by column chromatography using ethyl acetate-petroleum ether as eluant (1:10) to obtain the analytically pure product.

2,3-Diiodo-1,3-diphenyl-propan-1-one (75a): White solid (388 mg, 84%); mp. 110-111 °C; IR (KBr): 3062, 2990, 1687, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.14-8.09 (m, 2H), 7.85-7.35 (m, 7H), 7.26 (d, *J* = 8.8 Hz, 1H), 5.88 (d, *J* = 6.6 Hz, 1H), 5.69 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6, 139.2, 134.1, 129.5, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 60.8, 29.5. HRMS (ESI) m/z: calcd for $C_{15}H_{12}I_2O$: 484.8875 $[M+Na]^+$; Found: 484.8875.

3-(4-Chloro-phenyl)-2,3-diiodo-1-phenyl-propan-1-one (75b): White solid (401 mg, 81%); mp. 128-129 °C; IR (KBr): 3055, 2995, 1677, 1487, 1359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01-7.81 (m, 2H), 7.68-7.35 (m, 7H), 5.82 (d, *J* = 11.1 Hz, ½H), 5.64 (d, *J* = 11.1 Hz, ½H), 5.46 (d, *J* = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 137.6, 135.5, 134.3, 132.6, 129.6, 129.1, 128.9, 128.4, 56.8, 28.9; Anal. Calcd. for $C_{15}H_{11}ClI_2O$: C, 36.29; H, 2.23%. Found: C, 36.22; H, 2.13%.

2,3-Diiodo-3-(3-nitro-phenyl)-1-phenyl-propan-1-one (75c): White solid (416 mg, 82%); mp. 142-144 °C; IR (KBr): 3079, 1999, 1677, 1527, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.78-7.45 (m, 9H), 5.79 (dd, J_1 = 39 Hz, J_2 = 18 Hz, 1H), 5.54 (dd, J_1 = 39 Hz, J_2 = 21 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 148.4, 141.3, 139.2, 134.5, 134.2, 133.6, 129.7, 129.0, 128.9, 128.5, 56.6, 28.2; Anal. Calcd. for $C_{15}H_{11}I_2NO_3$: C, 35.53; H, 2.19; N, 2.76%. Found: C, 35.45; H, 2.14; N, 2.71%.

2,3-Diiodo-1-(4-methoxyphenyl)-3-phenylpropan-1-one (75d). Light pink gummy mass; 394 mg (80%); IR (KBr): 3068, 2985, 1682, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.96 (d, *J* 8.8 Hz, 2 H), 7.33-7.27 (m, 5 H), 6.88-6.85 (m, 2 H), 5.75 (d, *J* = 11.2 Hz, 1 H), 5.54 (d, *J* = 11.2 Hz, 1 H), 3.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz,): δ = 191.12, 164.34, 139.29, 129.39, 129.34, 129.15, 128.84, 128.79, 128.38, 128.10, 114.31, 60.94, 55.67, 29.32; Anal. Calcd for $C_{16}H_{14}I_2O_2$: C, 39.05; H, 2.87%. Found: C, 39.01; H, 2.80%.

2,3-Diiodo-3-phenyl-propionic acid (75e): White solid (333 mg, 83%); mp. 115-117 °C; IR (KBr): 3060, 3006, 1699, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.86 (br, 1H), 7.52-7.37 (m, 5H), 5.35 (d, *J* = 12 Hz, 1H), 4.89 (d, *J* = 12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 138.0, 128.9, 128.7, 128.3, 128.0, 127.7, 61.3, 24.7. Anal. Calcd. for $C_9H_8I_2O_2$: C, 26.89; H, 2.01%. Found: C, 26.82; H, 1.97%.

2,3-Diiodo-butyric acid (75f): Light grey gummy mass (275 mg, 81%); IR (KBr): 3080, 3024, 2987, 1712, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.17 (br, 1H), 4.48-4.32 (m, 2H), 1.79 (d, *J* = 12 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 55.6, 25.8, 24.6. Anal. Calcd. for $C_4H_6I_2O_2$: C, 14.13; H, 1.78%. Found: C, 14.07; H, 1.72%.

2,3-Diiodo-3-phenyl-propionic acid methyl ester (75g): White gummy mass (341 mg, 84%); IR (KBr): 3006, 2948, 1733, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.35 (m, 5H), 5.35 (d, *J* = 11.7 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 138.2, 129.4, 128.7, 128.0, 61.7, 53.2, 24.9. Anal. Calcd. for $C_{10}H_{10}I_2O_2$: C, 28.87; H, 2.42%. Found: C, 28.81; H, 2.37%.

1,2,4,5-Tetraiodo-1,5-diphenyl-pentan-3-one (75h): Light grey solid (608 mg, 82%); mp. 105-106 °C; IR (KBr): 3062, 3026, 2997, 1703, 1452, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.37 (m, 10H), 5.60-5.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 139.1, 129.3, 128.7, 128.1, 58.9, 33.3; Anal. Calcd. for $C_{17}H_{14}I_4O$: C, 27.52; H, 1.90%. Found: C, 27.43; H, 1.85%.

Typical procedure for the synthesis of (1,2-diiodo-2-nitro-ethyl)-benzene (75i): A mixture of nitroalkene (1 mmol, 149 mg), $NaIO_4$ (2 mmol, 426 mg) in 2 mL of DCM was taken in an open round bottomed flask at room temperature and then $NH_2OH.HCl$ (4 mmol, 276 mg) was added by portion for 10 min. After completion (TLC), the reaction mixture was diluted with a 1:1 mixture of water/DCM (15 mL) and the DCM layer was collected and dried over anhydrous Na_2SO_4. Crude product was obtained by evaporation of solvent, which was purified by column chromatography using ethyl acetate-petroleum ether as eluant (1:10) to obtain the analytically pure product. Light yellow gummy mass (306 mg, 76%); IR (KBr): 3077, 1993, 1675, 1522, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88-7.39 (m, 5H), 6.51 (d, *J* = 12 Hz, 1H), 5.55 (d, *J* = 12 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 128.8, 128.5, 126.4, 70.7, 33.6; Anal. Calcd. for $C_8H_7I_2NO_2$: C, 23.85; H, 1.75; N, 3.48%. Found: C, 23.81; H, 1.68; N, 3.42%.

3.25. Amidation reactions of terminal alkynes with benzenesulfonamide

Synthesis of compound (79): A mixture of the Ts-aziridine (**1a**, 0.5 mmol) and benzenesulfonamide (**76**, 0.5 mmol) was taken in 2 mL of CH_3CN in a sealed tube. Iodobenzene diacetate (PIDA, 1 equiv.) was added to the reaction mixture. Next, the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethylacetate (10 mL) and water (10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8% to 10%) as eluent.

General procedure for the synthesis of *α*-aminoketones (81): A mixture of the terminal alkyne (**80**, 0.5 mmol) and benzenesulfonamide (**76**, 0.5 mmol) was taken in 2 mL of CH_3CN in a sealed tube. Iodobenzene diacetate (PIDA, 0.25 equiv.) was added to the reaction mixture. Next, the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethylacetate (10 mL) and water (10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8% to 10%) as eluent.

Synthesis of 4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (81a) on gram scale: A mixture of phenylacetylene (**80a**, 5 mmol) and 4-methylbenzenesulfonamide (**76a**, 5 mmol) was taken in 10 mL of CH_3CN in a 25 mL of the round bottom flask. Iodobenzene diacetate (PIDA, 0.25 equiv) was added to the reaction mixture. Next, the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethylacetate (25 mL) and water (25 ml). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8% to 10%) as eluent to get the analytically pure product as white solid (**3a**, 1.08 g, 75%).

Synthesis of α-acetoxy ketone (82): A mixture of the terminal alkyne (**80,** 0.5 mmol) and iodobenzene diacetate (PIDA, 0.5 equiv.) was taken in 2 mL of CH_3CN in a sealed tube. Next, the reaction mixture was stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethylacetate (10 mL) and water (10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was collected and purified by column chromatography on silica gel using petroleum ether/ethyl acetate (5% to 6%) as eluent.

***N,N′*-(1-phenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (79):** White gummy (310 mg, 70%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 7.34−7.29 (m, 2H), 7.20−7.18 (m, 4H), 6.99−6.96 (m, 2H), 5.37 (bs, 1H), 4.82 (d, J = 6 Hz, 1H), 4.33−4.27 (m, 1H), 3.22−3.15 (m, 2H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.8, 143.6, 137.4, 136.6, 136.4, 129.8, 129.5, 128.9, 128.3, 127.2, 127.1, 126.5, 57.1, 48.2, 21.5; Anal. Calcd. For $C_{22}H_{24}N_2O_4S_2$: C, 59.44; H, 5.44; N, 6.30; Found: C, 59.58; H, 5.38; N, 6.39%.

4-Methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (81a) [305]: White solid (115 mg, 80%), mp: 116-118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.83 (m, 2H), 7.79-7.77 (m, 2H),

7.62-7.59 (m, 1H), 7.48-7.44 (m, 2H), 7.29-7.27 (m, 2H), 5.65 (t, J = 8.0 Hz, 1H), 4.46 (d, J = 4.4 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.7, 143.9, 136.3, 134.5, 134.0, 130.0, 129.1, 128.0, 127.3, 48.8, 21.6.

4-Methyl-*N*-(2-oxo-2-(*p*-tolyl)ethyl)benzenesulfonamide (81b) [293]: White solid (118 mg, 78%), mp: 120-121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.66 (m, 4H), 7.22-7.18 (m, 4H), 5.59 (t, J = 8.4 Hz, 1H), 4.35 (d, J = 4.8 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.1, 145.7, 143.9, 136.2, 131.4, 129.9, 129.8, 128.1, 127.3, 48.6, 21.9, 21.6.

4-Methyl-*N*-(2-oxo-2-(*m*-tolyl)ethyl)benzenesulfonamide (81c) [293]: White solid (127 mg, 84%), mp: 127-128 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.76 (m, 2H), 7.65-7.62 (m, 2H), 7.43-7.40 (m, 1H), 7.36-7.28 (m, 3H), 5.66 (t, J = 8.4 Hz, 1H), 4.44 (d, J = 4.4 Hz, 2H), 2.39 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.8, 143.9, 139.1, 136.2, 135.4, 133.9, 130.0, 129.0, 128.5, 127.3, 125.2, 48.8, 21.6, 21.4.

***N*-(2-(4-(*Tert*-butyl)phenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81d) [306]:** White solid (146 mg, 85%), mp: 117-119 °C; 1H NMR (CDCl3, 400 MHz): δ 7.79-7.76 (m, 4H), 7.48-7.46 (m, 2H), 7.29-7.27 (m, 2H), 5.68 (t, J = 8.8 Hz, 1H), 4.43 (d, J = 4.4 Hz, 2H), 2.39 (s, 3H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.2, 158.6, 143.8, 136.2, 131.3, 129.9, 128.0, 127.3, 126.1, 48.7, 35.4, 31.1, 21.6.

***N*-(2-(4-Acetylphenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81e) [297]:** White solid (143 mg, 87%), mp: 116-118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 2H), 7.94-7.92 (m, 2H), 7.79-7.77 (m, 2H), 7.31-7.28 (m, 2H), 5.63 (t, J = 8.4 Hz, 1H), 4.49 (d, J = 4.4 Hz, 2H), 2.63 (s, 3H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 197.2, 192.4, 144.0, 141.3, 137.0, 136.2, 130.0, 128.9, 128.3, 127.3, 49.2, 27.0, 21.7.

***N*-(2-(4-Fluorophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81f):** Colourless oil (128 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90-7.87 (m, 2H), 7.78-7.76 (m, 2H), 7.29-7.27 (m, 2H), 7.15-7.11 (m, 2H), 5.66 (t, J = 8.4 Hz, 1H), 4.43 (d, J = 4.4 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.2, 166.5 (d, $^{1}J_{C\text{-}F}$ = 256 Hz), 143.9, 136.2, 130.8 (d, $^{3}J_{C\text{-}F}$ = 10 Hz), 130.4 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 129.9, 127.3, 116.4 (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 48.7, 21.6. Anal. Calcd. For $C_{15}H_{14}FNO_3S$: C, 58.62; H, 4.59; N, 4.56%; Found: C, 58.68; H, 4.52; N, 4.67%.

***N*-(2-(3-Fluorophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81g):** White solid (125 mg, 82%), mp: 157-158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.63-7.61 (m, 1H), 7.55-7.52 (m, 1H), 7.48-7.43 (m, 1H), 7.33-7.28 (m, 3H), 5.63 (t, J = 8.4 Hz, 1H), 4.44 (d, J = 4.4

Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.7, 163.0 (d, $^{1}J_{C\text{-}F}$ = 248 Hz), 144.0, 136.1, 135.8 (d, $^{3}J_{C\text{-}F}$ = 7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 130.0, 127.3, 123.7 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 121.6 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 114.8 (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 49.0, 21.6. Anal. Calcd. For $C_{15}H_{14}FNO_3S$: C, 58.62; H, 4.59; N, 4.56%; Found: C, 58.52; H, 4.51; N, 4.48%.

***N*-(2-(4-Chlorophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81h) [302]:** White solid (131 mg, 77%), mp: 166-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.76 (m, 4H), 7.45-7.42 (m, 2H), 7.30-7.28 (m, 2H), 5.63 (t, J = 8.0 Hz, 1H), 4.42 (d, J = 4.8 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.6, 144.0, 141.1, 136.2, 132.2, 130.0, 129.5, 129.4, 127.3, 48.8, 21.6.

***N*-(2-(2-Chlorophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81i) [302]:** Colourless oil (122 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77-7.75 (m, 2H), 7.48-7.40 (m, 3H), 7.34-7.28 (m, 3H), 5.56 (t, J = 8.4 Hz, 1H), 4.43 (d, J = 4.0 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.1, 145.7, 143.7, 136.2, 131.4, 129.9, 129.8, 128.1, 127.3, 48.6, 21.9, 21.6.

***N*-(2-(4-Bromophenyl)-2-oxoethyl)-4-methylbenzenesulfonamide (81j) [302]:** White solid (150 mg, 78%), mp: 120-122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.72-7.69 (m, 2H), 7.63-7.59 (m, 2H), 7.30-7.28 (m, 2H), 5.60 (t, J = 8.4 Hz, 1H), 4.42 (d, J = 4.8 Hz, 2H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.8, 144.0, 136.2, 132.6, 132.5, 130.0, 129.9, 129.4, 127.3, 48.7, 21.7.

***4*-Methyl-*N*-(2-(3-nitrophenyl)-2-oxoethyl)benzenesulfonamide (81k):** Yellow solid (135 mg, 81%), mp: 107-108 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66-8.65 (m, 1H), 8.47-8.44 (m, 1H), 8.20-8.18 (m, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.71 (t, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 5.66 (t, J = 4.4 Hz, 1H), 4.53 (d, J = 4.8 Hz, 2H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.2, 148.6, 144.2, 136.1, 135.1, 133.5, 130.5, 130.0, 128.6, 127.3, 122.9, 49.2, 21.7. Anal. Calcd. For $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38%; Found: C, 53.81; H, 4.31; N, 8.46%.

***4*-Methyl-*N*-(2-oxo-2-(thiophen-3-yl)ethyl)benzenesulfonamide (81l) [303]:** White solid (126 mg, 86%), mp: 130-131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07-8.06 (m, 1H), 7.78-7.76 (m, 2H), 7.47-7.45 (m, 1H), 7.35-7.33 (m, 1H), 7.29-7.27 (m, 1H), 5.60 (t, J = 8.4 Hz, 1H), 4.34 (d, J = 4.8 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 186.9, 143.9, 138.6, 136.1, 133.1, 129.9, 127.3(2C), 126.4, 49.3, 21.6.

4-Methyl-*N*-(2-oxo-4-phenylbutyl)benzenesulfonamide (81m): White solid (137 mg, 87%), mp: 92-93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64-7.62 (m, 2H), 7.22-7.15 (m, 4H), 7.12-7.09

(m, 1H), 7.02-7.00 (m, 2H), 5.27 (t, J = 9.2 Hz, 1H), 3.70 (d, J = 4.8 Hz, 2H), 2.76 (t, J = 14.8 Hz, 2H), 2.59 (t, J = 15.2 Hz, 2H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 203.1, 143.9, 140.0, 136.2, 129.9, 128.7, 128.3, 127.3, 126.5, 51.7, 41.7, 29.5, 217. Anal. Calcd. For $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41%; Found: C, 64.42; H, 6.11; N, 4.48%.

4-Chloro-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (81n) [306]: White solid (128 mg, 83%), mp: 137-138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.82 (m, 4H), 7.64-7.60 (m, 1H), 7.49-7.45 (m, 4H), 5.73 (t, J = 8.4 Hz, 1H), 4.48 (d, J = 4.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.4, 139.6, 137.9, 134.7, 133.8, 129.6, 129.2, 128.7, 128.0, 48.7.

4-Chloro-*N*-(2-oxo-2-(*p*-tolyl)ethyl)benzenesulfonamide (81o): Colourless oil (132 mg, 82%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.74 (m, 2H), 7.68-7.66 (m, 2H), 7.41-7.37 (m, 2H), 7.21-7.18 (m, 2H), 5.68 (t, J = 8.8 Hz, 1H), 4.37 (d, J = 4.4 Hz, 2H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.0, 145.9, 139.5, 137.9, 131.3, 129.8, 129.6, 128.7, 128.1, 48.6, 21.9. Anal. Calcd. For $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33%; Found: C, 55.55; H, 4.28; N, 4.27%.

***N*-(2-(4-(*Tert*-butyl)phenyl)-2-oxoethyl)-4-chlorobenzenesulfonamide (81p):** White solid (155 mg, 85%), mp: 145-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.77 (m, 4H), 7.49-7.44 (m, 4H), 5.77 (t, J = 8.8 Hz, 1H), 4.45 (d, J = 4.8 Hz, 2H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 192.0, 158.8, 139.5, 137.9, 131.2, 129.6, 128.7, 128.0, 126.1, 48.6, 35.4, 31.1. Anal. Calcd. For $C_{18}H_{20}ClNO_3S$: C, 59.09; H, 5.51; N, 3.83%; Found: C, 59.19; H, 5.60; N, 3.92%.

4-Chloro-*N*-(2-(4-ethoxyphenyl)-2-oxoethyl)benzenesulfonamide (81q): White solid (137 mg, 78%), mp: 153-154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.80 (m, 4H), 7.47-7.45 (m, 2H), 6.93-6.90 (m, 2H), 5.74 (t, J = 8.4 Hz, 1H), 4.40 (d, J = 4.4 Hz, 2H), 4.12-4.07 (m, 2H), 1.44 (t, J = 13.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 190.6, 164.2, 139.5, 137.9, 130.4, 129.6, 128.7, 126.5, 114.8, 64.1, 48.3, 14.7. Anal. Calcd. For $C_{16}H_{16}ClNO_4S$: C, 54.32; H, 4.56; N, 3.96%; Found: C, 54.41; H, 4.65; N, 3.88%.

4-Chloro-*N*-(2-(4-fluorophenyl)-2-oxoethyl)benzenesulfonamide (81r): White solid (137 mg, 84%), mp: 124-126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.87 (m, 2H), 7.84-7.82 (m, 2H), 7.48-7.46 (m, 2H), 7.17-7.13 (m, 2H), 5.74 (t, J = 8.4 Hz, 1H), 4.45 (d, J = 4.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 190.9, 166.7 (d, $^{1}J_{C\text{-}F}$ = 256 Hz), 139.6, 137.9, 130.8 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 130.2 (d, $^{4}J_{C\text{-}F}$ = 2 Hz), 129.7, 128.7, 116.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 48.6. Anal. Calcd. For $C_{14}H_{11}ClFNO_3S$: C, 51.30; H, 3.38; N, 4.27%; Found: C, 51.23; H, 3.30; N, 4.18%.

***N*-(2-(4-Bromophenyl)-2-oxoethyl)-4-chlorobenzenesulfonamide (81s):** White solid (159 mg, 82%), mp: 138-139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.82 (m, 2H), 7.72-7.70 (m, 2H), 7.63-7.61 (m, 2H), 7.48-7.45 (m, 2H), 5.71 (t, J = 8.4 Hz, 1H), 4.44 (d, J = 4.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 191.6, 139.7, 137.9, 132.6, 132.5, 130.1, 129.7, 129.4, 128.7, 48.7. Anal. Calcd. For $C_{14}H_{11}BrClNO_3S$: C, 43.27; H, 2.85; N, 3.60%; Found: C, 43.38; H, 2.95; N, 3.67%.

4-Chloro-*N*-(2-oxo-2-(thiophen-3-yl)ethyl)benzenesulfonamide (81t): White solid (133 mg, 85%), mp: 119-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09-8.08 (m, 1H), 7.84-7.81 (m, 2H), 7.47-7.44 (m, 3H), 7.36-7.34 (m, 1H), 5.74 (t, J = 8.8 Hz, 1H), 4.37 (d, J = 4.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 186.8, 139.6, 138.5, 137.9, 133.2, 129.6, 128.7, 127.4, 126.4, 49.3. Anal. Calcd. For $C_{12}H_{10}ClNO_3S_2$: C, 45.64; H, 3.19; N, 4.44%; Found: C, 45.72; H, 3.28; N, 4.51%.

***N*-(2-Oxo-2-phenylethyl)benzenesulfonamide (81u) [304]:** White solid (105 mg, 77%), mp: 40-41 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.89 (m, 2H), 7.86-7.83 (m, 2H), 7.63-7.45 (m, 6H), 5.69 (t, J = 8.4 Hz, 1H), 4.48 (d, J = 4.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 192.6, 139.3, 134.6, 133.9, 133.1, 129.4, 129.1, 128.0, 127.3, 48.8.

***N*-(2-(4-(*Tert*-butyl)phenyl)-2-oxoethyl)benzenesulfonamide (81v):** Yellow oil (137 mg, 83%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.88 (m, 2H), 7.79-7.77 (m, 2H), 7.55-7.46 (m, 5H), 5.71 (t, J = 8.4 Hz, 1H), 4.45 (d, J = 4.4 Hz, 2H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 192.1, 158.7, 139.3, 133.0, 131.3, 129.3, 128.0, 127.2, 126.1, 48.7, 35.4, 31.1. Anal. Calcd. For $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23%; Found: C, 65.33; H, 6.30; N, 4.28%.

2-Oxo-2-phenylethyl acetate (82a) [275]: White Solid (75 mg, 84%), mp: 42-43 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.88 (m, 2H), 7.61-7.57 (m, 1H), 7.49-7.45 (m, 2H), 5.32 (s, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 192.3, 170.5, 134.3, 134.0, 129.0, 127.9, 66.2, 20.7.

2-Oxo-2-(*p*-tolyl)ethyl acetate (82b) [275]: White Solid (78 mg, 81%), mp: 84-85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.27-7.25 (m, 2H), 5.30 (s, 2H), 2.40 (s, 3H), 2.20 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 191.8, 170.5, 144.9, 131.8, 129.6, 127.9, 66.0, 21.8, 20.6.

2-(4-(*Tert*-butyl)phenyl)-2-oxoethyl acetate (82c) [364]: White Solid (100 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.84 (m, 2H), 7.50-7.48 (m, 2H), 5.32 (s, 2H), 2.22 (s, 3H), 1.33 (s,

9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.9, 170.6, 157.9, 131.7, 127.8, 125.9, 66.1, 35.3, 31.1, 20.7.

2-(3-Fluorophenyl)-2-oxoethyl acetate (82d): Yellowish oil (81 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 1H), 7.57-7.53 (m, 1H), 7.45-7.40 (m, 1H), 7.28-7.25 (m, 1H), 5.26 (s, 2H), 2.16 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.2, 170.3, 162.8 (d, $^{1}J_{C\text{-}F}$ = 248 Hz), 136.1 (d, $^{3}J_{C\text{-}F}$ = 6 Hz), 130.6 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 123.5 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 120.9 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 114.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 66.0, 20.4. Anal. Calcd. For $C_{10}H_9FO_3$: C, 61.23; H, 4.62%; Found: C, 61.29; H, 4.72%.

2-(4-Bromophenyl)-2-oxoethyl acetate (82e) [275]: White Solid (94 mg, 73%), mp: 82-83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.76 (m, 2H), 7.64-7.62 (m, 2H), 5.28 (s, 2H), 2.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 191.5, 170.5, 133.1, 132.4, 130.0, 129.4, 65.9, 20.6.

2-Oxo-2-(thiophen-3-yl)ethyl acetate (82f) [365]: Yellow Solid (77 mg, 84%), mp: 75-76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.09 (m, 1H), 7.53-7.51 (m, 1H), 7.36-7.34 (m, 1H), 5.19 (s, 2H), 2.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 186.8, 170.5, 138.7, 132.3, 126.9, 126.5, 66.3, 20.6.

3.26. Synthesis of selenoesters from *α*-aminocarbonyl derivatives

Synthesis of *α*-aminocarbonyl compound (83a): 2-Bromoacetophenone (5 mmol) was added to a mixture of *p*-toluidine (5 mmol) and $NaHCO_3$ (5 mmol) in ethanol at room temperature under argon atmosphere. The mixture was allowed to stirr vigorously for 6-8 h and then diluted with water (10 mL). The mixture was extracted with ethyl acetate and the organic layer was washed with water followed by dried over anhydrous Na_2SO_4. Then the mixture was concentrated under vacuum to give yellow solid of pure 1-phenyl-2-(*p*-tolylamino)ethan-1-one (**83a**).

General procedure for the synthesis of diselenides: To a stirred solution of Se^0 metal (2.0 mmol) and aryl iodide (1.0 mmol) in dry DMSO (2.0 mL) solvent CuO nanoparticles (10.0 mol%) was added; then KOH (2.0 equiv.) was added under nitrogen atmosphere at 90 ºC. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool, which was separated through column chromatographic to give pure diselenide compounds. The identity and purity of the product were ensured by ^{1}H and ^{13}C NMR spectroscopic analysis.

Synthesis of *Se*-Phenyl benzoselenoate (85a): A mixture of 1-phenyl-2-(*p*-tolylamino)ethan-1-one (**83a,** 1 mmol, 225 mg) and diphenyl diselenide (**84a,** 0.5 mmol, 312 mg) was taken in 2 mL of DCM in a sealed tube. $FeCl_3$ (10 mol%) and benzoyl peroxide (1 equiv) was added to the

reaction mixture. Next, the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). Then, the organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent, the crude product was collected and purified by column chromatography on silica gel (60−120 mesh) using *n*-hexane as eluent to afford the analytically pure product (**85a**) as yellow solid. *n*-Hexane was used as eluent for the column chromatography for all the synthesized compounds.

***Se*-Phenyl benzoselenoate (85a) [400]:** Yellow solid; mp. 40-42 °C, Yield: 84%, 220 mg; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.95-7.93 (m, 2H), 7.64-7.59 (m, 3H), 7.51-7.47 (m, 2H), 7.45-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.5, 138.7, 136.5, 134.0, 129.5, 129.2, 129.1, 127.5, 126.0.

***Se*-(*m*-Tolyl) benzoselenoate (85b):** Yellow solid; mp 71-73 °C, Yield: 80%, 220 mg; ^{1}HNMR ($CDCl_3$, 400 MHz): δ 7.95-7.92 (m, 2H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 2H), 7.43-7.39 (m, 2H), 7.34-7.30 (m, 1H), 7.26-7.24 (m, 1H), 2.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8, 139.4, 138.8, 137.0, 134.0, 133.5, 130.1, 129.1, 127.5, 125.6, 21.5. Anal. Calcd. For $C_{14}H_{12}OSe$: C, 61.10; H, 4.40%; Found: C, 61.18; H, 4.49%;

***Se*-Phenyl 4-methylbenzoselenoate (85c) [400]:** Yellow solid; mp 70-72 °C, Yield: 82%, 225 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.92 (m, 2H), 7.63-7.59 (m, 1H), 7.50-7.46 (m, 4H), 7.24 (d, J = 8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6, 139.4, 138.8, 136.4, 133.9, 130.4, 129.1, 127.5, 122.3, 21.5.

***Se*-(3-Fluorophenyl) benzoselenoate (85d):** Yellow solid; mp. 50-52 °C, Yield: 78%, 217 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.66-7.62 (m, 1H), 7.52-7.48 (m, 2H), 7.41-7.28 (m, 3H), 7.16-7.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.7, 162.7 (d, $^1J_{C\text{-}F}$ = 248 Hz), 138.4, 134.2, 132.0 (d, $^3J_{C\text{-}F}$ = 3 Hz), 130.6 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.2, 127.6 (d, $^4J_{C\text{-}F}$ = 14 Hz), 123.4, (d, $^2J_{C\text{-}F}$ = 22Hz), 116.4 (d, $^2J_{C\text{-}F}$ = 20 Hz). Anal. Calcd. For $C_{13}H_9FOSe$: C, 55.93; H, 3.25%; Found: C, 55.83; H, 3.34%.

***Se*-(4-Fluorophenyl) benzoselenoate (85e) [400]:** Yellow solid; mp 53-55 °C, Yield: 81%, 225 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.65-7.61 (m, 1H), 7.57-7.47 (m, 4H), 7.14-7.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.4, 163.6 (d, $^1J_{C\text{-}F}$ = 248 Hz), 138.5 (d, $^4J_{C\text{-}F}$ = 8 Hz) (2C), 134.1, 129.1, 127.5, 120.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 116.8 (d, $^2J_{C\text{-}F}$ = 21 Hz).

***Se*-(3-Chlorophenyl) benzoselenoate (85f):** Yellow solid; mp. 74-76 °C, Yield: 79%, 233 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.66-7.61 (m, 2H), 7.52-7.47 (m, 3H), 7.43-7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6, 138.3, 136.1, 134.9, 134.5, 134.3, 130.4, 129.4, 129.2, 127.5, 127.2. Anal. Calcd. For $C_{13}H_9ClOSe$: C, 52.82; H, 3.07%; Found: C, 52.93; H, 3.02%.

***Se*-(4-Chlorophenyl) benzoselenoate (85g) [400]:** Pale yellow solid; mp. 84-86 °C, Yield: 83%, 244 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91 (m, 2H), 7.66-7.61 (m, 1H), 7.53-7.48 (m, 4H), 7.41-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.1, 138.4, 137.7, 135.7, 134.2, 129.8, 129.2, 127.5, 124.1.

***Se*-(3-Bromophenyl) benzoselenoate (85h):** White solid; mp 65-68 °C, Yield: 77%, 261 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 8 Hz, 2H), 7.77-7.76 (m, 1H), 7.66-7.62 (m, 1H), 7.58-7.48 (m, 4H), 7.32-7.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6, 138.8, 138.3, 135.0, 134.3, 130.8, 129.2, 127.5, 126.1, 122.9. Anal. Calcd. For $C_{13}H_9BrOSe$: C, 45.91; H, 2.67%; Found: C, 45.84; H, 2.76%.

***Se*-(4-Bromophenyl) benzoselenoate (85i) [398]:** White solid; mp. 72-74 °C, Yield: 82%, 278 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.90 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.8, 138.4, 138.0, 134.2, 132.7, 129.2, 127.5, 124.8, 124.0.

***Se*-(3-(Trifluoromethyl)phenyl) benzoselenoate (85j) [400]:** White solid; mp. 52-54 °C, Yield: 76%, 250 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.92 (m, 2H), 7.87 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.70-7.63 (m, 2H), 7.57-7.49 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 139.9, 138.2, 134.4, 133.1 (q, J_{C-F} = 5.0 Hz), 131.9, 131.6, 129.7, 129.2, 127.6, 127.0, 126.0 (q, J_{C-F} = 6.0 Hz), 125.2, 122.5.

***Se*-(Thiophen-2-yl) benzoselenoate (85k):** Pale yellow gummy mass; Yield: 78%, 208 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 8.4 Hz, 2H), 7.65-7.61 (m, 2H), 7.52-7.48 (m, 2H), 7.29-7.28 (m, 1H), 7.17-7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.9, 137.9, 137.6, 134.3, 132.9, 129.2, 128.5, 127.6, 119.2. Anal. Calcd. For $C_{11}H_8OSSe$: C, 49.44; H, 3.02%; Found: C, 49.58; H, 3.11%;

***Se*-Benzyl benzoselenoate (85l) [401]:** Yellow oil, Yield: 75%, 207 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.89 (m, 2H), 7.61-7.56 (m, 1H), 7.47-7.43 (m, 2H), 7.39-7.36 (m, 2H), 7.31-7.27 (m, 2H), 7.23-7.20 (m, 1H), 4.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.6, 139.1, 139.0, 133.8, 129.2, 129.0, 128.8, 127.4, 127.1, 29.2.

***Se*-Butyl benzoselenoate (85m)**: Yellow oil, Yield: 61%, 139 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.592-7.90 (m, 2H), 7.60-7.56 (m, 1H), 7.47-7.43 (m, 2H), 3.11 (t, J = 14.8 Hz, 2H), 1.76-1.70 (m, 2H), 1.48-1.43 (m, 2H), 0.95 (t, J = 16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.2, 139.4, 133.6, 128.9, 127.3, 31.7, 29.2, 22.8, 13.8. Anal. Calcd. For $C_{11}H_{14}OSe$: C, 54.78; H, 5.85%; Found: C, 54.85; H, 5.94%.

***Se*-Phenyl 3-methylbenzoselenoate (85o) [398]:** Yellow oil, Yield: 78%, 214 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.56 (m, 2H), 7.44-7.41 (m, 2H), 7.25-7.17 (m, 5H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.5, 139.0, 138.8, 136.5, 134.8, 129.5, 129.1, 128.9, 127.9, 126.1, 124.7, 21.4.

***Se*-(*p*-Tolyl) benzoselenoate (85p) [400]:** White solid; mp. 95-97 °C; Yield: 81%, 222 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85-7.83 (m, 2H), 7.61-7.59 (m, 2H), 7.43-7.42 (m, 3H), 7.32-7.27 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.9, 145.0, 136.2, 136.2, 129.7, 129.5, 129.1, 127.6, 126.1, 21.9.

***Se*-Phenyl 4-fluorobenzoselenoate (85q):** Yellow gummy mass; Yield: 79%, 220 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.95 (m, 2H), 7.61-7.58 (m, 2H), 7.45-7.41 (m, 3H), 7.19-7.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.9, 166.3, (d, $^1J_{C\text{-}F}$ = 254 Hz), 136.4, 135.1 (d, $^3J_{C\text{-}F}$ = 2 Hz), 130.1, (d, $^4J_{C\text{-}F}$ = 9 Hz), 129.5, 129.3, 116.3 (d, $^2J_{C\text{-}F}$ = 22 Hz). Anal. Calcd. For $C_{13}H_9FOSe$: C, 55.93; H, 3.25%; Found: C, 55.86; H, 3.35%.

***Se*-Phenyl 3-chlorobenzoselenoate (85r):** White solid; mp. 73-75 °C; Yield: 77%, 227 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.70 (m, 1H), 7.64-7.62 (m, 1H), 7.42-7.38 (m, 3H), 7.27-7.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.5, 140.2, 136.3, 135.4, 133.8, 130.3, 129.6, 129.4, 127.3, 125.6, 125.5. Anal. Calcd. For $C_{13}H_9ClOSe$: C, 52.82; H, 3.07%; Found: C, 52.94; H, 3.16%.

***Se*-Phenyl 4-chlorobenzoselenoate (85s) [400]:** White solid; mp. 82-84 °C; Yield: 80%, 236 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86 (m, 2H), 7.60-7.57 (m, 2H), 7.48-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.4, 140.4, 137.1, 136.4, 129.6, 129.4 (2C), 128.8, 125.7.

***Se*-Phenyl 4-bromobenzoselenoate (85t) [400]:** White solid; mp. 96-98 °C; Yield: 78%, 265 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.78 (m, 2H), 7.64-7.62 (m, 2H), 7.60-7.57 (m, 2H), 7.45-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.6, 137.5, 136.4, 132.4, 129.6, 129.4, 129.1, 128.8, 125.6.

***Se*-(4-Chlorophenyl)-4-methylbenzoselenoate (85u):** White gummy mass; Yield: 75%, 231 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82-7.80 (m, 2H), 7.53-7.49 (m, 2H), 7.40-7.37 (m, 2H), 7.30-7.27 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 145.3, 137.8, 135.8, 135.6, 129.8, 129.7, 127.6, 124.2, 21.9. Anal. Calcd. For $C_{14}H_{11}ClOSe$: C, 54.30; H, 3.58%; Found: C, 54.39; H, 3.50%.

***Se*-(4-Chlorophenyl)-4-chlorobenzoselenoate (85v):** White gummy mass; Yield: 72%, 237 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.75 (m, 1H), 7.49-7.46 (m, 2H), 7.43-7.37 (m, 2H), 7.32-7.30 (m, 1H), 7.29-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.1, 145.2, 137.7, 135.9, 129.8, 129.5, 129.2, 128.8, 123.7. Anal. Calcd. For $C_{13}H_8Cl_2OSe$: C, 47.31; H, 2.44%; Found: C, 47.26; H, 2.37%.

***N*-Benzylbenzamide (85x) [399]:** White solid, mp. 105-107 °C, Yield: 77%, 162 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.79 (m, 2H), 7.51-7.27 (m, 8H), 6.58 (s, 1H), 4.64 (d, J = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 138.4, 134.5, 131.6, 128.8, 128.7, 128.0, 127.6, 127.1.

***N*-(4-Methoxybenzyl)benzamide (85y) [399]**: White solid, mp. 94-96 °C, Yield: 79%, 190 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79-7.77 (m, 2H), 7.45-7.37 (m, 3H), 7.28-7.26 (m, 2H), 6.86-6.83 (m, 2H), 6.64 (s, 1H), 4.55 (d, J = 5.2 Hz, 2H), 3.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 159.6, 134.5, 131.5, 130.5, 129.4, 128.6, 127.1, 114.1, 55.4, 43.6.

3.27. Synthesis of thioaminated naphthoquinones

Representative example for the synthesis of 2-(pyrrolidin-1-yl)-3-(*p*–tolylthio) naphthalene-1,4-dione (90a): A mixture of 1,4-naphthoquinone (**87**, 1 mmol), benzenethiol (**88a**, 1 mmol) and pyrrolidine (**89a**, 3 mmol) was stirred in presence of PIDA (1 equiv.) at 80 °C in 1,2-DCE (2 mL) for 12 h under open to air. After the completion of the reaction, confirmed by TLC, the mixture was cooled to room temperature and then diluted with saturated saline water (3 × 15 mL), saturated sodium thiosulfate solution (2 × 15 mL) and extracted with ethyl acetate. The combined organic layer was collected and dried over anhydrous Na_2SO_4. The residue was purified by column chromatography on silica gel to afford the desired products (eluent: ethyl acetate/petroleum ether).

2-(Phenylthio)-3-(pyrrolidin-1-yl)naphthalene-1,4-dione (90a): Yield: 88%, 294 mg; red solid; mp 60–62 °C; R_f=0.5 (EA: PE=7: 93); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08–8.06 (m, 1H), 7.91–7.89 (m, 1H), 7.68–7.64 (m, 1H), 7.59–7.55 (m, 1H), 7.20–7.16 (m, 2H), 7.14–7.11 (m, 2H), 7.07–7.03 (m, 1H), 3.88–3.84 (m, 4H),1.79–1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 184.4, 180.2,

155.9, 138.7, 134.1, 133.4, 131.9, 128.8, 126.4, 125.9(2C), 124.9, 104.6, 53.9, 25.5. Anal. Calcd. For C20H17NO2S: C, 71.62; H, 5.11; N, 4.18%; Found: C, 71.54; H, 5.12; N, 4.24%.

2-(Pyrrolidin-1-yl)-3-(*p*–tolylthio)naphthalene-1,4-dione (90b) [402]: Yield: 80%, 279 mg; red solid; mp 56.3–57.3 °C; R_f=0.5 (EA: PE=7: 93); 1H NMR ($CDCl_3$, 400 MHz): δ 8.08–8.06 (m, 1H), 7.91–7.89 (m, 1H), 7.68–7.64 (m, 1H), 7.59–7.55 (m, 1H), 7.05–6.99 (m, 4H), 3.88–3.85 (m, 4H), 2.25 (s, 3H), 1.79–1.76 (m, 4H); ^{13}C NMR (CDCl3, 100 MHz): δ 184.6, 180.5, 155.7, 135.1, 134.9, 134.2, 133.6, 132.1, 132.0, 129.7, 126.6, 126.4, 126.0, 105.9, 53.9, 25.6, 21.0.

2-(Cyclohexylthio)-3-(pyrrolidin-1-yl)naphthalene-1,4-dione (90c) [402]: Yield: 72%, 245 mg; red solid; mp 48.6–49.8 °C; R_f=0.5 (EA: PE=4:96); 1H NMR ($CDCl_3$, 400 MHz): δ 8.07–8.04 (m, 1H), 7.87–7.84 (m, 1H), 7.66–7.62 (m, 1H), 7.57–7.53 (m, 1H), 3.91–3.88 (m, 4H), 2.88–2.82 (m, 1H), 1.94–1.90 (m, 4H), 1.87–1.83 (m, 2H), 1.72–1.69 (m, 2H), 1.57–1.53 (m, 1H), 1.28–1.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 184.7, 181.2, 156.4, 134, 133.7, 132, 131.8, 126.3, 125.7, 108.5, 54.5, 46.2, 33.0, 26.2, 26.0, 25.8.

2-(Phenylthio)-3-(piperidin-1-yl)naphthalene-1,4-dione (90d): Yield: 83%, 289 mg; red solid; mp 73–75 °C; R_f=0.5 (EA:PE=7:93); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01–7.95 (m, 2H), 7.61–7.58 (m, 2H), 7.19–7.13 (m, 4H), 7.08–7.07 (m, 1H), 3.35–3.32 (m, 4H), 1.64–1.60 (m, 1H), 1.55–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.6, 181.8, 155.5, 137.0,134.0, 132.8, 132.4, 129.0, 127.7, 126.8, 126.6, 126.0, 108.9, 53.5, 27.0, 24.2. Anal. Calcd. For $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01%; Found: C, 72.12; H, 5.40; N, 4.07%.

2-Morpholino-3-(phenylthio)naphthalene-1,4-dione (90e): Yield: 71%, 252 mg; red solid; mp 119–121 °C; R_f=0.45 (EA:PE=8: 92); 1H NMR (CDCl3, 400 MHz): δ 8.08–8.06 (m, 1H), 8.04–8.02 (m, 1H), 7.71–7.67 (m, 2H), 7.26–7.22 (m, 4H), 7.19–7.16 (m, 1H), 3.76–3.73 (m, 4H), 3.47–3.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.2, 181.9, 153.8, 136.1, 134.2, 133.1, 132.7, 132.2, 129.1, 127.9, 126.9, 126.7, 126.5, 121.2, 67.5, 52.0. Anal. Calcd. For $C_{20}H_{17}NO_3S$: C, 68.36; H, 4.88; N, 3.99%; Found: C, 68.30; H, 4.80; N, 3.91%.

2-(Pyrrolidin-1-yl)naphthalene-1,4-dione (90g): Yield: 90%, 204 mg; red solid; mp 160–161 °C; R_f=0.45 (EA: PE=12:88); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05–8.03 (m, 1H), 7.98–7.96 (m, 1H), 7.70–7.65 (m, 1H), 7.59–7.55 (m, 1H), 5.71 (s, 1H), 3.92 (bs, 2H), 3.40 (bs, 2H),1.99–1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 183.4, 182.5, 149.1, 134.1, 133.3, 131.9, 131.7, 126.4, 125.5, 104.9, 51.1, 50. Anal. Calcd. For $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%; Found: C, 73.93; H, 5.68; N, 6.11%.

3.28. C3-Alkylation of 4-hydroxycoumarin

General procedure for the synthesis of compounds (92):

In presence of TsOH: A mixture of 4-hydroxycoumarin **91** (162 mg, 1 mmol), styrene **7** (1.5 mmol) and TsOH (0.034 g, 20 mol%) was stirred at 80 °C for 4-6 h (TLC control). After completion, the reaction mixture was cooled and extracted with ethyl acetate (3×15 mL) and water (2×10 mL). The organic layer was separated and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure on rotary evaporator, the crude product was purified by column chromatography on silica gel (60–120 mesh) using petroleum ether/ethyl acetate (94:6 to 92:8 v/v) as eluent to afford the pure products.

In presence of $BF_3{\cdot}OEt_2$: A mixture of 4-hydroxycoumarin **91** (1 mmol, 162 mg), styrene **7** (1 mmol) and $BF_3.OEt_2$ (20 mol%)was allowed to stir at 80 °C for 3.5 h. After completion indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and water. Then the mixture was dried over anhydrous Na_2SO_4 and the organic layer was filtered. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (6% to 8%) to afford the pure corresponding product **92**. The identity and purity of the product were confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

In presence of BAIL-1: A mixture of 4-hydroxycoumarin **91** (1 mmol, 162 mg), styrene **7a** (1.5 mmol) and **BAIL-1** (5 mol%) was allowed to stir at 100 °C for 3 h. After completion indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and water. Then the mixture was dried over anhydrous Na_2SO_4 and the organic layer was filtered. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (6% to 8%) to afford the pure corresponding product **92**. The identity and purity of the product were confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

4-Hydroxy-3-(1-phenylethyl)-2*H*-chromen-2-one (92a): White solid, mp. 203-205 ºC, 207 mg, Yield: 78%; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65-7.63 (m, 1H, ArH), 7.53-7.49 (m, 3H, ArH), 7.47-7.43 (m, 2H, ArH), 7.38-7.31 (m, 2H, ArH), 7.24-7.20 (m, 1H, ArH), 5.92 (s, 1H, OH), 4.76-4.71 (m, 1H, CH), 1.66 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 159.8, 152.6, 141.6, 132.0, 129.9, 128.1, 127.4, 124.0, 123.0, 116.5, 116.2, 110.2, 34.7, 16.6. Anal. Calcd. For $C_{17}H_{14}O_3$: C, 76.68; H, 5.30%; Found: C, 76.78; H, 5.34%.

4-Hydroxy-3-(1-(*o*-tolyl)ethyl)-2*H*-chromen-2-one (92b): White solid, mp. 163-165 ºC, 196 mg, Yield: 70%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.65 (m, 2H, ArH), 7.55-7.50 (m, 1H, ArH), 7.45-7.41 (m, 1H, ArH), 7.37-7.29 (m, 3H, ArH), 7.26-7.22 (m, 1H, ArH), 6.37 (s, 1H, OH), 4.73-4.68 (m, 1H, CH), 2.27 (s, 3H, CH_3), 1.72 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 159.8, 152.6, 140.1 139.0, 132.1, 131.8, 128.3, 127.6, 124.7, 123.9, 123.0 116.4, 116.1, 108.2, 33.4, 19.7, 17.4. Anal. Calcd. For $C_{18}H_{16}O_3$: C, 77.12; H, 5.75%; Found: C, 77.04; H, 5.78%.

4-Hydroxy-3-(1-(*p*-tolyl)ethyl)-2*H*-chromen-2-one (92c): White solid, mp. 166-168 ºC, 210 mg, Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70-7.68 (m, 1H, ArH), 7.52-7.47 (m, 1H, ArH), 7.38 (d, J = 8 Hz, 2H, ArH), 7.30-7.27 (m, 1H, ArH), 7.24-7.20 (m, 3H, ArH), 6.45 (s, 1H, OH), 4.72-4.66 (m, 1H, CH), 2.35 (s, 3H, CH_3), 1.65 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 159.9, 152.6, 138.5, 137.7, 131.8, 130.5, 127.3, 123.9, 123.0, 116.4, 116.3, 110.2, 34.3, 21.1, 16.7. Anal. Calcd. For $C_{18}H_{16}O_3$: C, 77.12; H, 5.75%; Found: C, 77.17; H, 5.82%

4-Hydroxy-3-(1-(4-methoxyphenyl)ethyl)-2*H*-chromen-2-one (92d): White solid, 168-170 ºC, mp. 227 mg, Yield: 77%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73-7.71 (m, 1H, ArH), 7.53-7.49 (m, 1H, ArH), 7.43-7.41 (m, 2H, ArH), 7.31-7.29 (m, 1H, ArH), 7.26-7.22 (m, 1H, ArH), 6.96-6.94 (m, 2H, ArH), 6.64 (s, 1H, OH), 4.71-4.65 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 1.67 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 159.8, 159.4, 152.7, 133.0, 131.9, 128.6, 123.9, 123.0, 116.5, 116.3, 115.3, 110.2, 55.5, 34.0, 16.9. Anal. Calcd. For $C_{18}H_{16}O_4$: C, 72.96; H, 5.44%; Found: C, 72.90; H, 5.35%.

3-(1-(4-Chlorophenyl)ethyl)-4-hydroxy-2*H*-chromen-2-one (92e): White solid, mp. 185-187 ºC, 222 mg, Yield: 74%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 1H, ArH), 7.55-7.50 (m, 1H, ArH), 7.42-7.35 (m, 4H), 7.31-7.27 (m, 1H, ArH), 7.25-7.23 (m, 1H, ArH), 6.36 (s, 1H, OH), 4.71-4.66 (m, 1H, CH), 1.66 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 159.9, 152.6, 140.4, 133.7, 132.2, 129.7, 128.8, 124.1, 123.0, 116.6, 116.0, 109.8, 34.0, 16.7. Anal. Calcd. For: $C_{17}H_{13}ClO_3$: C, 67.90; H, 4.36%; Found: C, 67.81; H, 4.45%.

3-(1-(3-Bromophenyl)ethyl)-4-hydroxy-2*H*-chromen-2-one (92f): White solid, mp. 205-207 ºC, 247 mg, Yield: 72%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.70 (m, 1H, ArH), 7.61-7.60 (m, 1H, ArH), 7.55-7.51 (m, 1H, ArH), 7.46-7.40 (m, 2H, ArH), 7.32-7.23 (m, 3H, ArH), 6.26 (s, 1H, OH), 4.73-4.68 (m, 1H, CH), 1.66 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.3, 159.8, 152.7, 144.5, 132.2, 131.1, 130.9, 130.6, 126.0, 124.1, 123.9, 122.9, 116.7, 116.0, 109.7, 34.3 16.6. Anal. Calcd. for $C_{17}H_{13}BrO_3$: C, 59.15; H, 3.80%; Found: C, 59.07; H, 3.88%.

3-(1-(4-Fluorophenyl)ethyl)-4-hydroxy-2*H*-chromen-2-one (92g): White solid, mp. 184-186 ºC, 207 mg, Yield: 73%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75-7.73 (m, 1H, ArH), 7.60-7.55 (m, 1H, ArH), 7.53-7.49 (m, 2H, ArH), 7.36 (d, J = 7.6 Hz, 1H, ArH), 7.35-7.28 (m, 1H, ArH), 7.19-7.14 (m, 2H, ArH), 6.15 (s, 1H, OH), 4.78-4.72 (m, 1H, CH), 1.71 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3 (d, J = 246 Hz), 159.8, 152.6, 137.3 (d, J = 2 Hz), 132.1, 129.1 (d, J = 7 Hz), 124.1, 123.0, 116.7 (d, J = 19 Hz), 116.6, 116.0, 109.9, 34.0, 16.9. Anal. Calcd. for $C_{17}H_{13}FO_3$: C, 71.82; H, 4.61%; Found C, 71.76; H, 4.68%.

4-Hydroxy-3-(1-phenylpropyl)-2*H*-chromen-2-one (92h): White solid, mp. 176-178 ºC, 190 mg, Yield: 68%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.64 (m, 1H, ArH), 7.53-7.47 (m, 3H, ArH), 7.44-7.40 (m, 2H, ArH), 7.34-7.30 (m, 2H, ArH), 7.24-7.20 (m, 1H, ArH), 6.12 (s, 1H, OH), 4.53 (t, J = 15.2 Hz, 1H, CH), 2.29-2.22 (m, 1H, CH_2), 2.12-2.05 (m, 1H, CH_2), 1.08 (t, J = 14.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 159.1, 151.0, 138.5, 132.0, 129.9, 127.9, 128.8, 124.0, 122.9, 116.8, 116.5, 108.3, 41.8, 24.1 12.4. Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75%; Found: C, 77.20; H, 5.87%.

3.29. Tandem regioselective synthesis of pyrano[3,2-*c*]coumarins

General procedure for the synthesis of pyrano[3,2-*c*]coumarins (93): To a mixture of 4-hydroxycoumarin (1 mmol) and *α,β*-unsaturated ketone (1 mmol), the 5 mol% **BAIL-1** was added and the mixture was stirred at 100 °C for 6 h (TLC). After completion of the reaction, water was added to the reaction mixture. Then the product was filtered off and the ionic liquid was recovered by evaporating the water. The recovered ionic liquid was reused for a subsequent fresh batch of the reaction after reactivation. The crude product was recrystallized from hot ethanol to afford the pure product.

Synthesis of 4-phenyl-2-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93a): To a mixture of 4-hydroxycoumarin (**91a**, 1.62 g, 10 mmol) and 3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (**74b**, 2.22 g, 10 mmol), the 5 mol% **BAIL-1** was added and the mixture was stirred at 100 ºC for 3 h (TLC). After completion of the reaction, water was added to the reaction mixture. Then the product was filtered off and the crude product was recrystallized from hot ethanol to afford the pure product as white solid in 80% yield (2.93 g).

4-Phenyl-2-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93a) [329]. White solid (307 mg, 84%), mp: 157-158 °C (lit. [329] mp: 156-158 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.58-7.54 (m, 1H), 7.45-7.43 (m, 2H), 7.39-7.31 (m, 4H), 7.27-7.22 (m, 3H), 5.79 (d, J = 5.2 Hz, 1H), 4.70 (d, J = 4.8 Hz, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$,

100 MHz): δ 161.6, 155.9, 152.9, 147.1, 143.8, 139.5, 132.1, 129.9, 129.5, 128.7, 128.6, 127.3, 124.7, 124.3, 122.8, 116.9, 114.7, 103.8, 103.0, 36.7, 21.5.

2,4-Diphenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93b) [329]. White solid (299 mg, 85%), mp: 171-172 °C (lit. [329] mp: 170-171 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-8.04 (m, 1H), 7.78-7.76 (m, 2H), 7.62-7.57 (m, 1H), 7.50-7.34 (m, 9H), 7.28-7.25 (m, 1H), 5.88 (d, J = 5.2 Hz, 1H), 4.74 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.5, 155.8, 152.8, 147.0, 143.6, 132.7, 132.1, 129.4, 128.8, 128.7, 128.6, 127.3, 124.8, 124.3, 122.8, 116.9, 114.6, 103.8(2C), 36.7.

2-Phenyl-4-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93c) [329]. White solid (293 mg, 80%), mp: 186-188 °C (lit. [329] mp: 188-189 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.64-7.62 (m, 2H), 7.59-7.54 (m, 1H), 7.44-7.30 (m, 6H), 7.27-7.23 (m, 3H), 5.79 (d, J = 4.8 Hz, 1H), 4.70 (d, J = 5.2 Hz, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.6, 155.9, 152.8, 147.0, 143.8, 139.4, 132.0, 129.9, 129.4, 128.7, 128.6, 127.3, 124.7, 124.2, 122.8, 116.9, 114.7, 103.8, 103.0, 36.7, 21.4.

4-(4-Fluorophenyl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93d) [403]. White solid (296 mg, 80%), mp: 143-145 °C (lit. [403] mp: 142-143 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.75-7.73 (m, 2H), 7.61-7.56 (m, 1H), 7.49-7.44 (m, 3H), 7.41-7.34 (m, 4H), 7.02-6.98 (m, 2H), 5.82 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.1 (d, $^1J_{C\text{-}F}$ = 244 Hz), 161.6, 155.9, 147.2, 139.4 (d, $^3J_{C\text{-}F}$ = 2 Hz), 132.6, 132.3, 130.2 (d, $^4J_{C\text{-}F}$ = 8 Hz), 129.5, 128.9, 128.6, 128.2, 124.8, 124.4, 122.8, 117.0, 115.5 (d, $^2J_{C\text{-}F}$ = 21 Hz), 114.6, 103.6, 36.0.

4-(4-Chlorophenyl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93e) [324]. White solid (296 mg, 80%), mp: 194-196 °C (lit. [324] mp: 196-197 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.75-7.72 (m, 2H), 7.60-7.56 (m, 1H), 7.49-7.43 (m, 3H), 7.40-7.33 (m, 4H), 7.29-7.27 (m, 2H), 5.80 (d, J = 4.8 Hz, 1H), 4.68 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.5, 155.9, 152.8, 147.2, 142.1, 133.1, 132.5, 132.3, 130.0, 129.5, 129.3, 128.8, 124.8, 124.4, 122.8, 116.9, 114.5, 103.3, 103.2, 36.2.

4-(4-Bromophenyl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93f) [403]. White solid (357 mg, 83%), mp: 170-171 °C (lit. [403] mp: 168-169 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.74-7.72 (m, 2H), 7.61-7.56 (m, 1H), 7.49-7.43 (m, 5H), 7.41-7.29 (m, 4H), 5.80 (d, J = 4.8 Hz, 1H), 4.68 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.5, 156.0,

152.9, 147.3, 142.7, 132.5, 132.3, 131.8, 130.4, 129.6, 128.9, 124.8, 124.4, 122.8, 121.3, 117.0, 114.5, 103.3, 103.2, 36.3.

4-(3-Nitrophenyl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93g) [403]. White solid (325 mg, 82%), mp: 185-186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25-8.24 (m, 1H), 8.12-8.04 (m, 2H), 7.82-7.73 (m, 3H), 7.64-7.59 (m, 1H), 7.52-7.35 (m, 6H), 5.80 (d, J = 5.2 Hz, 1H), 4.86 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.5, 156.5, 153.0, 148.7, 147.9, 145.8, 134.9, 132.7, 132.3, 129.8, 129.6, 128.9, 128.7, 124.9, 124.6, 123.5, 123.0, 122.5, 117.1, 114.3, 102.4, 36.8.

4-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93h) [329]. White solid (329 mg, 83%), mp: 176-177 °C (lit. [329] mp: 177-178 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.00 (m, 1H), 7.74-7.72 (m, 2H), 7.60-7.55 (m, 1H), 7.48-7.34 (m, 5H), 6.91-6.89 (m, 2H), 6.76-6.74 (m, 1H), 5.91 (s, 2H), 5.82 (d, J = 5.2 Hz, 1H), 4.63 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.6, 155.8, 152.9, 148.0, 146.9, 146.8, 137.8, 132.7, 132.1, 129.4, 128.8, 124.8, 124.3, 122.8, 121.9, 117.0, 114.7, 109.1, 108.4, 103.9, 103.8, 101.2, 36.4.

2-Phenyl-4-(thiophen-2-yl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93i) [403]. White solid (279 mg, 78%), mp: 170-172 °C (lit. [403] mp: 168-169 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 1H), 7.77-7.75 (m, 2H), 7.58-7.54 (m, 1H), 7.49-7.43 (m, 3H), 7.38-7.33 (m, 2H), 7.20-7.19 (m, 1H), 7.14-7.13 (m, 1H), 6.97-6.95 (m, 1H), 5.94 (d, J = 5.2 Hz, 1H), 5.05 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.7, 155.6, 152.8, 147.8, 147.7, 132.6, 132.3, 129.6, 128.9, 127.2, 125.7, 125.1, 125.0, 124.4, 122.9, 117.0, 114.7, 103.6, 103.0, 31.3.

4-(Furan-2-yl)-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93j): White solid (256 mg, 75%), mp: 126-127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02-8.00 (m, 1H), 7.75-7.73 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.36 (m, 5H), 7.32-7.31 (m, 1H), 6.33-6.31 (m, 1H), 6.26-6.25 (m, 1H), 5.85 (d, J = 5.2 Hz, 1H), 4.88 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.6, 156.7, 155.1, 151.0, 148.0, 142.1, 139.9, 132.3, 129.5, 128.8, 128.3, 124.9, 124.4, 122.9, 117.0, 114.7, 110.8, 106.8, 100.9, 30.4. Anal. Calcd For $C_{22}H_{14}O_4$: C, 77.18; H, 4.12%; Found: C, 77.12; H, 4.05%.

2-(4-Methoxyphenyl)-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93k) [331]. White solid (313 mg, 82%), mp: 154-155 °C (lit. [331] mp: 156-157 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.84 (m, 1H), 7.53-7.50 (m, 2H), 7.42-7.38 (m, 1H), 7.30-7.28 (m, 2H), 7.23-7.16 (m, 4H), 7.11-7.08 (m, 1H), 6.84-6.81 (m, 2H), 5.55 (d, J = 4.8 Hz, 1H), 4.52 (d, J = 4.8 Hz, 1H), 3.70 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.5, 160.4, 155.7, 152.7, 146.6, 143.8, 131.9, 128.6, 128.5, 127.1, 126.1, 125.1, 124.1, 122.6, 116.7, 114.6, 114.0, 103.7, 101.9, 55.4, 36.6.

2-(4-Chlorophenyl)-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93l) [331]. White solid (309 mg, 80%), mp: 171-173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95-7.93 (m, 1H), 7.63-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.38-7.34 (m, 5H), 7.30-7.17 (m, 4H), 5.78 (d, J = 4.8 Hz, 1H), 4.65 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.4, 155.7, 152.8, 146.1, 143.4, 135.2, 132.2, 131.2, 129.7, 129.0, 128.8, 128.5, 127.4, 126.0, 124.3, 122.7, 117.0, 114.5, 104.3, 36.7.

2-(4-Iodophenyl)-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93m*)*: White solid (378 mg, 79%), mp: 214-215 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.88 (m, 1H), 7.71-7.68 (m, 2H), 7.52-7.47 (m, 1H), 7.39-7.36 (m, 2H), 7.33-7.30 (m, 3H), 7.28-7.22 (m, 3H), 7.18-7.16 (m, 1H), 5.77 (d, J = 4.8 Hz, 1H), 4.61 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.4, 155.7, 152.8, 146.2, 143.3, 138.0, 137.9, 132.2, 128.8, 128.5, 127.4, 126.4, 124.3, 122.7, 117.0, 114.5, 104.5, 103.7, 95.2, 36.7. Anal. Calcd For $C_{24}H_{15}IO_3$: C, 60.27; H, 3.16%; Found: C, 60.21; H, 3.24%.

4-Phenyl-2-(thiophen-2-yl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93n): White solid (286 mg, 80%), mp: 201-202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 1H), 7.59-7.55 (m, 1H), 7.43-7.31 (m, 8H), 7.25-7.22 (m, 1H), 7.11-7.08 (m, 1H), 5.75 (d, J = 4.8 Hz, 1H), 4.68 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.4, 155.6, 152.9, 143.4, 143.1, 136.2, 132.2, 128.8, 128.6, 127.8, 127.4, 126.0, 124.4, 124.3, 122.8, 116.9, 114.4, 103.9, 102.8, 36.6. Anal. Calcd For $C_{22}H_{14}O_3S$: C, 73.73; H, 3.94%; Found: C, 73.78; H, 3.99%.

2,4-Di-*p*-tolyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93o) [328]: Light yellow oily (296 mg, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.00 (m, 1H), 7.63-7.61 (m, 2H), 7.58-7.51 (m, 2H), 7.39-7.24 (m, 5H), 7.12 (d, J = 8.0 Hz, 2H), 5.78 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 4.8 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.7, 155.8, 152.9, 147.0, 143.3, 141.0, 139.4, 137.0, 132.0, 129.8, 129.4, 128.5 (2C), 124.7, 124.2, 122.8, 116.9, 114.8, 103.2, 36.3, 21.4, 21.2.

2-(2-Methoxyphenyl)-4-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93p): White solid (329 mg, 83%), mp: 144-145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.94 (m, 1H), 7.76-7.73 (m, 1H), 7.54-7.51 (m, 1H), 7.40-7.37 (3H), 7.35-7.31 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.10-7.06 (m, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.07 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 5.2 Hz, 1H), 3.87 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.7, 157.3, 156.0, 152.8, 144.4, 141.0, 136.7, 131.8, 130.3, 129.3, 128.5, 128.4, 124.1, 122.9, 122.0, 120.6, 116.8, 114.9, 111.5, 108.5, 103.8, 55.7, 36.3, 21.2. Anal. Calcd For $C_{26}H_{20}O_4$: C, 78.77; H, 5.09%; Found: C, 78.67; H, 5.02%.

4-(2-Chlorophenyl)-2-(4-methoxyphenyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93q): White solid (341 mg, 82%), mp: 166-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 1H), 7.64-7.61 (m, 3H), 7.42-7.37 (m, 3H), 7.20-7.16 (m, 3H), 6.96-6.93 (m, 2H), 5.74 (d, J = 4.4 Hz, 1H), 5.21 (d, J = 4.4 Hz, 1H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.6, 157.3, 153.1, 146.8, 141.0, 133.1, 132.3, 131.1, 130.0, 129.6, 128.3, 127.9, 127.5, 126.3, 124.3, 122.8, 117.1, 114.5, 114.1, 102.2, 100.5, 55.5, 34.0. Anal. Calcd For $C_{25}H_{17}ClO_4$: C, 72.03; H, 4.11%; Found: C, 71.96; H, 4.04%.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93r): White solid (312 mg, 78%), mp: 155-157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (m, 1H), 7.67-7.65 (m, 2H), 7.58-7.55 (m, 1H), 7.40-7.32 (m, 4H), 7.01-6.96 (m, 4H), 5.67 (d, J = 4.8 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.0 (d, $^1J_{C\text{-}F}$ = 245 Hz), 161.6, 160.6, 155.8, 152.8, 147.0, 139.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 132.1, 130.2 (d, $^4J_{C\text{-}F}$ = 8 Hz), 126.2, 125.2, 124.3, 122.8, 116.9, 115.4 (d, $^2J_{C\text{-}F}$ = 21 Hz), 114.6, 114.2, 103.7, 101.7, 55.5, 36.0. Anal. Calcd For $C_{25}H_{17}FO_4$: C, 74.99; H, 4.28%; Found: C, 74.91; H, 4.34%.

9-Methyl-2,4-diphenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93s) [329]. White solid (289 mg, 79%), mp: 215-216 °C (lit.[37] mp: 216-218 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.73 (m, 3H), 7.47-7.36 (m, 6H), 7.33-7.29 (m, 2H), 7.24-7.22 (m, 2H), 5.84 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 4.8 Hz, 1H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.9, 156.0, 151.1, 147.1, 143.8, 134.1, 133.2, 132.9, 129.9, 129.4, 128.8, 128.7, 128.6, 128.3, 127.3, 124.9, 122.4, 116.7, 104.0, 36.8, 21.2.

9-Methyl-4-phenyl-2-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93t). White solid (312 mg, 82%), mp: 197-198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.83 (m, 1H), 7.76 (s, 1H), 7.63-7.61 (m, 2H), 7.42-7.37 (m, 3H), 7.31-7.28 (m, 3H), 7.24-7.22 (m, 2H), 5.78 (d, J = 4.8 Hz, 1H), 4.69 (d, J = 4.8 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.9, 155.9, 151.1, 147.2, 143.9, 139.4, 134.0, 133.1, 129.5, 129.4, 128.7, 128.6, 128.4, 127.6, 127.3, 124.8, 122.4, 116.7, 103.1, 36.8, 21.5, 21.2. Anal. Calcd $C_{26}H_{20}O_3$: C, 82.08; H, 5.30%; Found: C, 82.02; H, 5.35%.

2-(4-Methoxyphenyl)-9-methyl-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93u). White solid (321 mg, 81%), mp: 176-177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (s, 1H), 7.68-7.65 (m, 2H), 7.41-7.20 (m, 7H), 6.99-6.97 (m, 2H), 5.70 (d, J = 4.8 Hz, 1H), 4.68 (d, J = 5.2 Hz, 1H), 3.86 (s, 3H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.9, 160.5, 155.9, 151.1, 144.0, 134.0, 133.1, 128.7, 128.6, 127.2, 126.3, 125.5, 122.4, 116.7, 114.4, 114.2, 103.8, 102.2, 89.9, 55.6, 36.7,

21.2. Anal. Calcd For Chemical Formula: $C_{26}H_{20}O_4$: C, 78.77; H, 5.09%; Found: C, 78.67; H, 5.02%.

4-(4-Chlorophenyl)-9-methyl-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93v). White solid (332 mg, 83%), mp: 173-174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74-7.69 (m, 3H), 7.45-7.42 (m, 2H), 7.33-7.31 (m, 2H), 7.25-7.22 (m, 3H), 7.16-7.14 (m, 1H), 7.11-7.09 (m, 1H), 5.77 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 5.2 Hz, 1H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8, 156.0, 151.1, 142.3, 134.2, 133.4, 130.0, 129.5, 128.9, 128.4, 128.2, 127.9, 127.8, 125.8, 124.9, 122.4, 116.8, 114.4, 103.4, 36.2, 21.2. Anal. Calcd For $C_{25}H_{17}ClO_3$: C, 74.91; H, 4.27%; Found: C, 74.85; H, 4.21%.

4-(Benzo[*d*][1,3]dioxol-5-yl)-9-methyl-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93w). White solid (348 mg, 85%), mp: 205-206 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.72 (m, 3H), 7.49-7.36 (m, 4H), 7.24 (d, J = 8.4 Hz, 1H), 6.90-6.87 (m, 2H), 6.76-6.74 (m, 1H), 5.91 (s, 2H), 5.81 (d, J = 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8, 155.8, 151.1, 148.0, 147.0, 146.8, 138.0, 134.1, 133.2, 132.9, 129.4, 128.8, 124.9, 122.4, 121.9, 116.7, 114.3, 109.1, 108.4, 104.0, 103.7, 101.2, 36.4, 21.2. Anal. Calcd For $C_{26}H_{18}O_5$: C, 76.09; H, 4.42%; Found: C, 76.02; H, 4.34%.

8-Hydroxy-2,4-diphenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93x). White solid (287 mg, 78%), mp: 233-235 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.68 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.85-7.82 (m, 2H), 7.50-7.43 (m, 3H), 7.32-7.31 (m, 4H), 7.23-7.20 (m, 1H), 6.95-6.92 (m, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 4.8 Hz, 1H), 4.58 (d, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 161.7, 161.0, 156.1, 154.2, 145.4, 144.2, 132.1, 129.2, 128.8, 128.6, 128.0, 126.8, 124.4, 124.3, 113.5, 105.7, 104.1, 102.3, 99.3, 35.8. Anal. Calcd For $C_{24}H_{16}O_4$: C, 78.25; H, 4.38%; Found: C, 78.20; H, 4.29%.

8-Hydroxy-4-phenyl-2-(*p*-tolyl)-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93y). White solid (305 mg, 80%), mp: 244-245 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.69 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.31-7.26 (m, 7H), 6.95-6.92 (m, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.05 (d, J = 5.2 Hz, 1H), 4.56 (d, J = 4.8 Hz, 1H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 161.6, 160.9, 156.1, 154.0, 145.3, 144.2, 138.7, 129.3, 128.5, 127.9, 126.7, 124.2(2C), 113.4, 105.7, 103.1, 102.2, 99.2, 71.1, 35.7, 20.8. Anal. Calcd For $C_{25}H_{18}O_4$: C, 78.52; H, 4.74%; Found: C, 78.58; H, 4.64%.

4-(Benzo[*d*][1,3]dioxol-5-yl)-8-hydroxy-2-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromen-5-one (93z). White solid (338 mg, 82%), mp: 215-218 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.69 (s, 1H),

7.94 (d, J = 8.8 Hz, 1H), 7.83-7.81 (m, 2H), 7.49-7.42 (m, 3H), 6.94-6.91 (m, 1H), 6.87-6.82 (m, 2H), 6.76-6.74 (m, 2H), 6.08 (d, J = 4.8 Hz, 1H), 5.96 (s, 2H), 4.50 (d, J = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 100 MHz): δ 161.6, 161.0, 156.0, 154.1, 147.3, 146.1, 145.2, 138.3, 132.0, 129.2, 128.8, 124.3, 124.2, 121.1, 113.4, 108.5, 108.2, 105.7, 104.1, 102.2, 100.9, 99.3, 35.4. Anal. Calcd For $C_{25}H_{16}O_6$: C, 72.81; H, 3.91%; Found: C, 72.71; H, 3.84%.

***E*-factor (Environmental factor) calculations:**

For 93a: E factor = [0.162 g(**91a**) + 0.222 g(**74b**) – 0.307 g (product × yield)] /0.307 g = 0.250

For 93b: E factor = [0.162 g(**1a**) + 0.208 g(**74a**) – 0.299 g (product × yield)] /0.299 g = 0.237

3.30. *O*-Vinylation of carbonyl oxygen in 4-hydroxycoumarin

General procedure for the synthesis of compounds (94): A mixture of 4-hydroxycoumarin (**91**, 1 mmol), terminal alkyne (**80**, 1 mmol) and 20 mol% of $BF_3{\cdot}OEt_2$ was allowed to stir at 80 °C under the neat condition for 10 min. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with water and extracted with ethyl acetate. The combined organic layer was then washed and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. After that, the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate to afford desired product **94.**

2-((1-Phenylvinyl)oxy)-4*H*-chromen-4-one (94a): Yellow solid; 227 mg, Yield: 86%; mp. 58-60 °C; IR (KBr): 1681, 1222, 833, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.13 (m, 1H), 7.67-7.63 (m, 1H), 7.56-7.53 (m, 2H), 7.46-7.35 (m, 6H), 5.71 (s, 1H), 5.56 (d, J = 2.8 Hz, 1H), 5.20 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.4, 154.3, 153.9, 133.6, 132.4, 130.0, 129.0, 125.9, 125.6, 125.3, 123.0, 117.5, 102.4, 91.1. Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58%; Found: C, 77.17; H, 4.48%.

2-((1-(*p*-Tolyl)vinyl)oxy)-4*H*-chromen-4-one (94b): Yellow gum; 230 mg, Yield: 83%; IR (KBr): 1637, 1373, 1060, 616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.12 (m, 1H), 7.67-7.62 (m, 1H), 7.45-7.37 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 5.69 (s, 1H), 5.49 (d, J = 2.8 Hz, 1H), 5.14 (d, J = 2.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.4, 154.4, 153.9, 140.2, 133.5, 129.7, 129.6, 125.9, 125.5, 125.3, 123.1, 117.5, 101.5, 91.0, 21.4. Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%; Found: C, 77.74; H, 5.01%.

2-((1-(*m*-Tolyl)vinyl)oxy)-4*H*-chromen-4-one (94c): Yellow gum; 222 mg, Yield: 80%; IR (KBr): 1684, 1274, 816, 768 cm^{-1}^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.13 (m, 1H), 7.67-7.63 (m, 1H), 7.46-7.34 (m, 4H), 7.27-7.23 (m, 1H), 7.18 (d, J = 7.6 Hz, 1H), 5.70 (s, 1H), 5.52 (d, J = 2.8

Hz, 1H), 5.17 (d, J = 2.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.4, 154.5, 153.9, 138.8, 133.5, 132.4, 130.8, 128.9, 126.0, 125.9, 125.6, 123.1, 122.5, 117.5, 102.2, 91.0, 21.6. Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%; Found: C, 77.54; H, 5.14%.

2-((1-(4-Methoxyphenyl)vinyl)oxy)-4*H*-chromen-4-one (94d): Yellow gum; 250 mg, Yield: 85%; IR (KBr): 1685, 1260, 832, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.13 (m, 1H), 7.67-7.62 (m, 1H), 7.49-7.37 (m, 4H), 6.89-6.87 (m, 2H), 5.71 (s, 1H), 5.41 (d, J = 2.4 Hz, 1H), 5.08 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.5, 160.9, 154.2, 153.9, 133.5, 126.9, 126.0, 125.6, 125.0, 123.1, 117.5, 114.4, 100.4, 91.0, 55.5. Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80%; Found: C, 73.55; H, 4.89%.

2-((1-(4-Fluorophenyl)vinyl)oxy)-4*H*-chromen-4-one (94e): Yellow gum; 231 mg, Yield: 82%; IR (KBr): 1685, 1229, 833, 753 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.13 (m, 1H), 7.67-7.63 (m, 1H), 7.56-7.52 (m, 2H), 7.44-7.38 (m, 2H), 7.08-7.04 (m, 2H), 5.70 (s, 1H), 5.48 (d, J = 2.8 Hz, 1H), 5.17 (d, J = 2.8 Hz, 1H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.1, 163.6 (d,$^1J_{C\text{-}F}$ = 249 Hz), 153.9, 153.5, 133.6, 128.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 127.4 (d, $^4J_{C\text{-}F}$ = 9 Hz), 126.0, 125.7, 123.0, 117.5, 116.1 (d, $^2J_{C\text{-}F}$ = 22 Hz), 102.0, 91.2. Anal. Calcd. for $C_{17}H_{11}FO_3$: C, 72.34; H, 3.93%; Found: C, 72.40; H, 3.98%.

2-((1-(4-(*Tert*-butyl)phenyl)vinyl)oxy)-4*H*-chromen-4-one (94f): Yellow gum; 268 mg, Yield: 84%; IR (KBr): 1681, 1272, 833, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.12 (m, 1H), 7.66-7.62 (m, 1H), 7.49-7.43 (m, 3H),7.40-7.36 (m, 3H), 5.69 (s, 1H), 5.51 (d, J = 2.8 Hz, 1H), 5.14 (d, J = 2.8 Hz, 1H), 1.3 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 166.5, 154.3, 153.9, 153.3, 133.5, 129.5, 125.9(2C), 125.5, 125.1, 123.1, 117.5, 101.6, 91.0, 34.8, 31.2. Anal. Calcd. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29%; Found: C, 78.64; H, 6.20%.

2-((1-(Thiophen-3-yl)vinyl)oxy)-4*H*-chromen-4-one (94g): Brown gum; 218 mg, Yield: 81%; IR (KBr): 1695, 1275, 949, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17-8.14 (m, 1H), 7.68-7.64 (m, 1H), 7.46-7.39 (m, 3H), 7.35-7.33 (m, 1H), 7.24-7.22 (m, 1H), 5.77 (s, 1H), 5.42 (d, J = 2.8 Hz, 1H), 5.11 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 166.4, 153.9, 150.6, 134.6, 133.6, 127.3, 126.0, 125.6, 124.9, 123.3, 123.1, 117.5, 101.3, 90.8. Anal. Calcd. for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73%; Found: C, 66.54; H, 3.67%.

2-((1-(Cyclohex-1-en-1-yl)vinyl)oxy)-4*H*-chromen-4-one (94h): Yellow gum; 214 mg, Yield: 80%; IR (KBr): 1680, 1220, 828, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16-8.14 (m, 1H), 7.65-7.61 (m, 1H), 7.43-7.36 (m, 2H), 6.12 (t, J = 8.4 Hz, 1H), 5.67 (s, 1H), 5.03 (d, J = 2.4 Hz, 1H), 4.9 (d, J = 2.4 Hz, 1H), 2.19-2.16 (m, 2H), 2.12-2.08 (m, 2H), 1.73-1.67 (m, 2H), 1.60-1.54

(m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 167.3, 155.1, 153.8, 133.4, 128.8, 128.0, 125.9, 125.4, 123.1, 117.4, 100.6, 89.6, 25.4, 24.8, 22.2, 21.7. Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%; Found: C, 76.17; H, 6.10%.

2-((1-(1-Hydroxycyclohexyl)vinyl)oxy)-4*H*-chromen-4-one (94i): Yellow gum; 208 mg, Yield: 73%; IR (KBr): 3405, 1717, 1255, 845, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18-8.15 (m, 1H), 7.67-7.63 (m, 1H), 7.45-7.38 (m, 2H), 6.13 (t, J = 8 Hz, 1H), 5.68 (s, 1H), 5.04 (d, J = 2.4 Hz, 1H), 4.90 (d, J = 2 Hz, 1H), 2.21-2.17 (m, 2H), 2.13-2.09 (m, 2H), 1.75-1.69 (m, 2H), 1.64-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.7, 167.3, 155.2, 153.9, 133.4, 128.8, 128.0, 125.9, 125.5, 123.1, 117.5, 100.6, 89.7, 25.4, 24.9, 22.3, 21.8. Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%; Found: C, 71.23; H, 6.22%.

2-((1-Cyclopropylvinyl)oxy)-4*H*-chromen-4-one (94j): White gum; 180 mg, Yield: 79%; IR (KBr): 1695, 1275, 949, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18-8.16 (m, 1H), 7.66-7.62 (m, 1H), 7.42-7.38 (m, 2H), 5.83 (s, 1H), 4.84 (d, J = 2.4 Hz, 1H), 4.77 (d, J = 2.4 Hz, 1H), 1.64-1.57 (m, 1H), 0.83-0.77 (m, 2H), 0.75-0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 166.3, 158.4, 154.0, 133.5, 126.0, 125.6, 123.1, 117.5, 99.2, 91.0, 13.2, 6.2. Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%; Found: C, 73.58; H, 5.21%.

(*Z*)-2-((1-Phenylprop-1-en-1-yl)oxy)-4*H*-chromen-4-one+(*E*)-2-((1-phenylprop-1-en-1-yl)oxy)-4*H*-chromen-4-one (94k): Yellow gum; 216 mg, Yield: 78%; IR (KBr): 1682, 1225, 950, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15-8.12 (m, 0.32H), 8.11-8.09 (m, 0.91H), 7.67-7.64 (m, 0.26 H), 7.62-7.58 (m, 1.08 H), 7.50-7.47 (m, 3 H), 7.40-7.31 (m, 6H), 6.04-5.98 (m, 0.28H), 5.84-5.77 (m, 0.94H), 5.66 (s, 1H), 5.61 (s, 1H), 1.91 (d, J = 7.6 Hz, 3H), 1.83 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.4, 167.0, 153.9 (2C), 147.7, 147.4, 133.5, 133.4, 132.1, 129.3, 129.0, 128.7, 128.4, 125.9(2C), 125.5, 125.4, 124.7, 123.1, 117.5, 117.4, 116.2, 114.4, 90.6, 89.6, 12.9, 11.4. Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%; Found: C, 77.78; H, 5.02%.

6-Methyl-2-((1-phenylvinyl)oxy)-4*H*-chromen-4-one (94l): Yellow gum; 228 mg, Yield: 82%; IR (KBr): 1681, 1275, 815, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 1.6 Hz, 1H), 7.56-7.53 (m, 2H), 7.46-7.43 (m, 1H), 7.37-7.32 (m, 4H), 5.69 (s, 1H), 5.54 (d, J = 2.4 Hz, 1H), 5.18 (d, J = 2.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 166.3, 154.4, 152.1, 135.6, 134.6, 132.5, 129.9, 129.0, 125.4 (2C), 122.7, 117.2, 102.2, 91.0, 21.0. Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%; Found: C, 77.76; H, 5.17%.

6-Methyl-2-((1-(*p*-tolyl)vinyl)oxy)-4*H*-chromen-4-one (94m): Yellow gum; 233 mg, Yield: 80%; IR (KBr): 1681, 1277, 814, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 1.2 Hz,

1H), 7.45-7.42 (m, 3H), 7.32 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 5.68 (s, 1H), 5.47 (d, J = 2.4 Hz, 1H), 5.12 (d, J = 2.4 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 166.4, 154.5, 152.2, 140.1, 135.5, 134.6, 129.8, 129.7, 125.4, 125.3, 122.8, 117.2, 101.2, 91.0, 21.4, 21.0. Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52%; Found: C, 78.14; H, 5.63%.

2-((1-(4-Fluorophenyl)vinyl)oxy)-6-methyl-4*H*-chromen-4-one (94n): Yellow gum; 230 mg, Yield: 78%; IR (KBr): 1699, 1217, 946, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 1.2 Hz, 1H), 7.55-7.52 (m, 2H), 7.46-7.44 (m, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.08-7.03 (m, 2H), 5.69 (s, 1H), 5.46 (d, J = 2.8 Hz, 1H), 5.15 (d, J = 2.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 166.1, 163.7 (d, $^1J_{C\text{-}F}$ = 249 Hz), 153.6, 152.2, 135.7, 134.7, 128.8 (d, $^3J_{C\text{-}F}$ = 3 Hz), 127.4 (d, $^4J_{C\text{-}F}$ = 8 Hz), 125.5, 122.7, 117.2, 116.2 (d, $^2J_{C\text{-}F}$ = 22 Hz), 101.8, 91.2, 21.0. Anal. Calcd. for $C_{18}H_{13}FO_3$: C, 72.97; H, 4.42%; Found: C, 72.90; H, 4.34%.

6-Methyl-2-((1-(thiophen-3-yl)vinyl)oxy)-4*H*-chromen-4-one (94o): White gum; 215 mg, Yield: 76%; IR (KBr): 1672, 1165, 817, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 1.2 Hz, 1H), 7.46-7.42 (m, 2H), 7.34-7.31 (m, 2H), 7.23-7.21 (m, 1H), 5.75 (s, 1H), 5.40 (d, J = 2.8 Hz, 1H), 5.09 (d, J = 2.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 166.3, 152.2, 150.7, 135.6, 134.7(2C), 127.2, 125.4, 125.0, 123.3, 122.7, 117.2, 101.1, 90.9, 21.0. Anal. Calcd. for $C_{16}H_{12}O_3S$: C, 67.59; H, 4.25%; Found: C, 67.49; H, 4.17%.

2-((1-Cyclopropylvinyl)oxy)-6-methyl-4*H*-chromen-4-one (94p): White gum; 181 mg, Yield: 75%; IR (KBr): 1703, 1216, 948, 816 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.95 (m, 1H), 7.45-7.42 (m, 1H), 7.31-7.29 (m, 1H), 5.81 (s, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.75 (d, J = 2.8 Hz, 1H), 2.43 (s, 3H) 1.63-1.56 (m, 1H), 0.81-0.77 (m, 2H), 0.74-0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.7, 166.2, 158.5, 152.2, 135.5, 134.6, 125.4, 122.8, 117.2, 98.9, 91.0, 21.0, 13.2, 6.2. Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%; Found: C, 74.27; H, 5.74%.

6-Chloro-2-((1-phenylvinyl)oxy)-4*H*-chromen-4-one (94q): Yellow gum; 229 mg, Yield: 77%; IR (KBr): 1682, 1261, 817, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.10 (d, J = 2.4 Hz, 1H), 7.60-7.57 (m, 1H), 7.55-7.52 (m, 2H), 7.41-7.36 (m, 4H), 5.71 (s, 1H), 5.56 (d, J = 2.8 Hz, 1H), 5.20 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1, 166.5, 154.4, 152.2, 133.7, 132.3, 131.7, 130.1, 129.1, 125.6, 125.4, 124.2, 119.1, 102.5, 91.1. Anal. Calcd. for $C_{17}H_{11}ClO_3$: C, 68.35; H, 3.71%; Found: C, 68.45; H, 3.80%.

6-Chloro-2-((1-(*p*-tolyl)vinyl)oxy)-4*H*-chromen-4-one (94r): Yellow solid; 243 mg, Yield: 78%; mp. 64-66 °C; IR (KBr): 1720, 1264, 947, 816 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): 8.09 (d, J = 2.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.43-7.38 (m, 3H), 7.17 (d, J = 8 Hz, 1H), 5.69 (s, 1H), 5.49 (d,

J = 2.4 Hz, 1H), 5.13 (d, *J* = 2.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.0, 166.6, 154.4, 152.2, 140.3, 133.6, 131.6, 129.7, 129.5, 125.5, 125.3, 124.2, 119.1, 101.6, 91.0, 21.4. Anal. Calcd. for $C_{18}H_{13}ClO_3$: C, 69.13; H, 4.19%; Found: C, 69.19; H, 4.10%.

2-((1-(4-(*Tert*-butyl)phenyl)vinyl)oxy)-6-chloro-4*H*-chromen-4-one (94s): Yellow gum; 262 mg, Yield: 74%;); IR (KBr): 1682, 1265, 817, 775 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (d, *J* = 2.8 Hz, 1H), 7.60-7.57 (m, 1H), 7.47-7.44 (m, 2H),7.41-7.37 (m, 3H), 5.69 (s, 1H), 5.51 (d, *J* = 2.8 Hz, 1H), 5.14 (d, *J* = 2.8 Hz, 1H), 1.3 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1, 166.7, 154.4, 153.5, 152.2, 133.6, 131.6, 129.4, 126.0, 125.5, 125.1, 124.2, 119.2, 101.8, 91.0, 34.9, 31.3. Anal. Calcd. for $C_{21}H_{19}ClO_3$: C, 71.09; H, 5.40%; Found: C, 71.02; H, 5.31%.

6-Chloro-2-((1-(thiophen-3-yl)vinyl)oxy)-4*H*-chromen-4-one (94t): White solid; 231 mg, Yield: 76%; mp. 65-67 °C; IR (KBr): 1691, 1195, 822, 764 cm^{-1}^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, *J* = 2.8 Hz, 1H), 7.62-7.58 (m, 1H), 7.42-7.39 (m, 2H), 7.35-7.33 (m, 1H), 7.23-7.21 (m, 1H), 5.77 (s, 1H), 5.43 (d, *J* = 3.2 Hz, 1H), 5.11 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.2, 166.6, 152.2, 150.6, 134.4, 133.7, 131.7, 127.4, 125.6, 124.9, 124.2, 123.4, 119.2, 101.5, 90.8. Anal. Calcd. for $C_{15}H_9ClO_3S$: C, 59.12; H, 2.98%; Found: C, 59.04; H, 2.92%.

3.31. Mechanochemical synthesis of 4-hydroxy-3-thiomethylcoumarins using imidazolium zwitterionic molten salt

General procedure for the synthesis of compounds (96):

A grinding beaker (50 mL) and milling balls (4 × 10 mm) were set as a reaction chamber. For each reaction, a mixture of aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and thiol (1.2 mmol) along with 10 mol% of zwitterionic molten salt (**MS-1**) was milled for 1 h at 500 rpm at room temperature (a 30 min interval). After completion of the reaction (monitored by thin-layer chromatography), the obtained solid product was filtered off through a Büchner funnel, thoroughly washed with the mixture of ethanol and hexane (2:8) to remove the unreacted starting material, and recrystallized in a 9:1 mixture of ethanol and chloroform. When the product was not solid, the mixture of ethanol and hexane (2:8) was removed under reduced pressure *via* a rotary evaporator and the obtained crude product was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water (2 × 10 mL) and brine solution (2 × 5 mL) and dried over anhydrous Na2SO4. Then, it was concentrated under reduced pressure to obtain the crude residue which was subjected to column chromatography using petroleum ether−ethyl acetate as the eluent to obtain the analytically pure product.

4-Hydroxy-3-(phenyl(phenylthio)methyl)-2*H*-chromen-2-one (96a) [404]. Yield: 91%, 328 mg; white solid; mp 160−161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.30 (s, 1H), 7.92−7.90 (m, 1H), 7.54−7.46 (m, 5H), 7.38−7.23 (m, 8H), 6.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.7, 152.8, 136.9, 132.5, 132.1, 130.9, 129.6, 129.2, 128.5, 128.1, 124.1, 123.6, 116.6, 116.0, 102.3, 49.6.

4-Hydroxy-3-((phenylthio)(*p*-tolyl)methyl)-2*H*-chromen-2-one (96b) [404]. Yield: 87%, 326 mg; white solid; mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.31 (s, 1H), 7.95−7.92 (m, 1H), 7.57−7.53 (m, 1H), 7.51−7.49 (m, 2H), 7.43 (d, J = 8 Hz 2H), 7.34−7.28 (m, 5H), 7.19 (d, J = 8 Hz, 2H), 6.18 (s, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 162.7, 152.8, 138.5, 133.8, 132.5, 132.2, 130.9, 129.9, 129.6, 128.4, 128.0, 124.1, 123.6, 116.6, 116.1, 102.5, 49.3, 21.3.

4-Hydroxy-3-((2-methoxyphenyl)(phenylthio)methyl)-2*H*-chromen-2-one (96c). Yield: 84%, 328 mg; brown solid; mp 145−150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.64 (s, 1H), 7.96−7.94 (m, 1H), 7.52−7.47 (m, 4H), 7.32−7.28 (m, 4H), 7.24−7.22 (m, 2H), 6.97−6.93 (m, 2H), 6.32 (s, 1H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 162.5, 156.8, 152.6, 133.4, 132.1, 130.8, 129.7, 129.4, 128.0, 125.7, 123.9, 123.5, 121.2, 116.3, 116.2, 111.5, 102.4, 56.0, 45.7. Anal. Calcd for $C_{23}H_{18}O_4S$: C, 70.75; H, 4.65%. Found: C, 70.70; H, 4.60%.

4-Hydroxy-3-((4-methoxyphenyl)(phenylthio)methyl)-2*H*-chromen-2-one (96d). Yield: 88%, 343 mg; off-white solid; mp 115−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.30 (s, 1H), 7.92−7.89 (m, 1H), 7.55−7.50 (m, 1H), 7.47−7.42 (m, 4H), 7.31−7.27 (m, 3H), 7.25−7.23 (m, 2H), 6.88 (d, J = 8.8 Hz 2H), 6.14 (s, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 162.7, 159.7, 152.8, 132.5, 132.2, 130.8, 129.6, 129.3, 128.7, 128.4, 124.1, 123.6, 116.6, 116.1, 114.6, 102.5, 55.4, 49.1. Anal. Calcd for $C_{23}H_{18}O_4S$: C, 70.75; H, 4.65%. Found: C, 70.70; H, 4.71%.

3-((4-Chlorophenyl)(phenylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96e). Yield: 86%, 339 mg; white solid; mp 100−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.33 (s, 1H), 7.95−7.93 (m, 1H), 7.57−7.53 (m, 1H), 7.51−7.47 (m, 4H), 7.36−7.25 (m, 7H), 6.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 162.6, 152.8, 135.4, 134.3, 132.7, 131.6, 130.9, 129.7, 129.4, 129.3, 128.7, 124.2, 123.6, 116.6, 115.8, 101.9, 49.0. Anal. Calcd for $C_{22}H_{15}ClO_3S$: C, 66.92; H, 3.83%. Found: C, 66.85; H, 3.77%.

4-Hydroxy-3-(phenyl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96f) [404]. Yield: 89%, 333 mg; white solid; mp 134−135 °C (lit); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.42 (s, 1H), 7.94−7.92 (m, 1H), 7.52 (d, J = 7.6 Hz 3H), 7.40−7.28 (m, 6H), 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8 Hz, 2H),

6.11 (s, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.7, 152.9, 139.0, 137.1, 132.5, 131.5, 130.4, 129.2, 128.5, 128.3, 128.1, 124.1, 123.6, 116.6, 116.2, 102.4, 50.3, 21.3.

4-Hydroxy-3-(*p*-tolyl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96g). Yield: 88%, 342 mg; white solid; mp 140−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.43 (s, 1H), 7.95−7.92 (m, 1H), 7.54−7.50 (m, 1H), 7.43−7.38 (m, 4H), 7.31−7.28 (m, 1H), 7.24 (d, *J* = 8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 6.11 (s, 1H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 162.6, 152.8, 138.8, 138.3, 133.9, 132.4, 131.4, 130.3, 129.8, 128.4, 127.9, 124.0, 123.5, 116.5, 116.1, 102.5, 50.0, 21.2 (2C). Anal. Calcd for $C_{24}H_{20}O_3S$: C, 74.20; H, 5.19%. Found: C, 74.13; H, 5.13%.

4-Hydroxy-3-((4-methoxyphenyl)(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96h) [404]. Yield: 82%, 332 mg; white solid; mp 142−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.45 (s, 1H), 7.94−7.91 (m, 1H), 7.55−7.50 (m, 1H), 7.44−7.41 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.32−7.28 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8 Hz, 2H), 6.89−6.86 (m, 2H), 6.07 (s, 1H), 3.79 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 162.7, 159.6, 152.8, 138.9, 132.4, 131.4, 130.4, 129.3, 128.9, 128.4, 124.1, 123.6, 116.6, 116.2, 114.5, 102.6, 55.4, 49.8, 21.3.

4-Hydroxy-3-((4-hydroxyphenyl)(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96i) [404]. Yield: 67%, 261 mg; white solid; mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.5 (s, 1H), 7.97−7.95 (m, 1H), 7.58−7.54 (m, 1H), 7.40−7.32 (m, 5H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.09 (d, *J* = 8 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.06 (s, 1H), 5.71 (s, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 163.1, 156.0, 152.8, 138.9, 132.5, 131.4, 130.4, 129.5, 128.6, 128.4, 124.2, 123.6, 116.6, 116.2, 116.1, 102.5, 49.9, 21.3.

3-((4-Fluorophenyl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96j) [404]. Yield: 83%, 326 mg; white solid; mp 79−80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.47 (s, 1H), 7.95−7.92 (m, 1H), 7.56−7.47 (m, 3H), 7.38 (d, *J* = 8 Hz, 2H), 7.33−7.29 (m, 1H), 7.24 (d, *J* = 8 Hz, 1H), 7.09−7.01 (m, 4H), 6.07 (s, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.6, 162.6 (d, $^1J_{C–F}$ = 246 Hz), 152.8, 139.1, 132.8 (d, $^3J_{C–F}$ = 3 Hz), 132.6, 131.5, 130.5, 129.9 (d, $^4J_{C–F}$ = 8 Hz), 128.0, 124.2, 123.6, 116.6, 116.1 (d, $^2J_{C–F}$ = 22 Hz), 116.0, 102.2, 49.6, 21.2.

3-((4-Chlorophenyl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96k) [404]. Yield: 90%, 368 mg; white solid; mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.43 (s, 1H), 7.95−7.92 (m, 1H), 7.55−7.51 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.33−7.28 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.06 (s, 1H), 2.27 (s, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ 163.1, 162.6, 152.8, 139.2, 135.6, 134.3, 132.6, 131.5, 130.5, 129.5, 129.3, 127.9, 124.2, 123.6, 116.6, 116.0, 101.9, 49.7, 21.2.

3-((2-Bromophenyl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96l). Yield: 80%, 362 mg; white solid; mp 180−185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.08 (s, 1H), 8.01−7.99 (m, 1H), 7.68−7.66 (m, 1H), 7.57−7.53 (m, 1H), 7.50 (d, *J* = 8 Hz, 2H), 7.37−7.33 (m, 2H), 7.27−7.23 (m, 2H), 7.19−7.17 (m, 1H), 7.11 (d, *J* = 8 Hz, 2H), 6.27 (s, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 162.2, 153.0, 139.5, 136.3, 134.1, 132.6, 131.9, 130.5, 130.0, 128.7, 128.1, 125.4, 124.1, 123.7, 116.6, 116.1, 101.6, 51.9, 21.3. Anal. Calcd for $C_{23}H_{17}BrO_3S$: C, 60.93; H, 3.78%. Found: C, 60.97; H, 3.70%.

3-((4-Bromophenyl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96m) [404]. Yield: 87%, 394 mg; white solid; mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.39 (s, 1H), 7.94−7.91 (m, 1H), 7.56−7.52 (m, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.39−7.36 (m, 4H), 7.33−7.29 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.032 (s, 1H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 162.6, 152.9, 139.3, 139.2, 132.7, 132.3, 131.6, 130.5 129.8, 127.8, 124.2, 123.6, 122.5, 116.6, 116.0, 101.9, 49.8, 21.3.

4-Hydroxy-3-((4-(methylthio)phenyl)(*p*-tolylthio)methyl)-2*H*chromen-2-one (96n). Yield: 76%, 320 mg; greenish-white solid; mp 151−155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.42 (s, 1H), 7.94−7.92 (m, 1H), 7.55−7.50 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 3H), 7.07 (d, *J* = 8 Hz, 2H), 6.09 (s, 1H), 2.47 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 162.6, 152.8, 139.1, 139.0, 133.6, 132.5, 131.5, 130.4, 128.5, 128.2, 126.9, 124.1, 123.6, 116.5, 116.1, 102.2, 49.9, 21.2, 15.7. Anal. Calcd for $C_{24}H_{20}O_3S_2$: C, 68.54; H, 4.79%. Found: C, 68.54; H, 4.79%.

4-Hydroxy-3-(naphthalen-1-yl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96o). Yield: 84%, 356 mg; white solid; mp 203−205c °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.52 (s, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.00−7.97 (m, 1H), 7.92−7.89 (m, 1H), 7.85−7.83 (m, 1H), 7.70−7.66 (m, 1H), 7.59−7.35 (m, 3H), 7.49−7.47 (m, 2H), 7.42−7.27 (m, 3H), 7.14−7.12 (m, 2H), 6.81 (s, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 162.6, 152.9, 139.0, 134.4, 132.5, 132.0, 131.3, 131.0, 130.5, 129.7, 129.2, 128.9, 127.1, 126.3, 125.4, 124.1, 123.7, 123.6, 116.6, 116.2, 102.5, 47.1, 21.3. Anal. Calcd for $C_{27}H_{20}O_3S$: C, 76.39; H, 4.75%. Found: C, 76.45; H, 4.83%.

4-Hydroxy-3-(naphthalen-2-yl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96p) [404]. Yield: 81%, 344 mg; white solid; mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.47 (s, 1H), 7.98−7.96 (m, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.84−7.79 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 1H),

7.57−7.52 (m, 1H), 7.49−7.46 (m, 2H), 7.43 (d, *J* = 8 Hz, 2H), 7.32 (t, *J* = 7.6 Hz 1H), 7.26 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8 Hz, 2H), 6.28 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 162.7, 152.9, 139.0, 134.4, 133.4, 133.2, 132.5, 131.6, 130.5, 129.1, 128.3, 128.2, 127.8, 126.7, 126.6, 126.5, 126.2, 124.1, 123.7, 116.6, 116.2, 102.3, 50.6, 21.3.

3-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96q). Yield: 89%, 442 mg; white solid; mp 125−135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.12 (s, 1H), 8.00−7.97 (m, 1H), 7.57−7.53 (m, 1H), 7.47 (d, *J* = 8 Hz, 2H), 7.35−7.31 (m, 1H), 7.27−7.24 (m, 1H), 7.10 (d, *J* = 9.6 Hz, 3H), 6.82 (s, 1H), 6.17 (s, 1H), 5.97−5.94 (m, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 162.2, 153.0, 148.5, 147.9, 139.5, 132.6, 132.0, 130.6, 129.2, 128.0, 124.2, 123.7, 116.7, 116.3, 116.1, 113.9, 108.4, 102.2, 101.8, 52.1, 21.3. Anal. Calcd for $C_{24}H_{17}BrO_5S$: C, 57.96; H, 3.45%. Found: C, 57.88; H, 3.42%.

3-(Furan-3-yl(*p*-tolylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96r). Yield: 61%, 222 mg; brown gummy; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.78 (s, 1H), 7.90−7.88 (m, 1H), 7.54−7.50 (m, 1H), 7.44 (s, 1H), 7.40−7.39 (m, 1H), 7.37−7.30 (m, 2H), 7.29−7.27 (m, 1H), 7.26−7.22 (m, 1H), 7.05 (d, *J* = 8 Hz, 2H), 6.51 (t, *J* = 0.8 Hz, 1H), 6.04 (s, 1H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 162.6, 152.8, 144.0, 140.6, 139.0, 132.6, 131.9, 130.3, 129.9, 129.8, 127.7, 124.1, 123.5, 122.0, 116.6, 116.0, 110.2, 102.6, 41.2, 21.2. Anal. Calcd for $C_{21}H_{16}O_4S$: C, 69.21; H, 4.43%. Found: C, 69.26; H, 4.49%.

3-(Cyclohexyl(phenylthio)methyl)-4-hydroxy-2*H*-chromen-2-one (96s) [404]. Yield: 68%, 249 mg; colorless gummy, column chromatography done (eluent: ethyl acetate/petroleum ether = 3/97); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.88 (s, 1H), 7.74−7.72 (m, 1H), 7.39−7.34 (m, 1H), 7.28−7.25 (m, 2H), 7.16−7.02 (m, 5H), 4.80 (d, *J* = 6.8 Hz, 1H), 2.00−1.98 (m, 1H), 1.93−1.84 (m, 1H), 1.70−1.63 (m, 3H), 1.56−1.52 (m, 1H), 1.16−1.09 (m, 4H), 0.80−0.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.3, 162.4, 152.6, 132.1, 131.8, 130.7, 129.3, 129.1, 127.8, 123.9, 123.3, 116.3, 116.0, 102.7, 51.7, 42.5, 31.1, 31.0, 26.3, 26.2, 26.0.

4-Hydroxy-3-(1-(*p*-tolylthio)butyl)-2*H*-chromen-2-one (96t). Yield: 82%, 279 mg; colorless gummy; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.93 (s, 1H), 7.85−7.83 (m, 1H), 7.50−7.46 (m, 1H), 7.28−7.20 (m, 4H), 7.02−7.00 (m, 2H), 4.97 (t, *J* = 7.6 Hz, 1H), 2.22 (s, 3H), 1.95−1.89 (m, 2H), 1.62−1.49 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.4, 152.6, 138.3, 132.1, 131.2,

130.2, 127.9, 123.9, 123.3, 116.4, 116.2, 103.7, 45.5, 35.8, 21.1, 20.9, 13.9. Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.56; H, 5.92%; found: C, 70.51; H, 5.84%.

4-Hydroxy-3-((4-methoxyphenylthio)(*p*-tolyl)methyl)-2*H*-chromen-2-one (96u). Yield: 87%, 352 mg; white solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.46 (s, 1H), 7.96−7.94 (m, 1H), 7.55−7.50 (m, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 6.80−6.78 (m, 2H), 6.02 (s, 1H), 3.73 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 162.6, 160.3, 152.8, 138.2, 134.1, 134.0, 132.4, 129.8, 127.9, 124.0, 123.5, 122.3, 116.5, 116.1, 115.1, 102.5, 55.3, 51.1, 21.2. Anal. Calcd for $C_{24}H_{20}O_4S$: C, 71.27; H, 4.98%. Found: C, 71.32; H, 4.94%.

3-(((4-Chlorophenyl)thio)(*p*-tolyl)methyl)-4-hydroxy-2*H*-chromen-2-one (96v). Yield: 90%, 368 mg; white solid; mp 162−165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.03 (s, 1H), 7.94−7.92 (m, 1H), 7.59−7.55 (m, 1H), 7.45−7.41 (m, 4H), 7.35−7.26 (m, 4H), 7.21−7.19 (m, 2H) 6.19 (s, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 162.7, 152.8, 138.6, 134.6, 133.3, 132.7, 132.2, 130.7, 130.0, 129.8, 127.9, 124.2, 123.5, 116.6, 115.9, 102.2, 49.4, 21.2. Anal. Calcd for $C_{23}H_{17}ClO_3S$: C, 67.56; H, 4.19%. Found: C, 67.64; H, 4.23%.

4-Hydroxy-3-((4-methoxyphenyl)(naphthalen-2-ylthio)methyl)-2*H*-chromen-2-one (96w). Yield: 92%, 405 mg; white solid; mp 155−159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.34 (s, 1H), 7.94−7.89 (m, 2H), 7.77−7.72 (m, 3H), 7.57−7.44 (m, 6H), 7.28−7.19 (m, 2H), 6.92−6.90 (m, 2H), 6.33 (s, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 162.7, 159.7, 152.8, 133.7, 132.7, 132.5, 129.8, 129.6, 129.4, 128.5, 127.8, 127.7, 127.4, 126.9, 126.8, 124.1, 123.5, 116.5, 116.0, 114.6, 102.5, 55.4, 48.8. Anal. Calcd for $C_{27}H_{20}O_4S$: C, 73.62; H, 4.58%. found: C, 73.69; H, 4.67%.

3-((Benzylthio)(phenyl)methyl)-4-hydroxy-2*H*-chromen-2-one (96x) [404]. Yield: 79%, 296 mg; white solid; mp 110−112 °C; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.64 (s, 1H), 7.94−7.91 (m, 1H), 7.57−7.52 (m, 1H), 7.38−7.36 (m, 2H), 7.32−7.27 (m, 4H), 7.25−7.23 (m, 5H), 7.17−7.14 (m, 1H), 5.62 (s, 1H), 3.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 162.4, 152.9, 137.5, 135.9, 132.4, 128.9, 128.8, 128.7, 128.1, 127.8, 127.6, 124.0, 123.5, 116.4, 116.0, 101.4, 45.9, 37.6.

3-((Benzylthio)(4-methoxyphenyl)methyl)-4-hydroxy-2*H*-chromen-2-one (96y). Yield: 88%, 356 mg; greenish semisolid; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.65 (s, 1H), 7.94−7.92 (m, 1H), 7.60−7.56 (m, 1H), 7.35−7.30 (m, 4H), 7.28−7.26 (m, 4H), 7.19−7.17 (m, 1H), 6.83−6.80 (m, 2H), 5.58 (s, 1H), 3.85

(s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.5, 159.4, 153.0, 136.0, 132.5, 129.5, 129.1, 128.9, 128.8, 127.7, 124.1, 123.5, 116.5, 116.1, 114.4, 101.7, 55.3, 45.5, 37.7. Anal. Calcd for $C_{24}H_{20}O_4S$: C, 71.27; H, 4.98%. Found: C, 71.33; H, 4.94%.

3-((Benzylthio)(4-chlorophenyl)methyl)-4-hydroxy-2*H*-chromen-2-one (96z). Yield: 89%, 364 mg; colorless semisolid; column chromatography (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 7.88−7.85 (m, 1H), 7.53−7.49 (m, 1H), 7.28−7.22 (m, 4H), 7.20−7.16 (m, 6H), 7.12−7.09 (m, 1H), 5.50 (s, 1H), 3.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.3, 162.3, 152.9, 136.1, 135.6, 133.9, 132.6, 129.2, 129.0, 128.8, 127.7, 124.1, 123.5, 116.5, 115.9, 101.0, 45.2, 37.7. Anal. Calcd for $C_{23}H_{17}ClO_3S$: C, 67.56; H, 4.19%. Found: C, 67.63; H, 4.12%.

3-((Cyclohexylthio)(4-methoxyphenyl)methyl)-4-hydroxy-2*H*chromen-2-one (96a'). Yield: 70%, 277 mg; greenish semisolid; column chromatography done (eluent: ethyl acetate/petroleum ether = 10/90); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.03 (s, 1H), 7.96−7.94 (m, 1H), 7.59−7.55 (m, 1H), 7.35−7.30 (m, 4H), 6.84−6.81 (m, 2H), 5.71 (s, 1H), 3.76 (s, 3H), 2.84−2.78 (m, 1H), 2.17−2.13 (m, 1H), 1.89−1.71 (m, 4H), 1.31−1.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 162.7, 159.4, 153.0, 132.4, 130.2, 129.1, 124.1, 123.6, 116.6, 116.4, 114.4, 102.3, 55.4, 44.8, 43.8, 33.1, 32.7, 25.7. Anal. Calcd for $C_{23}H_{24}O_4S$: C, 69.67; H, 6.10%. Found: C, 69.77; H, 6.15%.

3-((Butylthio)(*p*-tolyl)methyl)-4-hydroxy-2*H*-chromen-2-one (96b'). Yield: 74%, 262 mg; colorless semisolid; column (eluent: ethyl acetate/petroleum ether = 5/95); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.88 (s, 1H), 7.96−7.94 (m, 1H), 7.59−7.55 (m, 1H), 7.35−7.30 (m, 4H), 7.12 (d, J = 8 Hz, 2H), 5.69 (s, 1H), 2.72−2.67 (m, 1H), 2.61−2.56 (m, 1H), 2.30 (s, 3H), 1.69−1.64 (m, 2H), 1.47−1.37 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 162.8, 153.0, 138.0, 135.0, 132.5, 129.7, 127.7, 124.1, 123.6, 116.6, 116.2, 101.5, 45.6, 32.5, 30.7, 22.0, 21.2, 13.7. Anal. Calcd for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26%. Found: C, 71.26; H, 6.21%.

4-Hydroxy-6-methyl-3-(phenyl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96c'). Yield: 93%, 361 mg; white solid; mp 132-135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.40 (s, 1H), 7.72 (s, 1H), 7.53−7.51 (m, 2H), 7.40−7.38 (m, 2H), 7.35−7.30 (m, 3H), 7.13 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8 Hz, 2H), 6.13 (s, 1H), 2.42 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.8, 151.0, 138.9, 137.0, 133.8, 133.5, 131.5, 130.4, 129.1, 128.4, 128.3, 128.1, 123.2, 116.3, 115.7, 102.1, 50.2, 21.2, 21.0. Anal. Calcd for $C_{24}H_{20}O_3S$: C, 74.20; H, 5.19%. Found: C, 74.24; H, 5.11%.

4-Hydroxy-3-((4-methoxyphenyl)(*p*-tolylthio)methyl)-6-methyl-2*H*-chromen-2-one (96d'). Yield: 83%, 347 mg; white solid; mp 142−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.40 (s, 1H),

7.70 (d, *J* = 1.2 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = Hz, 2H), 7.34−7.31 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8 Hz, 2H), 6.88−6.85 (m, 2H), 6.07 (s, 1H), 3.78 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 159.6, 151.0, 138.9, 138.8, 133.8, 133.4, 132.5, 131.4, 130.4, 129.4, 128.9, 128.5, 123.2, 116.3, 115.8, 114.5, 55.4, 49.8, 21.3, 21.1. Anal. Calcd for $C_{25}H_{22}O_4S$: C, 71.75; H, 5.30%. Found: C, 71.70; H, 5.37%.

3-((4-Chlorophenyl)(*p*-tolylthio)methyl)-4-hydroxy-6-methyl-2*H*chromen-2-one (96e'). Yield: 89%, 376 mg; white solid; mp138-142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.37 (s, 1H), 7.71 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.38−7.29 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.06 (s, 1H), 2.42 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 162.8, 151.0, 139.2, 135.6, 134.3, 134.0, 133.7, 131.6, 130.5, 129.5, 129.3, 127.9, 123.2, 116.4, 115.6, 101.8, 49.7, 21.2, 21.0. Anal. Calcd for $C_{24}H_{19}ClO_3S$: C, 68.16; H, 4.53%. Found: C, 68.10; H, 4.61%.

6-Chloro-4-hydroxy-3-(phenyl(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96f'). Yield: 90%, 368 mg; white solid; mp 145−148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 7.9 (d, *J* = 1.6 Hz, 1H), 7.51−7.49 (m, 2H), 7.47−7.45 (m, 1H), 7.39−7.31 (m, 5H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8 Hz, 2H), 6.08 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 161.9, 151.2, 139.2, 136.7, 132.4, 131.5, 130.5, 130.3, 129.7, 129.2, 128.6, 128.0, 123.2, 118.0, 117.2, 103.2, 50.4, 21.3. Anal. Calcd for $C_{23}H_{17}ClO_3S$: C, 67.56; H, 4.19%. Found: C, 67.67; H, 4.24%.

6-Chloro-4-hydroxy-3-((4-methoxyphenyl)(*p*-tolylthio)methyl)-2*H*-chromen-2-one (96g'). Yield: 65%, 285 mg; white solid; mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.55 (s, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.47−7.44 (m, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.89−6.86 (m, 2H), 6.02 (s, 1H), 3.79 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1, 161.7, 159.8, 151.2, 139.1, 132.4, 131.5, 130.5, 129.7, 129.3, 128.6, 128.2, 123.2, 118.0, 117.3, 114.6, 103.5, 55.5, 49.9, 21.3. Anal. Calcd for $C_{24}H_{19}ClO_4S$: C, 65.67; H, 4.36%. Found: C, 65.77; H, 4.43%.

6-Chloro-3-((4-chlorophenyl)(*p*-tolylthio)methyl)-4-hydroxy-2*H*chromen-2-one (96h'). Yield: 91%, 403 mg; white solid; mp 138−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 10.52 (s, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.48−7.45 (m, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 7.33−7.30 (m, 2H), 7.17 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8 Hz, 2H), 6.02 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 161.9, 151.2, 139.4, 135.3, 134.5, 132.6, 131.6, 130.5, 129.8, 129.4, 129.3, 127.6, 123.2, 118.1, 117.1, 102.8, 49.9, 21.3. Anal. Calcd for $C_{23}H_{16}Cl_2O_3S$: C, 62.31; H, 3.64%. Found: C, 62.38; H, 3.71%.

7-(Diethylamino)-4-hydroxy-3-(((4-methoxyphenyl)thio)(ptolyl)methyl)-2*H*-chromen-2-one 96i'). Yield: 85%, 403 mg; yellow solid; mp 112−115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 4 Hz, 1H), 7.44−7.40 (m, 4H), 7.14 (d, *J* = 8 Hz, 2H), 6.79 7.70 (d, *J* = 8 Hz, 2H), 6.60 (d, *J* = 8 Hz, 1H), 6.39 (s, 1H), 6.00 (s, 1H), 3.75 (s, 1H), 3.42−3.37 (m, 4H), 2.32 (s, 3H), 1.19 (t, *J* = 12 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 163.6, 160.0, 155.3, 151.1, 137.8, 134.7, 133.9, 132.7, 129.9, 129.5, 127.9, 124.4, 122.8, 114.9, 108.4, 104.2, 96.9, 55.3, 50.8, 44.8, 21.1, 12.4. Anal. Calcd for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.95%. Found: C, 70.78; H, 6.25; N, 2.86%.

CONCLUSIONS

The summary results obtained in the dissertation work on the study of the processes of direct functionalization of C(H)C and C(H)Y (Y = heteroatom) bond and concomitant transformations in the series of aziri(di)nes and epoxides, as well as their precursors and/or products of their transformations (styrene, acetylene, chalcones, 1,4-quinones, aldehydes and azomethines), the established patterns and conclusions and provisions formulated on their basis **can be considered as a significant scientific achievement in a field of organic chemistry**, which consists in the development of "green"/rational methods for the synthesis of biologically active molecules/drugs or their precursors/analogues, as well as important organic synthons, which are, as a rule, inaccessible by traditional synthetic methods. The approach is based on a detailed analysis of the possible directions of transformation of the above-mentioned substrates in various conditions, the identification of patterns of the "structure-property" type, and the establishment of patterns of reactions. The following important results were obtained as part of the work:

1. Transformations of aziri(di)nes and epoxides in reactions with *C-,N-,S-, O*-centered reagents, as well as halogenating agents, have been studied in details:

1.1. The possibility of direct C(sp^3)-H acyloxylation in 2-arylazirines under photoactivation conditions has been demonstrated for the first time;

1.2. The self-catalyzed synthesis of *N*-acyl-/*N*-formyl-*α*-aminoketones, as important synthons, has been demonstrated by the interaction of 3-aryl-2*H*-azirines/2-Me/Ph-3-aryl-2*H*-azirines with formic acid, as well as other organic acids;

1.3. The regioselective opening of the cycle in aziridines under the action of *C-,S-,O-* and *N*-nucleophiles catalyzed by Lewis and Brønsted acids, as well as CuO nanoparticles, has been demonstrated with the formation of *β*-substituted amines;

1.4. A method has been developed for the synthesis of substituted oxazolidines by AgOTf-catalyzed nucleophilic ring opening in aziridines in the absence of other external synthons;

1.5. Methods have been developed for the production of poorly available *β*-halogenated amines and *β*-haloalcohols by opening the aziridine or epoxy ring under the action of halogenating agents, including, for the first time, under the action of such a typical ones as allyl zinc halides generated *in situ*;

1.6. A method has been developed for obtaining *β*-(nitrooxy)-substituted *N*-Ts-amines by heating *N*-Ts-substituted aziridines with commercially available $Zn(NO_3)_2*6H_2O$ under the solvent-free conditions;

1.7. A method has been developed for the synthesis of substituted imidazoles by $HClO_4$-catalyzed opening of the aziridine ring under the action of nitriles under conditions of mechanosynthesis.

2. Transformations of azomethines and their derivatives in reactions with *C-,N-O*-centered reagents were studied and the possibilities of obtaining extensive series of acyclic derivatives, such as tertiary amines, 2,2'-(arylmethylene)bis(1*H*-pyrroles), 3,3'-(arylmethylene)bis(1*H*-indoles), as well as promising heterocycles, such as dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones, 1,2-disubstituted-1*H*-benzo[*d*]imidazoles, quinolines, were demonstrated.

3. Transformations of compounds with multiple bonds (ethylenes, acetylenes, *α,β*-unsaturated compounds, *etc*.) in reactions with *C-,N-,S-,O*-centered reagents, as well as halogenating agents, have been studied:

3.1. A wide range of important oranic synthons have been synthesized that are inaccessible by other methods, namely *vicinal* diiodolkanes, *β*-iodohydrins, their esters and acetates, *α*-acetoxyketones, *α*-sulfonylaminoketones, as well as cyclic products: cyclic acetals, enantiomerically pure 1,4-dioxanes, C3-benzylated coumarins, pyrano[3,2-*c*]coumarins, 4-hydroxy-3-thiomethylcoumarins, substituted 1,4-naphthoquinones and others;

3.2. Previously undescribed *O*-vinylation of the oxygen atom in 4-hydroxycoumarins under the action of terminal acetylenes was discovered;

3.3. The possibility of obtaining practically and biologically important selenoesters by reaction of *α*-aminocarbinyl compounds with diselenides has been demonstrated for the first time.

4. Using quantum chemical methods, the reactivity of the compounds studied in the work was evaluated and general patterns were revealed.

5. The biological activity of the obtained compounds was evaluated using molecular docking and *in silico* modeling methods and the most promising representatives were selected.

Recommendations and prospects for further development of the topic:

Among the obtained compounds, the search for ligands for metal cations, as well as potential fluorophores and chemosensors, is promising. Also, according to *in silico* screening data, it is advisable to search for compounds with antiviral as well as antitumor activity in the ranks of the obtained compounds. It is also necessary to expand the boundaries of the applicability of reactions under conditions of mechanosynthesis and catalyzed by ionic liquids, for example, for the implementation of multicomponent processes, including stereoselective reactions.

List of basic abbreviations

CAN	ceric ammonium nitrate
BAIL	Brønsted acidic ionic liquid
BDMS	bromodimethylsulfonium bromide
BHT	2,6-di-tertbutyl-4-methylphenol
CD	cyclodextrin
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	9,l0-dicyanoanthracene
DCE	1,2-dichloroethane
DCM	dichloromethane
DCN	1,4-naphthalenedicarbonitrile
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEM	diethyl malonate
DMA	dimethylacetamide
DMF	dimethylformamide
DMM	dimethyl malonate
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
EDA	ethyl diazoacetate
IBA	*o*-iodosobenzoic acid
IBX	*o*-iodoxybenzoic acid
IL	ionic liquid
OPD	*o*-phenylenedialdehyde
MCR	multicomponent reaction
MS	molten salt
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NPs	nanoparticles
PET	photoinduced electron transfer
PIDA	(diacetoxyiodo)benzene, phenyliodine(III) diacetate

PTSA	*p*-toluenesulfonic acid
TBAI	tetrabutylammonium iodide
TBDMSH	*tert*-butyldimethylsilane
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1- piperidinyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMGT	*N,N,N,N*-tetramethylguanidinium trifluoroacetate
TMGTf	*N,N,N,N*-tetramethylguanidinium triflate

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