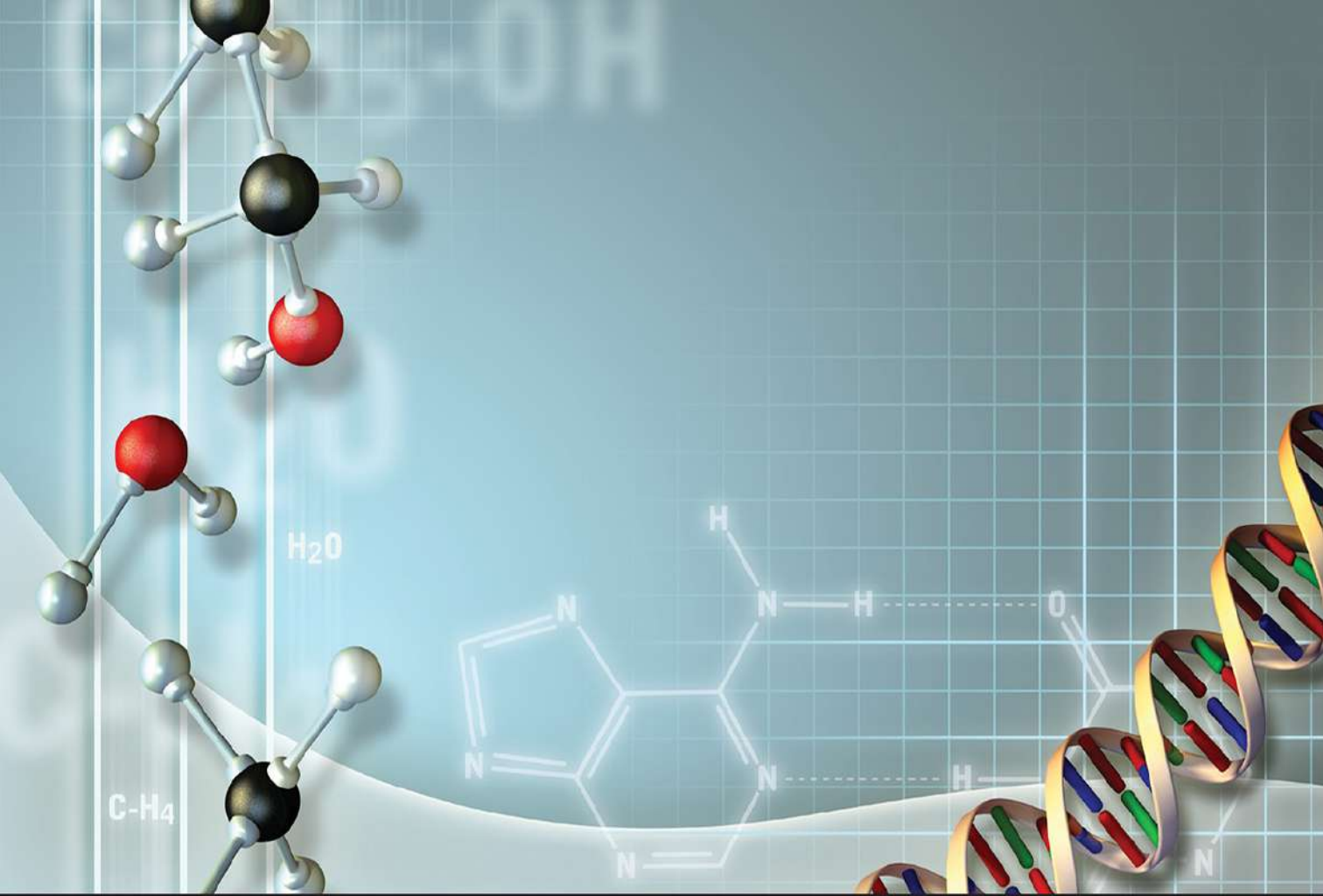

N-Sulfonated-*N*-Heterocycles

Synthesis, Chemistry, and Biological Applications

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Wafaa A. Zaghary is a Professor of Pharmaceutical Chemistry, the head and founder of the Pharmaceutical Chemistry Department, Faculty of Pharmacy, Helwan University. She is one of the expert Egyptian medicinal chemists, especially in the design and synthesis of new chemical scaffolds targeting cancer. In addition, she had been involved in the nano-nuclear pharmacy research and radiopharmaceutical fields. Prof. Zaghary with her group had discovered a novel tumor imaging agent with nano-graphene oxide sheets (2022), DNA gyrase and topoisomerase IV inhibitors (2021), Novel thienopyrimidine analogs as potent mGR-1 inhibitors with anticancer activity (2021), coumarin-based lead compound with CDK-4 inhibitory and anticancer activity (2021), Nano-selenium platforms as protective agents for hepatocellular carcinoma (2021), new aldose reductase inhibitors with anticancer action (2019), potential EGFR inhibitors (indazole, quinazoline, and quinolones) (2019). She has been involved in many research projects (Helwan University), (King Saud University), and (National Research Centre in Egypt). In 2018, She received the "outstanding research award" at Helwan University.

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Nadia H. Metwally is a Professor of Organic Chemistry in the Faculty of Science, Cairo University. Her research interests include the synthesis of N-sulfonated heterocyclic compounds and their applications, green chemistry, and medicinal chemistry. She supervised the work of

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Mona O. Sarhan is a lecturer of Radiopharmaceutical Chemistry at the Egyptian Atomic Energy Authority and an IAEA trained Radio-pharmacist. A member of the quality control team in the Egyptian-Chinese project for the production of Gel 99m-Technitium generators. Since 2018 she has been a visiting lecturer at different Egyptian Universities teaching medicinal chemistry and the basic concepts of drug design. Currently, her research interest links the fields of medicinal chemistry, organic chemistry, rational design, and radio-pharmacy to seek an opportunity to develop targeted therapeutics.

Elshimaa M. Abdelhafez, is Associate Professor of Medicinal Chemistry, Faculty of Pharmacy, Minia University, Minia, Egypt. In 2008, she received her master's degree from the Faculty of Pharmacy, Minia University, meanwhile, in 2013; her Ph.D. was in pharmaceutical medicinal chemistry as a channel scholarship between wake forest university, North Carolina, USA, and Minia University, Minia, Egypt. She has earned six national awards for publication from Minia University for the period 2016 to 2021. She published 28 works of literature in various international journals and 7 national papers. She writes and develops educational materials and contributes to teaching special topics in organic synthesis and medicinal chemistry for 18 years.

Rasha E. Elsayed, a senior research assistant at American University in Cairo (AUC), obtained her MSc degree in organic chemistry from Helwan University in 2019 under the supervision of Professor Galal Elgemeie. Her master research focused on the preparation of biologically active sulfonamide analogs and loading the most potent antibacterial compounds into nanofiber delivery systems for their use in wound healing. From 2017 till now, she worked as a research assistant on two scientific projects at the laboratory of Professor Tarek Madkour, at AUC, where she developed biodegradable polymer composites, in addition to functionalization of natural polymers. One of these projects is awarded the Silver Medal from the Academy of Scientific Research and Technology in 2018.

Chapter 1

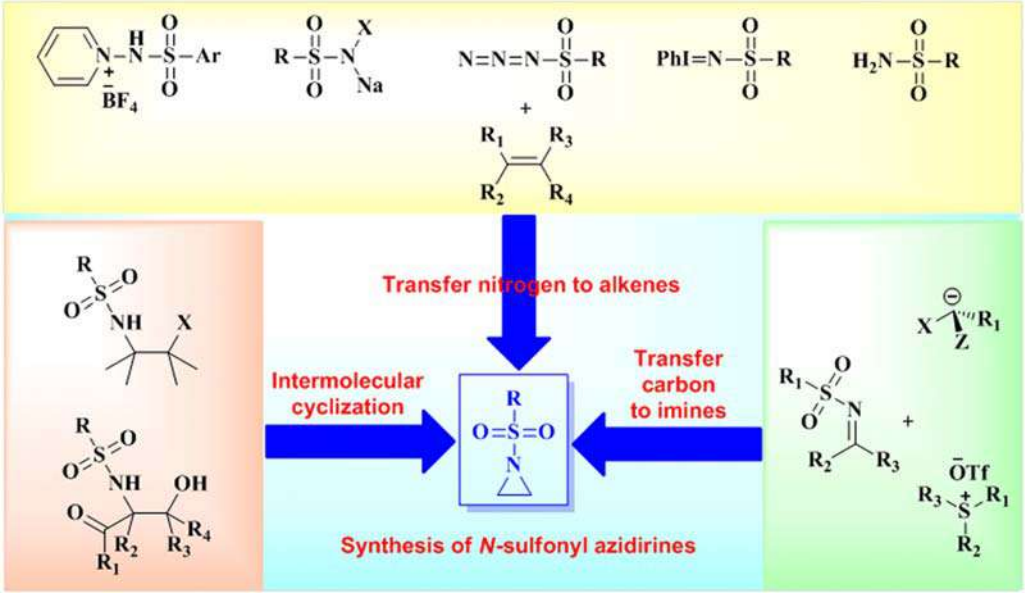
Synthesis of *N*-sulfonated aziridines

1.1 Introduction

Aziridines, three-membered aza-heterocycles, are fascinating compounds in organic synthesis. They function in some chemical reactions as precursors for specific end products and in others as target compounds to be synthesized. The significance of organic synthesis of aziridines is due to the complexity of synthesizing these three-membered rings [1−3]. Indeed, tremendous attention toward synthetic approaches for the construction of the aziridinyl system is due to the biological properties of some naturally occurring compounds containing such ring system [4−8] as well as the high strain of aziridinyl rings that make them willing to facilely undergo ring cleavage reactions for the synthesis of several useful compounds, including amines, amino alcohols, amino acids derivatives and other aza-heterocycles [9−11]. Nowadays more than before, many efficient synthetic methods have been developed for the preparation of aziridine-containing compounds [12−21]. Several reviews in the literature concerning the prepration and chemistry of aziridines have been published [22−26]. A review on the synthesis as well as the chemistry of ethynylaziridines and vinylaziridines was reported by Ohno [27] in 2014. At the same year, Leonardo et al. [28] recovered the latest progress in the stereoselective synthesis of aziridines. In 2016, an interesting review was demonstrating the substantial role of the cycloadditions of aziridines in synthesizing unsaturated *N*-heterocycles [29].

Among various functionalized aziridines, *N*-sulfonyl aziridines, in particularly, displayed numerous of transformations due to the ring strain of these aza-heterocycles and their electron-deficient nitrogen atom because of the presence of an electron-withdrawing sulfonyl group.

In this chapter, we reviewed the non-stereoselective and stereoselective preparation of *N*-sulfonyl aziridines focusing on pioneering synthetic approaches, mechanistic insights as well as their limitations, and recent advances in this field. The main strategies are presented for the construction of *N*-sulfonyl aziridine rings based on the transferring of nitrogen to alkenes, transferring of carbon to *N*-sulfonyl imines, and intramolecular cyclization of amine derivatives (Scheme 1.1). Herein, we focused primarily on presenting a detailed discussion on the aforementioned synthetic strategies.



SCHEME 1.1 Main synthetic strategies to *N*-sulfonyl aziridines.

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00006-9

1.2 Synthesis of *N*-sulfonated aziridines via transferring of nitrogen to alkenes

The main route for the construction of *N*-sulfonyl aziridines involves the transfer of nitrogen from suitable source nitrogen to alkenes. Different nitrogen sources under catalysis by either proper metal complexes or photoredox formed active species such as the electrophilic nitrene and nitrogen-centered radical species. The addition of such species to alkenes could facilely produce *N*-sulfonyl aziridines in good yield.

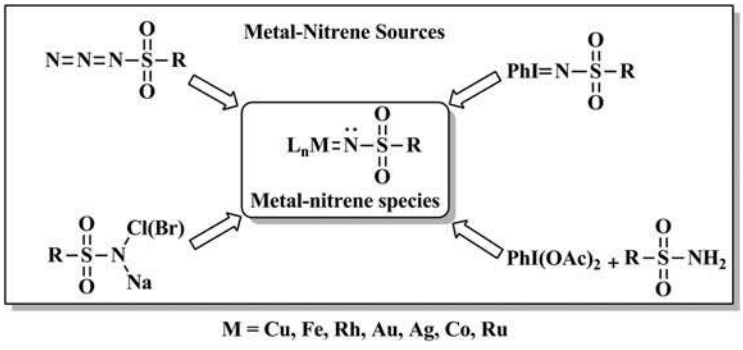
1.2.1 The addition of nitrene species to alkenes

Nitrenes, the nitrogen analog of carbenes, are considered reactive electrophiles because their nitrogen bears two electron lone pairs (electron-deficient nitrogen) and one electron-withdrawing substituent (EWG). The reactive nitrene intermediates are generated from diverse nitrene sources such as sulfonylimino iodinanes, sulfonamides, *N*-sulfonyl azides, and haloamine-T. This synthetic strategy could be achieved by utilizing a transition metals-based catalyst including copper, iron, rhenium, gold, cobalt, and rhodium. Usually, the aziridination of alkenes was achieved by utilizing transition metals (copper, iron, rhenium, gold, cobalt, and rhodium) complexing with suitable ligands (Ln) such as bis-oxazolines, phthalocyanines, and porphyrins. The use of chiral ligands in the aziridination process was essential for the production of extremely enantioenriched *N*-sulfonyl aziridines (Scheme 1.2).

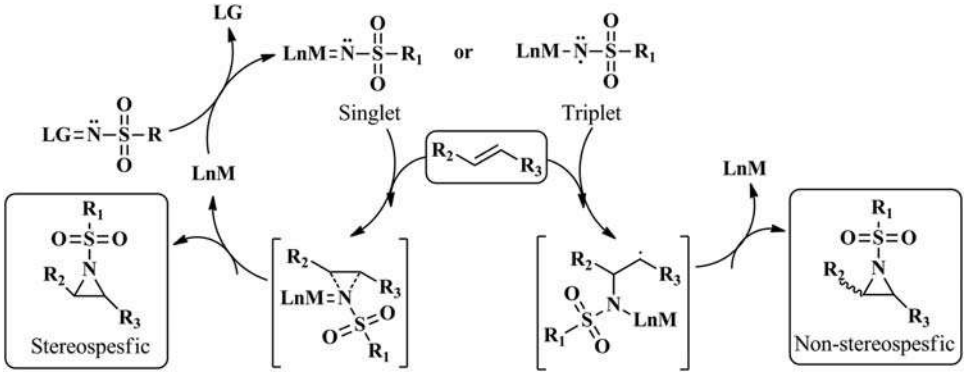
The metal−nitrene intermediates represent a substantial role in the catalytic transfer of nitrogen to alkenes. Even though the significance of the metal−nitrene intermediates in the synthesis of *N*-sulfonyl aziridines, there are still doubts about the mechanism of this type of reaction as well as the active metal−nitrene species nature involved. Nevertheless, the latest mechanistic studies reported that two possible electronic states (singlet and triplet) are accessible for the metal−nitrene species [30]. Assumedly, singlet species would react stereospecifically without changing the stereochemistry of olefins. In a contrary situation, triplet species couldn't react stereospecifically (Scheme 1.3). Nitrene transfer reactions have attracted continuing interest in the synthesis of *N*-sulfonyl aziridines. Consequently, we discussed in this section in detail of this type of reaction.

1.2.1.1 Nitrene transfer reactions using sulfonylimino iodinanes as nitrene precursors

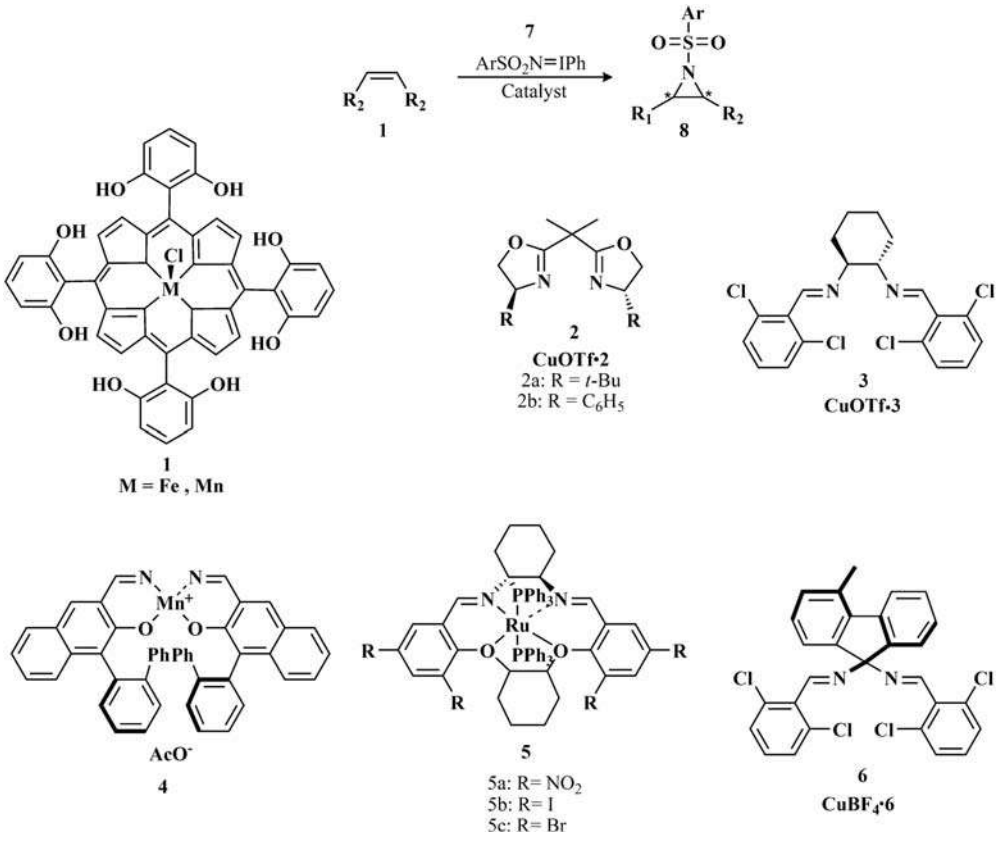
In previous studies, Mansuy and coworkers [31,32] demonstrated the effectiveness of Mn(III)- and Fe(III)−Porphyrin complexes **1** incatalyzing olefin aziridination using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (TsN = IPh) as nitrene source (Scheme 1.4). After that, Evans and coworkers [33] used copper(I) and copper(II) salts as alternative catalysts in olefin aziridination (Scheme 1.4). Subsequently,



SCHEME 1.2 Sulfonylimino iodinanes, sulfonamide, *N*-sulfonyl azides and haloamine-T as efficient nitrene precursors.



SCHEME 1.3 Mechanistic insights for non-stereoselective and stereoselective preparation of *N*-sulfonyl aziridines.

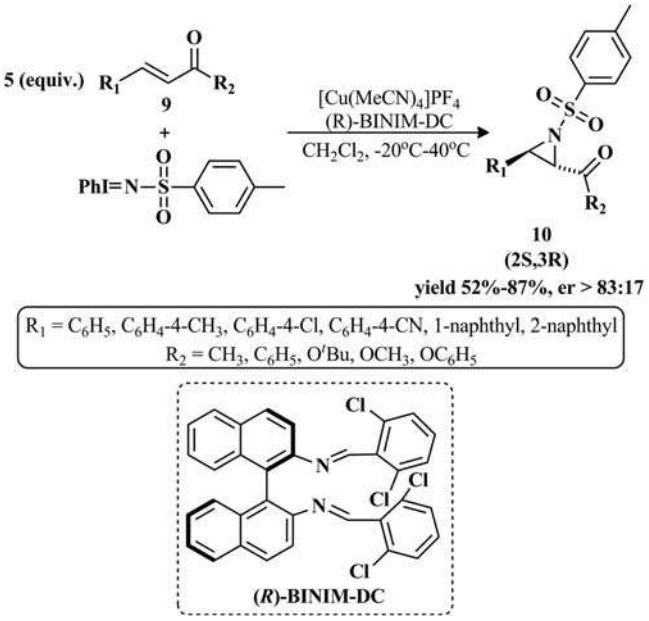


SCHEME 1.4 The earlier pioneer works for the aziridination of olefins using sulfonylimino iodinanes as nitrene precursors.

preliminary work on the catalytic asymmetric olefin aziridination utilizing chiral copper(I)−bis(oxazoline) complexes **CuOTf.2** was reported by the same group [34,35], providing aziridines with high enantioselectivity (Scheme 1.4). Copper diimine complex **CuOTf.3** was introduced by Li et al. [36] for highly enantioselective aziridination of dihydronaphthalene and 6-cyano-2,2-dimethylchromene (Scheme 1.4). Mn−salen catalyzed aziridination of styrene derivatives was described by Noda et al. [37] toward the synthesis of *N*-sulfonyl aziridines in moderate to high enantioselectivity (Scheme 1.4). Liang et al. [38] explored Ru(II)−salen complexes **5** to catalyze aziridination of cyclic olefins (Scheme 1.4). Gillespie et al. [39,40] introduced copper−biaryldimine complex **6** in enantioselective aziridination of cinnamate esters (Scheme 1.4).

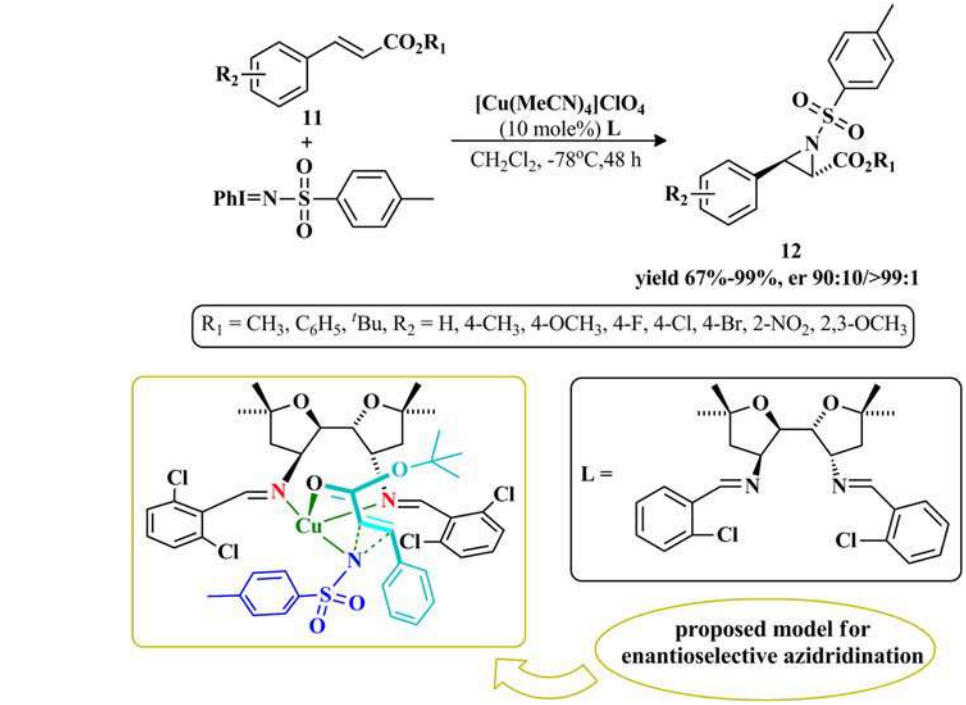
After the pioneering previous works, a tailor-designed catalytic combined system of Cu(I) salts with binaphthyldiimine ligand was employed for enantioselective aziridination of olefins [41]. In this regard, a wide variety of enantioenriched *N*-sulfonyl aziridines **10** were produced from chalcones and *trans*-cinnamyl esters under the catalysis of $[Cu(MeCN)_4]PF_6$ and BINIM-DC ligand (Scheme 1.5).

An innovative chiral C_2-symmetric 1,4-diamine, similar to Li's ligand, was synthesized from *D*-mannitol to investigate its catalytic activity for the transfering of metal−nitrene species to alkenes after complexation with

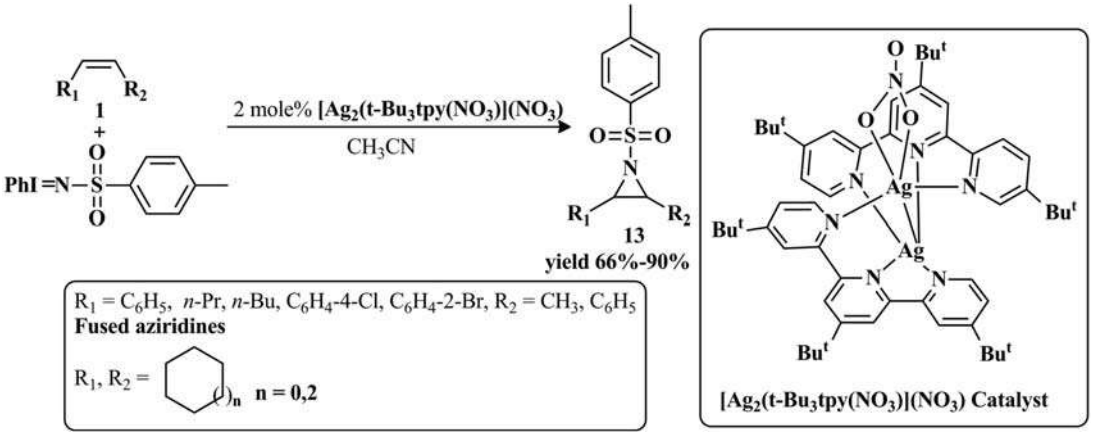


SCHEME 1.5 The developed catalytic system of $[Cu(MeCN)_4]PF_6$ and BINIM-DC for enantioselective aziridination of olefins.

copper(I) (Scheme 1.6) [42]. Although this strategy produced high yields and enantioenriched aziridines **12**, the requested alkenes was used in excess (5 equiv) **11** and the



SCHEME 1.6 The use of a novel chiral C_2-symmetric 1,4-diamine in transference of copper-catalyzed metal − nitrene species to alkenes and its proposed model for this transformation.



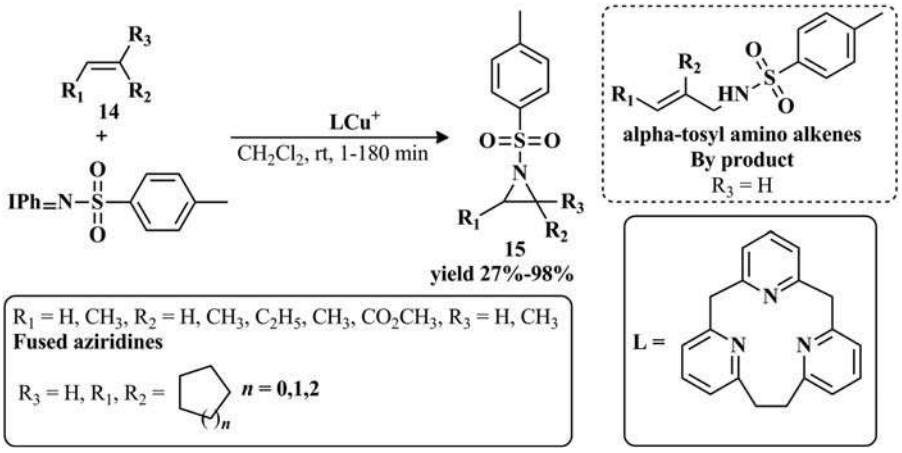
SCHEME 1.7 The advanced and unique disilver(I) catalytic complex for efficient olefins aziridination.

reaction was carried at low temperature (−78°C) which considered as major drawback. As illustrated in Scheme 1.6, the proposed model for the asymmetric motivation was represented in Scheme 1.6, involving the chelation of nitrogen atoms of the ligand and the olefin carbonyl group through copper−nitrene.

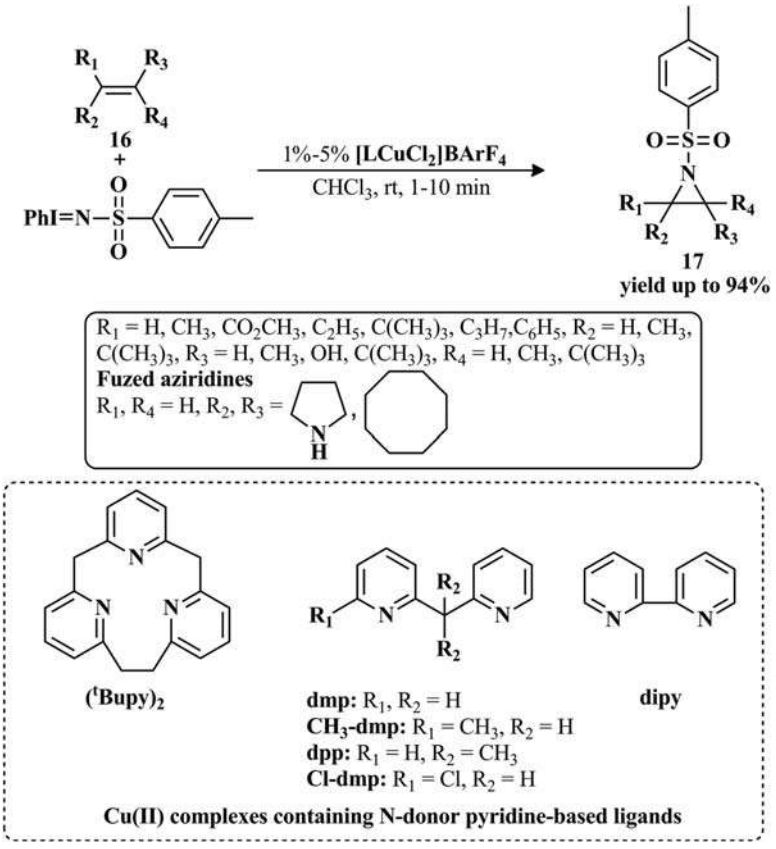
Cui et al. [43] demonstrated the efficacy of a unique disilver(I) complex as a catalyst in olefin aziridination. The unique characteristics of this complex in terms of the open coordination sites of the two silver(I) ions in this complex led to the easy formation Ag = NTs species when such complex reacted with PhI = NTs and transferred its tosyl (Ts) moiety to olefin to afford aziridines **13** in good yield (Scheme 1.7). Notably, the electronic interaction between the disilver(I) core helped in the generation of Ag = NTs species and tune its reactivity.

A pyridinophane macrocycle, an angular ligand, bound to copper was introduced by Vendnikov et al. [44] for efficient aziridination of mono-, di-, and trisubstituted olefins **14** (Scheme 1.8). However, in some cases, α-tosyl amino alkenes were obtained as a by-product. Nerveless, that fast rate of reaction (1−180 min) and high yield (up to 98%) could be a good feature.

A simple Cu(II) complexes containing *N*-donor pyridine-based ligands allowed the efficient aziridination of diverse activated and regular alkenes **16** with PhINTs in the presence



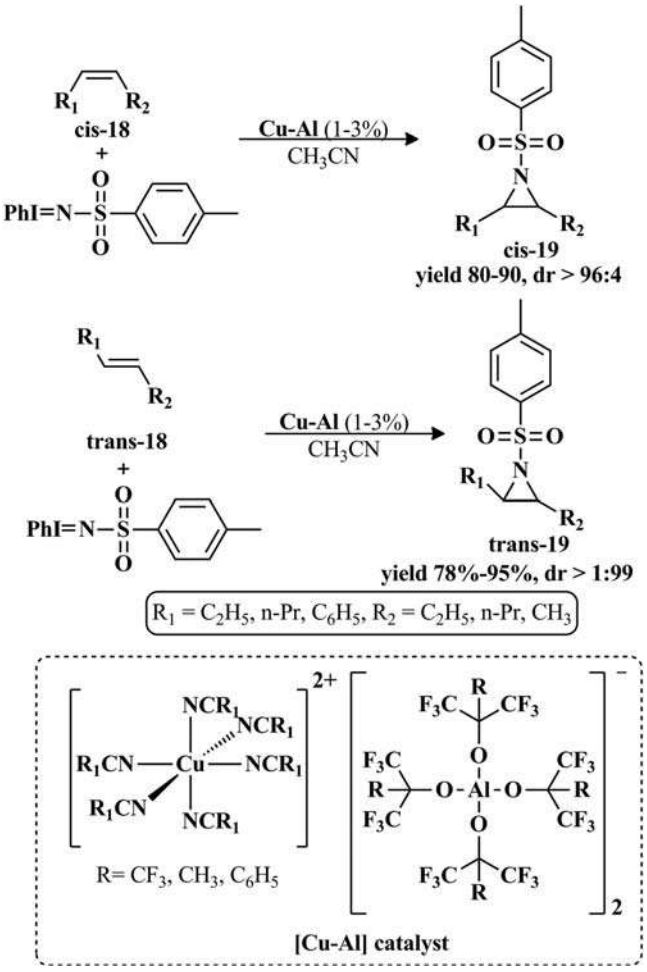
SCHEME 1.8 Copper-medicated aziridination of mono-, di-, and trisubstituted olefins using a regular pyridinophane macrocycle ligand.



SCHEME 1.9 The employ of Cu(II) Complexes containing *N*-donor pyridine-based ligands in catalyzing of the aziridination of olefins **1ecT6**.

of weakly coordinating solvent [45]. It was noted that sodium tetrakis(3,5-di(trifluoromethyl)phenyl)borate ($NaBArF_4$) increased moderately the catalytic potency as well as the effectiveness of the copper complexes. A verity of *N*-sulfonyl aziridines **17** was produced in good yield (Scheme 1.9).

A new advance in the stereoselective aziridination of alkenes was reported by Li et al. [46] in 2011. The weakly coordinating anions, perfluoroalkoxy aluminates [$Al(OC(CF_3)_2R)_4$]($R = CF_3$, Ph), were introduced with acetonitrile ligated copper (II) complexes for making the nitrene species more accessible to alkene coordination. The reactivity and stereoselectivity of the reaction depend on the weak coordinating capability of copper (II) complexes (Cu-Al). All *trans* olefins **trans-18** resulted in the desired *trans* disubstituted aziridines **trans-19** in excellent yields in the presence of PhINTs, while the aziridination of *cis*-disubstituted aliphatic olefins **cis-18** also showed high stereoselectivities, providing almost exclusively *cis*-aziridines **cis-19** (Scheme 1.10).

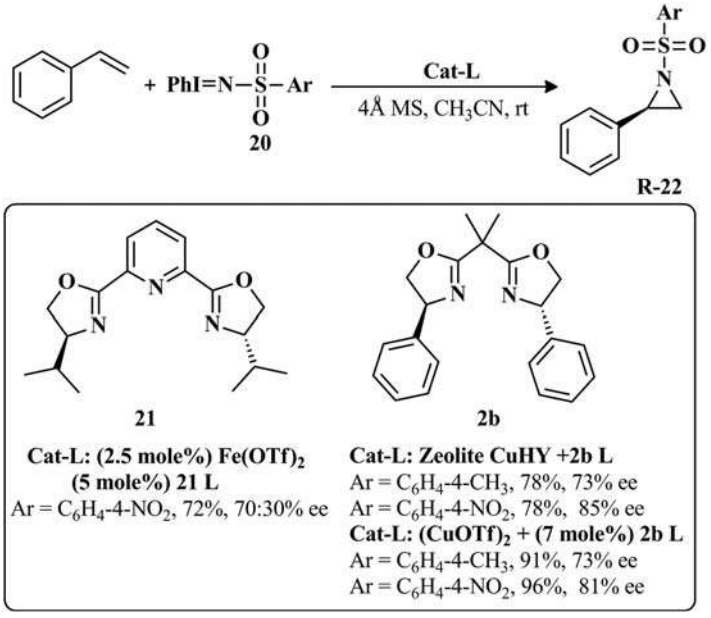


SCHEME 1.10 Stereoselective aziridination of olefins using acetonitrile ligated copper (II) complexes as robust catalysts.

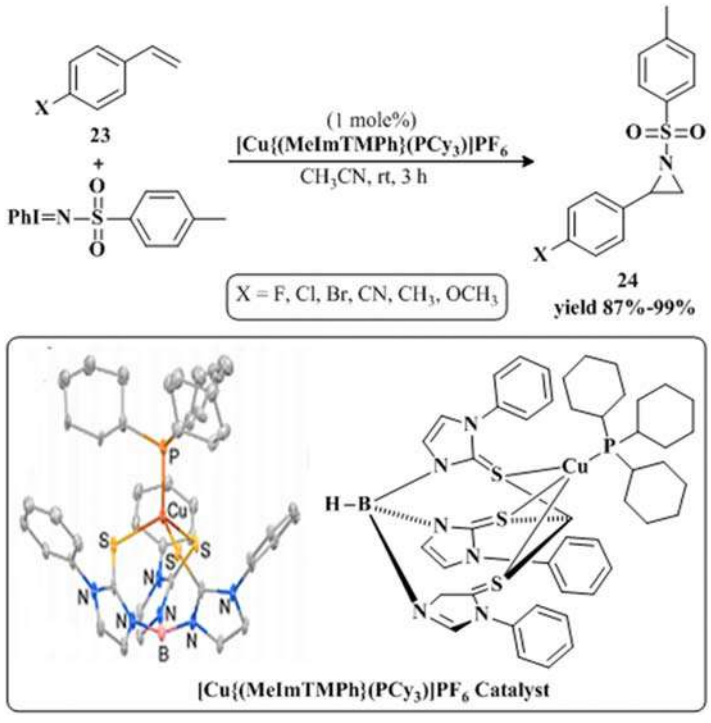
Attempts for the development of aziridination of styrene were done. Nakanishi et al. [47] revealed the catalytic activity and efficacy of a combined catalyst consisting of $Fe(OTf)_2$ and ligand **21** in the asymmetric olefin aziridination to yield *N*-tosyl aziridine **22** with high enantioselectivity (70:30 er) (Scheme 1.11). Gullick et al. [48–51] demonstrated better results by utilizing both homogeneous, copper (II) triflate and heterogeneous, copper-exchanged zeolite (CuHY) catalysts in conjunction with Evans' ligand **2b**. Interestingly, the heterogeneously catalyzed reaction seems to provide much better enantioselection compared with the homogeneously catalyzed asymmetric reaction. These catalytic systems furnish mostly the C_2 (*R*)-configured aziridines **R-22** (Scheme 1.11).

In continuation efforts for discovering more effective catalysts for styrene aziridination, tripodal *S*-ligand complex of copper(I) catalysts were especially synthesized for investigation of their efficiency in catalyzing aziridination of styrene derivatives **23** [52]. Such complex structure was confirmed by single X-ray diffraction as depicted in Scheme 1.12. The results obtained demonstrated that metal complex with tripodal S_3 ligand complex could serve as very extremely active catalysts for aziridination of styrene derivatives **23** with product yields of up to 99% (Scheme 1.12).

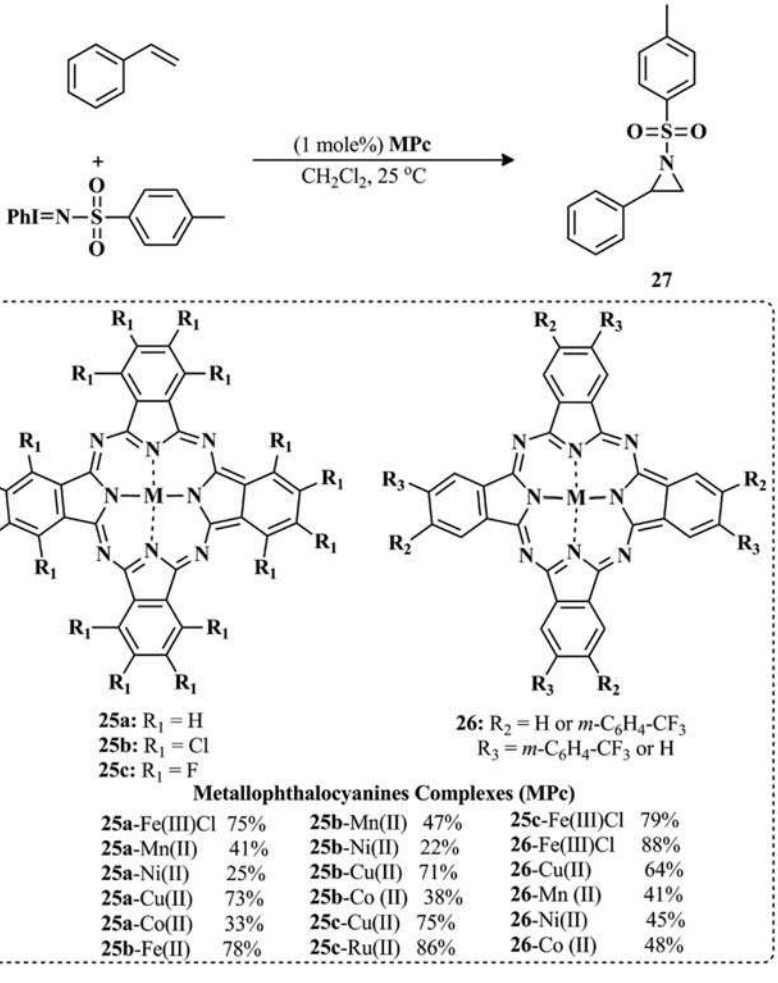
Yan et al. [53] demonstrated the efficiency of a series of substituted metallophthalocyanines complexes (MPc) for catalysis of nitrene transfer reactions. To assess the effects of diverse central metals as well as substituents of phthalocyanine ligands, eighteen different metallophthalocyanines complexes were employed in catalytic aziridination of styrene with PhI = NTs. It could be worth mentioning that **26**-FeCl catalyst led to the formation of *N*-sulfonyl aziridine **27** with an excellent yield, up to 88% (Scheme 1.13). As



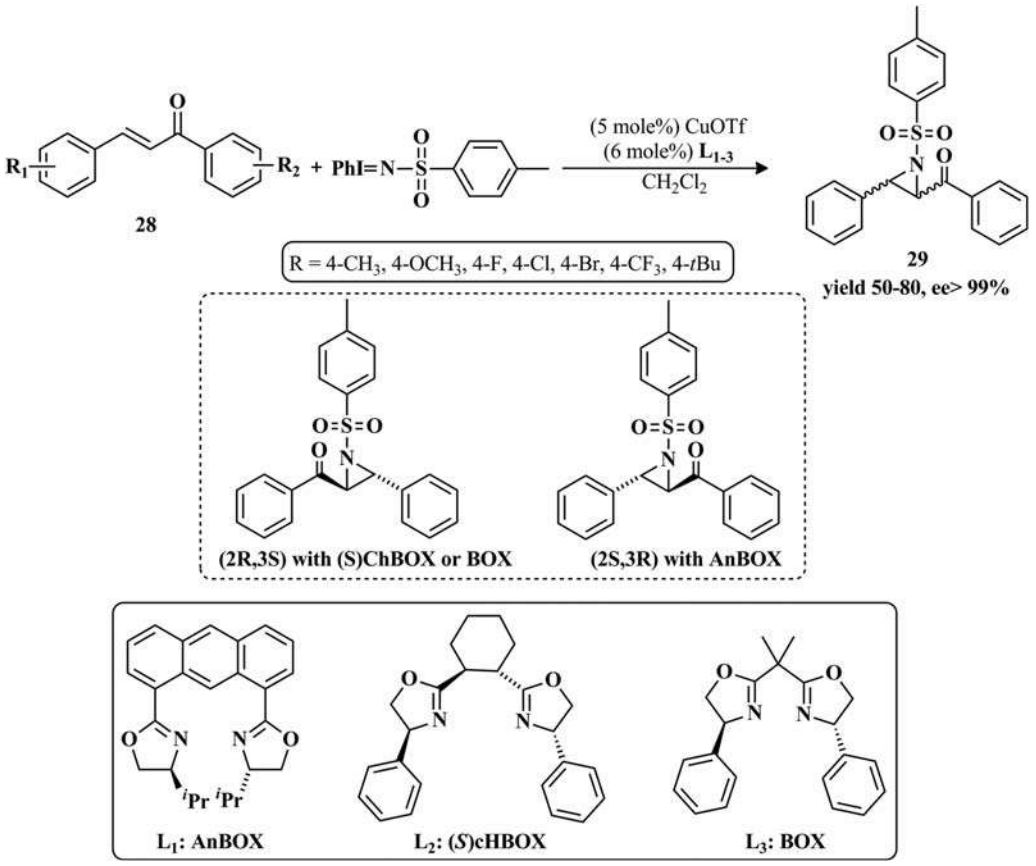
SCHEME 1.11 The influence of $Fe(OTf)_2$, copper (II) triflate and copper-exchanged zeolite catalysts in stereoselectivity of styrene aziridination.



SCHEME 1.12 Well-organized tripodal *S*-ligand complex of copper(I) catalysts in catalysis of styrene aziridination.



SCHEME 1.13 Successful aziridination of styrene using a set of metallophthalocyanines complexes as robust catalysts.



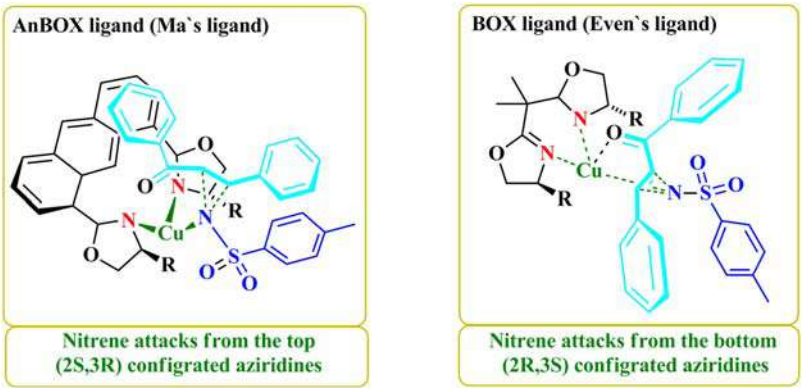
SCHEME 1.14 A combined catalytic system based on copper(II) triflate with cyclohexane-linked bis-oxazoline ligands in catalyzing enantioselective aziridination of chalcone derivatives.

consequence, this catalyst was highly robust toward the aziridination of styrene.

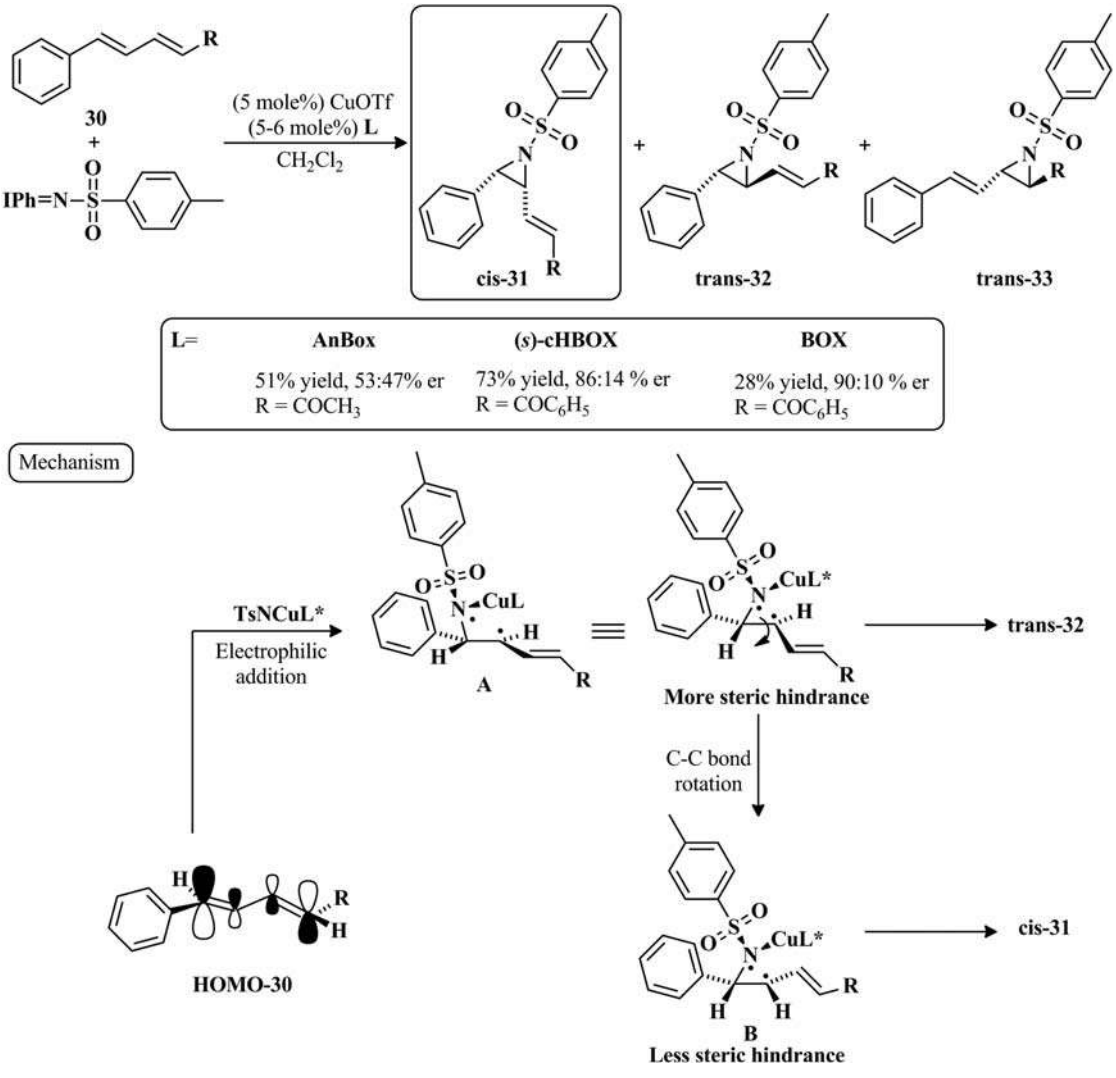
Ma et al. [54] explored that a successful enantioselective aziridination of chalcone derivatives with up to >99% ee was efficiently achieved under the catalysis of CuOTf with a series of cyclohexane-linked bis-oxazoline ligands. The chelate size in the reactive copper complex of bis-oxazolines can tune the enantioselectivity of asymmetric aziridination. Interestingly, the utilization of 1,8-bis-oxazolinylanthracene (AnBOX), as a ligand, afforded aziridines (**2*S*, 3*R*)-29** with enantioselectivity up to 99:1 er whereas an inverse stereo induction was observed with the cyclohexane-linked bis-oxazoline [(*S*)-*c*HBOX], resulting in enantiomeric aziridine (**2*R***, **3*S*)-29** (Scheme 1.14). The Evans' ligand(BOX) **2b** behaved in the same way as that of (*S*)-*c*HBOX (Scheme 1.14).

The proposed model for the aziridination process explained that the enantioselectivity was attributed to the direction of the metal−nitrene. It would be assumed that ligand of metal−nitrene species was attacked from the bottom of the asymmetric aziridination of chalcones utilizing AnBOX, leading to a 2*S*,3*R*-configuration in *N*-sulfonyl aziridines (Scheme 1.15). Interestingly, the enantioselectivity of the produced aziridines was found to be 2*R*,3*S*-configuration with BOX and (*S*)*c*HBOX ligands, supposing the metal−nitrene attack from the bottom as shown in Scheme 1.15.

Despite the limitation of 1,3-dienes in synthetic applications due to the symmetry of diene as well as the low cis/trans-selectivity, the same group [55] employed BOX, AnBOX, and *c*HBOX ligands in the asymmetric 1,3-diene aziridination. $\alpha,\beta,\gamma,\delta$-Unsaturated ketones **30** resulted in *cis*-γ,δ-aziridinated products **cis-31** in a yield of 28% with enantioselectivity up to 80% and diastereoselectivity with up to >99% by utilizing BOX ligand (Scheme 1.16). Upon employing the *c*HBOX ligand, the latter was obtained in a higher yield with lower enantioselectivity. Despite, the high regioselectivity of 1,4-diphenyl-1,3-butadiene aziridine, both *cis*- and *trans*-aziridines **31** and **32** were produced as major products (Scheme 1.16). As reported in Scheme 1.16, an electrophilic addition of the copper-nitrene TsN = CuL* with radical character to the HOMO orbital of the 1,3-butadienes **30** on the preferred terminal carbon was occurred, providing a diradical intermediate **A**, which generated the more stable intermediate **B** after C-C bond rotation. Finally, the cis-product **31** was yielded upon ring closure (Scheme 1.16).



SCHEME 1.15 The proposed model for enantioselective chalcone aziridination.



SCHEME 1.16 Copper(I)−bis(oxazoline) complexes in the asymmetric 1,3-diene aziridination.

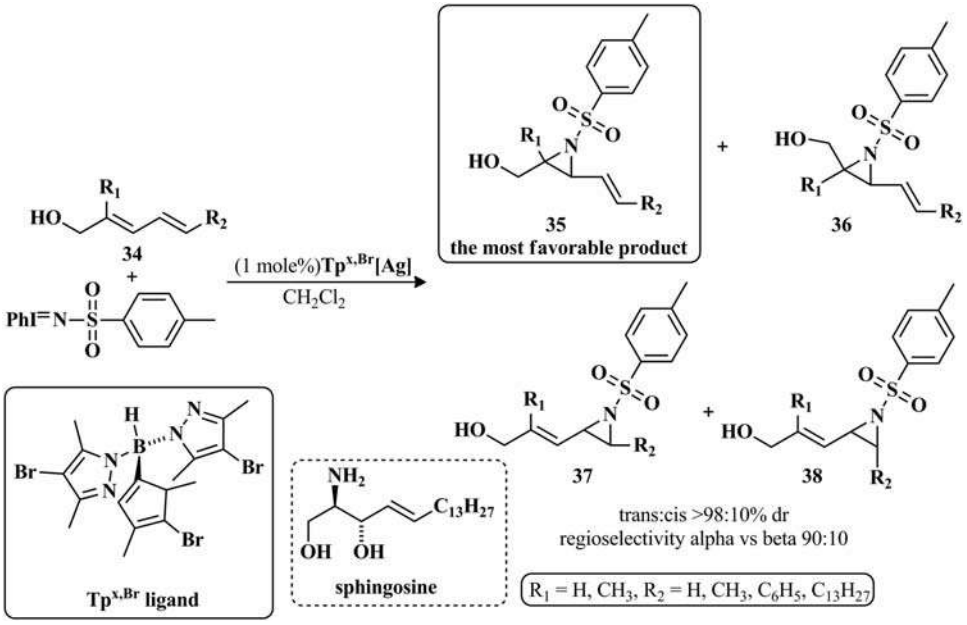
Llaveria et al. [56] investigated the efficacy of diverse complexes composed of the trispyrazolylborate ligand $TP^{x,Br}$ with a metal catalyst (M = Ag, Cu) to promote aziridination of 2,4-diene-1-ols **34**. Silver complexes bearing trispyrazolylborateligands (Tpx) catalyst allowed highly regioselective aziridination of the double bond (α), which is next to the hydroxyl moiety in 2,4-diene-1-ols **34**, resulting mainly in *trans*-aziridines **35** in excellent yields

(Scheme 1.17). It seemed that the free hydroxyl group was responsible for the regioselectivity (α vs β) of double bonds but not the effect on the stereoselectivity of this reaction (*cis* vs *trans*). Additionally, this new methodology was applied in the construction of racemic sphingosine.

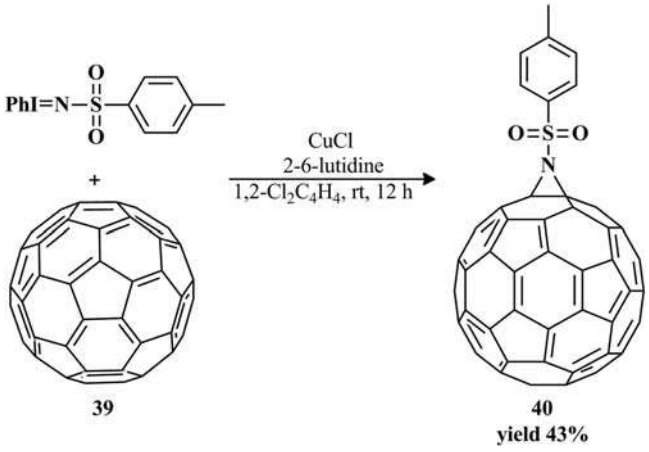
In the recent advance in metal-catalyzed olefin aziridination, Nambo et al. [57] explored the aziridination of the C_{60} fullerene **39** with iminophenyliodinane in the presence of copper chloride as a catalyst with 2,6 lutidine ligand to provide access for aziridinofullerene **40** in 43% yield (Scheme 1.18). Authors exhibited that the resulting aziridinofullerene **40** was a versatile precursor for the construction of a wide range of functionalized fullerenes.

Kiyokawa et al. [58] reported the novel metal-free catalytic aziridination of olefins **41** with *N*-tosyliminophenyliodinane (PhI = NTs) by employing a I_2/ tetrabutylammonium iodide (TBAI) catalyst system. In situ generation of $TBAI_3$ from I_2 and TBAI dramatically promoted the aziridination process. The stereochemistry of the aziridination reaction was also studied by using chiral olefins **43**. A mixture of *cis*/*trans* aziridines **44** was produced in good yield (Scheme 1.19).

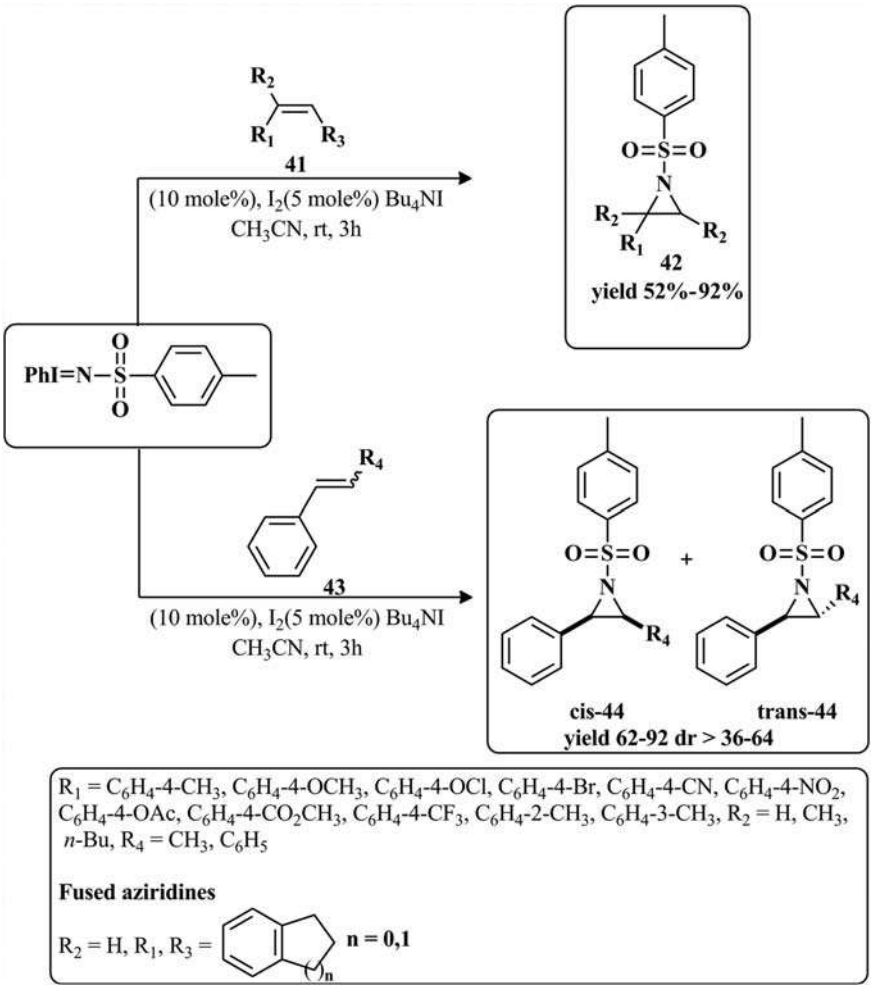
Despite the novelty of the metal-free catalytic aziridination strategy, this type of reaction was inadequate for the synthesis of aziridinofullerene. The azafulleroid **45** was selectively formed as the major product rather than the aziridinofullerene in the reaction of the fullerene C_{60} with *N*-tosyliminophenyliodinane in the presence of the same catalytic system in *o*-dichlorobenzene (Scheme 1.20) [58].



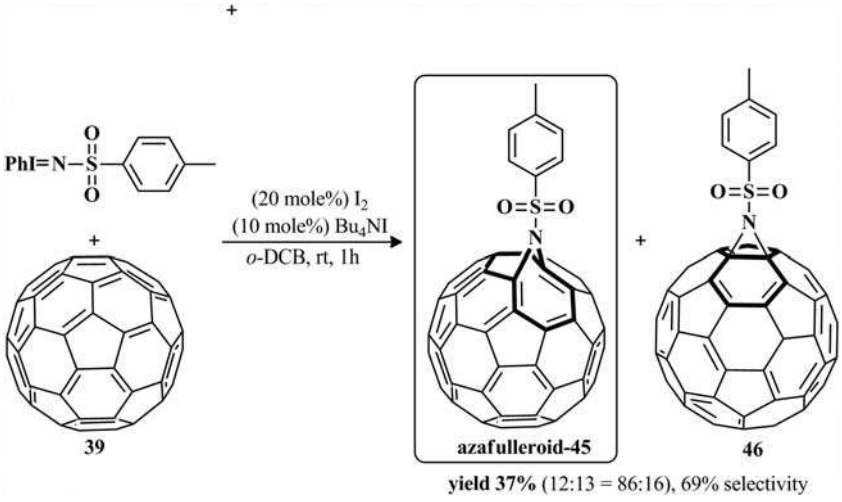
SCHEME 1.17 Promotion of aziridination of 2,4-diene-1-ols via silver complexes bearing trispyrazolylborate ligands.



SCHEME 1.18 Catalysis of aziridination of the C_{60} fullerene utilizing copper chloride and 2,6 lutidine.



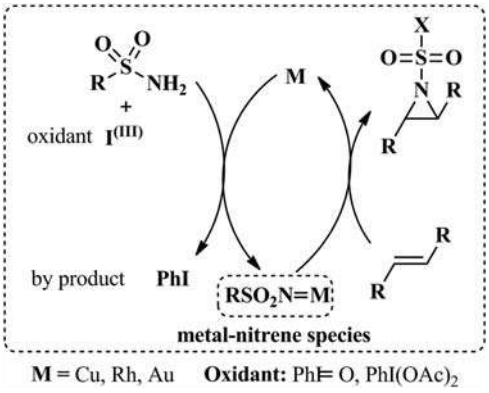
SCHEME 1.19 The use of the combined system consisting of iodine and tetrabutylammonium iodide in catalyzing aziridination of non-chiral and chiral olefins.



SCHEME 1.20 Synthesis of aziridinofullerene **45** through catalytic iodine/tetrabutylammonium iodide system.

1.2.1.2 Nitrene transfer reactions using sulfonamides as nitrene precursors

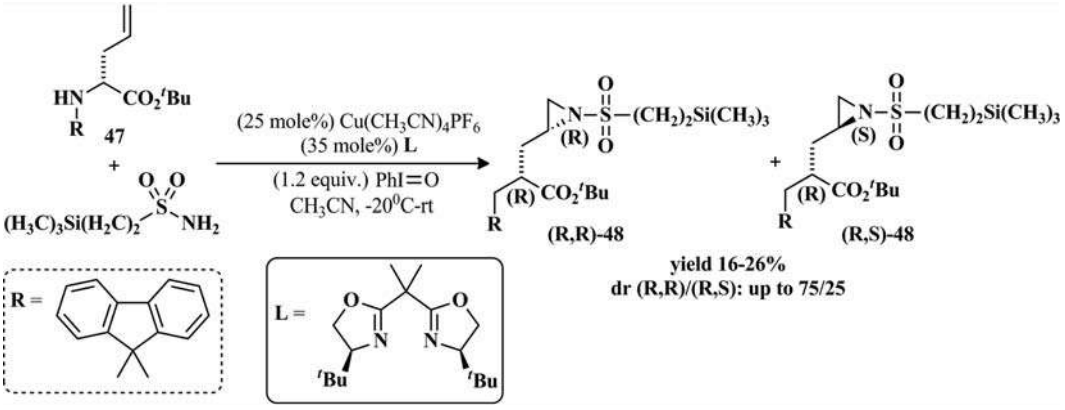
To expand the versatility of the direct olefin aziridination and avoid the troublesome removal of the *N*-arylsulfonyl group as well as the dull separation of the iminoiodinane, an alternative strategy was emerged based on utilizing sulfonamides as useful nitrene precursors in the metal-catalyzed olefin aziridination in the presence of an oxidant (Scheme 1.21). In this strategy, oxidation of *N*-sulfonyl amine with hypervalent iodine could be in situ generated the active metal−nitrene species.



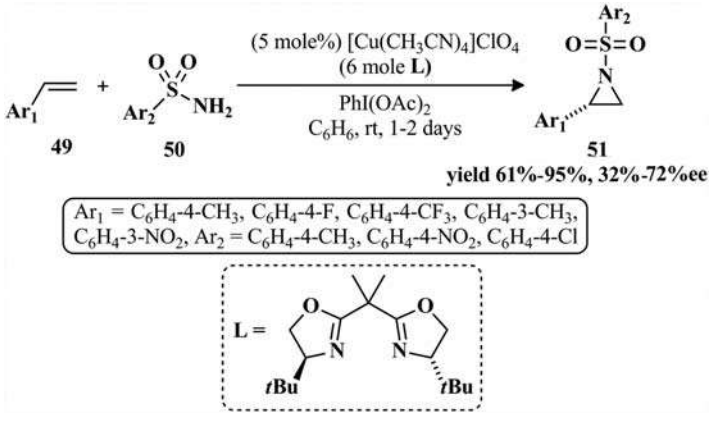
SCHEME 1.21 Sulfonamides as nitrene precursors in the metal-catalyzed olefin aziridination.

Sanie're et al. [59] reported the aziridination of α-allylglycine derivatives (***R*)-47** with 2-trimethylsilylethanesulfonamide ($SESNH_2$)utilizing $Cu(MeCN)_4PF_6$ as a copper source and iodosylbenzene as oxidant (Scheme 1.22). As a drawback, this reaction performed with low transformation (up to 26% only) as well as unpretentious diastereoselectivity (up to 67:33) with or without bis-oxazolinyl chiral ligand. The use of bis-oxazolinyl chiral ligand didn't have much effect on either the diastereomeric ratio (Dr) or yield of aziridines **48** (up to 75:25%).

Kwong et al. [60] also reported a chiral version of the aziridination olefin by introducing Evan's chiral bis(oxazoline) ligand to copper catalyst $[Cu(CH_3CN)_4]ClO_4$. Diverse sulfonamides **50** were used as nitrene sources to afford a verity of chiral aziridines **51** in medium to high yield (61%−95%) with modest to good enantioselectivity (up to 72%) (Scheme 1.23).



SCHEME 1.22 Aziridination of α-allylglycine derivatives (*R*)-47 with 2-trimethylsilylethanesulfonamide.



SCHEME 1.23 Copper-catalyzed aziridination of olefin **49** with sulfonamide **50** in the presence of chiral bis(oxazoline) ligand.

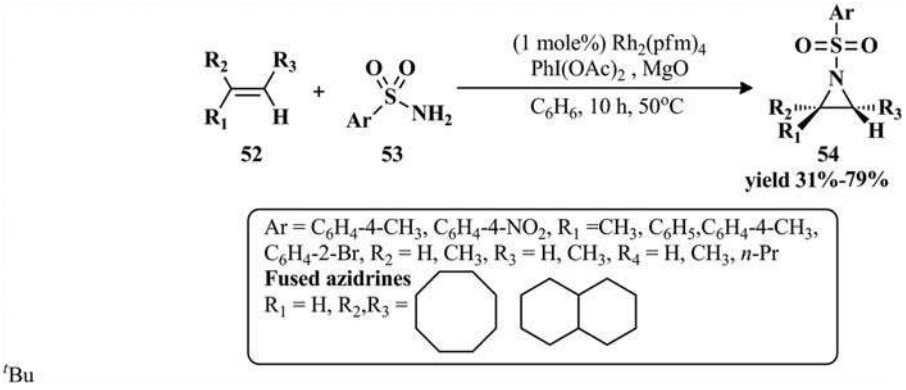
Keaney et al. [61] developed an enhanced microwave-assisted synthesis of rhodium perfluorobutyramide ($Rh_2(pfm)_4$) and investigated its effectiveness to catalyze aziridination of olefins **52** with sulfonamides **53** in the presence of phI $(OAc)_2$ as oxidant. The use of this catalyst resulted in the production of *N*-sulfonyl aziridines **54** in moderate to good yield (Scheme 1.24).

Han et al. [62] developed an external ligand-free copper-catalyzed aziridination reaction based on a chelation strategy for the first time. The coordination effects of 2-pyridinesulfonamide significantly facilitated the aziridination process via the favorable generation of a pyridyl-coordinated nitrenoid intermediate **55**, which efficiently added to olefin **1** (Scheme 1.25).

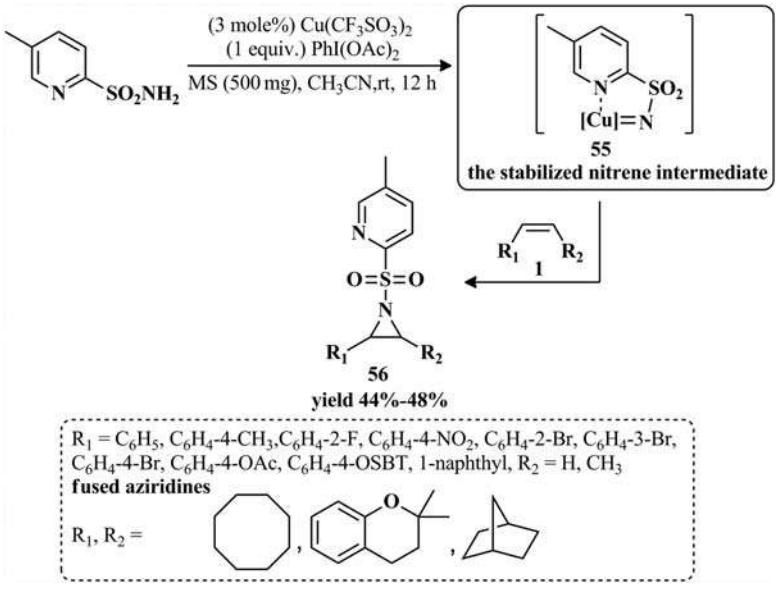
Li et al. [63] disclosed the first report on gold-catalyzed nitrene transfer reaction. The combination of a gold catalyst with pyridine-based ligand [Au $(tBu_3Tpy)](OTf)$ exhibited superior catalytic potency in aziridination of olefin **1** with sulfonamide **53**. Such an effective catalytic system could provide *N*-sulfonyl aziridines **57** in moderate to excellent yield (up to 95%) (Scheme 1.26).

1.2.1.3 Nitrene transfer reactions using N-sulfonyl azides as nitrene precursors

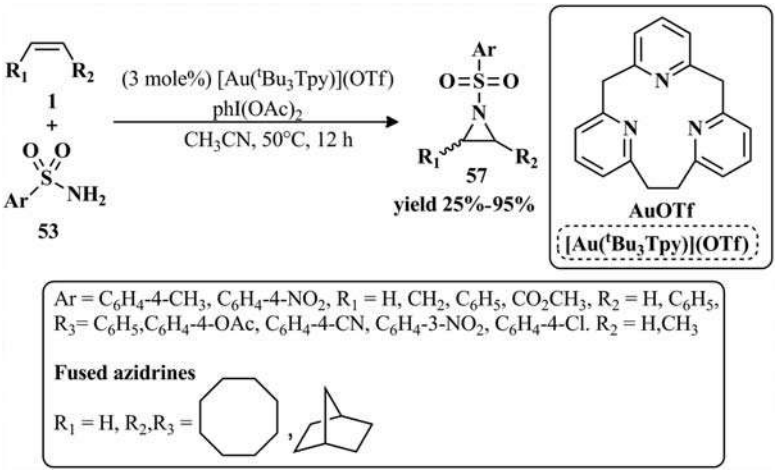
Azides are considered ideal metal−nitrene precursors owing to the simple generation of nitrene species via releasing harmless nitrogen gas. However, their drawback is that several synthetic steps are required for their preparation. Pioneering studies designed *N*-sulfonyl azides as privileged nitrenoid precursors and employed diverse cat-



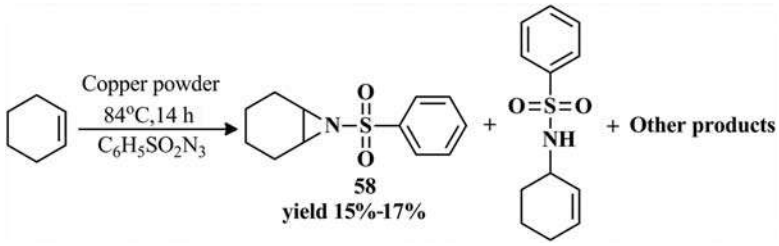
SCHEME 1.24 Rhodium perfluorobutyramide in catalysis of aziridination of olefins **52**.



SCHEME 1.25 Development of ligand-free copper-medicated aziridination of olefin via using of 2-pyridinesulfonamide as substrate.



SCHEME 1.26 Gold-catalyzed olefin aziridination in the presence of pyridine-based ligands.



SCHEME 1.27 First successful olefin aziridination through using *N*-sulfonyl azide as nitrenoid precursors.

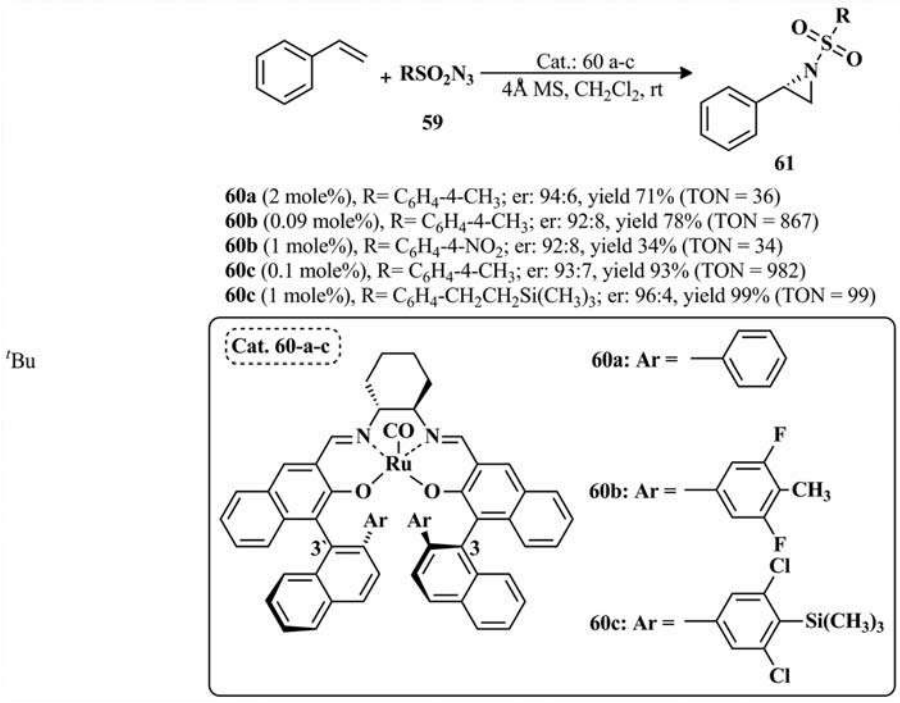
alysts for converting these azides into active species that are useful in the aziridination of olefins. The first synthesis of *N*-sulfonyl aziridine by using *N*-sulfonyl azide as nitrenoid precursors was reported by Kwart et al. [64,65] in 1965. Unfortunately, the selectivity of the reaction was very low, producing aziridine **58** with other products (Scheme 1.27).

Katsuki and coworkers [66–68] obtained noteworthy outcomes in the field of catalytic enantioselective aziridination via utilizing *N*-sulfonyl azides. Ruthenium–salen complexes were designed for catalysis of enantioselective aziridination of olefins in presence of *N*-sulfonyl azides as nitrene source. The newly designed ruthenium–salen complexes **60** demonstrated promising results in terms of producing highly enantioenriched chiral *N*-sulfonyl aziridines up to 96:4 er (Scheme 1.28). The authors introduced diverse aryl groups on the naphthyl groups connected at positions 3 and 3‘ to optimize the catalyst structure that had a high turnover number.

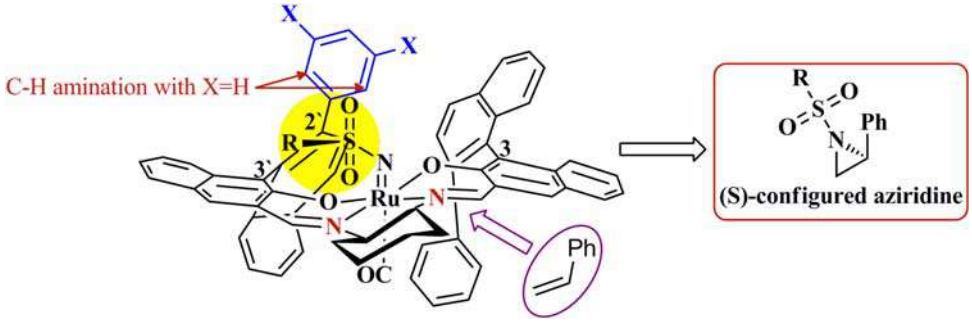
As shown in the proposed model for the asymmetric styrene aziridination via using the Ru–Salen complex (Scheme 1.29), the aryl group on the position 2" (in blue) that is close to the imino group drives the *N*-sulfonyl moiety (in green) to the front side. Styrene (in purple) approached the imino species alongside the Ru–N bond (in orange) from the back direction of the downward naphthalene ring of the ligand to minimize steric repulsion, resulting in the (*S*)-configured aziridine. X-ray analysis proved that *m*-chloro substituents improved the immovability of the catalyst to resist the undesired intramolecular C–H amination of the aryl group [69].

The most robust catalyst **60c** was employed for the extension of the scope of this reaction to aliphatic and aromatic olefins, vinyl ketones, *N*-methoxy-*N*-benzyl-2-propenamide, and benzyl acrylate **62** using $SESN_3$ as nitrene precursors. *N*-Sulfonyl aziridines **63** were obtained with medium to good yield with extreme levels of enantioselectivity (Scheme 1.30) [70]. However, low regioselectivity resulted in a nearly equimolar ratio between *N*-sulfonyl aziridines **65** and **66** when testing this catalyst in competitive aziridination of the *p*-vinylphenyl vinyl ketone.

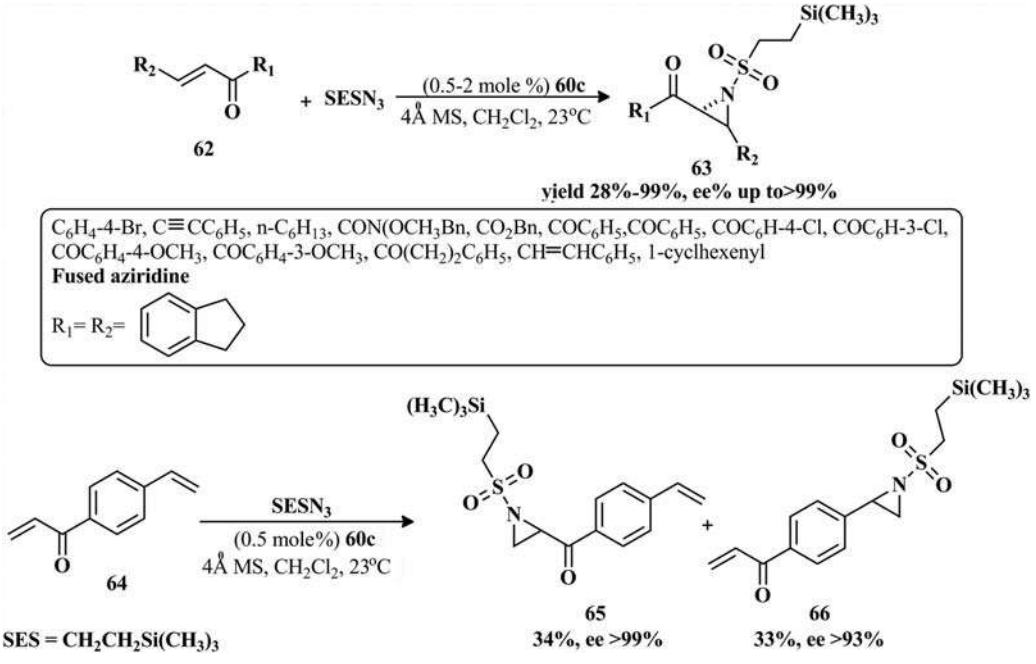
The same catalyst was also introduced for the asymmetric aziridination of 1-(2-hydroxy-5-methoxyphenyl) prop-2-en-1-one, providing the aziridinyl ketones **67** with extreme enantioselectivity (up to >99%). The latter served as useful chiral precursors in the preparation



SCHEME 1.28 Robust ruthenium − salen complexes in catalyzing aziridination of olefins.



SCHEME 1.29 The proposed model for the asymmetric aziridination of styrene.

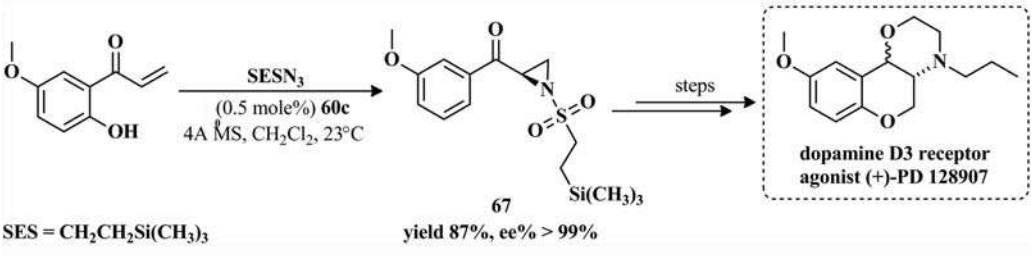


SCHEME 1.30 Enantioselective aziridination of aliphatic and aromatic olefins, vinyl ketones, *N*-methoxy-*N*-benzyl-2-propenamide and benzyl acrylate using ruthenium − salen complex catalyst.

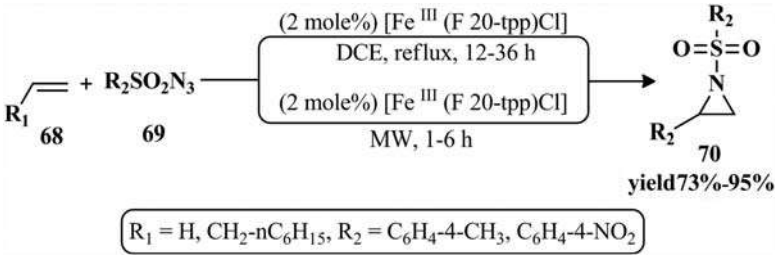
of dopamine D3 receptor agonist (+)-PD 128907 (Scheme 1.31) [71].

In addition to ruthenium−salen complexes, the perfluorinated tetraphenylporphyrin complex [Fe^{III}(F20-tpp)Cl] was found to be an active catalyst for nitrene transfer reactions utilizing *N*-sulfonyl azides **69** as nitrene precursors [72]. [Fe^{III}(F20-tpp)Cl] catalyst was capable of catalyzing aziridination of olefins **68**, providing access to aziridines **70** in excellent yield under thermal and microwave-assisted conditions (Scheme 1.32). Microwave-assisted aziridination time was decreased by up to 16-fold (12−36 vs 1.5−6 h) in comparison to thermal conditions, without significantly influencing substrate conversion or the product yield.

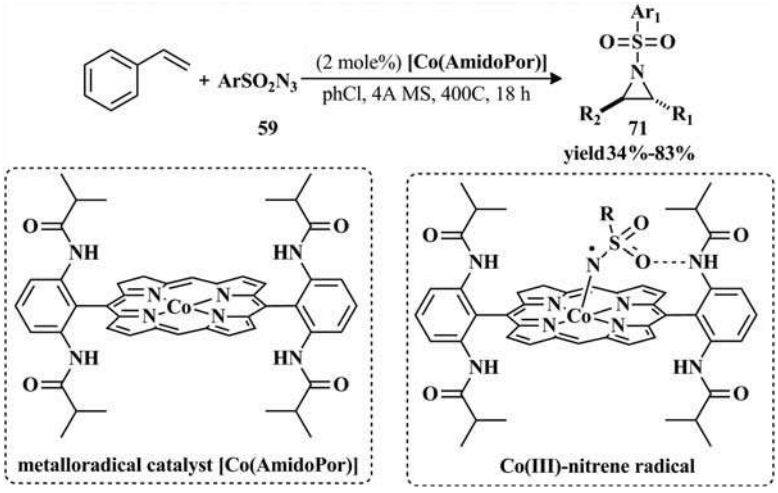
The novel radical aziridination was achieved by Zhang and coworkers [73−76], who provided an important contribution to the preparation of *N*-sulfonyl aziridines **71** by utilizing Co(II) complexes of porphyrins, analogs of metallophthalocyanines complexes, in radical styrene aziridination in the presence of *N*-sulfonyl azides **59** as nitrene source (Scheme 1.33). The DFT mechanistic study confirmed that the high catalytic efficacy of Co(II) complexes



SCHEME 1.31 Asymmetric aziridination of 1-(2-hydroxy-5-methoxyphenyl)prop-2-en-1-one.



SCHEME 1.32 The use of perfluorinated tetraphenylporphyrin complex in catalyzing the styrene aziridination with *N*-sulfonyl azides.



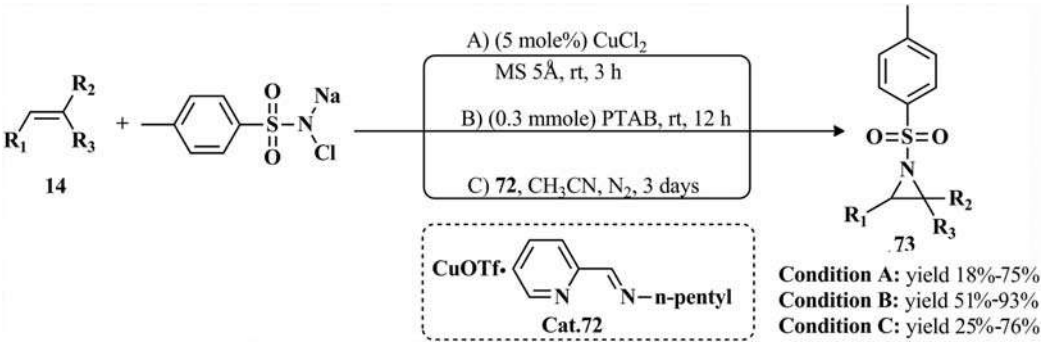
SCHEME 1.33 The capability of Co(II) complexes of porphyrins in catalysis of radical aziridination of olefin.

of porphyrins [Co(AmidoPor)] was associated with the formation of a stable key Co(III)-nitrene radical (α-Co(III)-aminyl radical) intermediate by hydrogen-bonding interaction between sulfonyl group of the azide and the amide group of the porphyrin ligand (Scheme 1.33).

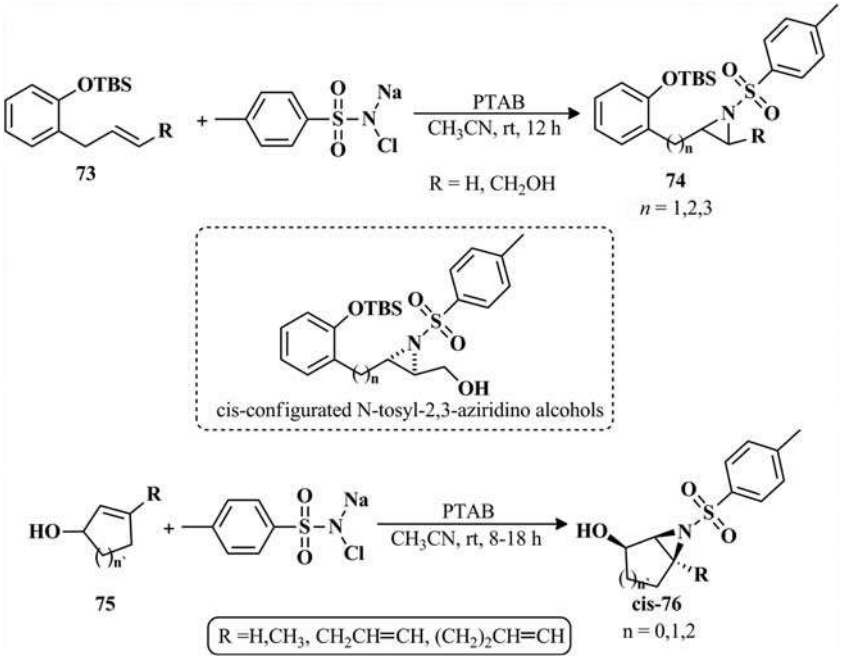
1.2.1.4 Nitrene transfer reactions using haloamine-T as nitrene precursors

In a previous investigation, Ando et al. [77] demonstrated that chloramine-T could be utilized as a nitrogen transfer reagent in the aziridination of olefins in presence of copper chloride as a catalyst (Scheme 1.34). To improve the yield of the aziridination process, phenyltrimethylammonium tribromide (PTAB) was employed as an alternative catalyst in this transformation. Albone et al. [78] introduced ligand **72** with copper(I) triflate as a catalytic system for aziridination of aryl olefins **14**, affording *N*-tosyl aziridines **73** in modest to good yield (Scheme 1.34).

Devi et al. [79] described aziridination of olefins **73** with chloramine-T trihydrate in presence of phenyltrimethylammonium tribromide (PTAB), providing access to functionalized aziridines **74**. A wide variety of olefins, including terminal alkenes and *E*-allylic alcohols, participated in this reaction. Interestingly, *E*-allylic alcohols converted to *N*-tosyl-2,3-aziridino alcohols in a completely diastereoselective fashion (Scheme 1.35). For access to fused aziridines, O'Brien and coworkers [80,81] demonstrated allylic alcohols **75** which could undergo a transformation under the above mentioned reaction condition, providing chiral



SCHEME 1.34 Effective aziridination of functionalized olefins **14** using haloamine-T as nitrene precursors by using different competitive catalysts.

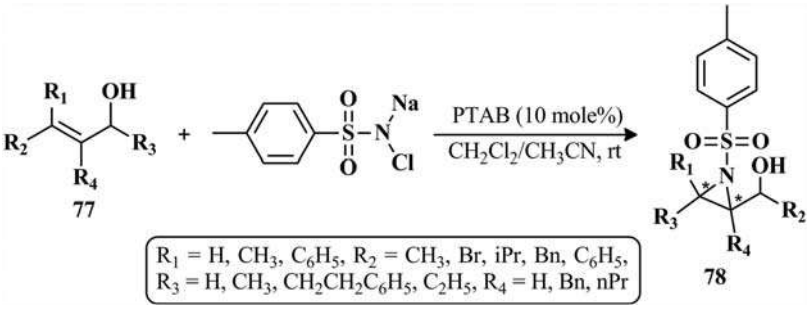


SCHEME 1.35 Diastereoselective aziridination of terminal alkenes and *E*-allylic alcohols with chloramine-T trihydrate.

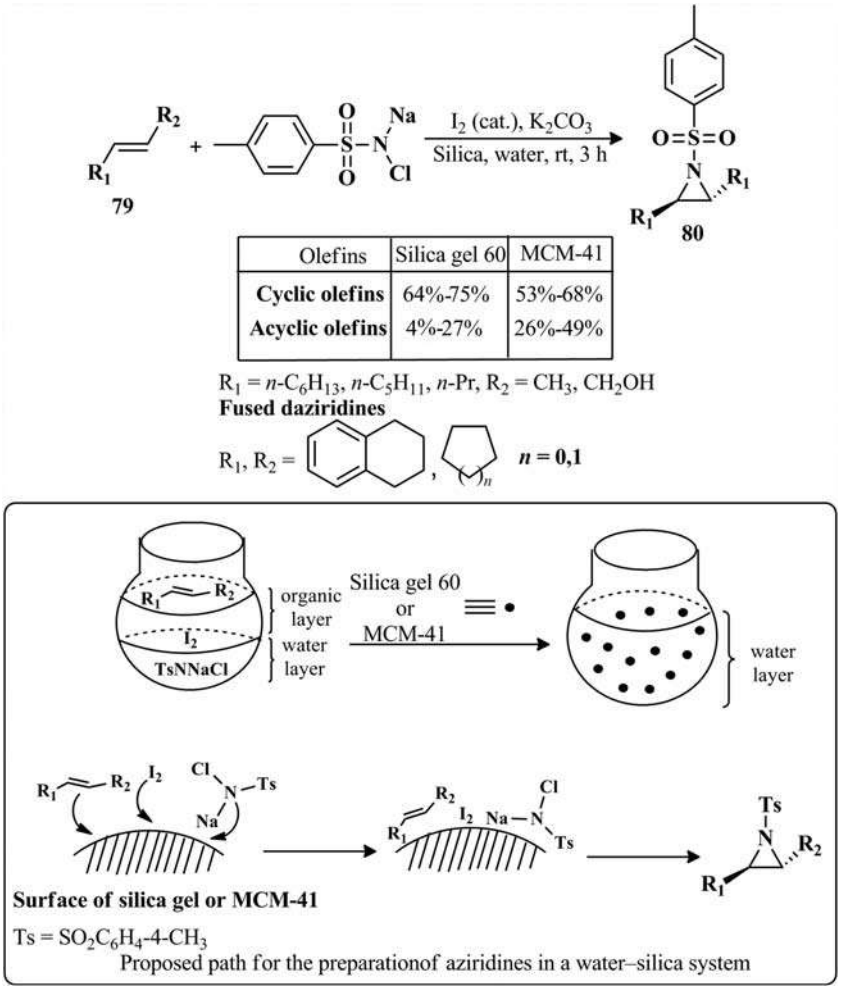
β-hydroxy aziridines **76** with good *cis*-selectivity (Scheme 1.35).

Recently, a diastereoselective aziridination of acyclic allylic alcohols **77** with chloramine-T was achieved under the same catalyst at room temperature in CH_2Cl_2/CH_3CN [82]. It is worth mentioning that aziridination of 2,3,3-trisubstituted allylic alcohols was achieved to produce α-hydroxy aziridines **78** with high selectivity ($>96:<4$) but (*E*)-2,2,3-trisubstituted allylic alcohols exhibited low reactivity (Scheme 1.36).

Chemical reactions in aqueous media signify attracted considerable attention for achieving more eco-friendly synthetic transformations. In this regard, Minakata et al. [83] reported the silica-mediated synthesis of *N*-tosyl aziridines **80** in aqueous media utilizing the iodine catalyst-chloramine-T system (Scheme 1.37).



SCHEME 1.36 Synthesis of selective α-hydroxy aziridines **78** via the aziridination of 2,3,3-trisubstituted allylic alcohols with chloramine-T.



SCHEME 1.37 Novel silica-mediated synthesis of *N*-tosyl aziridines in aqueous media in the presence of iodin eatalysts.

In this protocol, adsorption of the organic substrate to silica was performed via hydrophobic interactions between the organic molecule and the surface of the silica. Two different types of silica, silica gel 60 and mesoporous silicas with a hexagonal array of uniform mesopores (MCM-41) were used as solid support. A reaction of cyclic alkenes was achieved effectively by employing (MCM-41) due to its larger specific surface area compared with that of silica gel 60. However, the interaction of acyclic alkenes with the MCM-41 surface seemed to be difficult because of the high degree of freedom of acyclic alkenes as well as the low average pore size of the MCM-41 (Scheme 1.37).

The first report of aziridination of olefins under both ultrasound and microwave irradiation conditions was described by Chanda et al. [84]. This reaction was performed via using bromamine-T (TsNNaBr) as the nitrene source and copper halides as an effective catalyst in this transformation. This reaction was successfully achieved under ultrasound irradiation to afford *trans*-aziridine **82** selectively whereas a mixture of *trans* and *cis* isomers **82** was produced under microwave irradiation (Scheme 1.38).

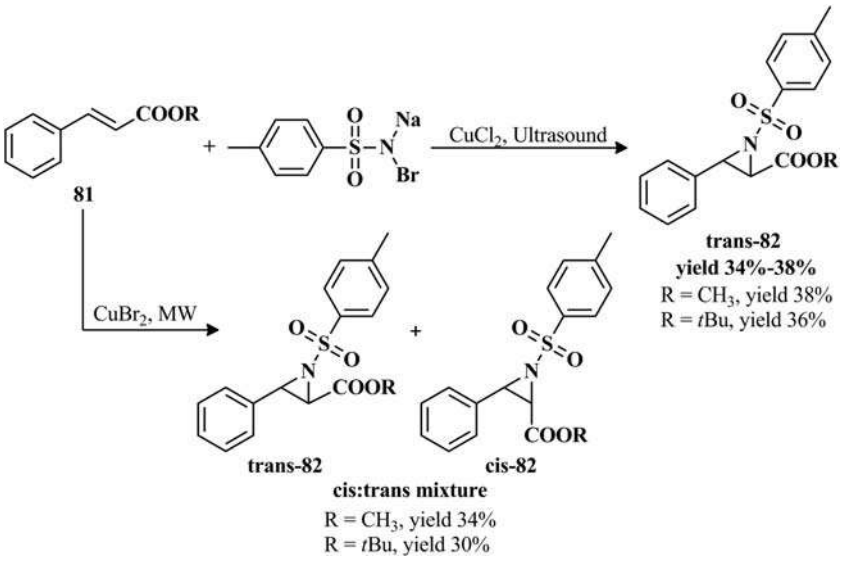
Zhang et al. [85] disclosed a novel efficacious aziridination protocol based on the employ of bromamine-T in the presence of porphyrin complexes including transition metal ions Fe^{III}, Co^{II} as catalysts. The use of metalloporphyrin complexes in this transformation paved the synthesis of *N*-sulfonated aziridine **83** in good to high yield (Scheme 1.39).

This prompted authors to investigate the more robust catalysts Co(TDClPP) and Fe(TPP)Cl in the aziridination of a wide diversity of mono- and disubstituted olefins **41**. However, the reaction proceeded with medium to low stereospecificity with 1,2-disubstituted olefins (Scheme 1.40) [86].

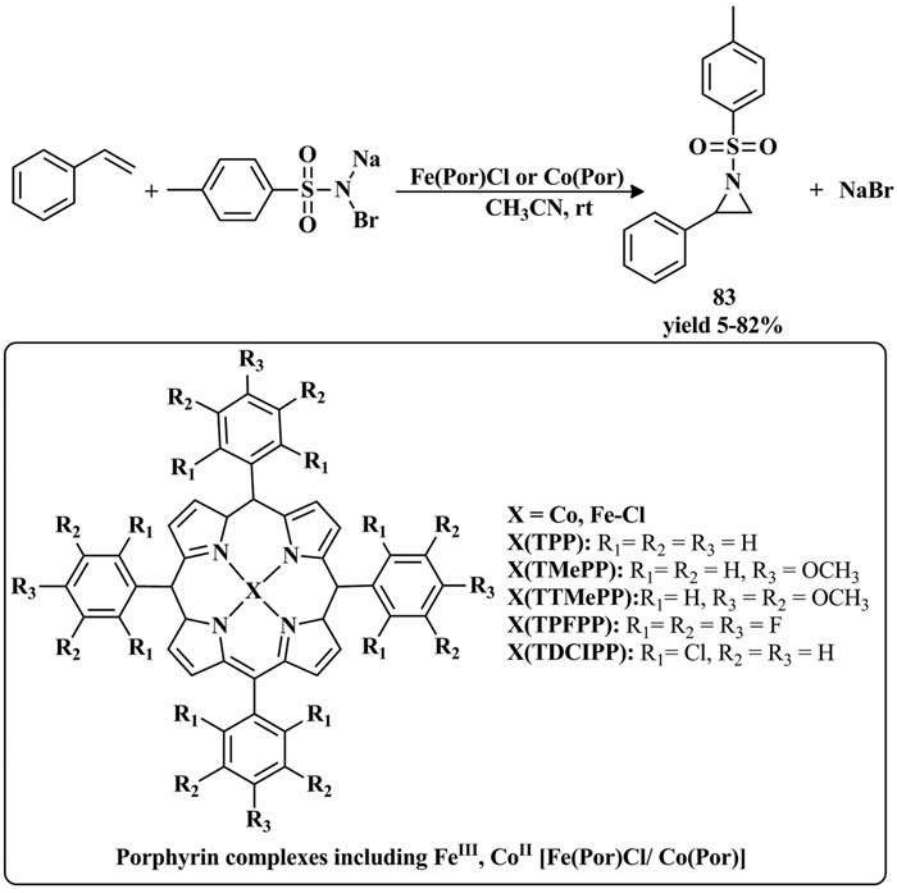
1.2.2 The addition of nitrogen-centered radical species to alkenes

Visible-light-induced photocatalysis has recently emerged as a concise applied technique in the synthesis of *N*-sulfonyl aziridines. In 2018, Yu et al. [13] developed a stereospecific aziridination of alkenes using *N*-tosyl 1-aminopyridium **85** as the nitrogen radical sources under photoredox catalysis, providing access to *N*-sulfonyl aziridines **90** (Scheme 1.41). In this protocol, the irradiation of the photoredox catalyst $Ir(ppy)_3$ generated the photoexcited species, which were oxidatively quenched by *N*-tosyl 1-aminopyridium to form the nitrogen-centered radical species **86** and (Ir^{IV}). The addition of the electrophilic radical to the alkene **87** gave intermediate **88**, which was oxidized by Ir^{IV} to afford the stabilized carboncation intermediate **89** with the regeneration of Ir^{III}. Finally, the intramolecular cyclization followed by deprotonation produced highly functionalized aziridines **90** with excellent diastereoselectivity (Scheme 1.41).

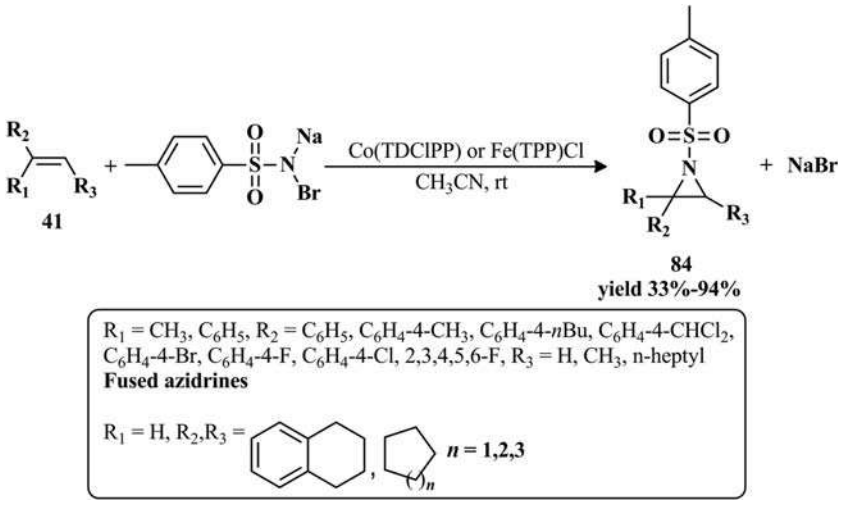
Takemoto and coworkers developed photo-induced aziridination of olefins under free-metal catalysis via introducing an ortho-coordinating substituent to *N*-sulfonyliminiodinanes **92** [87,88]. Such a stable in situ coordinating bond between the iodine atom and ortho



SCHEME 1.38 Ultrasound and microwave-assisted aziridination of olefin **81** with bromamine-T.

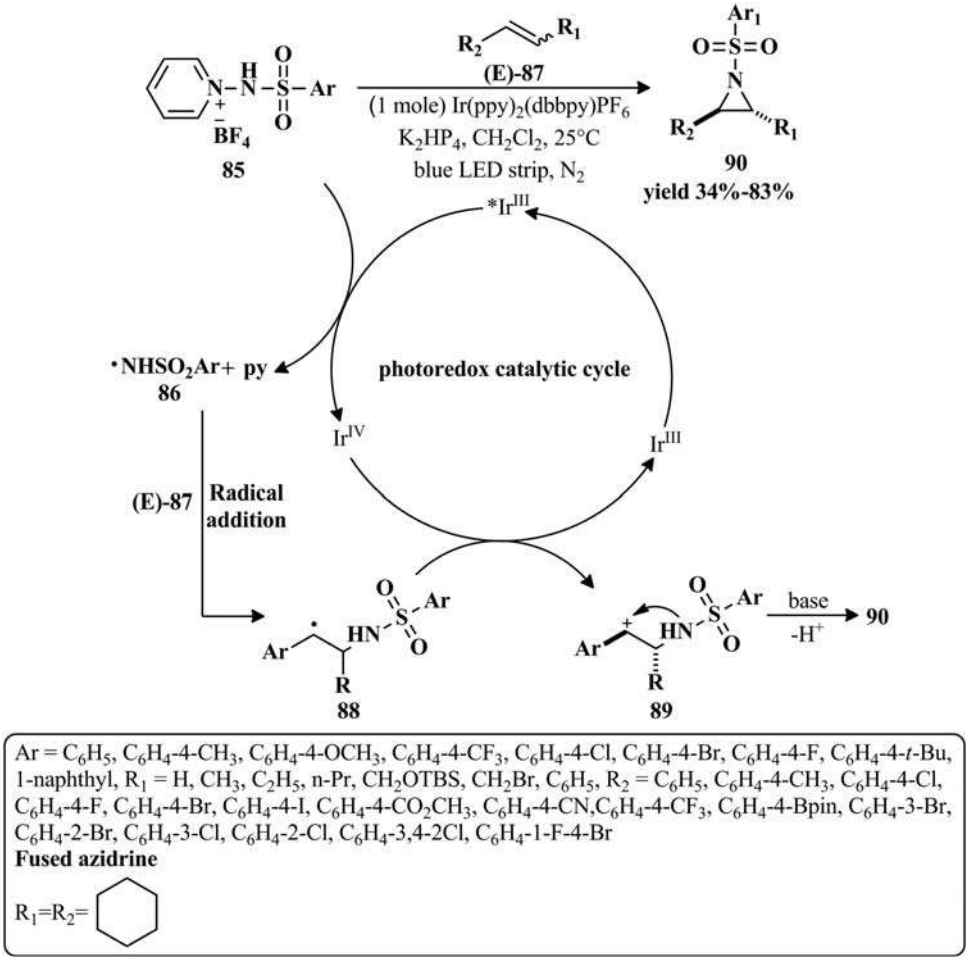


SCHEME 1.39 Introduction of metalloporphyrin complexes in the transformation of styrene to *N*-sulfonyl aziridine **83**.

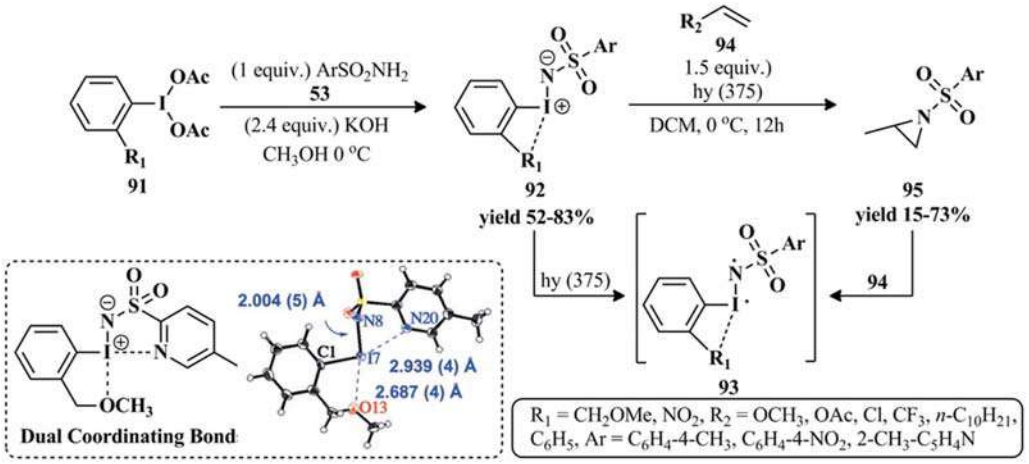


SCHEME 1.40 Efficient aziridination of mono- and disubstituted olefins using cobalt and iron complexes of porphyrins Co(TDClPP) and Fe(TPP)Cl as active catalysts.

substituent would stabilize the photoexcited state of the iminoiodinane **93** and avoid the formation of free nitrene. *N*-Ortho-methoxymethyl and nitro-substituted iminoiodinanes **92** were specifically used for this transformation due to their capability to form more stable coordinating bonds than the other substituents. Surprisingly, *N*-pyridinesulfonyl iminoiodinane revealed superior stability at room temperature



SCHEME 1.41 Visible-light-induced photocatalysis in the synthesis of *N*-sulfonyl aziridines.



SCHEME 1.42 Photo-induced aziridination of olefins *N*-orthomethoxymethyl and nitro-substituted iminoiodinanes **92**.

due to the dual coordinating bonds as proved in the single-crystal X-ray of its structure. The tailor-designed iminoiodinanes **92** was effectively obtained in moderate to extreme yields from the reaction of the corresponding sulfonamides **53** with 2-nitro or 2-methoxymethyliodobenzene diacetate in basic methanol solution. This approach produced aziridines **95** in low to moderate yield (Scheme 1.42).

1.3 Synthesis of *N*-sulfonated aziridines via transferring of carbon to *N*-sulfonyl imines

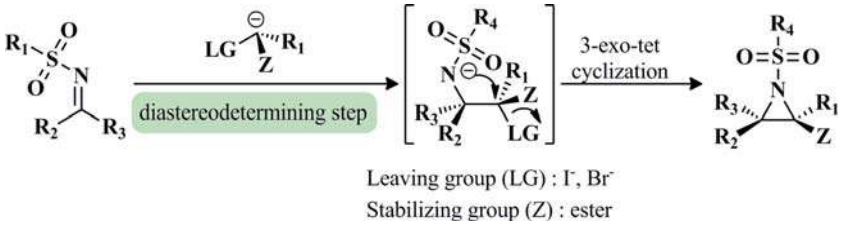
Among the strategies developed for the synthesis of *N*-sulfonyl aziridines, aziridination of *N*-sulfonyl imines has attracted considerable attention. Two main routes will be discussed here: (1) Direct aza-Darzens reaction and (2) The reaction of *N*-sulfonyl imines with sulfonium ylide.

1.3.1 Direct aza-Darzens reaction

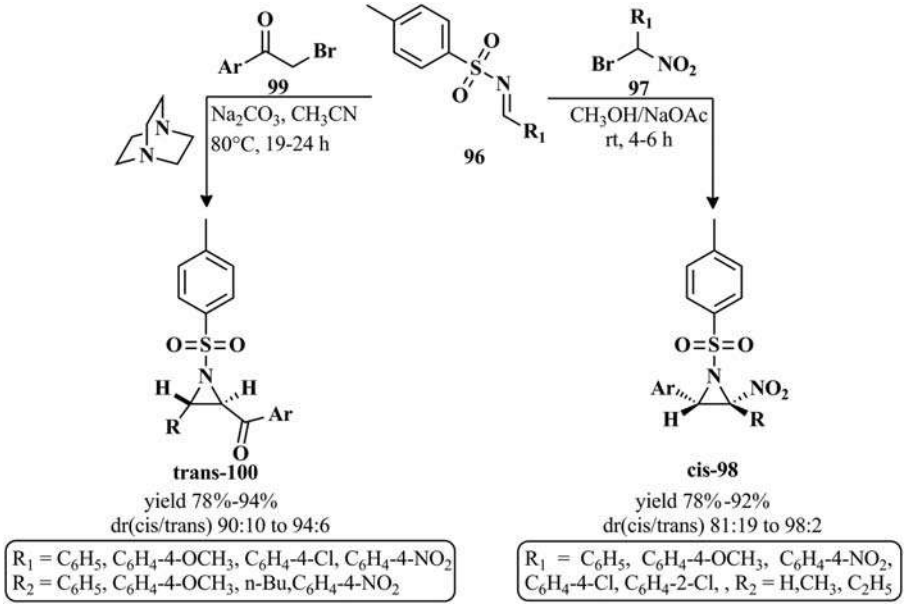
The aza-Darzens reaction, an essential approach for the construction of *N*-sulfonyl aziridines, involved reacting *N*-sulfonyl imines with stabilized anions tolerating α-leaving groups (generally halogens). In the aza-Darzens reaction, a nucleophilic attack of the anion on the imine bond (C = N) was achieved to generate the β-haloamine intermediate which efficiently underwent 3-*exo*-tet cyclization as represented in Scheme 1.43.

Many authors highlighted the potential of aza-Darzens reaction for straightforward access to *N*-sulfonyl aziridines from electron-deficient alkenes. Yadav et al. [89] disclosed the first expeditious nitroaziridination of *N*-tosylaldimines **96** with 1-bromonitroalkanes **97**. It was found that MeOH/NaOAc was the best solvent/base system to afford *N*-sulfonated aziridines **98** with high yield and cis-selectivity (Scheme 1.44). The same group [90] developed an organocatalytic aziridination reaction of *N*-tosyl imines **96** with phenacyl bromide derivatives **99** for providing chemically and pharmaceutically relevant *N*-tosyl aziridines **100** with *trans*-diastereoselectivities (Scheme 1.44).

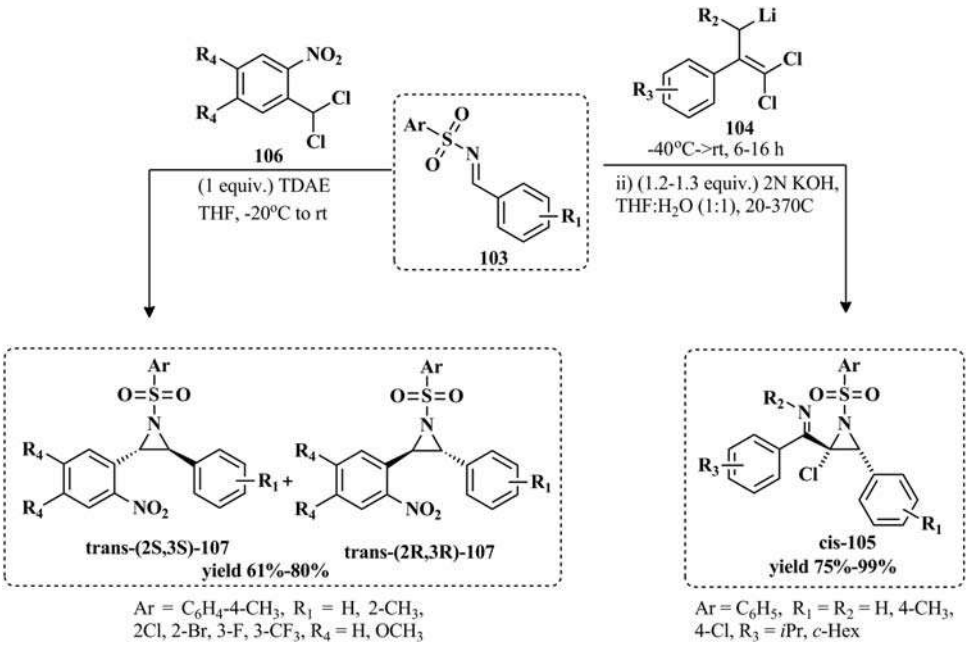
Direct aza-Darzens protocol involving the reaction of *N*-sulfonylaldimines **103** with 3,3-dichloro-1-azaallylic anions **104** was described by Colpaert et al. in 2011 [91]. This protocol was found to be very efficient to synthesize defined highly functionalized *cis*-3-aryl-2-chloro-2-imidoyl-1-(phenylsulfonyl)aziridines **105** as a new example of stable 2-chloroaziridines in excellent yield (up to 99%)



SCHEME 1.43 Mechanistic insights of direct aza-Darzens reaction.



SCHEME 1.44 Easy access to *N*-sulfonyl aziridines from electron-deficient alkenes **96** via aza-Darzens reaction.



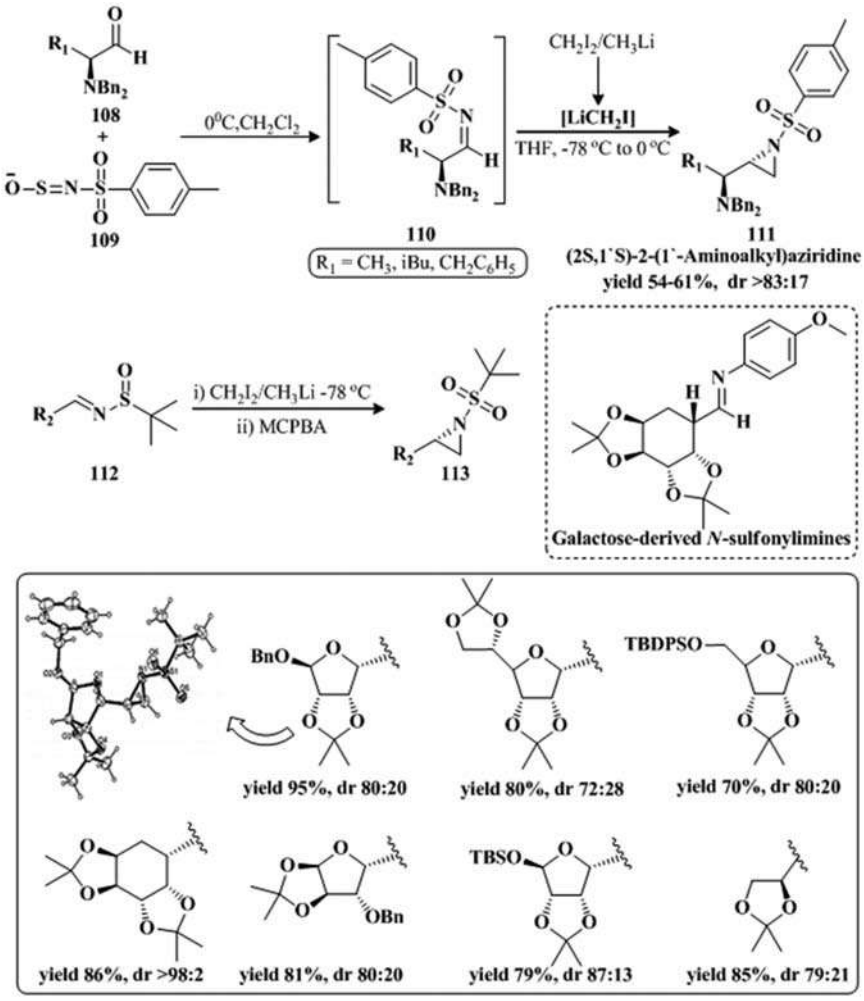
SCHEME 1.45 Direct aza-Darzens for efficient synthesis of chiral *N*-sulfonyl aziridines **105** and **107**.

(Scheme 1.45). Such aziridines **105** efficiently could undergo further transformations. In 2013, Khoumeri et al. [92] introduced tetrakis(dimethylamino)ethylene (TDAE), as an organic reducing agent, to reduce 1-(dichloromethyl)-2-nitrobenzene derivatives **106** to α-chlorocarbanion, which able to react with *N*-sulfonyl *N*-sulfonylaldimines **103** under the basic condition to yield a mixture of cis/trans isomers of *N*-sulfonyl aziridines **107** (Scheme 1.45).

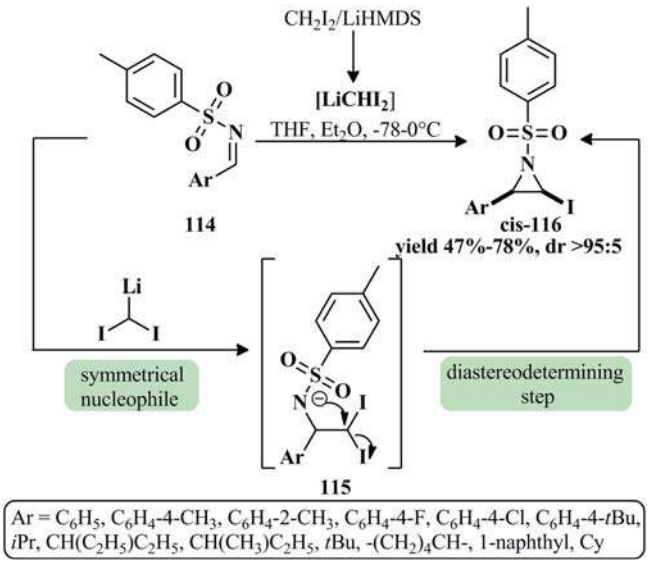
Concellón and coworkers [93–95] dealt with the lack of reactivity of in situ generated halomethyllithium compounds toward the poor electrophilic reagents such as imines via utilizing *N*-sulfonyl imines as a synthetic model of imines bearing *N*-EWGs. Indeed, the authors successed to provide access to enantiopure (2 *S*,1′*S*)-2-(1-aminoalkyl)aziridine **111** in moderate yield and extreme diastereoselectivity upon the addition of the in situ generated iodomethyllithium ($LiCH_2I$) to enantioenriched *R*-tosylated imines **110** derived from phenylalaninal **108** (Scheme 1.46). Taking into account the characteristic usefulness of this methodology, they decided to investigate its application for the aziridination of sugar-derived *N*-sulfonylimines. Unfortunately, no addition of iodomethyllithium to galactose-derived *N*-sulfonylimine was occurred and consequently galactose-derived aziridines didn't produce. Accordingly, an alternative way was performed to produce *N*-sugar-derived sulfonyl aziridines via the addition of iodomethyllithium to *N*-sulfinylimines that were used as an alternative substrate to *N*-sulfonylimines, followed by the oxidation of the resulting *N*-sulfinyl aziridines to *N*-sulfonyl aziridines **113** in the presence of oxidizing agent MCPBA (Scheme 1.46). Sugar-derived *N*-sulfonyl aziridines **113** were produced, as evidenced in single X-ray diffraction, in high yields with medium to good stereoselectivities under this reaction condition.

In 2013, Boultwood et al. [96] developed the conjugate addition-cyclization protocol analog to the aza-Darzens reaction involving the reaction of diiodomethyllithium with *N*-tosyl imines **114** to afford an unprecedented synthesis of *cis*-iodoaziridines **116**. Such protocol differed from the aza-Darzens reaction in terms of the diastereodetermining step. The diastereoselectivity of the produced aziridines **116** was determined in the initial addition of the aza-Darzens reaction (Scheme 1.47). The unstable substituted reagent $LiCHI_2$ acted as a symmetrical nucleophile, consequently, the initial addition step does not represent diastereodetermining. In this case, the cyclization step determined the diastereochemistry of *N*-sulfonyl aziridines by selecting one of two iodide leaving groups. $LiCHI_2$was in situ generated through deprotonating CH_2I_2 with LiHMDS at very low temperatures (−78°C−0°C) (Scheme 1.47).

An interesting paper, Wu et al. [97] pursued the advance of a synthetic protocol for the synthesis of highly functionalized aziridinyl diesters **118** by direct aza-Darzens aziridination of 2-bromomalonates **117** with *N*-



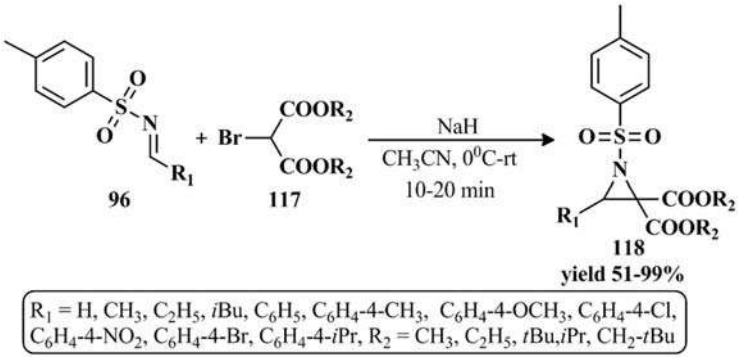
SCHEME 1.46 The preparation of enantiopure (2S,1′S)-2-(1-aminoalkyl)aziridine **111** and sugar-derived *N*-sulfonyl aziridines **113**.



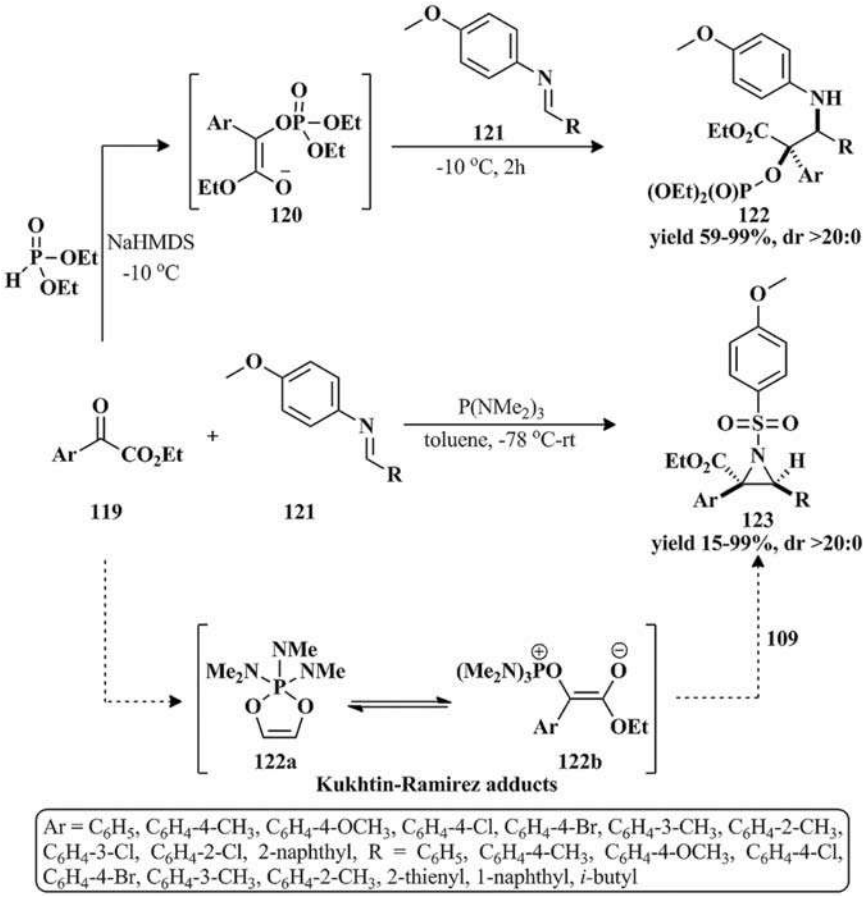
SCHEME 1.47 Unprecedented synthesis of *cis*-iodoaziridines via addition of diiodomethyllithium to *N*-tosyl imines **114**.

tosylimines **96** (Scheme 1.48). The wide substrate scope and high yield (up to 99%) required a feature for this reaction for exploration on a large scale.

Jiang and coworkers [98,99] made attempts to focus on the aziridination of α-ketoesters with *N*-sulfonyl imines. They speculated that the reaction might achieved through aza-Darzens reaction of *N*-sulfonyl imines **121** with α-phosphonyloxy enolates **120**. The latter was formed via base-promoted addition reaction of diethyl phosphite with α-ketoesters **119**, followed by [1,2]-phospha-Brook rearrangement (Scheme 1.49). However, the relative weak nucleophilicity of the nitrogen anion of *N*-sulfonyl imines prevents the aziridination and allowed a retro-Mannich reaction to produce



SCHEME 1.48 Direct aza-Darzens aziridination reaction for the preparation of highly functionalized aziridinyl diesters.



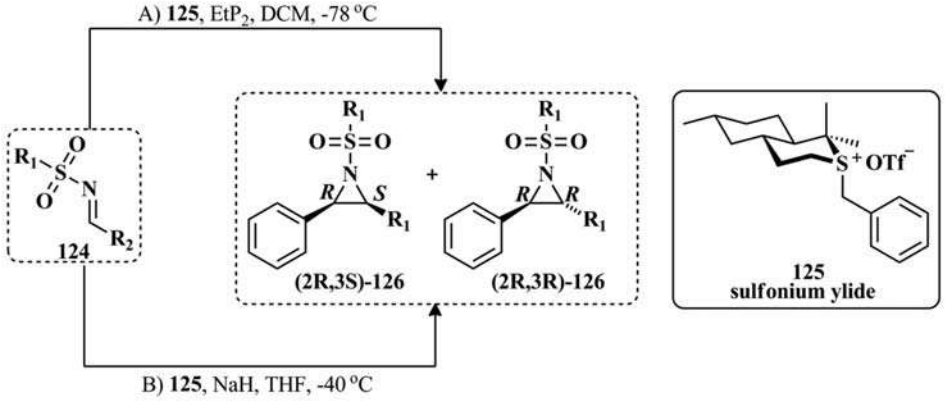
SCHEME 1.49 Successful attempts for the aziridination of α-ketoesters **119** with *N*-sulfonyl imines **121**.

α-hydroxy- and *N*-sulfonyl aza-amino acid derivatives **110** [98]. Alternatively, a polar-reversal strategy was achieved by using trivalent phosphorus reagents to provide efficient aziridination of α-ketoesters with *N*-sulfonyl imines. The addition of trivalent phosphorus reagent to α-ketoesters produced the reactive Kukhtin-Ramirez adducts **122a,b**, which are effectively intercepted by *N*-sulfonyl imines **121** in an aza-Darzens-like transformation, yielding aziridine-2-carboxylates **123** (Scheme 1.49) [99].

1.3.2 Reaction of *N*-sulfonyl imines with sulfonium ylides

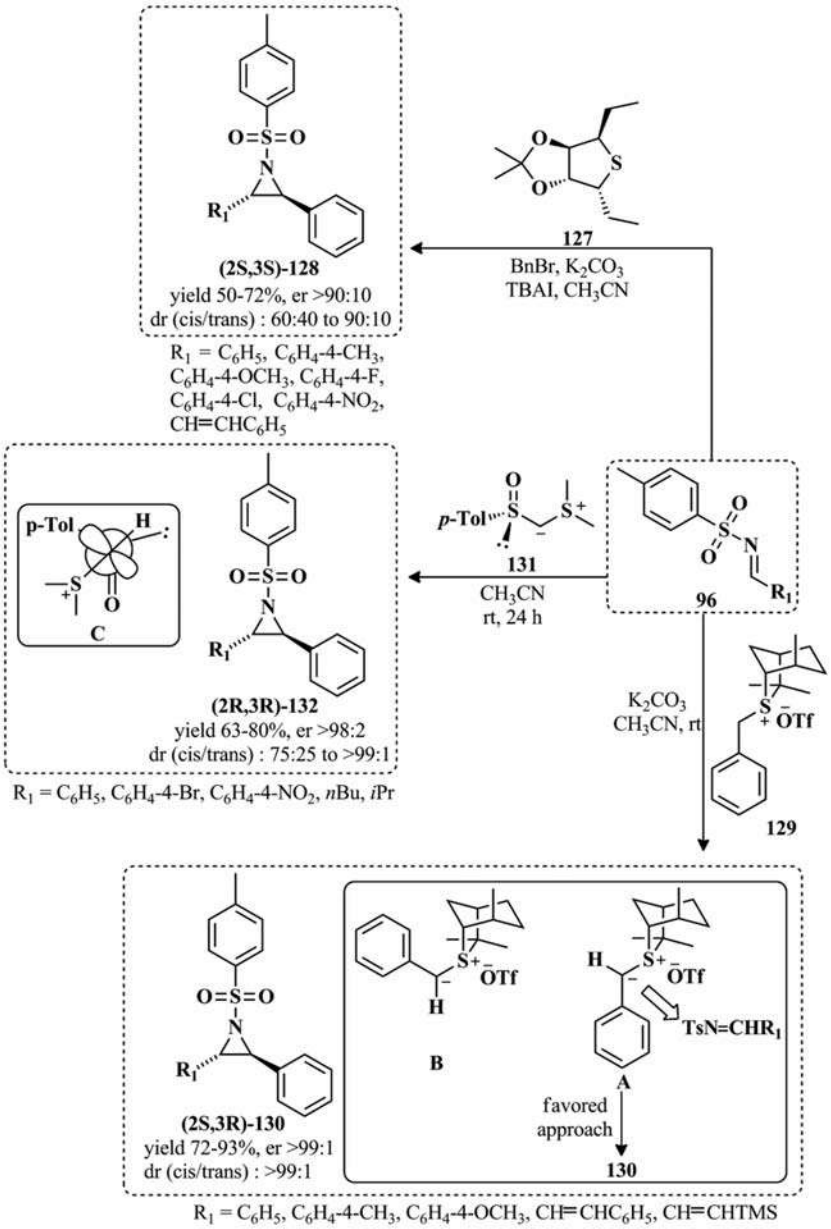
The sulfonium ylide-mediated aziridination of *N*-sulfonyl imines, the aza analog of the Johnson–Corey–Chaykovsky reaction, requires a particularly useful approach for the construction of enantiopure *N*-sulfonyl aziridines with moderate to good diasteroselectivity. Solladié-Cavallo et al. [100] described an asymmetric synthesis of 2,3-disubstituted *N*-tosyl aziridines **126** by the reaction of chiral sulfonium ylide **124** with *N*-tosylimine **125**. A phosphazene base (EtP_2) was used as a base to form the desired ylide in extreme enantioselectivity for both *cis*- and *trans*-aziridine products **126** (Scheme 1.50). Hameršak and coworkers [101,102], two different works, explored the efficiency of sodium hydride base as an alternative to the expensive and toxic phosphazene base EtP_2 without loss of yield, diastereoselectivity, or enantioselectivity. The influence of the *N*-imine substituents on the stereoselectivity in aziridination was also investigated. It was observed that the order of reducing trans-selectivity represented 2-(trimethylsilyl)ethanesulfonyl (SES) > toluenesulfonyl (Ts) > *o*-nitrobenzenesulfonyl (o-Ns) as shown in Scheme 1.50.

Gui et al. [103] explored the use of a chiral sulfonium ylide that formed in situ from the reaction of C2-symmetric sulfide **127** with benzyl bromide under basic conditions, in the aziridination of *N*-tosyl imines **96**. Tetrabutylammonium iodide (TBAI) was utilized as a phase-transfer catalyst to produce chiral *trans*-(*S*,*S*)-aziridines **128** in good yield with high enantioselectivities (Scheme 1.51). Illa et al. [104] employed alternative semistabilized ylide generated from benzyl sulfonium salt **129** for aziridination of *N*-tosyl imines **96**, furnishing with *trans*-(*R*,*R*)-aziridines **130** in high levels of enantioselectivity. The formed compounds could adopt the two possible conformers **A** or **B**, but conformer A was more favorable than conformer **B** due to steric reasons. The high enantioselectivity of aziridines **130** was attributed to a selective approach of *N*-tosyl imines **86** to the *Re*-face of this conformer because the methyl group flanked the *Si*-face (Scheme 1.51). Midura et al. [105] synthesized the stabilized ylide bearing an enantiopure sulfinyl group **131** and demonstrated its application in stereoselective aziridination of diverse *N*-tosyl imines **96**. The stereochemical course of this reaction was determined by the ylide



Condition A	Condition B
R_1 = C_6H_4-4-CH_3, R_2 = C_6H_5, C_6H_4-4-OCH_3, 1-naphthyl, *t*Bu, 9-phenanthryl, 9-anthryl	R_1 = $(CH_2)_2SiCH_3$, C_6H_4-4-CH_3, C_6H_4-2-NO_2, R_2 = C_6H_5, C_6H_4-4-OCH_3, 1-naphthyl, *t*Bu, 9-phenanthryl, 9-anthryl
yield 60-88%, er >99:1 dr (cis/trans) : 30:70 to 99:1	yield 31-88%, er >98:2 dr (cis/trans) 100:0 to 2:98 for R_2 =$(CH_2)_2SiCH_3$ 100:0 to 24:79 for R_2 =C_6H_4-4-CH_3 100:0 to 53:47 for R_2 = C_6H_4-2-NO_2

SCHEME 1.50 Sulfonium ylide-mediated aziridination of *N*-sulfonyl imines for asymmetric synthesis of 2,3-disubstiuted *N*-tosyl aziridines **126**.

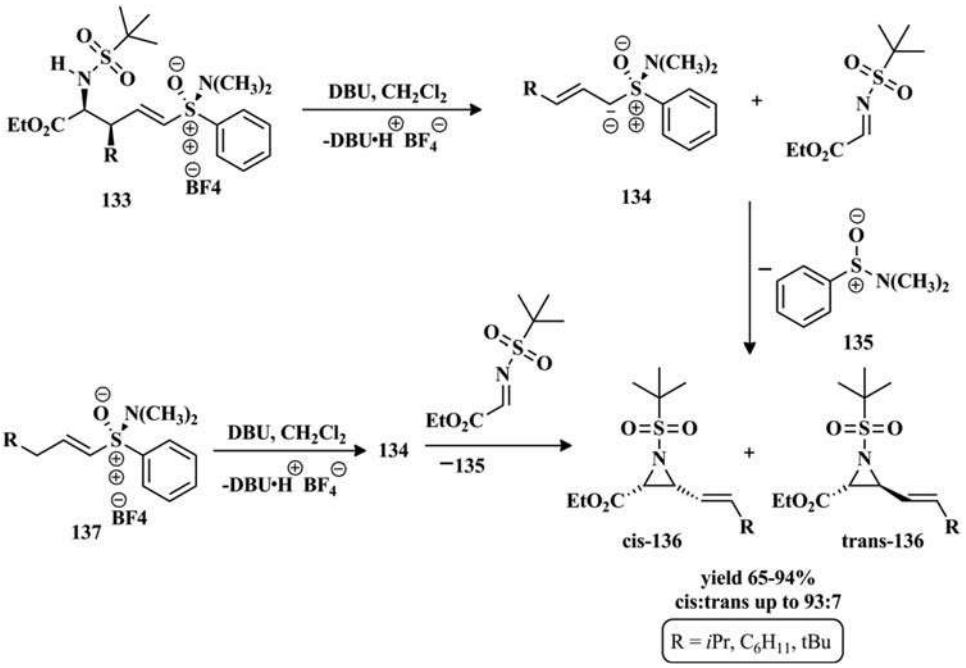


SCHEME 1.51 The employ of diverse chiral sulfonium ylides in aziridination of *N*-tosyl imines **96**.

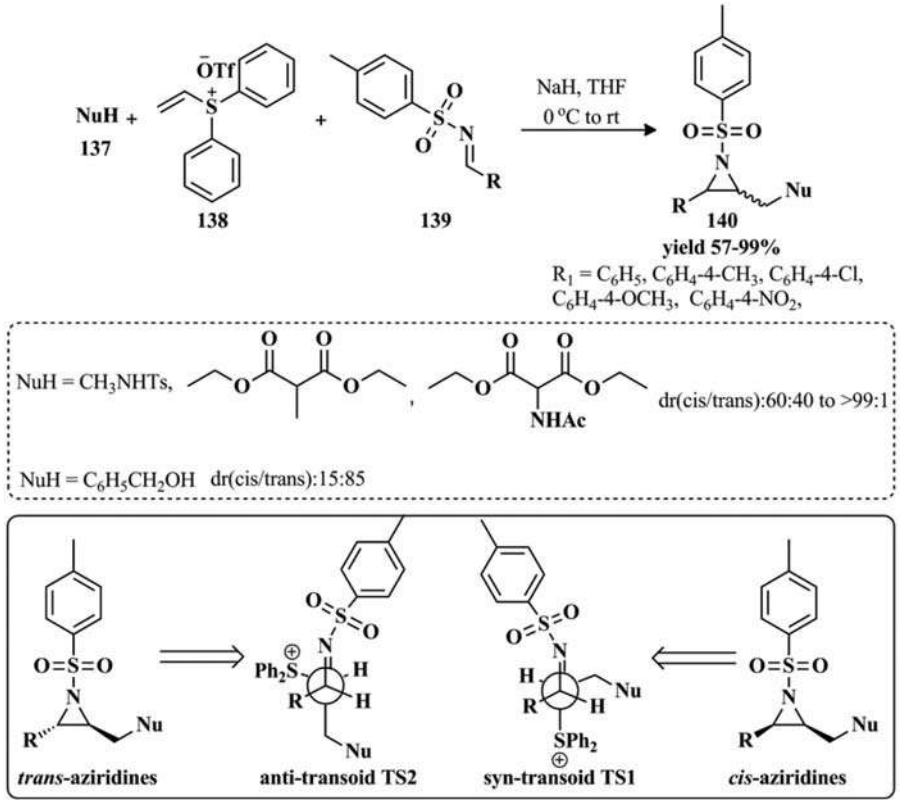
conformer **C**, delivering high selectivity for *cis*-(2*S*,3*R*)-aziridines **132** (Scheme 1.51).

Iska et al. [106] envisioned that aminosulfoxonium-substituted β,γ-unsaturated α-amino acids **133** would be a dual source of *N*-sulfonyl imines with sulfonium ylides upon treating with DBU. DBU, a non-nucleophilic base, deprotonated the N atom and, subsequently, formation of the corresponding anions was occured to produce allyl aminosulfoxonium ylides **134** and (*E*)-ethyl 2-((tert-butylsulfonyl)imino)acetate which directly reacted together affording alkenyl aziridine carboxylates **136** with moderate to extreme diastereoselectivity and enantioselectivity (Scheme 1.52). The same allyl aminosulfoxonium ylides **134** was also generated from 1-alkenyl aminosulfoxonium salts, as an alternative source, under the aforementioned condition. Alkenyl aziridine carboxylates were produced, and (*E*)-ethyl 2-((tert-butylsulfonyl)imino)acetate was externally added (Scheme 1.52).

An interesting paper, Kokotos et al. [107] reported the first study for trans/cis-selectivity in the reactions of non-stabilized sulfur ylides with *N*-tosyl imines. In a three-component reaction, the nucleophile **137** firstly reacted with the sulfonium salt **138** to generate a non-stabilized ylide,

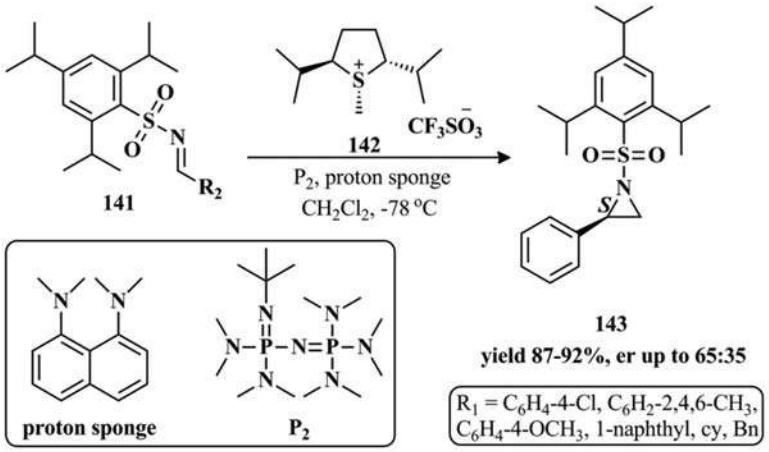


SCHEME 1.52 Synthesis of alkenyl aziridine carboxylates **136** via aminosulfoxonium-substituted β,γ-unsaturated α-amino acids **133**.

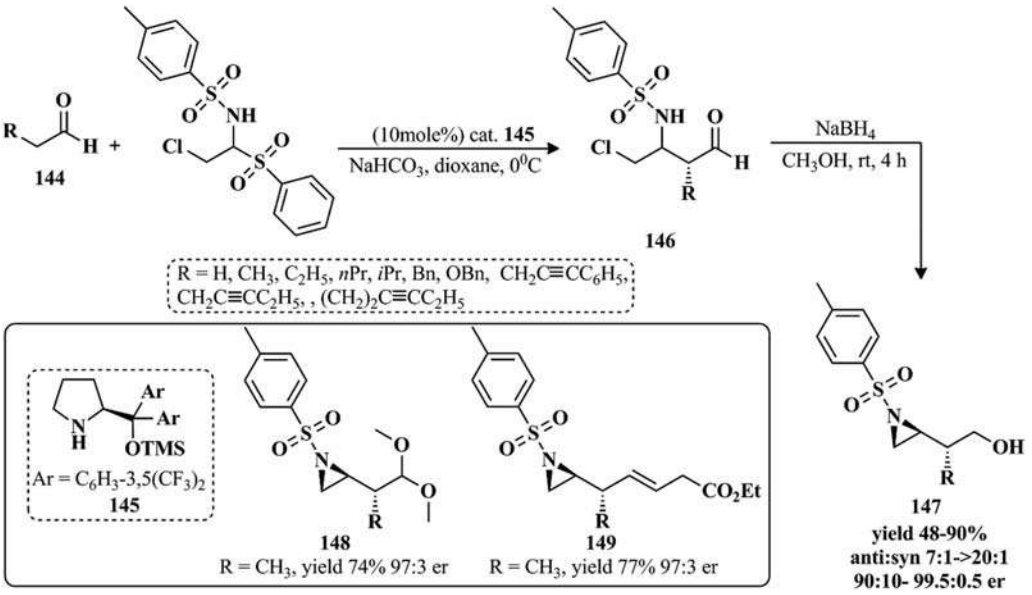


SCHEME 1.53 Three-component reaction to form a chiral tosylated aziridine **140**.

which then reacted with *N*-tosyl imine **139** to afford chiral tosylated aziridine **140** (Scheme 1.53). The $\pi-\pi$ interactions between the existing groups in a *syn*-transoid transition state TS1 resulted in *cis*-aziridines in almost all cases. However, the formation of a stabilizing hydrogen bond between the imine C−H in the anti-cisoid TS2 and the β-alkoxy group of the ylide caused the formation of *trans*-aziridines in the case of using alcohol as a nucleophile (Scheme 1.53).



SCHEME 1.54 Aziridination of triisopropylphenyl sulfonylimines **141** using chiral sulfonium salt **142** in the presence of proton sponge as an auxiliary base.



SCHEME 1.55 Successful synthesis of enantioenriched aziridines containing either α,β-hydroxyethyl moiety or acetal moiety **147-149**.

Recently, Kavanagh et al. [108] developed a novel ylide-based protocol involving a chiral sulfonium salt **142** with a strong base for the aziridination of triisopropylphenyl sulfonylimines **141** (Scheme 1.54). Despite the poor enantioselectivity of aziridine products **143**, this protocol required a rare example for the synthesis of chiral terminal aziridines. Proton sponge was utilized as an auxiliary base for scavenging triflic acid that was generated from the decomposition of **142**.

1.4 Synthesis of *N*-sulfonated aziridines via intramolecular cyclization of amine derivatives

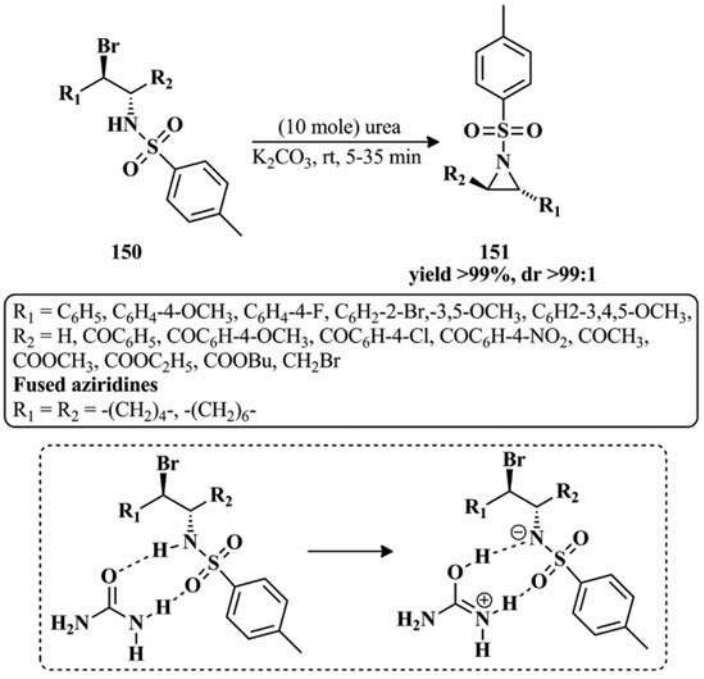
Although pioneering studies on the direct azidrination of olefins were generally described, a useful alternative strategy based on intramolecular cyclization of chiral amino alcohols as well as 1,2-vicinal haloamines was also represented. In 2011, Hayashi et al. [109] prepared synthetically useful enantioenriched aziridines containing α,β-hydroxyethyl moiety **147**. An enantioselective Mannich reaction of aliphatic *N*-(2-chloro-1-phenylsulfonylethyl)-*p*-toluenesulfonamide and aldehydes **144** in the presence of diarylprolinol silyl ether catalyst **145** led to the formation of the putative amino aldehyde intermediates **146**, which then easily reduced by using $NaBH_4$ to *N*-sulfonyl aziridines **147** (Scheme 1.55). Similarly, both aziridines containing an acetal moiety **148** and aziridines containing an α,β-unsaturated moiety **149** were also prepared (Scheme 1.55).

A facile and rapid methodology for the synthesis of *N*-tosyl aziridines **151** from 1,2-vicinal haloamines **150** via grinding the mixture of 1,2-vicinal haloamine **150**, anhydrous potassium carbonate, and a catalytic amount of urea in the air under solvent-free conditions (Scheme 1.56) [110]. Urea, which is considered a strong H-bond donor and acceptor, can form a hydrogen bond with the nitrogen of sulfonamide, leading to the transferring proton on the sulfonamide to the urea oxygen atom to form the nitrogen anion nucleophile.

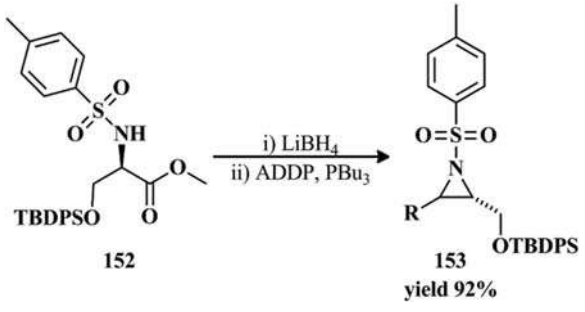
Two-step synthesis of enantiomerically pure silyl protected aziridine **153** from silyl protected ester **152** was achieved via ester reduction using $LiBH_4$, followed by mitsunobu condensation (Scheme 1.57) [111]. It was worth mentioning that such aziridines **153** could efficiently undergo [3 + 3] annelations under palladium catalysis for the stereoselective synthesis of another aza heterocyclic.

A well-organized protocol for the synthesis of *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonyl aziridine **155** from optically pure 2,3-epoxy-1,1,1-trifluoropropane was reported by Katagiri et al. [109]. In such protocol, the initial nucleophilic-ring opening of epoxide with $TsNH_2$ in the presence of lewis acid afforded chiral amino alcohol derivative **154**, which underwent intramolecular mitsunobu reaction to produce the desired aziridines **155** (Scheme 1.58).

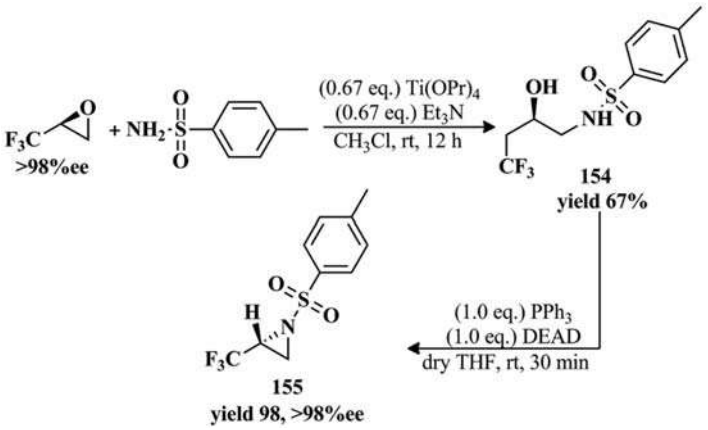
Very recently, Shabani et al. [112] reported an intramolecular Mitsunobu type reaction of tripeptide **158** for the synthesis of a novel aziridine-containing tripeptide



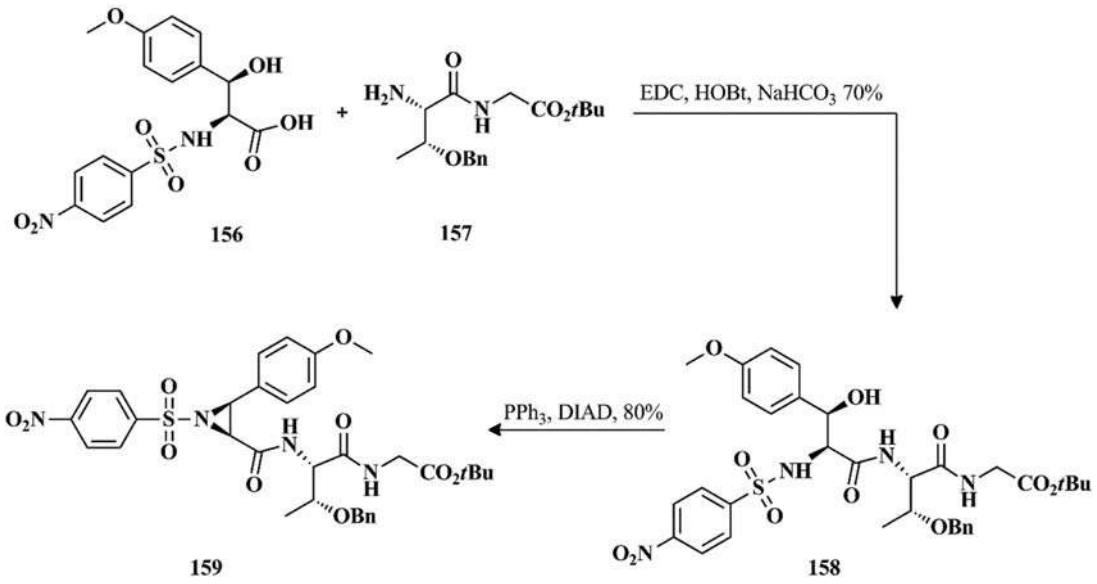
SCHEME 1.56 Rapid and facile synthesis of *N*-tosyl aziridines **151** from 1,2-vicinal haloamines **150**.



SCHEME 1.57 The two-step preparation of silyl protected aziridine **153** from silyl protected ester **152**.



SCHEME 1.58 Synthesis of *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonyl aziridine **155** from optically pure 2,3-epoxy-1,1,1-trifluoropropane.



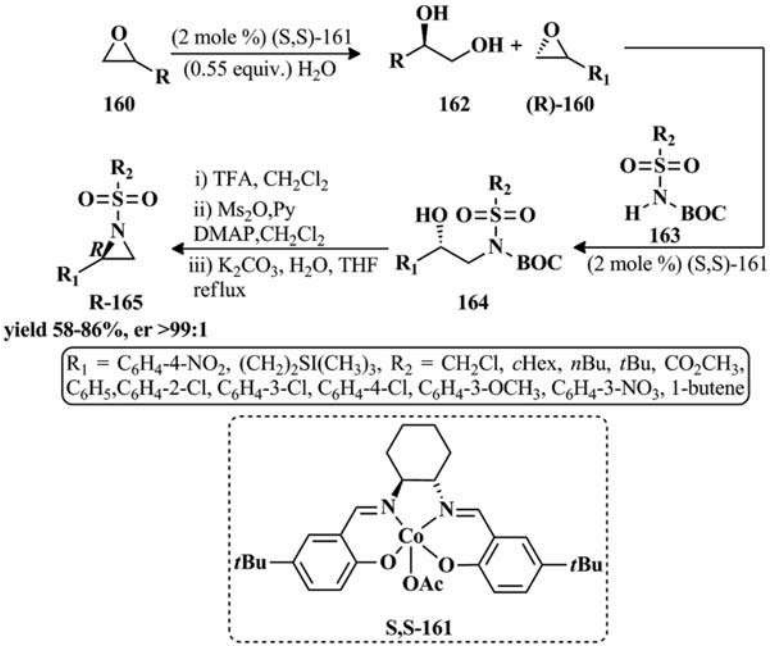
SCHEME 1.59 Synthetic strategy for synthesis of a novel aziridine-containing tripeptide **159**.

159 as a single stereoisomer. Tripeptide **158** was firstly prepared by coupling β-hydroxytyrosine **158** with dipeptide **157** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), a carboxyl activating agent (Scheme 1.59).

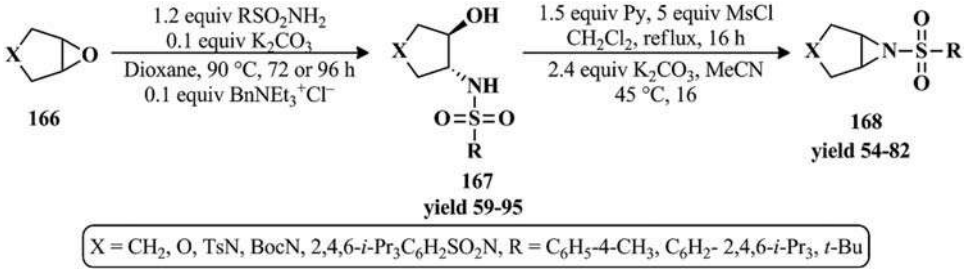
A novel and practical route toward enantiomerically enriched 1,2-amino alcohols derived from racemic epoxides ($\pm$)- was reported and their utility in the synthesis of aziridines **165** tolerating a labile *N*-sulfonyl group was descriped. The Co^{III}−Salen complex **S,S-161** was found to be effective in the hydrolytic kinetic resolution (HKR) of racemic terminal epoxides [113]. A highly selective HKR could be followed by ring opening of the unreacted enantiomer of the epoxide **R-160** supported by the same catalyst. Subsequently, a deprotection/mesylation/cyclization cascades provided terminal aziridines containing aliphatic and aromatic substituents **R-165** with high enantiomeric purity (up to >99%) (Scheme 1.60) [114].

Brien et al. [115] represented a high-yielding and adequate two-step preparation of *N*-Sulfonyl aziridines **168** derived from epoxides **166**. In this synthetic approach, epoxide ring opening with sulfonamides occurred to give amino alcohols **167** and sequent mesylation−cyclization to yield the fused aziridines **168** as the sole products without isolation of amino mesylate intermediate (Scheme 1.61).

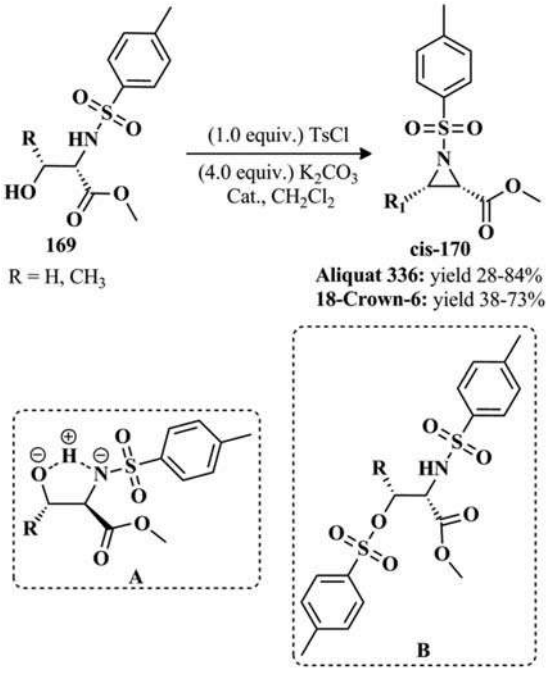
Marzorati et al. [116] developed one step phase-transfer catalyzed aziridination of β-hydroxy-α-aminoesters **169** (Scheme 1.62). The authors investigated two phase-transfer catalysts, including the quaternary ammonium salts (aliquat 336) and crown ethers (18-Crown-6) in this reaction. It



SCHEME 1.60 Two-step synthesis of chiral terminal aziridines **R-165** from racemic epoxides (±)-**160**.



SCHEME 1.61 Synthesis of fused aziridines **168** from epoxides **166** in two step reaction.



SCHEME 1.62 Aziridination of β-hydroxy-α-aminoesters **169**.

was observed that aliquat 336 was a more effective catalyst in aziridination of *N*-tosyl-*L*-threonine methyl esters or *N*-tosyl-*L*-serine **169** compared with 18-Crown-6. The mechanism of this reaction was assumed to be in four stages, firstly, the tosylated nitrogen of **169** was deprotonated at the film coated with potassium carbonate to generate intermediate **A**, which was facilely transported to the organic phase via the exchange between potassium cations and the quaternary ammonium (Q^+). Secondly, the transported intermediate **A** was *O*-tosylated in the organic phase. Thirdly, the tosylated nitrogen of the *N*,*O*-ditosylated aminoester **B** was deprotonated. After SN_2 ring closure, the favorable *cis*-aziridines **cis-170** were finally formed in the organic phase (Scheme 1.62).

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Chapter 2

Chemistry of *N*-sulfonated aziridines and their use in polymerization reactions

2.1 Introduction

Aziridines are one of the most useful building blocks in modern synthetic chemistry due to their high ring strain, similar to the other three-membered rings (epoxides, cyclopropanes) and consequently, aziridines can undergo a ring cleavage under comparatively mild conditions [1–11]. Considerable attention has increased in recent years to discovere valuable synthetic reactions that transform the aziridine ring into nitrogen-containing compounds, such as nucleophilic ring-opening, cross-coupling reactions, isomerizations, cycloadditions, and carbonylations [12–18]. Sulfonyl-activated aziridines are particularly attractive for their sufficient reactivity and remarkable efficacy in the preparation of an array of acyclic and cyclic nitrogen-containing compounds [19–21].

In this chapter, we provide a comprehensive overview on the chemistry of *N*-sulfonated aziridine, focusing on the recent development pathways, reaction conditions and mechanistic insights as well as stereo and regioselectivity (Fig. 2.1). Moreover, this chapter covers examples on the applications of *N*-sulfonated aziridines in living aza-anionic polymerization (Fig. 2.1). It is well-known that sulfonyl-activated aziridines can be polymerized anionically because of the superior electron-withdrawing sulfonyl group capability that allows them to facilitate the nucleophilic ring-opening reaction as well as inhibiting chain

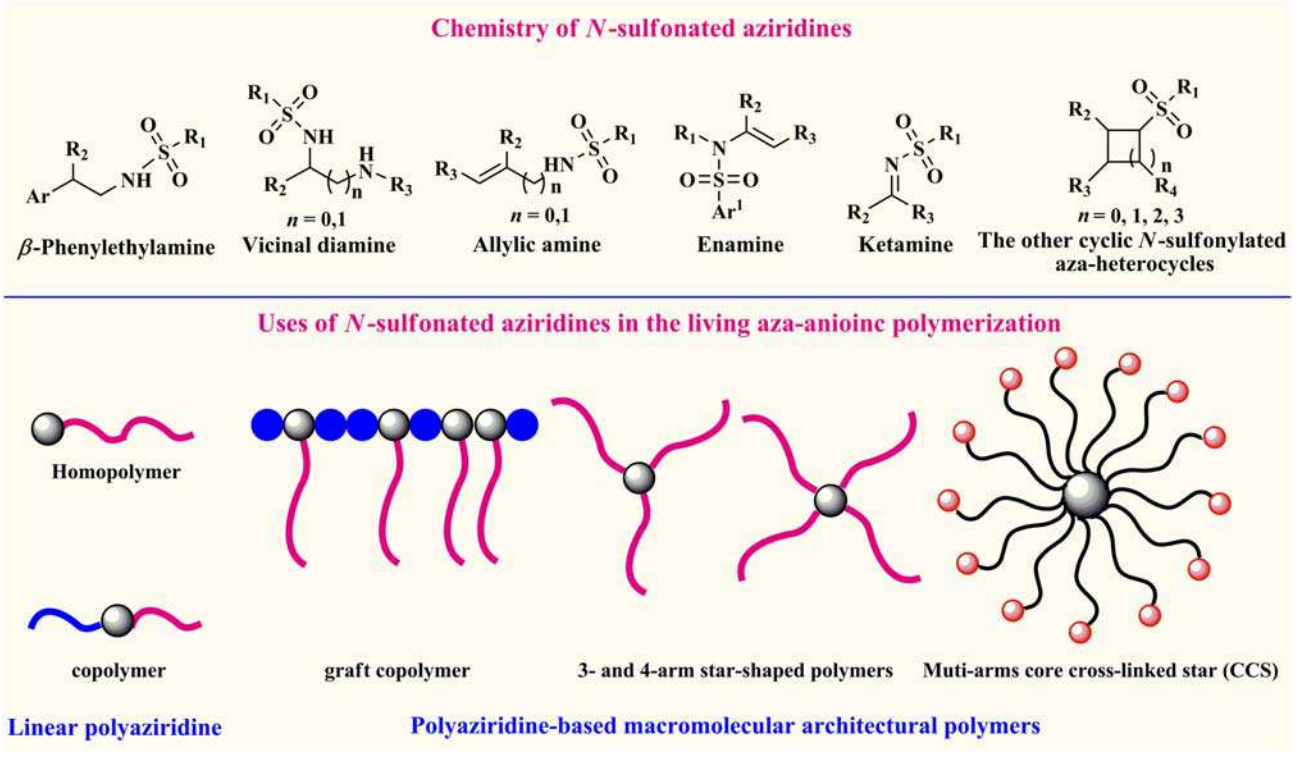


FIGURE 2.1 Reaction conditions and mechanistic insights of *N*-sulfonated aziridines and its important application in living aza-anionic polymerization.

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00001-X

branching. The great interest in synthesizing poly(*N*-sulfonylaziridine)s is due to the ability of such polymeric system to synthesize different polyamines after the removal of the sulfonyl group. To date, living anionic polymerization of sulfonyl-activated aziridines, followed by desulfonylation, is an efficient pathway rather than traditional routes toward well-defined linear polyethyleneimine and its derivatives. We report here all attempts in the desulfonylation process and its limitations as well as pioneering work in the preparation of macromolecular architectures through the living anionic polymerization of *N*-sulfonylaziridines.

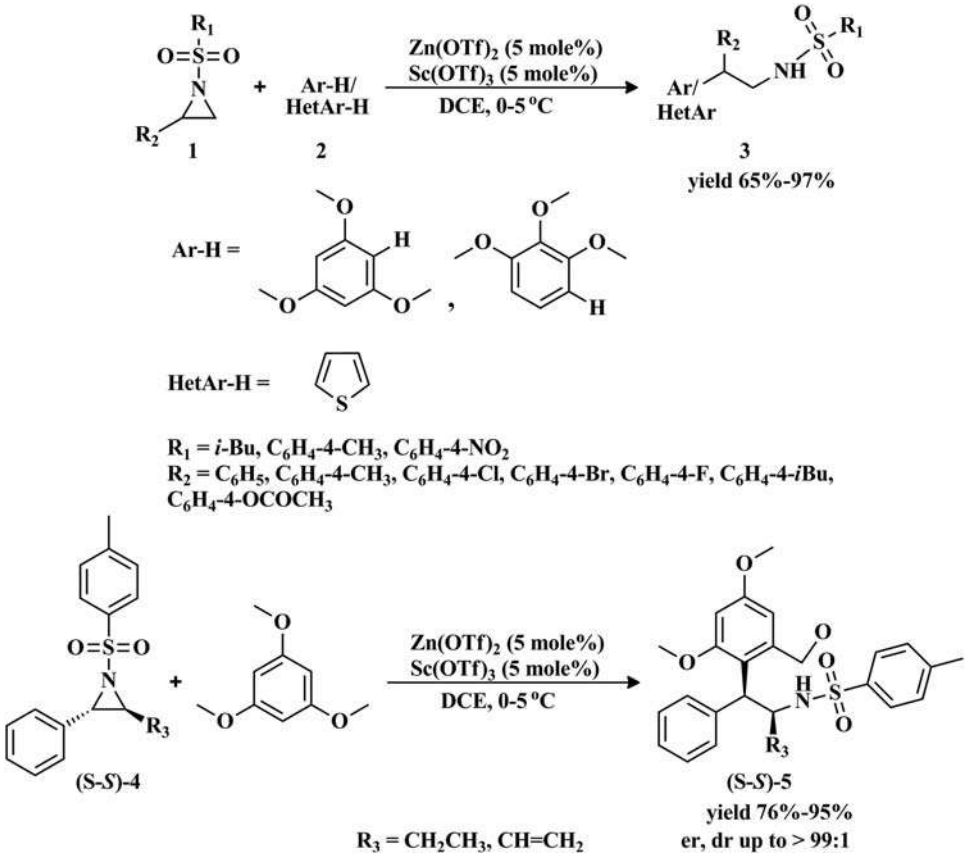
2.2 Chemistry of *N*-sulfonated aziridines

2.2.1 Ring-opening of *N*-sulfonated aziridines to acyclic amine derivatives

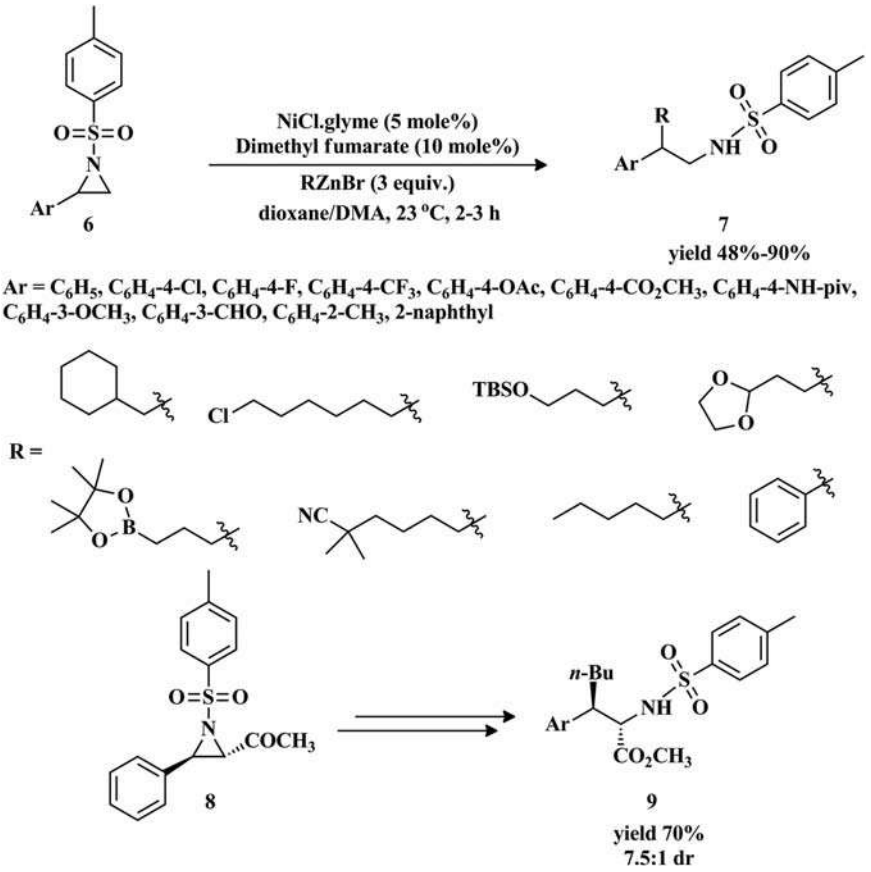
2.2.1.1 To β-phenylethylamine derivatives

β-Phenethylamines are present in a number of vital neurotransmitters and their extensive use in the synthesis of drug targets for diverse treatments (anxiety disorders, depression, Parkinson's, and Alzheimer's diseases) [22,23]. β-Phenethylamine is a basic structure of many small molecules with pharmacological characteristics and thus the pharmacological importance of β-phenethylamine encourages organic chemists to development of novel and efficient approaches for the preparation of β-phenethylamines analogs.

A novel synthetically β-phenethylamines analog **3** was reported by Ghorai *et al.* [24] who pronounced the catalytic efficiency of a mixture of Lewis acids $Zn(OTf)_2$ and $Sc(OTf)_3$ (1:1 ratio) in ring-opening of monosubstituted *N*-tosylaziridines **1** with different electron-rich arenes or heteroarenes **2** (Scheme 2.1). Authors employed such a strategy to prepare chiral arylethylamines **(S−S)-5** with good yield (up to >99%) and high levels of enantiocontrol as well as medium to excellent diasteroselectivity (er, Dr up to >99:1) using chiral disubstituted aziridine substrates **(S−S)-4**.



SCHEME 2.1 Synthesis of β-phenethylamines analog **3** *via* ring-opening of monosubstituted *N*-tosylaziridines **1**.



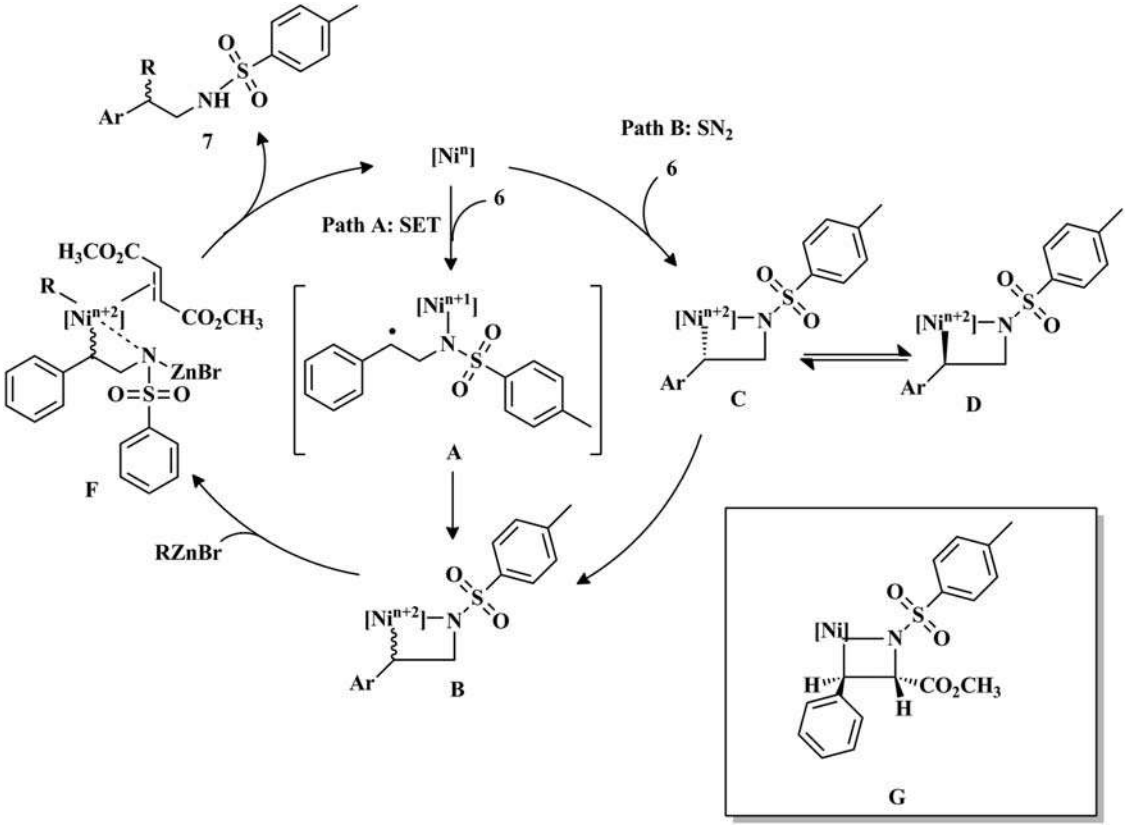
SCHEME 2.2 Negishi-type cross-coupling of *N*-sulfonated aziridines **6** with organozinc compounds to form β-arylethylamines **7**.

The transitional metal-medicated cross-coupling strategy played a significant role in the synthesis of β-phenethylamine analogs. A new catalytic system comprising an easy access nickel chloride as Ni(II) source and the dimethyl fumarate ligand to catalyze Negishi-type cross-coupling of *N*-sulfonated aziridines **6** with organozinc compounds was reported, affording β-arylethylamines **7** with extreme regioselectivivity (Scheme 2.2) [25]. Additionally, chiral 1,2-disubstituted aziridines **8** could participate in the cross-coupling with a highloading of the catalyst to yield β-arylethylamines with α-amino ester **9**. The formation C − C bond occurred with retention of configuration, delivering the coupling product at 7.5:1 Dr.

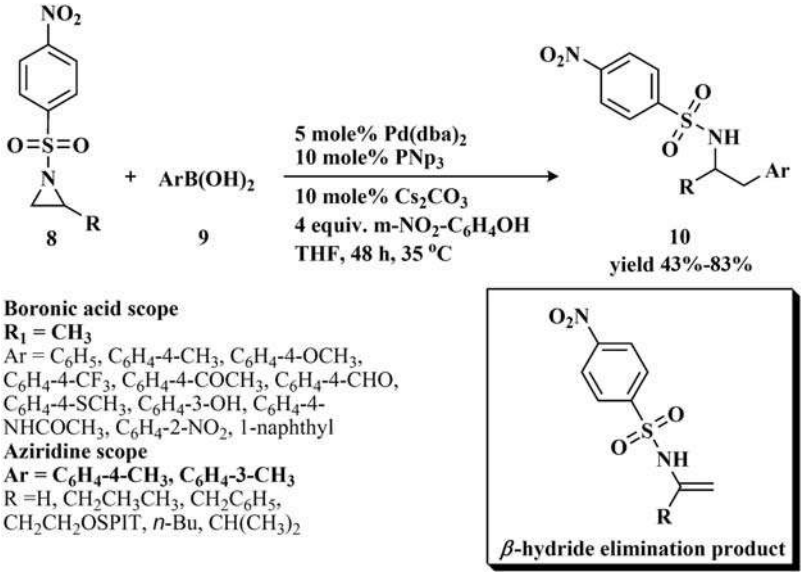
The proposed mechanism for this type of coupling proceeded through eitheran irreversible single-electron transfer (SET) oxidative addition of aziridine **6** to Ni(II) (Path A) or an S_N2-type oxidative addition accompanied by reversible homolysis of the Ni − C bond (Path B) (Scheme 2.3) [25]. Upon using chiral 1,2-disubstituted aziridine substrates **8**, the major diastereomer product was generated from the transazametallacycle intermediate **G**.

Commercial availability and excellent stability of organoboron compounds encouraged the organic chemists to introduce them as the coupling partners in Suzuki − Miyaura cross-coupling reactions with an array of *N*-sulfonated aziridines. Duda *et al.* [26] reported the first successful synthesis of β-arylethylamines *via* Suzuki coupling reaction of *N*-sulfonyl aziridines **8** with arylboronic acids **9** (Scheme 2.4). The use of sterically demanding ligand (triarylphosphine) was used to inhibit the formation of β-hydride elimination product and the presence of a catalytic amount of $CsCO_3$ allowed for obtaining the products with maximum yield. Moreover, a *m*-chlorophenol additive facilitated the transmetalation process.

The coupling reaction involved that the aziridine **8** was oxidatively added to Pd(0) to generate azametallacycle **A**, which is reversibly protonolyzed with *m*-nitrophenol to give the required Pd aryloxide **B** for transmetalation of the boronic acid **9**. Reductive elimination from intermediate C



SCHEME 2.3 Mechanistic insights of Negishi-type cross-coupling of *N*-sulfonated aziridines 6 with organozinc compounds.

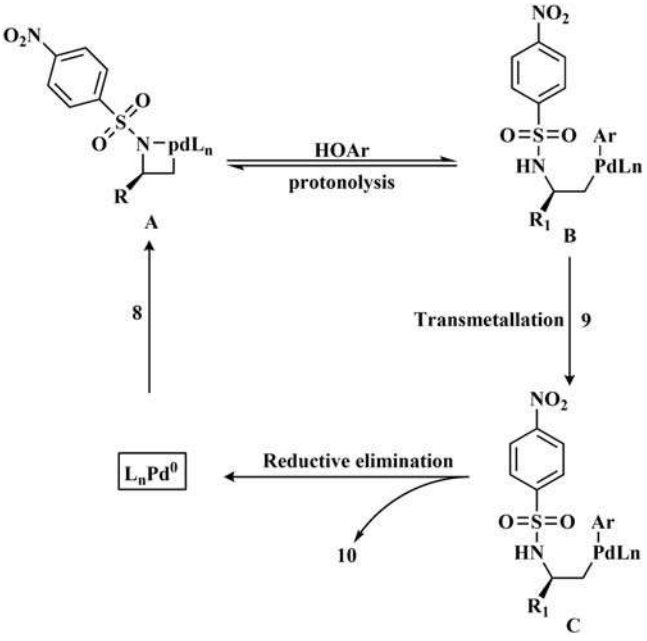


SCHEME 2.4. Suzuki coupling reaction of *N*-sulfonyl aziridines **8** with arylboronic acids **9**.

rapidly occurred to provide homoallylic amine **10** (Scheme 2.5) [26].

Under mild conditions, a palladium-catalyzed stereospecific and regioselective cross-coupling of enantiopure *N*-sulfonyl aziridines **R-11** and arylboronic acids **12** in the presence of sodium carbonate base provided an access to a set of enantioenriched β-arylphenethylamines **R-13** (Scheme 2.6) [27].

An efficient CuBr/xantphose catalytic system was developed for Suzuki cross-coupling reaction of *N*-tosyl aziridines **14** with neopentyl borane (Scheme 2.7) [28]. A catalytic amount of LiO^{t}Bu base and KI allowed accessing β-phenethylamine **15** at a high yield.

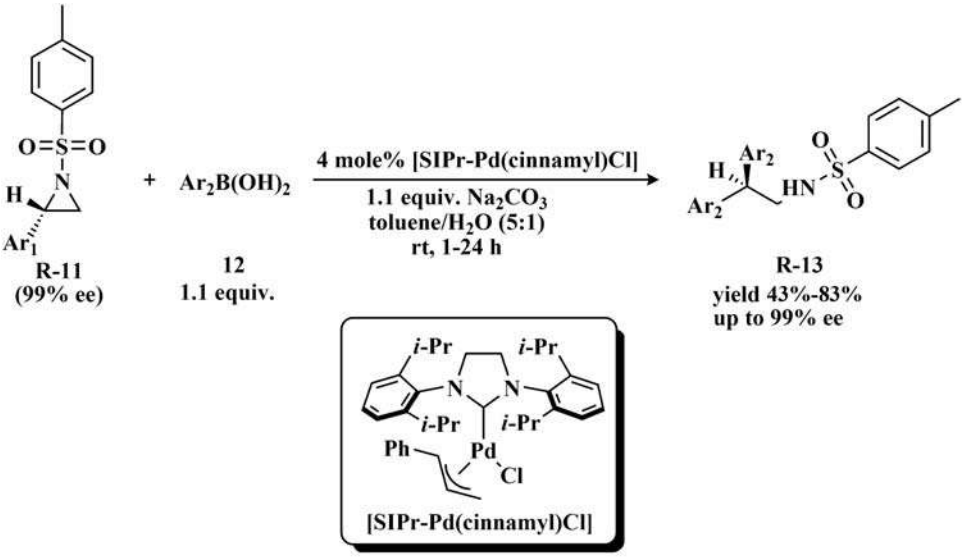


SCHEME 2.5 Mechanistic insights of Suzuki coupling reaction of *N*-sulfonyl aziridines **8** with arylboronic acids **9**.

2.2.1.2 To vicinal diamines

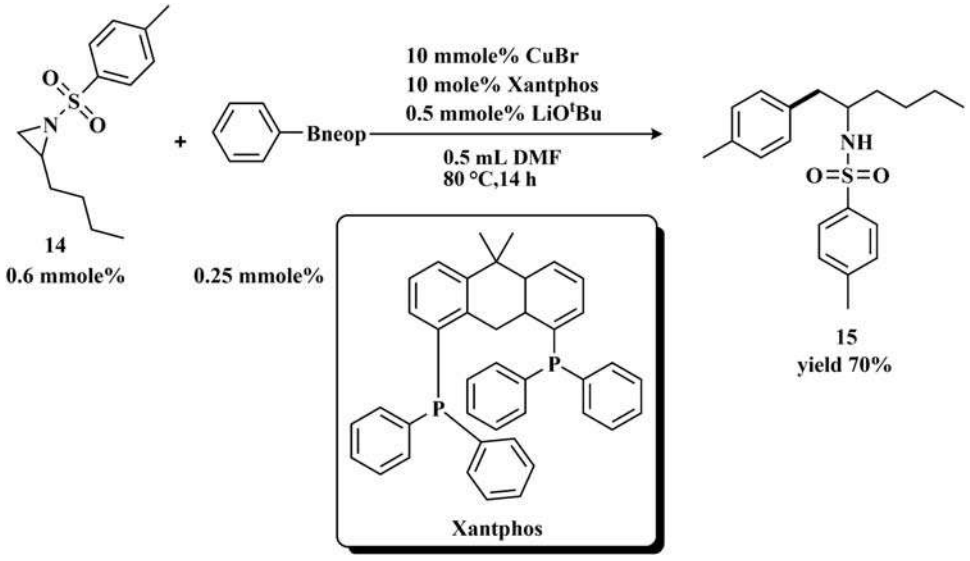
Diverse valuable natural products and chemotherapeutic agents are normally containing vicinal diamines in their structure, such as Oseltamivir [29], β-(methylamino)-l-alanine [30], and U-50,488 [31]. In addition, vicinal diamines are used as catalysts or chiral ligands for asymmetric synthesis [32–37]. Accordingly, the development of novel efficient methodologies for the preparation of vicinal diamines is highly desirable. The most straightforward and efficient methodology was reported to provide synthetically useful vicinal diamine derivatives based on the ring-opening of highly reactive *N*-*o*-Nosylated aziridines **16** with amide nucleophile, *N*-chloro-*N*-sodio-*tert*-butylcarbamate (Scheme 2.8) [38]. The ring-opening was achieved in a regioselective manner to make the ring-open product **17** in good yield. In contrast, the treatment of *N*-*o*-Nosylated aziridines **16** with benzylamine produced a 7:1 mixture ratio of vicinal diamine **18** and overalkylated vicinal diamine **19**. Upon using *tert*-butylcarbamate in the presence of NaOH, as an alternative condition, no conversion was observed at all and thus this indicated that the amide has validity as a proper nucleophile in such a transformation.

Recently, Yang *et al.* [39] developed a stereoconvergent transformation of racemic *N*-tosylaziridines to vicinal diamines under mild conditions. This included asymmetric aminolysis of racemic *N*-tosylaziridines **(±)-6** with secondary amine **20** using a combined catalytic system of Lewis acid ($[CH_3CN)_4Cu]PF_6$) and chiral (*S*)-BINAP ligand (Scheme 2.9). Such a complex

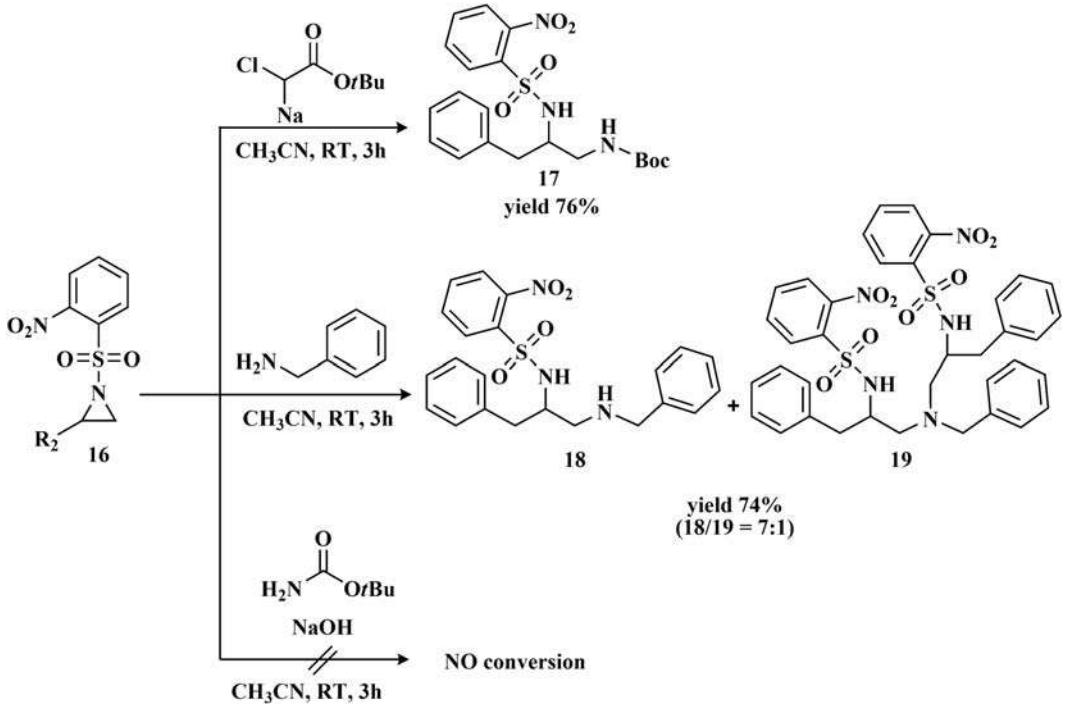


Ar_1 = C_6H_5, C_6H_4-4-OCH_3
Ar_2 = C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl, C_6H_4-4-F, C_6H_4-4-OCF_3, C_6H_4-4-NCH_3, C_6H_4-4-CO_2CH_3, C_6H_4-4-NO_2, C_6H_4-2-CH_3, 1-naphthyl, 2-thienyl, 2-benzofuran

SCHEME 2.6 A palladium-catalyzed cross-coupling of enantiopure 2-arylaziridines **R-11** with arylboronic acids **R-12**.



SCHEME 2.7 Suzuki cross-coupling reaction of *N*-tosyl aziridines **14** with neopentyl borane.

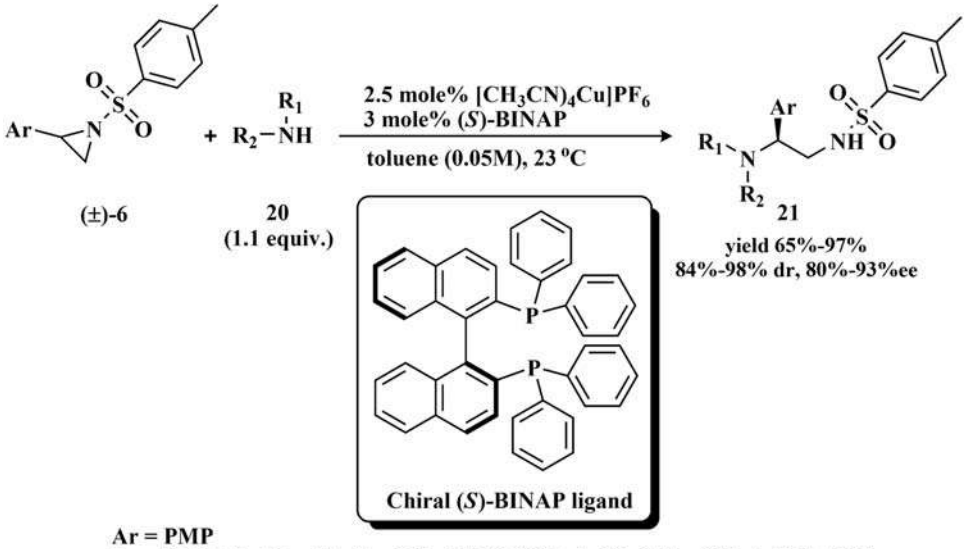


SCHEME 2.8 Ring-opening of the highly reactive *N*-*o*-nosylated aziridines **16** with amide nucleophile.

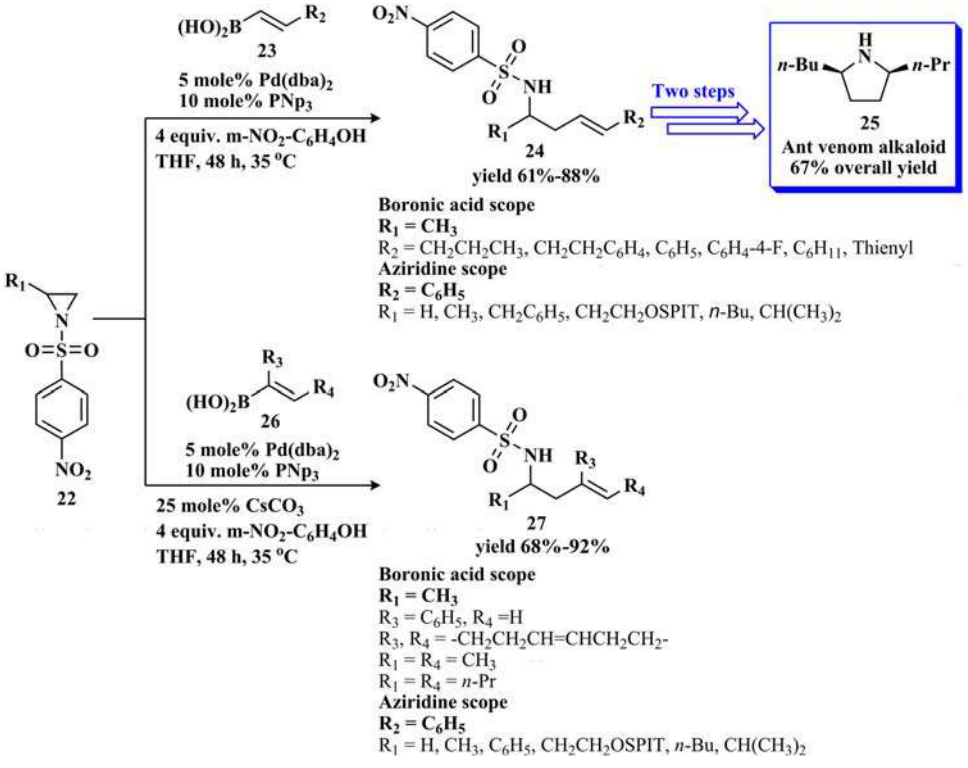
catalyst allowed for the synthesis of vicinal diamines **21** with extreme diastereo- and enantioselectivities (up to 98%Dr, up to 93%ee). Mechanistic studies highlighted that the stereoconvergent process was performed by the DYKAT type I.

2.2.1.3 To allyl amines and enamines

Allylic amines represent the most valuable synthetic intermediates' synthesis of nitrogen-containing compounds due to the possibility of the pendent double bond to participate in a range of additional useful transformations such as cycloaddition, hydrogenation, epoxidation, dihydroxylation, etc [40–44]. Suzuki cross-coupling approach of *N*-nosylaziridines and alkenylboronic species using palladium catalysis was reported [45]. The use of both terminal and internal alkenylboronic acids **23** and **26** as alkenylmetal species provided an array of 1,1-disubstituted and trisubstituted olefins **24** and **27**, respectively, in good to excellent yield (Scheme 2.10). Surprisingly, the addition of Cs_2CO_3 base in the



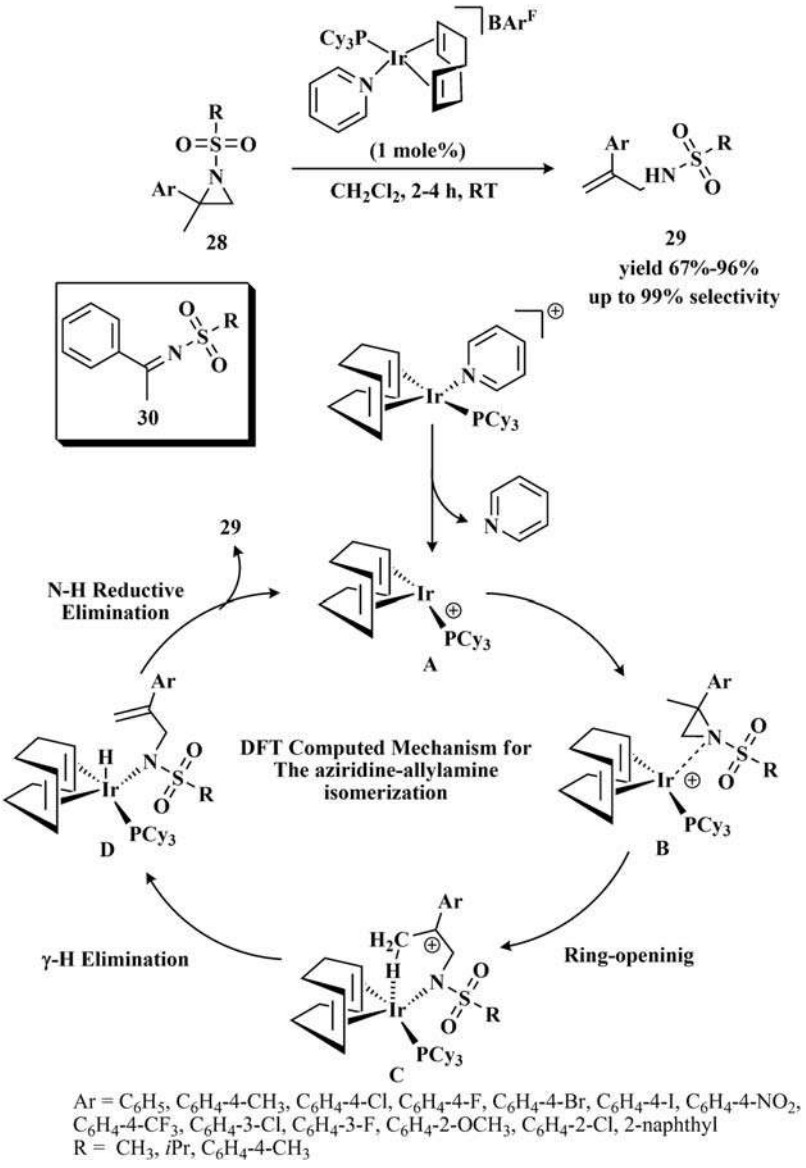
SCHEME 2.9 Asymmetric aminolysis of racemic *N*-tosylaziridines **(±)-6** with secondary amine **20**.



SCHEME 2.10 Suzuki cross-coupling approach of *N*-nosylaziridines **22** and alkenylboronic species using palladium catalysis.

coupling reactions of internal boronic acids **26** with *N*-nosylaziridines **22** resulted in the formation of product **27** in high yields, while the exclusion of the base allowed for an increase in the yields of the products in the case of using terminal boronic acids **23**. The synthesized homoallylic amines **24** were used as useful precursors for the preparation of a pyrrolidine natural product **25** with a 67% yield in two-step strategy. The coupling reaction was achieved similarly to the above-mentioned mechanism in Scheme 2.5.

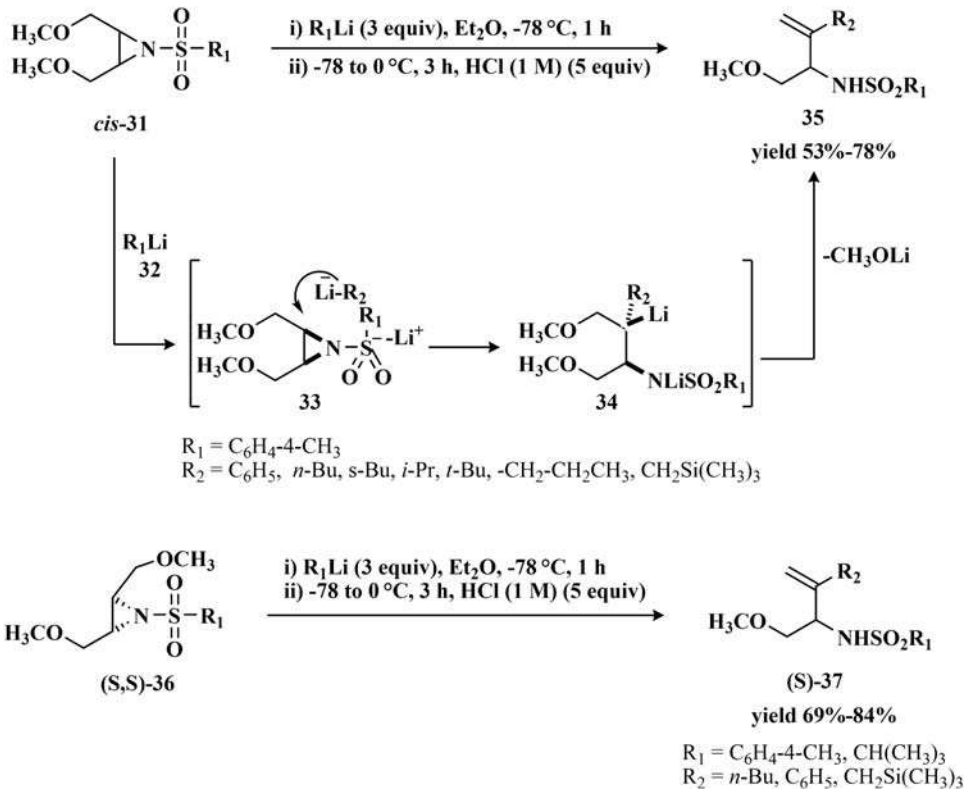
Crabtree's reagent was proved to be an efficient organoiridium catalyst in catalyzing the isomerization of *N*-sulfonyl aziridines with 2,2-disubstitution **28** to allylic amines



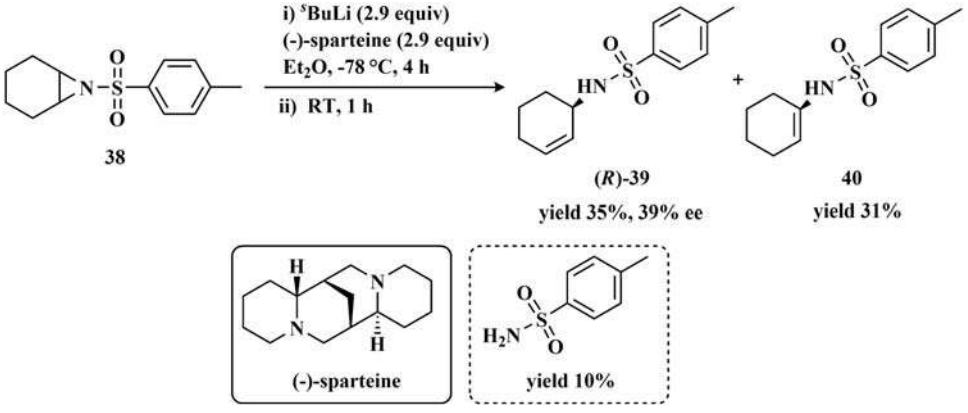
SCHEME 2.11 Organoiridium catalyzing reaction of *N*-sulfonyl aziridines with 2,2-disubstitution **28** to allylic amines **29** and its mechanisim.

29 (Scheme 2.11) [46]. The isomerization process took place with high selectivity of allyl amine **29** versus imine **30** (up to 99/1) in mild conditions taking no need to activate the Crabtree catalyst by hydrogen. A computational DFT study of the isomerization mechanism indicated that the mechanism was begun by approaching the aziridine **28** along with the reactive species **A**, giving a carbocation intermediate **B**. The ring-opening of the aziridine had taken place to form intermediate **C**. Subsequently, γ-H elimination from the intermediate **C** led to the formation of the amido hydride intermediate **D**, which underwent N − H reductive elimination to form the N − H bond and release of the desired allyl amine **29** (Scheme 2.11).

A wide range of organolithiums was introduced by Hodgson and coworkers to induce the alkylative ring-opening of *N*-sulfonated aziridinyl ether ***cis*-31**, providing access to allylic amines **35** with low to moderate yields [47,48]. The plausible mechanism for this transformation involves the useful reactive *N*-sulfonated aziridinyl ether ***cis*-31** facilely reacted with organolithiums **32** to generate the α-lithiated aziridines **33**. The latter underwent a 1,2-metalate shift to form the tertiary organolithium intermediate **34**. Subsequently, elimination with loss of MeOLi moiety resulted in the formation of the corresponding allyl amines **35** (Scheme 2.12) [47]. The use of enantiopure aziridines derived from *L*-tartaric



SCHEME 2.12 Ring-opening of *N*-sulfonated aziridinyl ether ***cis*-31** forming allylic amines 35 organolithium reagents.

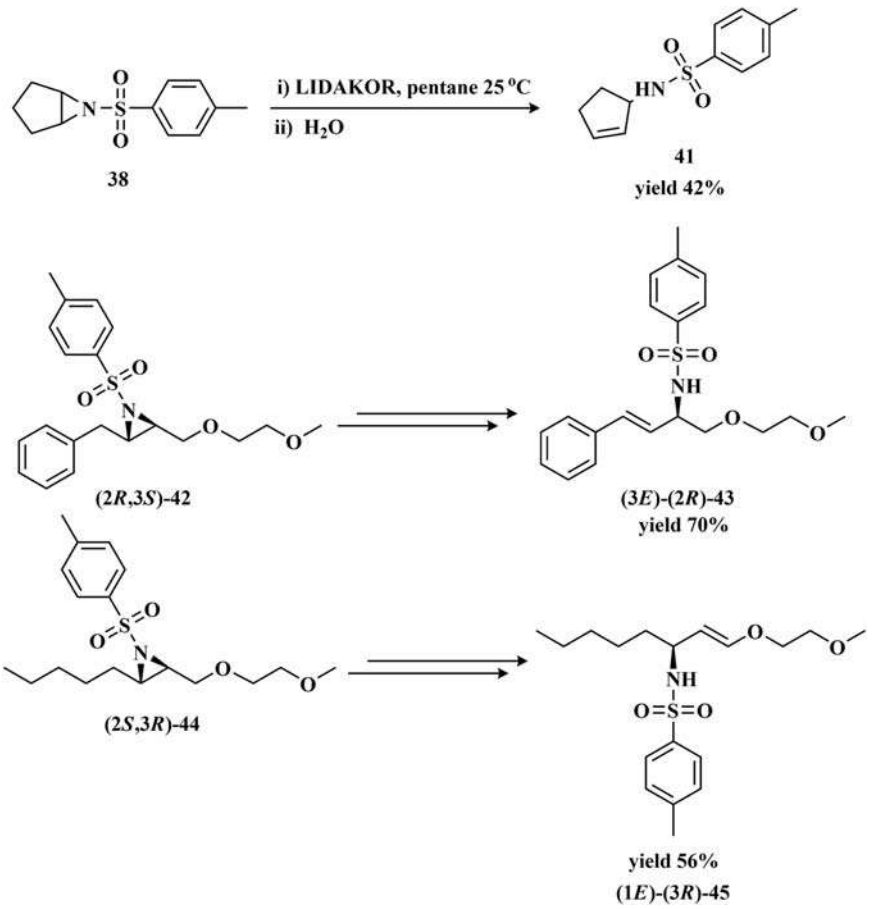


SCHEME 2.13 Rearrangement of *meso*-tosyl aziridine using (-)-sparteine as a ligand.

acid **(*S*, *S*)-36** led to the generation of allyl amine **(*S*)-37** without any loss in enantiopurity during the transformation (Scheme 2.12) [48].

The use of chiral ligand (-)-sparteine with *sec*-butyllithium led to the non-regioselective rearrangement of *meso-tosyl* aziridine to a mixture of enamine **39** and allylic amine **40** with the low enantioselectivity in the allylamine formation (39% ee) (Scheme 2.13) [49]. Later on, similar work by Brien and coworkers [50] has been carried out (Scheme 2.4) and the reaction formed $TsNH_2$ (yield 10%) as a by-product.

Mordini *et al.* [51] introduced an alternative combined system (LIDAKOR) based on a mixture of lithium diisopropylamide with potassium *tert*-butoxide in presence of pentane to induce the aziridine−allylamine rearrangement at room temperature to eliminate the need to use low temperature as in the case of *sec*-butyllithium (-)-sparteine. Bicyclic aziridine **38** was effectively converted into allylic amine **41** as a sole product but with a low yield (Scheme 2.14). Such rearrangement was achieved in a perfect regioselective manner and stereocontrol upon using chiral aziridine substituted with benzylic and alkoxy



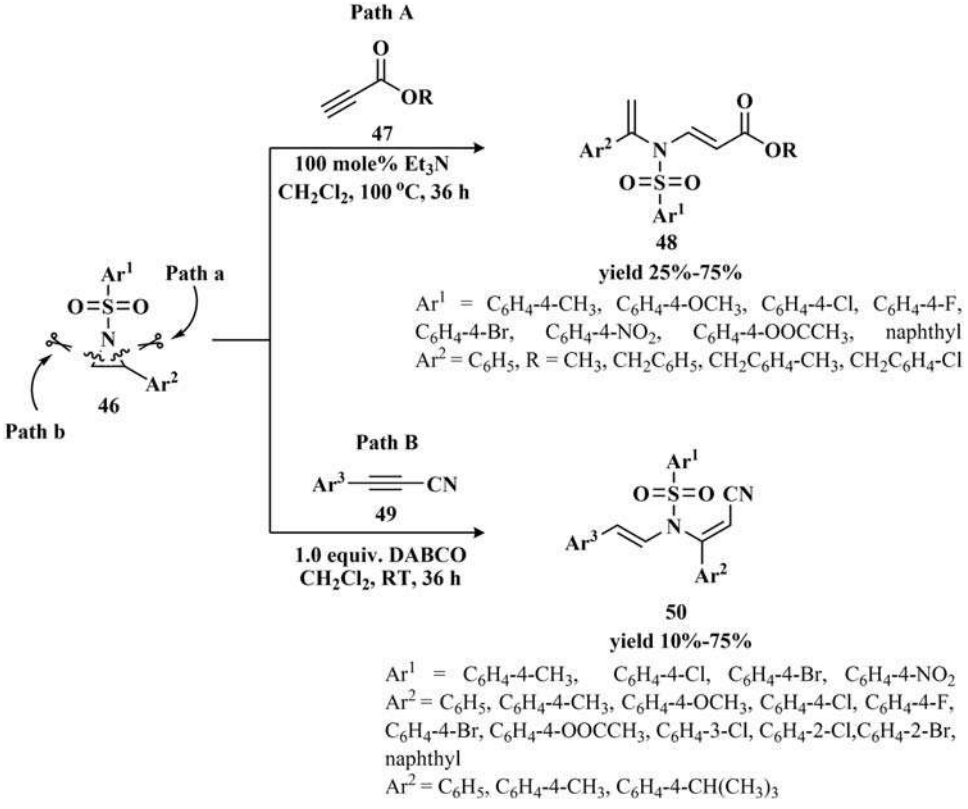
SCHEME 2.14 Rearrangement of bicyclic aziridine **38** into allylic amine **41** using LIDAKOR.

moieties **(2*R*,3*S*)-42**, yielding chiral allylic amines (Scheme 2.14). Deprotonating the benzyl methylene group of the benzyl substituted aziridrine **(2*R*,3*S*)-42** allowed the formation of allylic amine **(3*E*)-(2*R*)-43** in good yield (70%) and excellent regio- and stereocontrol while the regioselective deprotonation on the methylene adjacent to the alkoxy substituent **(2*S*,3R)-44** resulted in the preparation of *E*-isomer of the allylic amine **(1*E*)-(3*R*)-45** with 56% yield.

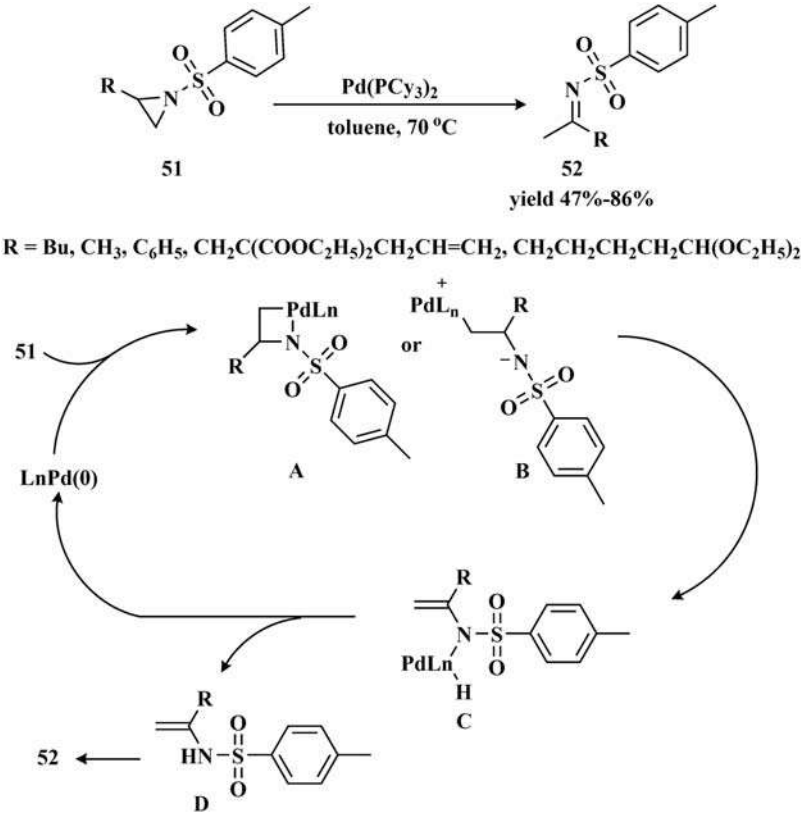
Wang and coworkers described, in two different reports, an efficient and robust approach for base-promoted *N*-sulfonylaziridines with electron-deficient alkyne nucleophiles in different two directions of C−N bond cleavage, affording structurally diverse functionalized enamines [52,53]. Employing of terminal alkynoates **47** to react with *N*-tosylaziridines **46** in the presence of the organic base Et_3N furnished with functionalized enamines **48** (Scheme 2.15, Pathway A) [52]. Interestingly, the ring-opening of *N*-sulfonylaziridines **46** with cyanoacetylenes **49** could be achieved through unexpected regioselective cleavage of the alternative C-N bond under the 1,4-diazabicyclo-[2.2.2]octane base catalysis (Scheme 2.15, Pathway B) [53]. A set of interesting functionalized enamines **50** was obtained in low to good yields. Such reaction products represent vital precursors in organic synthesis [54−56].

2.2.1.4 To Ketimines

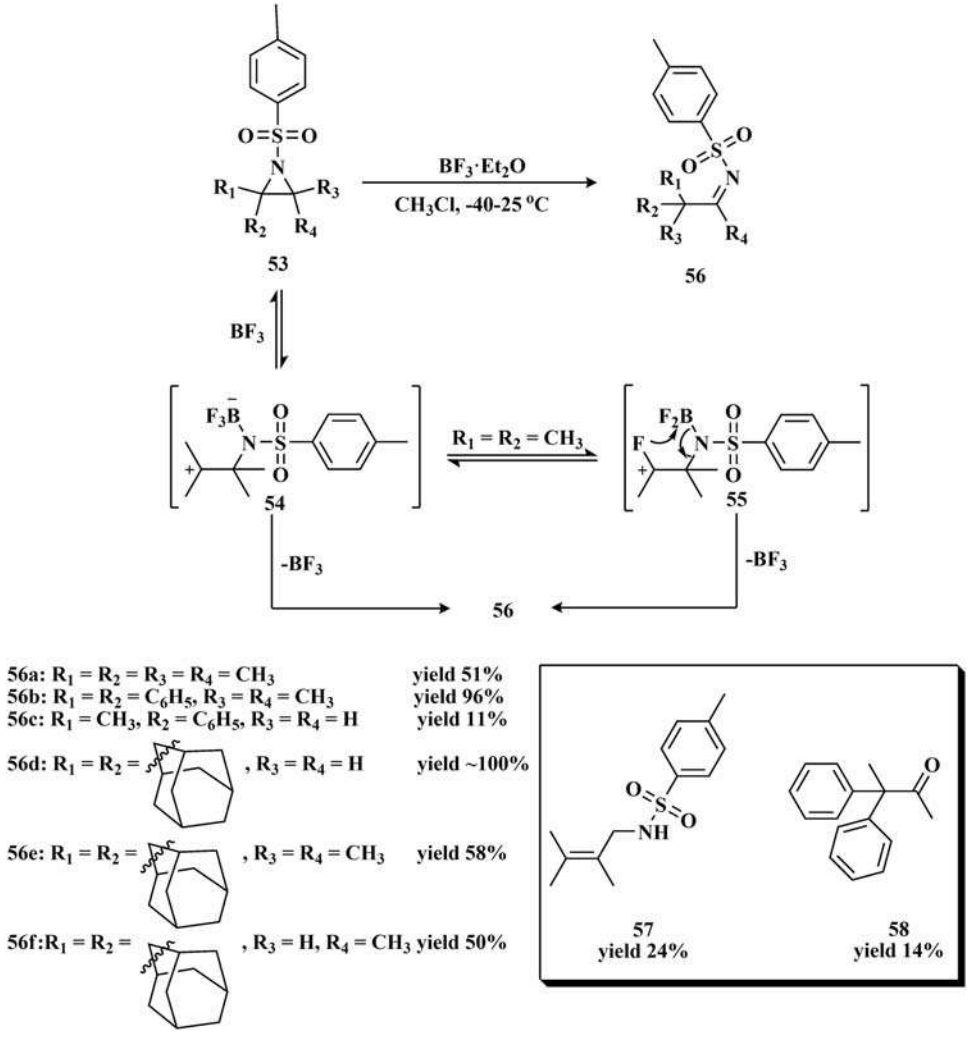
Isomerization of *N*-sulfonyl aziridines has been proved to be a mild and efficient methodology for providing access to *N*-sulfonylketimines [57]. An array of *N*-tosylketimines tolerated to ketones, esters, and acetals **51** were willing to participate in the reaction. The employment of $Pd(PCy_3)_2$ as a catalyst in the isomerization process resulted in the formation of *N*-sulfonylketimines **52** in low to high yield (Scheme 2.16). Notably, it was difficult to prepare highly functionalized ketimines under the same reaction condition. The plausible mechanism of the isomerization involved the S_N2-type oxidative addition of *N*-tosylaziridines, affording



SCHEME 2.15 *N*-Sulfonylaziridines with electron-deficient alkyne nucleophiles.



SCHEME 2.16 Isomerization of *N*-sulfonyl aziridines to *N*-sulfonylketimine by palladium catalyzed reaction and its mechansim.



SCHEME 2.17 Lewis acid in catalyzing aza-pinacol rearrangement of *N*-tosylaziridines **53** to form *N*-tosylketimine **56**.

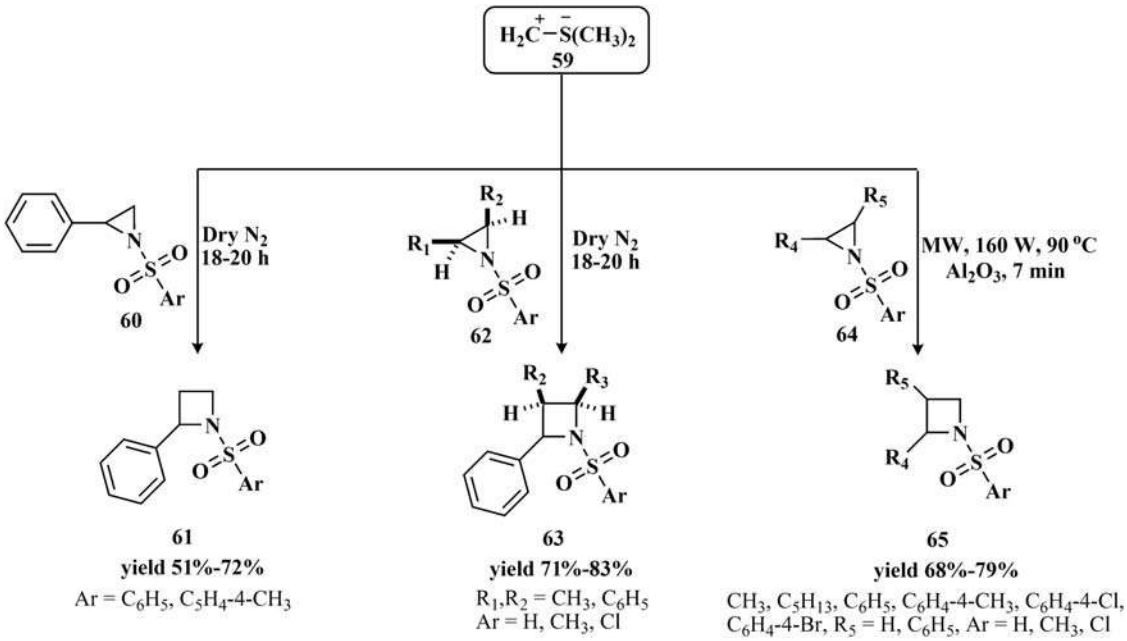
either azametallacyclobutane **A** or zwitterion **B**. β-Hydride elimination of these intermediates hydrido-palladium amido active species **C**, which eliminated reductively to form *N*-tosylenamine **D**. Tautomerization of the latter gave the desired product.

Sugihara *et al.* [58] demonstrated the efficacy of Lewis acid in catalyzing aza-pinacol rearrangement of *N*-tosylaziridines **53** to furnish *N*-tosylketimine **56** in satisfactory yields (Scheme 2.17). A mixture of ketamine **56a** and olefin **57** was produced when *tetra*-substituted *N*-tosylaziridine **53a** was subjected to Lewis acid $BF_3 \cdot Et_2O$ in chloroform at room temperature. In contrast, regioselective rearrangement occurred in the case of *di* and *tetra*-substituted aziridine substrates **53a-e** to obtain the corresponding ketamine **56a-e** as a sole product by an exclusive migration of the methyl group. Surprisingly, trisubstituted aziridines formed ketone **56f** as a major product, which was the hydrolyzed product of the corresponding imine formed due to a hydrogen migration. Treatment of the aziridines with $BF_3 \cdot Et_2O$ gave carbocation intermediates **54**, which would either directly convert the desired ketimines or a deprotonated form of the desired product according to the nature of the aziridine substrate. In the case of using aziridines with methyl group in R_1 and R_2 positions, the preferred pathway was deprotonation of carbocation intermediates **54**.

2.2.2 Ring-opening of *N*-sulfonated aziridines to other cyclic *N*-sulfonated aza-heterocycles

2.2.2.1 To N-sulfonated four-membered heterocycles

For many years, the unique structure and reactivity of the *N*-sulfonyl azidirine ring have attracted the interest of organic chemists. Therefore, a number of studies in



SCHEME 2.18 Conversion of *N*-sulfonyl aziridines to its corresponding *N*-sulfonyl azetidines using sulfur ylide.

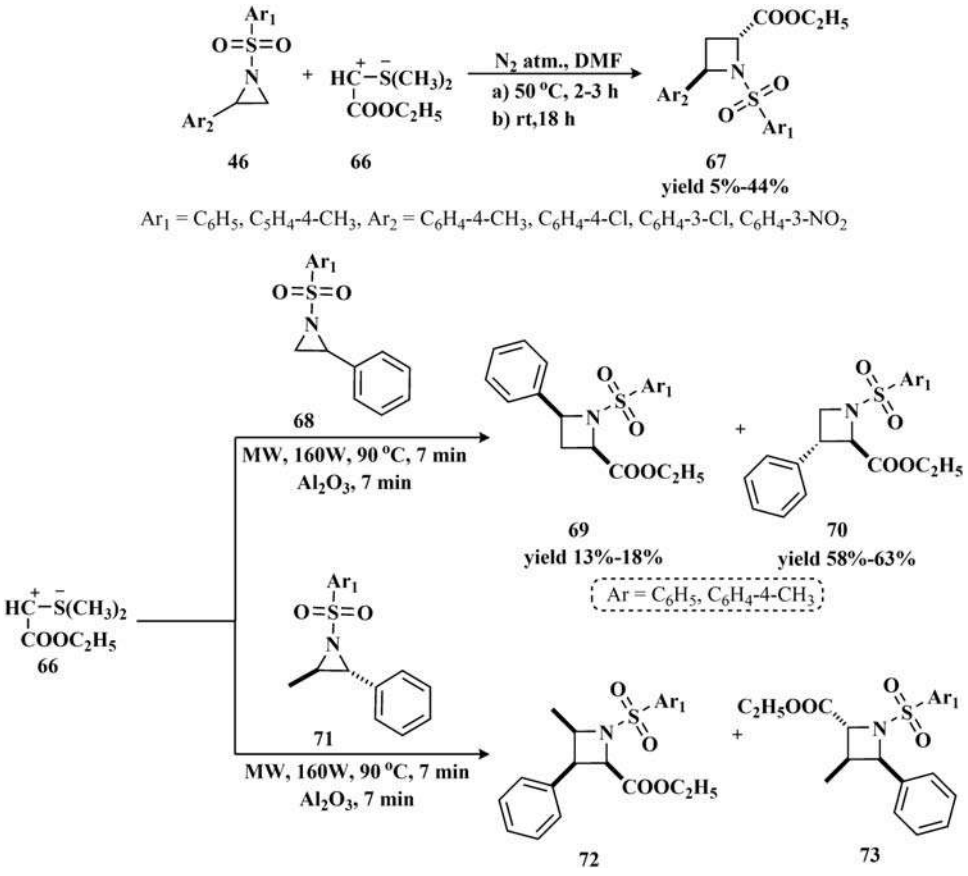
the literature investigated the ring enlargement of *N*-sulfonyl aziridines to its corresponding *N*-sulfonyl azetidines. During Nadir and coworkers study on *N*-sulfonyl aziridines, they noticed the transferring of the methylene group from the sulfur ylides **59** to *N*-sulfonyl aziridines which led to the formasion of a large variety of *N*-sulfonyl azetidines. Authors disclosed the first report on the preparation of azetidines **61** in moderate yield *via* a S_N2-type ring opening of *N*-sulfonyl aziridine **60** by sulfur ylide **59** through the elimination/cyclization process (Scheme 2.18) [59]. The stereochemical outcome of this reaction was further explored by using chiral aziridines **62** as a substrate. It was found that *cis*-2,3-disubstituted aziridines **62** gave *trans*-2,3-disubstituted azetidines **63** in good yield (Scheme 2.18) [60]. An alternative condition for this reaction was reported by utilizing microwave irradiation and surface mediation [61]. A one-pot reaction of *N*-arylsulfonyl aziridines **64** with sulfur ylide **59** under microwave irradiation on solid support Al_2O_3 furnished 2,3-disubstituted aziridines **65** in good yield (Scheme 2.18).

The use of the sulfur ylide bearing ethoxycarbonyl group **66** as methylene source provided access to diverse of *N*-sulfonyl azetidine 2-carboxylates **67** but in low to moderate yield (Scheme 2.19) [62]. A modified and well-yielded method for the preparation of azetidine 2-carboxylates was reported under microwave irradiation using Al_2O_3 as solid support media (Scheme 2.19) [63]. It was interested to observe that microwave irradiation not only increased the yield of azetidines but also altered the selectivity of the ylide attack, leading to the formation of *trans*-2,3-disubstituted azetidines **69** and **70** with high regioselectivity, but with a very low yield of azetidines **69**. This reaction was also extended to a regioselectively products of 3,4-disubstituted azetidine 2-carboxylates **72** and **73** (Scheme 2.19).

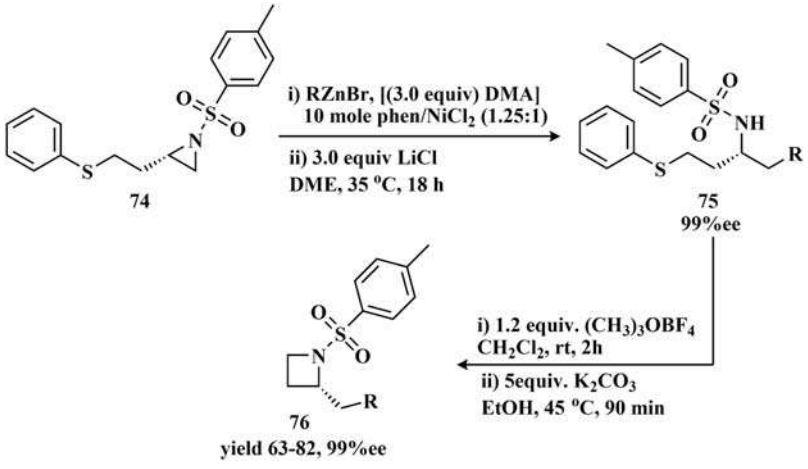
Jensen *et al.* [64] recently developed a highly effective synthetic route toward enantiomerically pure 2-alkyl azetidines **76** from aziridines **74** in two sequential steps. In the first step, the nickel-catalyzed ring-opening reaction of chiral terminal aziridines bearing aryl sulfide group **74** with aliphatic organozinc reagents afforded the ring-open product **75**. In the second step, treatment of **75** with Meerwein's salt and subsequent addition of potassium carbonate furnished the desired 2-substituted azetidine derivatives **76** with excellent enantiopurity (99% ee) (Scheme 2.20).

2.2.2.2 To *N*-sulfonated five-membered heterocyclic ring

As discussed before, aziridines could undergo a ring cleavage under mild conditions. Accordingly, extensive studies were reported to synthesize *N*-sulfonyl pyrroles *via* Lewis or Bronsted acid-catalyzed cycloaddition of aziridines with alkynes. In 2002, a rare method for stereocontrolled synthesis of *cis*-bicyclic lactams was reported by Madhushaw *et al.* [65]. An intramolecular [3 + 2] cycloaddition of alkynyltungsten complexes with its tethered aziridine **77** in the presence of $Bf_3.EtO_2$ as Lewis acid afforded bicyclic



SCHEME 2.19 Synthesis of *N*-sulfonyl azetidine 2-carboxylates.

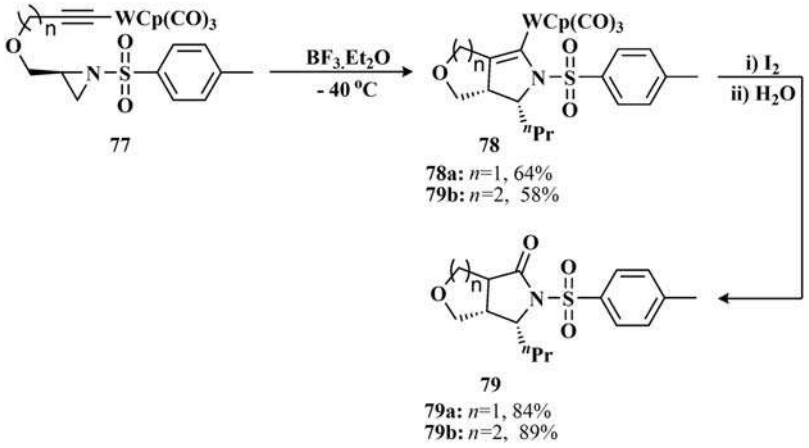


SCHEME 2.20 Synthesis of 2-alkyl azetidines **76** from aziridines **74**.

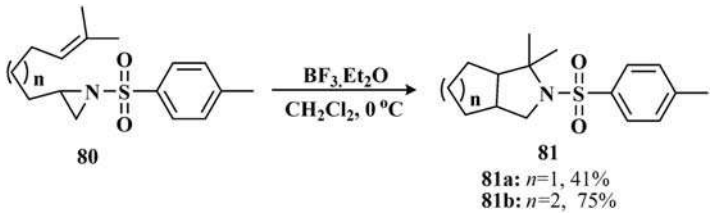
tungstenenamines **78** stereoselectively in moderate yields. After that, decomplexing these organometallics with I_2 in CH_2Cl_2, followed by hydrolysis, yielded only *cis*-fused bicyclic lactams **79** (Scheme 2.21).

Shortly after that, Bergmeier *et al.* [66] utilized the same catalyst to promote intramolecular [3 + 2] cycloaddition of olefinic aziridines **80** to furnish fused bicyclic pyrrolidines **81** in good yield (Scheme 2.22).

Xu *et al.* [67] reported a formal [3 + 2] cycloaddition reaction of vinylaziridines **82** and vinylketones **83** catalyzed by palladium to afford *N*-tosyl pyrrolidine **84**. No desired product was produced when vinylaziridine **82**



SCHEME 2.21 Synthesis of *N*-sulfonyl pyrroles *via* Lewis or Bronsted acid-catalyzed cycloaddition of aziridines with alkynes.



SCHEME 2.22 Intramolecular [3 + 2] cycloaddition of olefinic aziridines **80** producing fused bicyclic pyrrolidines **81**.

reacted with vinyl ketone **83** in the presence of $[Pd_2dba_3] \cdot CHCl_3/PPh_3$ catalyst only. However, a combination of $[Pd_2dba_3] \cdot CHCl_3/PPh_3$ and ligand $\mathbf{L_3}$ in the presence of KBr as additive afforded *N*-tosyl pyrrolidine **84** in good yield with highly diastereo- and enantioselectivity (Scheme 2.23). In addition, cyclic vinyl ketone **85** was also suitable substrate for this asymmetric [3 + 2] cycloaddition to provide the adduct **86** in 50% yield with 13:1 d.r. and 96%ee. Treatment of **86** with hydroxylamine furnished the *Z*-oxime **87** and *E*-oxime **88** in 31 and 54% yield, respectively. Protection of a tosyl group on the *E*-oxime **88** and subsequent Beckmann rearrangement in the presence of acetic acid yielded the bicyclic compound **89** over two steps (Scheme 2.23).

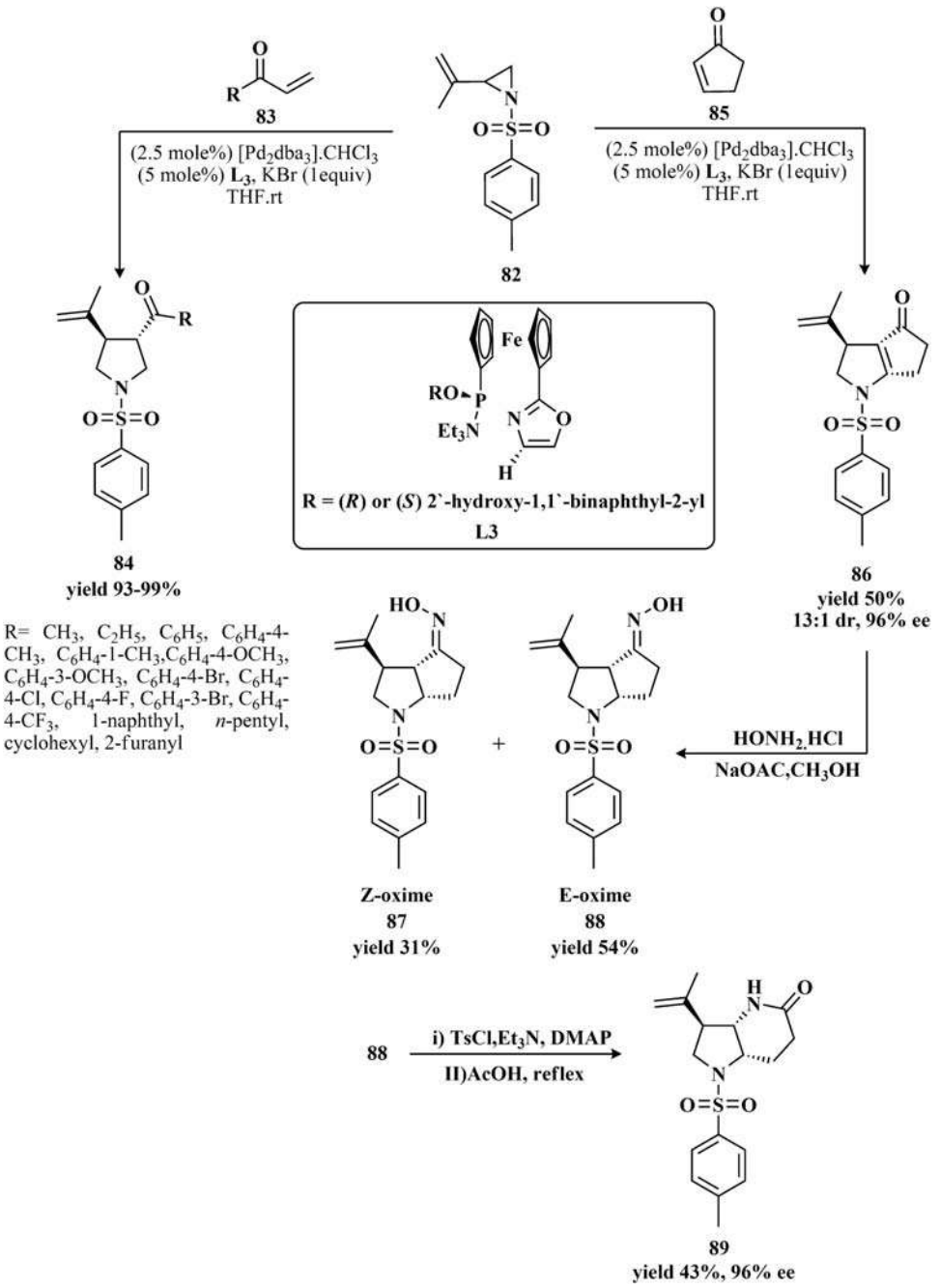
Craig *et al.* [68] reported an influential protocol based on the use of zinc bromide as a catalyst in cycloaddition reactions. Zinc bromide was found to be an effective catalyst in the [3 + 2] cycloaddition of *N*-sulfonylaziridines **90** with dialkyl-carbodiimides **91** to afford imidazolidine **92** (Scheme 2.24).

Zinc-catalyzed cycloaddition reaction of diester aziridine **93** with allyl isothiocyanate **95** was also reported. This reaction proceeds through the formation of azomethine ylides **94**, which reacts with allyl isothiocyanate **95** to form pyrrolidine **96** at 50% yield (Scheme 2.25) [68].

Continuous flow methodology has emerged as a powerful new technique in chemical synthesis. In 2015, Hsueh *et al.* [69] disclosed a novel method for imidazoline synthesis by formal [3 + 2] cycloaddition of aziridines **98** with nitriles **97** under continuous flow conditions (Scheme 2.26).

A number of functionalized protocols utilized *N*-tosylaziridinofullerene as a versatile platform for the formation of C60 and investigated the properties of these newly generated fullerene (C60) derivatives for their applications in materials science and medicinal chemistry. In 2013, Takeda *et al.* [70] reported a Lewis base-catalyzed [3 + 2] cycloaddition reaction of *N*-sulfonylated aziridinofullerene **100** with aryl isocyanates **101** for the preparation of the C60-fused imidazolidinones **102** (Scheme 2.27). However, the substrates were limited to aryl isocyanates, and alkyl-substituted C60-fused imidazolidinones could not be formed under this condition.

In continuation of the interest in functionalized fullerene, Xing *et al.* [71] are interested to develop new routes for the preparation cyclic diaminated [60] fullerenes **105** and **107** from *N*-tosylaziridinofullerene **103**. The double nucleophilic reaction of *N*-tosylaziridinofullerene **103** with various ureas **104** under the catalysis of Lewis base *N*-methylimidazole (NMI) afforded the

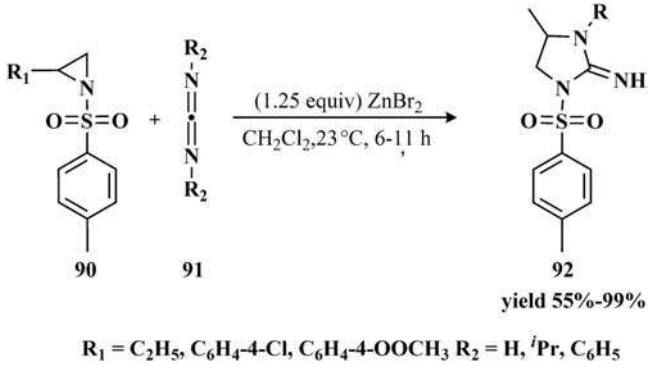


SCHEME 2.23 Cycloaddition reaction of vinylaziridines **82** and vinylketones catalyzed by palladium forming *N*-tosyl pyrrolidines.

anticipated product **105** (Scheme 2.28). Although this condition was suitable for alkyl ureas **104**, aryl ureas **106** gave a very low conversion under the same condition due to the lower nucleophilicity of aryl ureas **106** compared with that in alkyl ureas **104**. Replacement of NMI by DMAP furnished the desired product **107** in relatively good yields because DMAP has stronger basicity than NMI.

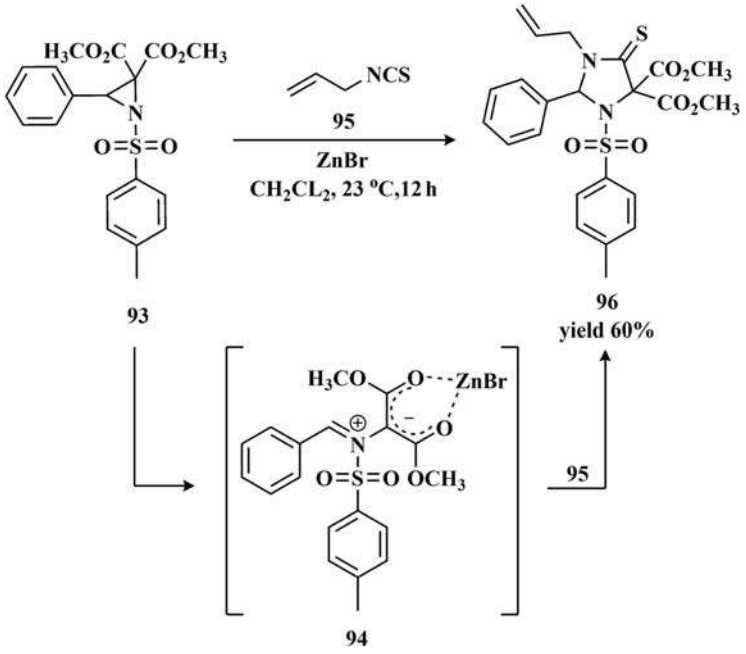
2.2.2.3 To N-sulfonated six-membered heterocyclic ring

Wang *et al.* [72] developed a novel and efficient Lewis acid-catalyzed [3 + 3]-annulation methodology for the construction of tetrahydroisoquinolines **109** and tetrahydro-β-carbolines **111** from readily available aziridines **1** and benzylic alcohols **108** and **110**, respectively, in good

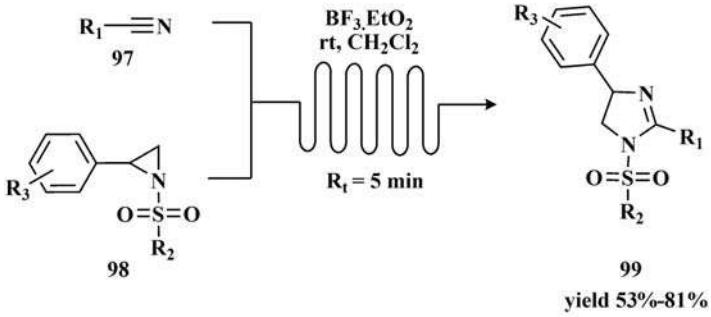


$R_1 = C_2H_5, C_6H_4\text{-}4\text{-}Cl, C_6H_4\text{-}4\text{-}OOCH_3$ R_2 = H, ^{i}Pr, C_6H_5

SCHEME 2.24 Cycloaddition of *N*-sulfonylaziridines **90** with dialkyl-carbodiimides **91**.

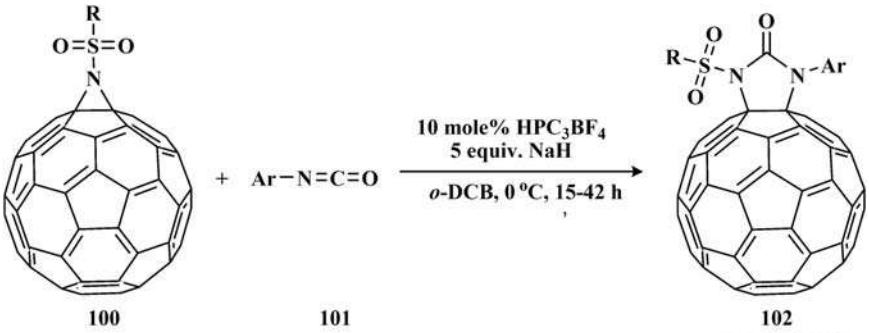


SCHEME 2.25 Zinc-catalyzed cycloaddition reaction of diester aziridine **93** with allyl isothiocyanate **95**.



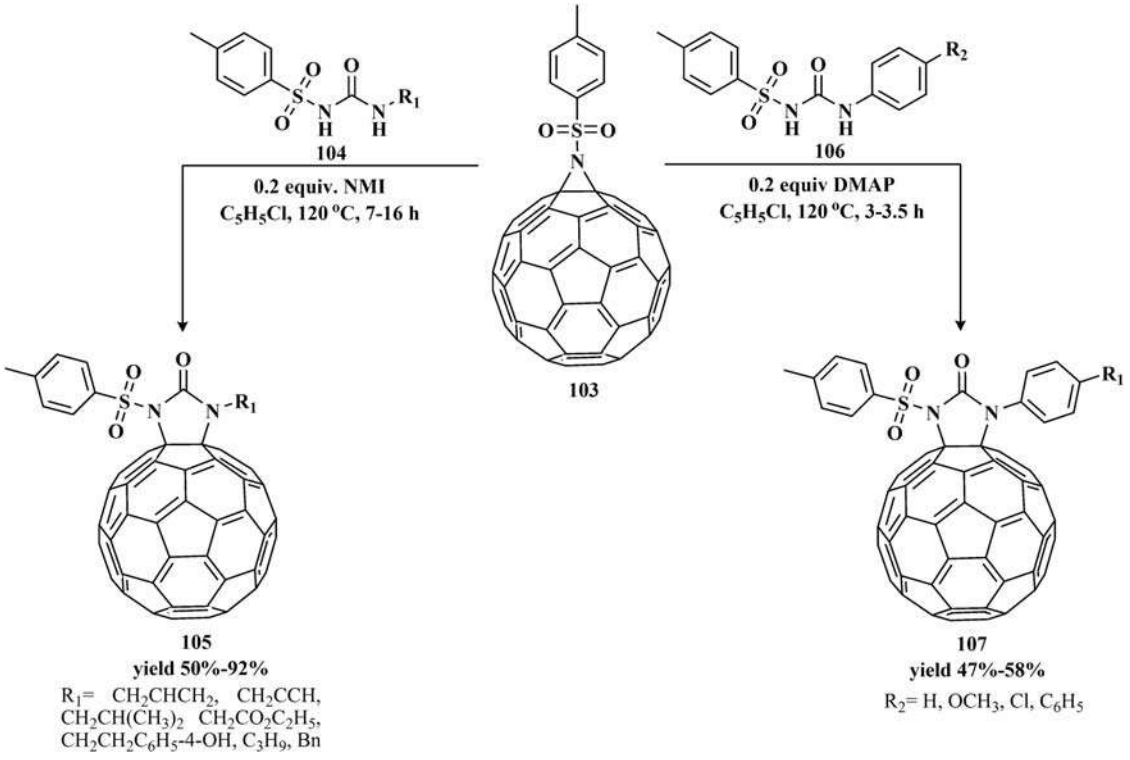
$R_1 = CH_3, C_6H_5, {}^t$Bu, ^{i}Pr, $R_2 = CH_3, C_2H_4\text{-}4\text{-}CH_3, C_2H_4\text{-}4\text{-}NO_2, C_2H_5,$
$R_3 = C_6H_5, C_6H_2\text{-}1,2,4,6\text{-}3CH_3$

SCHEME 2.26 Cycloaddition of aziridines **98** with nitriles **97** under continuous flow conditions.



R = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Br, C_6H_4-4-NO_2, Ar = $OSNC_6H_4$-4-OCH_3, $OSNC_6H_4$-4-Br, $OSNC_6H_4$-4-F, $OSNC_6H_4$-4-I, $OSNC_6H_4$-4-$CO_2C_2H_5$, $OSNC_6H_4$-3-Cl, $OSNC_6H_4$-3-NO_2, $OSNC_{12}H_7$

SCHEME 2.27 Lewis base-catalyzed [3 + 2] cycloaddition reaction of *N*-sulfonylated aziridinofullerene **100** with aryl isocyanates **101**.



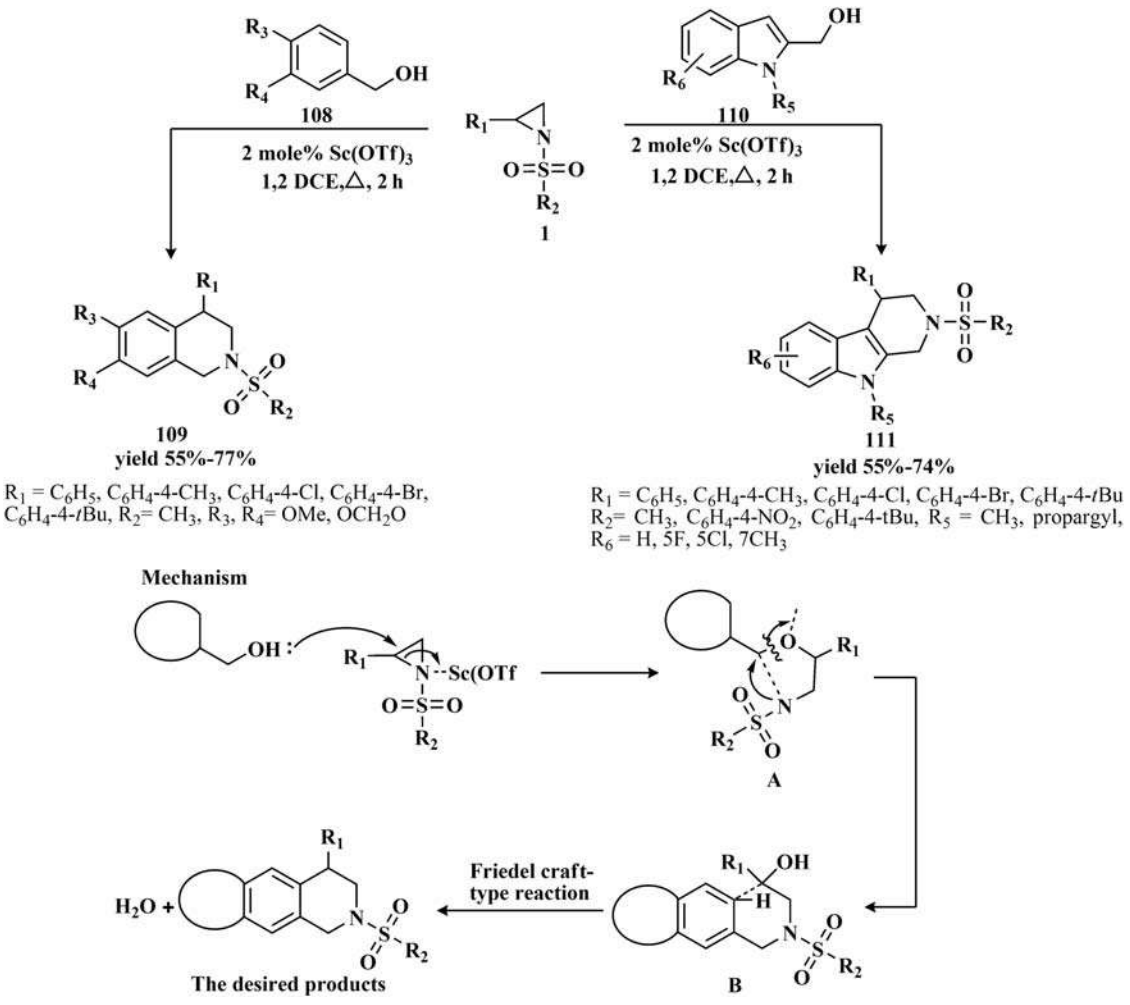
R_1= CH_2CHCH_2, CH_2CCH, $CH_2CH(CH_3)_2$ $CH_2CO_2C_2H_5$, $CH_2CH_2C_6H_5$-4-OH, C_3H_9, Bn

R_2= H, OCH_3, Cl, C_6H_5

SCHEME 2.28 Synthesis of cyclic diaminated fullerenes **105** and **107** from *N*-tosylaziridinofullerene **103**.

yield (Scheme 2.29). This reaction, a potential alternative to the classical Pictet–Spengler reaction, started with the nucleophilic ring-opening reaction of the aziridine **1** with the benzylic alcohol to give the intermediate **A** which then underwent an intramolecular amination of the benzylic ether to form **B** and followed by an intramolecular Friedel–Crafts-type alkylation to afford the desired products (Scheme 2.29). Notably, this methodology failed to obtain an optically pure product from enantiomerically pure aziridine presumably because of racemization of the aziridine in the presence of a Lewis acid.

In 2010, Zhang *et al.* [73] developed an effective protocol for the synthesis of a series of 1,2,3,4-tetrahydroisoquinolines in excellent yields *via* gold-catalyzed domino



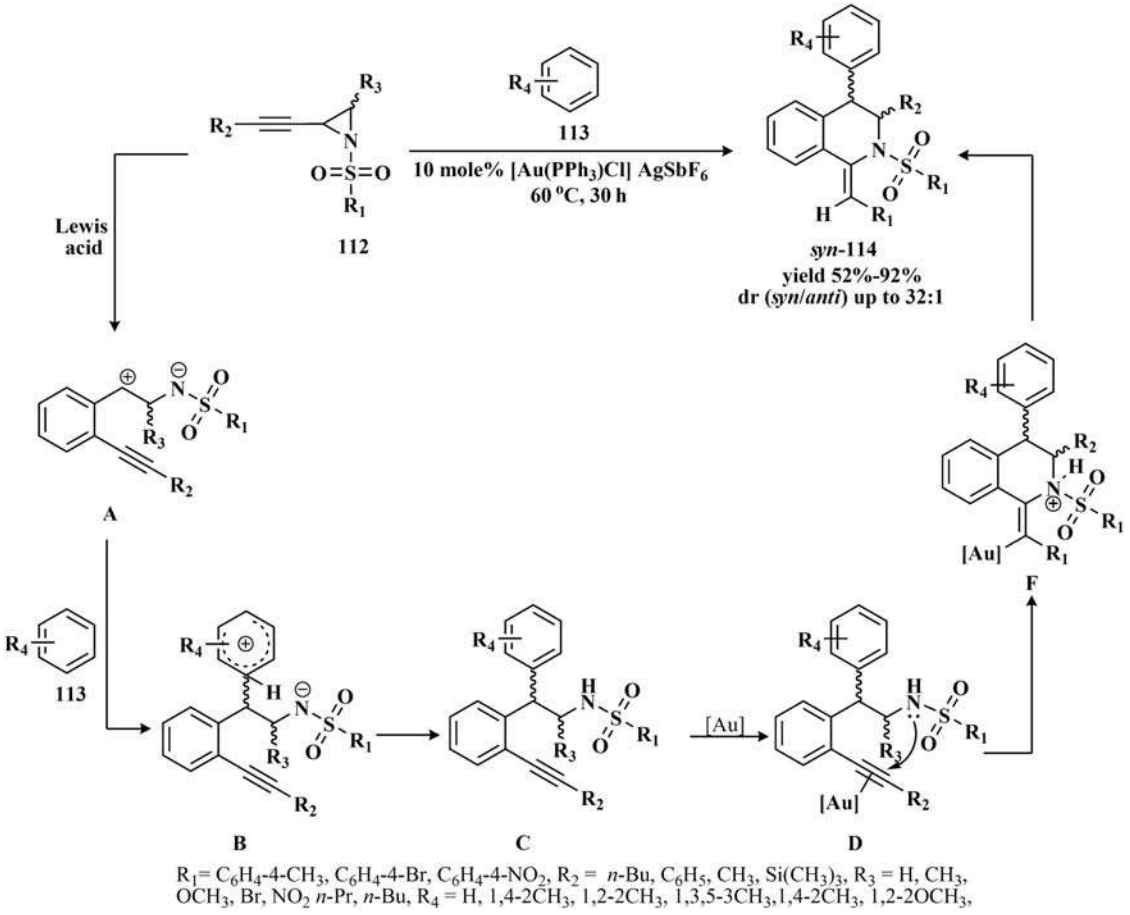
SCHEME 2.29 Synthesis of tetrahydroisoquinolines **109** and tetrahydro-β-carbolines **111** *via* Lewis acid-catalyzed [3 + 3]-annulation methodology.

reaction of aziridinyl alkynes **112** with a number of arenes **113** (Scheme 2.30). Mechanistically, it is proposed a zwitterionic species **A** was first generated from the aziridine by cleavage of the C−N bond and sequent Friedel−Crafts reaction of arene **113** with the benzylic cation to produce the intermediate **B** which afforded intermediate **C** by intramolecular proton transfer. Finally, a gold-catalyzed intramolecular nucleophilic attack of the nitrogen took place at the alkyne functionality to give D and the expulsion of the gold catalyst from intermediate **D** formed tetrahydroisoquinolines **syn-114** with in *syn* diastereoselectivity (Scheme 2.30).

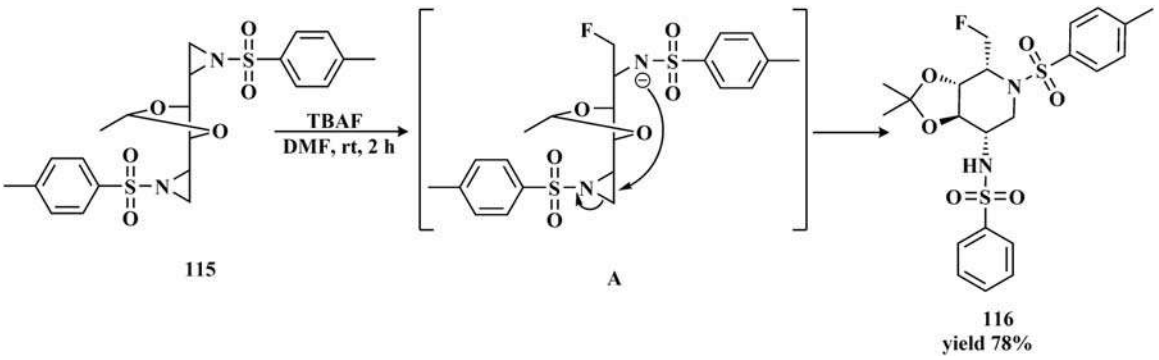
Interesting report by Dureault *et al.* [74], a chiral *N*, *N*′-ditosyl bis(aziridine) **115**, derived from *D*-mannitol, could transform to functionalized piperidines **116** in presence of TBAF, as a source of fluoride, by the opening of one aziridine moiety by fluoride ion followed by the intramolecular opening of the other aziridine moiety through the formation of the intermediate **A** (Scheme 2.31).

For emphasis on the effectiveness of Lewis acid BF_3.EtO as a catalyst, Xing *et al.* [75] employed BF_3.EtO to catalyze three-component reactions of aziridines **117**, arenes **118**, and aldehydes **119** for the synthesis of 1,4-disubstituted tetrahydroisoquinolines **120** (Scheme 2.32). This reaction involved sequential ring-opening of azidirine and pictet-splinger condensation to give a broad range of *cis*-1,4-disubstituted tetrahydroisoquinolines **120** with good regioselectivity in moderate yield. Abroad ranges of aziridine, arene, and aldehyde substrates participated in this reaction.

In 2014, a dimerization strategy of 2-trifluoromethyl-*N*-tosylaziridine **121** to the corresponding *trans*-2,5-disubstituted piperazine derivative **122** was serendipitously developed by Yoshiki *et al.* [76]. 2,5-Bis(trifluoromethyl)-1,4-bis(tosyl)piperazine **122** was produced as a single diastereomer when 2-trifluoromethyl-*N*-tosylaziridine was subjected to 1.5 equiv. of CsF and 1.5 equiv. of *t*-BuOTMS in DMSO at 80°C for 24 h (Scheme 2.33).



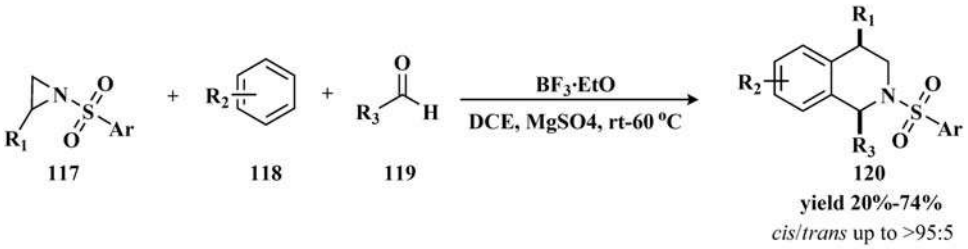
SCHEME 2.30 Snthesis of 1,2,3,4-tetrahydroisoquinoline through gold-catalyzed domino reaction of aziridinyl alkynes **112** with a number of arenes **113**.



SCHEME 2.31 Synthesis of functionalized piperidines **116** starting from ditosyl bis(aziridine) **115**.

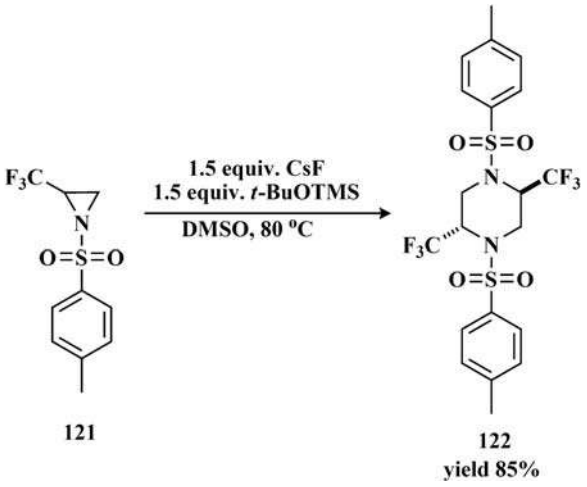
In 2017, three-component one-pot reactions of 2-trifluoromethyl-*N*-nosylaziridine **123**, primary amines , and vinylsulfonium salt **125** provides access to CF_3-containing piperazines **126** with excellent regioselectivity and in high yields which was described by Hirotaki *et al.* [77]. Similar result was obtained through the one-pot two reaction cascades that proceeded *via* ring-opening reaction of 2-trifluoromethylated *N*-nosylaziridine **123** with various primary amines to produce 1,2-ethylene diamine **123**, followed by the reaction with vinylsulfonium salts **125** (Scheme 2.34).

Samzadeh-Kermani [78] disclosed one-pot reaction included nitromethane, isothiocyanates **127**, and *N*-sulfonyl aziridines **51** for the formation of functionalized

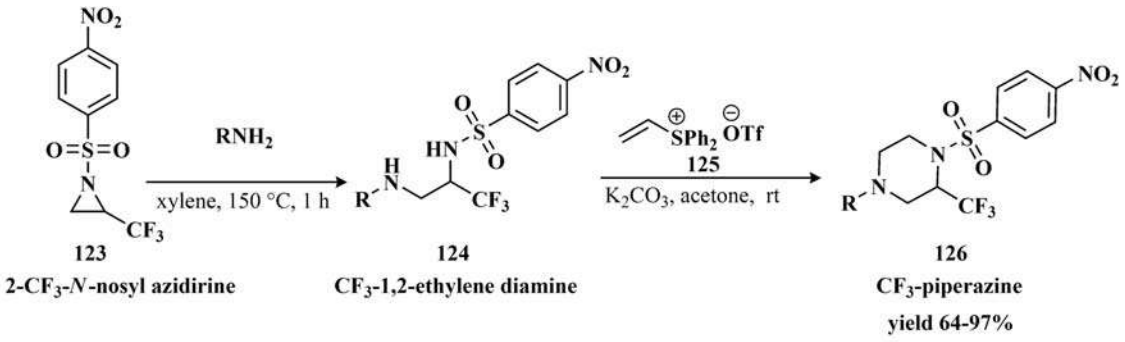


Ar = C_6H_4-4-CH_3, C_6H_4-4-Br, C_6H_4-4-NO_2, R_1= C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-F, C_6H_4-4-Cl, C_6H_4-4-Br, R_2 = H, OCH_3, 1,2-2OCH_3, 1,3-2OCH_3, 1,2,3-3OCH_3, Cl, 1-Br-3,4-OCH_3, R_3 = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl, C_6H_4-4-Br, C_2H_5, Bn, *i*Pr

SCHEME 2.32 Three-component reactions of aziridines **117**, arenes **118**, and aldehydes **119** for the synthesis of 1,4-disubstituted tetrahydroisoquinolines **120**.



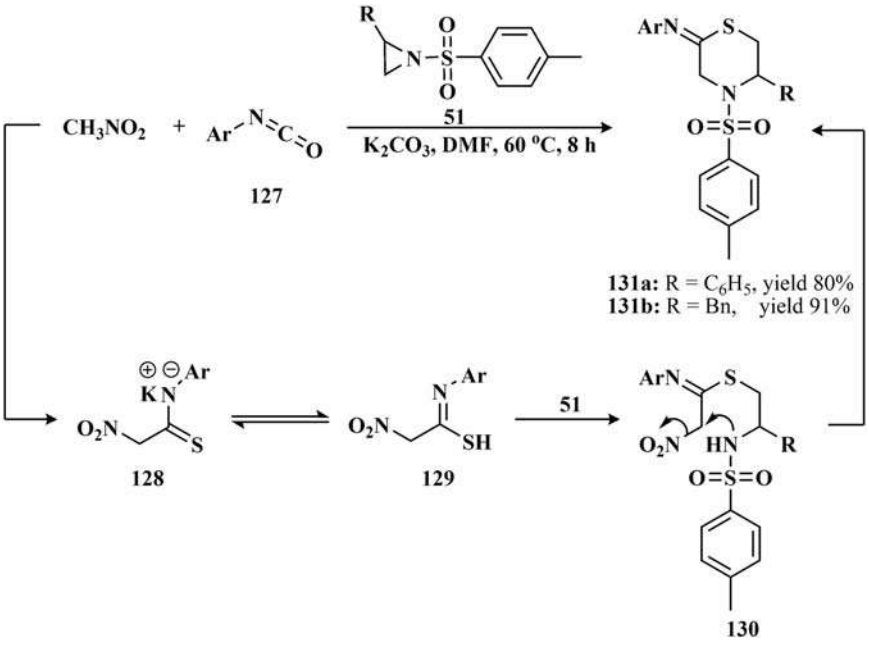
SCHEME 2.33 Dimerizartion of 2-trifluoromethyl-*N*-tosylaziridine to the corresponding *trans*-2,5-disubstituted piperazine derivative **121**.



R = C_6H_4-2-CH_3, C_6H_4-2-OCH_3, C_6H_{45}-2-Cl, C_6H_4-2-F, C_6H_4-3-CF_3, C_6H_4-4-Cl, C_6H_3-2,6-$(CH_3)_2$, C_6H_3-2,3-$(Cl)_2$, Bn, C_6H_3-3,5-$(CF_3)_2$, $CH_2(C_6H_5)_2$, *i*-Bu ,(2-methyl-1H-indol-5-yl, 4-[(3,4-methylenedioxyphenyl)methyl

SCHEME 2.34 Ring-opening reaction of 2-trifluoromethylated *N*-nosylaziridine **123** with primary amines, followed by vinylsulfonium salts.

thiomorpholines **131** under basic condition (Scheme 2.35). A plausible mechanism for this one-pot reaction initiated with the formation of the intermediate **128** from the coupling of nitromethane with the isothiocyanate group. This intermediate tautomized to give **129**, which efficiently could react with the aziridine to furnish the ring-opened product **130**. The latter underwent intramolecular cyclization reaction where the nitro group acted as the leaving group to afford the desired 1,4-thiomorpholine **131** (Scheme 2.35).



SCHEME 2.35 Synthesis of functionalized thiomorpholines **131** under basic condition by one-pot reaction.

2.2.2.4 To N-sulfonated seven-membered heterocyclic ring

Zhou *et al.* [79] reported an asymmetric and highly stereoselective approach toward the synthesis of azepane through a novel *N*-bromosuccinamide induced aminocyclization−aziridine ring-expansion cascade. At first, electrophilic addition of activated NBS to the double bond in aziridine **132** led to the formation of bromonium ion intermediate **A**. The latter underwent intramolecular nucleophilic attack *via* the ring nitrogen at the tertiary carbon in an S_N2-fashion followed by C−N bond cleavage of the aziridinium ion. Subsequently, the intermolecular nucleophilic attack on $NsNH_2$ furnished the desired product **133** in moderate yield (Scheme 2.36).

Shintani *et al.* [80] developed a palladium-medicated decarboxylative [4 + 3] cyclization of γ-methylidene-δ-valerolactone with *N*-tosyl aziridine to furnish *N*-tosyl azepanes **134** (Scheme 2.37). The development of asymmetric catalysis was also explored by using a chiral phorphoramidite ligand **B** to construct chiral *N*-sulfonyl azepane **135** with 85% enantiomeric excess in good yield.

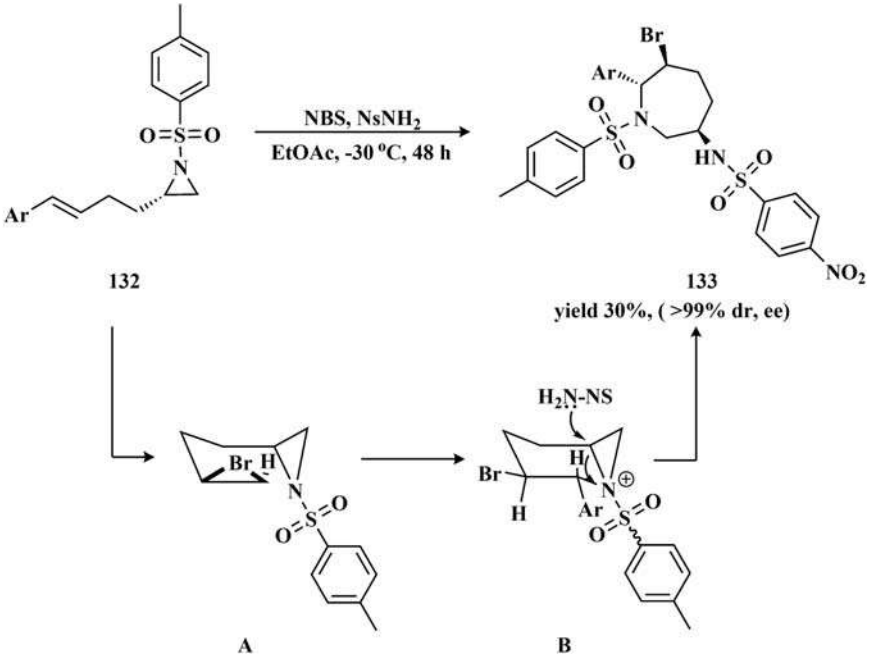
Moore *et al.* [81] demonstrated that allylic sulfonamide **138**, which was generated from a nucleophilic ring-opening of β-alkoxy aziridine **136** using organolithium reagent *n*-BuLi, underwent an intermolecular cyclization under mild Mitsunobu condition after removal of triisopropylsilyl group to provide fused-azepine **139** (Scheme 2.38). The synthetic utility of this methodology was the use of the synthesized fused-azepine **139** in the construction of the pentacyclic ring system of cephalotaxine alkaloide.

2.3 Uses of *N*-sulfonated aziridines in living aza-anionic polymerization

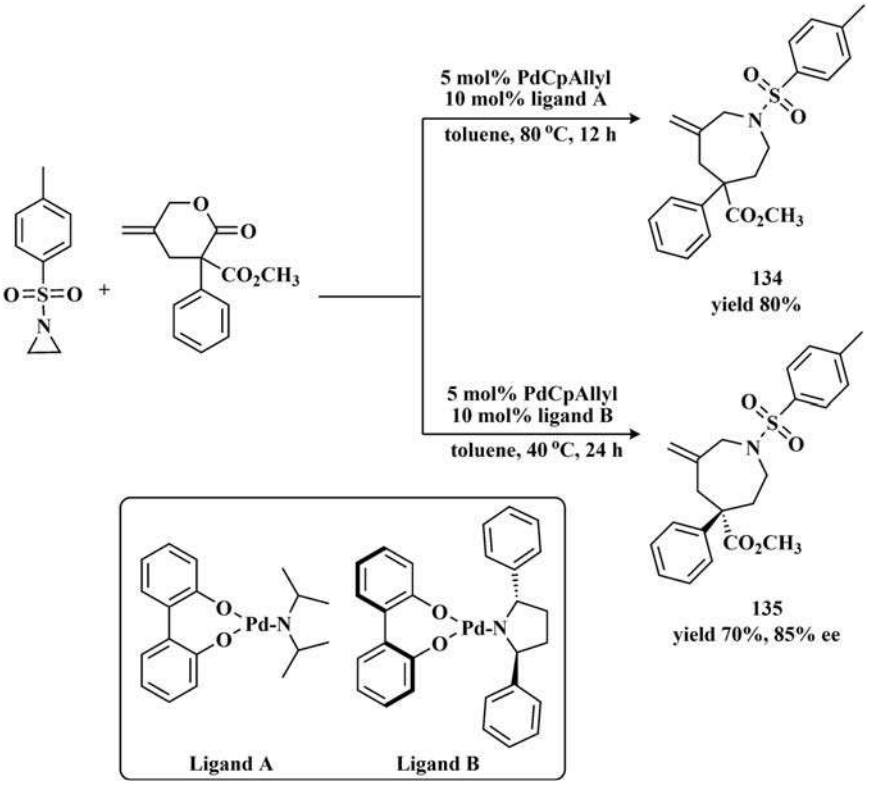
In light of the modern synthetic chemistry, *N*-sulfonylaziridines are valuable ring systems in the ring-opening polymerization (ROP) as compared with their oxygenated analogs, epoxides, due to their limitation in their ROP to form cationic ones that are not controlled and allow for the preparation of the interesting branched and hyperbranched poly(ethylenimine) derivatives.

Outstanding progress in the living anionic homopolymerization and copolymerization of different *N*-sulfonylaziridines, either in a sequential pattern or with well-known monomers, was done in recent years in the regard to its mechanism and the effect of monomers involved.

The classical route toward linear polyethyleneimine (PEI) represented the living cationic polymerization of 2-oxazolines and the subsequent hydrolysis. It was a challenge synthesizing linear PEIs attached with substitutents along with their backbone chains (e.g., linear polypropylene imine) through the polymerization of 4- or 5-substituents 2-oxazolines because of steric hindrance motives. Recent publications explored the possibility to synthesize PEI and its derivatives *via* desulfonylation of poly(*N*-sulfonylaziridines)s that are prepared from the

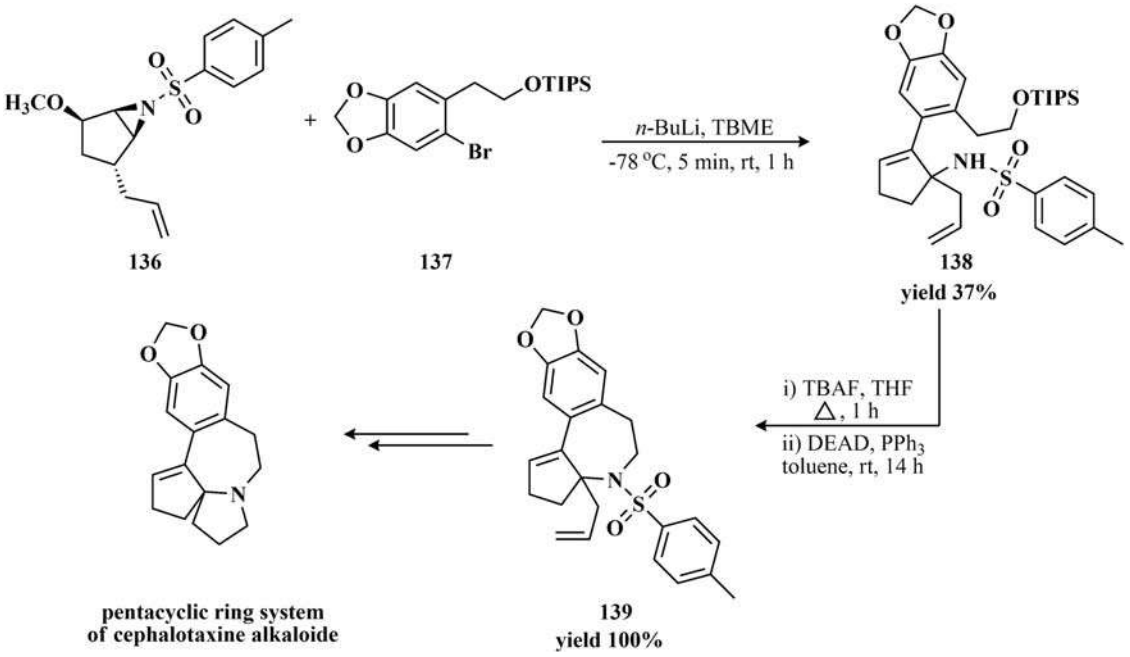


SCHEME 2.36 Aminocyclization–aziridine ring-expansion cascade.



SCHEME 2.37 Palladium-medicated decarboxylative [4 + 3] cyclization of γ-methylidene-δ-valerolactone with *N*-tosyl aziridine.

anionic polymerization of *N*-sulfonylaziridines. Well-defined PEI and its derivatives are stimulating materials, surfactants, polyelectrolytes, and transfection agents [82,83]. Currently, linear polyethyleneimine (L-PEI) is widely utilized for non-viral gene transfection because of its high efficacy [84].



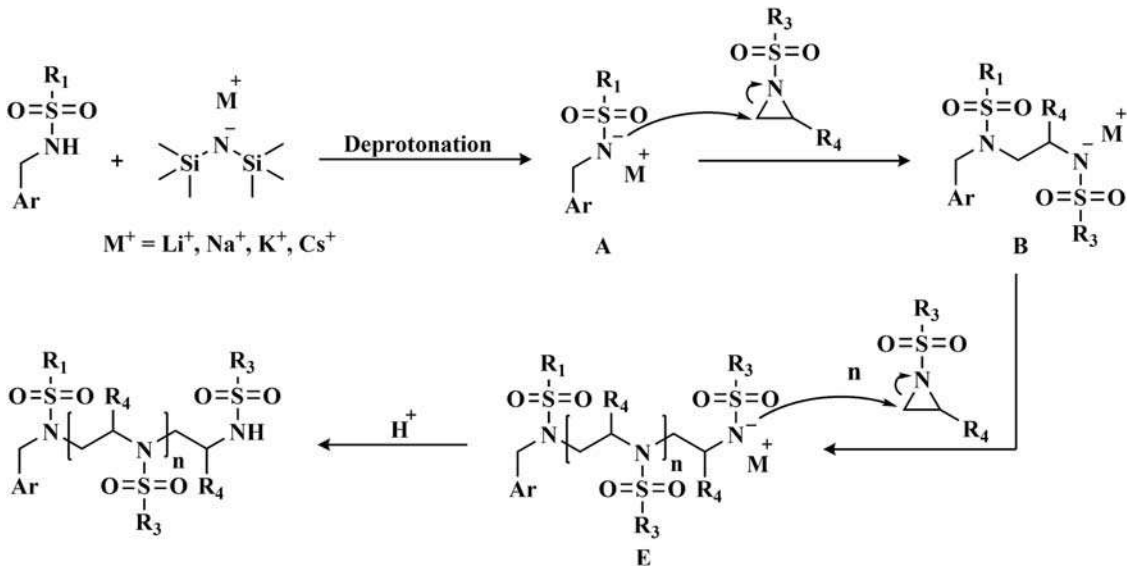
SCHEME 2.38 Synthesis of the pentacyclic ring system of cephalotaxine starting from allylic sulfonamide **138**.

2.3.1 Bis(trimethylsilyl)amides-catalyzed anionic ring-opening polymerization of *N*-sulfonated aziridines

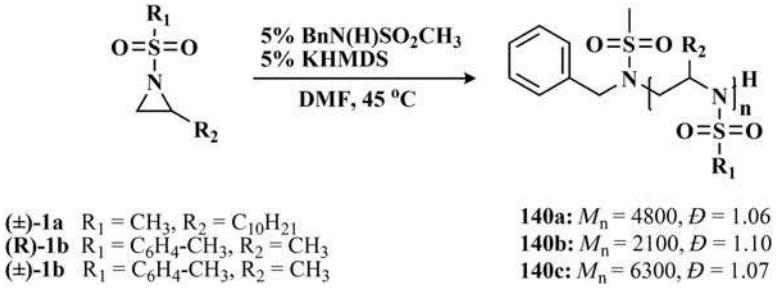
The living aza-anionic polymerization of sulfonamide-activated aziridine was typically achieved by using a stoichiometric amount of secondary *N*-sulfonamide initiators and alkali bis(trimethylsilyl)amides catalysts to furnish linear poly(*N*-sulfonylaziridine)s with diverse structures. The aza-anionic polymerization of *N*-sulfonyl aziridines can be initiated *via* a nucleophilic attack of the deprotonated secondary sulfonamide **A**, which can be generated *in-situ* in the presence of alkali bis(trimethylsilyl)amide, on the aziridine monomer at its less substituted ring side to form the propagating sulfonamide anion **B** (Scheme 2.39) [85]. Such aza-anion attacks at the next monomer and propagation remain continuous, as long as the monomer is still available. This type of anionic polymerization lives in the absence of any impurities and controlled termination is possible *via* the addition of an electrophile. It is worth mentioning that the electron-withdrawing sulfonyl group of the aziridine monomer allows for stabilizing the aza-anions in the growing chain through delocalization. In addition, its function is in facilitating the nucleophilic attack on aziridine rings.

Numerous of organic researchers were interested in the exploring of the performance of metallic initiator system in the polymerization of diverse *N*-sulfonated aziridines with over viewing the performed polymerization kinetics as well as their respective conditions. The first example of anionic ROP (ring-opening polymerization) of *N*-sulfonated aziridines was disclosed by Bergman, Toste *et al.* [86] in 2005. The authors attempted to initiate the anionic ROP of 2-*n*-decyl-*N*-mesylaziridine **(±)-1a** with *N*-benzyl methanesulfonamide in the presence of potassium bis(trimethylsilyl) amide (KHMDS). However, the resultant poly(2-*n*-decyl-*N*-mesylaziridine)s **140a** obtained in a very low molecular weight ($M_n = 4800$) and narrow polydispersity ($Đ = 1.06$). It was also determined that the use of the racemic of 2-methyl-*N*-tosylaziridine **(±)-1b** resulted in highly soluble atactic poly(2-methyl-*N*-tosylaziridine)s **140c**. On the contrary, identical tactic polymers **140b** were sparingly soluble at higher molecular weights upon using enantiopure monomer **(R)-1b**. Accordingly, the solubility of poly(*N*-sulfonylaziridine)s is greatly dependent on the tactility of the polymer (Scheme 2.40).

A systematic study on the aza-anionic polymerization of sulfonamide-activated aziridines was performed under different conditions (initiator, counter-ion variation, solvent, and temperature) [85]. It was observed that the polymerization of 2-methyl-*N*-mesylaziridine retained the living behavior at temperatures in the range of 20°C to 100°C. Furthermore, polar aprotic solvents DMSO and DMF revealed the high solvation capability of the living chain end and consequently the fastest polymerization. It was also noted that a novel bifunctional initiator, *N*,*N*′-(1,4-phenylenebis(methylene)) dimethanesulfonamide, produced poly(2-methyl-*N*-tosylaziridine)s with higher molecular weights and almost similar polydispersities compared with *N*-benzyl-sulfonamide.



SCHEME 2.39 Mechanism of the aza-anionic polymerization of *N*-sulfonyl aziridines.

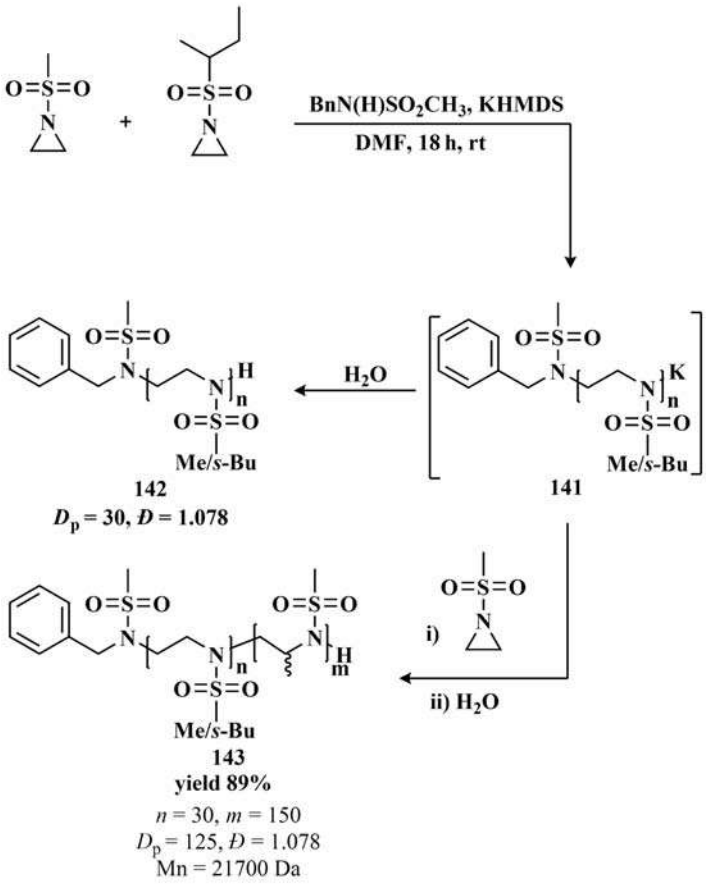


SCHEME 2.40 Anionic ring-opening polymerization of *N*-sulfonated aziridines **1a,b**.

Different bis(trimethylsilyl)amide salts of lithium, sodium, potassium, and cesium were used to study the influence of the respective counter ions on polymerization of both 2-methyl-*N*-tosylaziridine and 2-methyl-*N*-mesylaziridine. A slight variation was perceived in the following trend: $Cs^+ > Li^+ > Na^+ > K^+$ dependence on the binding between such counter ions with the propagating azaanions. Sulfonamide azaanions exhibited less binding to cesium and lithium cations compared to sodium and potassium.

2.3.1.1 Copolymerization of different N-sulfonylaziridine monomers

Competitive copolymerization of diverse *N*-sulfonylaziridine represents a powerful strategy for the preparation of random or gradient copolymers depending on the electronic nature of the sulfonyl substituents. Rupar *et al.* [87] studied the anionic copolymerization of two unsubstituted *N*-sulfonylaziridine, namely 1-(*sec*-butylsulfonyl)-aziridine (^{s}BsAz) with 1-(methylsulfonyl)aziridine (MsAz) as demonstrated in Scheme 2.41. It was established that the similarity in electronics of 1-(*sec*-butylsulfonyl)-aziridine (^{s}BsAz) with 1-(methylsulfonyl)aziridine (MsAz) resulted in the incorporation of both monomers into the copolymer with similar rates. Consequently, this allowed for the synthesis of random P(MsAz-r-sBsAz)$_{30}$ **142** with low molecular weight dispersity ($Đ = 1.078$). In spite of the fact that the ^{s}Bs group is bulkier compared with Ms, this didn't influence the polymerization rates of the two monomers, since the sulfonyl substituents are far enough from the position of nucleophilic attack on the aziridinyl ring. BnN(K)Ms-initiated copolymerization of the monomers was achieved to prepare Living P(MsAz-r-sBsAz)$_{30}$ **141**. The latter was then terminated by an excess amount of water. Due to the living nature of the copolymerization, a block copolymer P(MsAz-r-^{s}BsAz)$_{150}$-*b*-P(MeMsAz)$_{30}$ **143** can be successfully prepared *via* the addition of MsMAz to the copolymerization reaction after consummation of the monomers, following by adding of water (Scheme 2.41). Degree of polymerization D_p of the

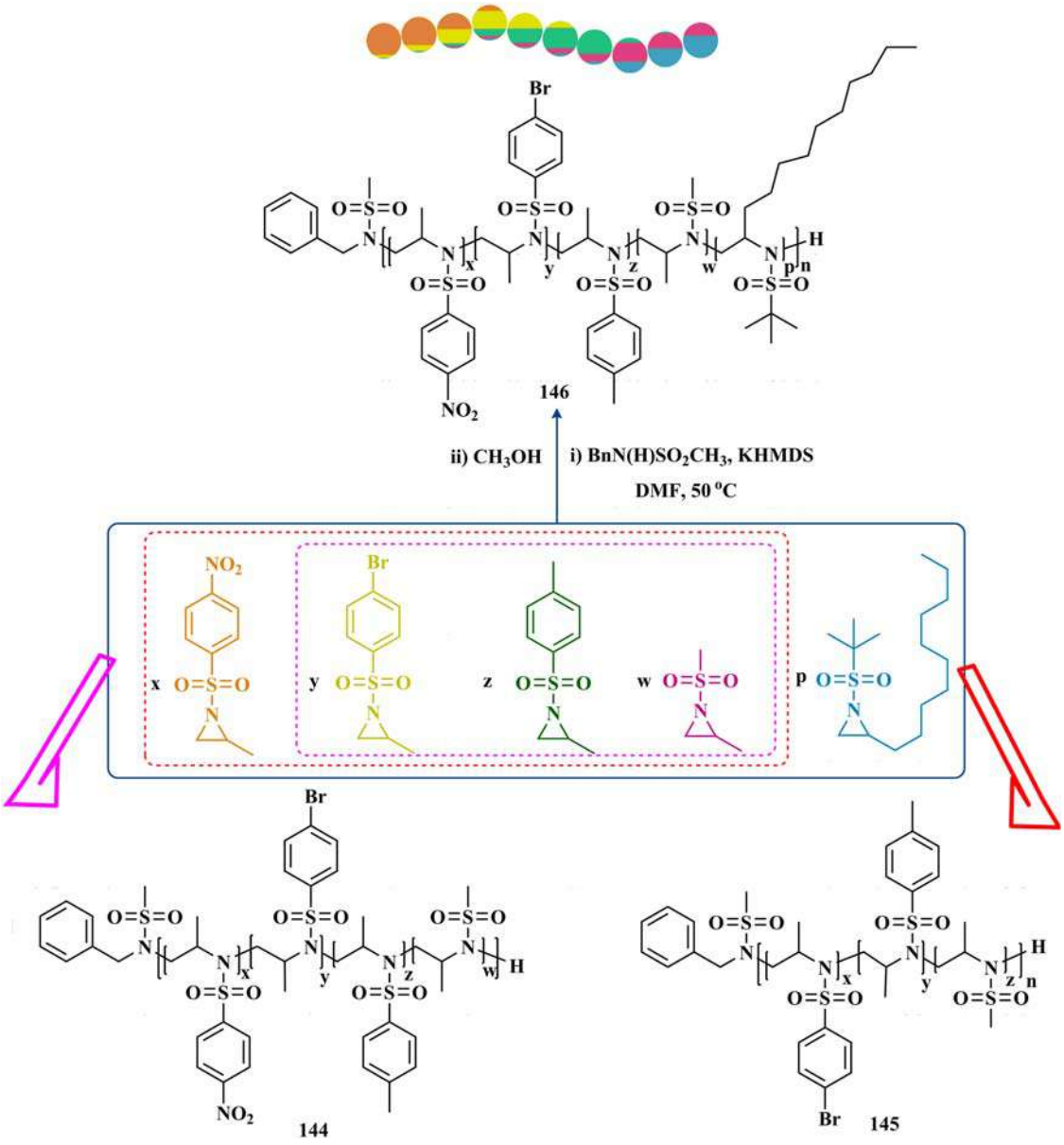


SCHEME 2.41 Anionic copolymerization of 1-(*sec*-butylsulfonyl)-aziridine (^{s}BsAz) with 1-(methylsulfonyl)aziridine (MsAz).

resulting copolymer **142** and block polymer**143** was determined *via* ^{1}H NMR end-group analysis.

Alternatively, Wurm and coworkers [88] explored how it affects the changes in the sulfonyl group electronic properties in the copolymerization of a series of 2-alkyl-*N*-sulfonylaziridines. Multi gradient copolymers were successfully prepared in a controlled fashion *via* one-pot copolymerization reactions, up to five diverse 2-alkyl-*N*-sulfonylaziridine monomers (Scheme 2.42). The terpolymerization of 2-methyl *N*-mesylaziridine (MsMAz), 2-methyl *N*-tosylaziridine (TsMAz), and 2-methyl *N*-brosylaziridine (BsMAz) provide access to terpolymer with sharp gradient incorporation of the three monomers (Scheme 2.42). The monomer incorporation was in the following order: BsMAz > TsMAz > MsMAz. Accordingly, the stronger electron-withdrawing sulfonyl groups could promote faster polymerization rates. When 2-methyl-*N*-nosyl aziridine (NsMAz) with robust electron-withdrawing nosyl group participated in the quarterpolymerization reaction of BsMAz, TsMAz and MsMAz, the polymerization rate constant of NsMAz was found to be twice than that of BsMAz. Therefore, the quick consumption of NsMAz was observed, followed by the sequential consummation of the other monomers as the above-mentioned trend to obtain quarterpolymer **p(NsMAz-co-BsMAz-co-TsMAz-co-MsMAz)**. For expansion of this work, the authors successfully prepared pentablock quintopolymers using five *N*-sulfonylaziridine monomers that differ in sulfonyl substituents (Scheme 2.42). A newly synthesized monomer, 2-decyl-*N*-*tert*−butylsulfonylaziridine (BusDAz), was subject to the quarterpolymerization reaction with the four aforementioned monomers (Scheme 2.42). It was noted that the monomer exhibited the slowest incorporation due to the less negative inductive influence of the busyl group as well as the steric hindrance of the decyl group. In this regard, the author investigated the effect of steric hindrance of 2-alkyl substituent individually on the incorporation rate *via* employing two monomers carrying an identical sulfonyl group (mesyl group) and a different alkyl group at position no. 2 of aziridinyl ring (decyl vs methyl) in quart polymerization reaction with NsMAz and BsMAz, The results demonstrated that a slight influence on the polymerization rates and subsequently ideal random distribution between two mesylated monomers in the polymer chain was monitored by utilizing the real-time NMR spectroscopy.

In an interesting recent report, the same group of authors determined the reactivity ratios for a library of



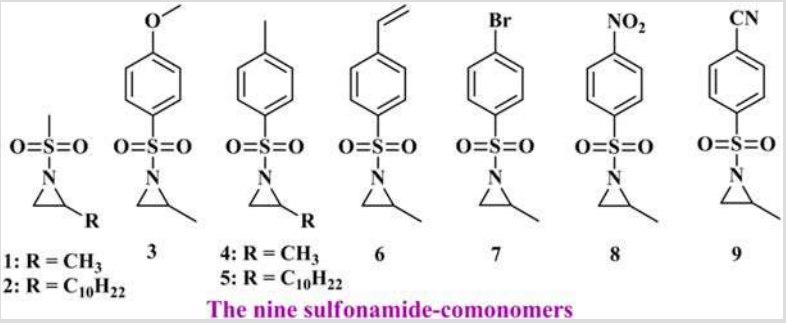
SCHEME 2.42 One-pot copolymerization reactions, up to five diverse 2-alkyl-*N*-sulfonylaziridine monomers.

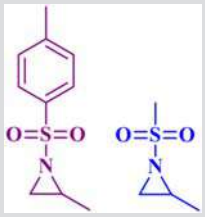
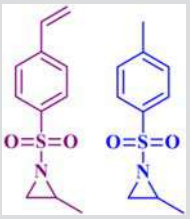
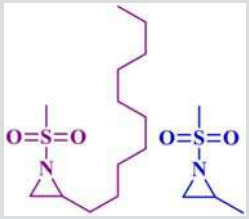
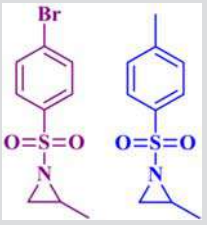
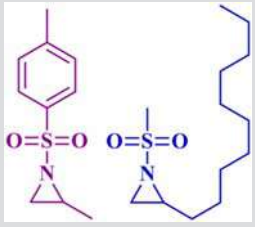
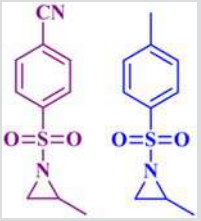
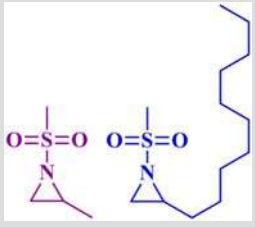
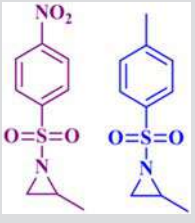
nine sulfonamide-comonomers using three nonterminal models (Jaacks, Frey, BSL) and the Meyer−Lowry terminal model (Table 2.1) [89]. It was proved the similarity of the obtained data, indicated that the copolymerization could be described with either nonterminal or terminal models and also the recorded reactivity ratios of commoners were correlated with the electron-withdrawing influences of the sulfonyl-activating groups. This family of *N*-sulfonylaziridines was utilized as commoner models for classification between soft, medium, and hard gradients for the resulting copolymers. It was noted that the competitive copolymerization of *N*-sulfonylaziridines with the same sulfonyl groups led to random copolymers [poly(**5**-co-**4**), poly(**2**-co-**1**)] as reported earlier (Table 2.1). Copolymers with a soft gradient profile were obtained for reactivity ratios of ≤ 2 and ≥ 0.5 for r_1 and r_2, respectively, as represented in the case of poly(**5**-co-**3**), poly(**6**-co-**5**), and poly(**7**-co-**5**) (Table 2.1). When reactivity ratios were closed to 5 for r_1 and 0.2 for r_2, the respective copolymers exhibited a medium gradient strength. Such medium gradient copolymers were shown in poly(**5**-co-**2**) and poly(**4**-co-**2**) (Table 2.1). Reactivity ratios resulting in hard gradients are usually in the range of $7.5 - 25$ for r_1 and $0.13 - 0.04$ for r_2. Similar situation was dominated in the case of poly(**8**-co-**4**) and poly(**9**-co-**4**). Upon further increasing the difference in reactivity

ratio of commoners, the resultant copolymer was similar to a real block copolymer that was prepared *via* sequential addition of monomer and this is represented in the case of poly(**9**-co-**2**) with reactivity ratios of r_1 and r_2 equaling to 76.31 and 0.01, respectively (Table 2.1).

A recent advance in the anionic polymerization of *N*-sulfonylaziridines was reported by the same authors who designed an approach based on physical separation of the comonomer pair in the emulsion compartment to force the commoners, which undergo perfectly random

TABLE 2.1 The reactivity ratios of nine sulfonamide-comonomers using three nonterminal models (Jaacks, Frey, BSL) and the Meyer – Lowry terminal model.

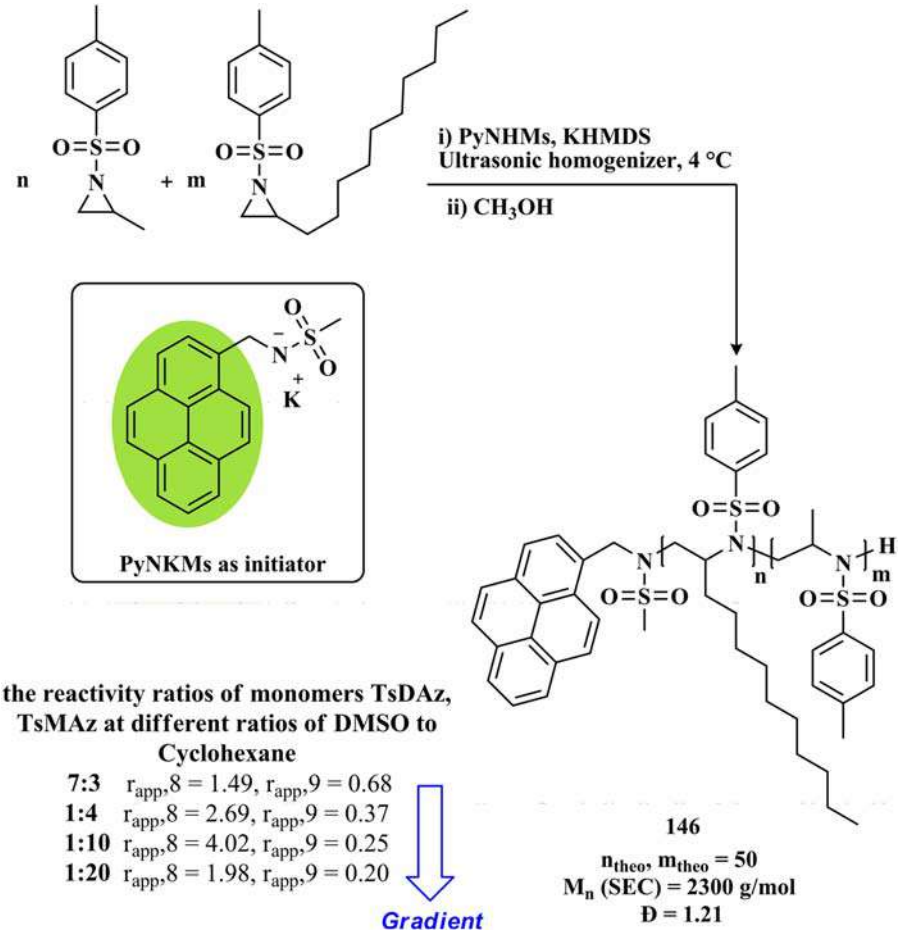


Commoners	Methods	Reactivity ratios R_1, R_2	Commoners	Method	Reactivity ratios R_1, R_2
	Jaacks	5.476, 0.182		Jaacks	1.681, 0.590
	Frey	5.526, 0.180		Frey	1.682, 0.594
	BSL	5.540, 0.181		BSL	1.675, 0.590
	M-L	5.634, 0.190		M-L	1.477, 0.495
	Jaacks	5.508, 0.181		Jaacks	4.245, 0.235
	Frey	5.493, 0.182		Frey	4.245, 0.235
	BSL	5.487, 0.182		BSL	4.245, 0.235
	M-L	5.461, 0.178		M-L	4.251, 0.236
	Jaacks	0.929, 1.074		Jaacks	13.791, 0.072
	Frey	0.900, 1.110		Frey	14.021, 0.071
	BSL	0.903, 1.106		BSL	14.084, 0.071
	M-L	n.c.		M-L	17.625, 0.199
	Jaacks	1.354, 0.737		Jaacks	22.664, 0.044
	Frey	1.359, 0.735		Frey	23.347, 0.042
	BSL	1.359, 0.735		BSL	23.081, 0.043
	M-L	1.426, 0.784		M-L	28.880, 0.132

copolymerization in solution, into the formation of gradient copolymers [90]. In this approach, the tosylated aziridine **TsMAz** is located in the DMSO droplets (the dispersed phase), while **TsDAz** with a long decyl tail is preferably soluble in the continuous phase (cyclohexane). Diluting the continuous phase with the DMSO droplets allowed for anionic polymerization, selectively, in the DMSO droplets (Scheme 2.43). By monitoring real-time ^{1}H NMR kinetics, the variation of the dispersed to continuous phase ratio was a vital factor in adjusting the gradient strength of the resulting copolymers. Upon increasing the dilution of the continuous phase, the reactivity ratios were changed gradually to form more prominent gradient copolymer structures. It was represented that the apparent reactivity ratios of the tosylated monomers (r_{app}(**TsDAz**) = 0.20 and r_{app}(**TsMAz**) = 4.98) in a 1:20-DMSO/cyclohexane emulsion resulted in producing the strongest gradient copolymer **146**. A florescent PyNHMs-initiator was selectively used as an initiator for the anionic polymerization in the presence of KHMDS to image the dispersed phase of the emulsion through confocal laser scanning microscope (CLSM).

2.3.2 Organocatalytic ring-opening polymerization of *N*-sulfonated aziridines

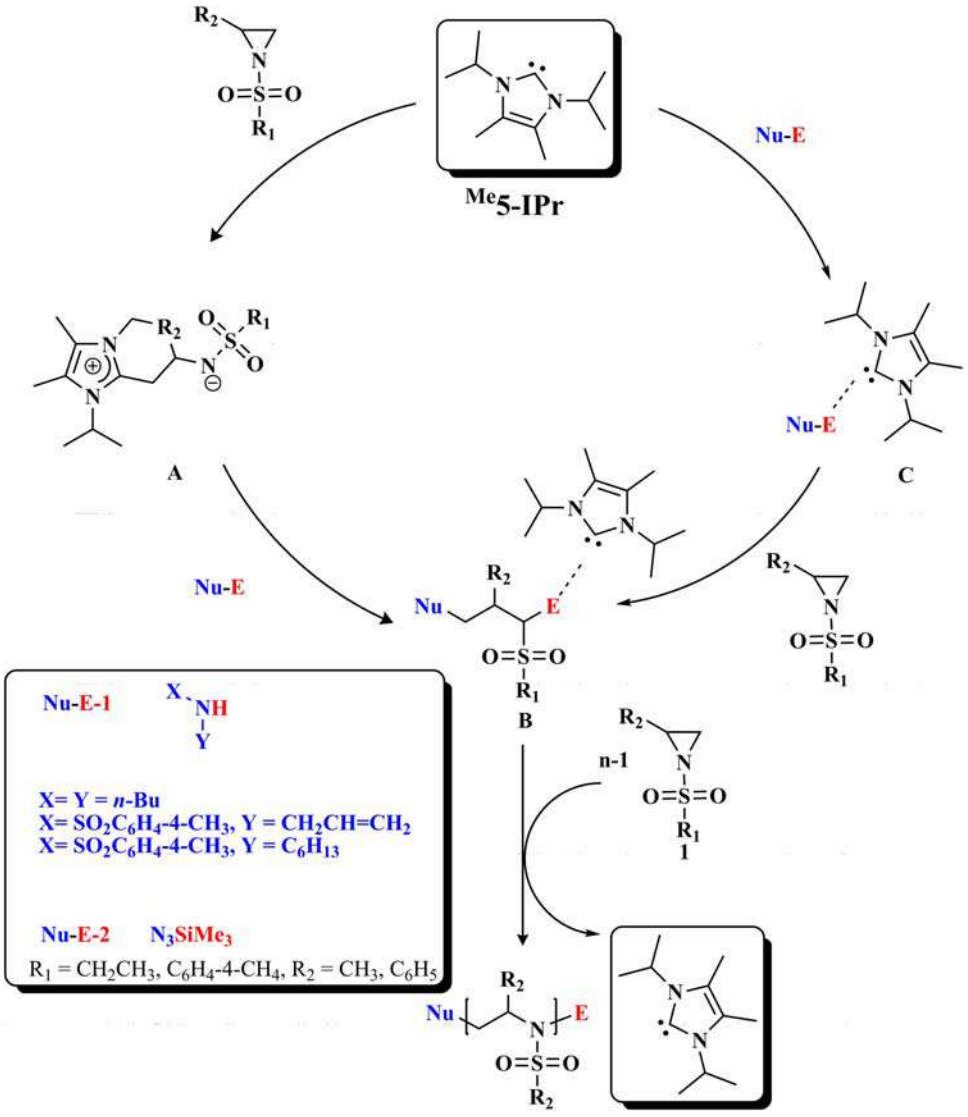
Most anionic polymerization of *N*-sulfonyl aziridines was limited to a metallic initiating system based on *N*-sulfonated amide and KHMDS. Therefore, there is considerable prominence to further exploring alternative strategies suitable for the ring-opining polymerization of *N*-sulfonylaziridines. The combination of the organocatalyst *N*-heterocyclic carbene with the non-activated secondary amines' initiator was considered an efficient, metal-free, and mild strategy for the anioinc ring-opining polymerization of *N*-sulfonyl aziridines. *N*-Heterocyclic carbenes usually represent robust catalysts in diverse types of polymerizations (zwitterionic ROP [91], step-growth polymerization [92], Group transfer polymerization [93–96], etc...) due to unconfined structural diversity as well as superior Brønsted-basicity and nucleophilicity characteristics. Two mechanisms, basic and nucleophilic mechanisms, are possible for carbene-catalyzed ROP of *N*-sulfonyl aziridines depending on the nature of aziridine monomer [97]. In the nucleophilic mechanism, *N*-heterocyclic carbene, 1,3-bis



SCHEME 2.43 Anionic polymerization of *N*-sulfonylaziridines using florescent PyNHMs-initiator and KHMDS.

(isopropyl)-4,5(dimethyl)imidazole-2-ylidene (Me5-Ipr), would directly attack the *N*-tosylaziridine monomer **146** to generate the imidazolium amidate **A**. The latter was then displaced using initiator **NuE** *via* concomitant protonation of the amidate **A**, as in the case of initiators **NuE-1** (or silylation as in case of initiator **NuE-2**). In addition, substitution of the imidazolium moiety *via* **Nu** to release the Me5-Ipr organocatalyst and activiation of another monomer were performed (Scheme 2.5). In the basic mechanism, the initiator would be deprotonated *via* Me5-Ipr. This is by the attack on the aziridine monomer by **Nu** (Scheme 2.44).

Carlotti, Taton and coworkers [98] introduced Me5-Ipr in the anionic homopolymerization of *N*-*p*-toluenesulfonylaziridines 2-phenyl or methyl substitutes (**TsMAz** or **TsPhAz**) in the presence of either di-*n*-butylamine or *N*-hexyl-*p*-toluenesulfonylamine as initiators (Scheme 2.45). It was noted that the molecular weights of the synthesized polyaziridines **147** were up to 11700 g/mol and dispersity ranged between 1.04 and 1.20. The polymerization completely occurred in the time range of 1−5 days in THF at 50°C dependent on the steric hindrance of the substitute for aziridine ring. Such methodology can further be applied to controlled polyaziridines-based block copolymers *via* sequence copolymerization of **TsMAz** and **TsPhAz** under *N*-heterocyclic carbene catalysis. Interestingly, the additional order of the two used monomers was affected by the molar masses of the prepared block copolymer. Interestingly, if the **TsMAz** was added first and then **TsPhAz**, the molar mass of the resultant block copolymer was twice that of the block copolymer prepared in the reverse addition order ($M_{n\ SEC} = 9000$ g/mol vs M_n



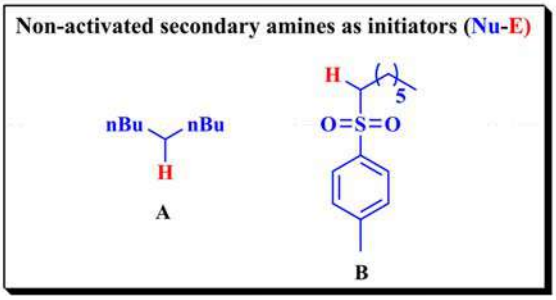
SCHEME 2.44 Mechanism of anionic polymerization of *N*-sulfonylaziridines under carbene-catalyzed reaction.

M: TsMAz (R = CH_3) Nu-E = A
[M]/[3]/[^{Me}5-Ipr]
10/1/0.1, $M_{n,SEC}$ = 1880, Đ = 1.07
20/1/0.1, $M_{n,SEC}$ = 2500, Đ = 1.06
50/1/0.1, $M_{n,SEC}$ = 6000, Đ = 1.06
100/1/0.1, $M_{n,SEC}$ = 11700, Đ = 1.04

M: TsPhAz (R = C_6H_5) Nu-E = A
[M]/[3]/[^{Me}5-Ipr]
20/1/0.1, $M_{n,SEC}$ = 2600, Đ = 1.06
50/1/0.1, $M_{n,SEC}$ = 6250, Đ = 1.12
100/1/0.1, $M_{n,SEC}$ = 10800, Đ = 1.15

M: TsMAz (R = CH_3) Nu-E = B
[M]/[3]/[^{Me}5-Ipr]
20/1/0.1, $M_{n,SEC}$ = 4500, Đ = 1.13
50/1/0.1, $M_{n,SEC}$ = 10600, Đ = 1.11
100/1/0.1, $M_{n,SEC}$ = 18 000, Đ = 1.16

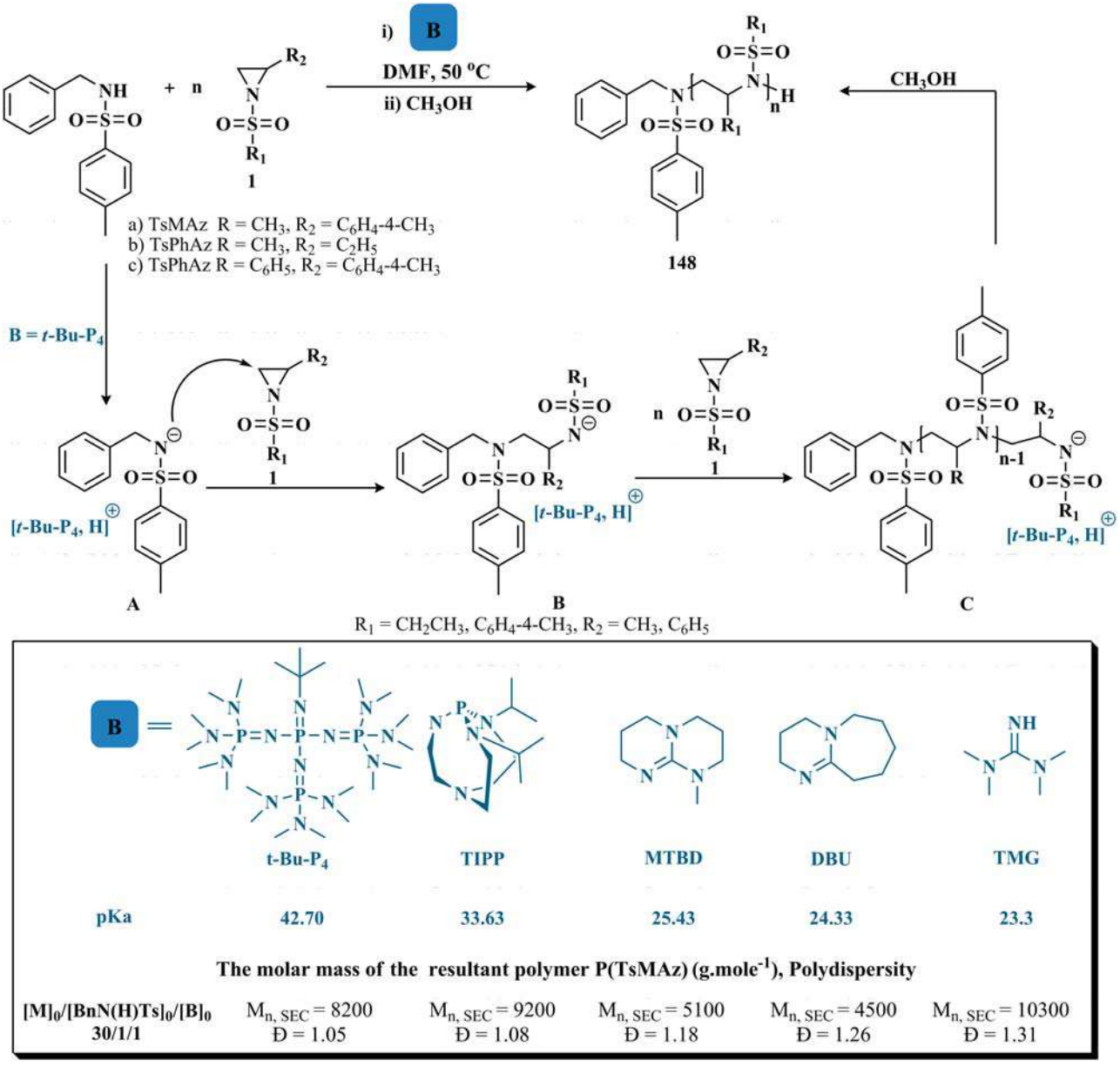
M: TsPhAz (R = C_6H_5) Nu-E = B
[M]/[3]/[^{Me}5-Ipr]
10/1/0.1, $M_{n,SEC}$ = 2100, Đ = 1.08
20/1/0.1, $M_{n,SEC}$ = 5000, Đ = 1.12
50/1/0.1, $M_{n,SEC}$ = 7200, Đ = 1.17
100/1/0.1, $M_{n,SEC}$ = 11000, Đ = 1.20



SCHEME 2.45 Anionic homopolymerization of *N*-*p*-toluenesulfonylaziridines.

$_{SEC}$ = 4500 g/mol) due to the higher reactivity of the monomer **TsMAz** compared with **TsPhAz**.

In addition, a range of organic superbases, namely *t*-BuP_4, TiPP, TMG, MTBD and DBU were used for their catalytic efficiency for the anionic polymerization of *N*-sulfonylaziridines (Scheme 2.46) [99]. The organo-medicated polymerizations of a variety of easily accessible *N*-sulfonylaziridines, TsMAz, TsPhAz, 2-methyl-*N*-ethylsulfonylaziridine (EsMAz), initiated *via* *N*-benzyl-*p*-toluenesulfonamide were performed at 50°C in DMF in the presence of the *N*-benzyl-*p*-toluenesulfonamide initiator (BnN(H)Ts) as shown in Scheme 2.45. The catalytic efficiency of the organic superbases correlated with their basicity (quantified *via* pKa of the conjugated acids). In the light of the catalytic efficacy of the used superbases, the use of *t*-Bu-P4 with inherent high basicity allowed for the synthesis of poly(*N*-sulfonylaziridine)s **148** with low molecular weight distributions ($Đ < 1.10$) and high molar masses surpassing 30 kg/mol in a short time (3.5 h). Using of TiPP base also revealed satisfactory results. However, the employ of the other three organic superbases in catalyzing the polymerizations led to a higher dispersity ($Đ$ up to 1.31) to obtain polymers compared with *t*-Bu-P4 and TiPP. Their increased nucleophilicity caused multiple initiators with variable initiating rates. The basic mechanism for the organocatalyzed polymerizations is through three steps (initiation, propagation and termination). The initiating species $[\text{t-Bu-P4,H}]^+ - /[\text{BnNTs}]^-$ **A** which is generated *via* deprotonation of the BnN(H)Ts initiator using *t*-Bu-P_4 as a base model, attached to the aziridine ring **1** to form the active species **B**. The propagation step started by the attack of the active species **B** on the other monomer substrate. The polymerization could be terminated by protonation of the living polyaziridine **C** using an excess amount of methanol.

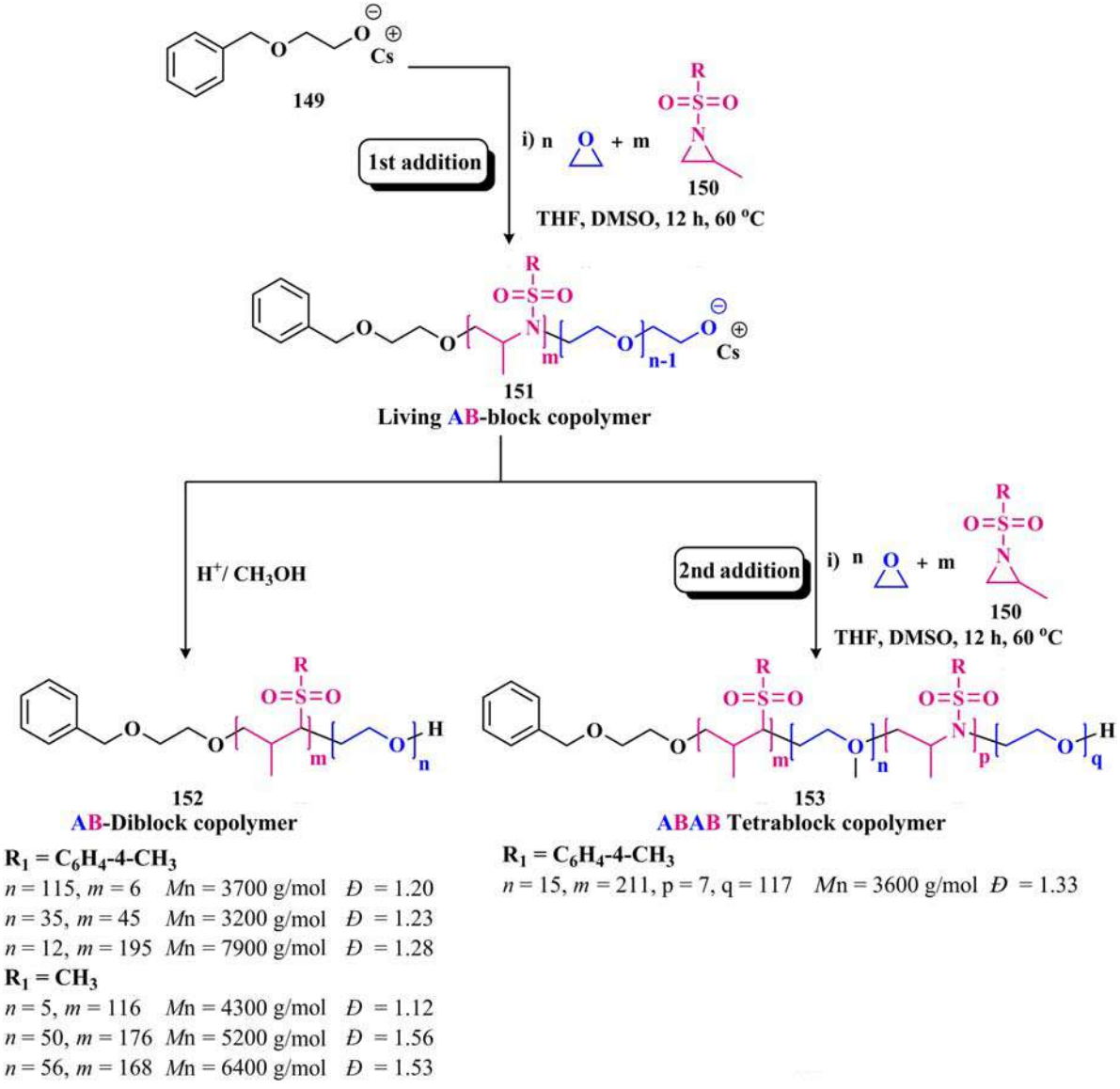


SCHEME 2.46 Anionic polymerization of *N*-sulfonylaziridines under diffrent bases.

2.3.3 Synthesis of copolymers and block copolymers of *N*-sulfonylaziridine monomers with different well-known monomers

An ideal strategy allowing for the fast synthesis of amphiphilic and stimulus-responsive block polymer based on the anionic copolymerization of *N*-sulfonylaziridines (MsMAz, TsMAz) with epoxides (EO) was recently described [100]. Thus, oxy-and aza-anionic ROP could be combined in such a strategy. The cesium alkoxides of 2-benzyloxyethanol **149** were utilized as an initiator for one-step and one-pot synthesis of di-block copolymer **152** with medium polydispersity ($Đ$ in the range of 1.12−1.56) as presented in Scheme 2.47. Interestingly, the unprecedented differences in reactivity ratios of commoners for an anionic copolymerization ($r_1 = 151$ and $r_2 = 0.013$ MsMAz /EO copolymer and $r_1 = 265$ and $r_2 = 0.004$ for TsMAz/EO copolymer) resulted in obtaining multi-block copolymers in an ideal crossover reaction. A sequential addition of the commoners to the living di-block copolymer chain **151** led to the formation of tetra-block copolymer **153** (Scheme 2.46).

The freshly prepared bifunctional PEO **155** from the oxy-anionic polymerization of EO using the cesium alkoxides of 1,4-bis(hydroxy-methyl)-benzene **154** was effectively initiated the anionic copolymerization of EO with MsMAz



$R_1 = C_6H_4\text{-}4\text{-}CH_3$

$n = 115, m = 6$ $Mn = 3700$ g/mol $Đ = 1.20$
$n = 35, m = 45$ $Mn = 3200$ g/mol $Đ = 1.23$
$n = 12, m = 195$ $Mn = 7900$ g/mol $Đ = 1.28$

$R_1 = CH_3$

$n = 5, m = 116$ $Mn = 4300$ g/mol $Đ = 1.12$
$n = 50, m = 176$ $Mn = 5200$ g/mol $Đ = 1.56$
$n = 56, m = 168$ $Mn = 6400$ g/mol $Đ = 1.53$

$R_1 = C_6H_4\text{-}4\text{-}CH_3$

$n = 15, m = 211, p = 7, q = 117$ $Mn = 3600$ g/mol $Đ = 1.33$

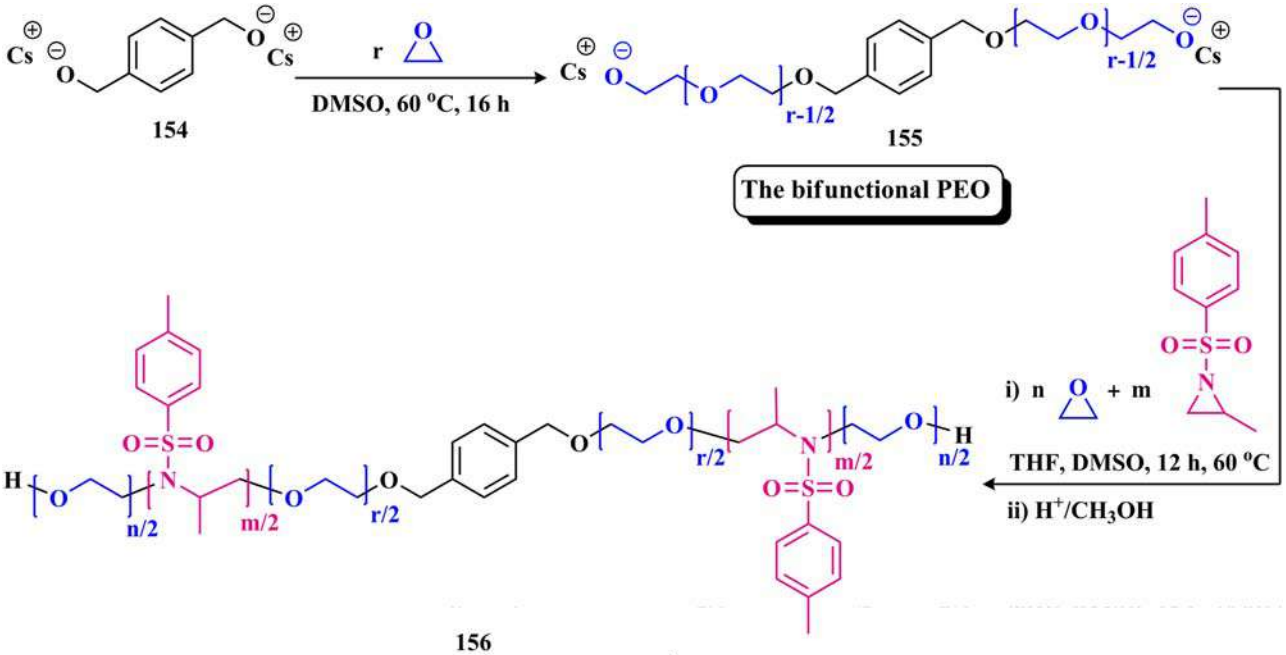
SCHEME 2.47 Oxy-and aza-anionic copolymerization reaction.

or TsMAz to prepare penta-block copolymer **156** (Scheme 2.48) [100]. Such type of amphiphilic copolymer can be utilized as surfactants for stabilization of emulsion polymerization or in the production of macromolecular architectures as well as nanostructures *via* self-assembly.

In addition to a block copolymer prepared *via* the copolymerization of polyaziridine (PAz) with epoxide, a stepwise methodology was designed for the preparation of PAz-*b*-PCL block copolymer **158** [101]. Firstly, telechelic poly(*N*-tosylaziridine) **157** was synthesized by the anionic polymerization of *N*-tosylaziridine in the presence of *N*-((pyridin-3-yl)methyl)-1,1-diphenylmethanimine as initiator and the catalyst KHMDS, following by hydrolysis. Secondly, the anionic ROP of ε-caprolactone with the telechelic polyaziridine **157** was achieved in the presence of the catalyst tin 2-ethyl hexanoate (Scheme 2.49).

A developed approach was proposed for providing PAz-*b*-PCL block copolymer **160** with high molecular weight ($M_{nSEC} = 42420$, $Đ = 1.14$) [102]. In such an approach, an alternative poly(*N*-tosylaziridine) with α-OH functionality **159** was synthesized *via* the anionic polymerization of *N*-tosylaziridine using 4-(hydroxymethyl)benzoic acid as initiator under superbasic condition which copolymerized anionically with ε-caprolactone to furnish with a well-controlled block copolymer **160** (Scheme 2.50).

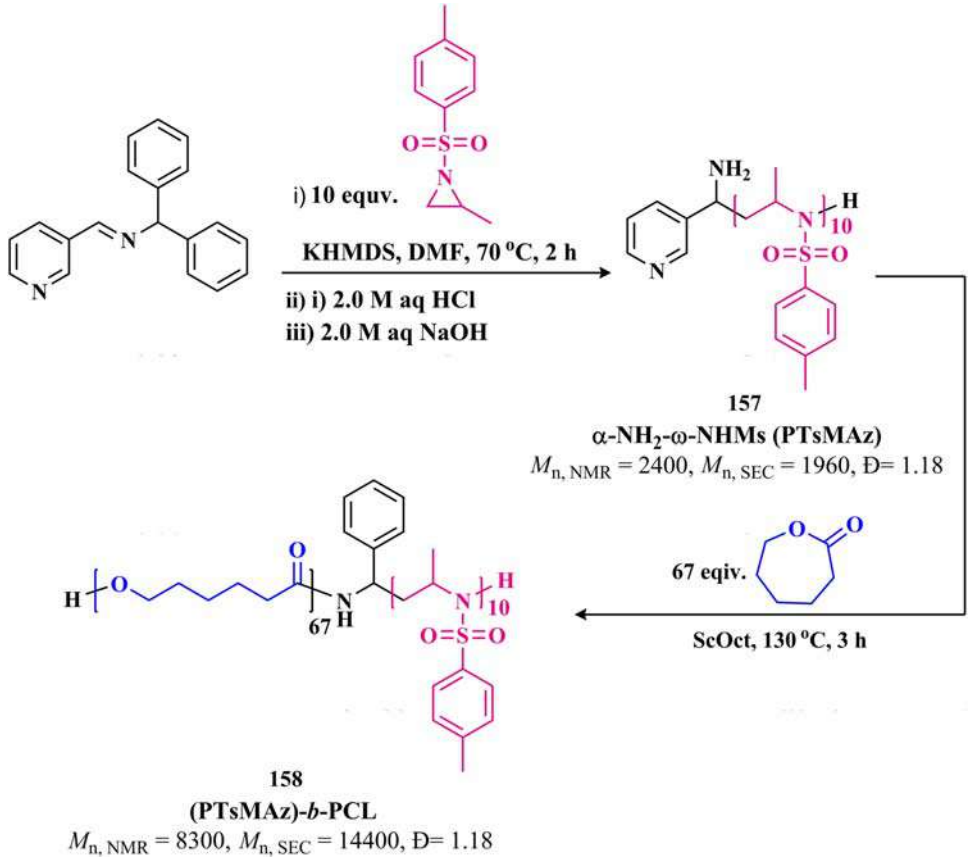
The double-headed initiator, 2-(methyl amino)ethanol, was selectively introduced in ^{Me}5-IPr-medicated ROP of TsMAz for the facile accessibility of telechelic α-hydroxy-ω-amino-poly(*N*-sulfonylaziridine) **161**, which



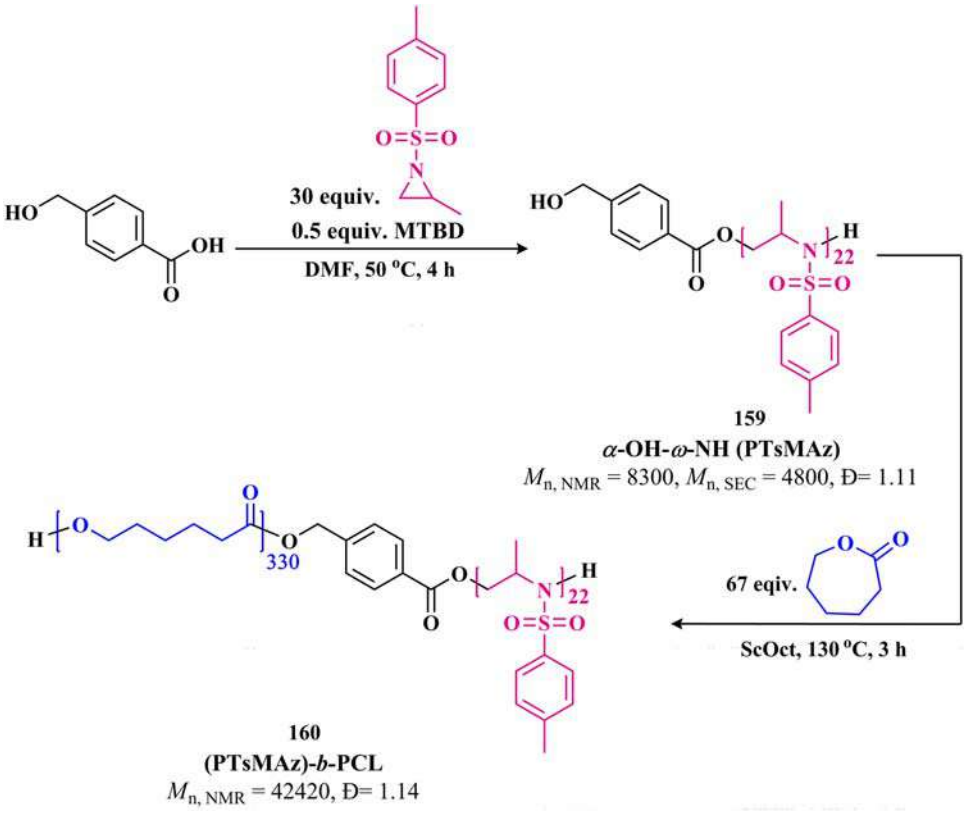
156

$P[(EO_{67}\text{-}b\text{-}TsMAz_5\text{-}b\text{-}EO_{95})]_2$ Mn = 4100 g mol^{-1} Đ = 1.15

SCHEME 2.48 Formation of penta-block copolymer **156** *via the anionic copolymerization of epoxide with aziridine derivatives.*



SCHEME 2.49 Synthesis of PAz-*b*-PCL block copolymer **158** through anionic ROP of ε-caprolactone with the telechelic polyaziridine 157.



SCHEME 2.50 Synthesis of well-controlled block copolymer **160**.

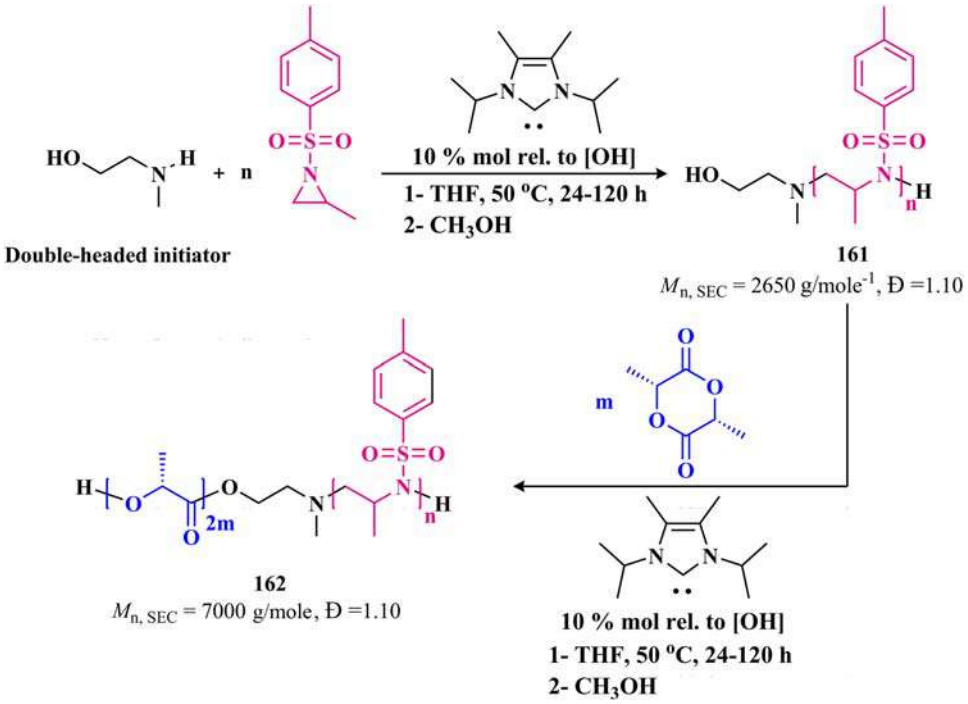
was used as macroinitiator for the preparation of poly(2-methyl-*N*-tosylaziridine)-*b*-poly(*L*-lactide) block copolymer **162** in the presence of *N*-heterocyclic carbene organocatalyst (^{Me}5-IPr) as illustrated in Scheme 2.51 [103].

2.3.4 Functionalized poly(sulfonylaziridine)s prepared via APOR polymerization of *N*-sulfonylaziridine

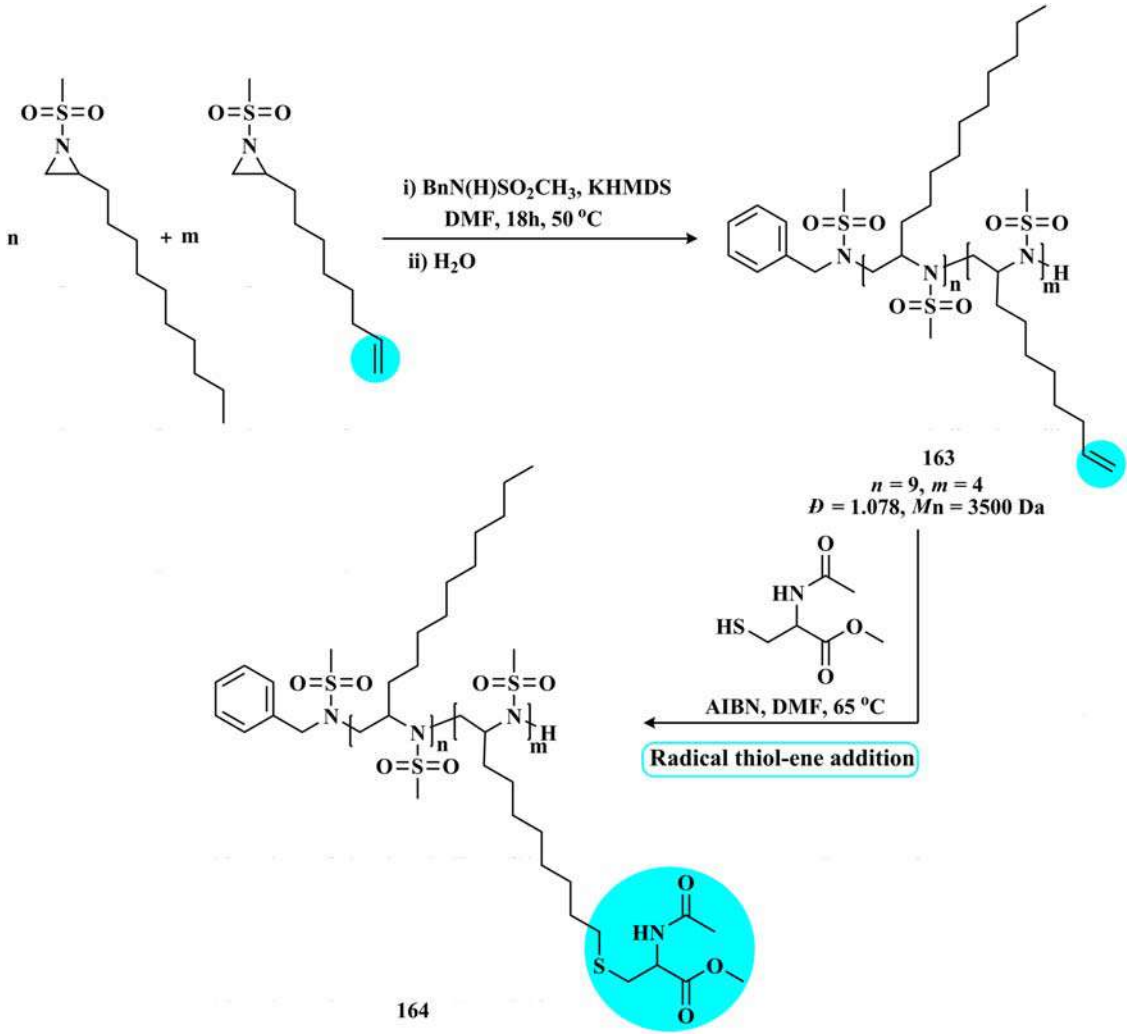
2.3.4.1 Polyaziridine-based linear in-chain functionalized polymers

The installation of functional groups as substituents in either the aziridine ring or the sulfonamide-activated group can be successfully achieved by providing access to interesting linear(*N*-sulfonylaziridine)s with in-chain functionality. In this section we demonstrated the easy accessibility of poly(*N*-sulfonylaziridine)s to being functionalized. The first attempt for functionalization of poly (sulfonylaziridine)s was conducted by Wurm and coworkers [104] who employed *N*-acetyl-*L*-cysteine methyl ester to react with pendant double bond of the copolymer **163** obtaining by the anionic copolymerization of 2-(oct-7-en-1-yl)-*N*-mesylaziridine and 2-*n*-decyl-*N*-mesylaziridine (Scheme 2.52). In this conjugation, a thiol-ene addition reaction was performed at 75°C in DMF in the presence of azobisisobutylnitrile (AIBN) as a radical source to furnish copolymer functionalized with a cysteine derivative **164**.

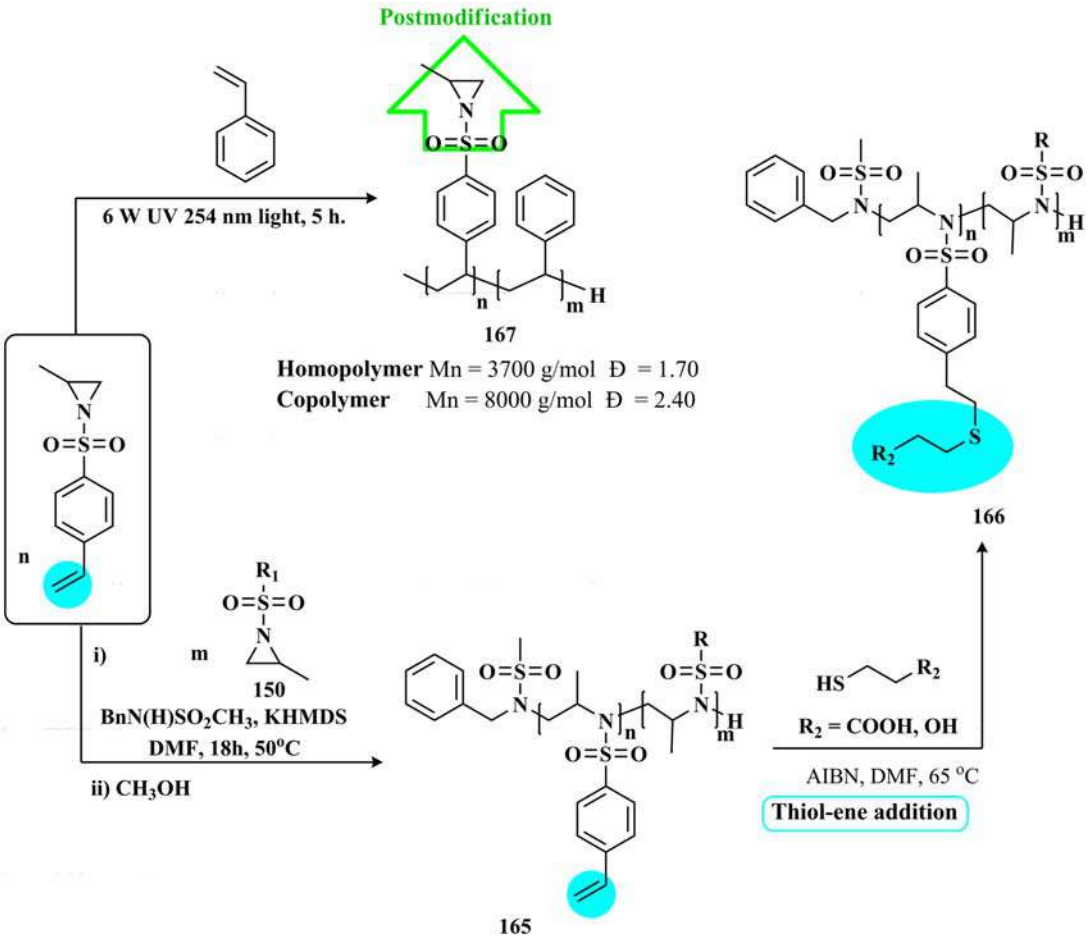
The use of a novel bivalent monomer, 4-styrenesulfonyl-(2-methyl)aziridine (StMAz), for both anionic and radical polymerization was reported by the same group (Scheme 2.53) [105]. After BnN(K)Ms-initiated anionic polymerization, the reactive vinyl groups of the resultant homo- and copolymers **165** could fully convertible *via* thiol-ene addition using mercaptopropionic acid or mercaptoethanol (Scheme 2.51). In radical polymerization, StMAz was subjected with the photoinitiator 2,2-dimethoxy-2-phenylacetophenone in benzene and exposed to UV irradiation for 5 h (Scheme 2.51). StMAz was also copolymerized radically with styrene under the same condition (Scheme 2.14). The pendent *N*-sulfonylaziridine moieties in the polymer side chains **167** could be efficiently post-modified *via* nucleophilic additions as described for other prepared polymers containing aziridinyl side groups [106–109].



SCHEME 2.51 Synthesis of poly(2-methyl-*N*-tosylaziridine)-*b*-poly(*L*-lactide) block copolymer **162**.



SCHEME 2.52 Synthesis of copolymer functionalized with a cysteine derivative **164** through the reaction of *N*-acetyl-*L*-cysteine methyl ester to react with pendant double bond of the copolymer **163**.



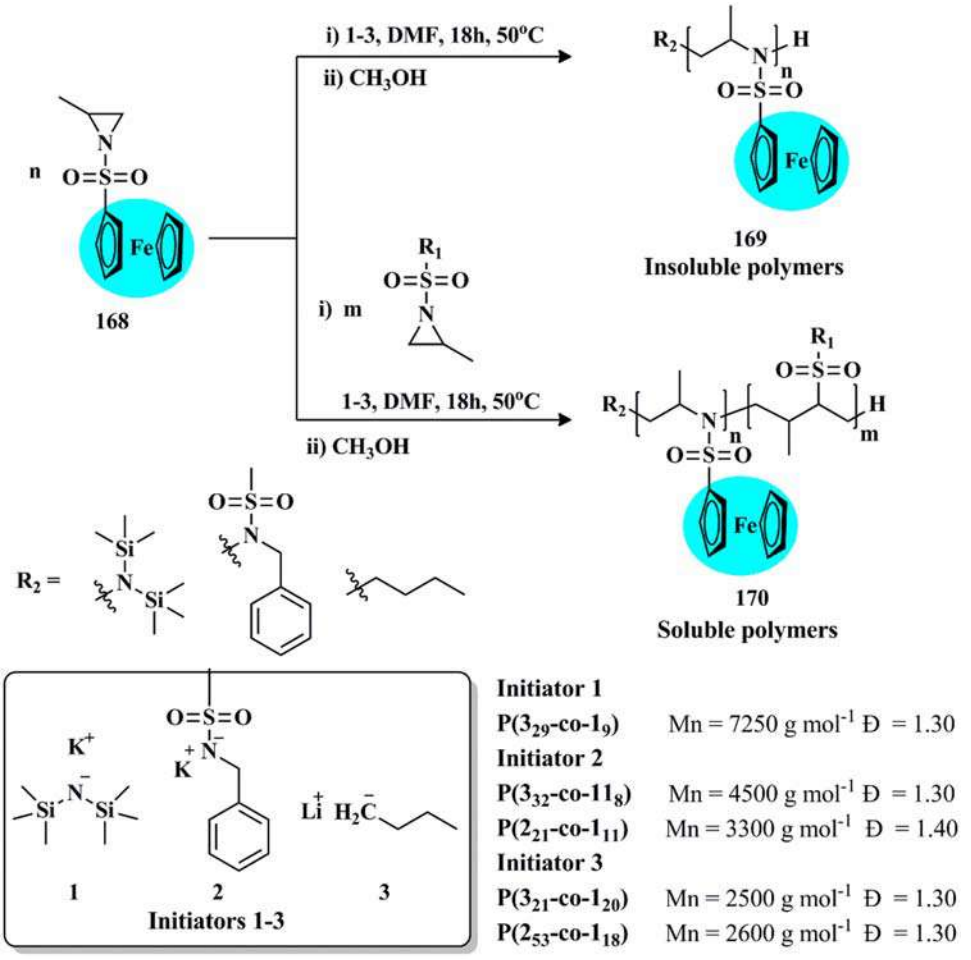
Homopolymer
$n = 30, m = 0$ $Mn = 4300$ g/mol $Đ = 1.27$
$n = 50, m = 0$ $Mn = 5000$ g/mol $Đ = 1.19$
Copolymer
$R_1 = C_6H_4$-4-CH_3
$n = 50, m = 5$ $Mn = 9000$ g/mol $Đ = 1.09$
$n = 50, m = 10$ $Mn = 10250$ g/mol $Đ = 1.11$
$R_1 = CH_3$
$n = 50, m = 5$ $Mn = 7050$ g/mol $Đ = 1.16$
$n = 50, m = 10$ $Mn = 7050$ g/mol $Đ = 1.22$

Fuctionalized homopolymer
$R_2 = OH, n = 30, m = 0$ $Mn = 7250$ g/mol $Đ = 1.14$
$R_2 = COOH, n = 50, m = 0$ Mn, $Đ$ = n.a.
Fuctionalized Copolymer
$R_1 = C_6H_4$-4-CH_3
$R_2 = OH, n = 50, m = 10$ $Mn = 13150$ g/mol $Đ = 1.13$
$R_2 = COOH, n = 50, m = 10$ $Mn = 5250$ g/mol $Đ = 1.50$
$R_1 = CH_3$
$R_2 = OH, n = 50, m = 10$ $Mn = 10800$ g/mol $Đ = 1.15$
$R_2 = COOH, n = 50, m = 10$ $Mn = 5000$ g/mol $Đ = 1.64$

SCHEME 2.53 Anionic and radical polymerization of 4-styrenesulfonyl-(2-methyl)aziridine (StMAz).

The novel *N*-ferrocenylsulfonyl-2-methylaziridine **168** was introduced as a monomer model for the synthesis of redox-responsive ferrocene-functionalized poly(*N*-sulfonylaziridine) *via* living anionic polymerization (Scheme 2.54) [110]. Such a monomer could be polymerized using diverse initiators (KHMDS **1**, KBnMs **2**, *n*-BuLi **3**). Notably, homopolymerization allowed for the synthesis of insoluble polymers **169**. However, the expected structure of homopolymer **169** was supported using both MALDI-TOF and solid-state NMR spectrums. Copolymerization with MsMAz or TsMAz led to the formation of soluble copolymers **170** with medium molecular weight dispersity ($Đ = 1.1-1.5$) as revealed in Scheme 2.53. This type of the resultant organometallic polymer has reversible oxidation/reduction properties *via* cyclic voltammetry in analogy to other polymers with ferrocene functionalities [111].

A fascinating alternative route was developed by the same group for in-chain functionalized poly(*N*-sulfonylaziridine) by protecting the reactive groups substituted with *N*-sulfonylaziridines prior to the polymerization, following by releasing the pendant reactive groups [112]. Similarly to the well-known ethoxy ethyl

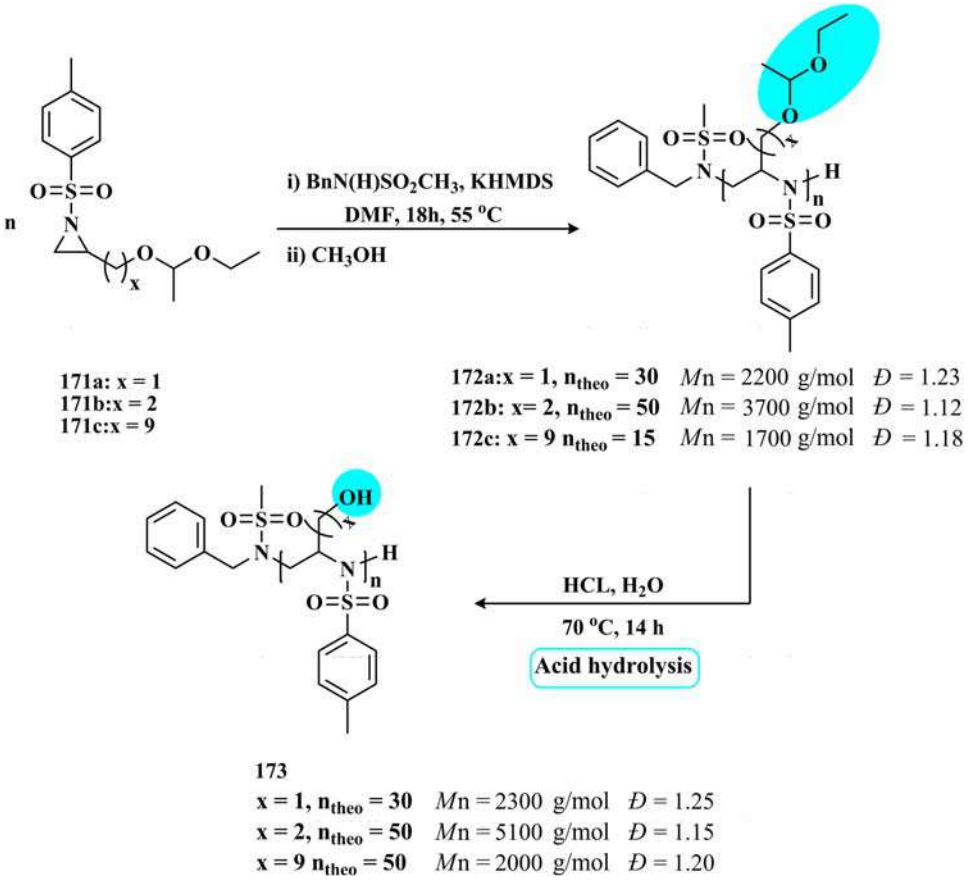


SCHEME 2.54 Synthesis of redox-responsive ferrocene-functionalized poly(*N*-sulfonylaziridine) *via* living anionic polymerization.

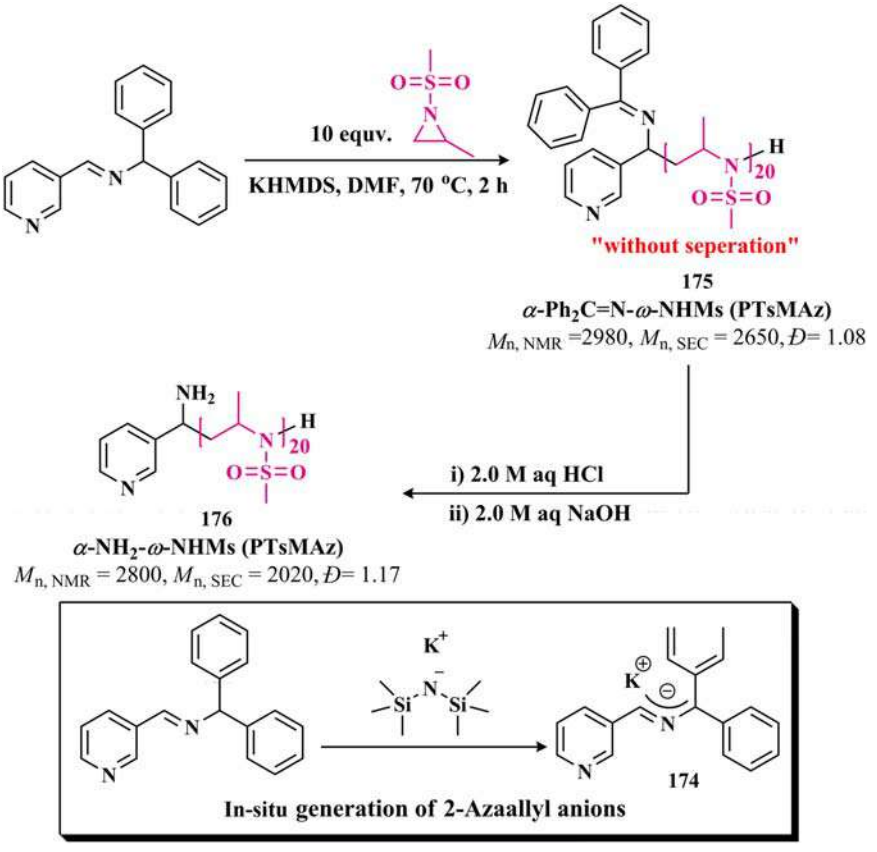
glycidyl ether (EEGE) monomer in oxyanionic polymerization for preparation of linear poly(glycerol), acetal-protected *N*-tosylated aziridine **171** was introduced to obtain polyhydroxyl-PEI-derivatives, **172** that represents the aza analog of linear poly(glycerol). Three acetal-protected *N*-tosylated monomers with methyl, ethyl and nonyl chain lengths **171** can be synthesized and polymerized *via* the living AROP (Scheme 2.55). The subsequent deportation was performed through a mild acidic hydrolysis to release hydroxyl groups in the side chain while leaving the sulfonyl groups along the backbone, affording multihydroxy polyamine derivative **173** (Scheme 2.54).

2.3.4.2 Polyaziridine-based linear chain-end functionalized polymers: Telechelic polyaziridines

Telechelic polymers tolerating more reactive end-groups are vital precursors for diverse macromolecular architectures [113]. The synthetic strategies are usually available for such telechelics based on introducing the reactive end-groups *via* either utilizing functional or switchable initiators or termination of the living chains of the polymer with a functional electrophile [114–118]. Particularly, in the common strategy for the synthesis of telechelic poly(*N*-sulfonylaziridine)s, aza-anionic polymerization of *N*-sulfonylaziridines was tolerant to a wide range of functional initiators, resulting in straightforward access to poly(*N*-sulfonylaziridine)s with chain-end functionality. A new conceptual methodology for the successful synthesis of amine-ended telechelic poly(*N*-sulfonylaziridine) was reported by Hadjichristidis and coworkers [101]. In this methodology, 2-azaallyl anions **174**, which are *in-situ* generated *via* deprotonating diphenylketimines with potassium bis(trimethylsilyl)amide, firstly initiated the anionic polymerization of MsMAz to generate α-diphenylketimine-α-aryl-ω-NH polyaziridine **175** and the latter was then post-modified to afford α-NH_2-α'-aryl-ω-NH polyaziridine **176** *via* hydrolysis of the imine moiety (Scheme 2.56).



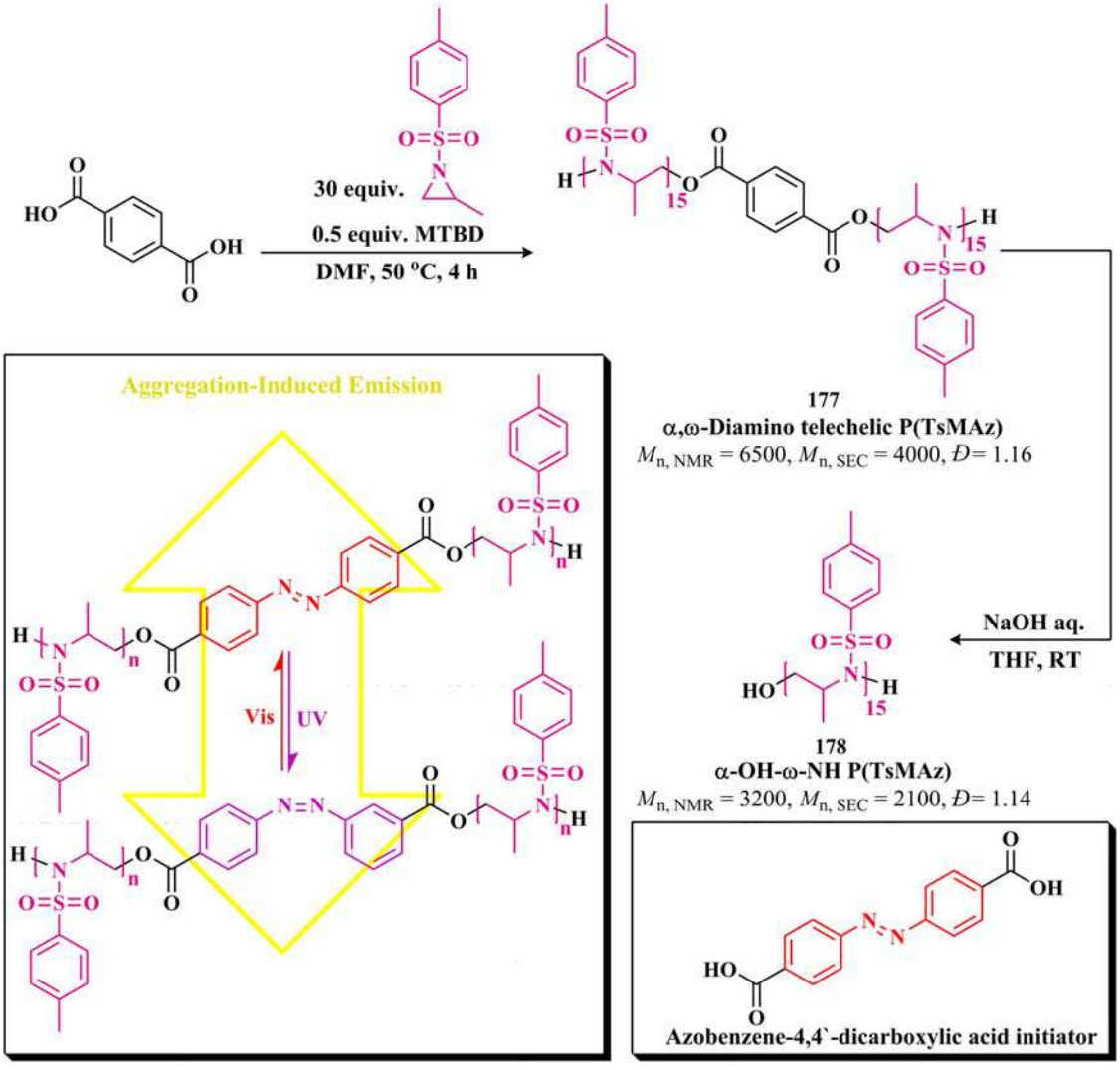
SCHEME 2.55 Synthesis of multihydroxy polyamine derivative **173** starting from acetal-protected *N*-tosylated aziridine **171**.



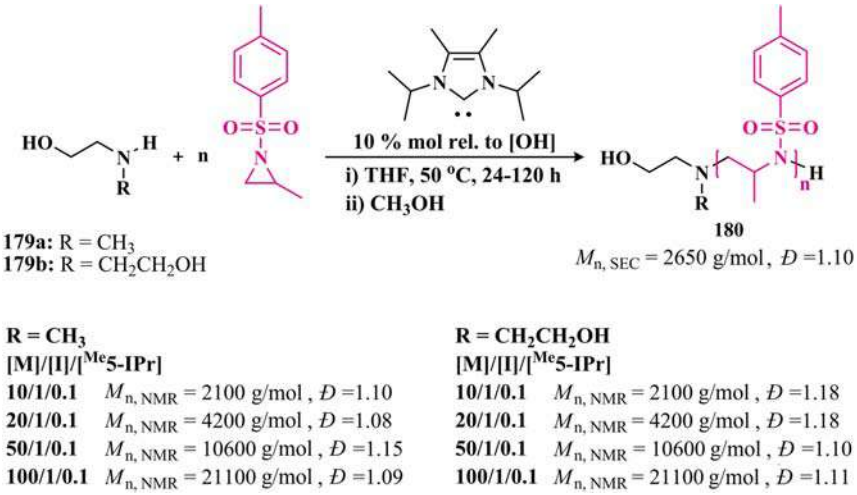
SCHEME 2.56 Anionic polymerization of MsMAz to form α-diphenylketimine-α-aryl-ω-NH polyaziridine **175** followed by hydrolysis forming of α-NH_2-α'-aryl-ω-NH polyaziridine **176**.

A well-organized metal-free system allowing for fast access to interesting telechelic poly(*N*-sulfonylaziridine) was developed by the same group [102]. Authors expanded the diversity of initiating system of the anionic polymerization of *N*-sulfonylaziridines into carboxylic acid-based compounds in the presence of the organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD). Terephthalic acid having two carboxylic groups was selectively used as an initiator for the preparation of linear α,ω-diamino telechelic polymer **177** ($M_{n,\ NMR} = 6500$, $M_{n,\ SEC} = 4000$, $Đ = 1.16$) as shown in Scheme 2.57. The benzoate ester group of the resultant polymer could facilely hydrolyze in aqueous solution of sodium hydroxide to divide into two segments of α-OH-ω-NH polyaziridines **178** with lower molecular weights (Scheme 2.56). The type of carboxylic acid initiator played a pivotal role in the shape and properties of the resultant polymer. The use of well-known azobenzene-4,4′-dicarboxylic acid in initiating the anionic polymerization of TsMAz provided photoresponsive azobenzene-containing polyaziridines. The weaker absorption intensity at 331 in the UV − vis absorption spectrum indicated that azobenzene chromophores were reversibly *trans*-to-*cis* isomerized after exposing to UV irradiation at 365 nm, similar to the other prepared polymers containing azobenzene [119,120].

The use of a series of double- or triple-headed amino alcohol initiators **179a,b** instead of carboxylic acids, allowed for initiating the anionic polymerization of



SCHEME 2.57 Synthesis of linear α,ω-diamino telechelic polymer **177** using terephthalic acid as an initiator for the anionic polymerization of *N*-sulfonylaziridines.



SCHEME 2.58 Anionic polymerization of TsMAz under the catalysis of *N*-heterocyclic carbene organocatalyst using double- or triple-headed amino alcohol initiators.

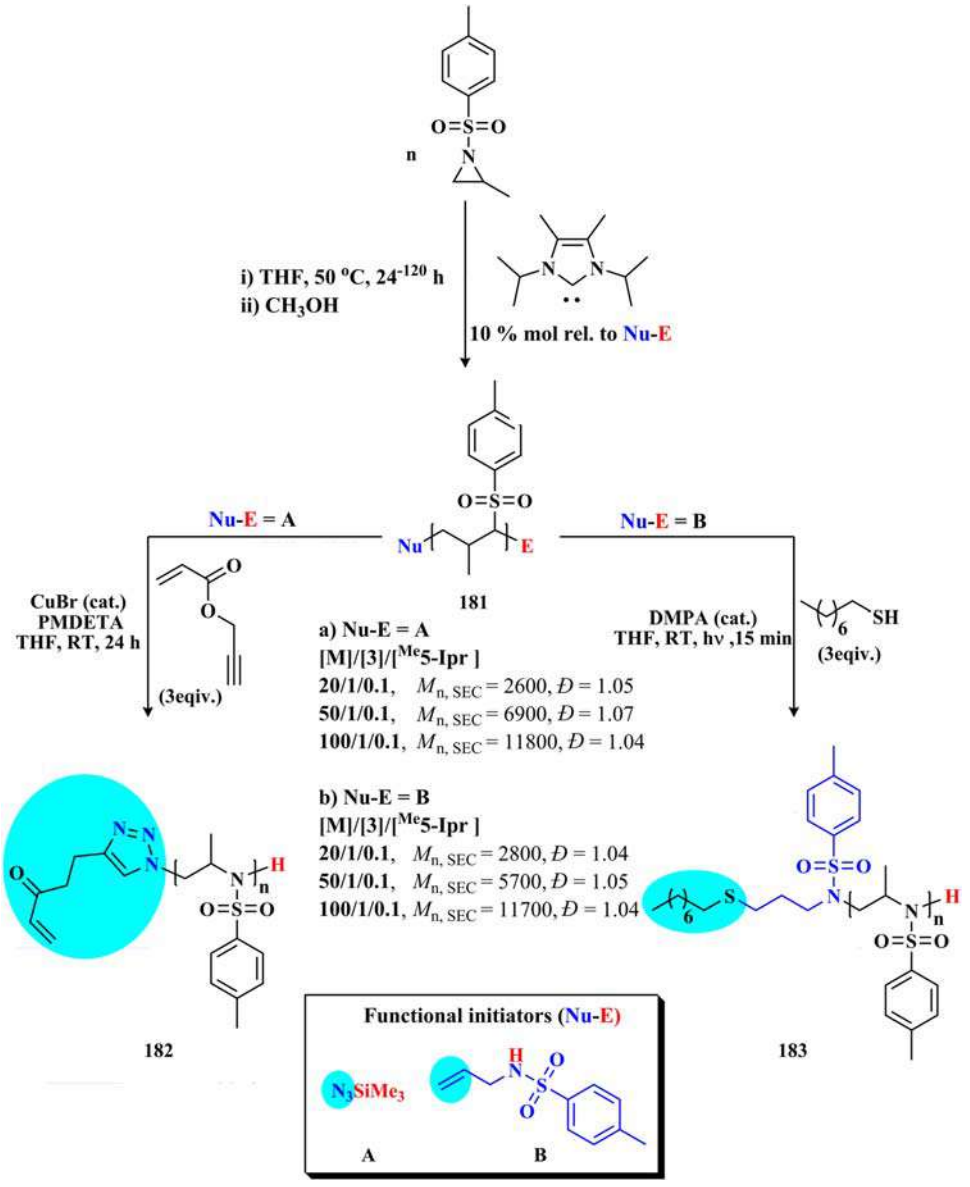
TsMAz under the catalysis of *N*-heterocyclic carbene organocatalyst, enabling the accessibility of either telechelic α-hydroxy-ω-amino- or α,α'-bis-hydroxy-ω-amino poly(*N*-sulfonylaziridine)s **180** with narrow molecular weight distributions ($Đ < 1.20$) (Scheme 2.58) [103].

The use of a commercially available trimethylsilyl azide **A** and allyl-functionalized *N*-tosyl secondary amine **B** allowed for providing access to poly(*N*-tosylaziridine)s containing α-N_3 and α-allyl functionalities **181**, respectively under the same catalysis [97]. The post-modification of the prepared α-N_3 poly(*N*-tosylaziridine) **181a** afforded acrylate-containing poly(*N*-tosylaziridine)s **182** through Cu-catalyzed Huisgen cycloaddition reaction with propargyl acrylate in the presence of PMDETA (Scheme 2.60). The synthesized α-allyl-functionalized poly(*N*-tosylaziridine)s **181b** was facilely undergone to DMPA-catalyzed thiol-ene reaction with octanethiol upon exposing to UV irradiation for 15 min, affording functionalized poly(*N*-tosylaziridine)s **183** (Scheme 2.59).

2.3.4.3 Recent synthetic developments of polyaziridine-based macromolecular architectural polymers

Carboxylic acid-based initiators represented tremendous candidates for the construction of diverse macromolecular architectures. Core cross-linked stars with 3-and 4-arms **184** and **185** were successfully synthesized using benzene-1,3,5-tricarboxylic acid and 1,1,2,2-tetra(4-carboxylphenyl) ethylene initiators, respectively (Scheme 2.61) [102]. Interestingly, the prepared 4-arm polyaziridine **185** exhibited aggregation-induced emission properties due to the presence of a luminogen core in its structure. The fluorescent spectrum in water/THF mixtures showed that the emission intensity reached the maximum of 90% water fraction. Additionally, the emission intensity increased 10-fold in comparison with the THF solution. When water was added to the THF solution, the molecular aggregation was induced and consequently, this enhanced the photoluminescenceintensity (Scheme 2.60).

Recently, the precise synthesis of core cross-linked stars (CCS) with multi-arms was recently achieved [101]. The α-diphenylketimine-α'-aryl-ω-NH poly(*N*-tosylazidirnes) **186** synthesizing by the anionic polymerization of TsMAz was employed as macroinitiator to initiate the 2-azaallyl anion-initiated polymerization of the double-headed tosyl diaziridyl ether of bisphenol A (TsDzEBA), forming CCS with outermost shell functionalities of benzophenone imine and triphenylphosphine **187** (Scheme 2.61). In order to overcome the issue of gelation due to the fast polymerization process, the organocatalyst phosphazene base *t*-Bu-P_4 as was utilized. Notably, Crossliker monomer TsDzEBA exhibited a vital role for inducing the star formation. Interestingly, the benzophenone imine moiety in the outer shell of the star could be converted into primary amine through hydrolysis, giving access to CCS **188** with high molecular weight ($M_{n,\,SEC} = 28040$) as well as mono-modal polydispersity (PDI = 1.23).

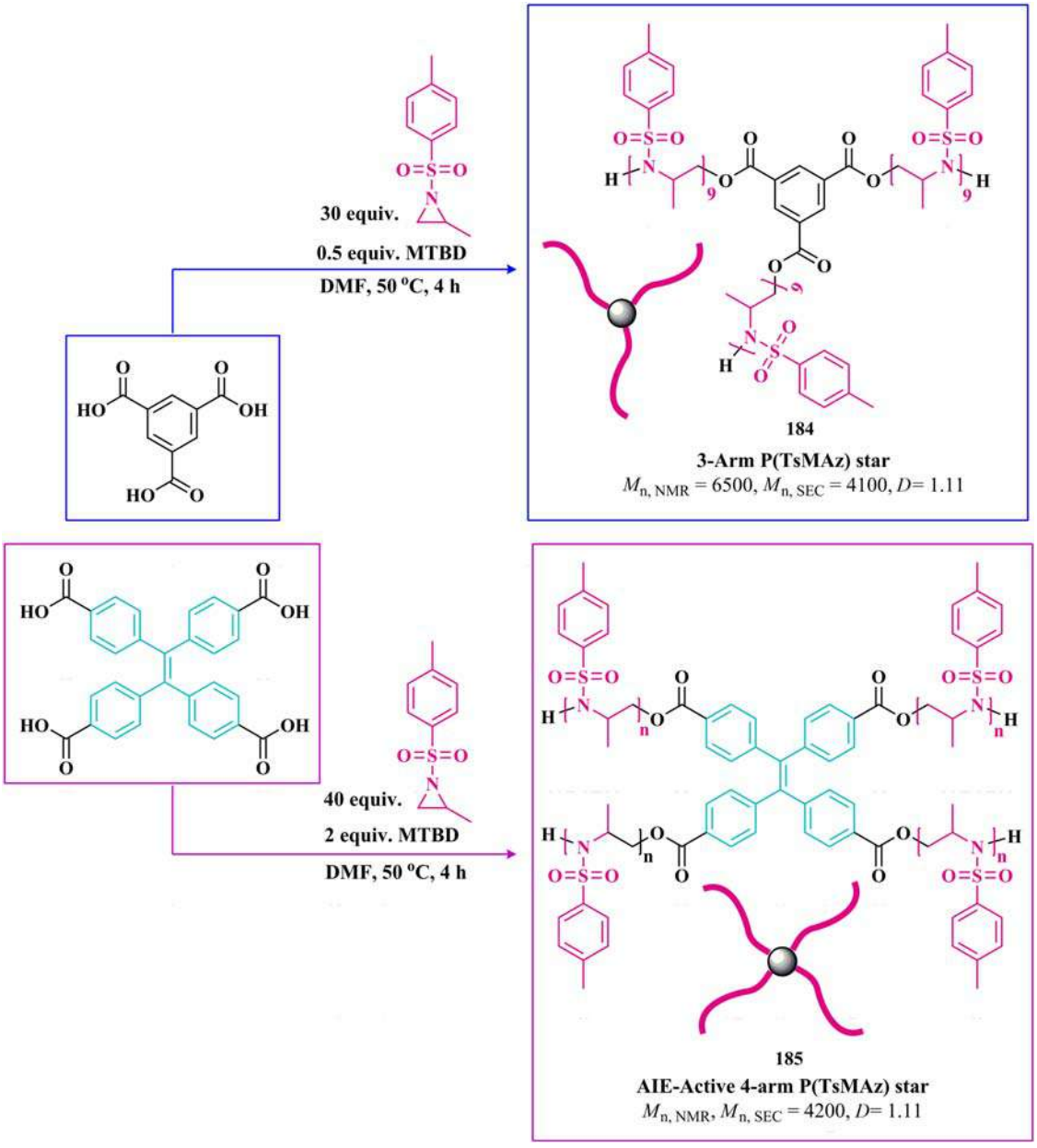


SCHEME 2.59 Synthesis of poly(*N*-tosylaziridine)s starting from trimethylsilyl azide **A** and allyl-functionalized *N*-tosyl secondary amine **B**.

In addition to star-shaped polymers, a well-organized stepwise methodology was introduced later for the successful preparation of graft copolymer architecture with poly (*N*-tosylaziridine) graft units [102]. For synthesis of narrow-dispersed macromolecule graft polymer **191**, a radom copolymer p(styrene-*co*-methacrylic acid) **190** was firstly prepared *via* nitroxide-medicated radical copolymerization of styrene with *tert*-butyl methacrylate, followed by hydrolysis and after that the prepared copolymer **191** successively initiated MTBD-organocatalyzed anionic polymerization of TsMAz (Scheme 2.62).

2.3.5 Desulfonation: easy access of linear polyamides from polyaziridine prepared via the anionic polymerization of *N*-sulfonylaziridine

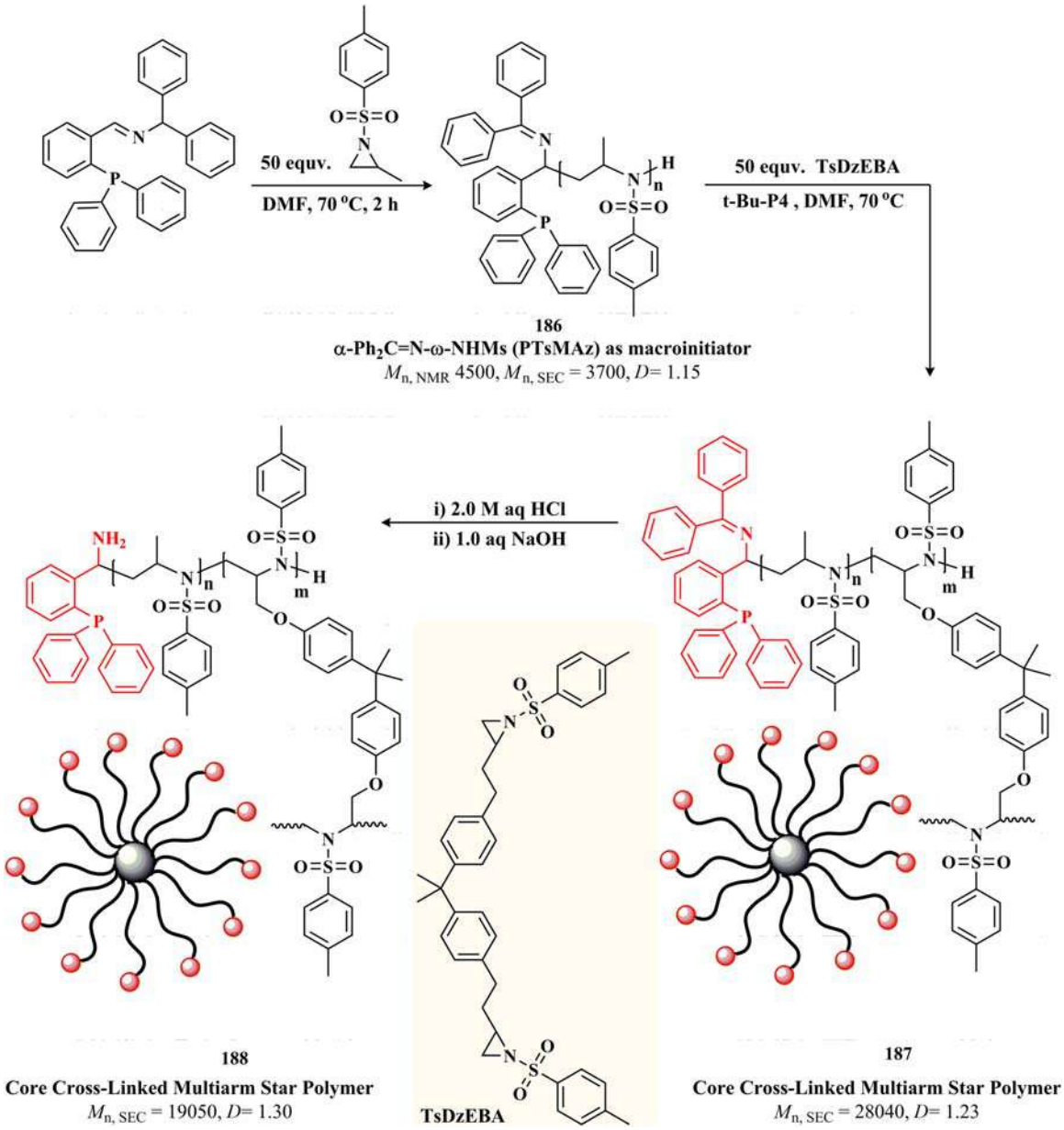
Several strategies for removal of sulfonyl moiety in compounds with low molecular weights were reported. The cleavage of the sulfonyl moiety on poly(*N*-sulfonylaziridine)s can be challenging, only four applications were reported. The desulfonylation in the presence of lithium naphthalenide (LiNp) was reported by the group of Bergman and Toste [86]. However, the



SCHEME 2.60 Synthesis of core cross-linked stars with 3-and 4-arms **184** and **185** using benzene-1,3,5-tricarboxylic acid and 1,1,2,2-tetra(4-carboxylphenyl)ethylene initiators.

obtained polymer did not show any data in regard to its spectral data and polydispersity. In the alternative methodology, the successful cleavage of tosyl groups connecting with the poly(styrene-*b*-tosylaziridine) **192** was described by Wurm and coworkers [104] *via* acidic hydrolysis. Such cleavage was performed using hydrobromic acid and phenol in boiling THF, providing the corresponding amino-deprotected block polymer **193** (Scheme 2.63).

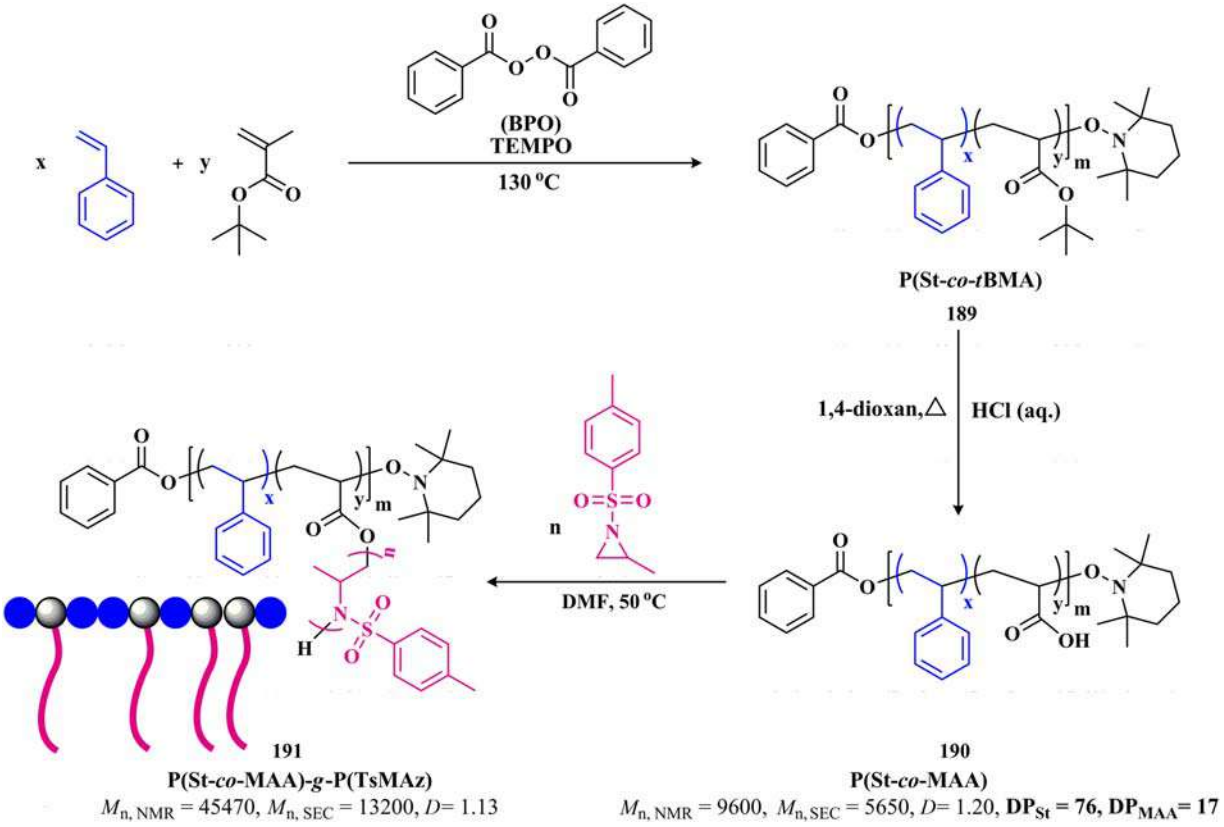
Recently, sulfonation could be achieved under reductive conditions. As an example, Ruper and coworkers [87] prepared *L*-PEI **194** *via* desulfonation of P(MsAz-r^{S}BsAz) random copolymer **142** in the presence of elemental lithium with *tert*-butanol in THF and hexamethylphosphoramide (HMPA) as illustrated in Scheme 2.64. The P(MsAz-r^{S}BsAz)-*b*-P(MsMAz) block copolymer **143** was transformed to poly(ethylenimine)-*block*-poly(propylenimine) **195** using a similar condition (Scheme 2.64). However, the required extremely low temperatures (−20°C to −5°C), as well as the toxicity of HMPA, could be drawbacks to such desulfonation's reaction, and consequently this methodology is not suitable for larger scale.



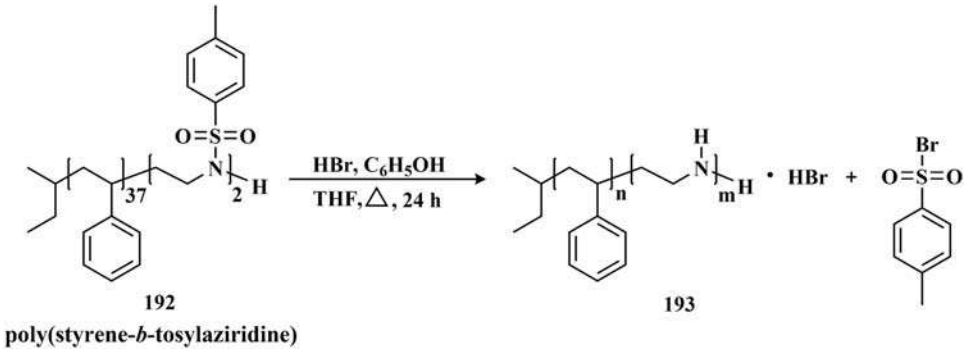
SCHEME 2.61 Synthesis of core cross-linked stars with multi-arms starting from the anionic polymerization of TsMAz.

In another example, the Wurm group was able to remove ca. 76% of the pendant sulfonyl groups along the backbone of the acetal-protected poly(*N*-sulfonylaziridine) **20c** could be removed using sodium bis(2-methoxyethoxy)aluminiumhydride (Red-Al) as a reductive agent (Scheme 2.65) [112]. Interestingly, the hydroxyl groups were also released upon treating the prepared acetal-protected polypropylenimine polymer **196** with concentrated HCl to afford multihydroxy polyethylenimine derivative **197** (Scheme 2.66).

Under the same desulfonation condition, the use of alternative polyaziridines **198** resulted in reductive removal of 80% of the tosylated groups (Scheme 2.66). A developed strategy was proposed for desulfonation of polyaziridines **198** based on hydrolytic cleavage of the sulfonyl moiety in the presence of *p*-toluenesulfonic acid (*p*-TsOH.H_2O) under microwave irradiation (300 W) [121]. The tosyl groups of P(TsMAz) **195b** were fully removed (100% conversion) to form linear polypropylenimine (L-PPI) **199** while 90% of mesyl groups connected with P(MsMAz) **195a were** cleaved, remaining intact mesyl-protected amine in the polymer chain.

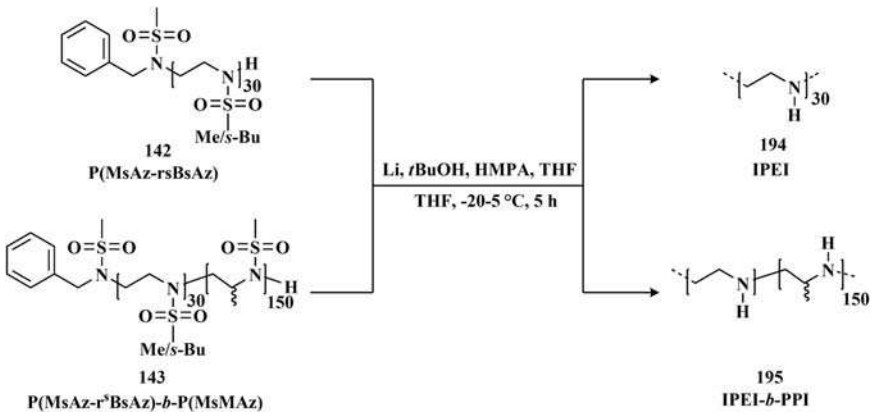


SCHEME 2.62 Synthesis of narrow-dispersed macromolecule graft polymer **191**.

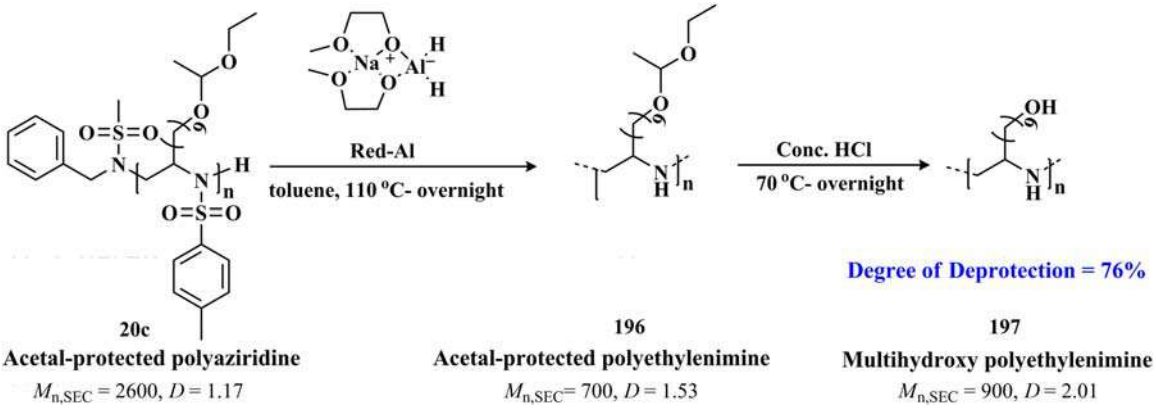


SCHEME 2.63 Desulfonation on poly(*N*-sulfonylaziridine)s by hydrobromic acid and phenol.

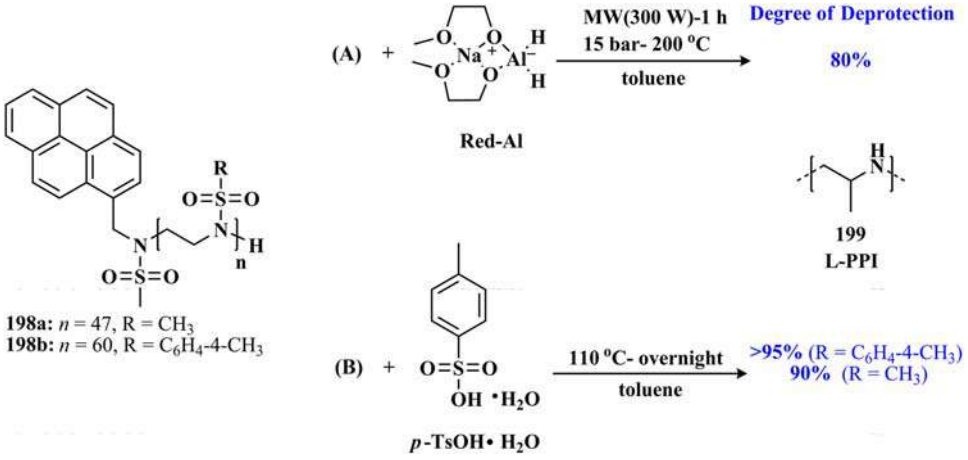
A free-harsh and fast approach for desulfonation of poly(*N*-sulfonylaziridine)s was developed [122]. The use of dodecanethiol in the presence of diazabicyclo-undecene (DBU) base and allowed for preventing scission of main-chain polymer as well as the removal of ≥98% of 4-cyanophenylsulfonyl groups, affording polyethylenimine **201** with high purity (Scheme 2.67). The desulfonation successfully proceeded *via* a nucleophilic attack from thiolate to the 4-cyanophenylsulfonyl group with electron-deficient characteristics to generate Meisenheimer complex **A**. Once such complex was formed, cyanobenzenesulfonyl groups could be directly cleaved to provide polyethylenimine **201** with thioether and sulfur dioxide as byproducts. Interestingly, the prepared *L*-PPI **201** was used in a gene transfection application. The cationic *L*-PPI nanoparticle can load the gene EGFP and efficiently transfer it to 293T cells. The maximum transfection efficiency was 16.1%. Hence, these promising results demonstrated that such *L*-PPI could be an alternative gene transfection reagent to well-known *L*-PEI that is prepared from the classical 2-oxazoline pathway [82,83,123].



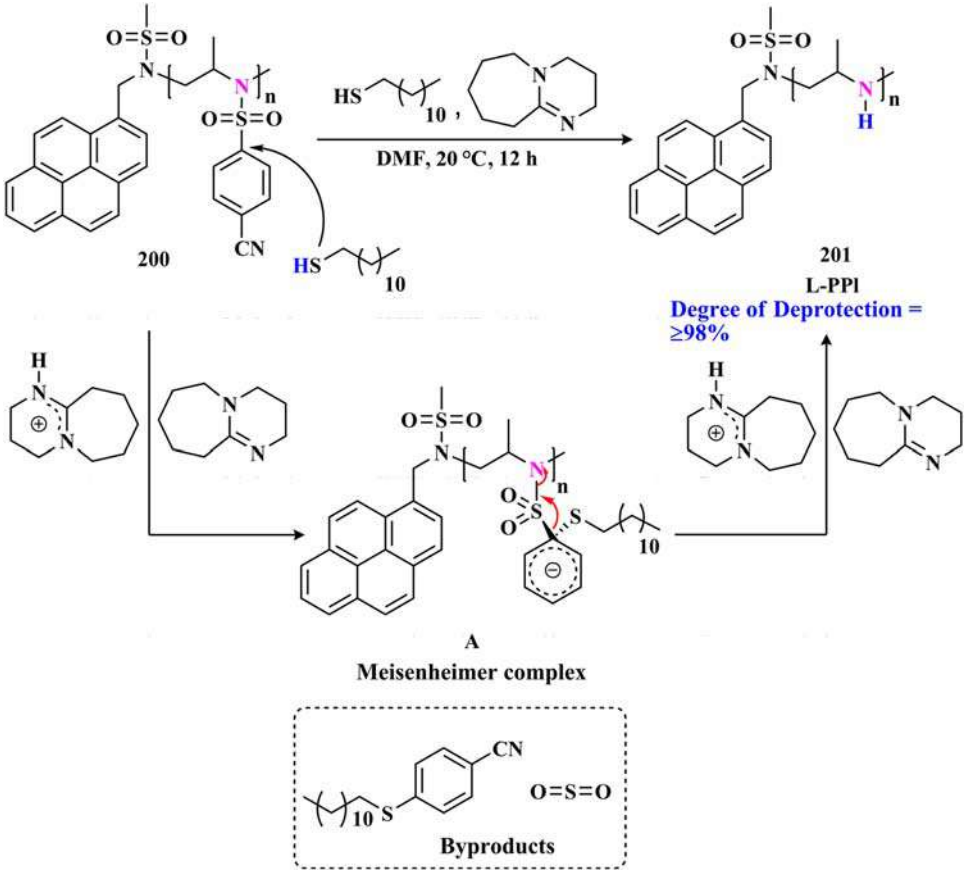
SCHEME 2.64 Desulfonation of P(MsAz-r^{s}BsAz) random copolymer **142** and P(MsAz-r^{s}BsAz)-*b*-P(MsMAz) block copolymer **143**.



SCHEME 2.65 Removal of sulfonyl group along the backbone of poly(*N*-sulfonylaziridine) **20c** using Red-Al.



SCHEME 2.66 Removal of tosyl group along the backbone of polyaziridines **198** using Red-Al.



SCHEME 2.67 Removal of 4-cyanophenylsulfonyl group from poly(*N*-sulfonylaziridine)s **200** using dodecanethiol and DBU.

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Chapter 3

Synthesis of *N*-sulfonated azetidines and β-lactemes and their applications

3.1 Introduction

Four-membered aza-heterocycles, sulfonyl-activated azetidines, and azetidin-2-ones were received little interest in comparison to the higher-membered aza-heterocycles but since the 90 s a considerable reversal occurred as a result of the isolation of diverse natural products bearing such motif as well as their pharmacological potencies [1–4]. The limitation of synthetic methods for the preparation of this type of ring system as well as the strained nature of the ring system represented a handicap to synthesizing the four-membered ring. Nevertheless, great efforts were done for developing novel synthetic routes toward bioactive compounds containing this particular type of ring system [5–10].

This chapter aims to cover the literature on *N*-sulfonyl azetidines and azetidin-2-ones and an overview of the synthetic methods available for the preparation of the particular aza-heterocycle. The azetidinyl ring bearing sulfonyl groups revealed sufficient reactivity toward a wide range of different transformations due to the ring strain associated with their four-membered ring and the electron-withdrawing nature of the nitrogen atom of the ring especially upon bearing an electron-withdrawing group like sulfonyl group. Therefore, a discussion on the reactivity of such type of functionalized four-membered ring in this chapter was also described. Furthermore, this chapter covers all successful efforts in the application of sulfonyl-activated azetidines in living aza-anionic polymerization. An indirect route was developed toward linear well-defined polyimine derivatives based on the desulfonylation of the prepared poly(*N*-sulfonyl azetidines)s instead of the most prominent traditional methodology being the oxazoline polymerization [11]. Moreover, the β-lactam-containing polymer was successfully prepared with a facile synthetic approach.

3.2 Synthesis of sulfonyl-activated azetidines and azetidin-2-ones

Diverse strategies are available for the construction of the stained four-membered aza-cyclic ring including cycloaddition reactions, intramolecular cyclization of amino alcohols or amine derivatives, ring contraction of 2-pyrrol-one, and crossed-benzoin/oxy-Cope rearrangement. In this part, each strategy and its mechanistic insights will be discussed in detail.

3.2.1 Ring expansion of sulfonyl-activated azidirine

Ring expansion of *N*-sulfonyl azidirine represents certainly one of the most powerful approaches for the preparation of the four-membered aza-heterocycles. In this section, we demonstrated the significant role of sulfonyl-activated aziridines in producing sulfonyl-activated four-membered aza-cyclic ring systems such as azetidine and azetidin-2-ones.

3.2.1.1 To sulfonyl-activated azetidine

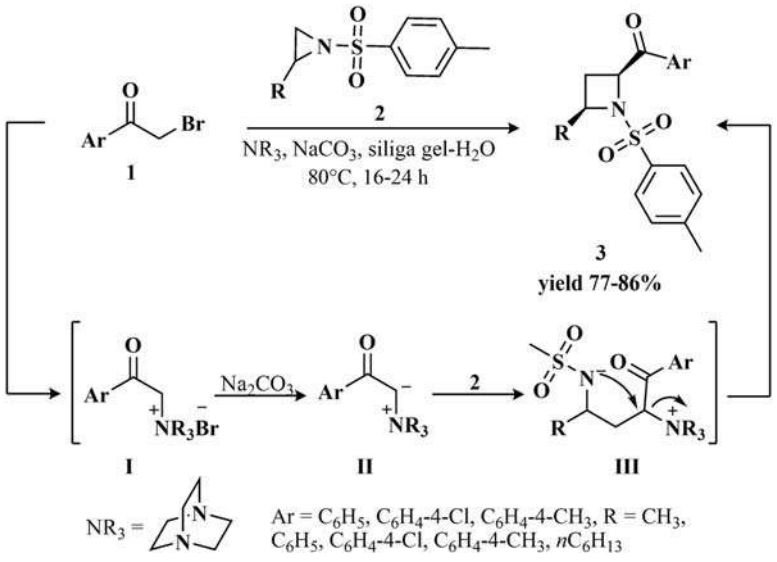
Important advances emerged in the transformation of sulfonyl-activated azidirines to sulfonyl-activated azetidines. In 2010, Garima et al. [12] disclosed a green synthesis of 2-aroyl-*N*-tosylazetidines **3** via tertiary amine-catalyzed ring-expansion of *N*-tosylaziridines **2** with 2-bromo-1-phenylethanone **1** in a silica gel-water system. In this reaction, a phenacyl bromide **1** underwent SN_2 displacement with the tertiary amine to generate a quaternary ammonium salt **I** which deprotonated in presence of $NaCO_3$ to afford nitrogen ylide **II**. A nucleophilic attack on the aziridine **2** by nitrogen ylide formed **III** and then the latter easily 4-*exo*-tetcyclized to furnish the desired *cis*-azetidine **3** (Scheme 3.1).

Lately, Kenis et al. [13] reported a regio- and stereospecific unprecedented synthesis of *cis*-2-CF_3-azetidines **5** from *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl) aziridine **4** through a sequence of a base-catalyzed ring-opening of *N*-sulfonyl aziridines **4** with aromatic oxygen nucleophile and intramolecular cyclization of the intermediate **I** (Scheme 3.2).

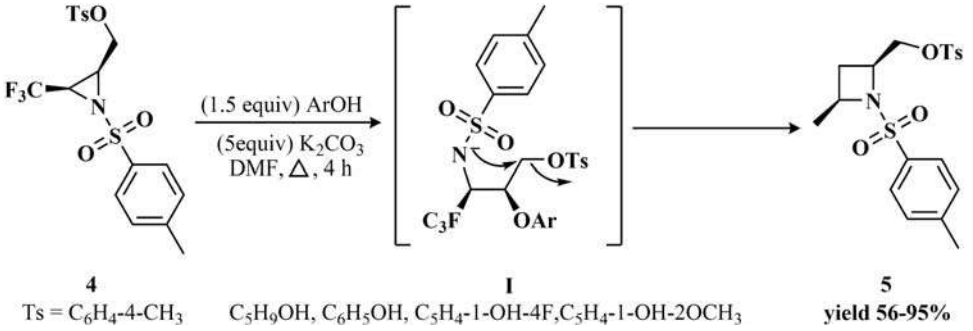
3.2.1.2 To sulfonyl-activated azetidin-2-ones (sulfonyl-activated β-lactam)

The β-lactam ring is considered the central motif of the main drugs utilized for the treatment of several bacterial infections such as ampicillin and amoxicillin [14]. The development of efficient and direct methodologies for the

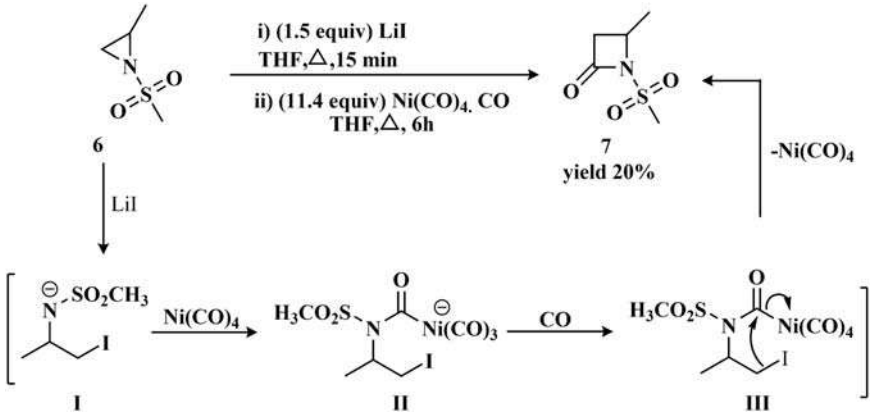
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00010-0



SCHEME 3.1 Synthesis of *cis*-azetidines **3**.



SCHEME 3.2 Synthesis of *cis*-2-CF3-azetidines **5**.



SCHEME 3.3 Synthesis of *N*-sulfonyl--lactams **7**.

synthesis of β-lactams is highly desirable [15–33]. In particular, several synthetic routes towards *N*-sulfonyl β-lactams from *N*-sulfonyl aziridines are extensively discussed. Chamchaang et al. [34] reported a complementary strategy to synthesize *N*-sulfonyl-β-Lactam **7** (Scheme 3.3). This strategy included a Ni-mediated carbonylation reaction which inserted the CO into the less substituted C–N bond of the aziridine ring **6**. Mechanistically, an initial SN_2-type ring-opening of the aziridine **6** with iodide nucleophile formed halide **I**. After that, nitrogen anion on **I** attacked one of the carbonyls of $Ni(CO)_4$ providing a carbonyl insertion between nitrogen and nickel followed by nickel reductive

elimination of the metal afforded the desired *N*-sulfonyl-β-lactams **7** (Scheme 3.3).

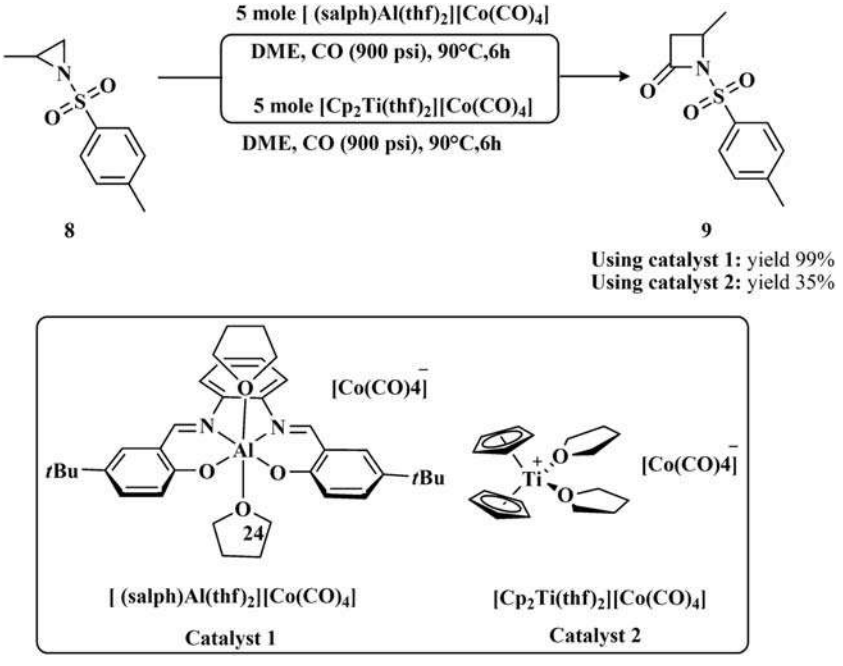
Mahadevan et al. [35] demonstrated the efficacy of two discrete sophisticated Co-carbonyl complexes to catalyze the carboxylation reaction of *N*-tosyl-2-methylaziridine **8** under mild conditions. Interestingly, it was observed that [(salph)Al(thf)$_2$][Co(CO)$_4$] catalyst was found to be extremely more effective than [Cp$_2$Ti(thf)$_2$][Co(CO)$_4$] catalyst. Initially, an SN$_2$-type ring-opening of the aziridine ring with [Co(CO)$_4$]$^-$ ion and sequent insertion of CO and intramolecular ring closure furnished *N*-sulfonyl β-lactam **9** in excellent yield (Scheme 3.4).

Tanner et al. [36] disclosed the first stereoselective synthetic route to *trans*3-vinyl β-lactam **11** via Pd(0)-mediated carbonylation reaction of optically pure *trans*-vinylaziridine **10** with the pressurized carbon monoxide. Hydrogenation of **11** was also reported to give the corresponding hydrogenated compound **12** in good yield (Scheme 3.5).

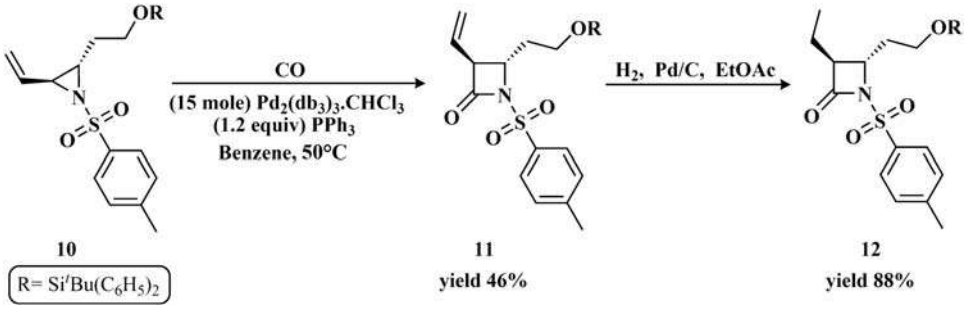
After that, Fontana et al. [37] utilized the same catalyst to promote the carbonylation reaction of *cis*- and *trans*-vinyl aziridines **13**. Notably, the β-allyl Pd intermediate **Ia** underwent a high degree of isomerization but when the reaction parameters were carefully controlled (temperature, [Pd], [CO]), *trans*-vinyl β-lactams **14** was formed with highly regioselectivity. It was found that both *cis*- and *trans*-vinyl aziridines **13** produced the same *trans*-β-lactams **14** due to π−σ−π isomerization before the formation of the *trans*-β-lactam derivatives (Scheme 3.6).

3.2.2 Synthesis of *N*-sulfonylazetidines via cycloaddition reactions

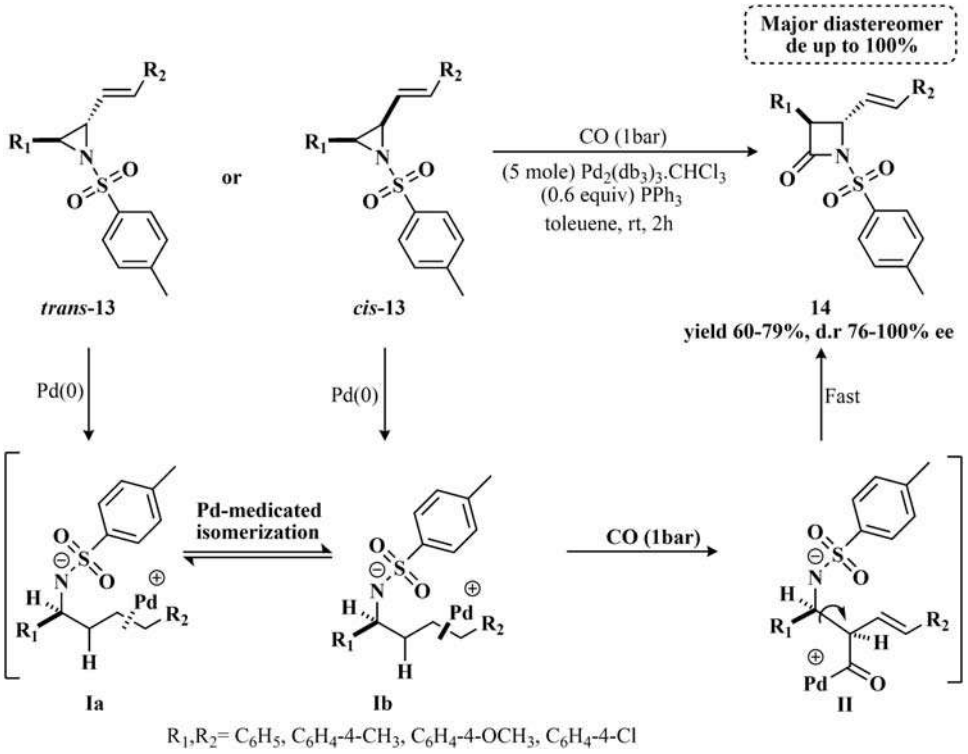
An interesting strategy featuring organocatalytic intermolecular [2 + 2] cycloaddition reaction of diverse *N*-tosylimines with allenoates catalyzed by novel bifunctional quinidine



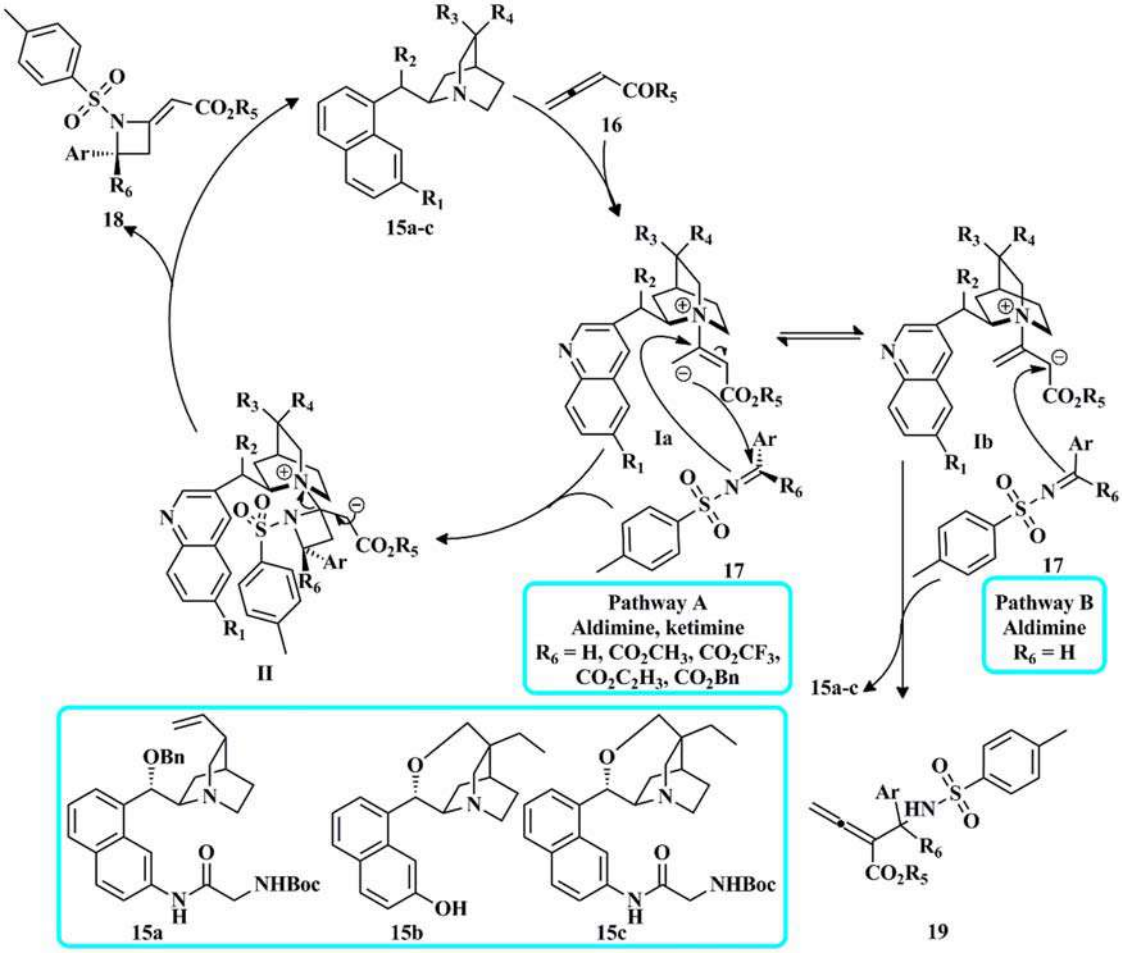
SCHEME 3.4 Synthesis of *N*-sulfonyl β-lactam **9**.



SCHEME 3.5 Synthesis of *trans* 3-vinyl β-lactam **11** and its corresponding hydrogenated compound **12**.



SCHEME 3.6 Synthesis of *trans*-β-lactams **14**.



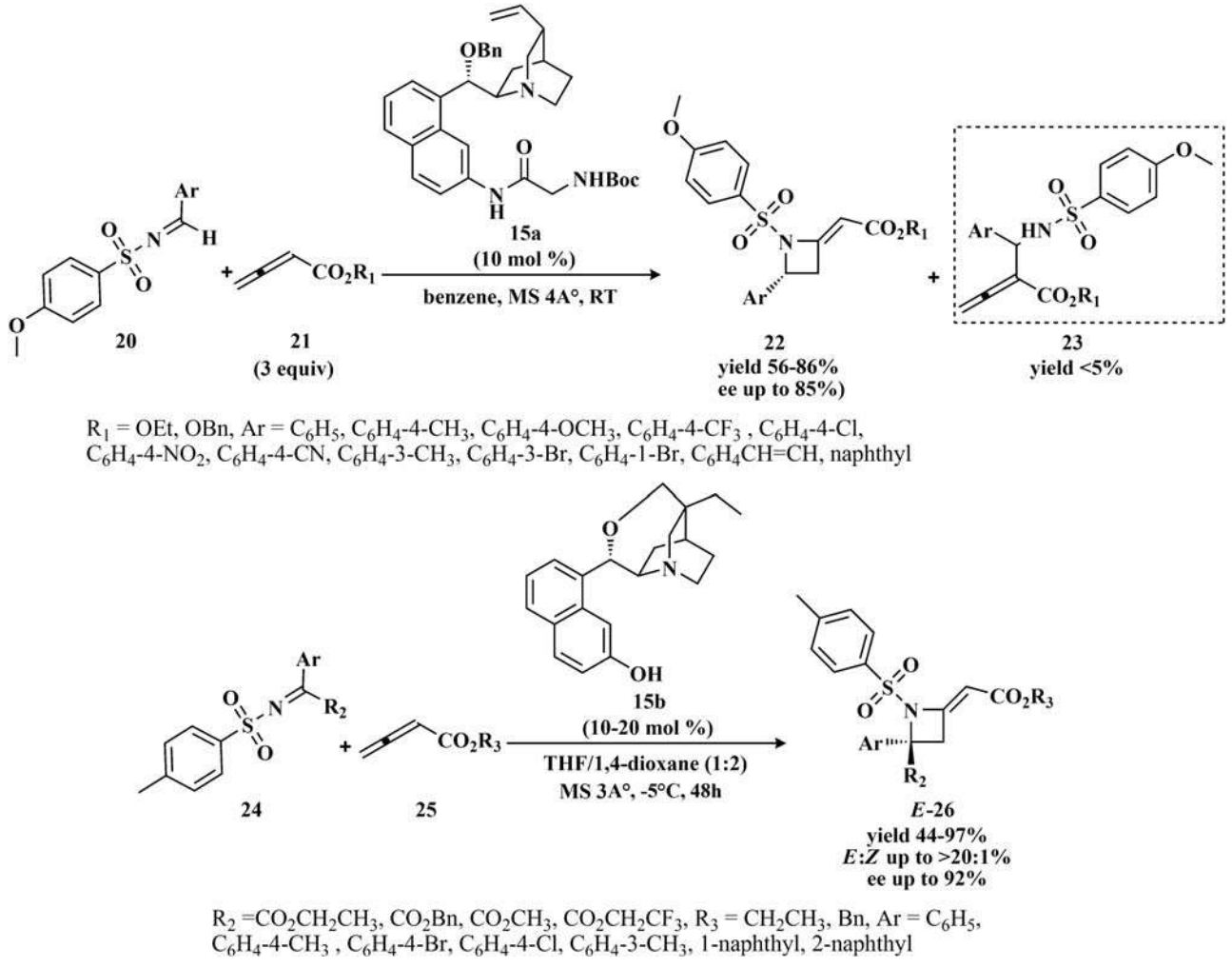
SCHEME 3.7 Synthesis of *N*-sulfonylazetidines **19** via a cycloaddition reaction.

derivative Lewis acid organocatalysts for the preparation of sulfonyl-activated azetidines with 2,4-disubstitution. Mechanistically, the addition of the catalyst **15a-c** to allenoate **16** generated the zwitterionic intermediate **Ia,b**, which might react with the imine **17** via two different pathways (Scheme 3.7) [38,39]. In the favored pathway **A**, the [2−2] cycloaddition of γ-carbanion **Ia** to the imine gave the intermediate **II**. Hydride elimination from the intermediate **II** provided the desired azetidine **18** with the regeneration of the used catalyst (Scheme 3.7). A second pathway **B** would occur to afford the aza Morita-Baylis-Hillman type product **19** in minimum yield through exaction of the catalyst (Scheme 3.7). The use of *N*-sulfonated ketamine as an imine model instead of aldimine avoided the formation of the aza Morita-Baylis-Hillman type product **19** probably due to the steric hindrance of the ketimine.

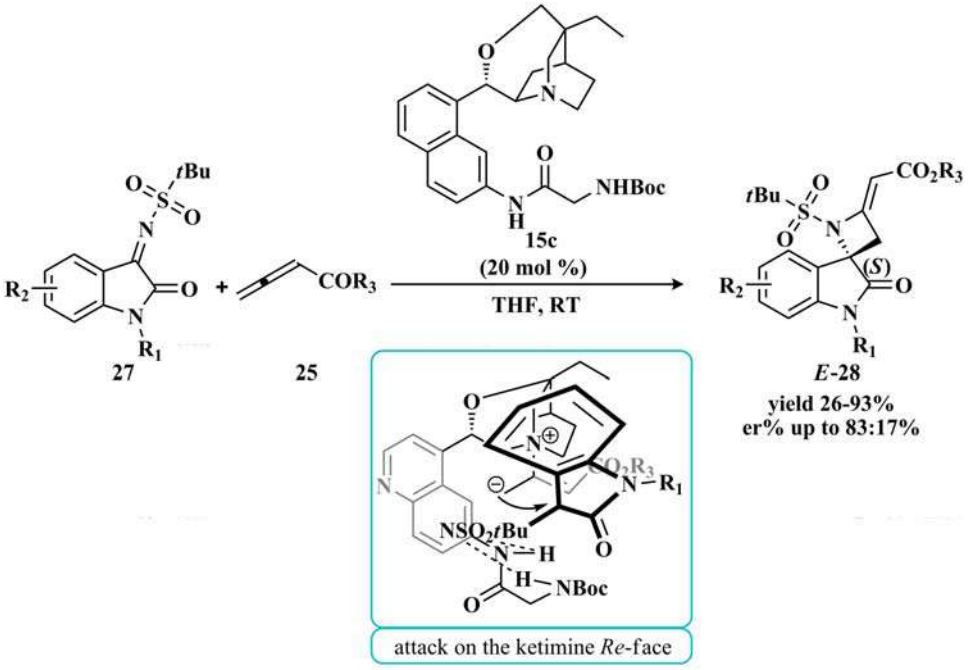
In 2011, Denis et al. [38] reported the first asymmetric synthesis of 2,4-disubstituted *N*-sulfonated azetidines **22**. An array of aromatic *N*-sulfonyl aldimines **20** could participate in cycloaddition reactions to furnished *R*-configured azetidines **22** with very traces of the aza Morita-Baylis-Hillman type product **23** (Scheme 3.8). After that, Takizawa et al. [39] introduced a wide range of *N*-sulfonated ketimines **24** in cycloaddition reaction with allenoates **25**, resulting in *N*-sulfonyl azetidines **26** as the sole products (Scheme 3.8).

Lately, such a strategy was successfully extended to the preparation of an interesting enantioenriched spirooxindole-based 4-methyleneazetidines **E-28** using isatin-derived *N*-tert-butylsulfonyl ketimines **27** as substrate model [40]. It was noted that the use of *N*-Boc glycinamide moiety at the position of C6′ in the catalyst led to the sufficient activation of the ketamine **27** through the formation of two hydrogen bonds with the ketamine. Based on this disposition, ketimine attacked its *Re*-face to the γ-carbanion to reduce the steric hindrance with the residue of the catalyst, resulting in the spiroazetidine in the *S*-configuration at the position of C3 of the oxindole ring as depicted in Scheme 3.9.

For highly functionalized azetidines, Meng et al. [41] developed the intermolecular [2 + 2] cycloaddition reaction of alkynyl ketones **29** with allyl *N*-tosylimines **30** in the presence

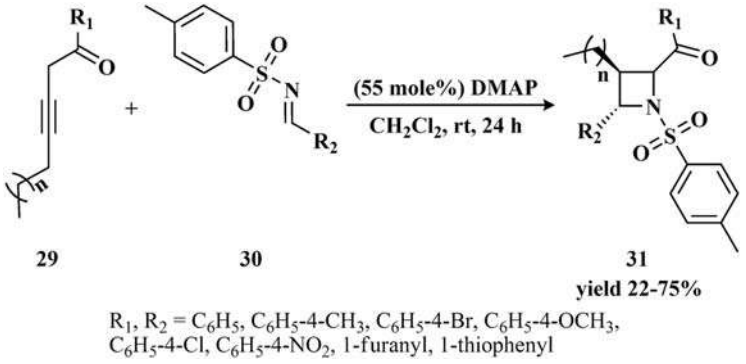


SCHEME 3.8 Synthesis of *N*-sulfonylazetidines **26** via cycloaddition reaction of *N*-sulfonated ketimines **24** with allenoates **25**.



$R_1 = CH_3$, Bn, Trt, *n*-Pr, *i*-Pr, C_6H_5, R_2 = H, 2-OCH_3, 2-Cl, 4-Cl, 6-Cl, $R_3 = CH_2CH_3$, Bn

SCHEME 3.9 Preparation of enantioenriched spirooxindole-based 4-methyleneazetidines **E-28** using isatin-derived *N*-tert-butylsulfonyl ketimines **27**.



R_1, $R_2 = C_6H_5$, C_6H_5-4-CH_3, C_6H_5-4-Br, C_6H_5-4-OCH_3, C_6H_5-4-Cl, C_6H_5-4-NO_2, 1-furanyl, 1-thiophenyl

SCHEME 3.10 Intermolecular [2+2] cycloaddition reaction of alkynyl ketones **29** with allyl *N*-tosylimines **30** to afford sulfonyl azetidines **31**.

of Lewis base. It was observed that DMPA was effective in this reaction as Lewis base to afford sulfonyl-activated azetidines **31** in moderate to good yields (Scheme 3.10).

3.2.3 Synthesis of sulfonyl-activated azetidines and azetidin-2-ones via intramolecular cyclization of amine derivatives or amino alcohols

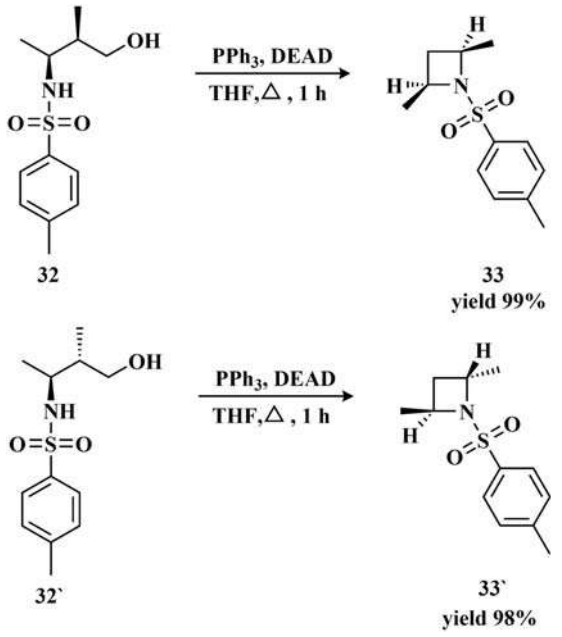
3.2.3.1 To N*-sulfonyl azetidines*

The intramolecular cyclization of amino alcohols or amine derivatives is a sample and facile strategy for non-stereoselective and stereoselective sulfonyl-activated azetidines. Ibuka et al. [42] reported an intramolecular cyclization alkyl alcohols **32,32′** under Mitsunobu condition to form the corresponding chiral 2,3-disubstituted azetidines **33**,**33′**, respectively as single diastereomers in excellent yields (Scheme 3.11).

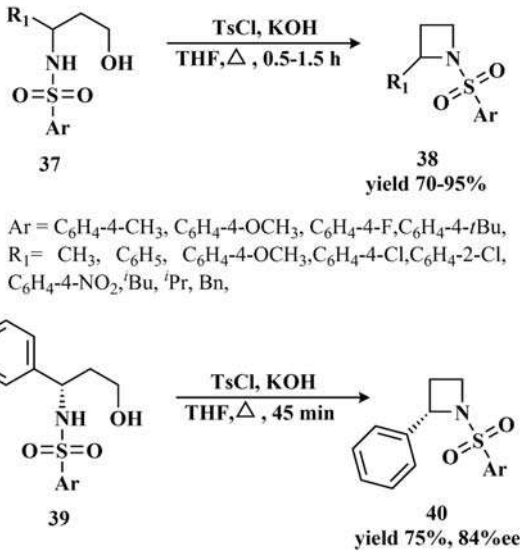
In continuing to explore the synthesis of chiral azetidines, Ohno et al. [43] successfully synthesized highly substituted ethynylazetidines bearing three chiral centers through intramolecular Mitsunobu reactions of chiral 1,3-amino alcohols in good to excellent yields (Scheme 3.12). Studies of Stereochemistry of the resulting azetidines proved that the *syn*,*syn*-amino alcohol **34** and the *anti*,

anti-amino alcohols **34**` afforded the desired ethynylazetidines **35** while the *anti*,*syn*-amino alcohol **34**` gave **35** in 57% yield and elimination product **36** in 42% yield (Scheme 3.12).

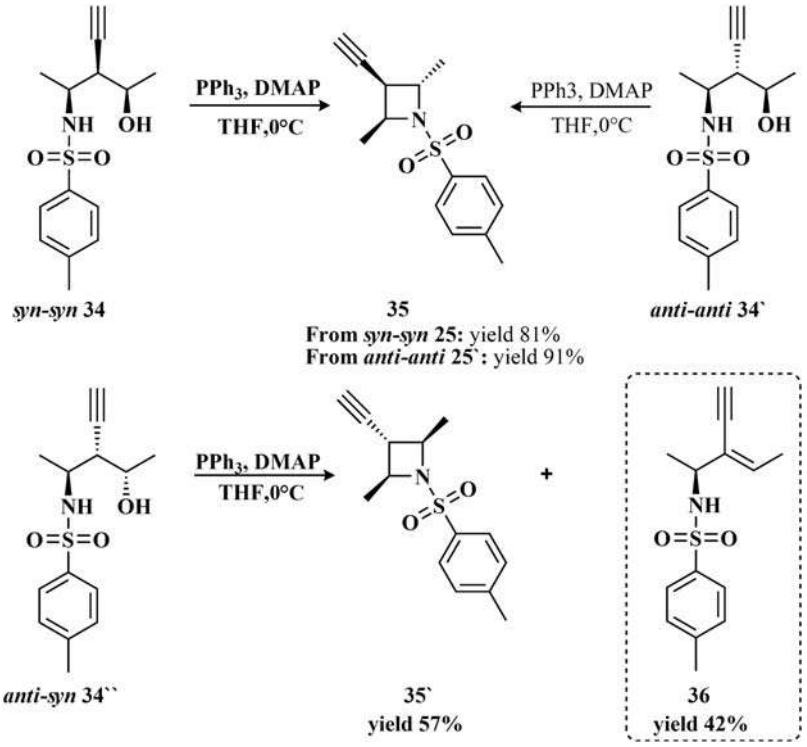
Ghorai et al. [44] devoted considerable efforts to easily and directly synthesize 2-substituted *N*-sulfonyl azetidines **38** via the intramolecular cyclization of γ-amino alcohols **37** using tosyl chloride and excess KOH in THF at refluxing condition. After a successful demonstration of this strategy for the synthesis of a variety of *N*-sulfonyl azetidines **38**, the authors expanded their protocol for the synthesis of chiral 2-substituted azetidines **40** by employing enantiomerically pure (*R*)-γ-amino alcohols **39** as the source of chirality (Scheme 3.13).



SCHEME 3.11 Intramolecular cyclization of alkyl alcohols **32,32**` under Mitsunobu condition to form the corresponding chiral 2,3-disubstituted azetidines **33,33**.



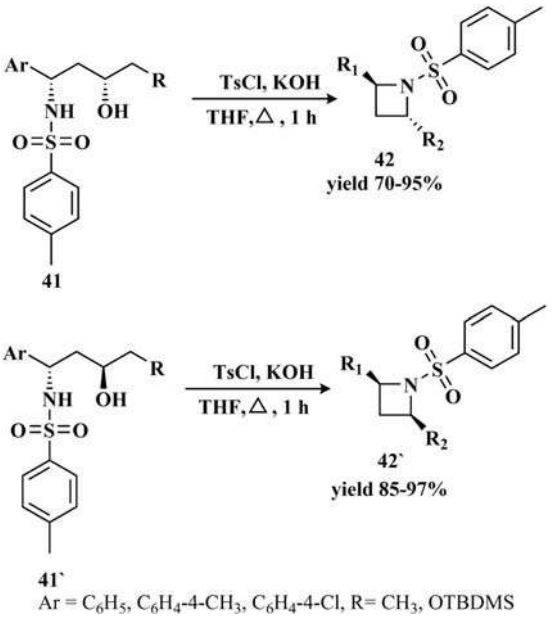
SCHEME 3.13 Synthesis of 2-substituted *N*-sulfonyl azetidines **38** and **40** via the intramolecular cyclization of γ-amino alcohols **37** and **39**.



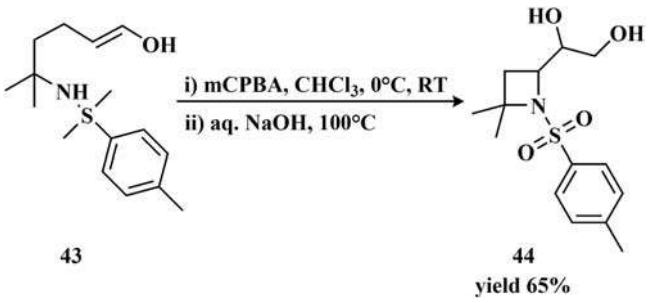
SCHEME 3.12 Synthesis of ethynylazetidines **35** and **35**`through intramolecular Mitsunobu reactions of chiral amino alcohols **34** and **34**.

Additionally, The pure diastereomers **41**,**41`** were also individually reacted with tosyl chloride and KOH in THF to afford diastereopure 2,4-disubstituted-*N*-tosyl azetidines **42** and **42`** respectively, in excellent yield (Scheme 3.14) [45].

Breternitz et al. [46] reported a facile method for the preparation of 2,4-substituted azetidine via epoxidation of the allyl alcohol **43**, followed by cyclization with sodium hydroxide furnished azetidine **44** (Scheme 3.15).



SCHEME 3.14 Synthesis of diastereo pure 2,4-disubstituted-*N*-tosyl azetidines **42** and **42`**.



SCHEME 3.15 Preparation of 2,4-substituted azetidine **44** via epoxidation of the allyl alcohol **43**.

Tiecco et al. [47] described a facile route for the stereocontrolled synthesis of 2,3-substituted *N*-sulfonyl azetidines **46** through the oxidation of *N*-Arylsulfonyl selenides **45** followed by the intramolecular substitution reaction of the produced phenylselenonyl group by the nitrogen atom in the intermediate **I** (Scheme 3.16).

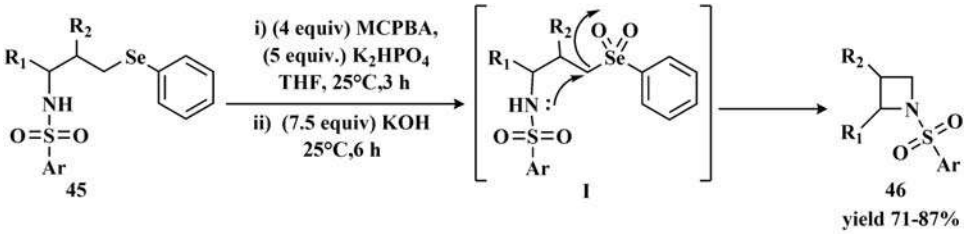
3.2.3.2 N-*sulfonyl azetidinone (*N-*sulfonyl* β-*lactam)*

Intramolecular cyclization of amino alcohols or amine derivatives also emerged for the synthesis of β-lactam ring linked to sulfonyl moiety. Kang et al. [48] reported a facile method for the construction of chiral β-lactam **48** from β,δ-dihydroxy amide **47**. Bissilylation of β,δ-dihydroxy amide **47** with tert-butyldimethylsilyl chloride and the sequent reaction of the bis-silylated amide with Boc-anhydride in the presence of DMAP and trimethylamine as strong bases furnished *t*-butoxycarbonylamide **48** which easily Intramolecular cyclized to the highly substituted β-lactam **49** (Scheme 3.17).

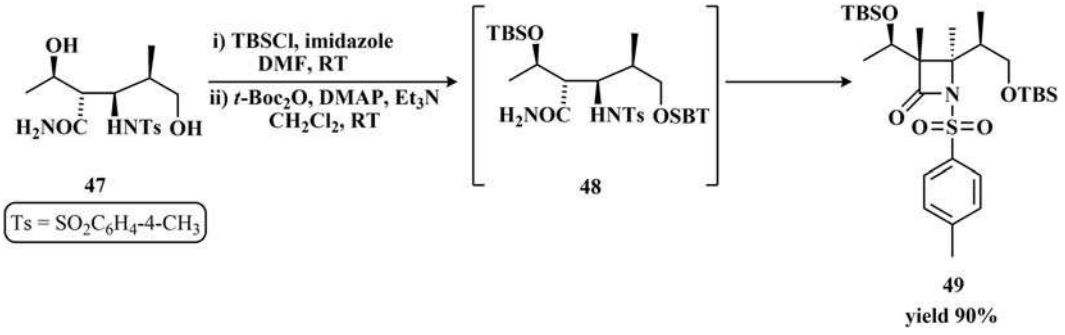
In continuing to explore the synthesis of chiral β-lactams, a rare method for synthesis of the β-lactam **51** was reported by Tanner et al. [49] via Jones oxidation and intramolecular cyclization sequence in the presence of DCC and 4-pyrrolidinopyridine (Scheme 3.18).

3.2.4 Synthesis of *N*-sulfonyl azetidine via ring contraction of 2-pyrrol-one

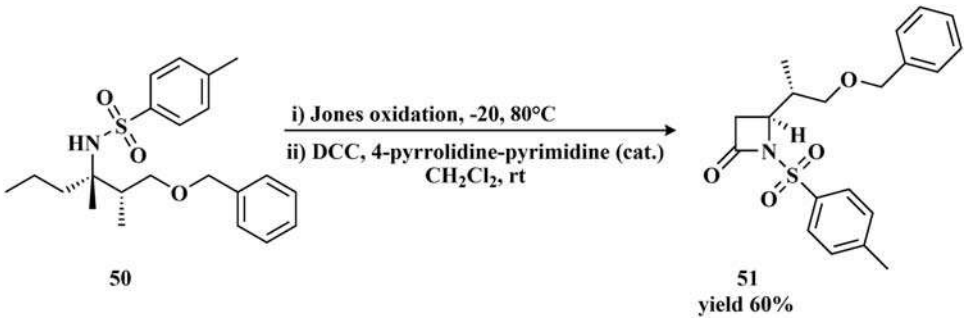
A simple and robust one-pot nucleophilic addition − r-ing contraction of α-bromo *N*-sulfonylpyrrolidinones **52** afforded *N*-sulfonyl azetidine **53** in good yield [50]. Various nucleophiles were efficiently incorporated into the azetidine derivatives in the presence of potassium carbonate as a base. To better understand the stereochemical outcome of the reaction, the rearrangement of enantiopure *trans*- and *cis*-α-bromo sulfonylpyrrolidinone **54** was studied. In presence of K_2CO_3 as a base, the *trans*-pyrrolidinone **trans-54** afforded the *trans*-azetidine **trans-55** with an excellent 7.3:1 diastereomeric ratio (dr) in only 1.5 h (Scheme 3.19). In contrast, the pure cis-pyrrolidinone **cis-54** afforded the *trans*-azetidine **trans-55** as the major isomer (5.1:1), but after



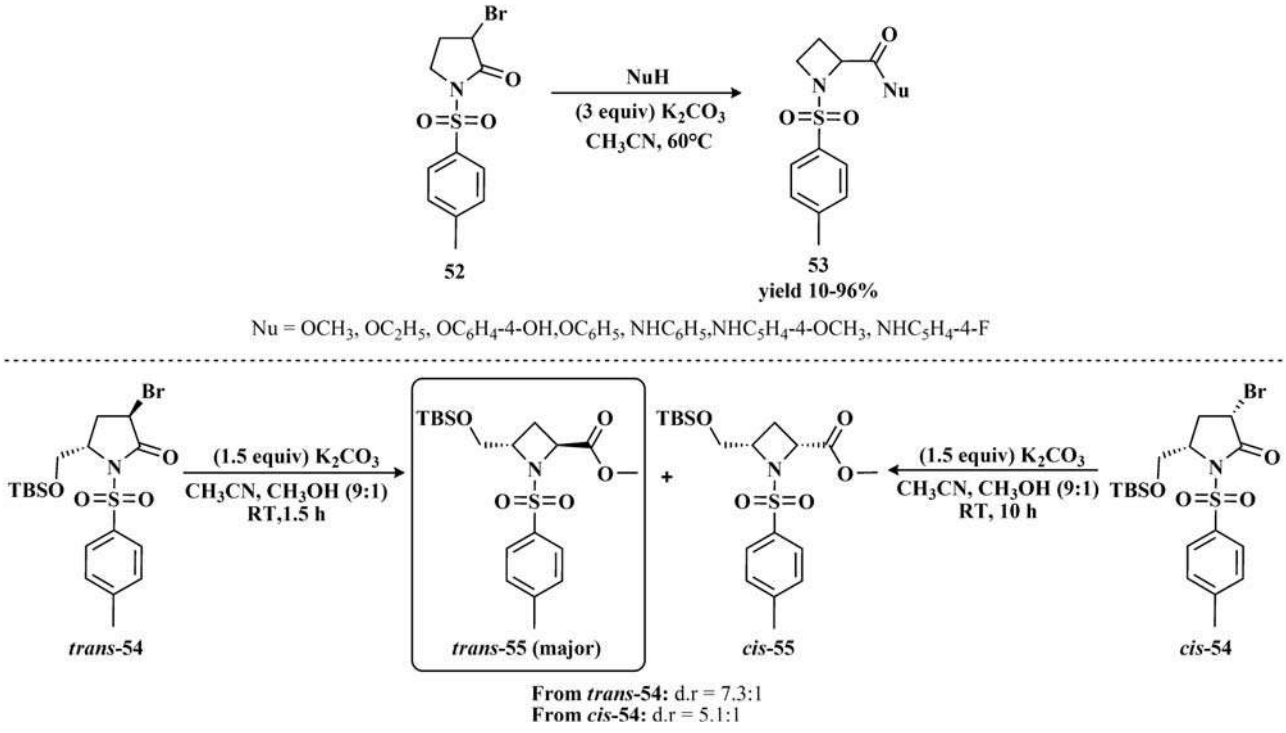
SCHEME 3.16 Synthesis of 2,3-substituted *N*-sulfonyl azetidines **46** through the *N*-Arylsulfonyl selenides **45**.



SCHEME 3.17 Synthesis of chiral β-lactam 49 from β,δ-dihydroxy amide **47**.



SCHEME 3.18 Synthesis of the β-lactam **51** via Jones oxidation and intramolecular cyclization of tosyl derivative **50**.



SCHEME 3.19 Synthesis of *N* sulfonyl azetidine **53** and **55** via α-bromo *N*-sulfonylpyrrolidinones **52** and **54**.

10 h. This result confirmed that the ring contraction was much faster for the substrate *trans*-pyrrolidinone **trans-54** than that of *cis*-pyrrolidinone **cis-54** because the *cis* isomer firstly epimerized to its *trans* isomer (Scheme 3.19).

3.2.5 Synthesis of bicyclic β-lactams via a crossed-benzoin/oxy-cope rearrangement

An isolated example of an investigation of the capability of *N*-heterocyclic carbene (NHC) for the promotion annulations

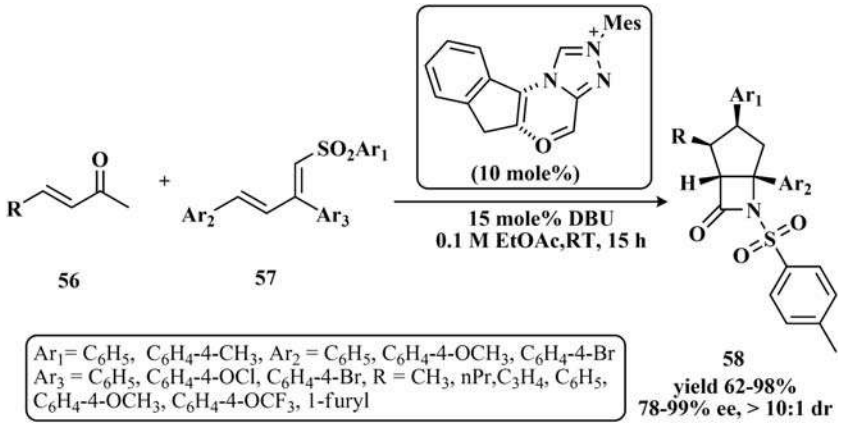
of enals with unsaturated *N*-sulfonyl ketimines was reported by Ha et al. [51] in 2008. NHC-catalyzed reactions of enals **56** with *N*-sulfonyl ketimines **57** furnished enantiomerically pure bicyclic β-lactams **58** with highly enantio and diastereoselectivity via a cascade process featuring a crossed-benzoin/oxy-Cope rearrangement. A variety of enols, 3-alkyl enals, and 3-aryl enols **56** could participate as substrates in this reaction (Scheme 3.20).

3.3 Chemistry of sulfonyl-activated azetidine and azetidin-2-ones

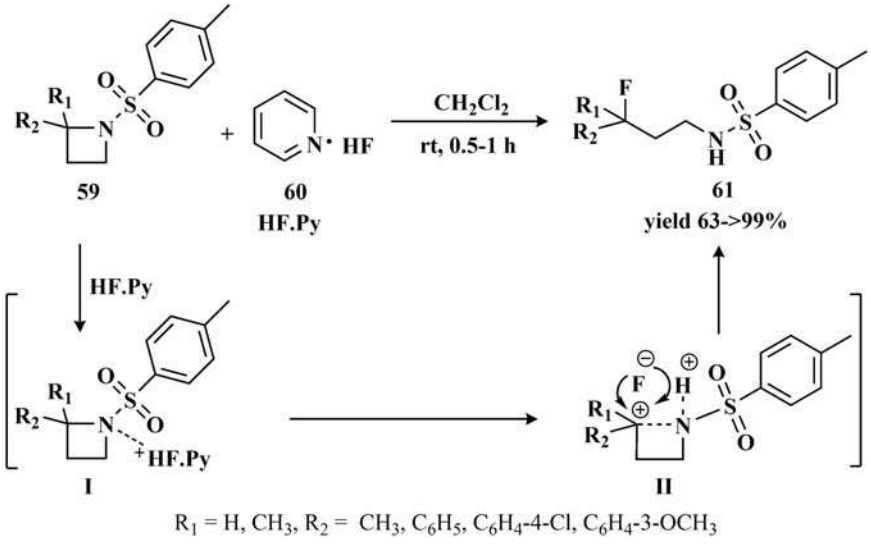
3.3.1 To acyclic amine derivatives

N-sulfonyl azetidine and azetidin-2-ones were widely employed as valuable building blocks in the preparation of a wide range of functionalized acyclic amine derivatives because of the inherent reactivity of their strained ring system [52–56]. A novel approach for the preparation of γ-fluorinated amines **61** with extreme regioselectivity was disclosed via ring-opening nucleophilic hydrofluorination of highly functionalized *N*-sulfonylazetidines **59** (Scheme 3.21) [57]. The Olah's reagent was used as a fluoride source, affording the desired product **61** with good to excellent yield. The proposed mechanism involves the coordination of pyridine–HF with azetidine nitrogen, followed by intermolecular SN_1-type ring opening through fluorion (Scheme 3.22).

The superior catalytic efficacy of Lewis acid $BF_3 \cdot OEt_2$ allowed for fast and facile ring-opening of *N*-sulfonylazetidines **62** with an array of hydrazones **63** to furnish an interesting hydrazonyl amine derivatives **64** in high yield (Up to 98%) [58]. This reaction was took place with the formation of a new C–N bond by a regiospecific addition of hydrazine nitrogen to the azetidine benzylic position (Scheme 3.23).



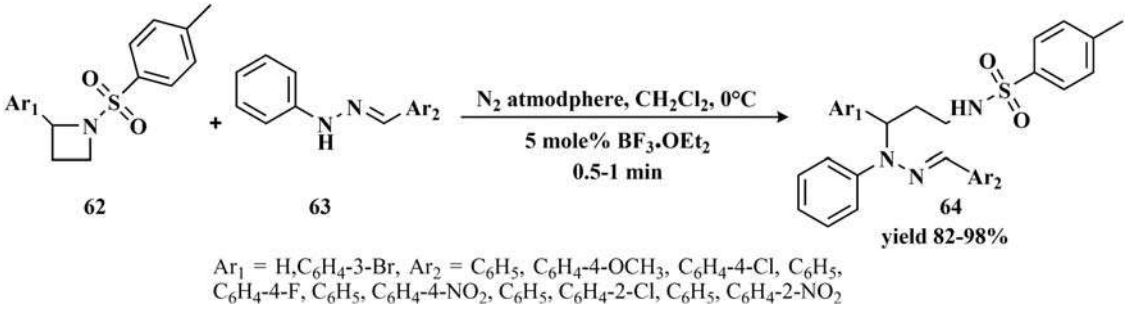
SCHEME 3.20 Synthesis of bicyclic β-lactams **58** through reaction of enals **56** with *N*-sulfonyl ketimines **57**.



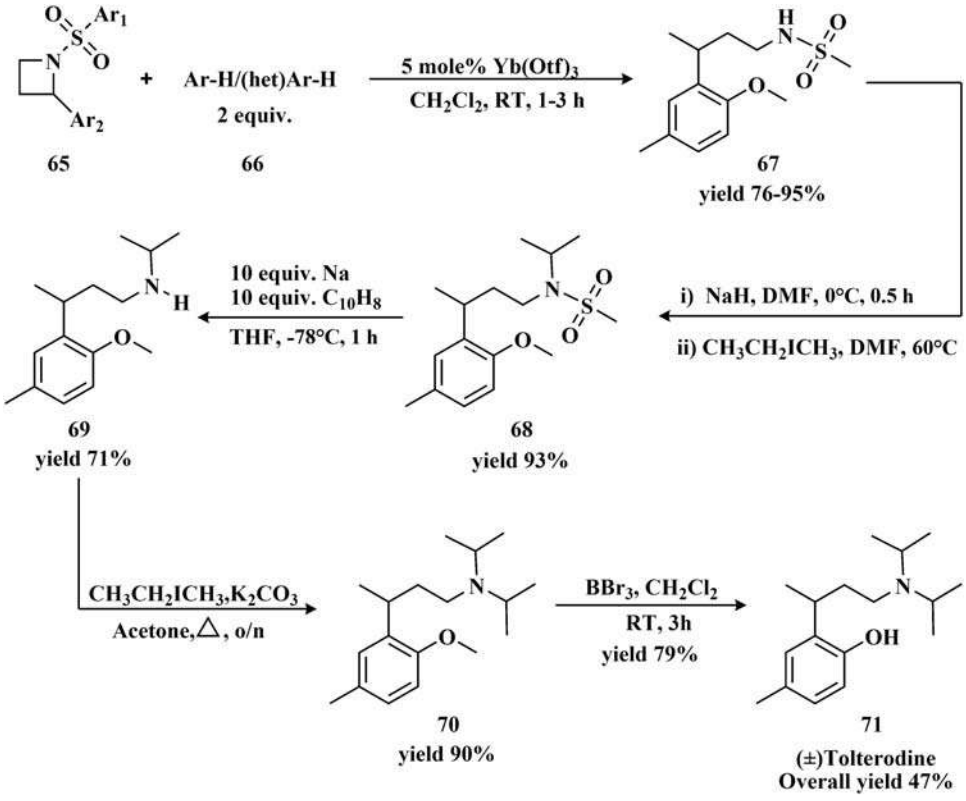
SCHEME 3.21 Preparation of γ-fluorinated amines **61** via ring-opening nucleophilic hydrofluorination of *N*-sulfonylazetidines **59**.

A simple and facile synthetic methodology allowing access to racemic 3,3-disubstituted propylamines **67** based on SN_2-type ring-opening of *N*-sulfonated azetidines **65** with electron-rich arenes/heteroarene nucleophiles **66** under Lewi acid catalysis was accomplished [59]. This methodology was applied in the racemic synthesis of tolterodine antimuscarinic drug **71** in 47% overall yield (Scheme 3.24). It involved the following four reaction steps: (1) alkylation of nitrogen atom on the ring-opened product **67** with isopropyl iodide, (2) detosylation of the alkylated product **68**, (3) second alkylation of the resultant secondary amine **69** was achieved, (4) the methoxy group on the benzene ring of the corresponding tertiary amine **70** was demethylated(Scheme 3.24).

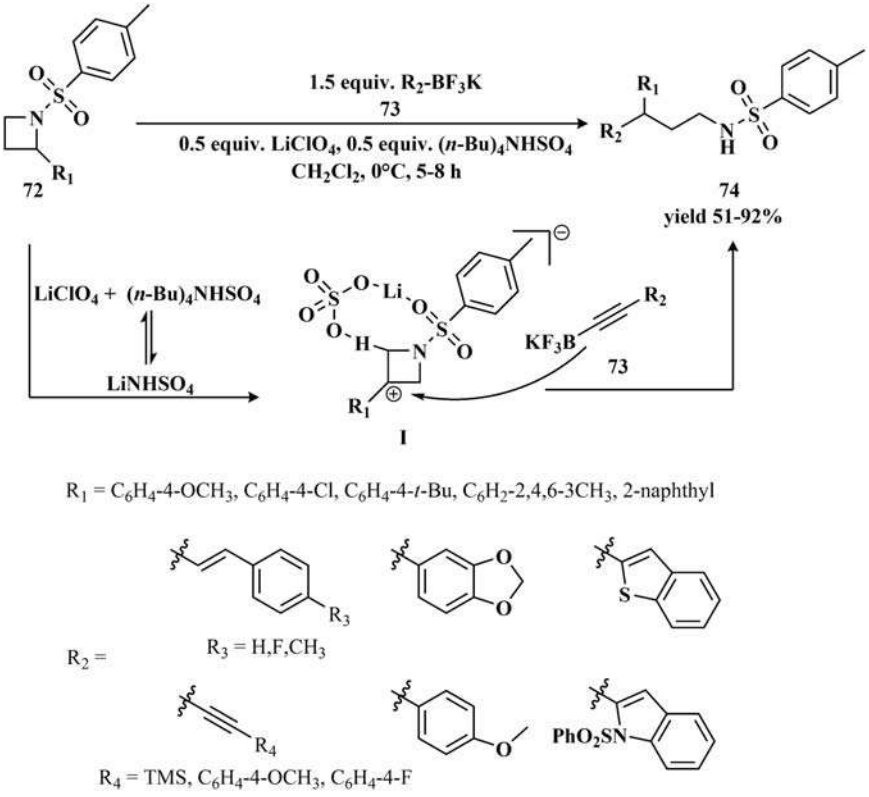
The employ of organotrifluoroborate salts **73** as active nucleophiles allowed for providing an array of γ,γ-substituted amines **74** through azetidine ring-opening (Scheme 3.25) [60]. The Lewis acid $LiClO_4$ was used to activate the ring-opening process. The use of Brønsted acid $(n\text{-Bu})_4NHSO_4$ as a co-catalyst resulted in an acceleration of reaction rate due to the possibility of in-situ formation of bifunctional catalyst $LiHSO_4$ through ion exchange between $(n\text{-Bu})_4NHSO_4$ and $LiClO_4$. The so-formed $LiHSO_4$ could coordinate with azetidine **72** to generate active species **I**. The nucleophilic attack of organotrifluoroborate salts **73** on the carbocation of the azetidine ring led to ring-opening and C−C bond formation, affording the desired amine products **74** with satisfactory yields (Scheme 3.25).



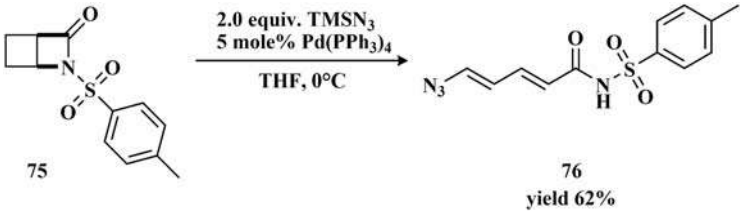
SCHEME 3.22 Ring-opening of *N*-sulfonylazetidines **62** with hydrazones **63** to produce hydrazonyl amine derivatives **64**.



SCHEME 3.23 Synthesis of tolterodine antimuscarinic drug **71** via ring-opening of *N*-sulfonated azetidines **65**.



SCHEME 3.24 Synthesis of γ,γ-substituted amines **74** through ring-opening of azetidine **72**.



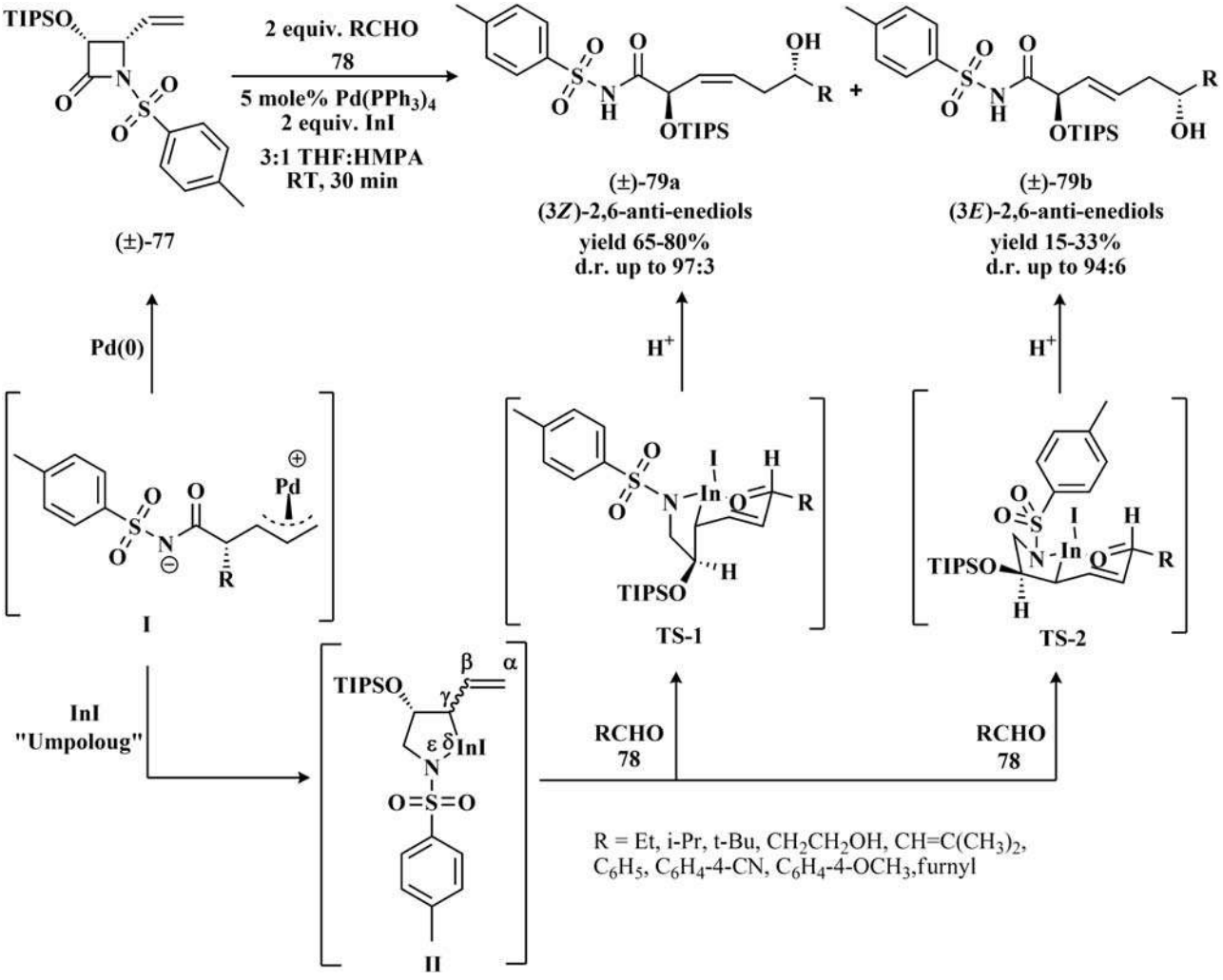
SCHEME 3.25 Conversion of *N*-sulfonated azetidine **75** into *E, E*-dienyl azide **76**.

A two-step domino reaction consisting of palladium-medicated allylic alkylation employing trimethylsilyl azide TMSN as azide source was achieved from *N*-sulfonated azetidine **75**, affording *E*, *E*-dienyl azide **76** (Scheme 3.26) [61].

Treatment of carbonyl compounds with diverse allylmetal reagents is considered the most effective approach for the C−C bond formation in organic synthesis [62−64]. Recently, Zambron and co-workers demonstrated that the easy access 4-b

vinylazetidin-2-ones bearing strongly electron-withdrawing sulfonyl group **(±)-77** could undergo C−N bond cleavage utilizing Pd(0) catalyst to generate the π-allylpalladium complexes **I** [65]. Umpolung of the latter via the reductive transmetalation in the presence of InI gives ε-amido-allylindiums **II**, which can react with a range of aliphatic and aromatic aldehydes **78** to afford (3*Z*)- and (3*E*)-2,6-*anti*-enediol products **79a,b** (Scheme 3.27). The addition of ε-amido-allylindiums **II** to aldehydes **78** occurred through rigid, bicyclic **TS-1** and **TS-2** transition states, in which the position of the group next to the indium was either axial or equatorial depending on the applied conditions to give different ratios of (3*Z*)- and (3*E*)-2,6-*anti*-enediols **79a,b**. In most cases, (3*Z*)-2,6-*anti*-enediols **79a** were the major products (Scheme 3.27).

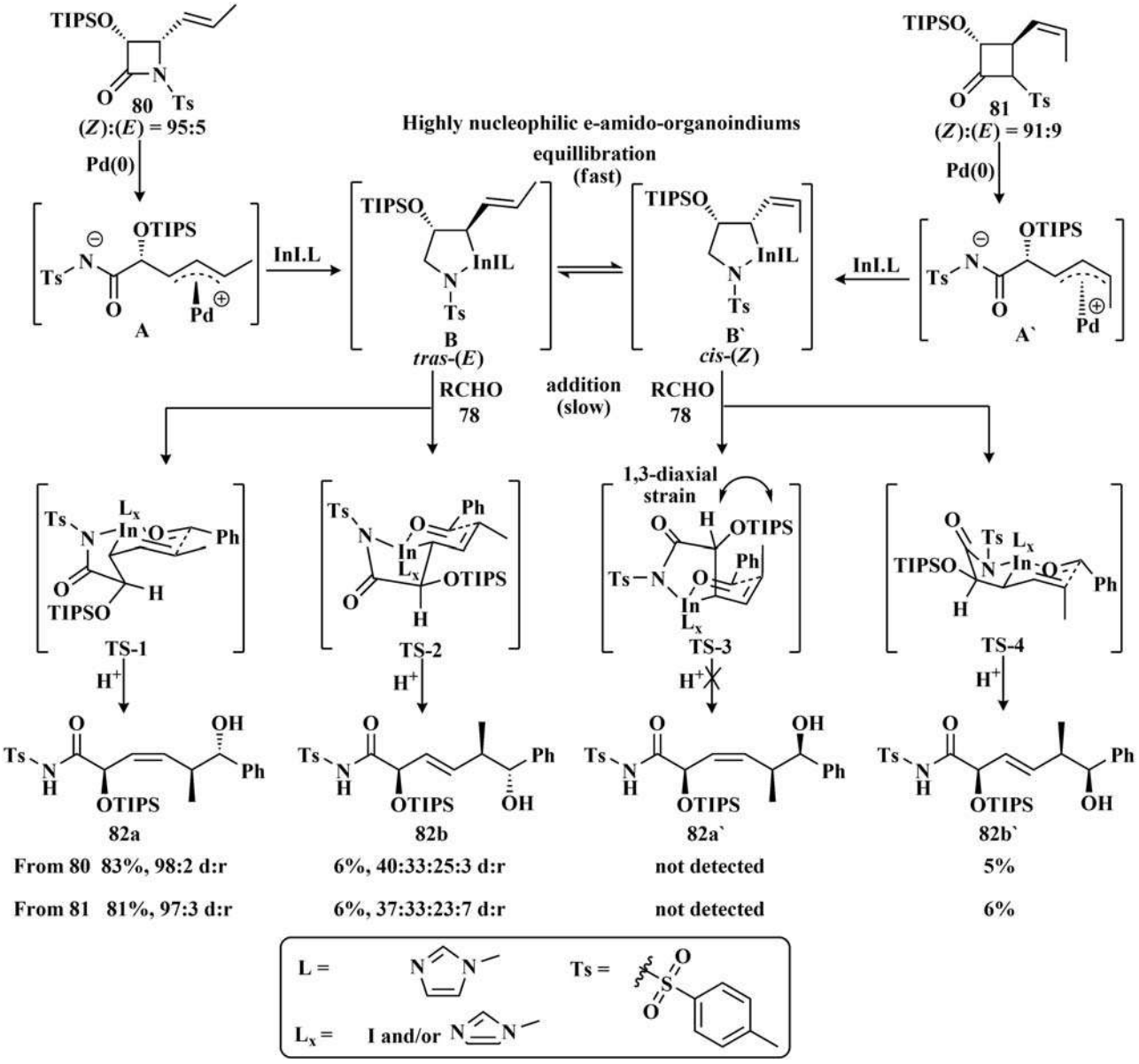
The same group explored the influence of *N*-methylimidazole ligand in allylations of β-lactam-derived organoindiums with aldehydes [66]. As a result, the coordination of the ligand to the amphiphilic InI accelerated the transmetalation step as well as enhanced



SCHEME 3.26 Synthesis of (3*Z*)- and (3*E*)-2,6-*anti*-enediols **79a,b** via C-N bond cleavage of 4-vinylazetidin-2-ones bearing sulfonyl group (±)-**77**.

nucleophilicity of ε-amido-organoindiums **B** or **B′**. The useful application of *N*-methylimidazole in this transformation enabled β-lactams with variously substituted allyl fragments **80,81,83,84** to successfully participate (Scheme 3.28). A detailed study on the influence of aldehyde structures, C3 β-Lactam and allyl moiety substitutions, β-lactams configuration, and chirality on the yield and in the stereochemistry and yield of the products was performed. An interesting observation on the reaction outcome upon studying the starting four isomers of β-lactam differing in the C═C bond configuration. Surprisingly, the use of *trans*-4-(*Z*)-propenyl-β-lactam **81** furnished almost the same mixture of (3*Z*)-2,5-*syn*-2,6-*anti*-enediol **82a** and (3*E*)-2,5-*anti*-2,6-*syn*-enediol **82b** as previously utilized *cis*-4-(*E*)-propenyl-β-lactam **80**. In the reactions of β-lactams **80** or **81**, the significant difference in energy between *trans*-(*E*)- and *cis*-(*Z*)-organoindiums led to shifting the equilibrium far toward the preferred *trans*-(*E*)-isomer (Scheme 3.28). Transition states **TS-1** and **TS-2** were more favored compared with **TS-3** and **TS-4** in the addition step, affording enediols **82a** and **82b**. A great majority in the formation of enediol **82a** with excellent stereoselectivity (98:2 Dr) because of the group next to the indium at the axial position. Owing to acute 1,3-diaxial strain in case of transition state **TS-3**, minor *cis*-(*Z*)-ε-amidoallylindium **B′** exclusively reacted with aldehyde through transition state **TS-4** to give (*E*)-substituted enediol **82b′** (Scheme 3.28).

In contrast to β-lactams **80** or **81**, the employ of *trans*-(*E*)- and *cis*-(*Z*)-substituted isomers **83,84** provided enediolproducts **85a,b** of totally different ratios and configurations. Cis-(*E*) and *trans*-(Z)-ε-amido-allylindiums **B** or **B′** existed in similar concentrations because of their comparable energies and this resulted in a reduction in stereoselectivity [66]. The reaction of *cis*-(*E*)-ε-amido-allylindium with aldehyde via **TS-5** and **TS-6** transition states provided the corresponding enediols **85a** and **85b′** with 33% and 12% yields, respectively. a 1,3-diaxial

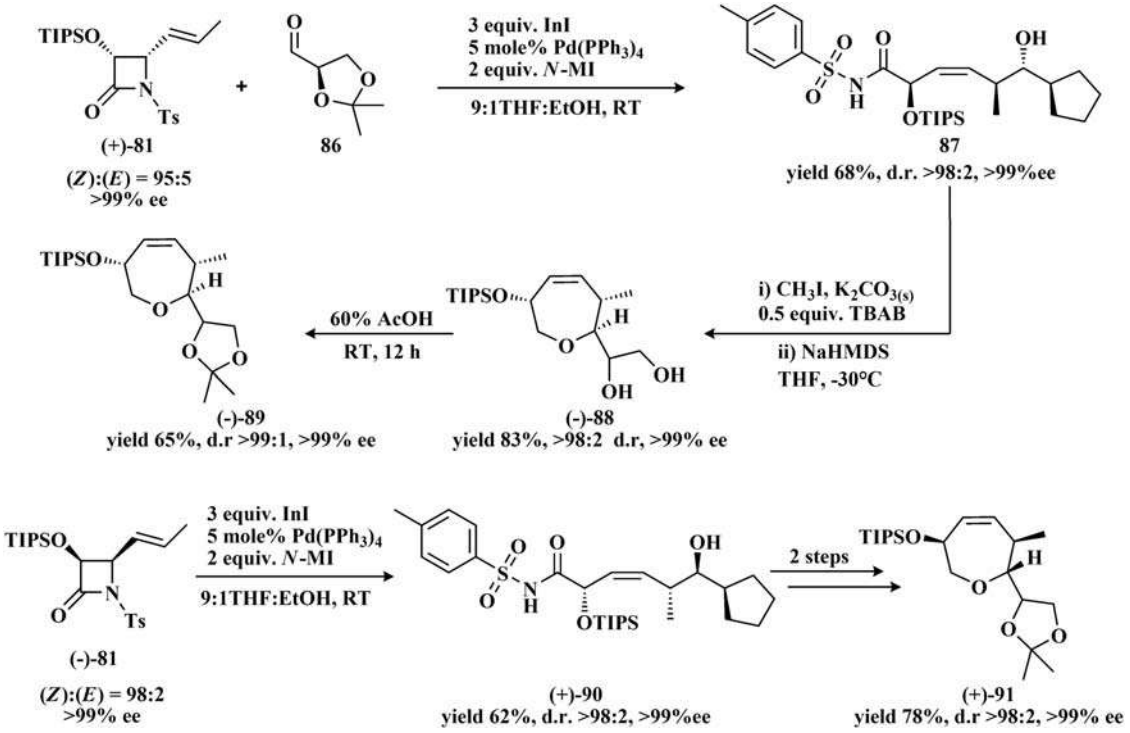


SCHEME 3.27 Synthesis of enediols **82a, 82b** and **82b´** using propenyl-*β*-lactams **80** and **81**.

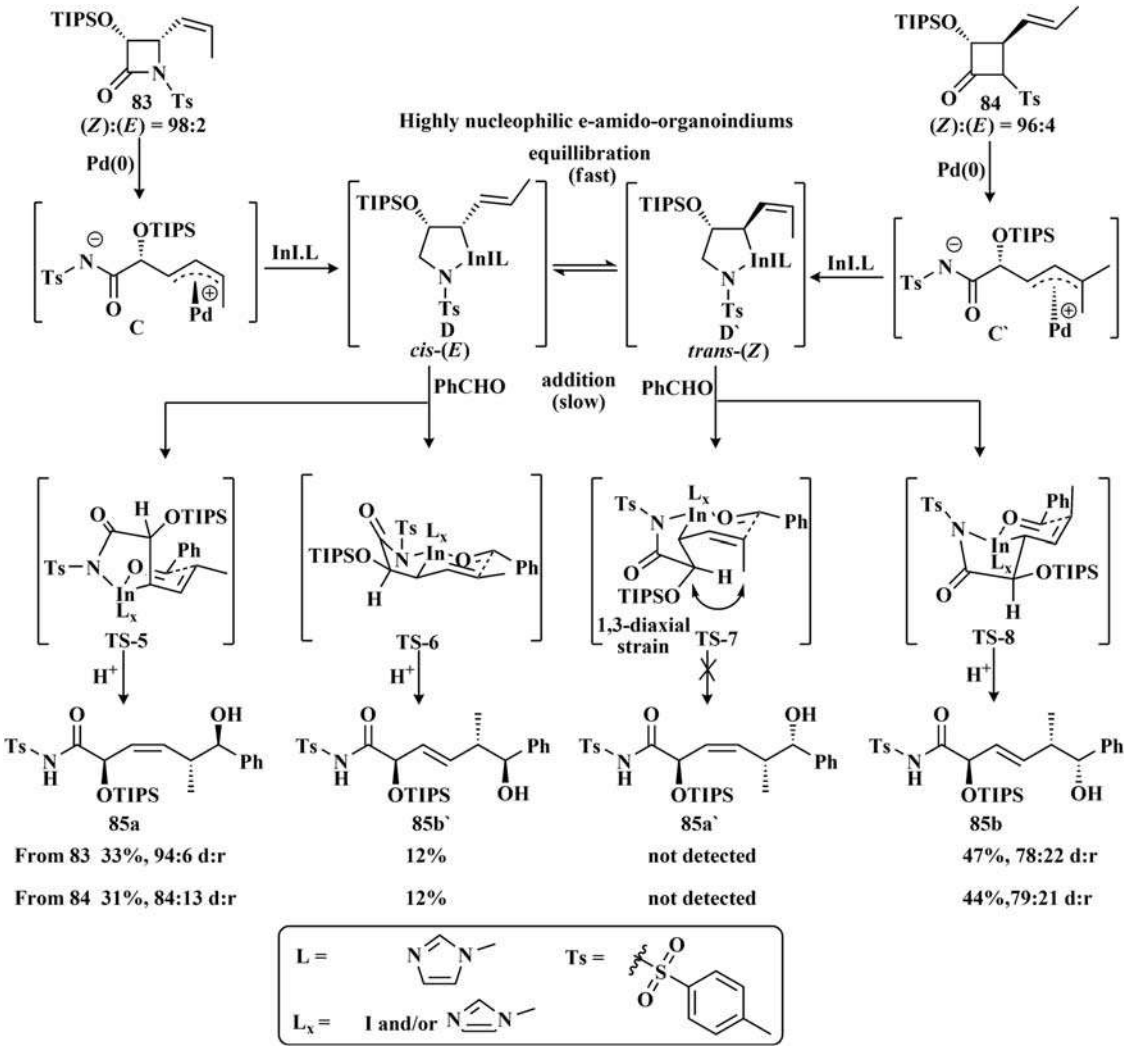
strain in transition state **TS-7** resulted in the reaction of *trans*-(*Z*)-*ε*-amidoallylindium only through transition state **TS-8** to obtain a 47% yield of (*E*)-substituted enediol **85b** (Scheme 3.29).

The synthetic utility of the prepared enediol **(-)-81** was exemplified in the synthesis of chiral caprolactone containing three stereogenic centers [66]. *N*-alkylation, hydrolysis of the N−C bond, and cyclization cascade reactions yielded chiral caprolactone **(−) − 87**, which then acidified with acetic acid to furnish (4*Z*)-3,6-*syn*-3,7-*anti*-caprolactones **(−) − 89** respectively (Scheme 3.21). Under the same conditions, the enediol isomer **(+) − 81** provided the corresponding caprolactone **(+) − 91** with excellent regio- and stereoselectivity (Scheme 3.21).

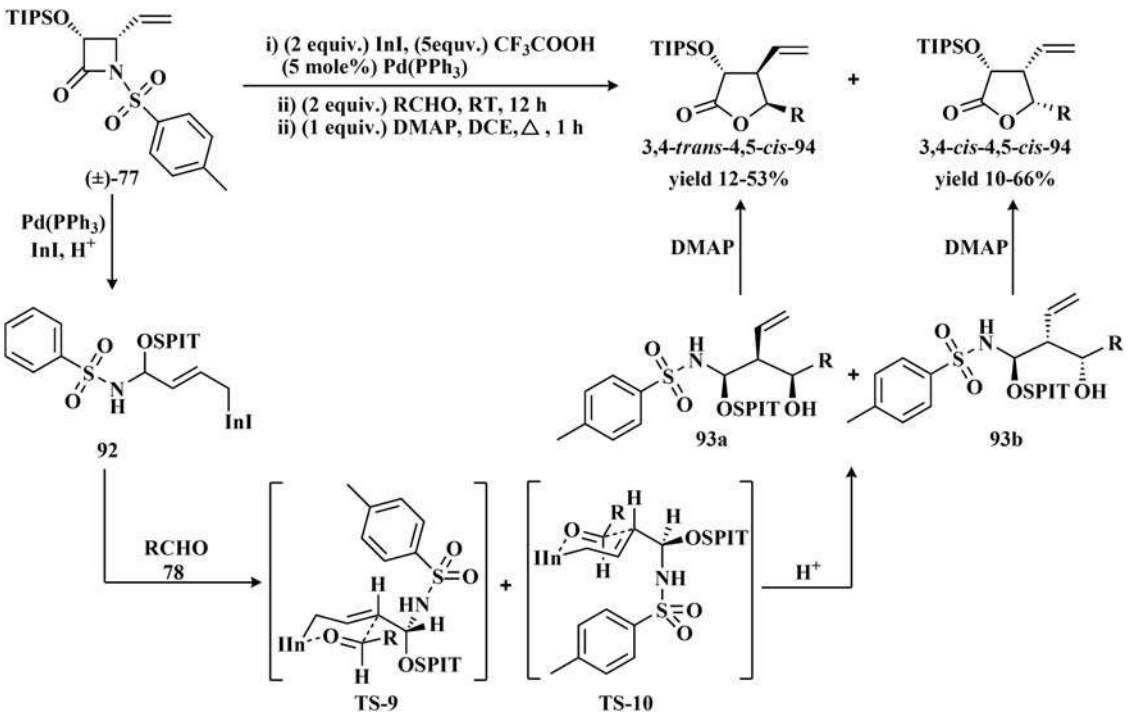
Further elaboration on the allylation of aldehydes with *β*-lactams-derived *ε*-amido-allylindiums was performed by the same group based on studying the addition of a Brønsted acid CF_3COOH as a proton source during the reaction [67]. Interestingly, it was observed that regioselectivity of the allylation could be effectively inverted to enable access to branched *γ*-adducts (1,3-diols) 93a,b instead to *σ*-adduct as previously demonstrated. Without any isolation, *γ*-adducts **93a,b** were facilely converted via intramolecular $TsNH_2$ substitution into extremely desirable *γ*-butyrolactones **94** possessing three stereogenic centers under DMAP nucleophilic catalysis (Scheme 3.30). A mixture of chiral 1,3-diols 93a,b was obtained from the addition of aldehydes with linear *ε*-amido-allylindium **92**



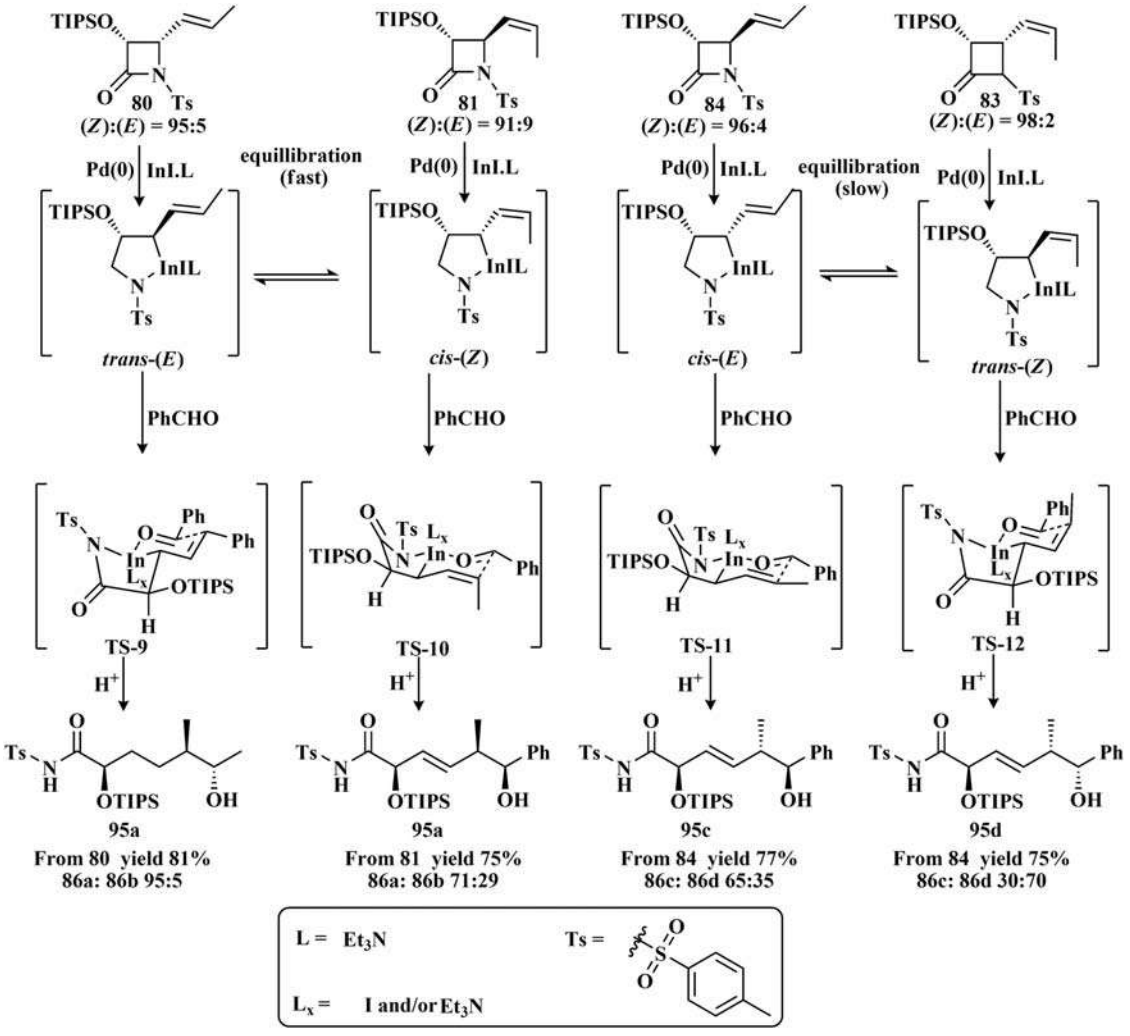
SCHEME 3.28 Synthesis of enediols **85a,b** and **85b´** using propenyl-β-lactams **83** and **84**.



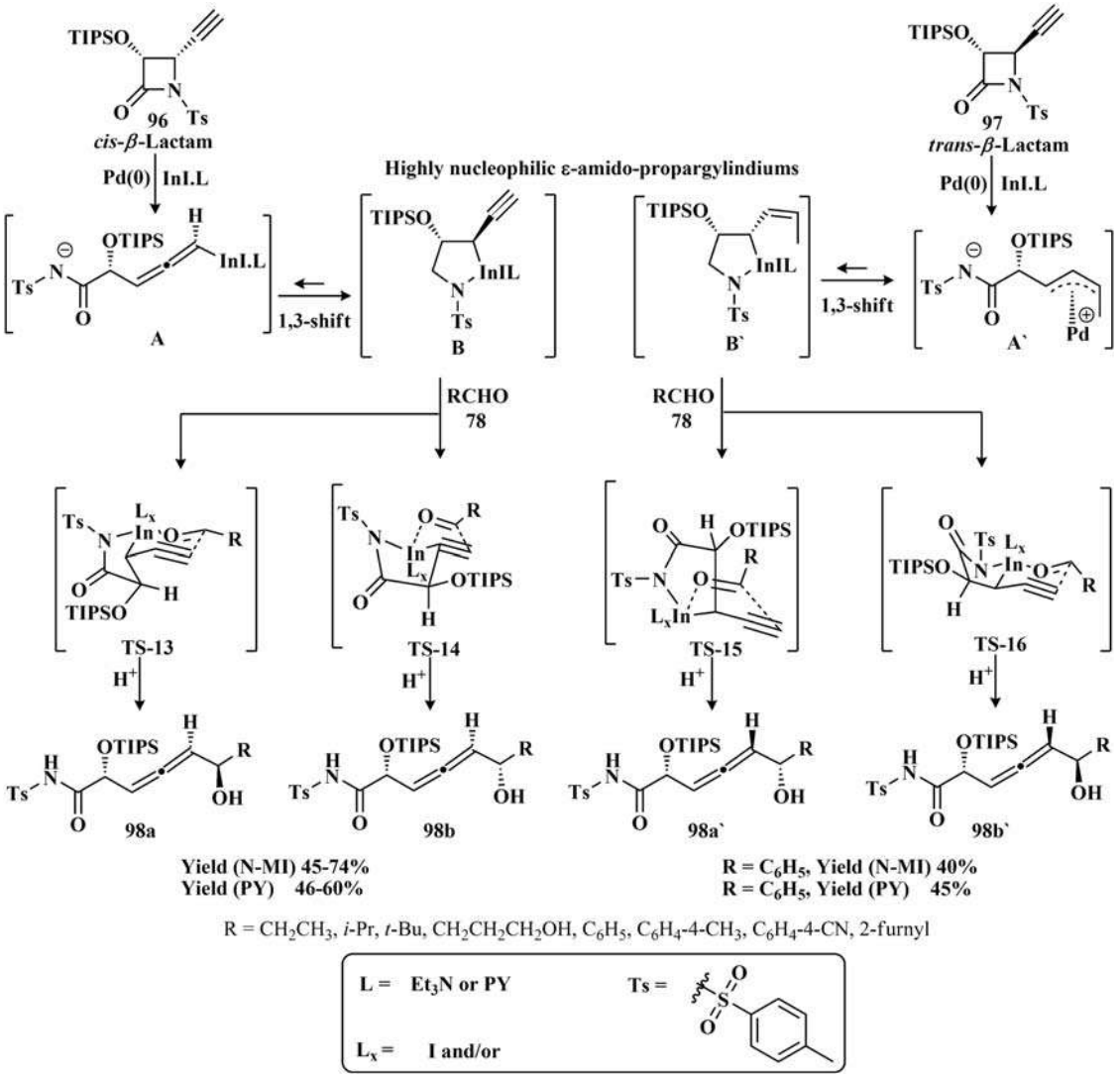
SCHEME 3.29 Synthesis of chiral caprolactone (−)-**89** and (+)-**91** using propenyl-β-lactams **81**.



SCHEME 3.30 Synthesis of γ-butyrolactones **94** using β-lactams **77**.



SCHEME 3.31 Synthesis of enediols **95a,b,c,d** using β-lactams **80,81,82,83**.

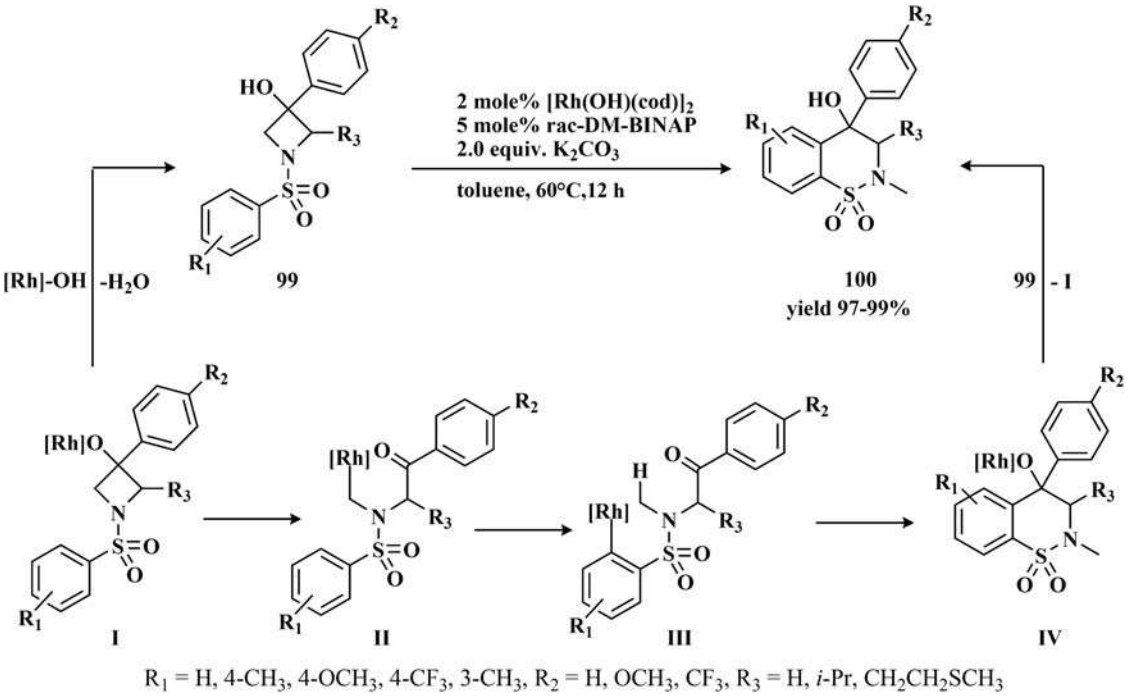


SCHEME 3.32 Synthesis of allenediols **98a,a´,b,b´** using 4-Ethynyl-β-lactams **96,97**.

via the two transition states TS-9 and TS-10. Subsequent protonation of the *N*-Ts moiety resulted in the formation of 3,4-*trans*-4,5-*cis*-**93** and 3,4-*cis*-4,5-*cis*-**93** with different rations (Scheme 3.30).

The switch of *N*-ligand from *N*-methylimidazole to the Et_3N varied diastereoselectivity in allylations of β-lactam-derived organoindiums with aldehydes. In contrast to previously prepared (3*Z*)-enediols, the developed (3*E*)-selective variant was obtained in modest to high yields (Scheme 3.31) [68]. Depending on the chirality of the applied β-lactams, it was assumed that the addition of the four isomeric *trans*-(*E*), *cis*-(*Z*), cis-(*E*), and *trans*-(*Z*) cyclic ε-amido-allylindiums to aldehyde through the corresponding rigid transition states **TS-9 − TS-12** where the position of the group next to the indium was equatorial (Scheme 3.31). However, with the relative fast equilibration between *cis*-(*Z*) and *trans*-(*E*) cyclic ε-amido-allylindiums, apparently disparity between them was observed so the equilibration moved to the thermodynamically favored *trans*-(*E*) and (3*E*)-2,5-*syn*-2,6-*anti*-enediol **95a** was produced as the major product in case of the applied β-lactam **80** and **81** (Scheme 3.31). Regarding to β-lactam **83** and **84**, the slower equilibration between the rest of *cis*-(*E*), and *trans*-(*Z*) cyclic ε-amido-allylindiums led to the formation of one of the two different enediols **95 c,d** in predominance, depending on the β-lactam chirality (Scheme 3.31).

The 4-Ethynyl-β-lactams **96,97** as precursors of stable ε-amido-propargylindiums **B,B`** were introduced to react with diverse aliphatic and aromatic aldehydes **78** using a catalytic system of $Pd(PPh_3)_4$ with *N*-methylimidazole *N*-MI or pyridine (PY) ligand in the presence of InI, affording 2,6-*syn*- or 2,6-*anti*-allenediols **98** (Scheme 3.32) [69]. The cleavage of the C4 − N bond in



SCHEME 3.33 Rearrangement of *N*-arenesulfonylazetidin-3-ols **99** into benzosultams **100**.

β-lactam using Pd(0) catalyst generated π-propargylpalladium(II) species **A,A`, which** underwent reductive transmetalation **to give** cyclic ε-amido-propargylindiums with the InI · PY or InI · *N*-MI complexes (Scheme 3.32).

3.3.2 To benzosultams

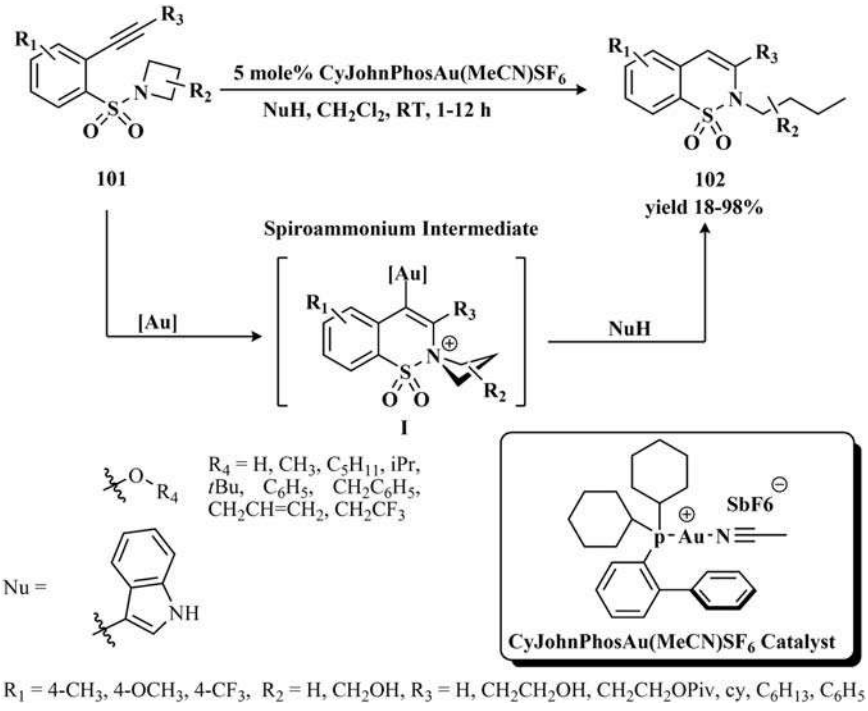
Benzosultams, bicyclic sulfonamides, represent privileged skeletons in different chiral catalysts and pharmaceutical compounds [70–74]. Diverse transformations were developed for the synthesis of such important compounds [75–87]. Among the developed transformations, novel and tailor-designed routes toward benzosultam derivatives from *N*-sulfonylazetidines were explored. Ishida et al. [88] reported rearrangement of *N*-arenesulfonylazetidin-3-ols **99** into benzosultams **100**. This rearrangement was promoted by a combined catalytic system consisting of the rhodium catalyst $[Rh(OH)(cod)]_2$ and *rac*-DM-BINAP as a chiral ligand, affording benzosultams **100** in enantiopure forms (Scheme 3.33). Mechanistically, exchanging the hydroxy group of **99** was firstly onto the rhodium hydroxide occurred to form rhodium alkoxide **I**. The subsequent β-carbon elimination and the cleavage of the C–H bond generated alkylrhodium II, which underwent a 1,5-rhodium shift to afford arylrhodium **III**. The benzosultam skeleton was constructed via intramolecular *6-exo* addition to the carbonyl in the intermediate **IV**. Finally, exchanging the generated rhodium alkoxide D with the hydroxy moiety of another azetidinol **99** gave the benzosultam **100** with the formation of the intermediate **I** (Scheme 3.33).

Pertschi et al. [89] recently reported an alternative strategy for the preparation of benzosultams **102** from *N*-(2-alkynyl)-phenylsulfonyl azetidine substrates **101** via gold(I)-medicated ammonium formation, followed by the ring-opening of the so-formed spiroammonium intermediate **I** using external nucleophiles (alcohols and indoles). This strategy was compatible with the wide range of the substrates and nucleophiles and obtained low to high yields of benzosultams **102** (Scheme 3.34).

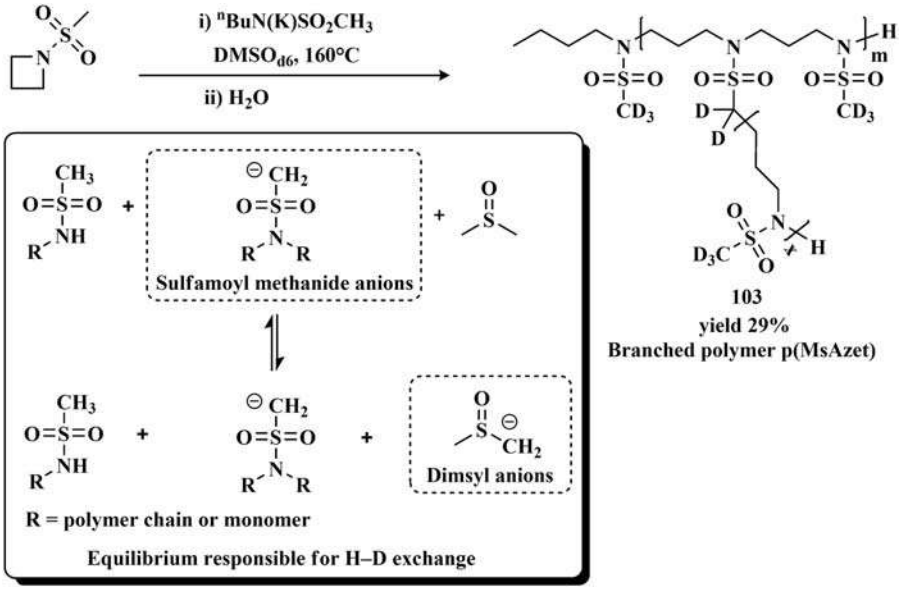
3.4 Sulfonyl-activated azetidine and azetidin-2-ones in polymerization application

3.4.1 Synthesis of poly(*N*-sulfonylaziridine)s via anionic polymerization

Based on the progress achieved with *N*-sulfonylaziridine polymerizations [90–92], Rupar and co-workers demonstrated significant results in anionic ring-opening polymerization (AROP) of *N*-sulfonylazetidines. The initial findings for *N*-sulfonylazetidine polymerization were described using *N*-(methanesulfonyl)azetidine (MsAzet) as a monomer model [93]. MsAzet can be initiated by ^{n}BuN(K)Ms to afford p(MsAzet) with a low yield (29%)



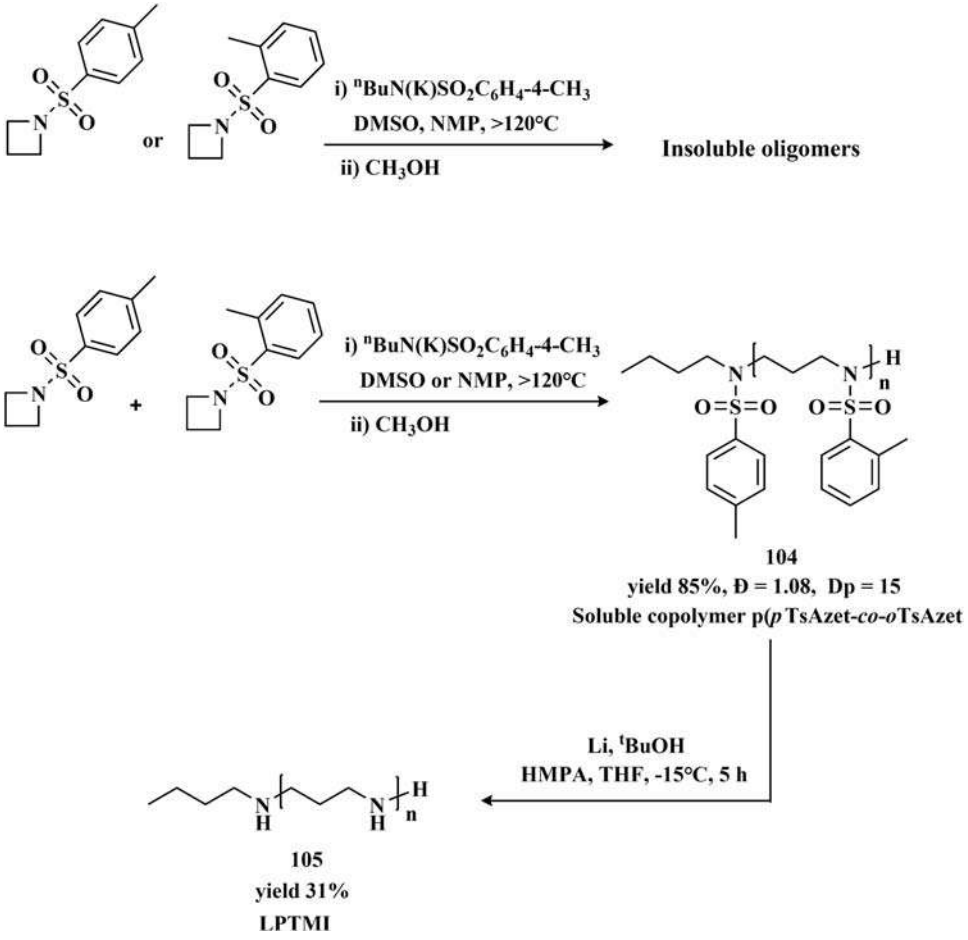
SCHEME 3.34 Preparation of benzosultams **102** from *N*-(2-alkynyl)-phenylsulfonyl azetidines **101**.



SCHEME 3.35 Synthesis of sulfonylazetidine polymer **103**.

as shown in Scheme 3.35. However, Unlike the AROP of *N*-sulfonylaziridine, an elevated temperature (160°C) was required for the azetidine polymerization. Unfortunately, the resulting polymer **103** proved to be branched owing to chain transfer to the methanesulfonyl group. H−D exchange of sulfonyl group protons is evident that such chain transfer took place via the deprotonation of methanesulfonyl groups to generate sulfamoyl methanide anions, which in turn initiated a new chain of polymer (Scheme 3.35). A minimal transfer to DMSO via dimsyl anions formation was also evidenced (Scheme 3.35). During the polymerization, it was found that the numeral active chain ends were constant and this demonstrated the possibility of sulfonylazetidine polymerization to be living and controlled if chain transfer can be repressed.

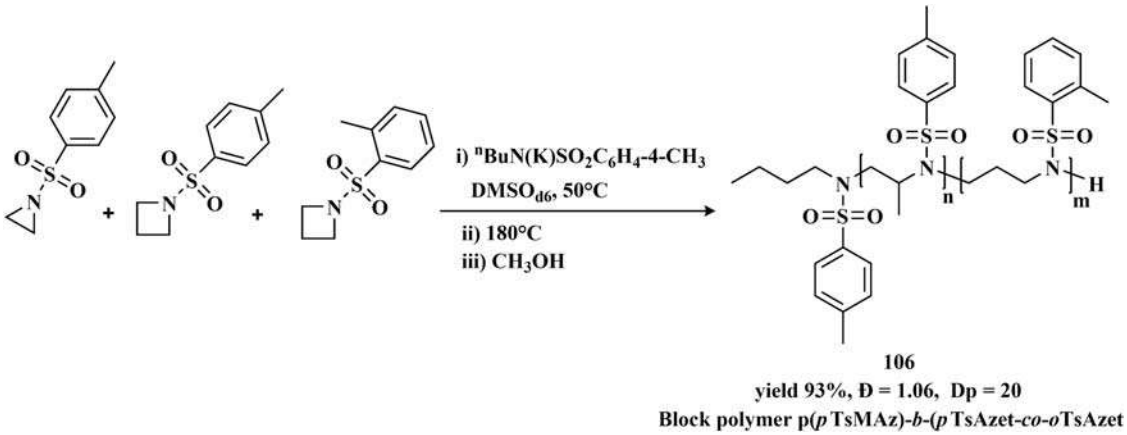
The author's attention was turned to polymerizing alterative azetidine monomer, *N*-(tolylsulfonyl)azetidines



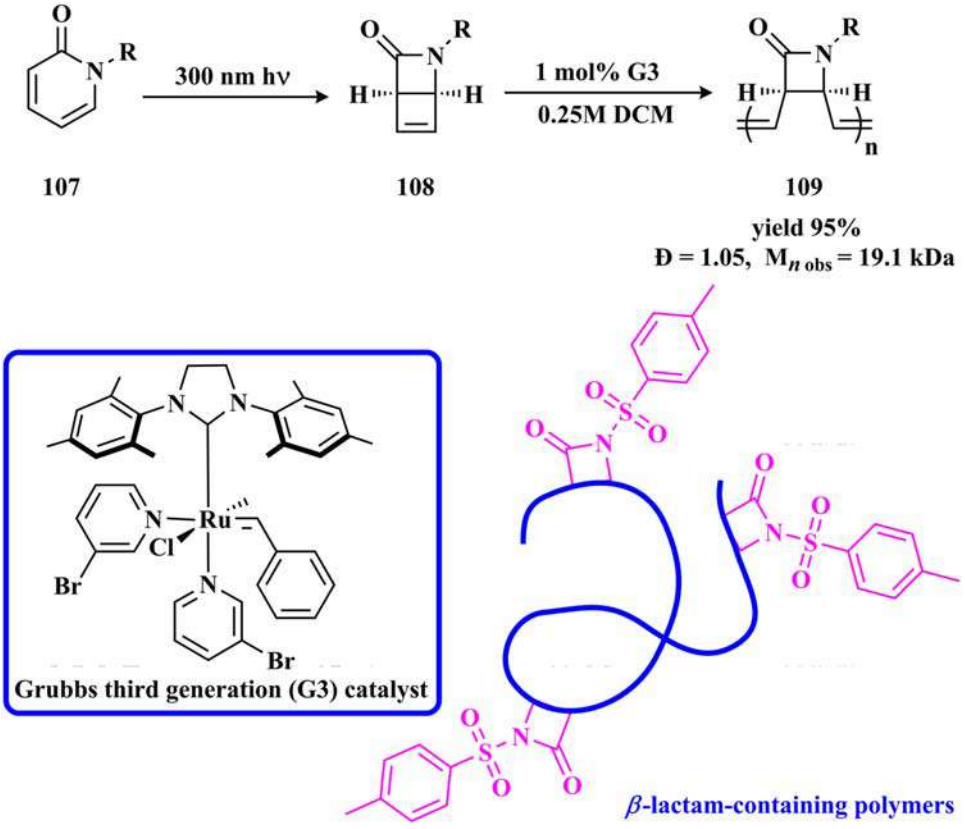
SCHEME 3.36 Anionic copolymerization of *p*TsAzet with *o*TsAzet to form copolymer p(*p*TsAzet-*co*-*o*TsAzet) **104**.

(*p*TsAzet), containing protons unlikely to be activated under the same polymerization condition [94]. Initial attempts were done for the homopolymerization of the two different monomers, *p*TsAzet and *N*-(*o*-tolylsulfonyl) azetidine (*o*TsAzet). Similar to *N*-sulfonylaziridine homooligomers [90,91], the homopolymerization of the azetidine monomers resulted in the precipitation of insoluble homooligomers with low molecular weight from solution (Scheme 3.36). Inspired by recent advances in the copolymerization of sulfonylaziridines for obtaining soluble copolymers, the *p*TsAzet with *o*TsAzet was copolymerized anioincally to form p(*p*TsAzet-*co*-*o*TsAzet) **104** as a target soluble copolymer with narrow dispersity (Scheme 3.36). The *o*TsAzet/*p*TsAzet copolymerization was first-order concerning the concentration of monomer only and the number of active chain ends was kept to be constant. More importantly, the first example of an interesting linear poly(trimethylenimine) LPTMI **105** with well-controlled molecular weight as well as low dispersity was described via reductive removal of the tosyl groups of the resultant copolymer p(*p*TsAzet-*co*-*o*TsAzet) **100** as demonstrated in Scheme 3.36. Therefore, the construction of polyimine derivatives could be offered as biomedical materials in potential applications.

Additionally, the same group exploited the high-temperature barrier in the polymerization of *N*-sulfonylazetidine to obtain block copolymers without any homopolymer impurities in a closed system via the combination of the monomers, *p*TsMAz, *o*TsAzet, and *p*TsAzet, in solution at the time (Scheme 3.37) [95]. Due to the variances in reactivities of the monomers, the selective polymerization of *p*TsMAz was achieved at low temperatures (Up to 50°C) while *o*TsAzet and *p*TsAzet could not polymerize at the same temperature. Once *p*TsMAz was completely consumed, an increase in the temperature occurred to reach 180°C for polymerization of the sulfonylazetidine monomers, *p*TsAzet and *o*TsAzet, affording block copolymers p(*p*TsMAz)-*b*-p(*p*TsAzet-*co*-*o*TsAzet) **106** as presented in Scheme 3.37. This allowed for the preparation of extreme performance block copolymer without necessitating the sequential addition of the monomers via living anionic polymerization.



SCHEME 3.37 Copolymerization of the monomers, *p*TsMAz, *o*TsAzet, and *p*TsAzet, to form copolymers p(*p*TsMAz)-*b*-p(*p*TsAzet-*co*-*o*TsAzet) **106**.



SCHEME 3.38 Synthesis of β-lactam-containing polymer **109**.

3.4.2 Synthesis of β-lactam-containing polymers via metathesis polymerization

β-Lactam-fused cyclobutene **108** prepared via photochemical valence isomerization of pyridone **107** was especially used as a model monomer substrate in metathesis polymerization, enabling access to novel polymer with β-lactam functionality **109** (Scheme 3.38) [96]. The polymerization was achieved using Grubbs third-generation (G3) catalyst in dichloromethane solvent. The termination of the polymerization process occurred with ethyl vinyl ether to afford novel β-lactam-containing polymer **109** with low dispersity ($Đ < 1.30$). it was noted that no sign of ring-opening of the pendant β-lactam along the polymer backbone under this polymerization condition as confirmed by NMR and IR spectroscopies. Additionally, the variation of the ratio of the initial monomer-to-catalyst from 25 to 200 resulted in a linear increase in the

prepared polymer molecular weight from 4.3 to 33.3 kDa, as detected by GPC.

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Chapter 4

N-Sulfonated *N*-azoles: Synthesis, chemistry and biological applications

4.1 Introduction

Natural products that contain functional groups with heteroatom-heteroatom linkages (X−X, where X = N, O, S, and P) are a small yet intriguing group of metabolites. Functional groups containing X−X bonds are found in all major classes of natural products and often impart significant biological activity [1]. Pyrroles are ubiquitous structural motifs in pharmaceutical agents and smart materials [2]. Oxazoles have been elucidated as potential antibacterial, antifungal, anticancer, antiviral, and antioxidation agents, monoamine oxidase inhibitors, *etc*. Indolyl-oxazole derivatives [3−5] are an important class of oxazole-type natural products, and these natural compounds and their derivatives have been demonstrated to exhibit broad biological and pharmaceutical activities. Thiazole is a good pharmacophore nucleus due to its various pharmaceutical applications. Its derivatives have a wide range of biological activities, such as antioxidant, analgesic, and antimicrobial, including antibacterial, antifungal, antimalarial, anticancer, antiallergic, antihypertensive, antiinflammatory, and antipsychotic activities [6]. From the point of view that sulfonated drug metabolites may be pharmacologically more active than their respective parent drugs, the synthesis of *N*-sulfonated heterocycles would be of interest in the field of synthetic new drugs [7,8]. In this chapter, we focus our attention on only one *N*-sulfonated five-membered ring, which includes five important classes named *N*-sulfonated- pyrroles, -isoxazoles, -oxazoles, -isothiazole, and −thiazole derivatives. That chapter also sheds light on their synthesis and their interesting biological aspects.

4.2 *N*-Sulfonated pyrroles

4.2.1 Synthesis

4.2.1.1 N-*Sulfonyl triazole as a α-imino metallocarbene precursor in the synthesis of* N-*sulfonyl pyrroles and their derivatives*

Transition metal-catalyzed denitrogenative transannulation of *N*-sulfonyl triazoles **1** has considerable attention as a new concept for the synthesis of pyrroles since *N*-sulfonyl triazoles can effectively decompose in the presence of a suitable metal catalyst (e.g., rhodium(II)catalysts) [9] as shown in Scheme 4.1. The resulting highly electrophilic α-imino metallocarbenes **3** undergo a variety of synthetically useful transannulations, including transannulation reactions, cyclopropanation, C−H functionalization, X−H (X = heteroatoms) bond insertions, and other reactions based on the inherent metal carbenes properties. In the last few years, several new transannulation reactions and cyclopropanations have been reported, leading to a convenient route to *N*-sulfonyl aza-heterocycles.

4.2.1.2 Transannulation reactions of N-*sulfonyl triazoles with alkynes*

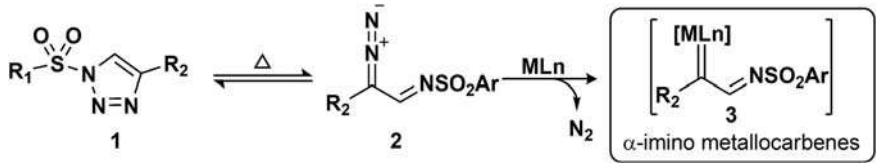
In 2009, Murakami et al. [9] prepared tetrasubstituted pyrroles **5** and **7** *via* transannulation of *N*-sulfonyl triazoles **1** with internal alkynes **4** (Scheme 4.2). It was noted that the combination of a [Ni(cod)$_2$] catalyst with the electron-rich, bulky phosphine ligand P(nBu)Ad$_2$, and AlPh$_3$ as a Lewis acid additive was an efficient condition for, the transannulation of *N*-sulfonyl triazoles with symmetrical internal alkynes whereas the utilize of unsymmetrical alkynes gave a mixture of regioisomers. However, terminal alkynes failed to participate in the reaction due to a facile self-oligomerization side process. Shortly after this, Chattopadhyay et al. then reported the transannulation of *N*-tosyl triazoles **1** with terminal alkynes **6** utilizing a dual rhodium/silver catalyst system to produce 2,4-disubstituted pyrroles **7**. Several numerous C-4 substituted triazoles and electron-rich terminal alkynes participated in the reaction (Scheme 4.2).

In 2013, Shi et al. [10] developed the intramolecular version of this reaction by using alkynyl *N*-tosyltriazoles **8** as a substrate for easy access to a range of 5,5-fused pyrroles **9**, including tetrahydropyrrolo and spiro systems (Scheme 4.3).

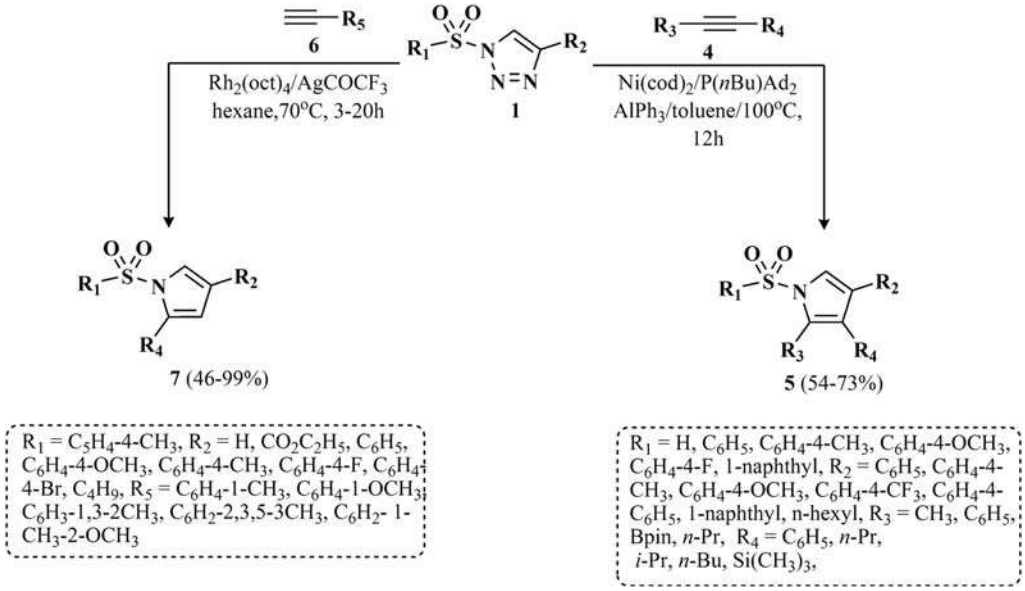
4.2.1.3 Transannulation reactions of N-*sulfonyl triazoles with alkenes*

In 2013 [11], a nickel(0)-catalyzed transannulation reaction of 1-sulfonyl-1,2,3-triazoles **1** with Undeca-1,2-diene

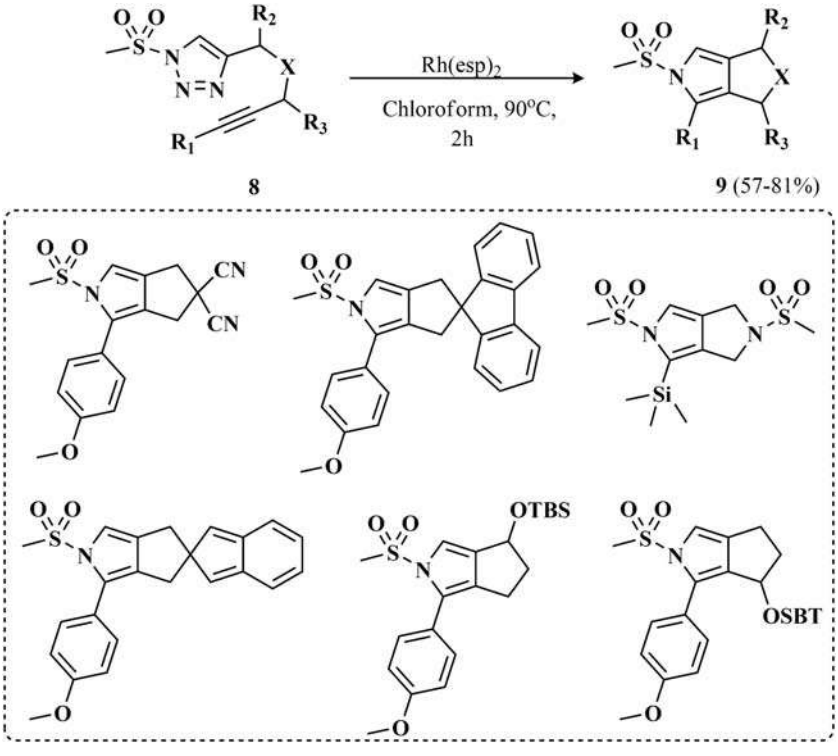
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00002-1



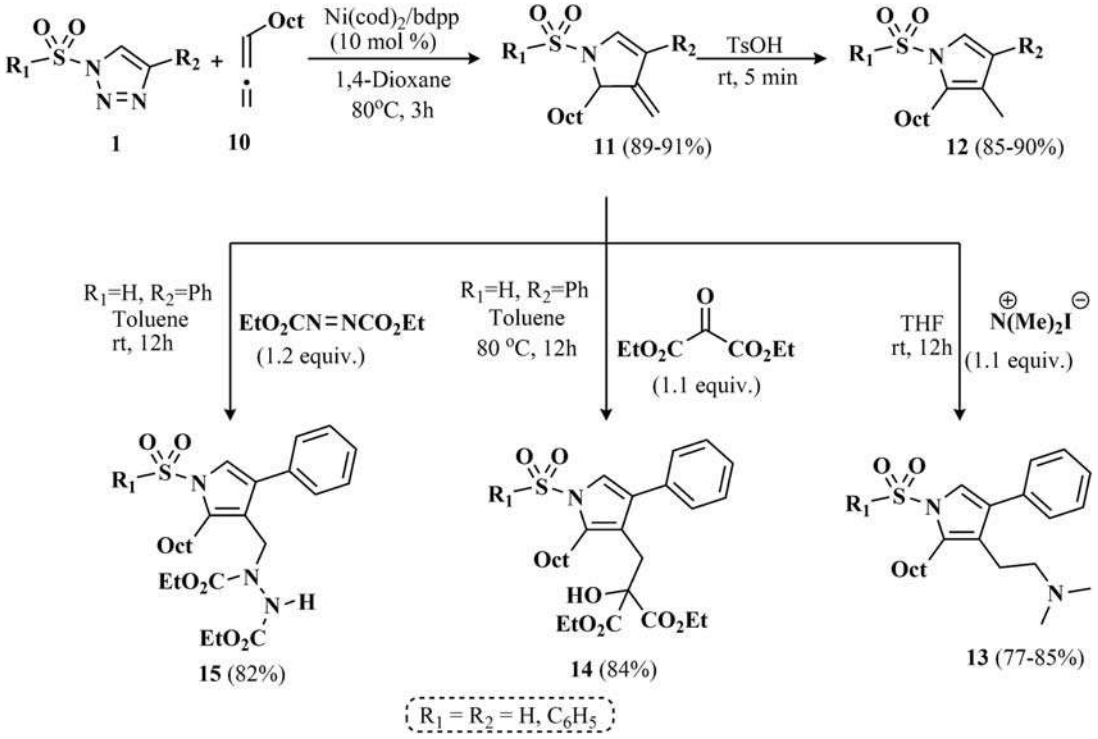
SCHEME 4.1 Decomposition of *N*-sulfonyl triazoles in the presence of rhodium(II)catalysts into *N*-sulfonated pyrroles.



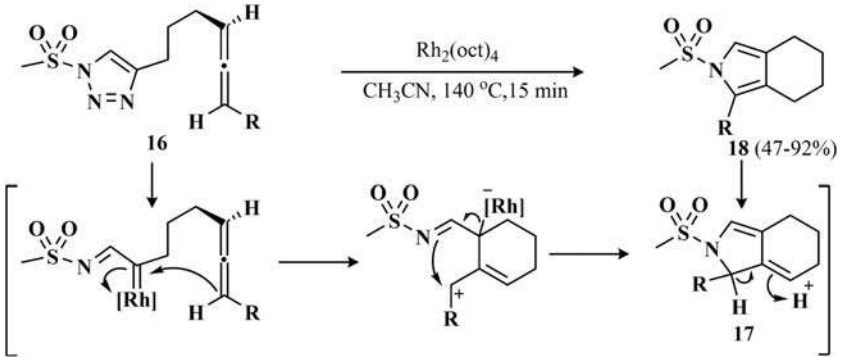
SCHEME 4.2 *N*-Tosyl pyrroles **5** and **7** from *N*-tosyl-1,2,3-triazoles **1**.



SCHEME 4.3 Alkynyl *N*-tosyltriazoles **8** as a substrate for easy access to a range of fused pyrroles **9**.



SCHEME 4.4 Transannulation reactions of *N*-sulfonyl triazoles **1** with alkenes into *N*-sulfonyl pyrroles **13**–**15**.



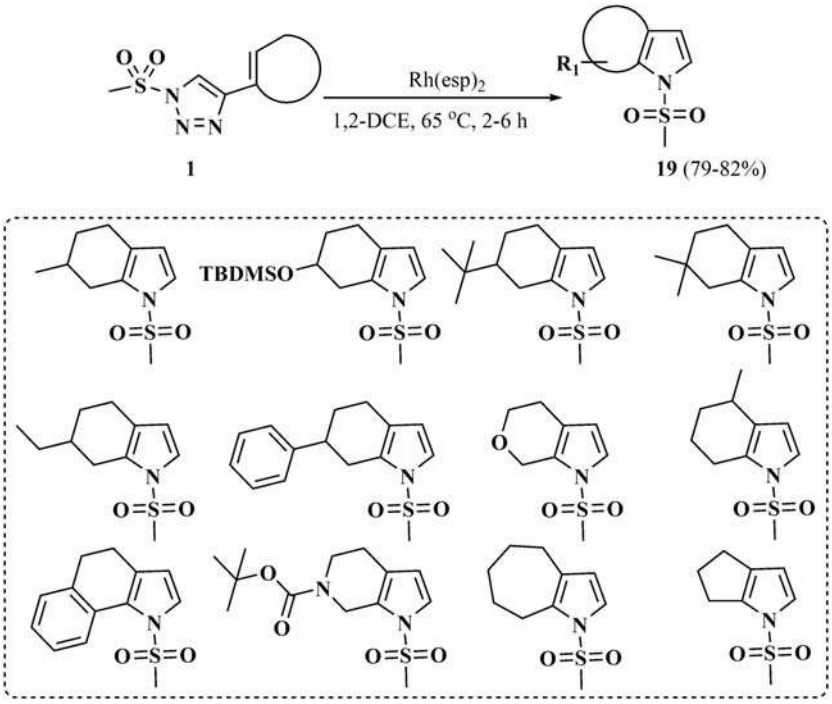
SCHEME 4.5 Rh(II)-catalyzed transannulation reaction of *N*-sulfonyl triazoles bearing allene moieties **14** into *N*-tosyl pyrroles **18**.

10 was reported by Miura el al. [11] to afford isopyrrole intermediates **11**. The latter could be further faithfully converted to 3-methylene-2,3-dihydropyrroles **12** in the acidic condition through double bond transposition or participate in sequent alder-ene reactions with proper enophiles such as Echenmoser's salt, diethyl ketomalonate, and diethyl azodicarboxylate to furnish polysubstituted pyrroles **13**, **14**, and **15**, respectively (Scheme 4.4).

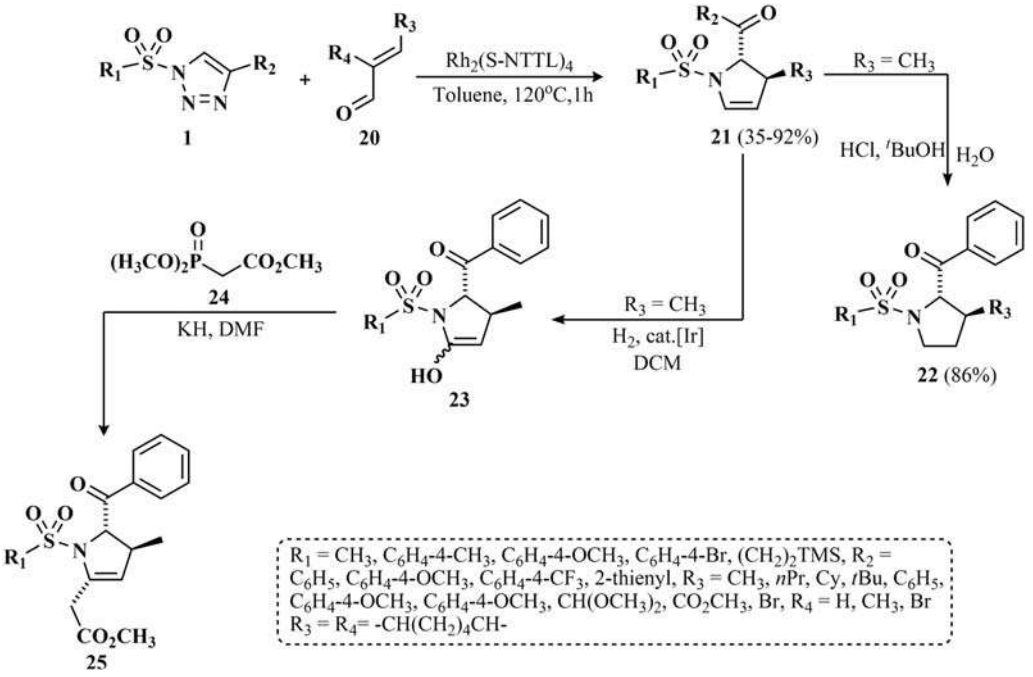
Schultz et al. [12] developed an intramolecular Rh(II)-catalyzed transannulation reaction of *N*-sulfonyl triazoles bearing allene moieties **16** (Scheme 4.5). The pendant allene moieties interacted with electrophilic α-alkyl imino metallocarbenes followed by cyclization to dihydropyrroles **17**. Dihydropyrroles **17** were isomerized to the desired pyrroles **18** (Scheme 4.5).

Alford et al. [13] successfully synthesized 2,3-fused pyrroles **19** from 4-alkenyl-*N*-sulfonyl triazoles **1**. It was found that 4-alkenyl-*N*-sulfonyl triazoles **1** could facilitate participation in a rhodium(II)-catalyzed 4π-electrocyclization with the adjacent alkenyl moieties to form 2,3-fused pyrroles **19** in good yield (Scheme 4.6).

Miura et al. [14] disclosed a stereoselective method for the synthesis of *trans*-2,3-disubstituted 2,3-dihydropyrroles **21** by denitrogenative annulation of *N*-sulfonyl triazoles **1** with various α,β-unsaturated aldehydes **20** in presence of Rh_2(S-NTTL)$_4$ as a catalyst. *Trans*-2,3-disubstituted 2,3-



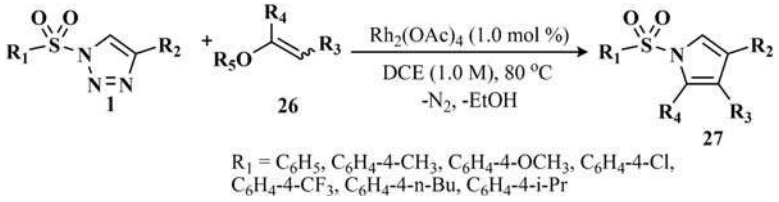
SCHEME 4.6 Synthesis of 2,3-fused pyrroles **19** from 4-alkenyl-*N*-sulfonyl triazoles **1**.



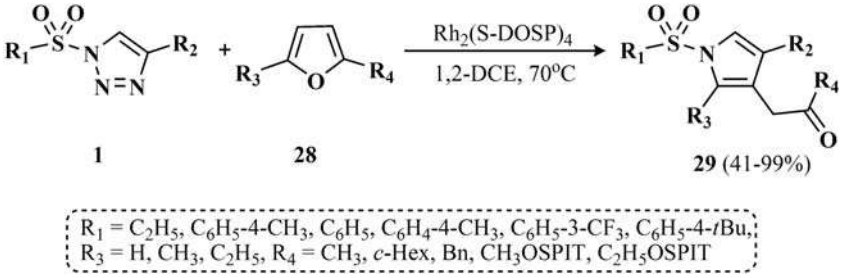
SCHEME 4.7 Synthesis of trisubstituted *N*-tosyl pyrroles **25**.

dihydropyrrole **21** was then hydrogenated using Crabtree's catalyst to produce **22** (Scheme 4.6). On the other hand, 2,3,5-trisubstituted pyrrolidine **23** was diastereoselectively formed from **21** *via* a sequence of hydration under acidic conditions, Horner–Wadsworth–Emmons olefination, and an aza-Michael reaction (Scheme 4.7). Alkylation of **23** using methyl 2-(dimethoxyphosphoryl)acetate (**24**) afforded *N*-tosyl pyrroles **25** (Scheme 4.7).

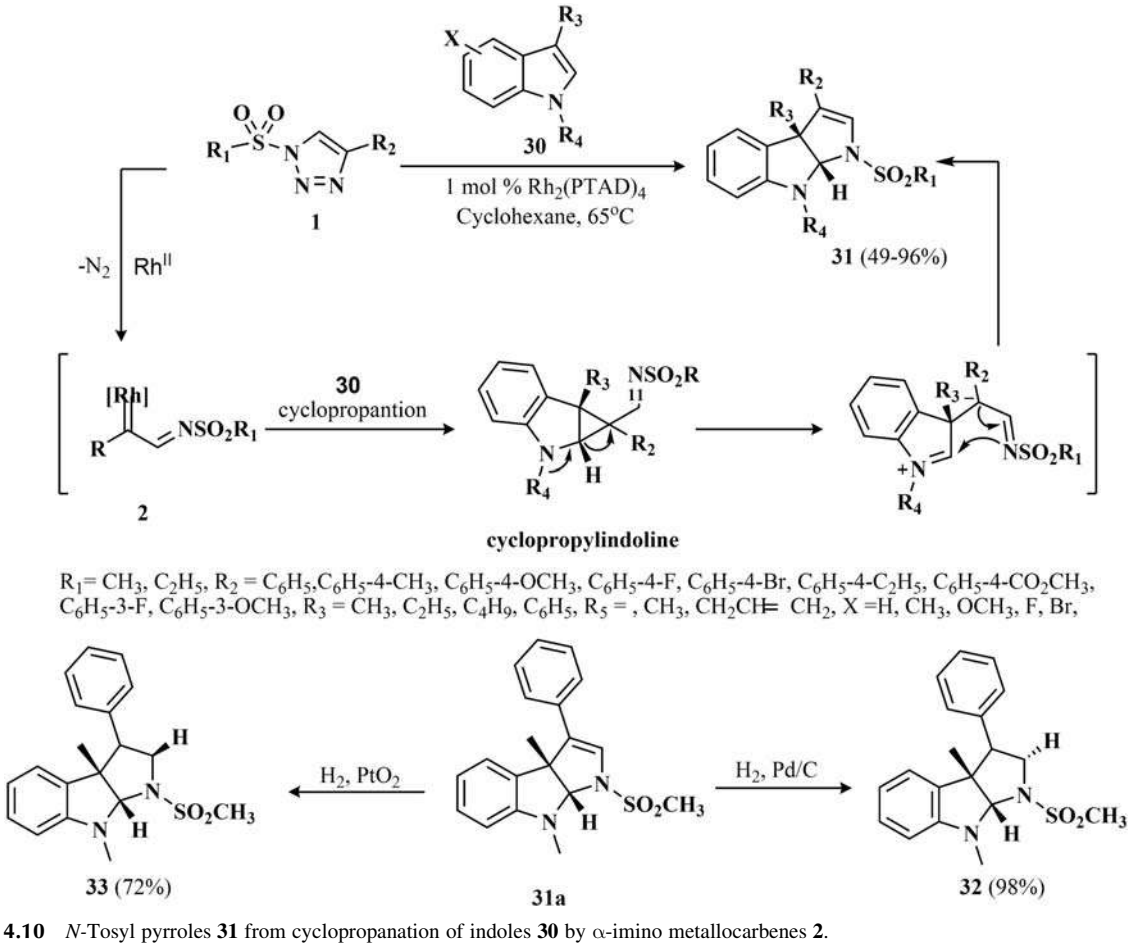
Rhodium (II)-catalyzed denitogentive transannulation of 1-sulfonyl-1,2,3-triazoles **1** with alkenyl alkyl ether **26** [15] was found to be a highly effective method for the preparation of polysubstituted pyrroles **27** (Scheme 4.7).



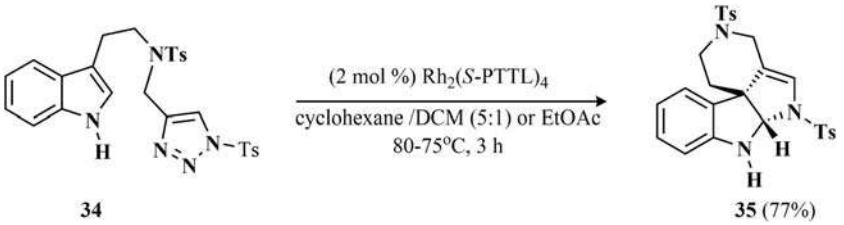
SCHEME 4.8 Rhodium (II)-catalyzed denitogentive transannulation of 1-sulfonyl-1,2,3-triazoles **1** with alkenyl alkyl ether **26** to *N*-tosyl pyrroles **27**.



SCHEME 4.9 Trisubstituted pyrroles **29** from a rhodium(II)-catalyzed transannulation of *N*-sulfonyl triazoles **1** with 2,5-disubstituted furans **28**.

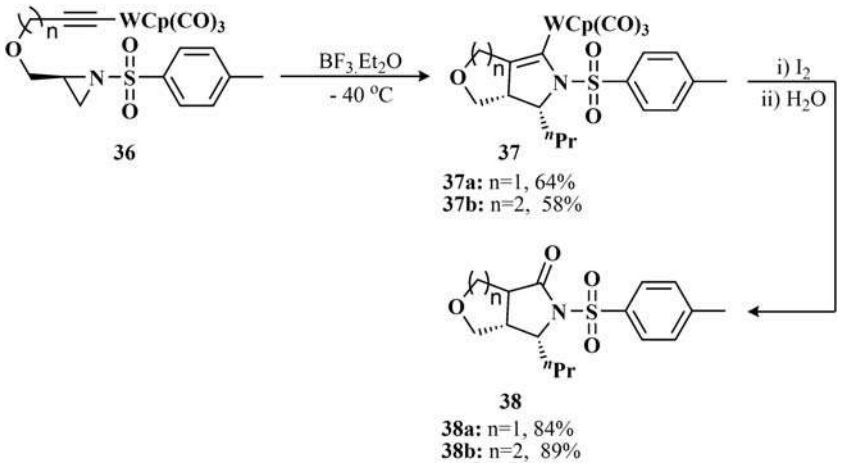


SCHEME 4.10 *N*-Tosyl pyrroles **31** from cyclopropanation of indoles **30** by α-imino metallocarbenes **2**.



34 35 (77%)

SCHEME 4.11 Synthesis of 3,6-ditosyl-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole **35**.

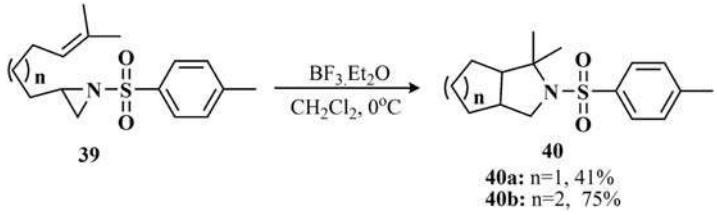


36 37 38

37a: n=1, 64%
37b: n=2, 58%

38a: n=1, 84%
38b: n=2, 89%

SCHEME 4.12 Tethered aziridine in the synthesis of *N*-tosyl pyrroles **38**.



39 40

40a: n=1, 41%
40b: n=2, 75%

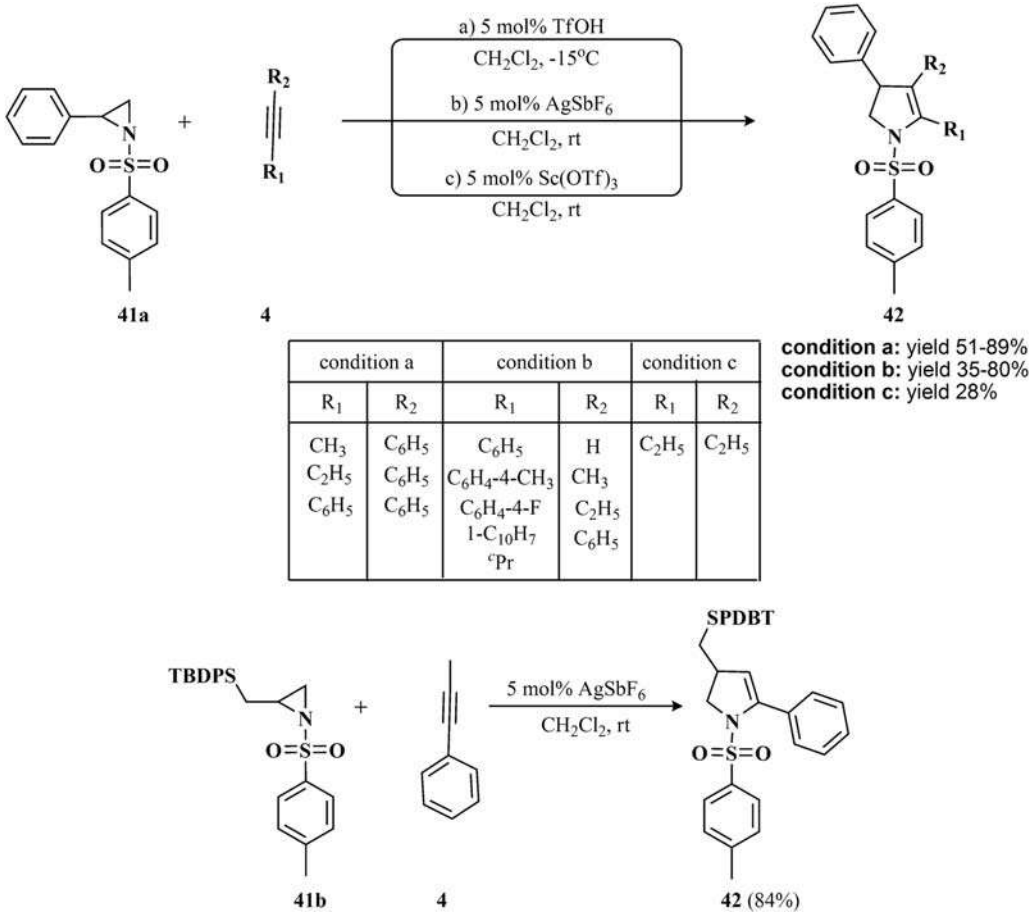
SCHEME 4.13 Intramolecular [3 + 2] cycloaddition of olefinic aziridines **39** to pyrrolidines **40**.

Under optimized conditions, they studied the variation of the sulfonyl group in the N_1 of triazoles and investigated the effect of substituents of alkenyl alkyl ether [15] (Scheme 4.8).

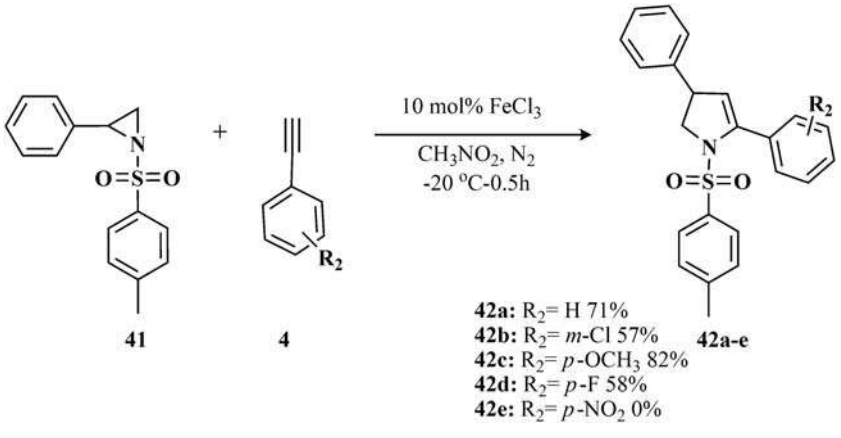
Parr et al. [16] synthesized trisubstituted pyrroles **29** from a rhodium(II)-catalyzed transannulation of *N*-sulfonyl triazoles **1** with 2,5-disubstituted furans **28** (Scheme 4.9). The reaction proceeded through an initial [3 + 2] annulation to form bicyclic hemiaminals, followed by a furan ring opening. This reaction was extended to use a range of furan derivatives but when the furan was unsymmetrically substituted, mixtures of regioisomers were formed (Scheme 4.8).

N-Tosyl pyrroles **31** were obtained *via* cyclopropanation of the double bond of indoles **30** by α-imino metallocarbenes **2** (Scheme 4.10). The reaction involved ring opening of **31** followed by cyclization [17]. Hydrogenation of pyrroloindoline **31a** with Pd/C gave the corresponding saturated **32**, while the use of PtO_2 provided the diastereomeric product **33** (Scheme 4.10).

In continuation of this type of transformation, Zhang et al. [18] developed intramolecular cyclopropanation of indolyltriazoles **34** followed by ring expansion for the construction of uniquely polycyclic pyrroloindolines **35** (Scheme 4.11). To optimize the reaction conditions, it was started to screen different Rh(II) complexes, temperature as well as solvents, using **35** as the model substrate. When the reaction was catalyzed by $Rh_2(Piv)_4$ (2 mol%) in DCM (dichloromethane) for 3 h at different temperatures, the corresponding product **35** was obtained at 21%−30% yields. On changing the solvent to DCE and performing the reaction at 80°C, the yield of **35** was only 8%, and by further increasing the reaction temperature to 110°C, the reaction was very complex with no desired product detected. Other achiral dirhodium tetracarboxylates were also investigated, and all of these catalysts turned out to be of poor efficiency in this reaction. When Rh_2(*S*-PTTL)$_4$ was employed as a catalyst, the yield of **35** increased to 75%. Other chiral



SCHEME 4.14 TfOH and $AgSbF_6$ promoted the reaction between *N*-tosyl aziridine **41** with substituted-acetylene **4**.

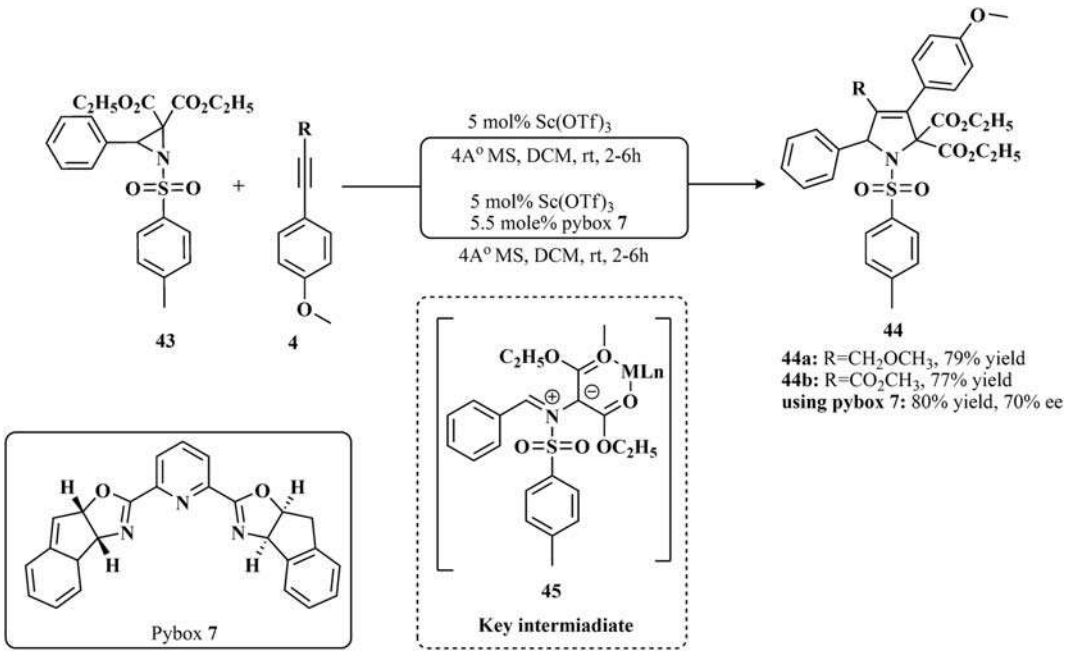


SCHEME 4.15 $FeCl_3$ promotes the reaction between *N*-tosyl aziridine **41** with aryl acetylenes **4**.

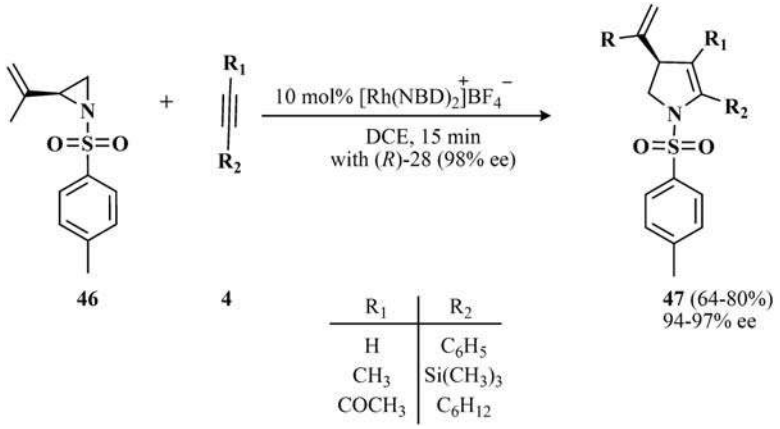
rhodium catalysts such as Rh_2(*S*-NTTL), Rh_2(*S*-DOSP)$_4$, and Rh_2(*S*-TBSP)$_4$ were found less effective than Rh_2(*S*-PTTL)$_4$, affording the desired product **35** in 28% and 71% yields, respectively. Next, solvent effects were tested and it was found that using a mixed solvent of cyclohexane and DCM (5 : 1) would benefit the formation of **35** (77%).

4.2.1.4 N-*sulfonyl aziridines as a precursor for synthesis* N-*sulfonyl pyrroles and their derivatives*

Aziridines undergo a ring cleavage reaction under relatively mild conditions. Therefore, extensive studies were reported to synthesize *N*-sulfonyl pyrroles *via* Lewis or



SCHEME 4.16 $Sc(OTf)_3$ promotes the reaction between *N*-tosyl aziridine **43** with acetylene **4**.



SCHEME 4.17 Rhodium-catalyzed intermolecular cycloaddition of vinyl aziridine **46** with acetylenes **4**

bronsted acid-catalyzed cycloaddition of aziridines with alkynes [19]. Previously and in 2002, a rare method for the stereocontrolled synthesis of *cis*-bicyclic lactams was reported by Madhushaw et al. [20]; initially, an intramolecular [3 + 2] cycloaddition of alkynyl tungsten complexes with its tethered aziridines **36** in presence of BF_3. EtO_2 as Lewis acid afforded bicyclic tungstenenamines **37** stereoselectively in moderate yields. After that, decomplexing these organometallics with I_2 in CH_2Cl_2, followed by hydrolysis, yielded only *cis*-fused bicyclic lactams **38a,b** (Scheme 4.12) [20].

Shortly after that, Bergmeier et al [21] utilized the same catalyst to promote intramolecular [3 + 2] cycloaddition of olefinic aziridines **39** to furnish fused bicyclic pyrrolidines **40** in good yield (Scheme 4.13).

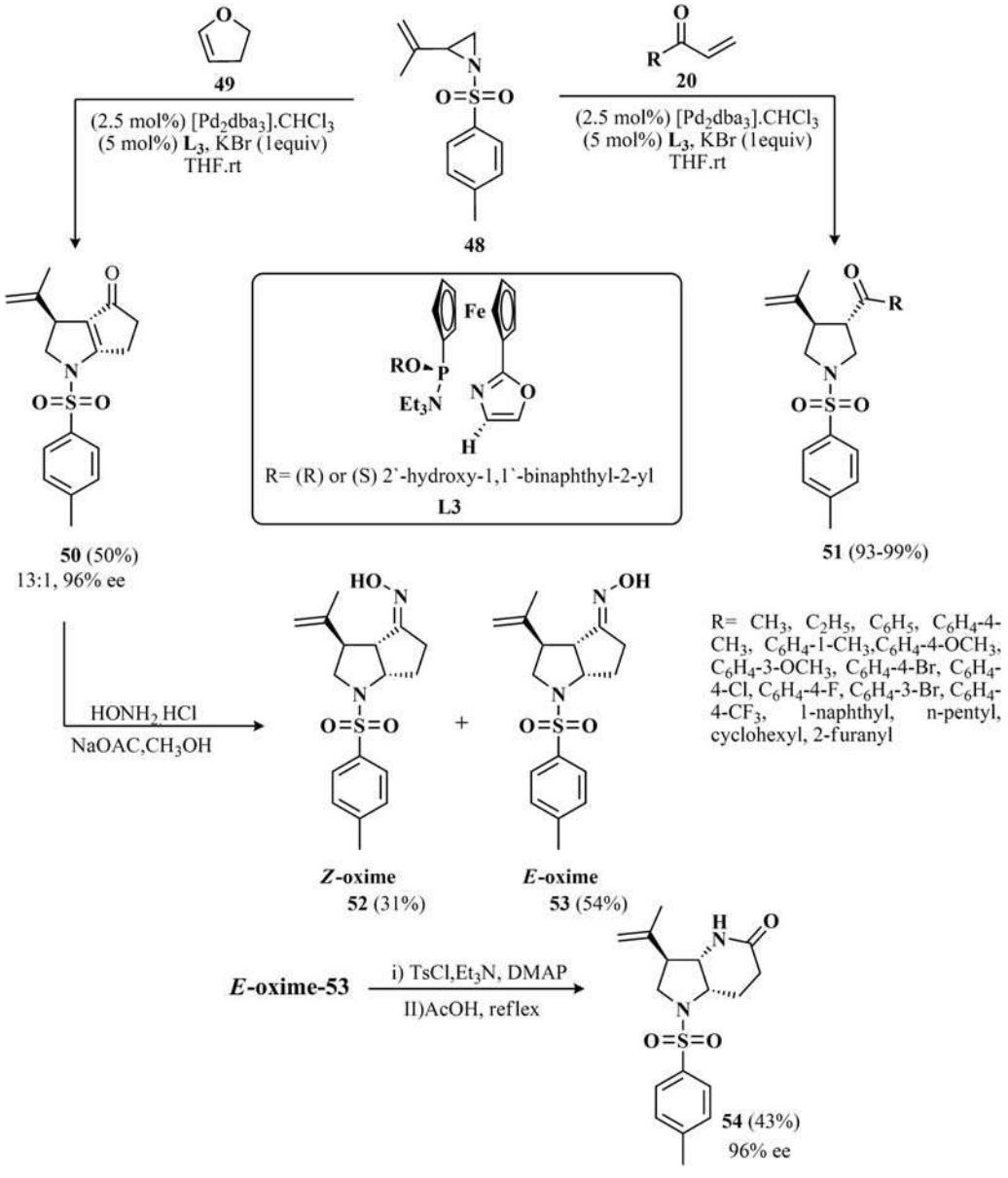
In pioneering works, several authors highlighted the potential of the conjugate addition-cyclization reaction for direct access to pyrollines from alkynes (Scheme 4.14). In 2009, Wender et al. [22] demonstrated the ability of several Lewis acids, TfOH and AgSbF6, which were effectively found to catalyze intermolecular [3 + 2]cycloadditions of arylaziridines **41a** with different alkynes **4** (Scheme 4.14). Both terminal and internal alkynes could participate in cycloaddition reactions to form 2,3-dihydropyrroles **42** as a single regioisomer (Scheme 4.14). The reaction is not limited to arylaziridine **41a**, but also alkylaziridine **41b** bearing a β-silyl group could react with prop-1-yn-1-ylbenzene (**4**) in the presence of $AgSbF_6$ to form **42** in 84% yield (Scheme 4.14).

In the same year, Wang et al. [23] reported that $FeCl_3$-promoted formal [3 + 2]cycloaddition of phenyl aziridines **41a** with terminal aryl alkynes **4** to furnish functionalized 2-pyrrolines **42** in moderate to high yields (Scheme 4.15). Zwitterionic 1,3-dipole, which was generated from $FeCl_3$-catalyzed ring opening of arylazidirine, reacted with terminal aryl to yield 2-pyrrolines **42** (Scheme 4.15).

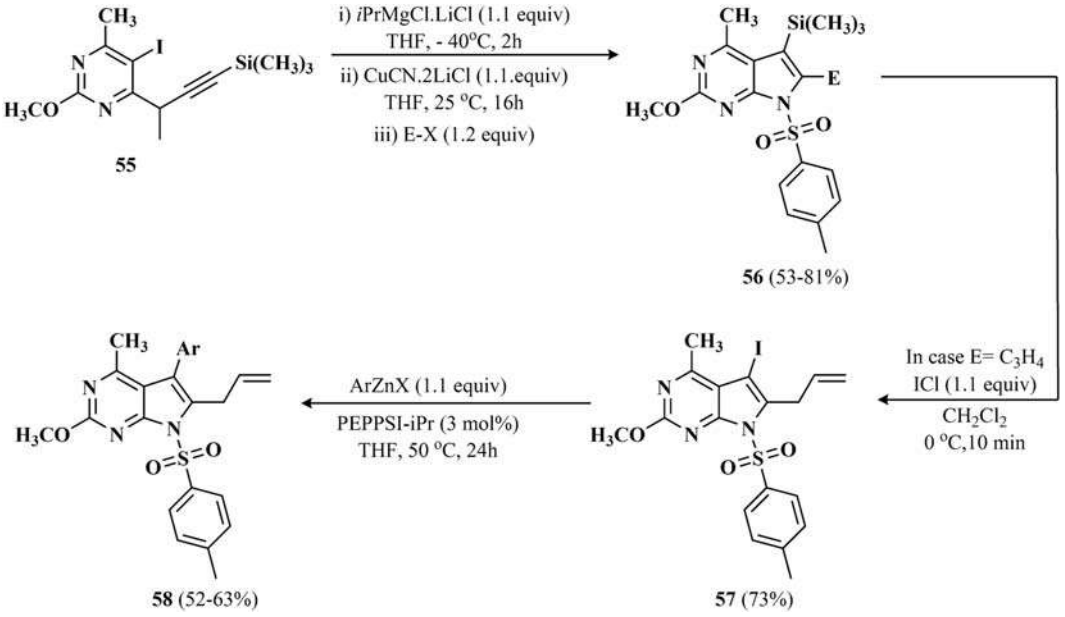
In 2011, Li et al. [19] pioneered the use of $Sc(Otf)_3$ as Lewis acid to catalyze the formal [3 + 2] cycloadditions of *N*-tosyl arylaziridinyl dicarboxylates **43** with alkynes **4** (Scheme 4.16). Azomethine ylides **45**, which was easily generated from *N*-tosylaziridines *via* CC bond heterolysis, reacted with 4-ethynylanisole (**4**) to form regions of a highly substituted 3-pyrroline **44** in good yield as a single regioisomer. Moreover, Treatment of **43** and **4** with 5 mol% Lewis acid $Sc(OTf)_3$ and 5.5 mol% Pybox **7** ligand afforded the desired product **44** in moderate enantioselectivity (Scheme 4.16).

In 2016, the rhodium-catalyzed intermolecular cycloaddition of vinyl aziridines **46** with alkynes 4 emerged as a practical method for the synthesis of pyrrolines **47** in good to excellent yield (Scheme 4.17) [24].

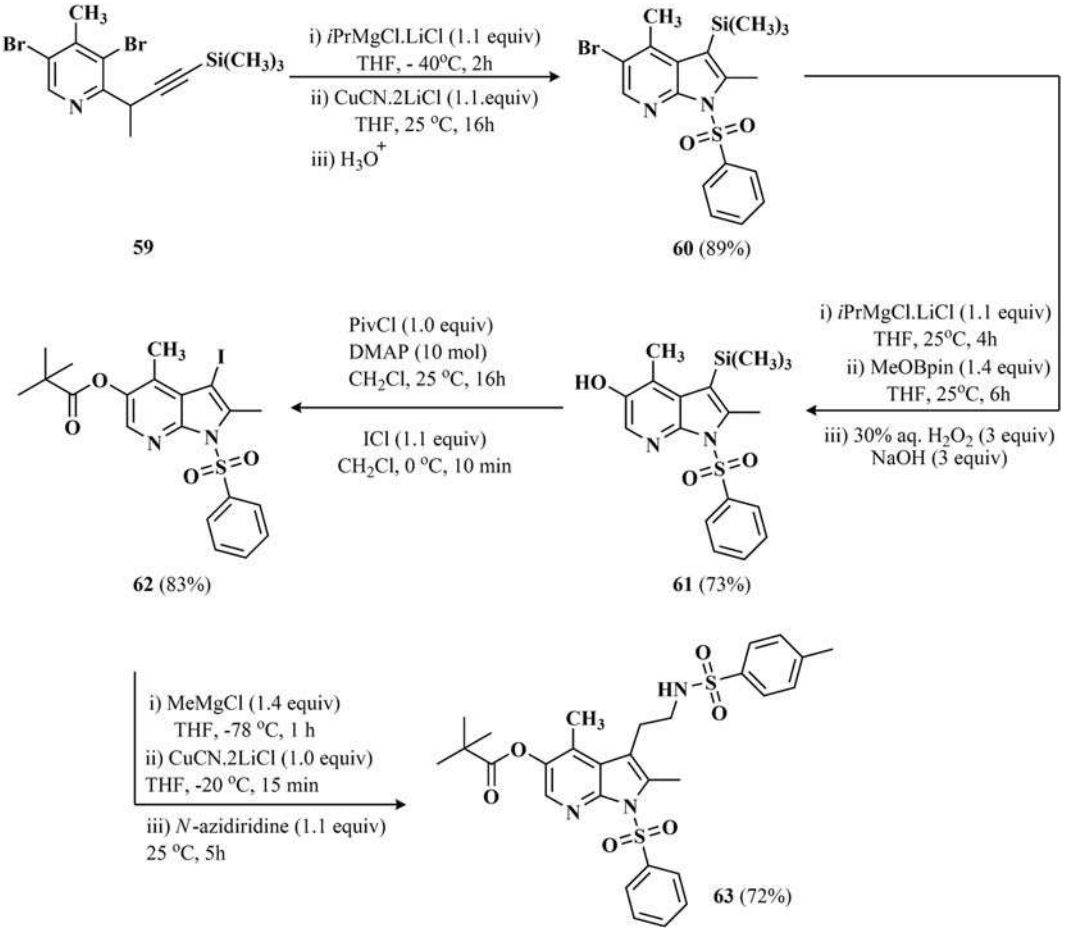
Xu et al. [25] reported a palladium-catalyzed [3 + 2] cycloaddition of the vinyl aziridines **48** and 2,3-dihydrofuran **49** or vinyl ketones **20** to afford *N*-tosyl pyrrolidines **50** and **51**, respectively (Scheme 4.18). The combination of $[Pd_2dba_3] \cdot CHCl_3/PPh_3$ and ligand $\mathbf{L_3}$ in the presence of KBr as an additive afforded an *N*-tosyl pyrrolidine in



SCHEME 4.18 Pd-catalyzed intermolecular cycloaddition of vinyl aziridine **48** with vinyl ketones **20** and **49**.



SCHEME 4.19 Copper-mediated carbomagnesiation procedure for the synthesis of functionalized pyrrolo[2,3-*d*]pyrimidine **58**.



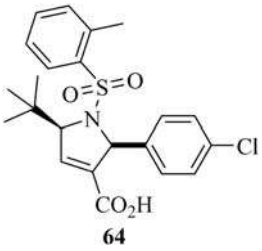
SCHEME 4.20 Convenient synthesis of 7-azaserotonine derivative **63**.

good yield with highly diastereo- and enantioselectivity. Treatment of **50** with hydroxylamine furnished the *Z*-oxime **52** and *E*-oxime **53** in 31 and 54% yield, respectively (Scheme 4.18). Protection of a tosyl group on the *E*-oxime **53** and subsequent Beckmann rearrangement in the presence of acetic acid yielded the bicyclic compound **54** over two steps (Scheme 4.18).

4.2.1.5 N-Sulfonyl ynamides as a precursor in the synthesis of fused N-sulfonyl pyrroles and their derivatives

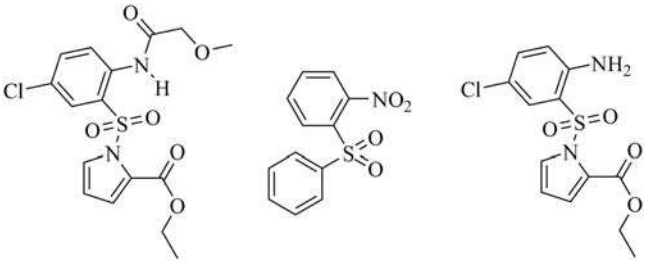
In 2016, Nickel et al. [26] synthesized functionalized pyrrolo[2,3-*d*]pyrimidines **58** *via* copper-mediated carbomagnesiation of *N*-sulfonyl ynamide **55** and sequent reaction with various electrophiles such as allylic halides or acid chlorides (Scheme 4.19). The 3-TMS-substituted pyrrolo [2,3-d]pyrimidine **55** can be readily transformed into the corresponding iodide to **57** by using ICl to the 3-iodocompound **56** and followed by Negishi cross-couplings with various zinc reagents using PEPPSI-IPr as a catalyst to arylated product **58** (Scheme 4.18).

The previous method was expanded to synthesize the 7-azaserotonine derivative **63** [26], which is related to the natural hormone serotonin, from ynamide. The azaindole **60** (Scheme 4.20) was formed *via* a sequence of regioselective Br−Mg exchange with *i*PrMgCl · LiCl, a transmetalation with CuCN · 2LiCl, and an intramolecular carbocupration to **59**. A second Br−Mg exchange followed by a borylation with methoxyboronic acid pinacol ester and subsequent oxidation gave the 5-hydroxyazaindole **61** (Scheme 4.20). Protecting the free phenolic hydroxyl group with pivaloyl chloride and subsequent iodination with ICl gave 3-iodoazaindole **62**. Lastly, the *N*-sulfonyl azaserotine derivative **63** was afforded through I−Mg exchange of **62** with MeMgCl, transmetalation with CuCN.2LiCl, and an opening of the *N*-tosyl aziridine sequence (Scheme 4.20).



64

FIGURE 4.1 Structure of *N*-tosyl prrole **64** as anticancer agent.



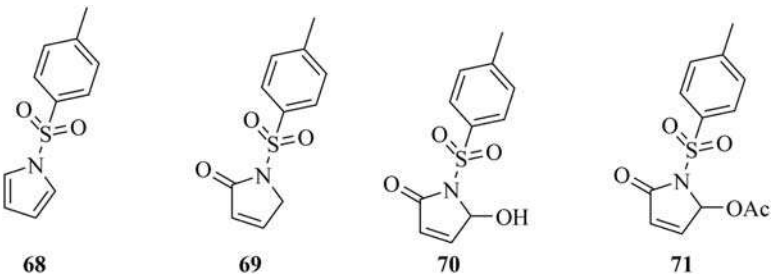
PAS (65) NPPS (66) PPTD (67)

FIGURE 4.2 Structures of *N*-tosyl pyrroles **65**, **66** and **67** as antiviral agents.

4.2.2 Biological activity of *N*-tosyl pyrroles

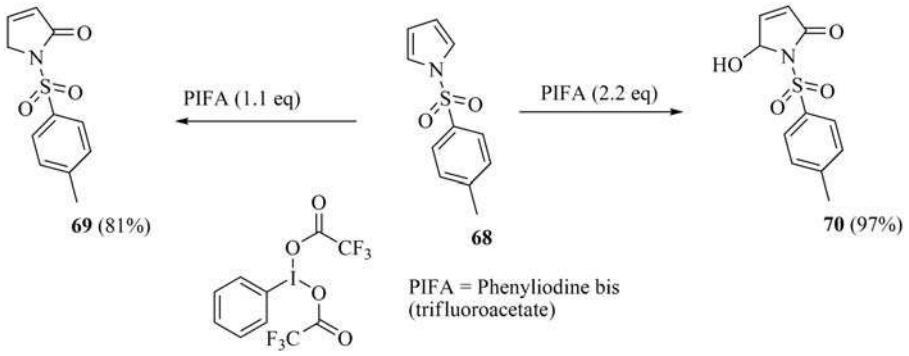
4.2.2.1 Anticancer activity

The development of FTase inhibitors (FTIs) as anticancer agents has been the focus of much academic and industrial research.6 Upon blocking FTase, however, the human oncogenic Ras isoform *K*-RasB is geranylgeranylated by protein GGTase-I.7 Geranylgeranylation functionally substitutes the farnesylation of Ras proteins. This phenomenon suggests that to effectively block Ras processing, the development of selective inhibitors of GGTase-I (GGTIs) is required just as important as the development of FTIs. In the in vitro assay, active compounds were sought for their ability to inhibit the geranylgeranylation of both RhoA and K-Ras4B. Fig. 4.1 displays the compound **64** (Fig. 4.1) that exhibited the highest activities obtained so far. Compound **64** exhibited specific inhibition of GGTase-I; that is, it did not inhibit FTase at concentrations at which they inhibited GGTase-I by more than 90% [27].

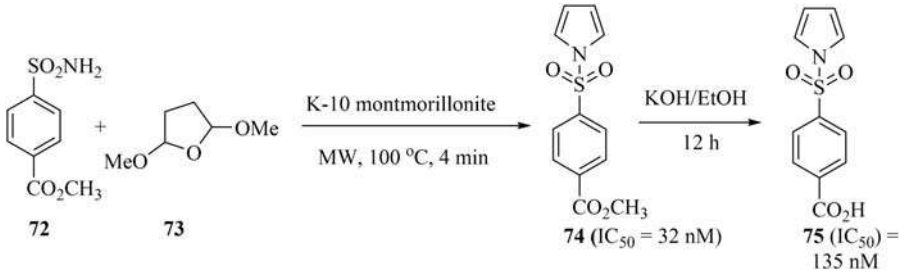


68 69 70 71

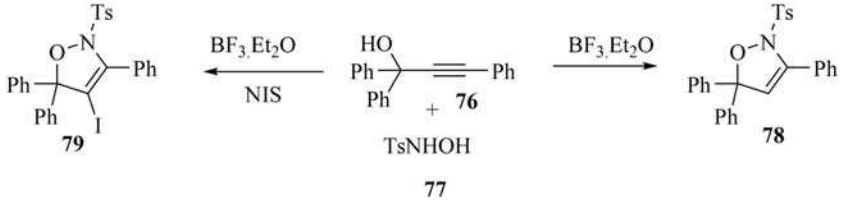
FIGURE 4.3 Structures of compounds **68**−**71** as cytosolic isozyme hCA II.



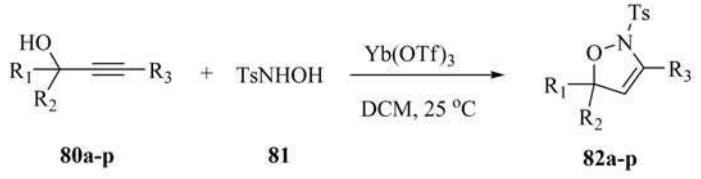
SCHEME 4.21 Synthesis of compounds **69** and **70** with PIFA (phenyliodine bis(trifluoroacetate)).



SCHEME 4.22 Synthesis of compounds **74** and **75**.



SCHEME 4.23 Synthesis of *N*-tosyl isoxazoles **78** and **79**.



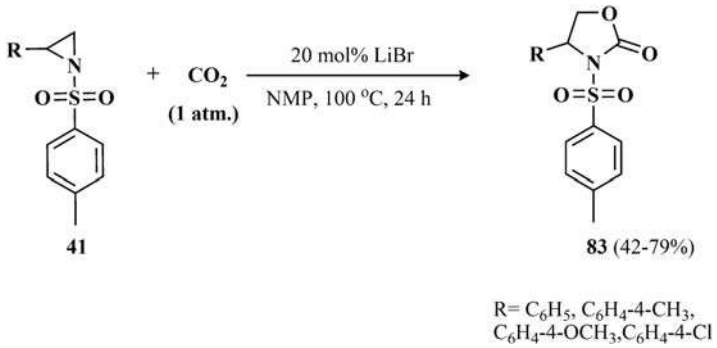
Reaction conditions: Compound **77** (0.6 mmol), **78** (0.5 mmol), $Yb(OTf)_3$ (0.05 mmol), solvent (5 mL).

SCHEME 4.24 $Yb(OTf)_3$ catalyzed the synthesis of *N*-tosyl isoxazole **82a-p**.

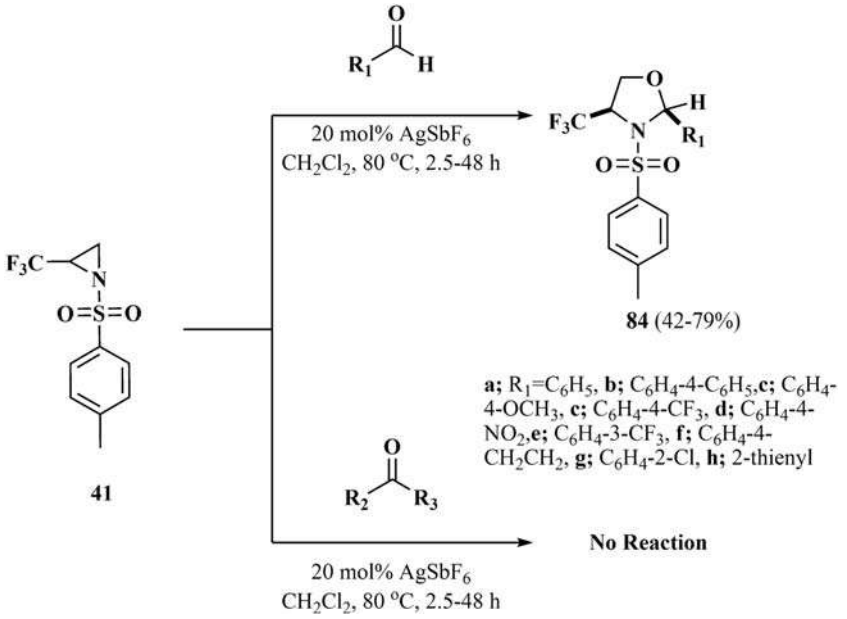
4.2.2.2 Antiviral activity

Compounds **65** and **67** showed high antiviral activity (Fig. 4.2) when tested in MT-4 cells infected with HIV-1 [28]. Pyrrol aryl sulfone (PAS, **65**) and PBTDs **67** were found as the NNRTI class discovered during studies on the known antiretroviral RT inhibitors related to nitrophenyl phenyl sulfone (NPPS, **66**) (Fig. 4.2). SAR studies on PAS derivatives led to looking into the structural requirements for high antiviral potency, namely the presence of a *p*-chloroaniline moiety and an ethoxycarbonyl group at position 2 of the pyrrole nucleus.

All compounds **68**–**71** had better inhibitory activity against the rapid cytosolic isozyme hCA II Kinetic investigation indicated that all the investigated compounds act



SCHEME 4.25 Synthesis of *N*-tosyl oxazoles **83**.



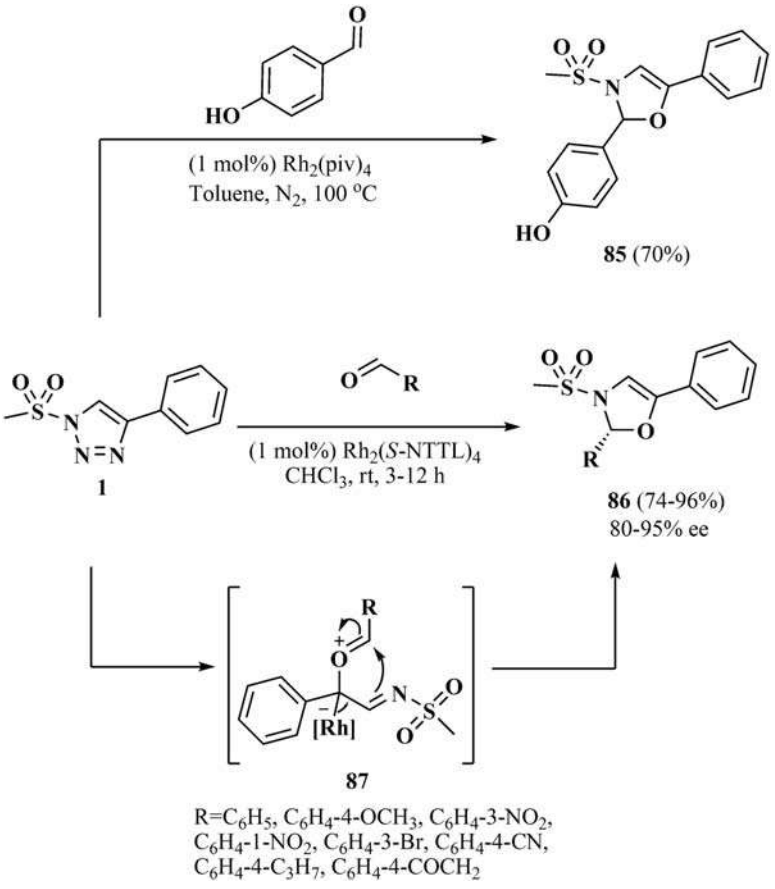
SCHEME 4.26 Synthesis of *N*-tosyl oxazoles **84a-h**.

as non-competitive inhibitors with 4-NPA as substrate, that is they bind in different regions of the active site cavity as compared to the substrate. However, the binding site of 4-NPA itself is unknown, but it is presumed to be in the same region as that of CO_2, the physiological substrate of this enzyme [29] (Fig. 4.3).

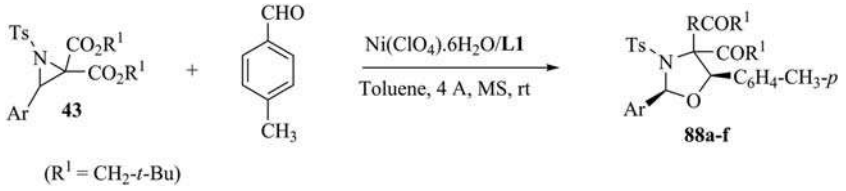
Compounds **69** and **70** were synthesized [30] taking 1 equiv of 1-tosyl-pyrrole **68**, which was then subjected to 1.15 and 2.2 equiv of PIFA. Using 1 equiv of 1-tosyl-pyrrole and 1.15 equiv of PIFA, 1-tosyl-1*H*-pyrrol-2(5*H*)-one **69** was obtained with 81% yield and 5-hydroxy-1-tosyl-1*H*-pyrrol-2(5*H*)-one **70** with 19% yield (Scheme 4.21). When 1-tosyl-pyrrole was reacted with 2.2 equiv of PIFA, 5-hydroxy-1-tosyl-1*H*-pyrrol-2(5*H*)-one **70** was obtained at a 97% yield (Scheme 4.21). Both reactions were initiated at 5 °C and stirred for 10 h at room temperature [30].

Similar results of compounds **68**−**70** were obtained on the inhibitory effects on the esterase activity of hCAs I and II. The acetazolamide was used as a reference compound in experiments for comparison reasons. The inhibition of hCAs I and II with tosyl pyrroles **68**−**70**, by an esterase assay, with 4-nitrophenyl acetate (4-NPA) as substrate:

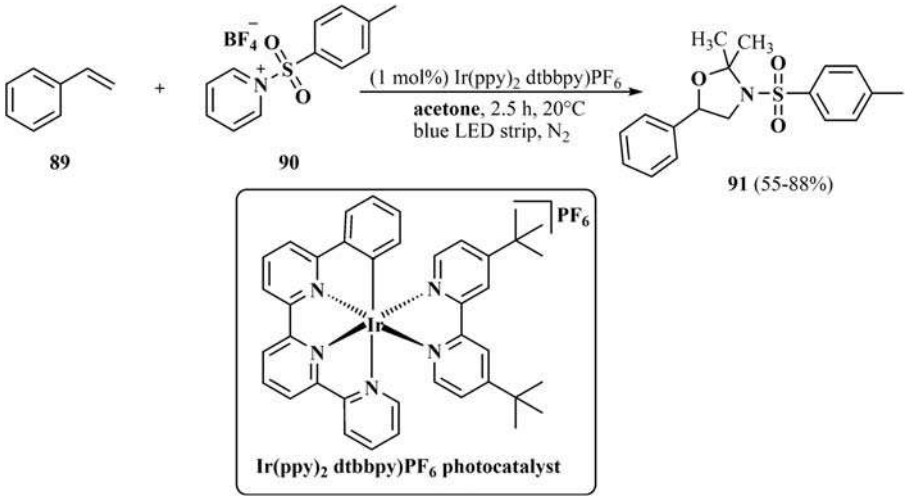
1. Against the slow cytosolic isozyme hCA, I compound **68** behaves as a moderate inhibitor, with Ki values in the range of 37.3−42.4 mM. The second group of derivatives, including compound **70**, showed better inhibitory activity as compared to the previously mentioned tosyl pyrroles, with Ki values of 14.6−25.7 mM. Thus, the nature of the groups strongly influences hCA I inhibitory activity.
2. A better inhibitory activity has been observed with compound **70** investigated for the inhibition of the



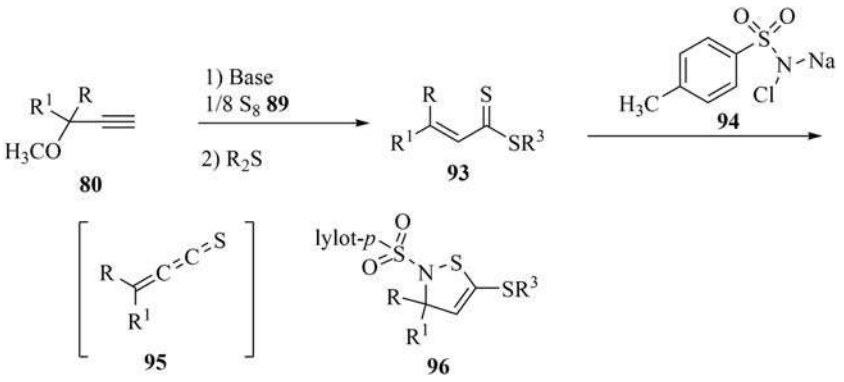
SCHEME 4.27 Synthesis of *N*-tosyl oxazoles **85** and **86** using Rh^I



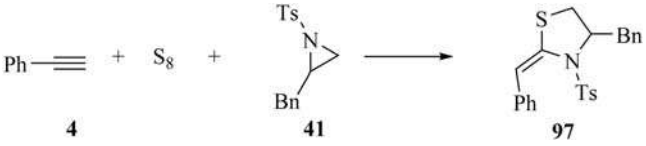
SCHEME 4.28 Synthesis of *N*-tosyl oxazoles **88** using $Ni(ClO_4)0.6H_2O$.



SCHEME 4.29 $Ir(ppy)_2(dtbbpy)PF_6$ catalyzes the formation of *N*-tosyl oxazole **91**.



SCHEME 4.30 A convenient method describes the formation of *N*-tosyl-1,2-thiazoles **96**.



SCHEME 4.31 *N*-Tosyl thiazoles **97** formed from the reaction of phenylacetylene (**4**), elemental sulfur, and aziridine **41**.

rapid cytosolic isozyme hCA II. Thus, the two derivatives, which were compounds **68** and 69, showed weak hCA II inhibitory activity with Ki-s in the range of 23.1−37.5 mM [30].

1-(4-Carbomethoxyphenylsulfonyl)-1*H*-pyrrole **75** was prepared from 4-carbomethoxy-phenylsulfonamide **72** (1 mmol) and 2,5-dimethoxytetrahydrofuran **73** (1.5 mmol) were mixed in Et_2O (3 mL). K-10 montmorillonite (500 mg) was then added. After stirring for 5 min, the solvent was evaporated to produce a dry mixture of reactants adsorbed at the catalyst surface. The dry mixture was transferred to a reaction tube and irradiated in a focused microwave reactor at 100°C. The reaction temperature was determined and maintained by a built-in infrared temperature detector−controller. After satisfactory conversion, Et_2O (10 mL) was added to the cold mixture, and the product was separated from the catalyst by filtration. The product was isolated as colorless crystals and purified by flash chromatography to give 198 mg **74** [31]. The resulting **74** was then subjected to a mixture of KOH/EtOH and then hydrolysis to give **75** (Scheme 4.22) [31].

Compounds **74** and **75** were tested as anti-leukemia. The respective IC_{50} values were found to be 32 and 135 nm. It appears that the computer-based systematic inhibitor design resulted in compounds that are more potent than AMP by approximately two orders of magnitude. Our data indicate that the *N*-sulfonylpyrroles **74** and **75** gave significantly lower IC_{50} values. A docking study showed that compound **72** exhibits enhanced hydrophobic interactions with Val 160, Leu30, and Leu34 of FBPase; its sulfate group oxygen atoms interact with Arg 140 and Tyr113, as well as the backbone of Thr 31. The most striking difference from AMP was the number of new interactions established in the hydrophobic interior of the AMP binding pocket [31].

4.3 Synthesis of *N*-tosyl isoxazoles and their derivatives

4.3.1 Synthesis

Previously it was reported that $BF_3.Et_2O$ catalyzed reaction of propargylic alcohol **76** and *N*-tosyl hydroxylamine **77** was examined (Scheme 4.23). As was expected, 2,5-dihydroisoxazole **78** was isolated at 54% yield when **76** was treated with **77** in the presence of $BF_3.Et_2O$ in dichloromethane (DCM) at room temperature for a short time [32]. It was found that 4-iodo-2,5-dihydroisoxazole **79** was obtained during the reaction of **76** and **77** in a mixture of $BF_3.Et_2O$ and NIS (Scheme 4.22).

With the optimized reaction conditions between **80** and **81** [32], the substrate diversity was subsequently tested for this transformation. Fortunately, $Yb(OTf)_3$ in DCM at 25°C, was found as the best condition for aryl and alkyl substituents of **80** (Scheme 4.24). The triaryl substituted propargyl alcohols and the diaryl substituted propargyl alcohol could undergo this cascade process to afford the corresponding 2,5-dihydroisoxazoles in moderate to excellent yields (30%−95%). The reaction proceeded smoothly with various aryl groups on the propargyl alcohols. When 2,4-diphenylbut-3-yn-2-ol was used as the substrate, no desired product was obtained as it was consumed completely. In cases of various substituents on R_3, groups with the nature of the electron-withdrawing increased the yields in comparison with the electron-donating groups, while the sterically hindered 3-(2-bromophenyl)-1,1-diphenylprop-2-yn-1-ol gave relatively lower yield. Aliphatic alkyne could also afford the desired product at 46% yield, while terminal alkyne failed to afford the desired product.

4.4 Synthesis of *N*-tosyl oxazoles and their derivatives

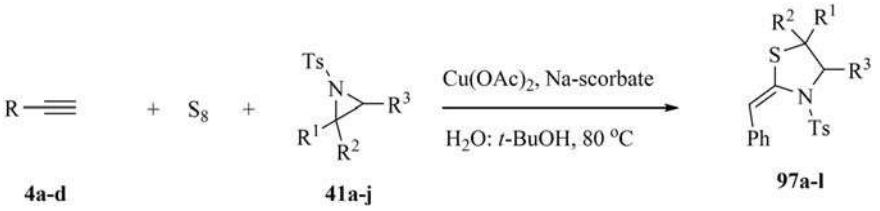
4.4.1 Synthesis

In 2004, Sudo et al. [33] utilized lithium bromide as a catalyst for promoting the insertion of carbon dioxide into aziridine **41** under high pressure. Under this condition, *N*-tosyl aziridine **41** was found to be a useful substrate for cycloaddition of carbon dioxide to yield *N*-tosyl-1,3-oxazolidine-2-ones **83** (Scheme 4.25). It was noted that electron-donating substituents at the 2-position of *N*-tosylaziridine tended to accelerate the reaction [33].

In 2011, Maeda et al. [34] successfully prepared *N*-tosyl-1,3-oxazolidines **84** from *N*-tosyl aziridine **41** under mild conditions (Scheme 4.26). 2-Trifluoromethyl-*N*-tosylaziridine could react with various aldehydes in the presence of a catalytic amount of $AgSbF_6$ to furnish *cis*-4-trifluoromethyl-2-substituted-*N*-tosyl-1,3-oxazolidines **84** with excellent regio- and stereoselectivity. In contrast to aldehydes, no reactions between **41** and ketones take place under the same reaction conditions (Scheme 4.26). Different reaction conditions were carried out using benzaldehyde ($R = C_6H_5$) and **41** as starting substances.

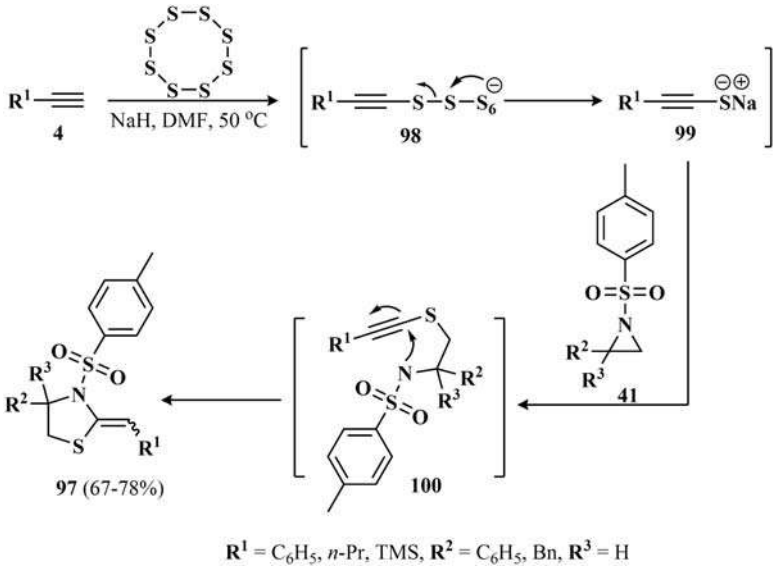
Zibinsky et al. [35] used $[Rh_2(piv)_4]$ for the synthesis of *N*-tosyl-1,3-oxazolines **85** and **86** (Scheme 4.27). *N*-Tosyl-1,3-oxazoline **85** was formed *via* $Rh_2(piv)_4$-catalyzed reaction of 4-hydroxy-benzaldehyde with *N*-mesyl 1,2,3-triazoles **1** under a nitrogen atmosphere. Another derivative of Rh(II) $Rh_2(S\text{-}NTTL)_4$, was applied to numerous aldehyde derivatives which were reacted with **1** to give **86** (Scheme 4.27). This reaction proceeds by intramolecular cyclization of ylide intermediates **87**, which is generated from Rh(II)-stabilized reaction of imino metallocarbenes with an aldehyde to afford 3-sulfonyl-4-oxazolines **86** at excellent yields with high levels of enantioselectivity. Investigation of the reaction conditions revealed that lowering the temperature from 100°C to ambient resulted in longer reaction times without significantly affecting the yield of oxazoline **86**.

Several chiral catalysts were also examined at various temperatures and in combination with various sulfonyl

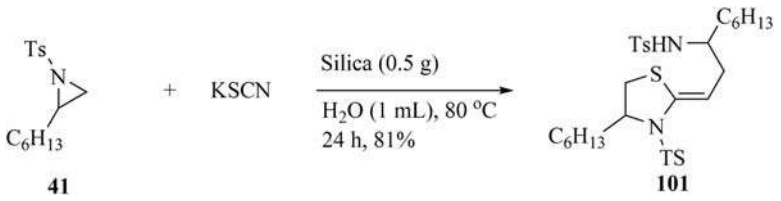


4a-d 41a-j 97a-l

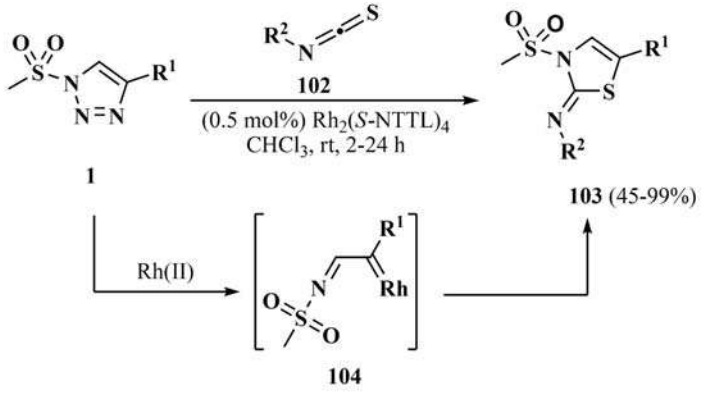
SCHEME 4.32 General reactions of acetylenes **4a-d** with sulfur and **41a-j** in preparation of *N*-tosyl thiazoles **97a-l**



SCHEME 4.33 NaH as a strong base in the reaction of **4**, sulfur, and **41**.



SCHEME 4.34 Synthesis of *N*-tosyl thiazolidine **101**.



R^1 = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-2-CH_3, 1-thienyl, -$(CH_2)_4$CH CH-, 1-naphtyl-4`-OCH_3, **R**^{2} = C_6H_5, COC_6H_5, C_6H_4-4-Cl, C_6H_4-4-Br, COC_6H_4-4-Cl, C_6H_4-4-OCH_3, CH_2CH_2Cl, C_6H_3-3,5-$2CF_3$, C_6H_4-2-Br,

SCHEME 4.35 Rh(II)- catalyzed the reaction of *N*-tosyl triazoles **1** with heterocumulenes **102**.

groups at N^1 of triazole **1**, resulting in the enantioselective version of the reaction. Optimal enantioselectivity was obtained in reactions of 1-mesyl-1,2,3-triazoles **1** performed at ambient temperature with the [Rh_2{(*S*)-nttl}$_4$] catalyst (1 mol%). Among the solvents tested, chloroform provided oxazoline products with consistently high yield and enantioselectivity.

Aziridine **41** and p-methylbenzaldehyde reacted smoothly in toluene to furnish the desired cycloadduct **88** (Scheme 4.28) at 83% yield with a promising 66% ee under the catalysis of $Ni(ClO_4)_2 \cdot 6H_2O$/Bn-Box (**L1**) [36]. The use of *i*-Pr-Box (**L2**), Ph-Box (**L3**), or *t*-Bu-Box (**L4**) as the chiral ligand resulted in lower ee, and **L4** caused a heavy decrease in yield due to the bulky steric effect. The indane-Pybox **L5** led to a slow transformation and only 46% yield with 21% ee was obtained. These results indicated that substituents on the Box ligand affected the reactivity and enantioselectivity significantly.

As shown in Scheme 4.29, a mixture of styrene **89**, acetone, and *N*-Ts-protected 1-aminopyridinium **90** was readily converted to the corresponding *N*-tosyl oxazoles **91** using Ir photo-catalysts [37]. $Ir(ppy)_2(dtbbpy)PF_6$ was found as the best photo-catalyst compared with the other Ir catalysts. The advantage of the previous transformation was that it helped to generalize the synthesis of various *N*-tosyl oxazoles.

4.5 Synthesis of *N*-tosyl-1,2-thiazole and its derivatives

4.5.1 Synthesis

Substituted propargyl methyl ether **80** reacted in the presence of a base (i.e. BuLi or *t*-BuOK) with elemental sulfur **92** and chloramine-T **94** to give *N*-tosyl-1,2-thiazoles **96** (Scheme 4.30). These reactions were assumed to proceed through in situ generations of some heterocumulene-like intermediates **95** related to propadienethiones **93** and the subsequent nucleophilic addition by chloramine-T **94**. Accordingly, it was described in the synthesis of 2-alkenecarbodithioate esters **93** through a plausible pathway involving the in situ generations of intermediates **95**. In conclusion, the procedure describes a successful conversion of compounds **93** into isothiazoles **96** *via* [4 + 1] type oxidative ring closure process using sodium chloro(tosyl)amide **94** [38].

4.6 Synthesis of *N*-tosyl thiazole and its derivatives

4.6.1 Synthesis

In 2019, Khalaj et al. [39] reported that the formation of *N*-tosyl thiazoles **97** was performed by the reaction

employing phenylacetylene **4**, elemental sulfur, and aziridine **41** using CuI and $(i\text{-Pr})_2$EtN in MeCN (Scheme 4.31). After 22 h of stirring at 80°C, the desired product **97** was obtained at a 14% yield. Other copper salts also promote the reaction. However, the yields were comparatively lower. It was delightedly found that 10 mol% loading of *N*-heterocyclic carbene copper (I) catalyst (IPr) CuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazole-2-ylidene) was turned out to effectively suppress by-product formation. The result was dramatically improved when the reaction was performed in the presence of $CuSO_4$ pentahydrate and sodium ascorbate. However, trace amounts of side-product of acetylide and aziridine were also detected. A Cu(II)/ascorbate screen showed that Cu $(OAc)_2$ gave superior yields in comparison to other copper (II) salts. These results demonstrated that the insertion of elemental sulfur into copper-acetylide species proceeds significantly faster than that of aziridine using $Cu(OAc)_2$.

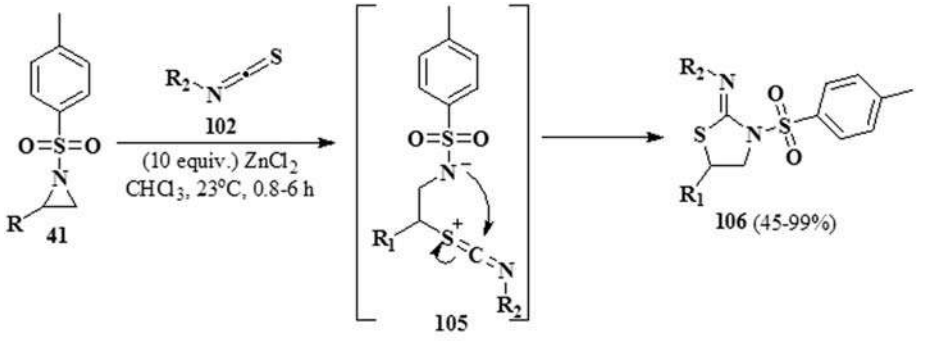
Utilizing the previous study, the authors also reported that a mixture of $Cu(OAc)_2$, Na-ascorbate, and H_2O:*t*-BuOH could be applied as a general reaction for preparing *N*-tosyl thiazoles **97** (Scheme 4.32). Therefore, the reaction of various acetylenes **4a-d** with elemental sulfur and aziridines **41a-j** in the presence of a mixture of Cu $(OAc)_2$, Na-ascorbate, and H_2O:*t*-BuOH formed compounds **97a-l** [39] (Scheme 4.32).

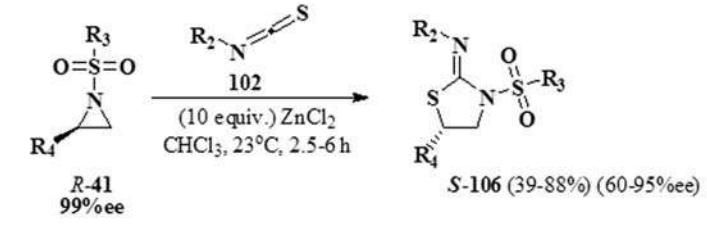
Previously, NaH was used as a base in a one-pot reaction involving *N*-tosyl aziridine **41**, terminal alkynes **4**, and elemental sulfur. Initially, the terminal alkyne **4** reacted with elemental sulfur in the presence of NaH/DMF to afford anionic adduct **98** and subsequent loss of S_7 to form the ionic intermediate **99**. Finally, this intermediate reacted with *N*-tosyl aziridine 41, furnishing 97, which easily gave intermediate **100** and then cyclized to form the desired thiazolidine **97** [40] (Scheme 4.33).

Minakata et al. [41] devised an environmentally benign route for the synthesis of iminothiazolidines **101** *via* ring opening followed by cyclization of 2-substituted-*N*-tosylaziridine **41** with a water-soluble nucleophile potassium thiocyanate in the silica-water medium. (Scheme 4.34) [41].

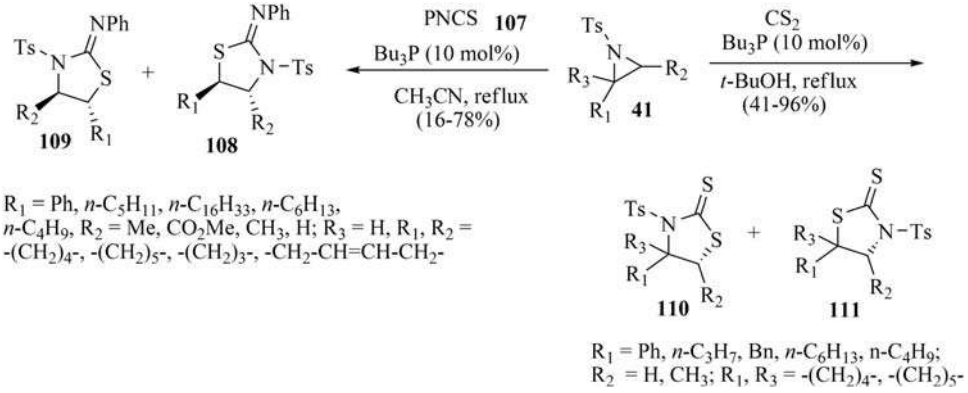
In 2013, Chuprakov et al. [42] conducted Rh(II)-catalyzed[3 + 2] cycloaddition reaction of highly reactive metal-stabilized azavinyl carbenes, which conveniently generated from readily available 1-mesyl-1,2,3-triazoles **1**, with heterocumulenes **102**, causing an apparent swap of 1,2,3-triazole core for thiazole **103** *via* the proposed formation of intermediate **101** (Scheme 4.35).

To the extent of [3 + 2] cycloaddition strategy, Lewis acid (i.e. $ZnCl_2$) mediated [3 + 2] cycloaddition of *N*-sulfonylaziridines **41** with heterocumulenes **102** *via* formation of Zwitterionic 1,3-dipole intermediate **105** was described [43]

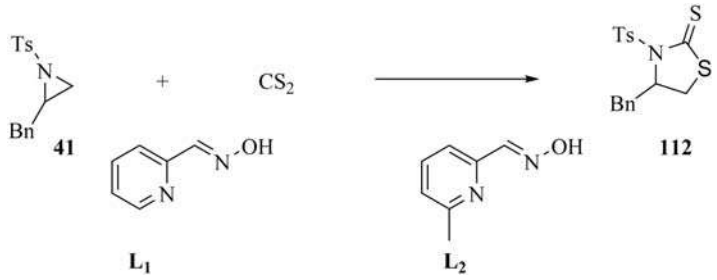




SCHEME 4.36 Lewis acid-catalyzed the reaction of *N*-tosyl aziridines **41** with heterocumulenes **102**.



SCHEME 4.37 Synthesis of *N*-tosyl thiazolidines **110** and **111**



SCHEME 4.38 A convenient synthesis of compound **112**.

(Scheme 4.36). The reaction proceeded to give **106** to 45%–99% (Scheme 4.36). The stereochemical study of this reaction was described by employing chiral substituted *N*-sulfonylaziridines (*R*)-**41**. enantioenriched 2-iminothiazolidines (**S**)-**106** was produced in excellent yield with reversion in configuration (Scheme 4.36).

It was reported [44] on the organophosphine-catalyzed cyclization reaction of aziridines **41** with isothiocyanates **107** in the presence of Bu_3P to afford thiazolidinone derivatives **108** and **109** as in a regioisomeric ratio 5:2 (Scheme 4.37). On applying the previous procedure using CS_2, the reaction proceeded to give products **110** and **111** (Scheme 4.37).

The reaction was initially examined using 2-benzyl-1-tosylaziridine **41** and CS_2 in the presence of MeONa (10% mol) (Scheme 4.38) [45]. When the reaction was carried out by stirring in THF at 40°C for 4 h, it afforded 4-benzyl-3-tosylthiazolidine-2-thione **112** in 42% yield. To optimize the reaction conditions, a variety of solvents and catalysts were examined. Among the solvents examined, DMF was superior to other solvents. Reaction in non-polar solvents like toluene led to very low conversion. Reaction conducted in a protic solvent gave the desired product a moderate yield, most likely due to the lower nucleophilicity of ethoxide ion in a protic solvent. Ethers and a chlorinated solvent were not efficient in this transformation. Polar-aprotic solvents improved the yield appreciably, an outcome we attribute to the greater solubility power of polar compounds. Reaction conducted in H_2O resulted in very low conversion. No reaction took place in the absence of the catalyst even at higher temperatures. Tetrabutylammonium methoxide achieved a higher conversion, most likely due to better solubility in the organic solvent than that of MeONa. Catalyst screening showed that 2-pyridine carboxaldehyde oxime **L1** afforded the desired product an excellent 94% yield, but the 6-methyl analog **L2** afforded the desired product a lower yield of 76%. It could be deduced that the steric issue on catalyst structure influences the reaction process. Pyridine *N*-oxide failed to promote the desired reaction and resulted in a complicated mixture. It is worth mentioning that no reaction took place at ambient [45].

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Chapter 5

Synthesis of *N*-sulfonated *N*-diazoles, their chemistry and biological assessments

5.1 Introduction

Imidazole is one of the most prominent, five-membered, nitrogen-containing, heterocyclic scaffolds and it is nucleus forms the main structure of some well-known components of human organisms, that is, the amino acid histidine, Vit-B12, a component of DNA base structure and purines, histamine, and biotin. It is also present in the structure of many natural or synthetic drug molecules, that is, cimetidine, azomycin, and metronidazole. Imidazole-containing drugs have a broader scope in remedying various dispositions in clinical medicine [1]. Moreover, pyrazole is an aromatic heterocyclic system that belongs to the azole class. The first pyrazole isolated from natural sources was 3-nnonyl-1*H*-pyrazole, extracted from Houttuynia cordata, a common plant from tropical Asia. β-(1-pyrazolyl) alanine can be found in watermelon seeds [2]. A large number of synthetic pyrazoles have been synthesized and approved for use, including fipronil [3], an insecticide; tartrazine [4], an azo dye employed as food coloring; sildenafil [5], used to treat erectile dysfunction; [4] dipyrone [6], a potent analgesic and antipyretic agent [7], celecoxib and tepoxalin a COX-2 selective nonsteroidal antiinflammatory drugs (NSAIDs) [8]. Heterocycles of thiadiazole and oxadiazole have a wide chemical transformation potential and have various pharmacological potentials, such as antitumor [9,10], antibacterial [11], anti-tuberculosis [12], and antiviral [13]. It is known as a pharmacopoeial fragment, anesthetics [14], antiinflammatory and analgesic action [15]. In addition, this class of compounds identified inhibitors of telomerase [16], histone deacetylase HDAC [17], and FAK family of kinases (focal adhesion kinases) [18] as potential antitumor agents, inducers of mitochondrial-mediated apoptosis [19,20].

5.2 Synthesis of *N*-sulfonylimidazole and its derivatives

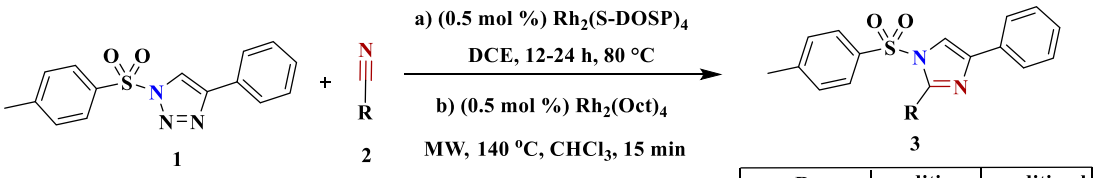
Hornaff et al. [21] used microwave irradiation and conventional methods to establish a transannulation reaction of C4-substituted *N*-sulfonyl triazole **1** with nitriles **2** to produce 1-sulfonyl-2,4-disubstituted imidazoles **3**. Both protocols were found to be equally effective in producing high yields of imidazoles (Scheme 5.1).

Chen et al. [22] developed a photoredox-induced functionalization of alkenes that yielded good substituted imidazolines **6**. A three-component reaction proceeded through radical addition and a formal [3 + 2] annulations cascade starting from alkenes **4**, 1-((4-methyl phenyl)sulfonamido)pyridin-1-ium tetrafluoroborate and nitriles **5**. This approach produces good to excellent yields, mild conditions, and readily available starting materials (Scheme 5.2).

Fokin et al. [23] developed a novel method for the production of imidazolines **9** through an Rh(II)-catalyzed transannulation reaction of 1-sulfonyl-1,2,3-triazoles **7** with heterocumulenes **8**. Metal-stabilized azavinyl carbenes, which are conveniently produced from stable and commonly accessible 1-mesyl-1,2,3-triazoles, are used as reactive intermediates in this formal [3 + 2] cycloaddition synthesis. This innovative method provides a modular sequence for the formal addition of "S−C−N" and "N−C−N" fragments to the acetylenic triple bonds, resulting in valuable families of five-membered nitrogen-containing heterocycles, in addition to a simple synthesis of triazoles (Scheme 5.3).

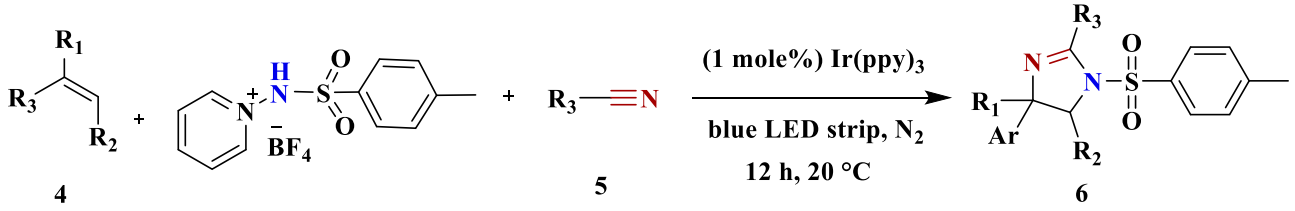
Jeon et al. [24] developed rhodium(II)-catalyzed denitrogenative coupling of *N*-sulfonyl-1,2,3-triazoles **10** with ambiphilic β-enamino esters **11** and **12** to furnish 2,5-dihydro-1*H*-imidazoles **13** and **14**, respectively. Moreover, the reaction proceeds with high diastereoselec-

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00014-8



R	condition a	condition b
C_6H_5	85%	82%
4-$OMeC_6H_4$	72%	87%
4-$NO_2C_6H_4$	69%	76%

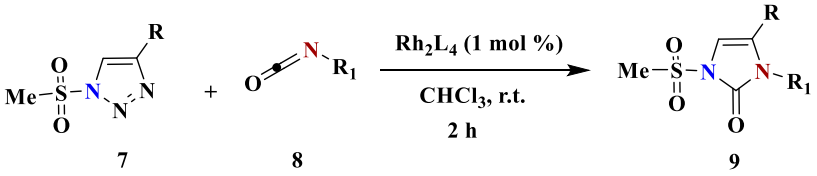
SCHEME 5.1 Synthesis of 1-sulfonyl-2- substituted-4-phenylimidazoles **3**.



$R_1 = R_2 = H$, $R_3 = Me$, Ar = Ph (95%), 2-MeC_6H_4 (97%), 3-MeC_6H_4 (90%), 4-MeC_6H_4 (86%), 2-ClC_6H_4 (88%), 3-Cl C_6H_4 (83%), 4-ClC_6H_4 (95%), 4-BrC_6H_4 (71%), 4-FC_6H_4 (95%), 4-(*i*Bu)C_6H_4 (84%)

$R_1 = R_2 = H$, Ar = Ph, R_3 = Et (95%), cyclopropyl (85%), Ph (22%)

SCHEME 5.2 Synthesis of substituted imidazoles **6**.



R = Ph, R_1 = Ph (95%), 4-ClC_6H_4 (84%), 4-$OMeC_6H_4$ (94%), 4-BrC_6H_4 (94%), 4-$NO_2C_6H_4$ (53%), 4-FC_6H_4 (89%), 4-$CF_3C_6H_4$ (83%), cyclohexyl (95%), 4-butyl (97%).

R = 3-FC_6H_4, R_1 = Ph (92%), 4-BrC_6H_4 (94%)

R = 3-FC_6H_4, R_1 = CH_2Ph (93%)

R = 4-MeC_6H_4, R_1 = 3-FC_6H_4 (85%), Cl-propyl (90%)

R = 4-OMeC6H4, R_1 = 4-ClC_6H_4 (85%), 4-$BrCH_2CH_2$ (92%)

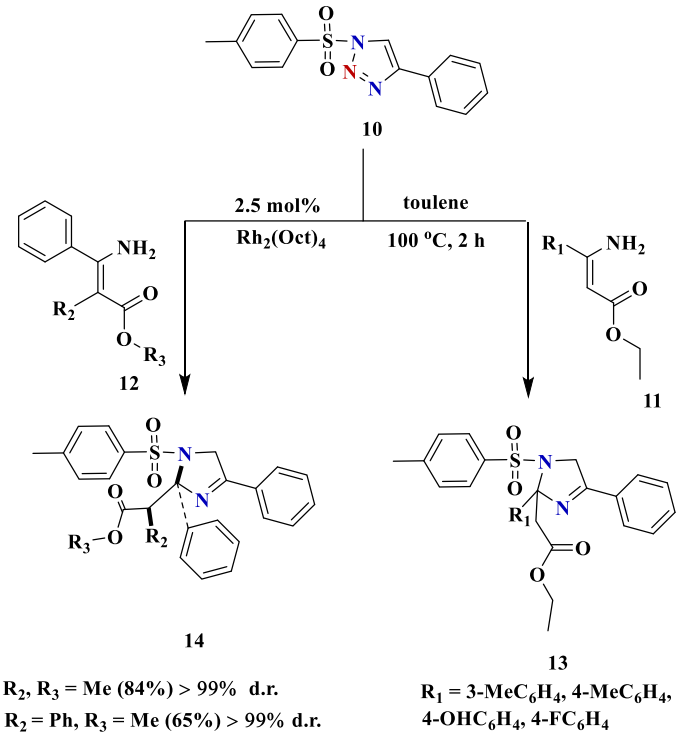
SCHEME 5.3 Synthesis of imidazolines **9**.

tivity for α-substituted β-enamino esters (R_3 = Me) to give a single diastereomer (Scheme 5.4).

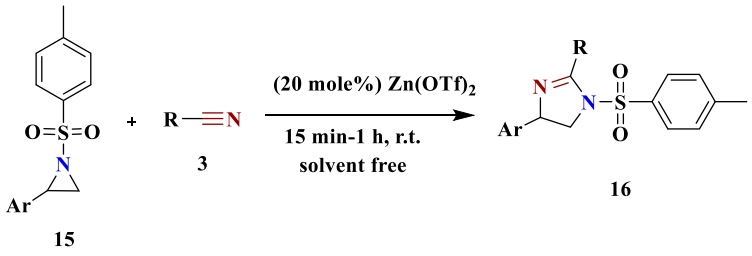
Singh et al. [25] described a good method for the synthesis of 2-substituted4-aryl-*N*-tosyl-1*H* imidazolines **16** through a formal [3 + 2] cycloaddition of *N*-tosylaziridines **15** with nitriles **3** in Lewis acid $Zn(OTf)_2$ at room temperature solvent-free The reaction proceeds in a Ritter fashion. After studying chiral aziridine, it was concluded that the reaction can proceed at SN_1 (2-aryl-*N*-sulfonylaziridines) or SN_2 (alkyl-*N*-tosylazidins) (Scheme 5.5).

Continuous flow methodology has emerged as a powerful new technique in chemical synthesis. In 2015, Shipman et al. [26] disclosed a novel method for imidazoline synthesis **18** by a formal (3 + 2) cycloaddition of aziridines **17** with nitriles **3** in DCM under continuous flow conditions at room temperature (Scheme 5.6).

Several Lewis acids including $BF_3.ETO_2$, Et_3OBF_4, $Cu(TOf)_2$, and TiF_4 were investigated for ring opening of aziridines with nitriles. Prasad et al. [27] successfully prepared 2,4-disubstituted imidazolines **19** from 2-aryl



SCHEME 5.4 Synthetic route of *N*-sulfonyl 2,5-dihydroimidazoles **13** and **14**.

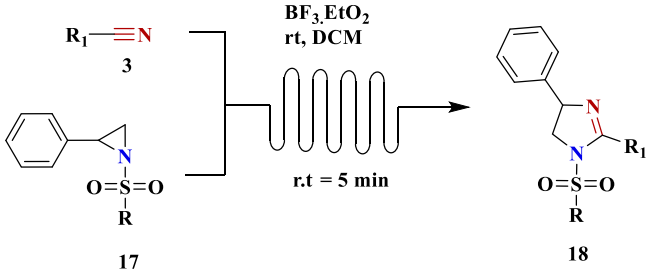


Ar = Ph, R = Ph (69%), Me (63%), iPr (51%), $PhCH_2$ (80%), 4-$FC_6H_4CH_2$ (85%), $ClCH_2$ (64%), $BrCH_2$ (61%)

Ar = 2-BrC_6H_4, R = Me (58%%), Ph (56%), $PhCH_2$ (60%)

Ar = 2-ClC_6H_4, R = Ph (79%%), $PhCH_2$ (76%)

SCHEME 5.5 Synthesis 2-substituted 4-aryl-*N*-tosyl-1*H* imidazolines **16**.



Ar = Ph, R = Me, R_1 = Me (73%), Ph (58%), ^{t}Bu (48%)

Ar = Ph, R = 4-MeC_6H_4, R_1 = Me (73%)

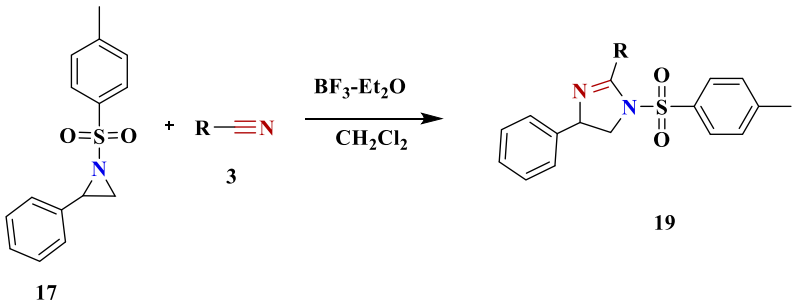
Ar = 2,4,6-$(Me)_3C_6H_2$, R = 4-MeC_6H_4, R_1 = Me (53%)

SCHEME 5.6 Formation of imidazolines by flow conditions **18**.

aziridines **17** with nitriles **3** in BF_3-Et_2O. The reaction proceeds *via* a [3 + 2] cycloaddition reaction at room temperature in a very short time (Scheme 5.7).

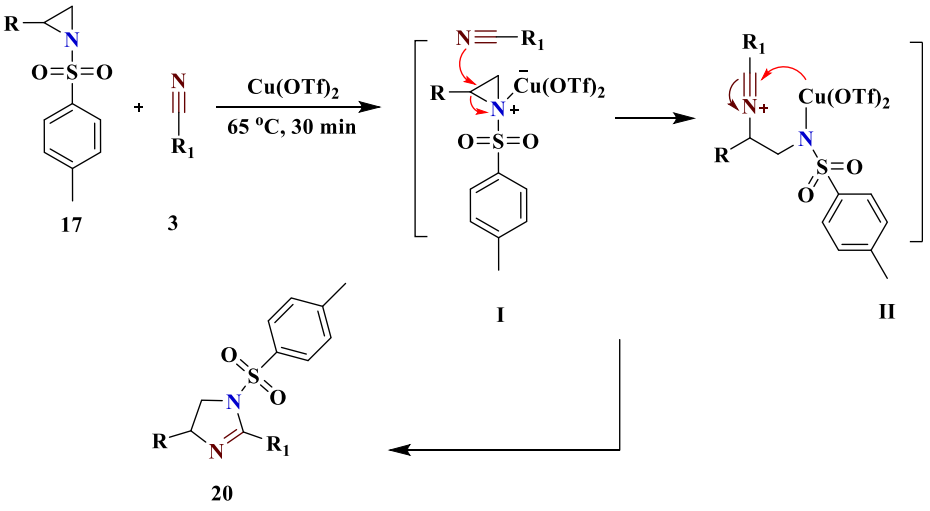
In 2006, Ghorai et al. [28] used $Cu(OTf)_2$ as an alternative catalyst for promoting [3 + 2] cycloaddition reaction of arylaziridines **17** with nitriles **3** to furnish imidazolines **20** in good yield. A mechanism for the cycloaddition is proposed to rationalize the formation of a nonracemic imidazoline from optically pure aziridine (Scheme 5.8).

In 2014, Hanamoto et al. [29] developed a mild and efficient [3 + 2] cycloaddition reaction of 2-(trifluoromethyl)-*N*-tosylaziridine **17** with various nitriles **3** in the presence of a catalytic amount of TiF_4 as the Lewis acid to yield the corresponding 4-(trifluoromethyl)-1,3-imidazolines



R = Me (75%), Et (72%), iPr (76%), Ph (67%), $CH_2C_6H_4$-2-Me (65%), $CH_2C_6H_4$-3-Me (49%), $CH_2C_6H_4$-3,6-$(Me)_2C_6H_3$ (55%%), Ph (56%), $PhCH_2$ (60%), CH2C6H4-3-OMe (60%), 2-$CH_2C_6H_4$-4-F-C_6H_4, (51%%), $PhCH_2$ (76%), $CH_2C_6H_4$-2-CF_3 (49%), CH_2Cl (48%), CH_2Br (47%)

SCHEME 5.7 Synthesis of disubstitutes imidazoles **19**.



R = Ph, R_1 = Me (82%), Ph (67%), 4-EtC_6H_3CN (62%)

R = 4-MeC_6H_4, R_1 = Me (77%), Ph (62%)

R = 4-ClC_6H_4, R_1 = Me (72%), Ph (61%)

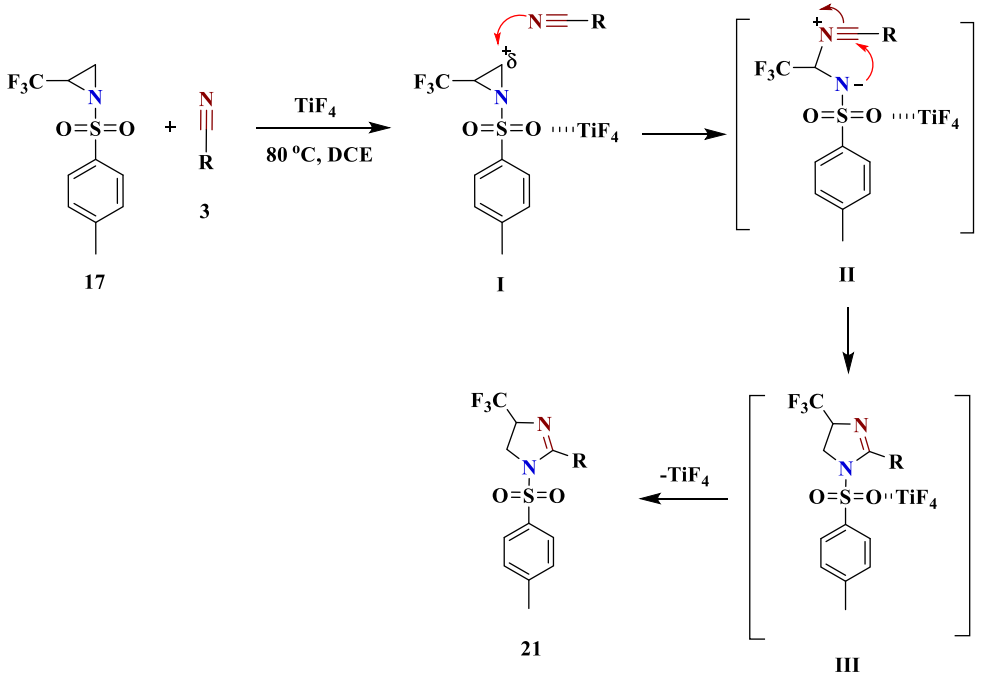
SCHEME 5.8 Synthetic pathway of imidazolines **20**.

21 with excellent regioselectivity. The mechanism of the formation of compounds **21** was proceeded initially, by the aziridine is activated by TiF4 to form the polarized aziridine ring **I**, which is attacked by the nitrile to afford the betaine intermediate **II**, followed by the intramolecular ring closure to generate the 1,3-imidazoline **III**. The regioselectivity of the product may be controlled by the CF_3 group because of its strong electron-withdrawing property during the ring-opening stage (Scheme 5.9).

Craig et al. [30] reported an influential protocol based on the use of zinc bromide as a catalyst in cycloaddition reactions. Initially, zinc bromide was found to be an effective catalyst in the [3 + 2] cycloaddition of *N*-sulfonylaziridines **17** with dialkyl carbodiimides **22** to afford imidazolidine **23** (Scheme 5.10).

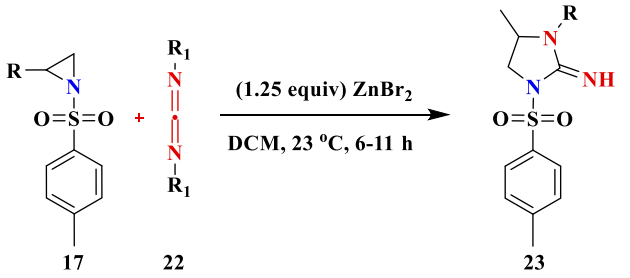
Additionally, the zinc-catalyzed cycloaddition reaction of diester aziridine **24** with allyl isothiocyanate **25** was also investigated in this protocol. This reaction proceeded through the formation of azomethine ylide intermediate **I**, which facilely reacted with allyl isothiocyanate **25** to form dimethyl 1-allyl-2-phenyl-5-thioxo-3-tosylimidazolidine-4,4-dicarboxylate **26** in 50% yield [30] (Scheme 5.11).

Several functionalization protocols utilized *N*-tosylaziridinofullerene as a versatile platform for functionalization on the sphere of C60 and investigated the properties of these newly generated fullerene C60 derivatives for their applications in materials science and medicinal chemistry constitute. In 2013, Takeda et al. reported the reaction of *N*-sulfonylated aziridinofullerene **27** with aryl



R = Me (82%), *i*Pr (32%), *t*Bu (35%), $ClCH_2$ (32%), Ph (85%), $PhCH_2$ (80%), 2-MeC_6H_4 (85%), 3-MeC_6H_4 (81%), 4-MeC_6H_4 (91%), 4-ClC_6H_4 (69%), 2-naphthyl (93%), 2-thienyl (62%), 9-antharyl (62%)

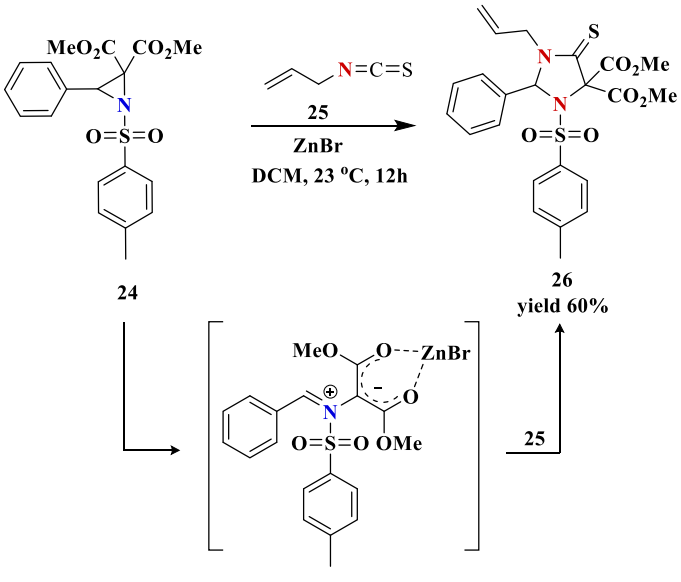
SCHEME 5.9 Synthesis of 4-(trifluoromethyl)-1,3-imidazolines **21**.



R = Ph, R_1 = H (61%), iPr (55%), Ph (96%)

R_1 = Ph, R = 4-$OAcC_6H_4$ (99%), 4-ClC_6H_4 (87%)

SCHEME 5.10 Synthesis of iminoimidazoline **23**.

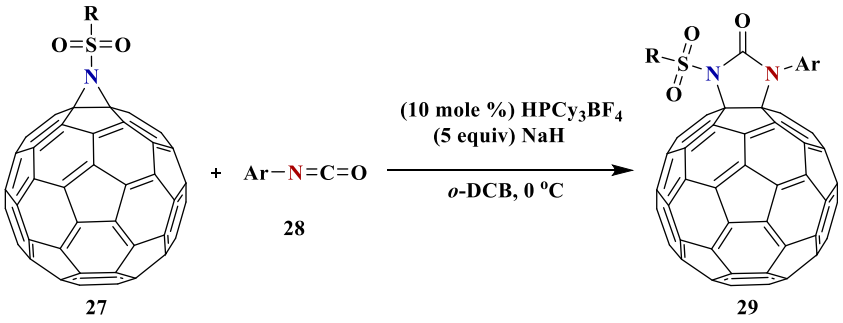


SCHEME 5.11 Synthetic route of dimethyl 1-allyl-2-phenyl-5-thioxo-3-tosylimidazolidine-4,4-dicarboxylate **26**.

isocyanates **28** and tricyclohexylphosphonium tetrafluoroborate ($HPCy_3BF_4$) in *o*-dichlorobenzene afforded the C60-fused imidazolidinones **29** (Scheme 5.12) [31].

[2] Yang et al. [32] developed an efficient preparation of fulleroimidazolidinones **32** through the $Cu(OAc)_2$-promoted intermolecular diamination reaction of fullerene C60 **30** with disubstituted ureas **31** by involving the cleavage of two N−H bonds and formation of two C−N bonds (Scheme 5.13).

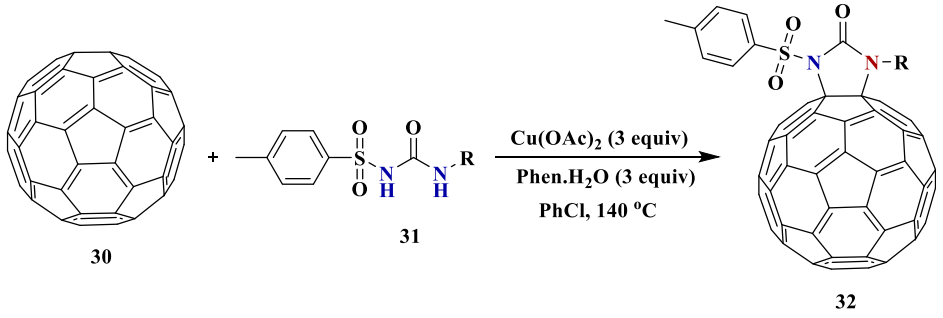
In continuation of the interest in the chemical functionalization of fullerene, Xing et al. [33] are interested to develop new routes for the preparation of cyclic diaminated (60) fullerenes from *N*-tosylaziridinofullerene. The double nucleophilic reaction of *N*-tosylaziridinofullerene **33** with various ureas **34** and **35** under the catalysis of Lewis base *N*-methylimidazole (NMI) afforded the anticipated product **36** and **37**, respectively. However, this condition was suitable for aryl ureas. Aryl ureas gave a very low conversion under this condition due to their lower



R = MeC_6H_4, Ar = $nBuC_6H_4$ (62%), $OMeC_6H_4$ (70%), FC_6H_4 (73%), ClC_6H_4 (83%), BrC_6H_4 (71%), IC_6H_4 (78%), $COOEtC_6H_4$ (74%)

Ar = naphthyl, R = Me (64%), Ph (75%), 4-$NO_2C_6H_4$ (92%), 4-$MeOC_6H_4$ (785%), 2-$NO_2C_6H_4$ (91%), 4-BrC_6H_4 (65%)

SCHEME 5.12 Generation of new fullerene C60 derivatives **29**.



R = *n*-Bu (21%), $CH_2C_6H_4$ (23%), CH_2COOEt (12%), $CH_2CH(OMe)_2$ (19%), 4-MeC_6H_4 (9%)

SCHEME 5.13 Preparation of fulleroimidazolidinones **32**.

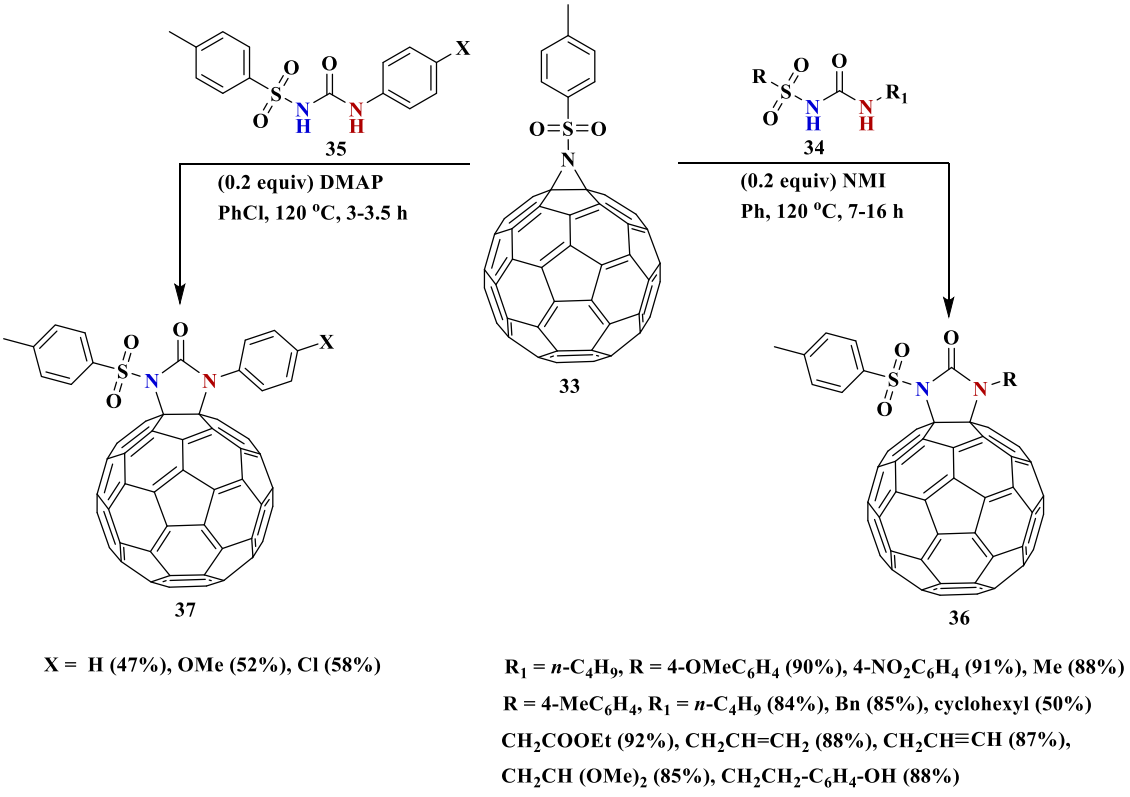
nucleophilicity compared with that in alkyl ureas. Replacement of NMI by 4-dimethylaminopyridine (DMAP) furnished the desired product in relatively good yield because DMAP has stronger basicity than NMI (Scheme 5.14).

Recently, Ye et al. [34] reported an updated synthesis of imidazole-1-sulfonyl azide from sulfuryl diimidazole to prevent the formation of hydrazoic acid or sulfuryl diazide. Thus, sulfuryl diimidazole **38** was treated with methyl trifluoromethanesulfonate (MeOTf) in DCM for 2 h to form intermediate **39** which reacted with sodium azide in a mixture of ethyl acetate and water at zero °C for one hour to furnish imidazole-1-sulfonyl azide **40** with 88% yield (Scheme 5.15).

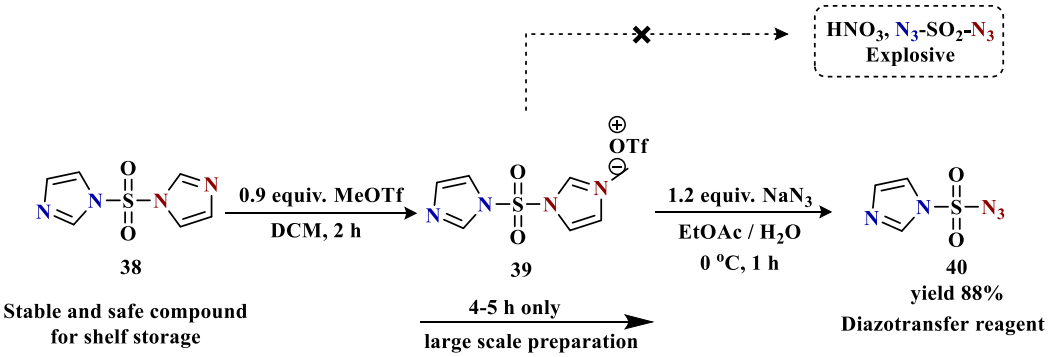
Mamedov et al. [35] found that the addition of sulfonyl chloride to the amino, rather than the carbamoyl group produced the monosulfonamides. The arylsulfonylcarbamoylguanidines **42** (obtained by the reaction of 4-methyl or 4-bromophenylsulfonyl chloride **41**, carbamoylguanidine and sodium hydroxide solution (30%) in a mixture of benzene and water with stirring at 40°C−50°C was added to chloroacetonitrile in ethanol containing 20% sodium hydroxide solution to form 1-arylsulfonyl-2-carbamido-3-aminoimidazoles **43a,b**. While carrying out the reaction in the presence of morpholine arylsulfonyl-2-carbamido-4,5-diphenylimidazoles **44a,b** were obtained (Scheme 5.16).

Kun et al. [36] described efficient *N*-sulfonylation of imidazoles **45** under mild conditions to obtain *N*-sulfonylimidazoles **46** in moderate to good yield using fluorobenzenesulfonimide (NFSI) as the sulfonyl source (Scheme 5.17).

Peddinti et al. [37] described a novel green protocol for the synthesis of *N*-sulfonylimidazoles **48** using iodine as a catalyst under solvent-free conditions. This method involves the oxidative coupling of sulfonyl hydrazides **47** and imidazoles in the presence of a catalytic amount of iodine using *tert*-butylhydroperoxide (TBHP) as the oxidizing agent. The mechanism of formation of *N*-sulfonylimidazole is proposed in Scheme 5.18. Initially, TBHP generates the *tert*-butoxyl radical and iodide ion in the presence of iodine. Then in the presence of *tert*-butoxyl



SCHEME 5.14 Formation of cyclic diaminated (60) fullerenes **36** and **37**.

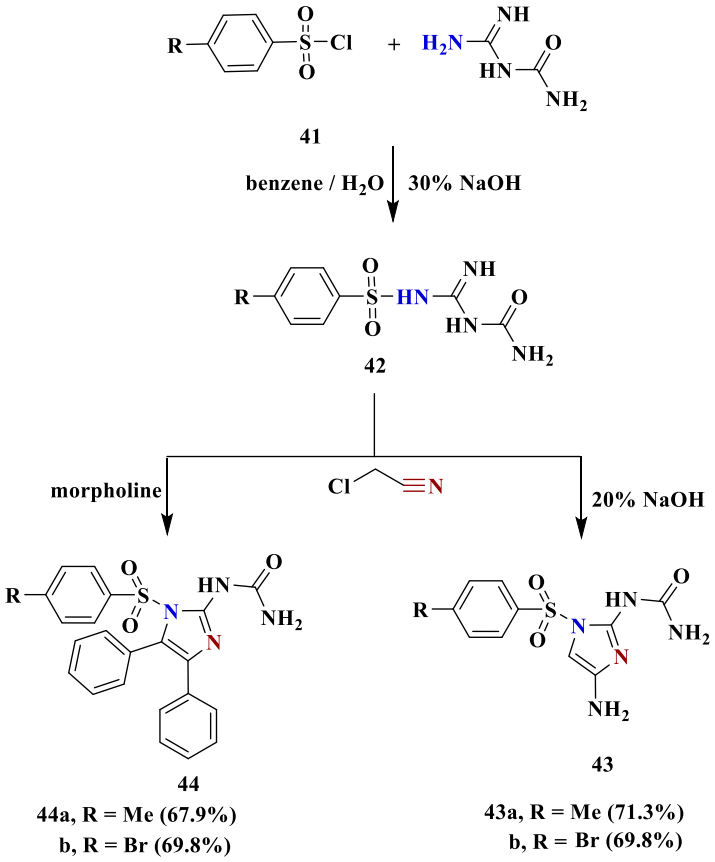


SCHEME 5.15 Synthesis of imidazole-1-sulfonyl **40**.

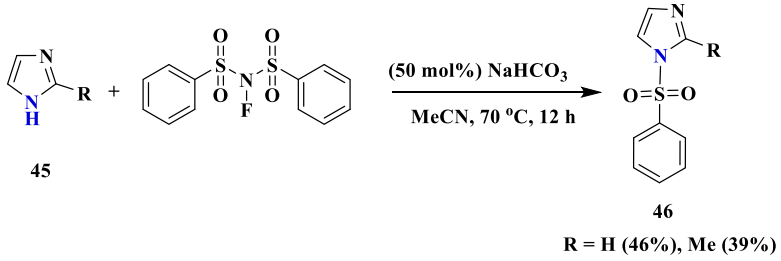
radical, the aryl sulfonyl hydrazide produces the intermediate **I** due to the removal of hydrogen and then reacts with *tert*-butoxyl radical to form intermediate **II**. The intermediate **II** has then converted to the aryl sulfonyl radical **III** due to the removal of the molecular nitrogen. In the presence of iodine, the arylsulfonyl radical **III** is converted to an arylsulfonyl cation **IV**, which can act as an electrophile. Arylsulfonyl cation **IV** combines with imidazole to yield *N*-sulfonylimidazole derivatives (Scheme 5.18).

Pasha et al. [38] developed a simple, facile, and efficient procedure for the synthesis of *N*-tosyl-1*H*-pyrazole **48** using *p*-toulene sulfonyl chloride (TsCl) in the presence of atomized sodium in an EtOH-THF mixture in high yield for 8 min under sonic conditions (Scheme 5.19).

A new series of 1-(arylsulfonyl)-2-methyl-4-nitro-1*H*-imidazole was synthesized **49** by Emanuel et al. [39] through alkylation of 2-methyl-4-nitro-1*H*-imidazole with various sulfonyl chlorides **41** in DCM containing potassium hydroxide, DMAP, and TEA at 40°C with stirring. The new compounds were screened against three unicellular parasites and the results showed that the sulfonamide derivatives have antiamoebic activity. Toxicity analysis showed that these compounds were not cytotoxic to the MDCK cell line (Scheme 5.20).



SCHEME 5.16 Synthetic pathway of 1-arylsulfonyl-2-carbamido-3-aminoimidazoles **43**.



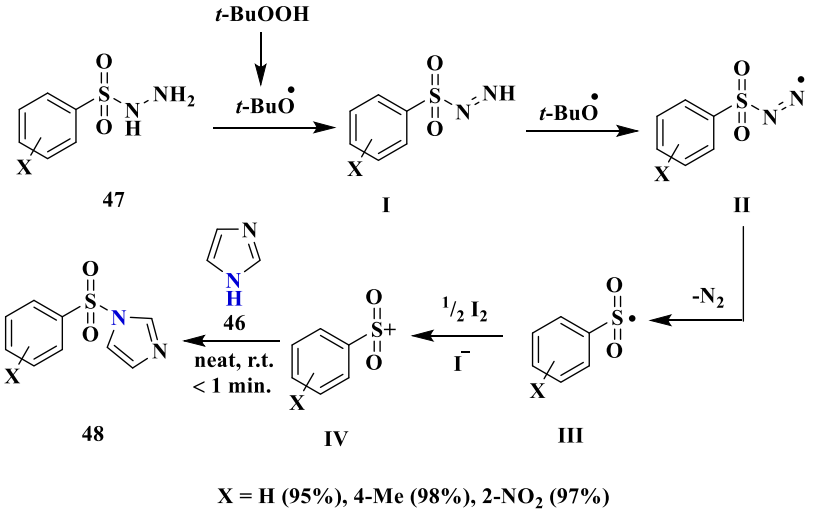
SCHEME 5.17 *N*-Sulfonylation of imidazoles **45**.

Yotphan et al. [40] found a convenient protocol for the formation of *N*-tosyl-1*H*-pyrazole **48** with 60% yield from 1*H*-imidazole **45** and sodium sulfinates using an I_2-catalyzed oxidative amination strategy. Sodium percarbonate, a dry carrier for hydrogen peroxide, is used as an oxidizing agent in this reaction, making it easy to organize and process the reaction (Scheme 5.21).

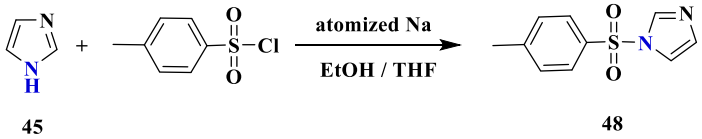
The reaction of 4-formylcoumarin **50** and benzil with ammonium acetate in the presence of acid catalysts furnished the desired coumarin-imidazole hybrid molecules **51** in good yields under the conventional method. Improvement in product yields was observed by employing a microwave (MW)-assisted method for short reaction time. The reaction of compound **51** with *p*-toluenesulfonyl chloride in the presence of triethylamine (TEA) at 0°C−5°C afforded *N*-sulfonyl imidazoles **52** with excellent yield. Also, the synthesized compounds **52** were evaluated for their antibacterial, antifungal, and antiinflammatory activities (Scheme 5.22) [41].

5.3 Uses of *N*-sulfonylimidazole derivatives

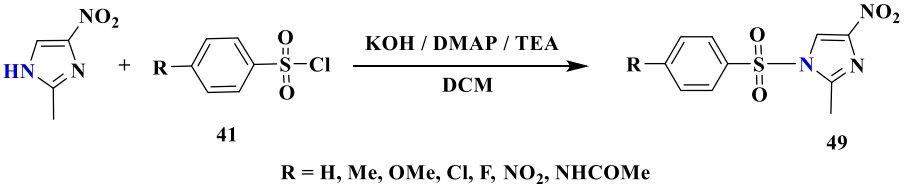
Chen et al. [42] proposed a novel transformation of *N*-arylsulfonylimidazoles **53** to diaryldisulfides **54** *via* imidazolyl as a leaving group using sodium borohydride and I_2/1,10-phen in dioxane. The reaction mechanism provides for efficient



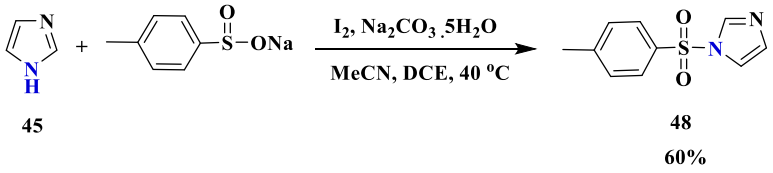
SCHEME 5.18 Synthesis of *N*-sulfonylimidazoles **48** under solvent-free conditions.



SCHEME 5.19 Preparation of *N*-tosyl-1*H*-pyrazole **48** using *p*-toulene sulfonyl chloride.



SCHEME 5.20 Synthesis of 1-(arylsulfonyl)-2-methyl-4-nitro-1*H*-imidazoles **49**.



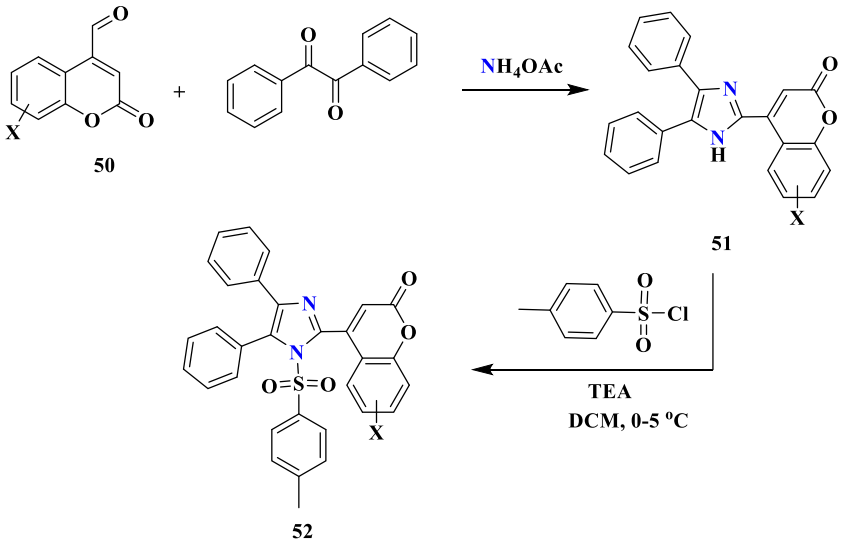
SCHEME 5.21 Formation of *N*-tosyl-1*H*-pyrazole **48**.

reductive coupling of phenyl sulfonyl imidazoles catalyzed by I_2/ 1,10-phenanthroline and the formation of the S−S coupling products in moderate to good yields (Scheme 5.23).

Rad et al. [43] achieved the reaction of primary alcohols **55**, potassium thiocyanate, and *N*-(p-toluenesulfonyl) imidazole (TsIm) **48** as a coupling agent in the presence of triethylamine in anhydrous DMF at 70°C to give the corresponding isothiocyanate derivatives **56** in rapid, simple, high yield and without isomerization (Scheme 5.24).

One-pot synthesis of 2-azetidinones **59** was discussed from cyclocondensation of Schiff bases **57** and substituted acetic acid **58** with *N*-tosylimidazole **48** in presence of trimethylamine at room temperature in DCM in good to excellent yields (Scheme 5.25) [44].

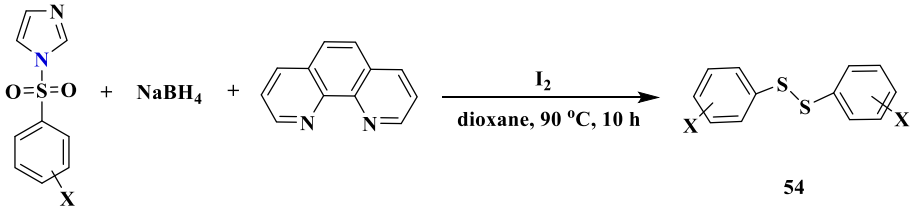
Velavan et al. [45] demonstrated an expeditious synthesis of 2-imidazo-1-yl substituted pyridines **61** in moderate to good yields by Amberlyst-15 catalyst from pyridine-*N*-oxides **60** with *N*-tosylimidazole **48**. This method completely avoids transition metals and, in addition to the first report on acid-catalyzed Reissert-Henze reaction, these results further demonstrate the value of acid catalysis in improving the leaving group ability of imidazole in organic synthesis. The mechanism of formation 2-imidazo-1-yl substituted pyridines is proceeds



50 51 52

X = 6-Me, 7-Me, 6-OMe, 6-Br, 6-Cl, 7,8-Benzo

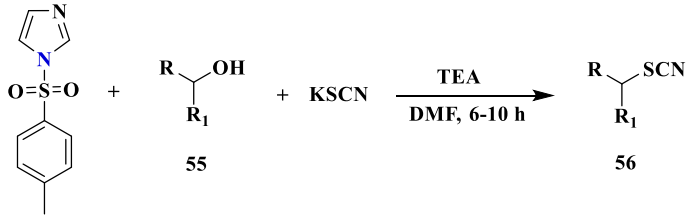
SCHEME 5.22 Synthesis of coumarin-imidazole hybrid molecules **51**.



53 54

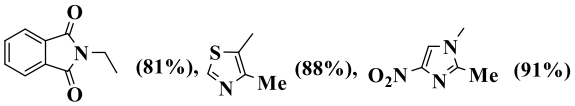
X = H (82%), 2-Me (88%), 4-Me (90%), 2,4,6-^{i}Pr (95%), ^{t}Bu (86%), 4-OMe (47%), 4-Cl (91%), 2-NO_2 (80%), 3-NO_2 (89%), 3-NO_2,4-Me (97%), 3-Br (94%), 4-Br (94%), 4-F (83%)

SCHEME 5.23 Transformation of *N*-arylsulfonylimidazoles **53** to diaryldisulfides **54**.



48 55 56

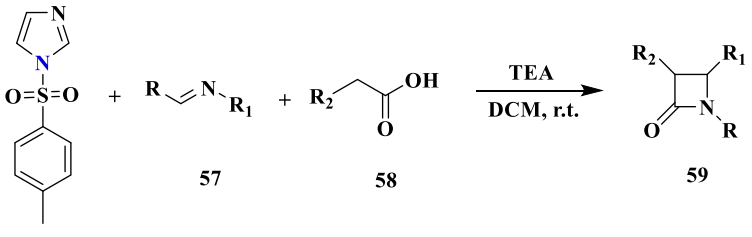
R_1 = H, R = n-heptyl (93%), $PhCH_2$ (92%), $PhCH_2CH_2$ (94%), 4-$ClC_6H_4CH_2$ (86%), 4-MeC_6H_4 (90%), 2,4-$(Cl)_2C_6H_3$ (81%), 4-$ClC_6H_4OCH_2$ (89%), $PhCOCH_2$ (68%), 4-$OMeC_6H_4COCH_2$ (73%), furyl (75%)



(81%), (88%), (91%)

R_1 = Me, R = Ph (40%), $PhCH_2CH_2$ (30%)

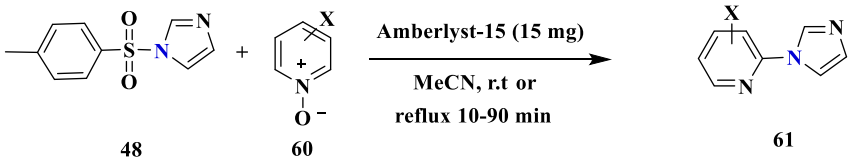
SCHEME 5.24 Isothiocyanate derivatives **56** from *N*-(p-toluenesulfonyl) imidazole **48**.



48 57 58 59

R = R_1 = Ph, R_2 = PhO (91% *cis*)
R = 4-$MeOC_6H_4$, R_1 = 2,4-$(Cl)_2C_6H_3$, R_2 = Ph (94% *cis*)
R = 4-$MeOC_6H_4$, R_1 = 3,4,5-$(OMe)_3C_6H_2$, R_2 = PhthN (85% *trans*)
R = 4-EtC_6H_4, R_1 = 2,4-$(Cl)_2C_6H_3$, R_2 = PhO (85% *cis*)
R = 4-EtC_6H_4, R_1 = 2,4-$(Cl)_2C_6H_3$, R_2 = PhthN (91% *trans*)
R = 4-EtC_6H_4, R_1 = 2,4-$(Cl)_2C_6H_3$, R_2 = 2,4-$(Cl)_2C_6H_2O$ (80% *cis*)
R = 4-EtC_6H_4, R_1 = 3,4,5-$(OMe)_3C_6H_2$, R_2 = 2,4-$(Cl)_2C_6H_2O$ (81% *cis*)
R = 4-EtC_6H_4, R_1 = 3,4,5-$(OMe)_3C_6H_2$, R_2 = PhthN (76% *trans*)

SCHEME 5.25 One-pot synthesis of 2-azetidinones **59**.



48 60 61

X = H (63%), 2-OMe (53%), 3-Cl (60%), 3,5-$(Cl)_2$ (45%), 2,5-(Br) (45%), 4-CN (61%)

SCHEME 5.26 Synthesis of 2-imidazo-1-yl substituted pyridines **61**.

48 62 63 64

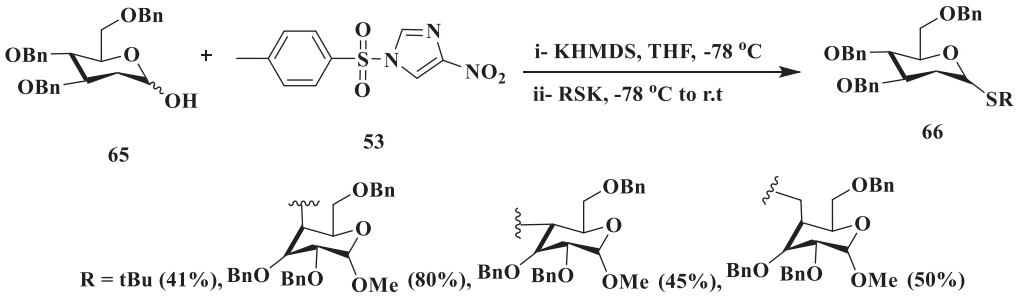
R = 4-MeC_6H_4, R_1 = *i*Pr (80%), octyl (87%), 4-MeC_6H_4 (88%), 2-ClC_6H_4 (80%),
3-FC_6H_4 (89%), 4-BrC_6H_4 (90%), 1-phenylethyl (82%), cyclohexyl (79%)
R = Ph, R_1 = Pr (93%), 2-phenylethyl (91%)
R_1 = benzyl, R = Me (88%), 2-ClC_6H_4 (79%), 4-$OMeC_6H_4$ (88%), 4-$NO_2C_6H_4$ (91%)

SCHEME 5.27 Efficient method for one-pot synthesis of *N*-alkyl sulfonamides **64**.

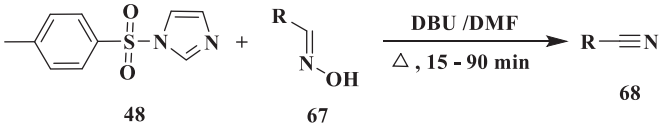
through acidic proton from the sulfonic acid group of amberlyst-15 protonates the imidazole nitrogen, thus making it a very good leaving group compared to the unprotonated imidazole. C-2 Substituted product was observed in most cases arising out of the intramolecular attack by the imidazole leaving group (Scheme 5.26).

Rad et al. [46] described a facile and efficient method for one-pot synthesis of *N*-alkyl sulfonamides **64** in good to excellent yields from various salts of potassium sulfonylamide **62** and alcohols **63** using *N*-(p-toluenesulfonyl) imidazole (TsIm) **48** and trimethylamine in reflux DMF. This technique is highly effective for the reaction of structurally different primary and secondary alcohols as well as potassium sulfonylamides (Scheme 5.27).

Bennett et al. [47] found that treating 2-deoxysugar hemiacetals **65** with 4-nitro-1-tosyl-1*H*-imidazole ($TsImNO_2$) **53** in potassium bis(trimethylsilyl)amide (KHMDS) results in situ formation of a species that reacts with *S*- and *O*-nucleophiles to form glycoside products **66** exclusively as β-anomers. The reaction presumably proceeds through the formation of a glycosyl tosylate, which reacts through an SN_2 or SN_2-like manifold (Scheme 5.28).

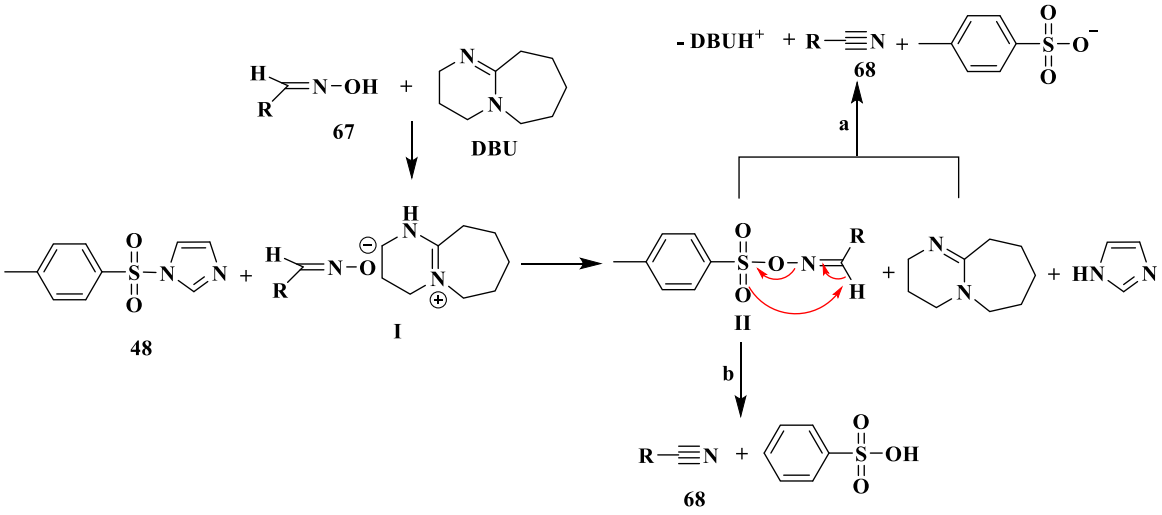


SCHEME 5.28 Synthesis of glycosides **66** from 4-nitro-1-tosyl-1*H*-imidazole.



R = *n*-Pr (86%), *n*-Bu (86%), Ph (91%), 4-MeC$_6$H$_4$ (94%), 2-OMeC$_6$H$_4$ (92%), 4-OMeC$_6$H$_4$ (95%), 4-ClC$_6$H$_4$ (96%), 2,4-(Cl)$_2$C$_6$H$_3$ (91%), 3-NO$_2$C$_6$H$_4$ (87%), 4-CNC$_6$H$_4$ (89%), Me$_2$NC$_6$H$_4$ (93%), 4-pyridyl (91%), thienyl (90%), *N*-methylpyrrole (87%), benzyl (85%)

SCHEME 5.29 Dehydration of aldoximes to nitriles **68** using TsIm.



SCHEME 5.30 Mechanism of formation of nitriles **68**.

Rad et al. [48] developed a simple method for dehydration of aldoximes to nitriles using *N*- (*p*-toluenesulfonyl) imidazole (TsIm). In this method, TsIm **48** with aldoximes **67** were refluxed in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and DMF to afford the corresponding nitriles **68** in good yields. The essential features of this method are short reaction times, good product yields, simple experimental procedures, and versatility (Scheme 5.29).

The mechanism of formation of nitriles **68** from TsIm **48** and oxime **67** in the presence of DBU suggests that a preliminary acid-base reaction of DBU with oxime **67** produces the adduct DBU-oxime **I**. Adduct **I** reacts with TsIm **48** to form *O*-tosyl-aldoxime **II** as a major intermediate. Two pathways (A and B) were hypothesized for the formation of nitriles **68**. In path **a**, the transformation occurs due to 1,2-elimination, but in path **b**, the transformation is achieved due to 1,4-elimination in a concerted process [48] (Scheme 5.30).

An efficient and selective method for the esterification of alcohols with *N*-(*p*-toluenesulfonyl)imidazole (TsIm) is described. In this method, alcohols **69** were refluxed with a mixture of sodium benzoate and TsIm **48**, in the presence of triethylamine and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI) in DMF to afford the corresponding esters **70** in good

yields. This methodology is highly efficient for structurally different alcohols that are selective for ROH: 1 > 2 > 3 [49] (Scheme 5.31).

Tan et al. [50] used 1-(*p*-tosyl)-imidazole **48** along with β-cyclodextrin **71** in the synthesis of highly pure mono-6-tosyl-β-cyclodextrin (TsO-CD) **72** with a good yield (Scheme 5.32).

5.4 Chemistry of *N*-sulfonylpyrazoles

5.4.1 Synthesis of *N*-sulfonylated pyrazoles

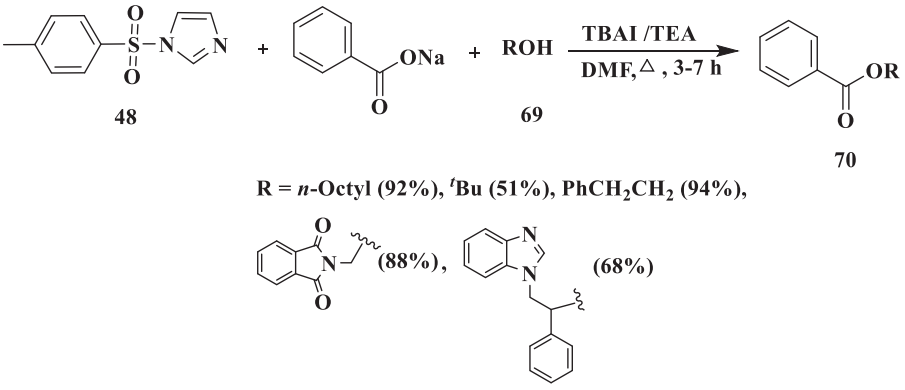
A novel strategy for the synthesis of various 3,5-dimethyl-1-(substituted sulfonyl)-4-tosyl-1*H*-pyrazoles **74** through the reaction of sulfonyl hydrazides **73**, acetylacetone, and sodium sulfinate in the presence of molecular iodine and potassium hydrogen phosphate for 22 h at room temperature in acetonitrile. Sulfonyl hydrazides and sodium sulfinate improve the diversity of the desired substituted sulfonyl-4-tosylpyrazoles by providing a sulfonyl group in the reaction (Scheme 5.33) [51].

A mild and rapid approach was developed by Zhang et al. [52] for the construction of fully substituted sulfonyl pyrazoles in one step. Thus the reaction of tosylhydrazides **73** with acetylacetone in the presence of *tetra*-butylammonium iodide (TBAI), TBHP and cobalt (II) acetate $[Co(OAc)_2]$ in pyridine afforded 3,5-dimethyl-1,4-bis (substituted *N*-sulfonyl-1*H*-pyrazoles) **75** with good yields. This transformation allows for use of a wide range of substrates, including aromatic and heteroaromatic sulfonyl hydrazides with a wide range of functional groups, using readily available starting materials and ease of operation (Scheme 5.34).

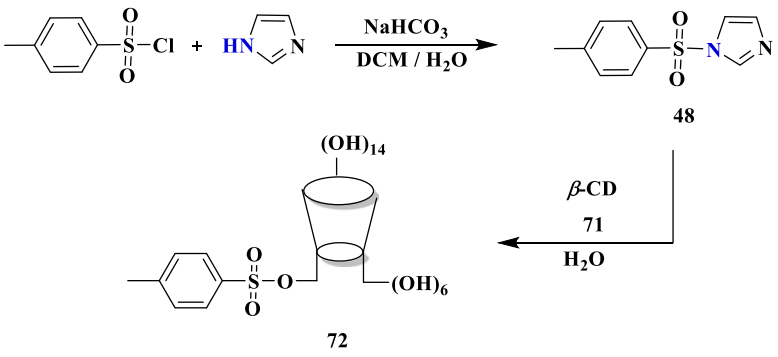
Ashraf et al. [53] demonstrated the reactions of 1,3-diketones **76** with 4-methylbenzenehydrazine **73** in methanol for 12 h under reflux afforded 3,5-disubstited *N*-tosylpyrazoles **77** (Scheme 5.35).

3,5-Dimethyl-4-substituted-*N*-sulfonylpyrazoles **79** were prepared *via* solventless condensation of 4-methyl benzenesulfonylhydrazide **73** with 1,3-diketones **78** in the presence of a catalytic amount of Sc $(OTf)_3$ at room temperature. Additionally, the catalyst could be recovered easily after the reactions and reused without evident loss in activity. The protocol presents a simple work-up, short reaction time, environmentally benign, easy recovery and reuse of metal triflate, and mild reaction conditions with good yield (Scheme 5.36) [54].

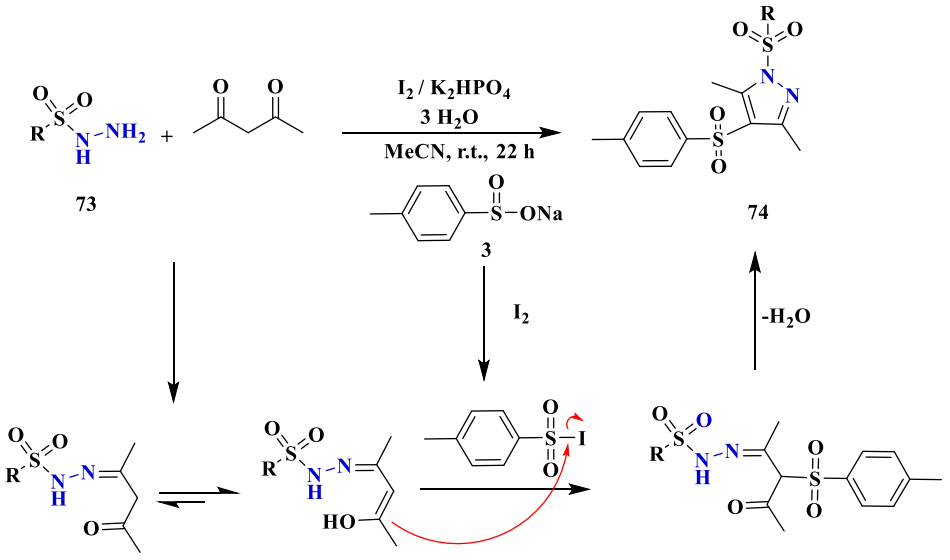
Reaction of thiophene-2-sulfonohydrazide **80** with ethyl diacetylacetate **81** in ethanol under reflux for 2 h afforded the 4-carbethoxy-3,5-dimethyl-l-(thiophene-2'-sulfonyl)pyrazole **82** (Scheme 5.37) [55].



SCHEME 5.31 Synthesis of ester **70** from TsIM.

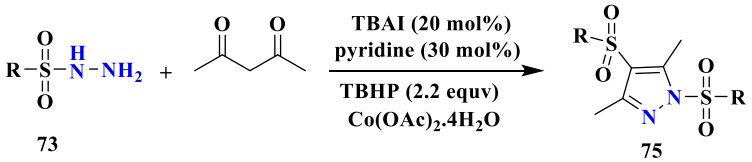


SCHEME 5.32 Synthesis of mono-6-tosyl-β-cyclodextrin **72**.



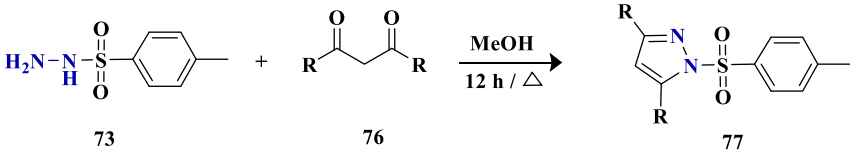
R = ^{i}Pr (45%), Ph (59%), 3-MeC6H4 (66%), 4-MeC_6H_4 (83%), 4-$^{t}BuC_6H_4$ (51%)4-$OMeC_6H_4$ (66%), 4-FC_6H_4 (67%), 4-ClC_6H_4 (66%), 2,4,6$(Me)_3C_6H_2$, 4-BrC_6H_4 (54%),4-$NO_2C_6H_4$ (53%), 4-CNC_6H_4 (63%), 2-ClC_6H_4 (52%), 2-thienyl (51%), naphthyl (56%), quinolyl (51%)

SCHEME 5.33 Formation of 3,5-dimethyl-1-(substituted sulfonyl)-4-tosyl-1*H*-pyrazoles **74**.



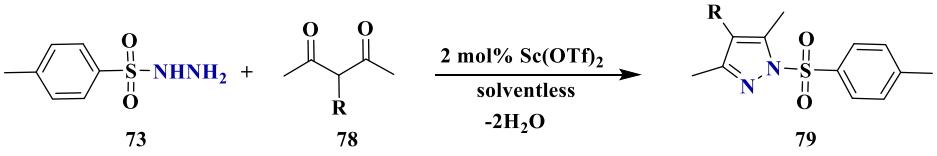
R = Bu (10%), Bn (10%), Ph (74%), 4-$OMeC_6H_4$ (82%), 4-ClC_6H_4 (80%), 4-FC_6H_4 (89%), 3-BrC_6H_4 (79%) 4-$CF_3C_6H_4$ (80%), 3-$NO_2C_6H_4$ (83%), naphthyl (91%), 2-theinyl (82%), quinolyl (52%)

SCHEME 5.34 Construction of fully substituted sulfonyl pyrazoles **75** in one step.



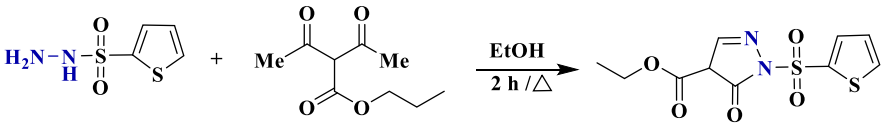
R = Me (35%), Ph (32%)

SCHEME 5.35 Synthesis of 3,5-disubstited *N*-tosylpyrazoles **77**.



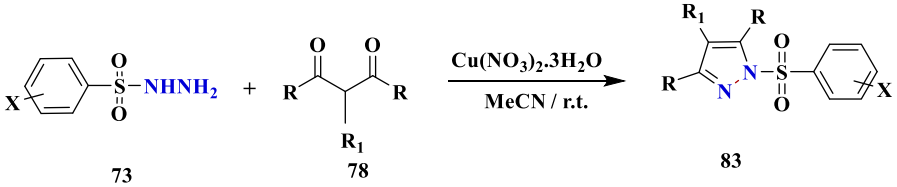
R = H (99%), Cl (82%)

SCHEME 5.36 Preparation of 3,5-dimethyl-4-substituted-*N*-sulfonylpyrazoles **79**.



80 81 82

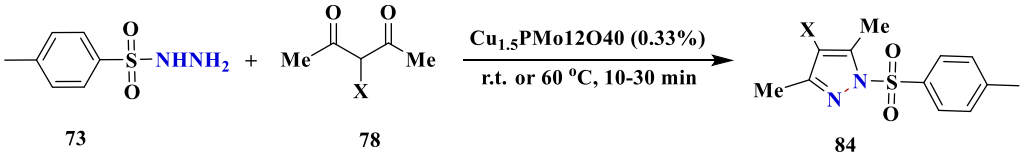
SCHEME 5.37 Synthesis of 4-carbethoxy-3,5-dimethyl-l-(thiophene-2'-sulfonyl)pyrazole **82**.



73 78 83

X = 4-Me, R = Me, R_1 = Et (82%)
X = 4-Me, R_1 = H, R= Me (81%), Et (82%), ^{t}Bu (73%), Ph (68%)
X = 4-Br, R_1= H, R = Me (89%)
X = R = R_1 = H (71%)
X = R = Me, R_1 = 4-Cl (84%)
X = iPr, R = Me, R_1= H (80%)

SCHEME 5.38 Synthesis of fully substituted pyrazoles **83**.



73 78 84

X = H (99%), Me (99%), Cl (94%)

SCHEME 5.39 Generation of 3,5-dimethyl-4-substituted pyrazole derivatives **84**.

Wang et al. [56] developed an efficient method for the synthesis of fully substituted pyrazoles **83** through the condensation of various sulfonyl hydrazides **73**, 1,3-diketones **78** in the presence of copper nitrate [$Cu(NO_3)_2$] in acetonitrile at room temperature for 15 min. The reaction is general with good functional group compatibility, giving the corresponding substituted pyrazoles in good to excellent yields in short reaction times (Scheme 5.38).

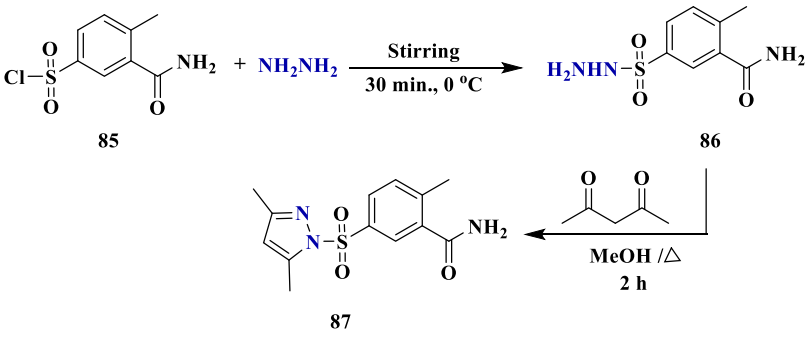
Yu et al. [57] demonstrated a convenient and direct preparation of 3,5-dimethyl-4-substituted pyrazole derivatives **84** in 99% yield by the condensation and cyclization of 4-methylbenzenesulfonylhydrazide **73** and 1,3-diketones **78** in the presence of 0.33 mol% poly acid salt $Cu_{1.5}PMo_{12}O_{40}$ for 10 min−30 min at room temperature or 60°C. This solvent-free and halogen-free catalytic system represents an effective economic and environmentally friendly method for the construction of substituted *N*-sulfonylpyrazoles (Scheme 5.39).

3-Carbamoyl-4-methylbenzenesulfonyl chloride **85** was converted to the 5-(hydrazineylsulfonyl)-2-methylbenzamide **86** through the reaction with hydrazine hydrate. The compound **85** reacts with acetylacetone in refluxing methanol for two hours to afford the 5-[3,5-(dimethyl-1*H*-pyrazol-1-yl)sulfonyl]-2-methylbenzamide **87** (Scheme 5.40) [58].

Treatment of phenoxyacetamide **88** with chlorosulfonic acid gave the 4-sulfonyl chloride **89**, which reacted with hydrazine hydrate to afford the phenoxyacetamide 4-sulfonyl hydrazide **90**. Condensation of hydrazide **90** with acetylacetone in refluxing ethanol for 6 h yielded the 4-[(3,5-dimethylpyrazol-l-yl)sulfonyl]phenoxy acetamide **91** through cyclization reaction (Scheme 5.41) [59].

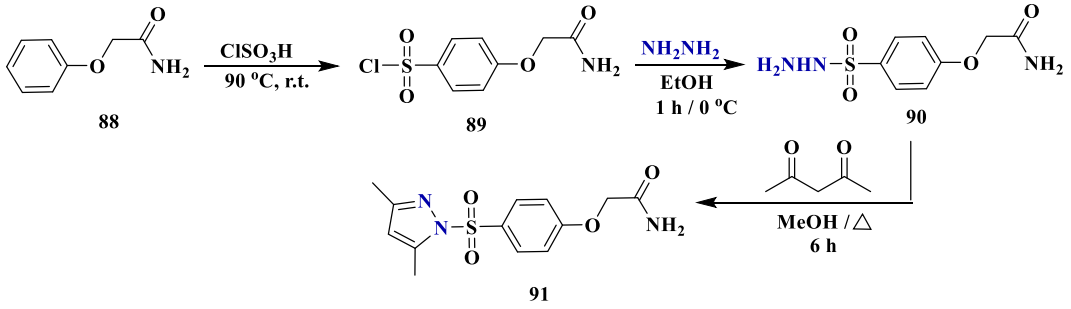
Sanghapal et al. [60] developed a new method for direct *N*-heterocyclization of sulfonylhydrazines **92** with metal-diketones namely copper(II)acetylacetonate [$Cu(acac)_2$] for the synthesis of various 3,5-dimethyl-*N*-sulfonyl pyrazoles **93** in excellent yields under microwave irradiation for 5 min at 100°C. This method was also applicable to various sulfonyl hydrazines, which are very important functional moieties in drug discovery (Scheme 5.42).

Liu et al. [61] demonstrated the reaction of 3-oxo-3-phenylpropanenitrile **94** with phenylsulfonyl hydrazide, and *N*-iodosuccinimide (NIS) for 6 h at room temperature to yield the cyclized 3-phenyl-1-(phenylsulfonyl)-1*H*-pyrazol-5-amine **95** with 69% yield. This protocol presents



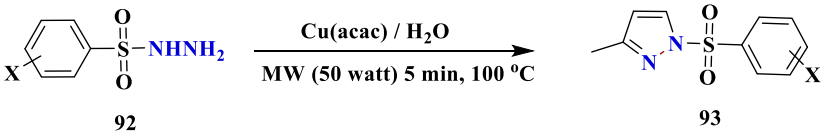
85 86 87

SCHEME 5.40 Formation of 5-[3,5-(dimethyl-1*H*-pyrazol-1-yl)sulfonyl]-2-methylbenzamide **87**.



88 89 90 91

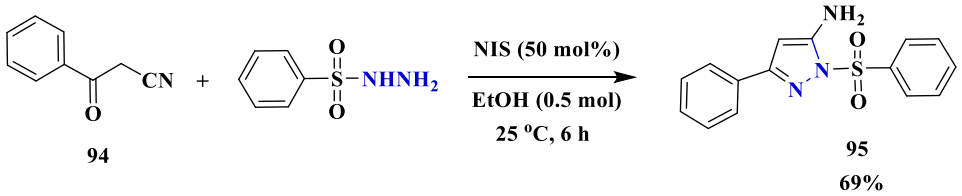
SCHEME 5.41 Synthesis of 4-[(3,5-dimethylpyrazol-l-yl)sulfonyl]phenoxy acetamide **91**.



92 93

X = 4-Me (92%), 4-OMe (89%), 3,4-$(OMe)_2$ (90%), 2-MeO-6-Br (97%), 2,3,4,5,6-$(Me)_5$ (93%), 4-F (85%), 3-F_3C (83%), 2-F_3CO (82%), 4-F_3CO (89%), 3,5-$(OCF_3)_2$ (88%), 4-CN (91%), naphthyl (88%)

SCHEME 5.42 *N*-Heterocyclization of sulfonylhydrazines **92** to 3,5-dimethyl-*N*-sulfonyl pyrazoles **93**.



94 95 69%

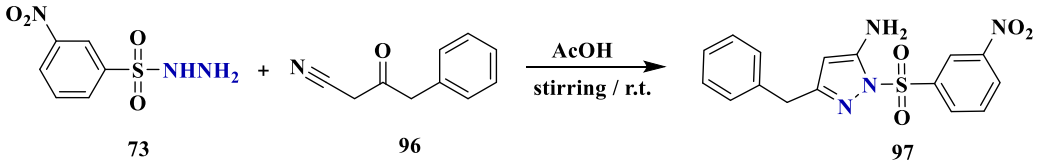
SCHEME 5.43 Formation of cyclized 3-phenyl-1-(phenylsulfonyl)-1*H*-pyrazol-5-amine **95**.

good functional group tolerance and mild reaction conditions (Scheme 5.43).

Bai et al. [62] synthesized 3-benzyl-1-(3-nitrophenylsulfonyl)-1*H*-pyrazol-5-amine **97** from the reaction of 4-nitrobenzene sulfonyl hydrazide **73** and 3-oxo-4-phenylbutanenitrile **96** in glacial acetic acid under stirring at room temperature for 6 h with yield 60% (Scheme 5.44).

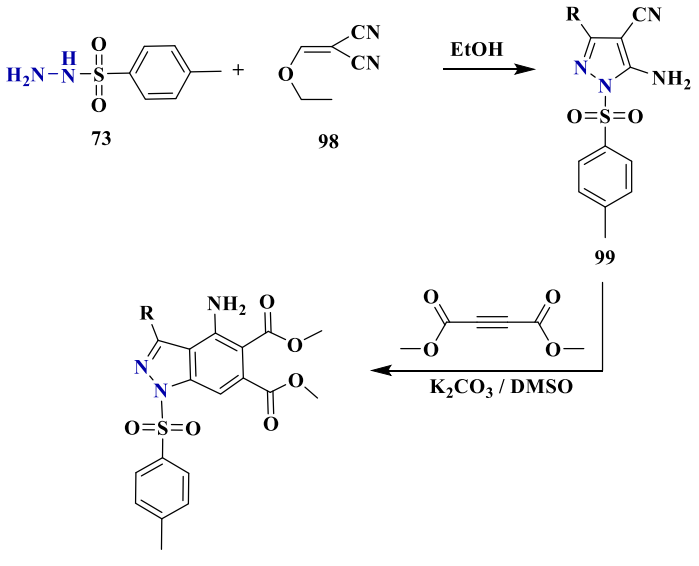
Tomrnaga et al. [63], developed the synthesis of 1,3-disubstituted 5-aminopyrazole-4-carbonitriles **99** from ethoxymethylene malononitrile **98** with 4-methylbenzenesulfonyl hydrazide **73**, which then reacted with dimethyl acetylenedicarboxylate in the presence of potassium carbonate in dimethylsulfoxide to give the corresponding dimethyl-1,3-disubstituted pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates **100** (Scheme 5.45).

wQuinoline sulfonyl hydrazide **101** was cyclized with each ethyl cyanoacetate, and ethyl acetoacetate afforded the corresponding 5-amino-2-((8-hydroxyquinolin-5-yl)sulfonyl)-2,4-dihydro-3*H*-pyrazol-3-one **102** and 2-((8-hydroxyquinolin-5-yl)sulfonyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one



73 96 97

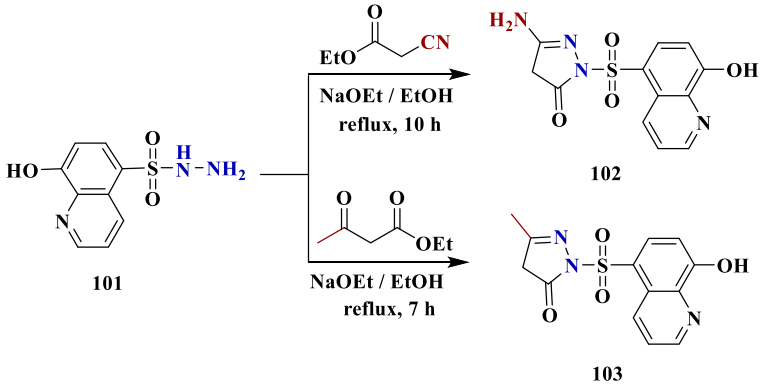
SCHEME 5.44 Synthesis of 3-benzyl-1-(3-nitrophenylsulfonyl)-1*H*-pyrazol-5-amine **97**.



73 98 99 100

R = H (38%), SMe (45%)

SCHEME 5.45 Synthesis of 1,3-disubstituted 5-aminopyrazole-4-carbonitriles **99**.



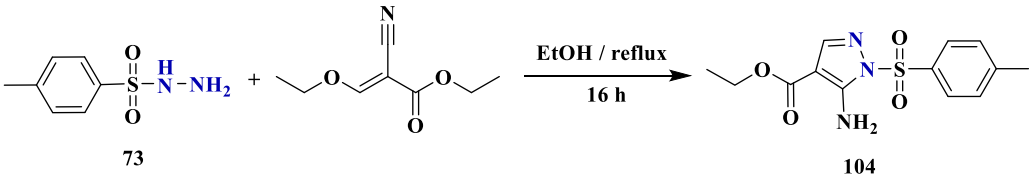
101 102 103

SCHEME 5.46 Synthesis of 8-hydroxyquinolin-5-yl-*N*-sulfonylpyrazol-3-ones **102** and **103**.

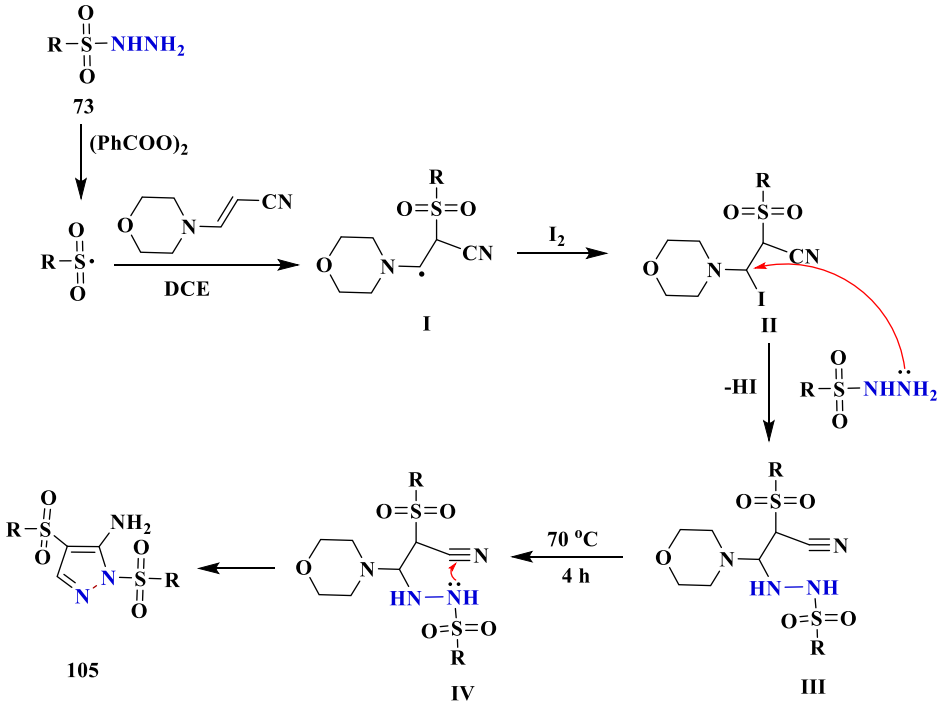
103, respectively which exhibited in vitro schistosomicidal activity against *S.* mansoni adult worms (Scheme 5.46) [64].

The reaction of 4-methylbenzenesulfonohydrazide **73** with (*E*)-ethyl 2-cyano-3-ethoxyacrylate was conducted in the presence of ethanol at reflux for 16 h afforded ethyl 5-amino-1-tosyl-1*H*-pyrazole-4-carboxylate **104** with 65% yield (Scheme 5.47) [65].

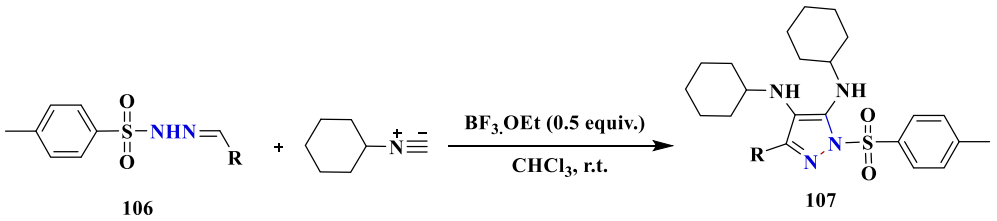
Cheng et al. [66] reported the tandem reaction of sulfonyl hydrazides **73** with 3-morpholinoacrylonitrile in the presence of iodine-benzoyl peroxide (I_2/BPO), which offers an efficient approach for the synthesis of aromatic, heteroaromatic and aliphatic 1,4-(arylsulfonyl-5-aminopyrazoles) **105**. A possible mechanism is hypothesized as depicted in Scheme 5.47. Initially, sulfonyl radical is formed by the removal of nitrogen from sulfonyl hydrazine in the presence of benzoyl peroxide and iodine. Subsequently, the in situ formed sulfonyl radical attacks the double bond of **1** to afford the radical intermediate **I**. The reaction of intermediate **I** with I_2 or iodine radical generates the corresponding



SCHEME 5.47 Ethyl 5-amino-1-tosyl-1*H*-pyrazole-4-carboxylate **104**.



SCHEME 5.48 Mechanismatic path way of 1,4-(arylsulfonyl-5-aminopyrazoles) **105**.



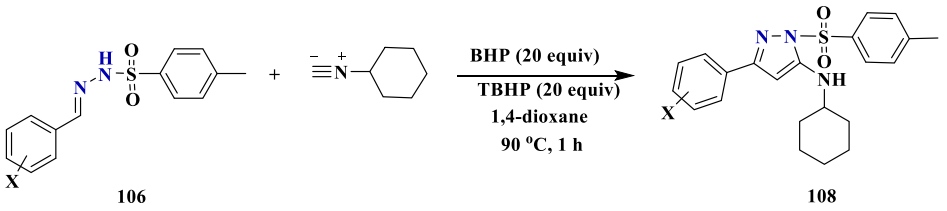
R = Ph (61%), 2-EtC$_6$H$_4$ (46%), 2-MeC$_6$H$_4$ (88%), 4-MeC$_6$H$_4$ (82%), 4-OMeC$_6$H$_4$ (87%), 3,4-(OMe)$_2$C$_6$H$_3$ (85%), 2-ClC$_6$H$_4$ (81%), 3-ClC$_6$H$_4$ (74%), 4-ClC$_6$H$_4$ (72%), 2-BrC$_6$H$_4$ (77%), 2-NO$_2$C$_6$H$_4$ (13%), 2-thienyl (49%)

SCHEME 5.49 Preparation of N^4, N^5-dicyclohexyl-3-aryl-1-tosyl-1*H*-pyrazole-4,5-diamines **107**.

iodide **II**, which is attacked by sulfonyl hydrazide to form **III**. The intermediate **III** loses one molecule of morpholine to give the intermediate **IV** and subsequently occurs the intermolecular cyclization and isomerization to give the target product **105** (Scheme 5.48).

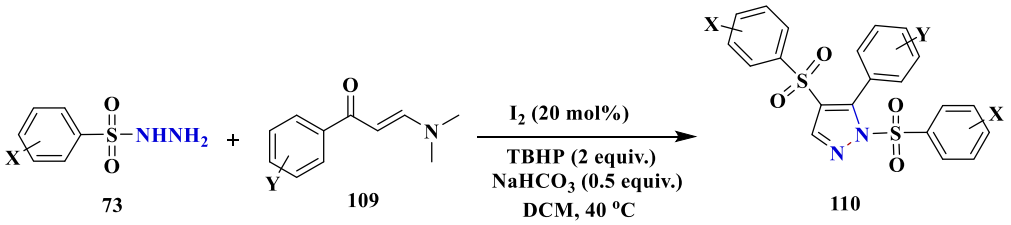
Tang et al. [67] demonstrated a facile method for the preparation of N^4, N^5-dicyclohexyl-3-aryl-1-tosyl-1*H*-pyrazole-4,5-diamines **107** from *N*-tosylhydrazones **106** and cyclohexyl isocyanide in the presence of $BF_3 \cdot OEt_2$ in chloroform at room temperature. This strategy proceeded smoothly, and the reaction conditions showed good compatibility with different substituents. The present reaction mechanism was proposed as acid-promoted [3 + 1 + 1] cyclization (Scheme 5.49).

Wang et al. [68] developed iodine-*tert*-butyl hydroperoxide (I_2-TBHP)-catalyzed formal [4 + 1]-annulation of *N*-sulfonyl hydrazine derivatives **106** with cyclohexyl isocyanide in 1,4-dioxane for 1 h at 90°C for the synthesis of



X = H (85%), 4-Me (79%), 4-MeO (77%), 4-F (88%), 3-Br (76%), 3-I (78%), 4-CN (77%), 4-FC_3 (72%), ,4-$(Cl)_2$ (79%)

SCHEME 5.50 Formal [4 + 1]-annulation of *N*-sulfonyl hydrazine derivatives **106**.



Y = H, X = H (70%), 4-MeO (78%), 2-Cl (62%), 4-Cl (68%), 4-Br (72%), 4-F (63%)

X = 3,4-$(Cl)_2$, Y = 4-MeO (68%)

SCHEME 5.51 Synthesis of 4-sulfonyl-*N*-sulfonyl-5-substituted pyrazoles **110**.

3,5-disubstitued-*N*-sulfonylpyrazoles **108** in good yields *via* in situ generations of azo-alkene. This metal-free approach is realized through conjugate addition (C−C bond formation) and zwitterionic cyclization (C−N bond formation) (Scheme 5.50).

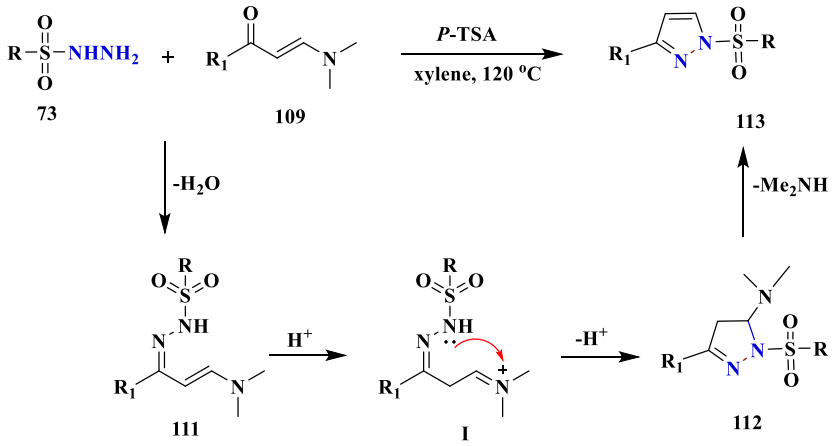
The synthesis of 4-sulfonyl-*N*-sulfonyl-5-substituted pyrazoles **110** have demonstrated by Tian et al. [69] by the reactions of sulfonyl hydrazines **73** with *N, N*-dimethyl enaminones **109** catalyzed by molecular iodine in the presence of TBHP and sodium bicarbonate in acetonitrile at 40°C. The produced substituted pyrazoles **110** have been constructed through the tandem C(sp^2)-H sulfonylation and a pyrazole annulation without using any transition-metal catalyst or reagent (Scheme 5.51).

In another report, the rapid synthesis of 3-substituted *N*-sulfonyl pyrazoles **113** was achieved by reacting sulfonyl hydrazines **73** with *N, N*-dimethyl enaminones **109** using *p*-toluene sulfonic acid (*p*-TSA). A plausible mechanism of formation of compounds **113** is shown in Scheme 5.51. Carbonyl-tosyl hydrazine of sulfonyl hydrazine **73** initially condensed with *N, N*-dimethyl enaminone **109** affords **111**, and subsequently, incorporate with proton leads to intermediate **I**, which generates pyrazolines **112** through loses a proton *via* intramolecular nucleophilic cyclization. The final product **113** is formed from **112** due to the elimination of the dimethyl amine molecule (Scheme 5.52) [70].

The cascade reactions between sulfonyl hydrazines **73** and NH_2-functionalized enaminones **114** were developed by Guo et al. [71] for the synthesis of 4,5-disubstituted 1,3-bis (arylsulfonyl)-1*H*-pyrazoles **115** in good to excellent yields. The reaction proceeds well *via* cascade C-H sulfonylation and pyrazole annulation in pure water in the presence of molecular iodine, TBHP, and $NaHCO_3$ at room temperature (Scheme 5.53).

Romagnoli et al. [72] designed two series of *N*-tosyl-3,4-diaryl-1*H*-pyrazoles **121** and **125** containing 3,4,5-trimethoxy rings at either C-3 or C-4. Thus, the reaction of enaminones **116** and **109** with hydrazine hydrate in ethanol afforded pyrazole derivatives **117** and **122**, respectively. Monobromination at 4-position of the pyrazole nucleus of compounds **117** and **122** using *N*-bromosuccinimide in DMF afforded the corresponding 3-aryl-4-bromo-1*H*-pyrazole analogs **118** and **123**, respectively. The pyrazole hydrogen of these latter compounds was replaced with a tosyl group by treatment with *p*-toluenesulfonyl chloride (TsCl) in a mixture of dichloromethane and pyridine to obtain the corresponding *N*-tosyl-4- bromopyrazoles **119** and **124**, respectively. The brominated products were subjected to a Suzuki cross-coupling process in the presence of arylboronic acids **120** under heterogeneous conditions $PdCl_2$(DPPF) and CsF in 1,4-dioxane at 65°C, to afford the corresponding 3,4-diaryl pyrazole derivatives **121** and **125**, respectively. The synthesized 3,4-diaryl pyrazole derivatives **121** and **125** were designed and prepared as analogs of cis-rigidified combretastatin A-4 (CA-4) and showed in vitro antiproliferative activity against six different cancer cell lines. The selected compounds were evaluated for high activity inhibitory effects on tubulin polymerization, cell cycle effects, and in vivo potency (Scheme 5.54).

Wang et al. [73] developed a $Zn(OTf)_2$-promoted cyclization reaction of 2- (dimethylamino)malononitrile **126** with tosylhydrazones **127** affording an efficient



R = Ph, R_1 = Ph (60%), 4-MeC_6H_4 (65%), 4-$OMeC_6H_4$ (65%), 2-ClC_6H_4 (59%),4-ClC_6H_4 (58%), 4-FC_6H_4 (64%), 4-$CF_3C_6H_4$ (52%), 4-$NO_2C_6H_4$ (51%), 2-OHC_6H_4 (45%), 1,1`-biphenyl (51%), styryl (46%), 2-thienyl (50%), 1-adamantanyl (55%)

R = 4-MeC_6H_4, R_1 = Ph (61%), 4-MeC_6H_4 (64%), 4-$OMeC_6H_4$ (62%), 4-ClC_6H_4 (56%), 4-ClC_6H_4 (56%), 4-FC_6H_4 (58%), 2-furyl (50%)

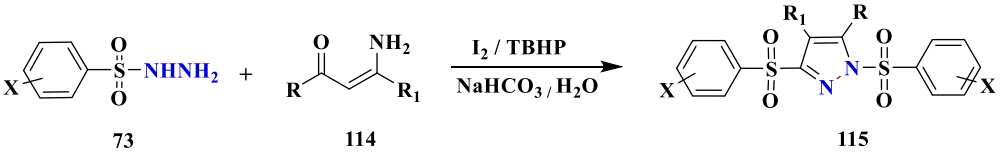
R = 4-BrC_6H_4, R_1 =4-MeC_6H_4 (65%), 4-$OMeC_6H_4$ (62%)

R = 4-$^tBuC_6H_4$, R_1 = 4-$OMeC_6H_4$ (64%)

R = 2-FC_6H_4, R_1 = 4-$OMeC_6H_4$ (66%)

R = 2-Naphthyl, R_1 = 4-MeC_6H_4 (53%)

SCHEME 5.52 Mechanism of formation of 3-substituted *N*-sulfonyl pyrazoles **113**.



R = Ph, R_1 = Me, X = H (76%), 2-Me (78%), 4-Me (80%), 4-Cl (85%), 4-Br (82%, 4-F (82%)

R = R_1 = Me, X = H (71%), 2- Me (74%), 4-OMe (78%), 4-Cl (80%), 2,4,6-$(Me)_3$ (67%), 4-Cl (83%)

R = R_1 = Et, X = 4-Me (65%), 4-OMe (70%), 4-Cl (68%), 4-F (77%), 4-CF_3 (70%)

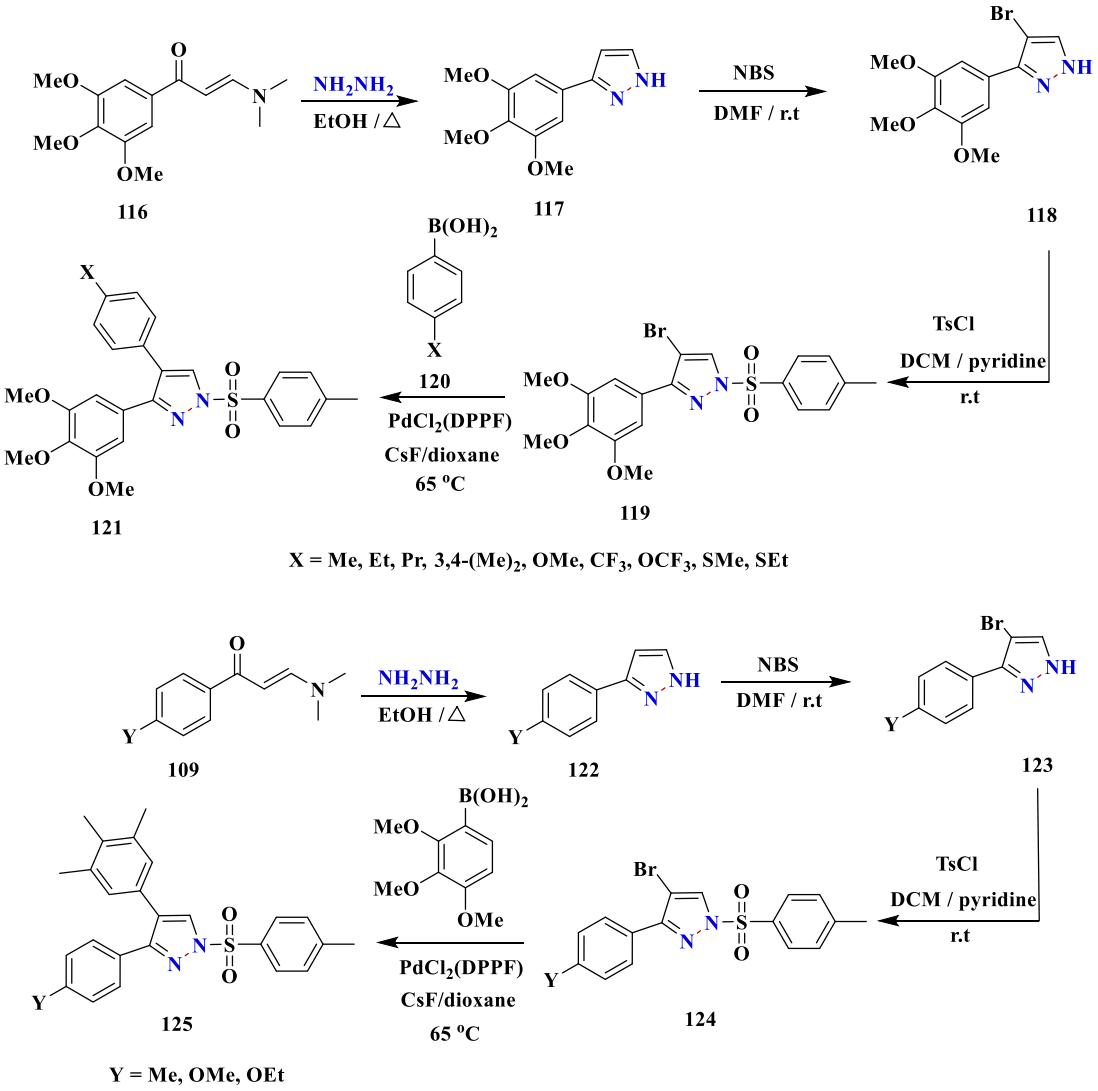
SCHEME 5.53 Formation of 4,5-disubstituted 1,3-bis (arylsulfonyl)-1*H*-pyrazoles **115**.

strategy for the synthesis of 3-substituted 1-tosyl-1*H*-pyrazoles **128** in good yields. A suggested mechanism of formation of compounds **128** as shown in Scheme 5.55.

Ito et al. [74] described the formation of pyrazoles by the reaction of *N*-(phenyl sulfonyl)benzohydrazonyl chloride with enamines, which proceeds through the two-step way involving the nucleophilic process. Thus, the reaction of **129** with ethyl or allyl 3-(diethyl amino)crotonates **130a,b** in tetrahydrofuran at room temperature afforded the 4-ethoxycarbonyl or 4-allyloxycarbonyl-5-methyl-3-phenyl-1-phenyl sulfonyl pyrazoles **131a,b** with good yields (Scheme 5.56).

Liu et al. [75] reported a novel synthesis of 3-arylpyrazoles **133** bearing *N*-sulfonyl and 5-alkylthio groups *via* the reactions of sulfonyl hydrazines **73** with ketene dithioacetals **132** using *p*-toulenesulfonic acid as an acid catalyst in tetrahydrofuran at 65°C as mild heating conditions in an air atmosphere (Scheme 5.57).

Zhou et al. [76] developed an iodine-catalyzed [3 + 2] cycloaddition/ring-opening reaction of 1,1- sulfonyl hydrazides **73** with diacylcyclopropane in the presence of 20 mol% iodine in acetonitrile at 70°C, to afford the functionalized *N*-sulfonylpyrazoles **134** with a hydroxyl functional group in moderate to excellent yields with high regioselectivity. The proposed mechanism for pyrazole formation proceeds initially, in which sulfonyl hydrazide **73** reacts with diacylcyclopropane to form sulfonylhydrazone **I**, which undergoes intramolecular condensation to give intermediate **II**. Intermediate **II** is then reacted with iodine to afford intermediate **III** and at the same time



SCHEME 5.54 Synthetic routes of *N*-tosyl-3,4-diaryl-1*H*-pyrazoles **121** and **125**.

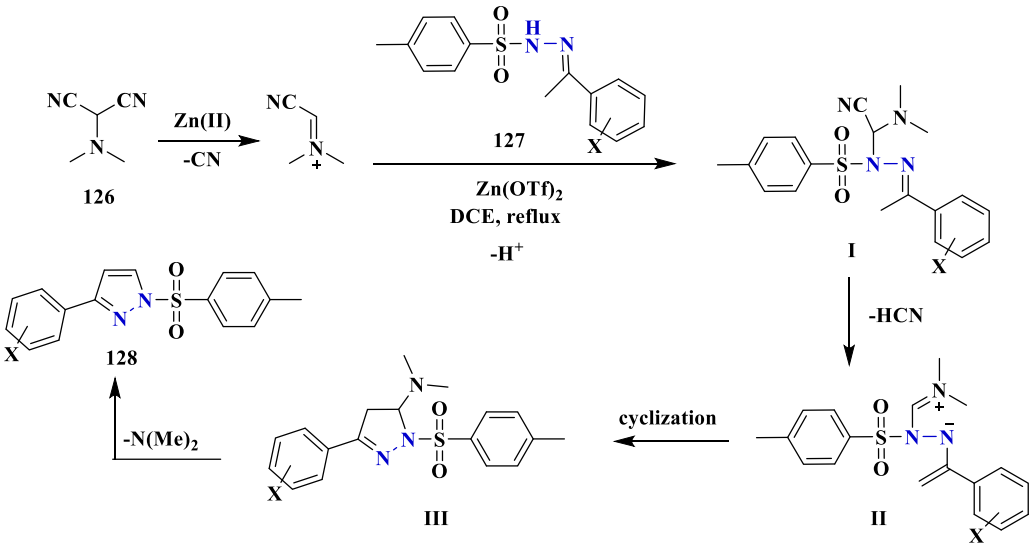
iodine is converted into hypoiodic acid. Due to the ring tension, intermediate **III** undergoes ring opening to give intermediate **IV**, which is attacked by the previously removed hydroxyl anion to form 1-(1-(substituted sulfonyl)-3-methyl-5-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-ols **134** (Scheme 5.58).

Kovalchuk et al. [77,78] established the reaction of tosylhydrazine **73** with 3-aryl-1-(2-methyloxiran-2-yl) prop-2-en-1-ones **135** leads to 3-[(*E*)-2-arylvinyl]-4-methyl-1-tosyl-1*H*-pyrazoles **136** and 3-aryl-1-(2-methyloxiran-2-yl)-3-tosylpropan-1-ones **137**. The latter is formed as a result of rearrangement of the intermediate hydrazino alcohols **I** and/or addition of *p*-toluenesulfinic acid, which formed during the decomposition of tosylhydrazine **73**. It was shown that the reaction of 3-aryl-1-(2-methyloxiran-2-yl)-3-tosylpropan-1-ones **137** with an excess of tosylhydrazine **73** leads to 3-(2-aryl-2-tosylethyl)-4-methyl-1-tosyl-1*H*-pyrazoles **138**. The proposed mechanism for the formation of compounds **3**, **4**, and **5** is shown in Scheme 5.59.

Rao et al. [79] described a new efficient and one-pot method for the synthesis of functionalized *N*-sulfonylpyrazoles **140** from 4-methylbenzenesulfonyl hydrazide **73** with ethoxycyclobutanones **139** at ambient temperature using a small amount of $SnCl_4$ in DCM. The reaction demonstrates excellent reactivity, complete regioselectivity, and high yields (Scheme 5.60).

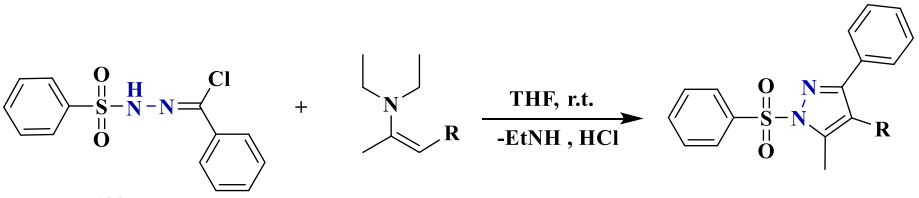
An efficient method for synthesized 4-iodo-5-phenyl-1-tosyl-3-(trifluoromethyl)-1*H*-pyrazole **142** with 94% yield was achieved by the cyclization of 4-methyl-*N*'-(1,1,1-trifluoro-4-phenylbut-3-yn-2-ylidene)benzenesulfonohydrazide **141** in the presence of sodium bicarbonate in acetonitrile at room temperature for one day using molecular iodine (Scheme 5.61) [80].

Chen et al. [81] established simple method for the preparation of 4,5-disubstituted-*N*-tosylpyrazoles **145**



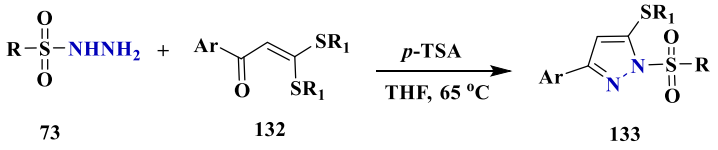
X = H (92%), 2-Me (80%), 3-Me (78%), 4-Me (73%), 4-OMe (91%), 3,4-$(OMe)_2$ (69%), 4-CN (55%)
2-Cl (86%), 3-Cl (83%), 4-Cl (83%), 4-Br (87%), 4-F (88%), 4-F_3C (86%), 3,5$(CF_3)_2$ (63%)

SCHEME 5.55 Use of $Zn(OTf)_2$ as catalyst in the synthesis of 3-substituted 1-tosyl-1*H*-pyrazoles **128**.



131a, R = COOEt (89%)
b, R = $COOCH_2CH{=}CH_2$ (87%)

SCHEME 5.56 Synthesis of 4-ethoxycarbonyl or 4-allyloxycarbonyl-5-methyl-3-phenyl-1-phenyl sulfonyl pyrazoles **131a,b**.

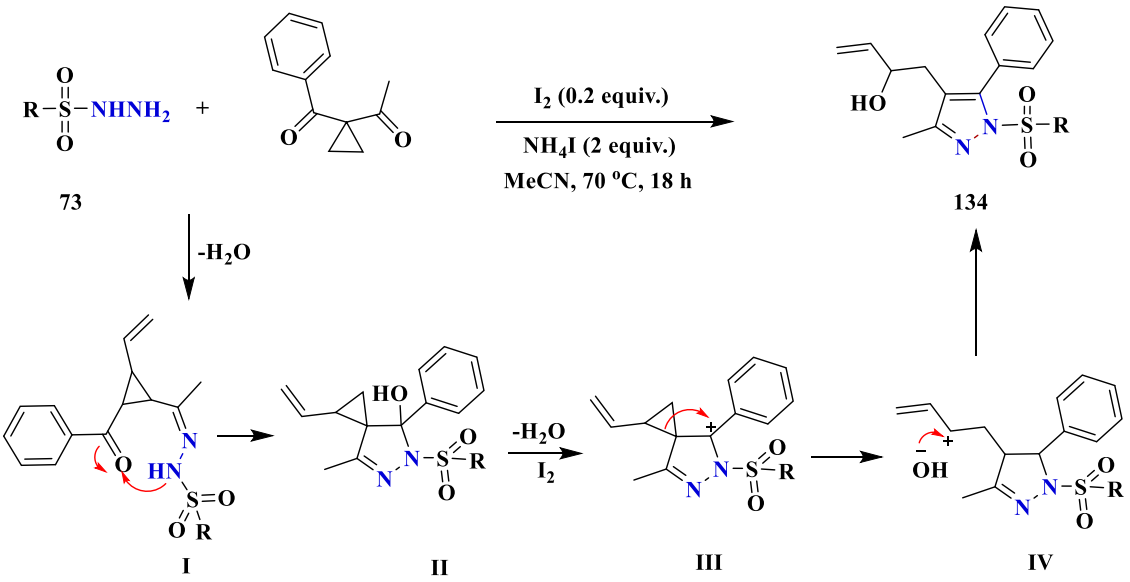


R_1 = Me, R = 4-MeC_6H_4, Ar = Ph (72%), 4-MeC_6H_4 (71%), 4-$OMeC_6H_4$ (69%), 4-ClC_6H_4 (75%), thienyl (65%)
R_1 =Me, Ar = 4-C_6H_4, R = Ph (66%), 3-MeC_6H_4 (73%), 4-MeC_6H_4 (66%), 4-ClC_6H_4 (63%), 2-FC_6H_4 (64%)
R_1 = Et, R = 4-MeC_6H_4, Ar = Ph (67%), 4-MeC_6H_4 (67%), 4-ClC_6H_4 (68%)

SCHEME 5.57 Formation of 3-arylpyrazoles **133** bearing *N*-sulfonyl and 5-alkylthio groups **133**.

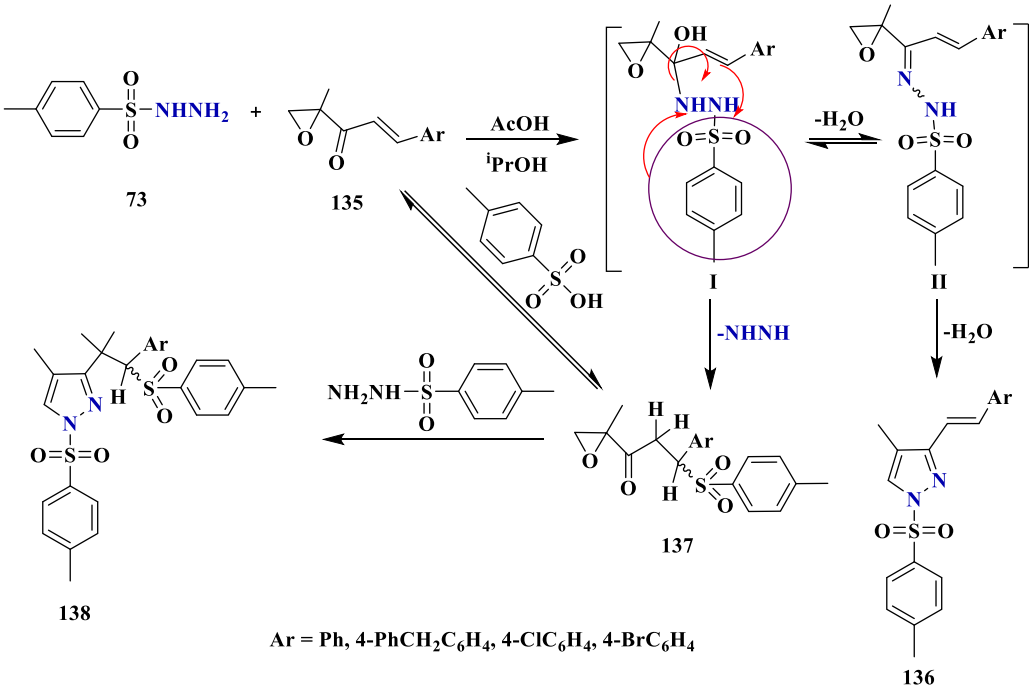
through Sonogashira coupling/cyclization of *N*-propargyl sulfonylhydrazones **143** with aryl iodide derivatives **144** using bis(triphenylphosine)palladium(II) dichloride/ copper(I)iodide [Pd (II)/Cu (I)] catalyst in a one-pot reaction. This protocol provides an expedient method to construct substituted-*N*-tosylpyrazole rings with a wide range of substrates under mild conditions (Scheme 5.62).

Chen et al. [82] developed a new strategy for the synthesis of (*E*)-4-benzylidene-4,5-dihydro-1*H*-pyrazoles **148** through tandem intermolecular addition-intramolecular cyclization of *N*-propargylic sulfonylhydrazones **146** with aryl acetals **147** in the presence of ferric chloride in DCE at 80°C. A plausible mechanism for this reaction is postulated that the aryl acetals initially react with $FeCl_3$ to form the oxocarbonium cation $PhCH=OEt^+$ **I** and the anion $FeCl_3(OEt)$. Cation **I** then reacts with *N*-propargylic sulfonylhydrazones **146** to generate vinyl cation **II**, which is subjected to intramolecular nucleophilic attack by the nitrogen atom to yield the intermediate pyrazole **III**. The pyrazole ring intermediate **III** is then hydrolyzed with water to give **IV**. Intermediate **IV** reacts again



R = Et (57%), Bu (57%), Bn (67%), cyclopropyl (65%), Ph (61%), 4-MeC_6H_4 (75%), 4-$OMeC_6H_4$ (65%), 4-ClC_6H_4 (71%), 4-BrC_6H_4 (73%), 4-FC_6H_4 (65%), 4-IC_6H_4 (59%), 4-$NO_2C_6H_4$ (43%), 4-AcNH (48%)

SCHEME 5.58 Synthetic pathway of 1-(1-(substituted sulfonyl)-3-methyl-5-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-ols **134**.

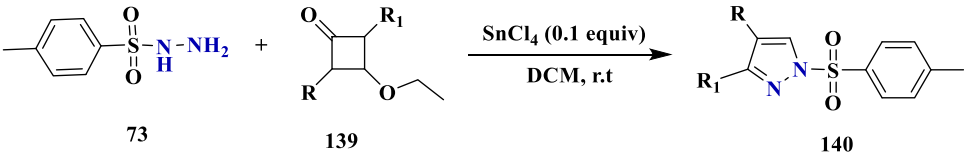


Ar = Ph, 4-$PhCH_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

SCHEME 5.59 Pathway of formation of 3-(2-aryl-2-tosylethyl)-4-methyl-1-tosyl-1*H*-pyrazoles **138**.

with $FeCl_3$ to produce carbon cation intermediate **V**. Then stabilization through the elimination of an H^+ results in the products **148** (Scheme 5.63).

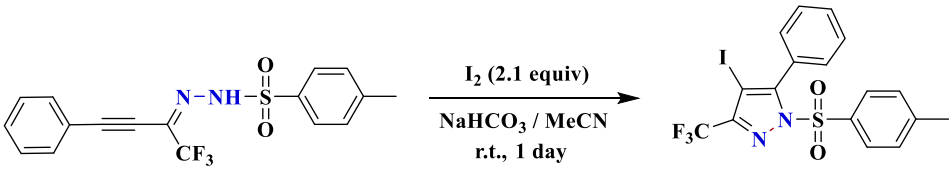
Chen et al. [83] developed a simple and green method for the synthesis of 3,5-disubstituted-*N*-tosylpyrazoles **149** in good to excellent yields from α,β-alkynyl *N*-tosylhydrazones **146** and diisopropylamine ($^iPr_2NH$) under metal- and solvent-free conditions at room temperature using a grind-stone protocol. The proposed mechanism of pyrazoles **149** formation proceeds through an intramolecular



73 139 140

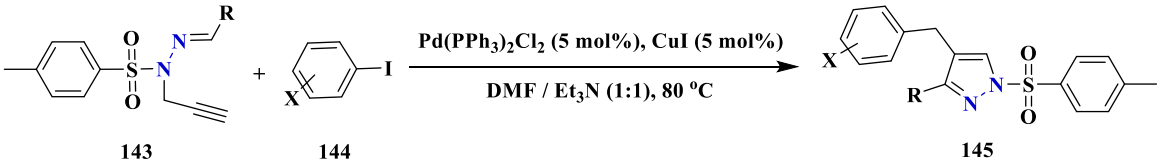
R = H, R_1 = Me (77%), Et (76%), ^{i}Pr (91%), Bn (85%),
CH_2Bn (85%), cyclohexayl (89%), cyclopentyl (87%)
R = Me, R_1 = Et (88%), ^{i}Pr (82%)

SCHEME 5.60 Synthesis of functionalized *N*-sulfonylpyrazoles **140**.



141 142

SCHEME 5.61 Synthesis of 4-iodo-5-phenyl-1-tosyl-3-(trifluoromethyl)-1*H*-pyrazole **142** using iodine.



143 144 145

R = 4-BrC_6H_4, X = 2-CN (85%), 4-CN (93%), 4-EtOOC (84%), 4-F_3C (78%)
X = 2-CN, R = 4-FC_6H_4 (88%), 4-MeC_6H_4 (78%), 4-OMeC_6H_4 (63%), naphthyl (81%)
X = 4-NO_2, R = 4-ClC_6H_4 (84%)
X = 4-CN, R = Et (83%), CF_3 (87%), thienyl (64%)

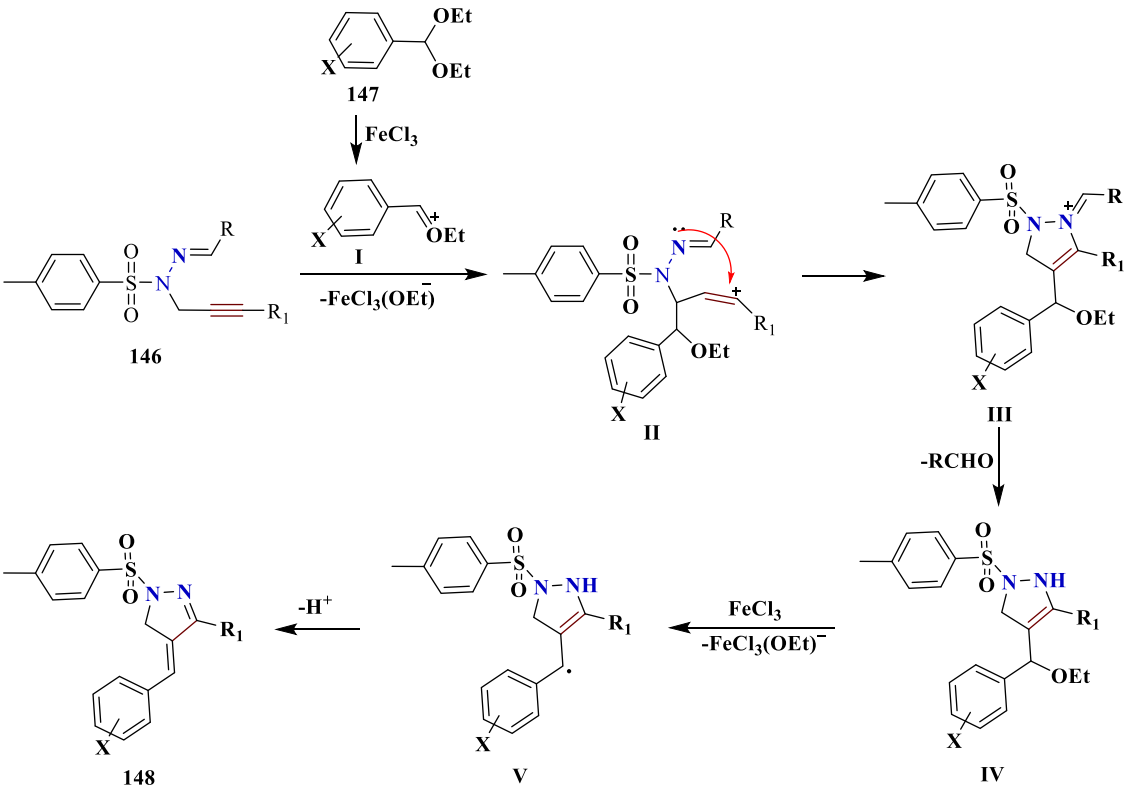
SCHEME 5.62 Bis(triphenylphosine)palladium(II) dichloride/copper(I)iodide catalyzed synthesis of 4,5-disubstituted-*N*-tosylpyrazoles through Sonogashira coupling/cyclization.

electrophilic cyclization process. Initial base-promoted deprotonation of alkyne **146** gives intermediate **I**, which then undergoes intramolecular electrophilic cyclization, and protonation affords the desired products **149** (Scheme 5.64).

Xiao et al. [84] developed an efficient ligand-free Pd (II)-catalyzed aminoacylation reaction of the inactivated alkenes in β,γ- and γ,δ-unsaturated hydrazones **150** with diaryliodonium tetrafluoroborate (Ar_2IBF_4) **151** as both aryl source and terminal oxidant. This protocol features great functional group compatibility, uses convenient materials as well as mild reaction conditions, and provides different 3,5-substituted-*N*-tosyl-4,5-dihydro-1*H*-pyrazoles **152** (Scheme 5.65).

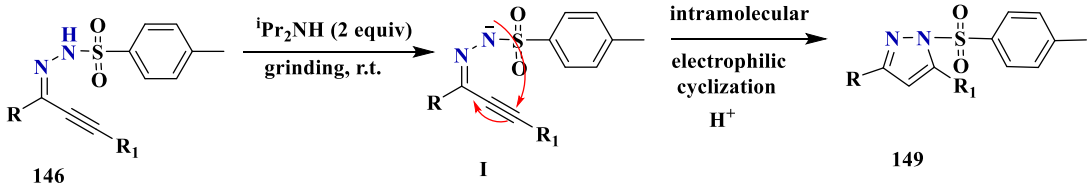
Lixin et al. [85] developed the first palladium-catalyzed aminomethylamination/aromatization of β,γ-unsaturated hydrazones namely, (*E*)-4-methyl-*N*′-(1-phenylbut-3-en-1-ylidene)benzene-sulfonohydrazide **153** with *N, N, N', N'*-tetrabenzylmethanediamine in the presence of 1,3-bis (diphenylphosphino)-propane (DPPP) in DCM for 24 h at 80°C. The reaction proceeds *via* activation of the C−N bond, resulting in various substituted *N, N*-dibenzyl-2-(3-substituted-1-tosyl-1*H*-pyrazol-5-yl)ethan-1-amine **154** which is of interest in medicinal chemistry. This reaction offers a novel strategy for the construction of aromatic heterocycles from aminoalkenes in the absence of external oxidizing agents and bases under the palladium catalysts. Mechanistic studies suggest that the aminal not only acts as a source of aminomethyl groups but also acts as an internal base and formal oxidizer to promote aromatization (Scheme 5.66).

An efficient synthesis of various substituted-*N*-tosylpyrazole derivatives through metal-free oxidative C−H cycloamination of vinyl hydrazones was developed by Zhu et al. [86]. The reaction usually completes within 5 min at ambient temperature in the air in good to excellent yields. Thus, (*Z*)-1-phenyl-2-[(*E*)-4-phenylbut-3-en-2-ylidene]hydrazine **155** was converted into substituted-*N*-tosylpyrazoles **156** in the presence of phenyliodine



X = H, R_1 = H (89%), 4-OMeC_6H_4 (80%), 4-ClC_6H_4 (85%), 4-BrC_6H_4 (80%), 4-FC_6H_4 (74%), naphthyl (50%), cyclopropyl (49%), cyclohexacyl (64%)

SCHEME 5.63 Synthesis of (*E*)-4-benzylidene-4,5-dihydro-1*H*-pyrazoles **148** through tandem intermolecular addition-intramolecular cyclization.



R_1 = R = ^{i}Pr (79%), Ph (92%), 4-MeC_6H_4 (77%), 4-MeOC_6H_4 (83%), 2-ClC_6H_4 (87%), 4-ClC_6H_4 (89%), 3,4-(Cl)$_2C_6H_3$ (74%), 4-BrC_6H_4 (74%), 2-FC_6H_4 (81%), 4-FC_6H_3 (73%), PhCH_2CH_2 (80%), naphthyl (91%)

R = Ph, R_1 = 4-MeC6H4 (77%), 4-EtC_6H_4 (90%), 4-ClC_6H_4 (84%), 4-BrC_6H_4 (87%), 2-FC_6H_4 (80%), 4-C_6H_4 (84%)

R = *n*-pentyl, R_1 = 4-FC_6H_4 (49%)

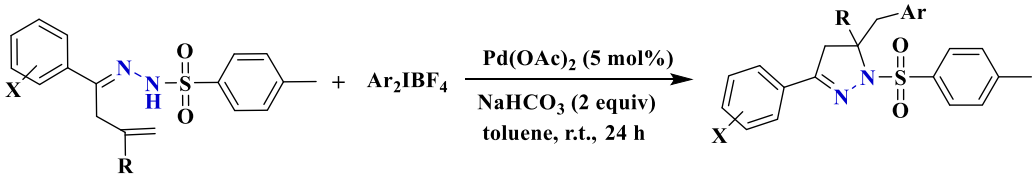
R = Me, R_1 = Et (90%)

SCHEME 5.64 Green method for the synthesis of 3,5-disubstituted-*N*-tosylpyrazoles **149**.

(III) diacetate and 1,1,1,3,3,3-hexafluoro-2-propanol (Scheme 5.67).

Zhan et al. [87] synthesized a series of fully substituted-*N*-sulfonyl pyrazoles **158** in moderate to good yields from *N*-allenic sulfonylhydrazones **157** using 20 mol% of ferric chloride, as a catalyst in DCM. This protocol is characterized by simplicity, mild reaction conditions, and the absence of by-products (Scheme 5.68).

Wang et al. [88] reported a straightforward strategy for the synthesis of 4-arylmethylene-1-(arylsulfonyl)-3,5-disubstituted-1*H*-pyrazoles **160** from propargyl alcohols **159** with *N*-sulfonylhydrazones **106** through a Lewis acid-catalyzed tandem reaction. A possible mechanism for this reaction was proposed, initially, assisted by a Lewis acid, **159** was converted to allenic carbocation **I** *via* Meyer Schuster rearrangement. Then **I** trapped in situ by **106** to



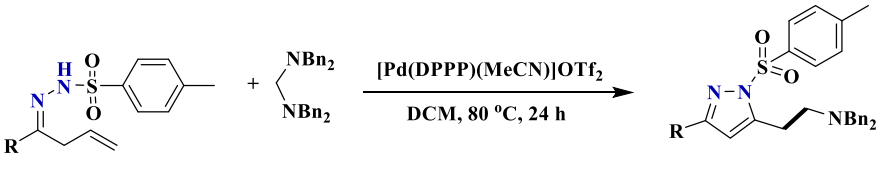
150 151 152

Ar = R = Ph, X = H (83%), 2-Me (37%), 4-Me (80%), 3-Cl (70%), 4-Cl (72%), 4-Br (80%)

X = H, Ar = Ph, R = Me (37%), 4-OMeC$_6$H$_4$ (91%), 4-ClC$_6$H$_4$ (93%), 2,4-(Cl)$_2$C$_6$H$_3$ (41%), 4-BrC$_6$H$_4$ (75%)

X = H, R = Ph, Ar = 4-CNC$_6$H$_4$ (80%), 4-ClC$_6$H$_4$ (74%), 1-naphthyl (62%)

SCHEME 5.65 Ligand-free Pd(II)-catalyzed aminoacylation reaction of the inactivated alkenes in β,γ- and γ,δ-unsaturated hydrazones.



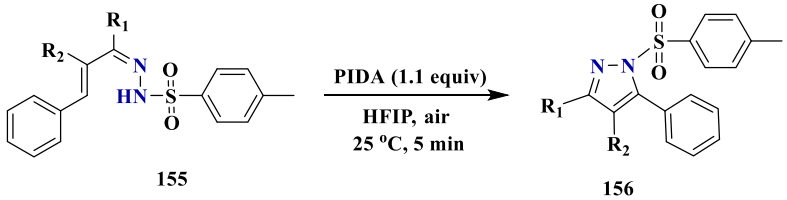
153 154

R = ^{i}Pr (60%), ^{t}Bu (77%), Ph (84%), 3-MeC$_6$H$_4$ (77%), 4-MeC$_6$H$_4$ (72%), 2-MeOC$_6$H$_4$ (57%), 3-OMeC$_6$H$_4$ (81%)

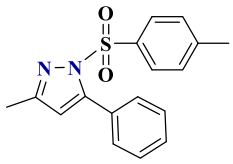
4-OMeC$_6$H$_4$ (80%), 3,5-(OMe)$_2$C$_6$H$_3$ (83%), 4-ClC$_6$H$_4$ (79%), 3,4-(Cl)$_2$C$_6$H$_3$ (79%), 3-BrC$_6$H$_4$ (77%), 4-BrC$_6$H$_4$ (87%)

2-FC$_6$H$_4$ (81%), 3-FC$_6$H$_4$ (75%), 4-CF$_3$C$_6$H$_4$ (80%), 2-naphthyl (80%), 2-thienyl (72%), 3-indol (75%)

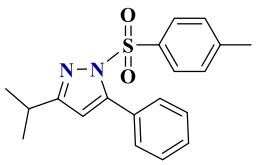
SCHEME 5.66 Palladium-catalyzed aminomethylamination/aromatization of β,γ-unsaturated hydrazones.



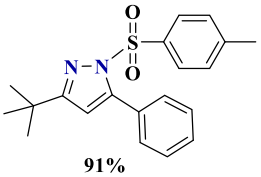
155 156



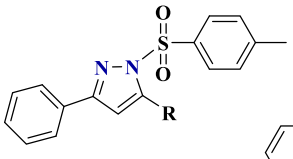
61%



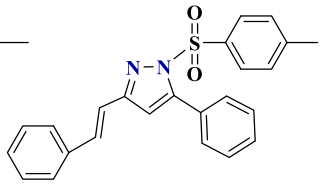
81%



91%



R =Ph (96%)
R = Me (82%)



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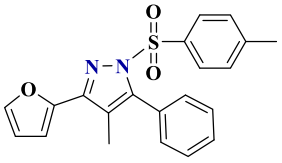

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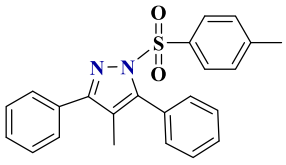
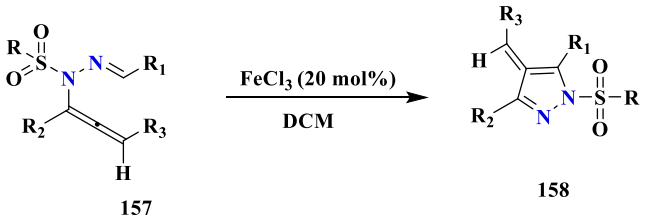


95%

SCHEME 5.67 Synthesis of *N*-tosylpyrazoles through metal-free oxidative C−H cycloamination of vinyl hydrazones.



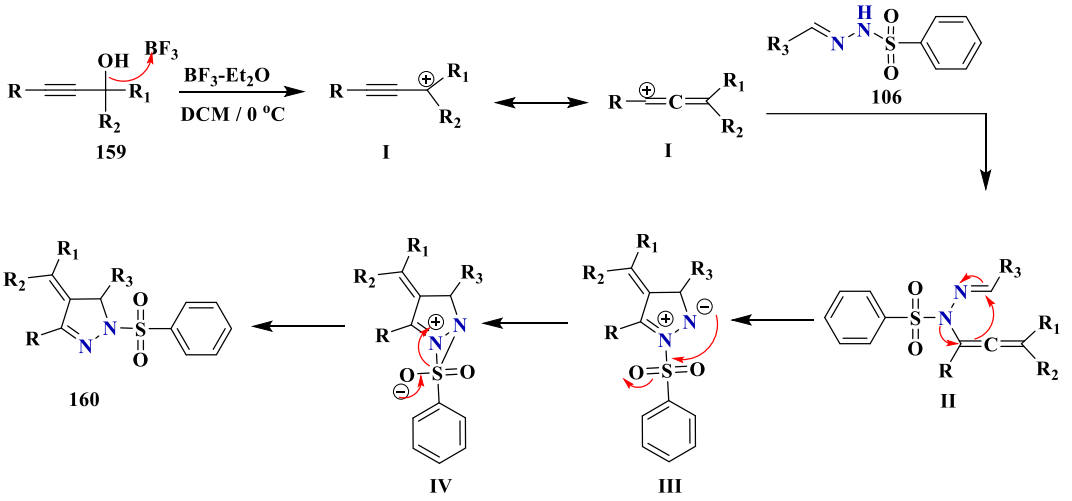
$R_1 = R_2 = R_3$ = Ph, R = Ph (84%), 4-MeC_6H_4 (83%), 4-$OMeC_6H_4$ (63%), 4-BrC_6H_4 (72%)

R = 4-Me, $R_2 = R_3$ = Ph, R_1 = 4-$OMeC_6H_4$ (82%), 4-FC_6H_4 (63%), 4-CNC_6H_4 (74%), naphthyl (95%), 2-theinyl (90%)

R = 4-MeC_6H_4, $R_1 = R_3$ = Ph, R_2 = 4-BrC_6H_4 (76%)

R = Ph, $R_1 = R_3$ = Ph, R_2 = 4-$OMeC_6H_4$ (73%)

SCHEME 5.68 Synthesis of fully substituted-*N*-sulfonyl pyrazoles **158**.



R = H, $R_1 = R_2 = R_3$ = Ph (66%),

R = H, $R_1 = R_2$ = 4-ClC_6H_4, R_3 = Ph (72%)

R = H, $R_1 = R_2$ = 4-MeC_6H_4, R_3 = Ph (55%)

R = H, $R_1 = R_3$ = Ph, R_2 = Me (41%)

R = n-Bu, R1 R3 = Ph, R2 = Ph (37%)

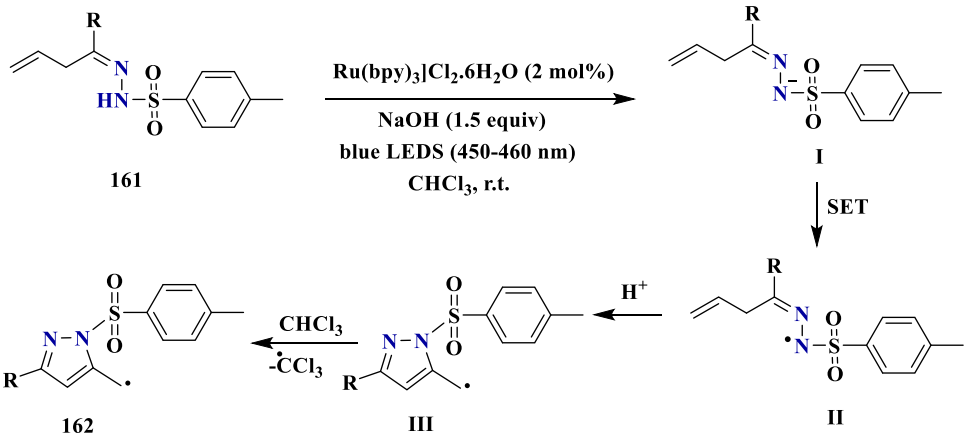
R = R1 = R2 = R3 = Ph (50%)

R = H, $R_1 = R_2$ = Ph, R_3 = 4-MeC_6H_4 (74%), 3,4-$Me_2C_6H_3$ (73%), 2-BrC_6H_4 (60%), 4-BrC_6H_4 (63%), 4-$NO_2C_6H_4$ (43%), $PhCH_2$ (33%), 1-naphthyl (74%), n-Pentyl (30%)

SCHEME 5.69 Straightforward strategy for the synthesis of 4-arylmethylene-1-(arylsulfonyl)-3,5-disubstituted-1*H*-pyrazoles **160**.

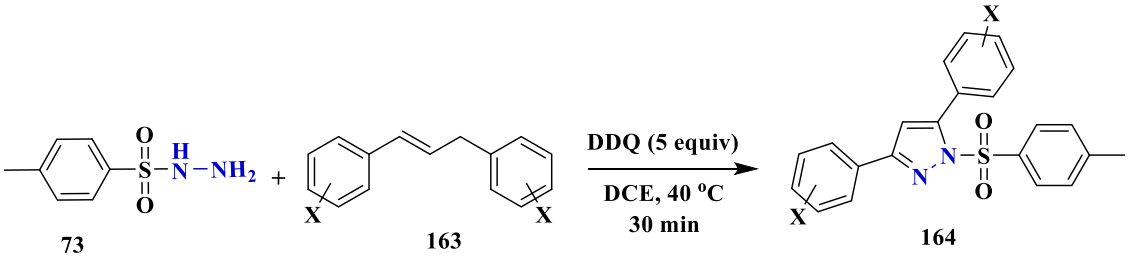
form *N*-sulfonylallenamide **II**. Because of the electron-donating nature of the nitrogen, the internal carbon of allene was electron-rich and could nucleophilically attack the electron-deficient carbon of the hydrazone. Thus, a cyclized intermediate **III** was constructed. Finally, intramolecular migration of the sulfonyl group led to the formation of the desired products **160** (Scheme 5.69).

Chen et al. [89] demonstrated a visible-light photocatalytic generation of *N*-centered hydrazonyl radicals for the first time from alkene tosylhydrazones **161**. This protocol provides efficient access to intramolecular alkene hydroamination and oxyamination, to afford the corresponding 3,5-disubstituted *N*-tosylyrazoles **162** in good yields. Importantly, the protocol involves deprotonation of an NH bond and photocatalytic oxidation to an *N*-centered radical, thus obviating the need to prepare photolabile amine precursors or the stoichiometric use of oxidizing reagents. A possible reaction mechanism was proposed as shown in Scheme 5.70. Deprotonation of the sulfonylhydrazone **161** under basic conditions to afford the anionic intermediate **I**. Single-electron oxidation of **I** by the excited state of the photocatalyst ($*[Ru(bpy)_3]2^+$) gives the *N*-centered radical **II** through a reductive quenching process. A 5-*exo*-trig cyclization of **II** affords the C-centered radical **III**. Subsequent hydrogen transfer from $CHCl_3$ to **III** gives the product **162**, together with



R = ^{i}Pr (74%), ^{t}Bu (84%), cyclohexcyl (76%), Ph (80%), $PhCH_2$ (62%), $PhCH_2CH_2$ (69%), 4-MeC_6H_4 (71%), 3-$MeOC_6H_4$ (68%), 2-ClC_6H_4 (73%), 2,4-$(Cl)_2C_6H_3$ (67%), 3-BrC_6H_4 (63%), 4-BrC_6H_4 (68%), 3-FC_6H_4 (77%), 4-FC_6H_4 (88%), 4-CF3C_6H_4 (70%)

SCHEME 5.70 Formation of 3,5-disubstituted *N*-tosylyrazoles **162** through **visible-light photocatalytic**.



X = H (80%), 2-Me (68%), 3-Me (79%), 4-Me (93%), 2-OMe (79%), 3-OMe (81%), 4-OMe (93%), 3,4-$(Me)_2$ (85%), 2-F (44%), 3-F (47%), 4F (7%), 4-Cl (63%), 4-Br (62%), 3F,4-F (75%)

SCHEME 5.71 Preparation of *N*-tosyl-3,5-diarylpyrazoles using DDQ under neutral and mild oxidative conditions.

the generation of trichloromethyl radical. The formed trichloromethyl radical can regenerate the photocatalyst ($[Ru^{-}(bpy)_3]_2^{+}$) through a single-electron-transfer process (Scheme 5.70).

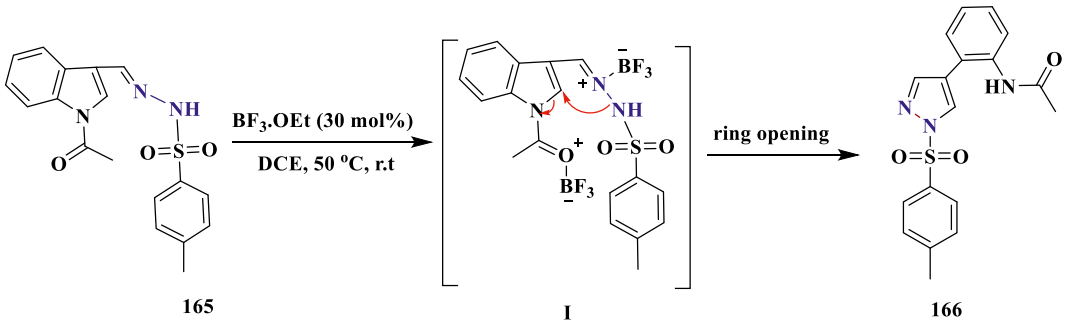
Zhang et al. [90] described a simple method for the synthesis of *N*-tosyl-3,5-diarylpyrazoles **164** from *p*-toluenesulfonyl hydrazide **73** with 1,3-diarylpropenes **163** *via* cascade intermolecular formation of C(sp^3)-*N* bond, oxidation and formation of C(sp^2)-*N* bond under neutral and mild oxidative conditions using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 5.71).

Manna et al. [91] demonstrated an unusual transformation of 1-acyl-1*H*-indole **165** to *N*-(2-(1-tosyl-1*H*-pyrazol-4-yl)phenyl)acetamide **166** *via* an aromatic ring-opening protocol in the presence of $BF_3.OEt_2$ at 50°C. The reaction involves the C_2-N_1 bond opening and concomitant cyclization reaction of the $C_2 = C_3$ bond of the indole moiety with the tosylhydrazone which proceeds under transition-metal and ligand-free conditions (Scheme 5.72).

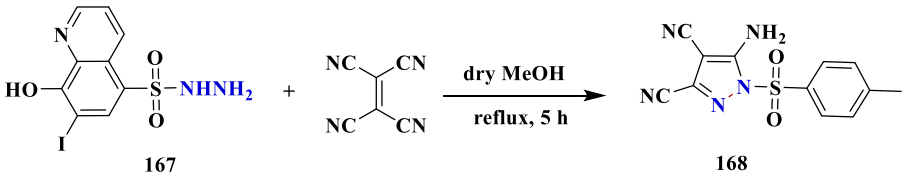
Heterocyclization of 8-hydroxy-7-iodoquinoline-5-sulfonohydrazide **167** with tetracyanoethylene in dry methanol afforded 5-amino-1-(8-hydroxy-7-iodoquinoline-5-sulfonyl)-1*H*pyrazole-3,4-dicarbonitrile **168** (Scheme 5.73) [92].

Xia et al. [93] described *N*-halosuccinimide mediated direct S-N bond formation between sodium sulfonates and substituted pyrazoles. Thus the reaction of sodium sulfonates **169** with pyrazoles **170** in the presence of *N*-halosuccinimide NXS (X = Br, I) as a halogen source in ethyl acetate at room temperature afforded *N*-sulfonyl-4-haloyrazoles **171**. A possible reaction pathway proceeds, initially, sodium sulfinates interacted with NXS to generate sulfonyl halide. Then, a nucleophilic reaction of pyrazoles **170** with sulfonyl halide would form the product. The halogenation could occur before or after the sulfonylation during the reaction (Scheme 5.74).

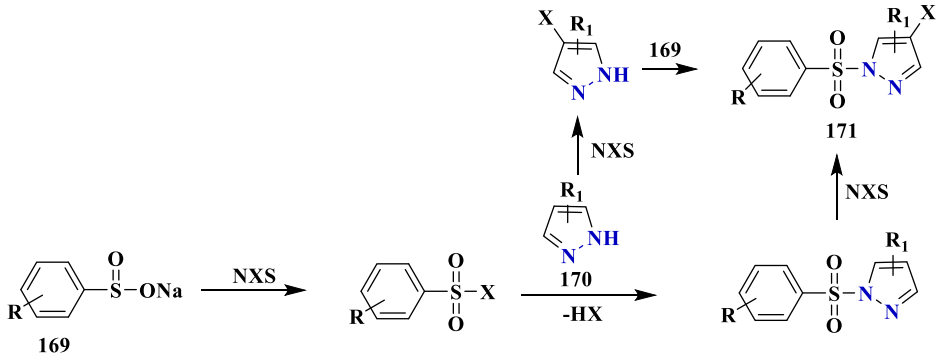
Pelcman et al. [94] developed the synthesis of *N*-1,3-disubstituted pyrazole-3-carboxanilides **176** that are good inhibitors of the human 15-LOX-1. Heating pyrazole-3-carboxylic acid **172** with $SOCl_2$ in tetrahydrofuran (THF)



SCHEME 5.72 Transformation of 1-acyl-1*H*-indole to *N*-(2-(1-tosyl-1*H*-pyrazol-4-yl)phenyl)acetamide *via* an aromatic ring-opening protocol.



SCHEME 5.73 Synthesis of 5-amino-1-(8-hydroxy-7-iodoquinoline-5-sulfonyl)-1*H*pyrazole-3,4-dicarbonitrile **168**.

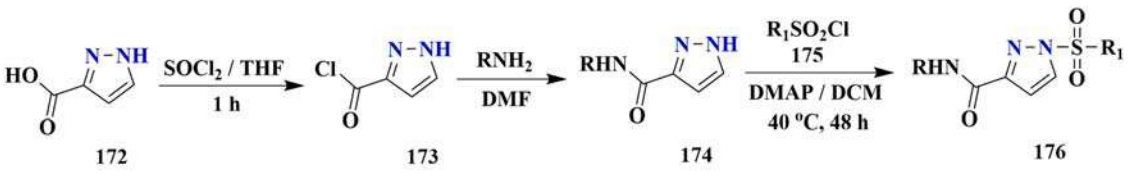


R = R_1 = H, X = I (60%)
R = H, X = Br, R_1 = Me (66%), Cl (85%), F (72%)
R = H, R_1 = OMe, X= Br (71%), I (73%)
R = H, R_1 = NO_2, X = I (62%)
R = 3-Me, R_1 = Me, X = Br (62%)
R = pyridyl, R_1 = Me, X = Br (98%), I (87%)
R = 3-Br, R_1 = Me, X = Br (96%), I (87%)
R = Ph, R_1 = Me, X = Br (91%), I (64%)

SCHEME 5.74 *N*-Halosuccinimide mediated direct S-N bond formation between sodium sulfonates and pyrazoles.

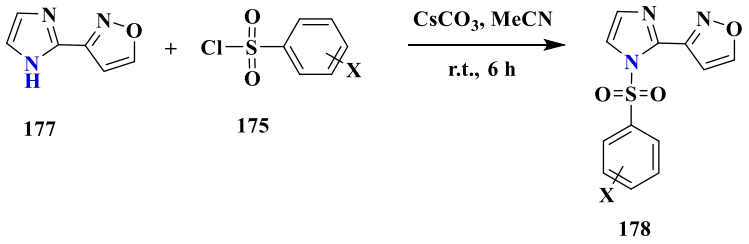
affords the corresponding acid chloride **173**, which is reacted with neat amine in the microwave or *N, N*-dimethylformamide to afford the corresponding carboxamides **174**. Sulfonylation of **174** with arylsulfonyl chlorides **175** in the presence of 4-dimethylaminopyridine (DMAP) in DCM at room temperature gives the final products **176** (Scheme 5.75).

Dende et al. [95] prepared a series of 2-(isoxazol-3-yl)-1*H*-imidazole sulfonamide derivatives **178** by the reaction of 2-(isoxazol-3-yl)-1*H*-imidazole **177** with various aryl sulfonyl chlorides **175** in the presence of Cs_2CO_3 in acetonitrile for 6 h at room temperature. In addition, these compounds were tested for their anticancer activity against four human cancer cell lines: MCF-7 (breast cancer), A549 (lung cancer), Colo-205 (colon cancer), and A2780 (ovarian cancer) using MTT assay, and etoposide was used as a positive control. Some compounds have shown more potent anticancer activity against human cancer cell lines (Scheme 5.76).



R = 2-Cl,4-FC$_6$H$_3$, R $_1$= 3-CF$_3$C$_6$H$_4$, N(Me)$_2$C$_6$H$_4$

SCHEME 5.75 Synthesis of *N*-1,3-disubstituted pyrazole-3-carboxanilides **176**.



X = H, 4-Me, 4-OMe, 4-Cl, 4-Br, 3-NO$_2$, 4-NO$_2$, 4-CN, 3,4-(Cl)$_2$, 2,4,5-(OMe)$_3$

SCHEME 5.76 Formation of 2-(isoxazol-3-yl)-1*H*-imidazole sulfonamide derivatives **178**.

Desideri et al. [96] designed and synthesized a series of (*N*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methyl)anilines **182**. Thus, the treatment of 3-phenyl-1*H*-pyrazole-4-carbaldehydes **179** with the benzenesulfonyl chlorides **175** in the presence of sodium hydride in tetrahydrofuran at room temperature for 12 h, afforded the respective 3-phenyl1-(phenylsulfonyl)-1*H*-pyrazole-4-carbaldehydes **180**. The latter carbaldehydes **180** condensed with substituted anilines **181** provided the corresponding Schiff bases **182**, reduced by sodium borohydride to yield the desired products **183**. The new derivatives were evaluated in cell-based assays for their cytotoxicity and antiviral activity against a large panel of RNA and DNA viruses of public health significance. Generally, the tested compounds did not display cytotoxicity toward the cell lines used. The majority of derivatives **183** were able to interfere with YFV and RSV replication in the micromolar range showing a marked improvement in potency and selectivity concerning the reference inhibitors 6-azauridine and ribavirin, respectively. To improve the anti-Flaviviridae activity of compounds **183** were assayed against a large panel of viruses belonging to Flaviviridae, Picornaviridae, Paramyxoviridae, Rhabdoviridae, Reoviridae, Retroviridae, Herpesviridae, and Poxviridae families (Scheme 5.77).

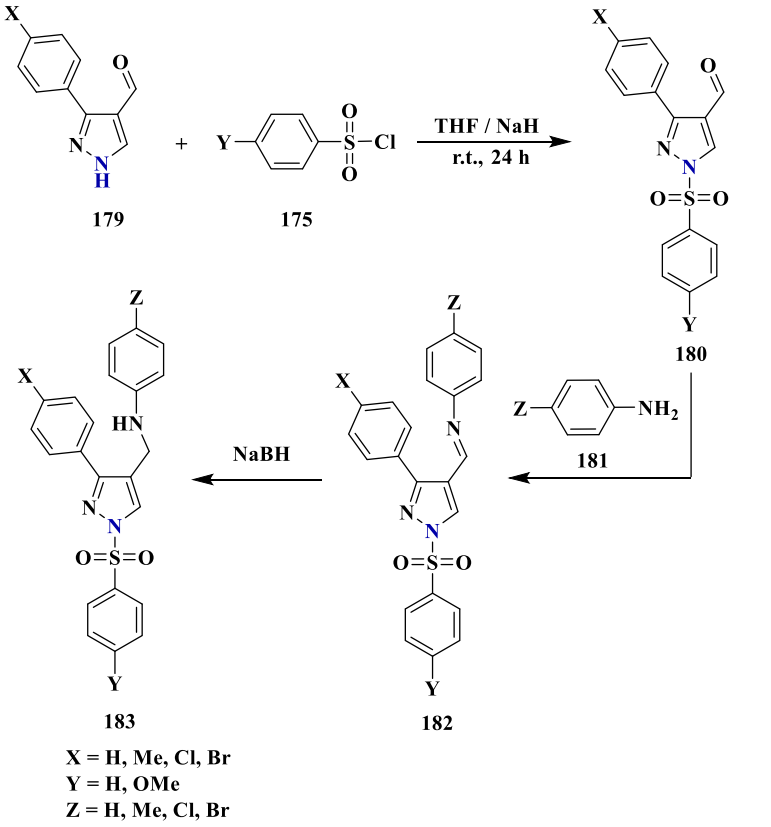
Isopropyl-2-chlorosulfonyl benzoate **184** reacted with 3 (5)aminopyrazoles **185** in dry benzene in the presence of trimethylamine to give 5-amino-3-phenyl-1-(2-isopropoxycabonyl benzene sulfonyl)pyrazoles **186** (Scheme 5.78) [97].

Tahir et al. [98] described the synthesis of 5-methyl-1-tosyl-1*H*-pyrazol-3-yl 4-methylbenzenesulfonate **188** from the reaction of 5-methyl-1H-pyrazol-3-ol **187** with 4-methyl benzenesulfonyl chloride **175** in anhydrous tetrahydrofuran (THF) and sodium hydride (NaH) at room temperature under stirring for 2 h (Scheme 5.79).

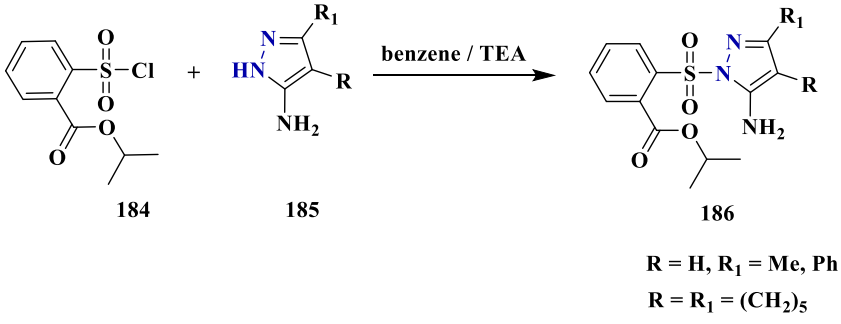
Sivla et al. [99] investigated the reactivity of (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles **189** as dienes in the Diels-Alder cycloaddition reaction. It is shown that the reaction of pyrazoles **189** with *p*-toluene sulfonyl chloride in anhydrous pyridine at room temperature for afforded (*E*)-5-styryl-1-tosyl-3-(2-tosyloxyphenyl)-1*H*-pyrazoles **190** in good isolated yields together with the corresponding mono-tosylated derivatives **191** as by-products. The tosylation of pyrazoles bearing strong electron-withdrawing groups (nitro group) was difficult and led to substantial degradation (Scheme 5.80).

New *N*-sulfonyl-pyrazolyl benzenesulfonamide derivatives **195** were prepared and some compounds showed a significant in vitro activity against Leishmania amazonensis. These pyrazolyl benzenesulfonamide derivatives did not show any toxicity in murine macrophages. The synthesis of sulfonamide derivatives **195** was performed by chlorination of 4-hydroxyquinolines **192** with phosphorus oxychloride at 120°C for 24 h, affording the 4-chloroquinolines **193** which react with an excess of hydrazine in diethylene glycol at 90°C−100°C for 1 h generate intermediate 4-hydrazinoquinolines I, which on raising the temperature to 130°C−140°C, react further over six hours to favor the rearrangement, affording the products **194**. The pyrazolyl benzenesulfonamides **195** were performed through a substitution reaction between 2-(1*H*-pyrazol-3-yl)anilines **194** and excess of sulfonyl chlorides **41** in tetrahydrofuran in the presence of trimethylamine (Scheme 5.81) [100].

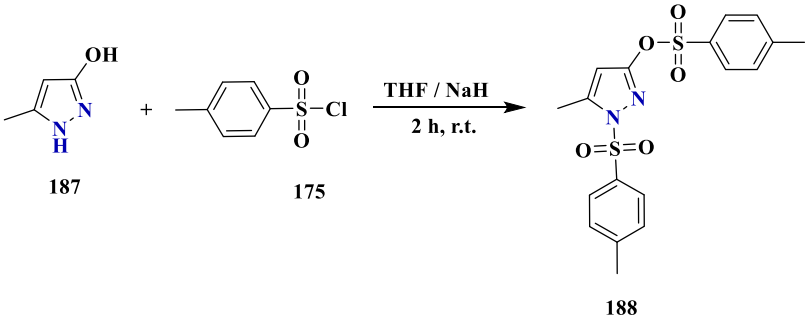
Elgemeie et al. [101−103] demonstrated novel 5-amino-1-arylsulfonyl-4-pyrazolin-3-ones **197A** or the tautomeric 5-amino-1-arylsulfonyl-3-hydroxypyrazole structures **197B**



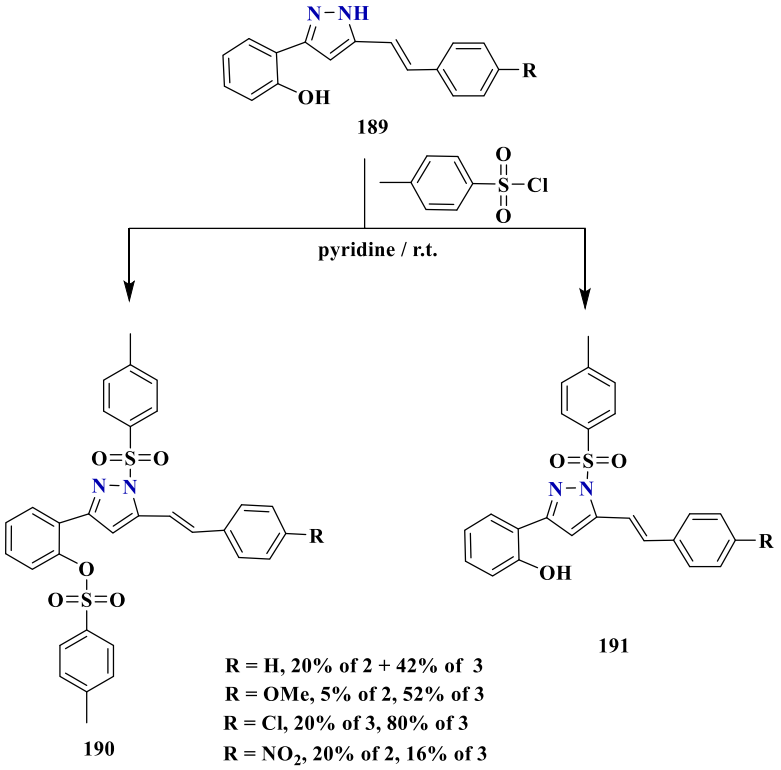
SCHEME 5.77 Synthetic routes of 2-(isoxazol-3-yl)-1*H*-imidazole sulfonamide derivatives **178**.



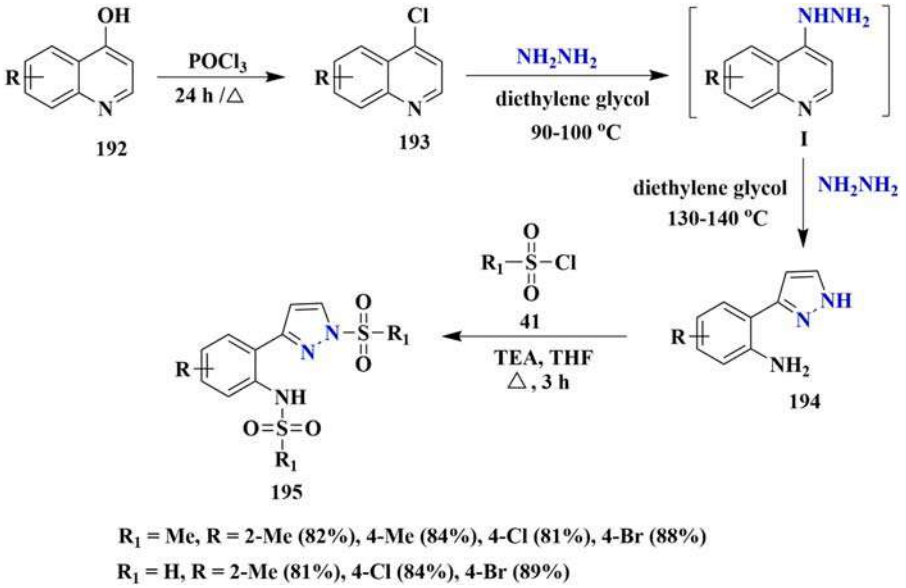
SCHEME 5.78 Synthesis of 5-amino-3-phenyl-1-(2-isopropoxycabonyl benzene sulfonyl)pyrazoles **186**.



SCHEME 5.79 Synthesis 5-methyl-1-tosyl-1*H*-pyrazol-3-yl 4-methylbenzenesulfonate **188**.

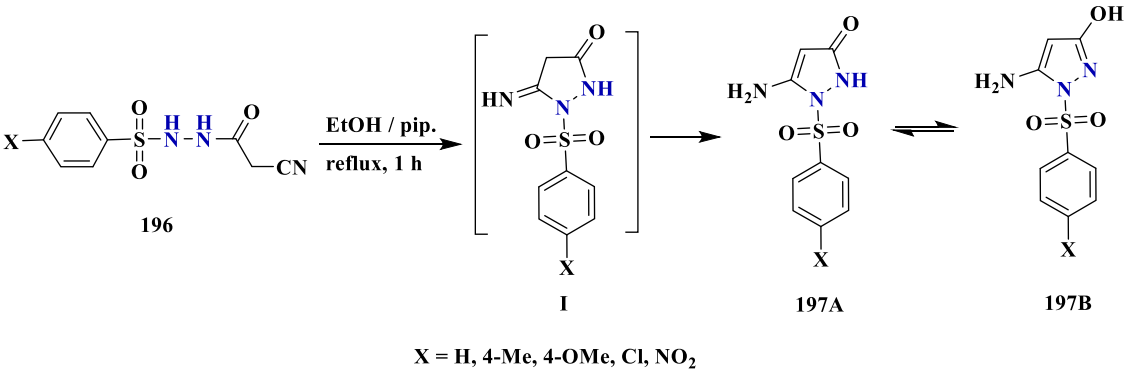


SCHEME 5.80 Diels-Alder cycloaddition reaction of (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles.

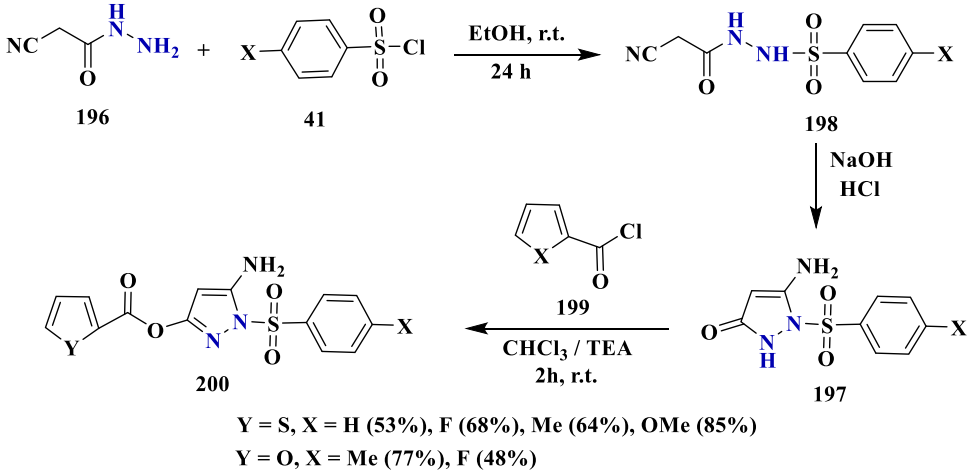


SCHEME 5.81 Synthesis of pyrazolyl benzenesulfonamides **195**.

via the refluxing cyanoaceto-*N*-arylsulfonylhydrazides **196** in ethanol containing catalytic amounts of piperidine undergo intramolecular cyclization. The hydroxy form **197B** would be expected to be more stable, because of the weakened basicity of the ring nitrogen at the 2-position, in turn arising from the adjacent heteroatom and the oxygen at the 3-position, however, spectral studies indicated the presence of the NH tautomer in solution for all products and the structure of



SCHEME 5.82 Synthesis of 5-amino-1-arylsulfonyl-4-pyrazolin-3-ones and their tautomeric forms.



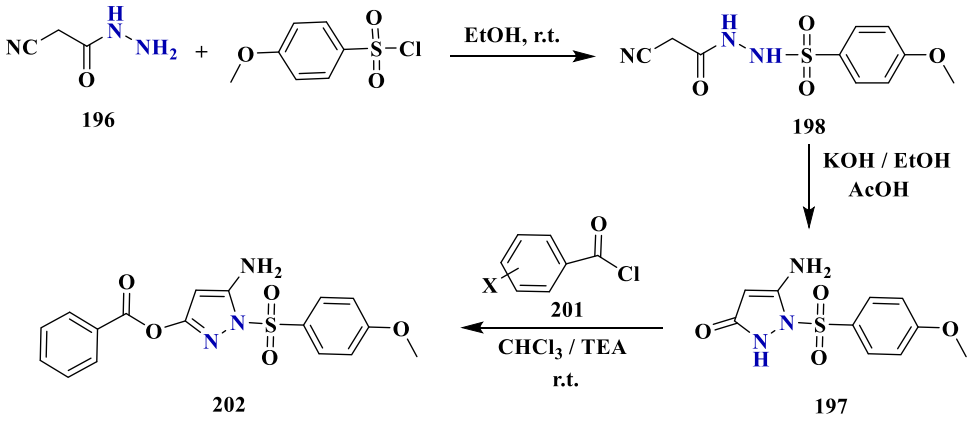
SCHEME 5.83 Synthesis *N*-sulfonyl substituted pyrazoles **197 as alternate substrates for the cysteine protease cathepsin B**.

5-amino-1-phenylsulfonyl-4-pyrazolin-3- one **197A** was confirmed by X-ray crystallography (Scheme 5.82).

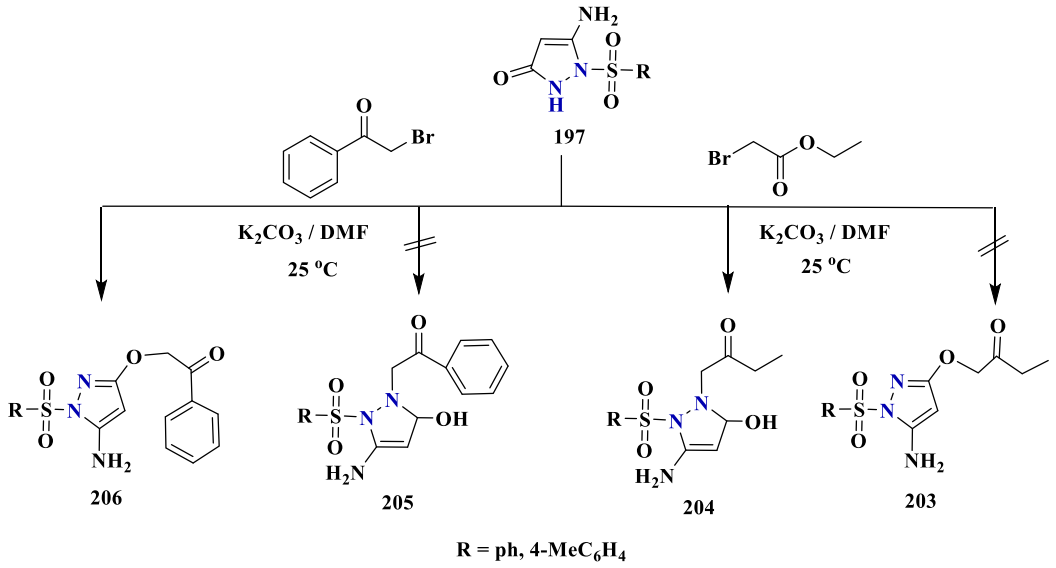
Michael et al. [104] studied the synthesis of *N*-sulfonyl substituted pyrazoles **197**, which act as alternate substrates for the cysteine protease, cathepsin B from the reaction of cyanoacetohydrazide **196** with 4-arylbenzenesulfonyl chlorides **41** in ethanol yielded the sulfonamide **197**. Cyclization of sulfonamide **198** to pyrazolone **197** was achieved in sodium hydroxide solution, followed by neutralization with HCl. Lastly, pyrazolone **197** was treated with heteroylcarbonyl chlorides **199** to obtain the pyrazole esters **200**. Synthesis and evaluation of related analogs revealed the potential reactivity of the ester functionality with the nucleophilic enzyme active site cysteine to form a transient thiphenoyl-enzyme intermediate. Initially, the similar reactivity of dithiothreitol (DTT) and cysteine in the bioassay confounded the high throughput screen and subsequent assay results due to the nucleophilic properties of the thiol sulfur. Thus, the biological and chemical communities need to consider the potential of DTT and cysteine to act as nucleophiles in assay systems where substrates contain electrophilic functionality (Scheme 5.83).

Michael et al. [105] described a series of pyrazole ester derivatives as allosteric inhibitors of WNV NS2B-NS3 proteinase. Thus, the reaction of cyanoacetohydrazide **196** with 4-methoxyphenylsulfonyl chloride **41** in ethanol yielded *N'*-(2-cyanoacetyl)-4-methoxybenzenesulfonohydrazide **198** which precipitated from the solution. Cyclization of compound **198** to 5-amino-1-((4-methoxyphenyl)sulfonyl)-1,2-dihydro-3*H*-pyrazol-3-one **197** was achieved in an ethanolic solution of KOH, followed by neutralization with AcOH. Lastly, pyrazolone **197** was treated with arylcarbonyl chlorides **201** to obtain the 5-amino-1-((4-methoxyphenyl)sulfonyl)-1*H*-pyrazol-3-yl benzoates **202**. The pyrazolone esters **202** were investigated in vitro against WNV NS2B-NS3 and the results showed that the compounds are inhibitors of WNV NS2B-NS3 proteinase with greatly improved stability in the assay medium (Scheme 5.84).

Recently Metwally et al. [106,107] discovered the alkylation of 5-amino-1-((4-arylphenyl)sulfonyl)-1,2-dihydro-3*H*-pyrazol-3-ones **197** with each ethylbromoacetate



SCHEME 5.84 Formation of pyrazole esters as allosteric inhibitors of WNV NS2B-NS3 proteinase.



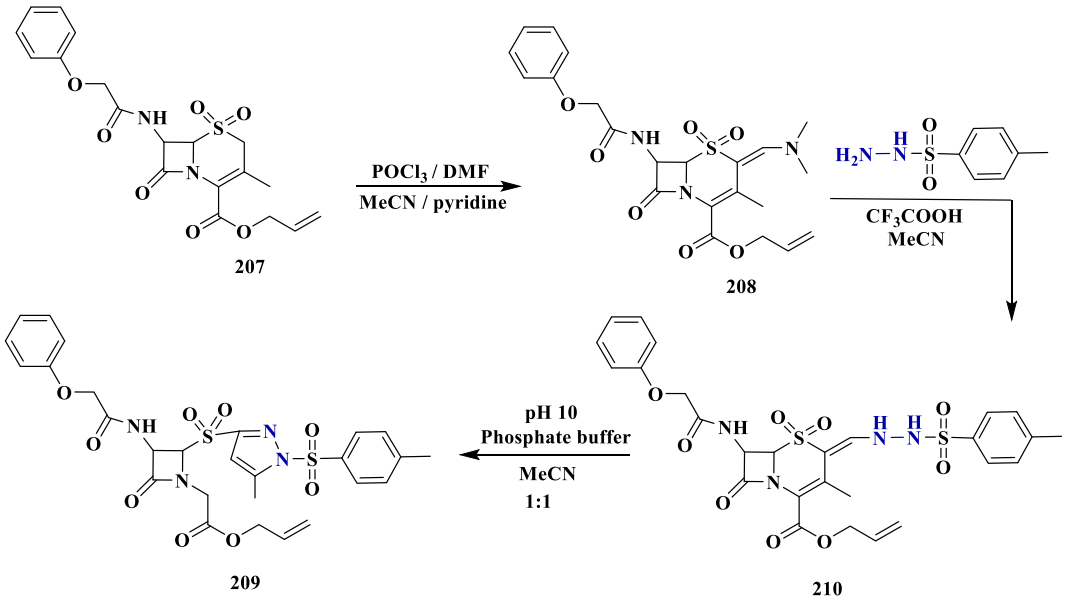
SCHEME 5.85 *N*- and *O*-alkylation of 5-amino-1-((4-arylphenyl)sulfonyl)-1,2-dihydro-3*H*-pyrazol-3-ones.

and phenacylbromide in the presence of solid potassium carbonate in DMF afforded the *N*- and *O*-alkyl-*N*-sulfonylated pyrazoles **204** and **206**, respectively. The formation of *N*-alkylates confirmed was confirmed by X-ray crystallography (Scheme 5.85).

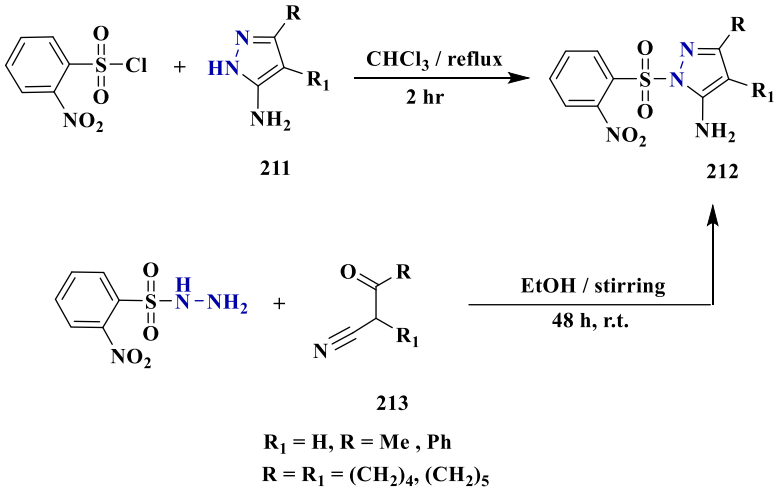
Lunn et al. [108] found that the tosylhydrazone derivative undergoes rearrangement involving a cephalosporin dehydrothioazine ring cleavage giving *N*-tosylpyrazole derivative. Thus the reaction of cephalosporin sulfonate **207** with vilsmeier reagent and pylidine in acetonitrile gave the enamine derivative **208**, which then reacted with 4-methylbenzenesulfonohydrazide in trifluoroacetic acid and acetonitrile to afford the *N*-tosylhydrazone derivative **209**. The latter hydrazone undergoes ring cleavage and yielded *N*-tosylpyrazole derivative **210** (Scheme 5.86).

The reaction of 2-nitrobenzene sulfonyl chloride with 3(5)aminopyrazoles **211** in refluxing chloroform in the presence of trimethylamine for two hours afforded the *N*-(2-nitrosulfonylbenzene-5-aminopyrazoles) **212**. Also, the compounds **212** were obtained by the reaction of 2-nitrobenzene sulfonyl hydrazide with β-ketonitriles **213** in ethanol under stirring at room temperature for 4 h (Scheme 5.87) [109].

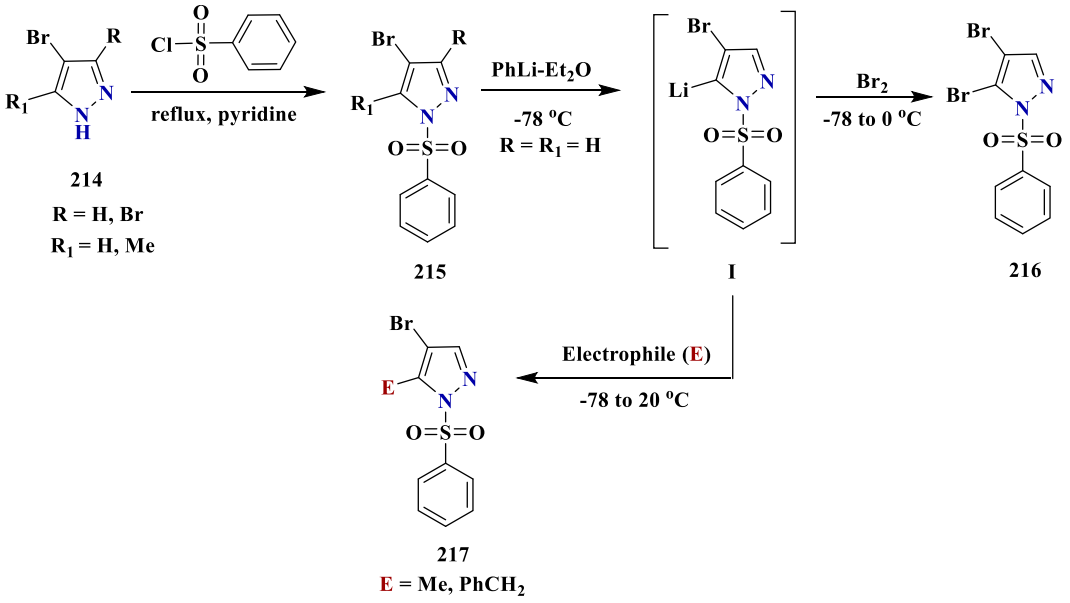
Holzer et al. [110] synthesized 4-bromo-1-phenylsulphonylpyrazole **215**, from 4-bromopyrazoles **214** and benzenesulphonyl chloride in boiling pyridine, which can be metallated regioselectively with phenyl lithium to form 5-lithio intermediate **I**, which it is quenching with bromine at −78°C lead to 4,5-dibromo-*N*-sulfonylbenzene-1*H* pyrazole **216**. 4-Bromo-1-phenylsulphonyl-5-substituted pyrazoles **217** was obtained by treating



SCHEME 5.86 Synthesis of *N*-tosylpyrazole derivative **209** *via* cephalosporin dehydrothioazine ring cleavage.



SCHEME 5.87 Proposed reaction of *N*-(2-nitrosulfonylbenzene-5-aminopyrazoles) **212**.



SCHEME 5.88 Alkylation reaction of 4-bromopyrazoles.

5-lithio intermediate **I** with an appropriate electrophile (Scheme 5.88).

Turnbul et al. [111] described the directed lithiation of 1-benzenesulfonylpyrazole **46** with *t*-butyllithium (Me_3CLi) in anhydrous THF at −78°C under an atmosphere of nitrogen and subsequent reaction with electrophiles yields the corresponding 5-substituted *N*-sulfonylbenzene-pyrazoles **218** in moderate to excellent yield (Scheme 5.89).

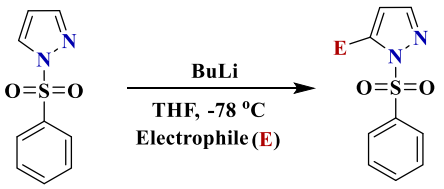
The reaction of 5-[3'-methyl-5'-oxo-4',5"-dihydro-pyrazol-l-yl-sulfonyl]-8-quinolinol **219** with the selected aldehydes **220** in the presence of triethylamine results in novel series of 5-(4'-arylidene-3'-methyl-5-oxo-4',5'-dihydropyrazol-1-yl-sulfonyl)-8-quinolinols **221**. Antibacterial activities of newly synthesized heterocyclic ligands and metal chelate Cu^{+2}, Hg^{+2}, Fe^{+3} chelates showed variable activities against some bacteria used (Scheme 5.90) [112].

5.5 Chemistry of *N*-sulfonylthiadiazole derivatives

5.5.1 Chemistry of thiadiazole moiety

There are various types of thiadiazole rings are present:

- 1, 2, 4-Thiadizole
- 1, 3, 4-Thiadizole
- 1, 2, 5-Thiadizole
- 1, 2, 3-Thiadizole



E = I, Me, Bn, CH_2=$CHCH_2$, Me_3Si, Bu_3Sn, COOH, CMe_2OH

SCHEME 5.89 Synthesis of 5-substituted *N*-sulfonylbenzenepyrazoles **218**.

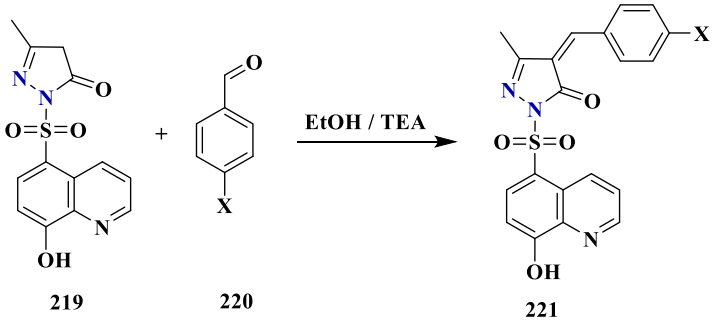
5.6 Synthesis of 1,3,4-thiadiazole and 1,2,3-thiadiazole derivatives

Schenone et al. [113,114] synthesized a series of *N*-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides **224** with good to excellent yields. The compounds **224** were prepared from arylbenzenesulfonyl hydrazides **73** with different acylisothiocyanates **222** in anhydrous THF at room temperature for three days to afford the corresponding acylthiosemicarbazides **223** in good yields. Compounds **223** were cyclized with phosgene in anhydrous THF, in the presence of dry sodium acetate, necessary to eliminate hydrochloric acid evolving during the reaction. The synthesized compounds were tested in vivo for their analgesic and antiinflammatory activities. All the new compounds possess good antalgic action in the acetic acid writhing test and some terms of the series showed also fair antiinflammatory activity in the carrageenan rat paw edema test. Ulcerogenic and irritative action on the gastrointestinal mucose, in comparison with indomethacin, is low (Scheme 5.91).

Oteleanu et al. [115−117] described the reaction of 4-acetamidobenzenesulfonyl chloride **225** with 5-(alkylthio)-1,3,4-thiadiazol-2(3*H*)-imines **226** in molar ratio 2:1 in a mixture of acetone-water to yield *N*-(4-(*N*-(3-((4-acetamidophenyl)sulfonyl)-5-(alkylthio)-1,3,4-thiadiazol-2(3*H*)-ylidene)-sulfamoyl)phenyl)acetamide **227** (Scheme 5.92).

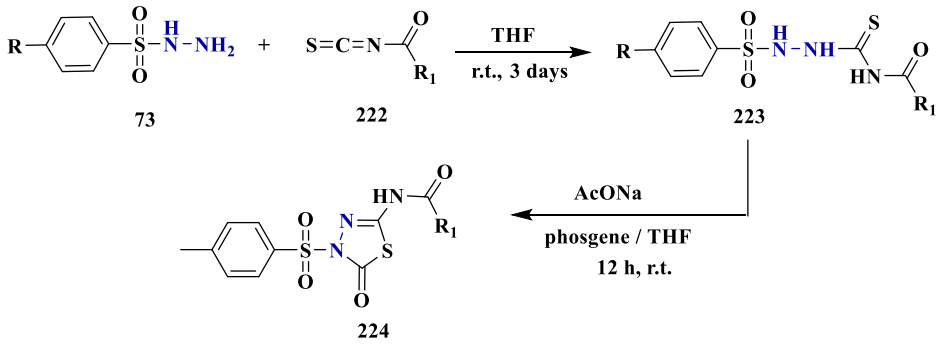
Acylation of 2-alkoxy-5-amino-l,3,4-thiadiazoles **228** with arenesulphonyl chlorides **41** was best done in a mixture of acetone and pyridine. Under these conditions *p*-acetoamidobenzenesulphonyl chloride **225** and *p*-nitrobenzenesulphonyl chloride gave the sulfonamides **229** (R_2 = AcNH or NO_2). With toluene-*p*-sulphonyl chloride and with *p*-chlorobenzenesulphonyl chloride, however, diacyl derivatives **229** ($R_1 = R_2$) were usually obtained (Scheme 5.93) [118].

Reaction of 2-amino-5-methyl-1,3,4-thiadiazole **230** with 4-acetamidobenzenesulfonyl chloride **225**



X = H, Me, OMe, Cl, NO_2

SCHEME 5.90 Formation of 5-(4"-arylidene-3'-methyl-5-oxo-4',5'-dihydropyrazol-1-yl-sulfonyl)-8-quinolinols **221**.

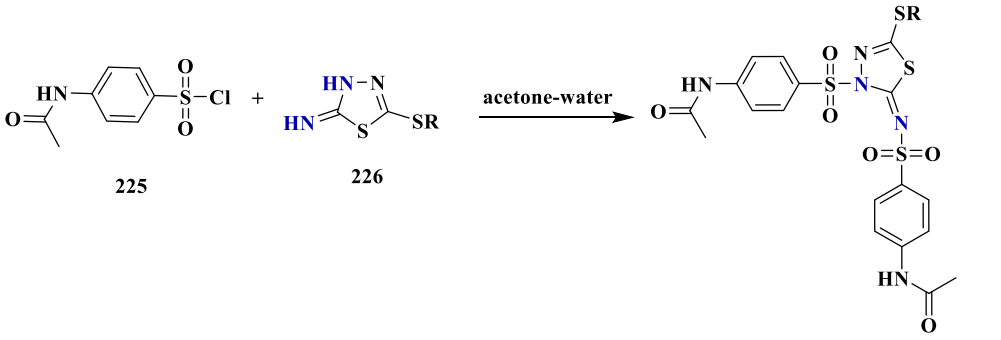


73 222 223 224

R = H, R_1 = Ph (89%), 4-MeC_6H_4 (91%), 4-OMeC_6H_4 (81%), 4-ClC_6H_4 (81%), 2-FC_6H_4 (90%), 3-FC_6H_4 (68%), 4-FC_6H_4 (71%), 2,4-$(F)_2C_6H_3$ (59%), 4-$CF_3C_6H_4$ (71%), 2-Furoyl (80%)

R = Me, R_1 = Ph (60%), 4-MeC_6H_4 (55%), 4-OMeC_6H_4 (90%), 4-ClC_6H_4 (81%), 2-FC_6H_4 (70%), 3-FC_6H_4 (60%), 4-FC_6H_4 (73%), 2,4-$(F)_2C_6H_3$ (75%), 4-$CF_3C_6H_4$ (75%), 2-Furoyl (58%)

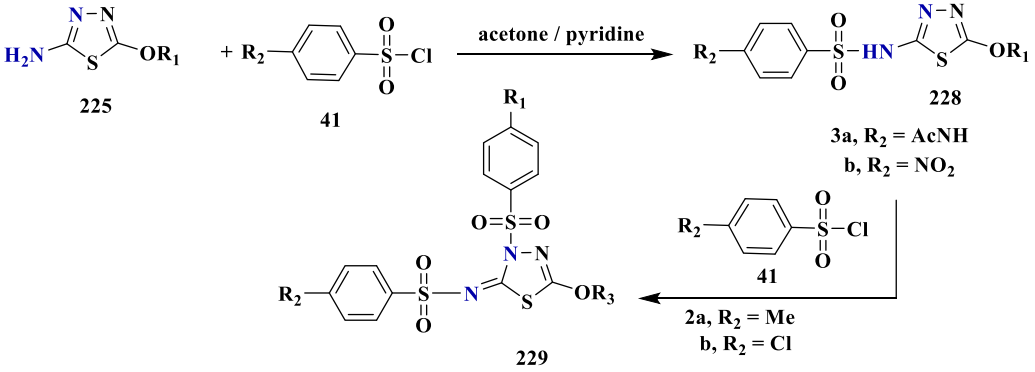
SCHEME 5.91 Synthesis of *N*-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides **224**.



225 226 227

R = H, $C_{1\text{-}4}$ alkyl

SCHEME 5.92 The reaction of 4-acetamidobenzenesulfonyl chloride **225** with 5-(alkylthio)-1,3,4-thiadiazol-2(3*H*)-imines.



225 41 228

3a, R_2 = AcNH
b, R_2 = NO_2

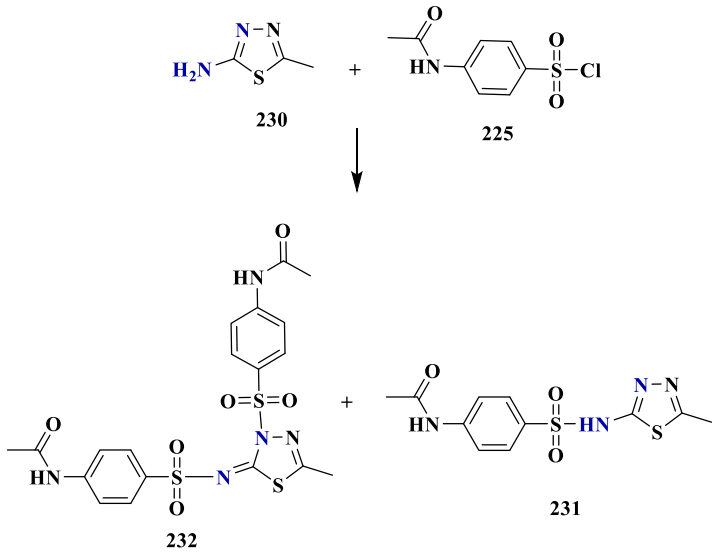
41 229

2a, R_2 = Me
b, R_2 = Cl

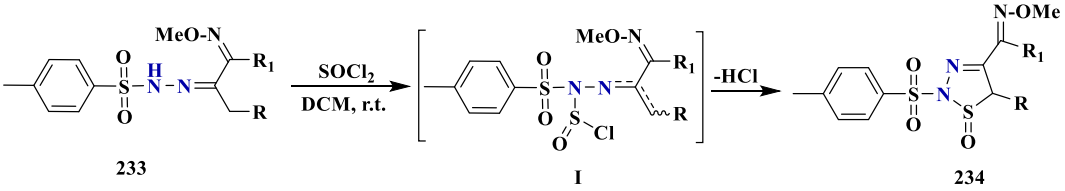
SCHEME 5.93 Acylation of 2-alkoxy-5-amino-l,3,4-thiadiazoles.

afforded *N*-[4-(*N*-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl]acetamide **231** and *N*-(4-(*N*-(3-((4-acetamidophenyl)sulfonyl)-5-methyl-1,3,4-thiadiazol-2(3*H*)ylidene)sulfamoyl)-phenyl)-acetamide **232** (Scheme 5.94) [119].

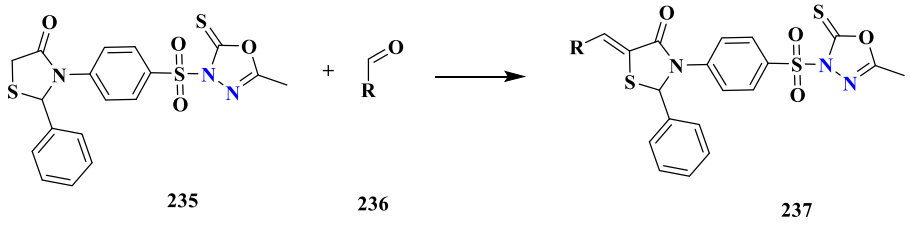
Kobori et al. [120] investigated the Hurd-Mori reaction of *p*-toulenesulfonylhydrazones **233** with thionyl chloride in DCM under reflux given Δ^3−1,2,3-thiadiazolin-l-ones **234** as each sole isolable product through the intermediate **I** (Scheme 5.95).



SCHEME 5.94 The reaction of 2-amino-5-methyl-1,3,4-thiadiazole with 4-acetamidobenzenesulfonyl chloride.



SCHEME 5.95 Formation of Δ^3−1,2,3-thiadiazolin-l-ones *via* Hurd-Mori reaction of *p*-toulenesulfonylhydrazones.



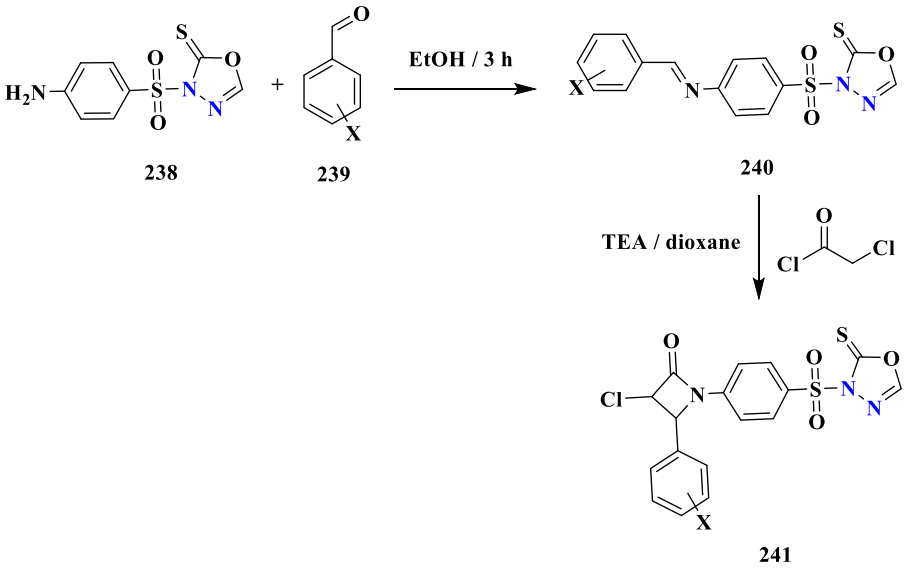
SCHEME 5.96 Synthesis of 5-(substitutedmethylene)-3-(4-(5-methyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)-2-phenylthiazolidin-4-ones.

5.7 Chemistry of *N*-sulfonyl-1,3,4-oxadiazoles

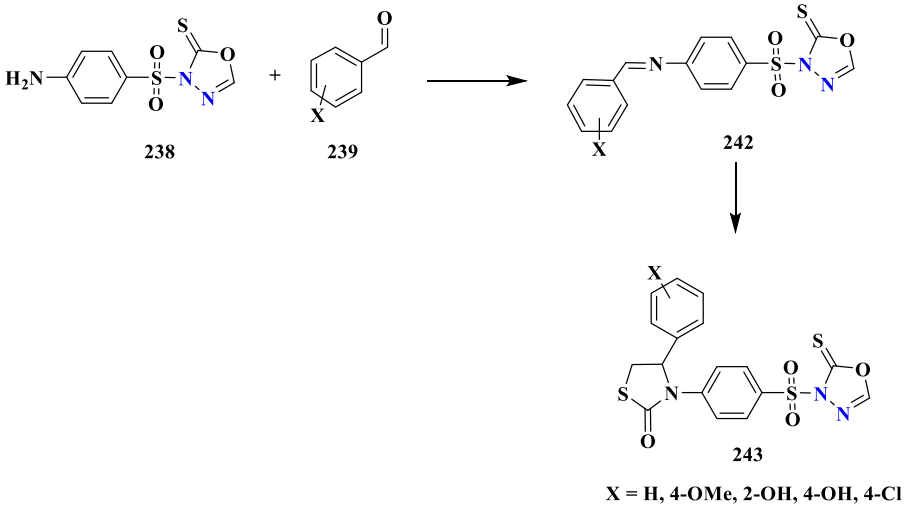
3-(4-(5-Methyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)-2-phenylthiazolidin-4-one **235** reacts with aromatic aldehydes **236** yield 5-(substitutedmethylene)-3-(4-(5-methyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)-2-phenylthiazolidin-4-ones **237**. The biological evaluation revealed that all compounds showed good to moderate biological. activity against employed bacterial and fungal strains (Scheme 5.96) [121].

3-(4-Aminophenylsulfonyl)-1,3,4-oxadiazole-2(3*H*)-thione **238** undergoes facile condensation with different aryl aldehydes **239** in refluxing ethanol afforded the corresponding 3-(4-(substituted benzylideneamino)-)-1,3,4-oxadiazole-2(3*H*)-thione **240** (X = H, 2-HO, 4-HO, 4-MeO, 4-Cl) in good yields. Cyclocondensation of compounds **240** with chloroacetyl chloride in 1,4-dioxane in the presence of trimethylamine yields 3-chloro-4-substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)azetidin-2-one **241**. The synthesized compounds **241** showed moderate antibacterial and antifungal activities (Scheme 5.97) [122].

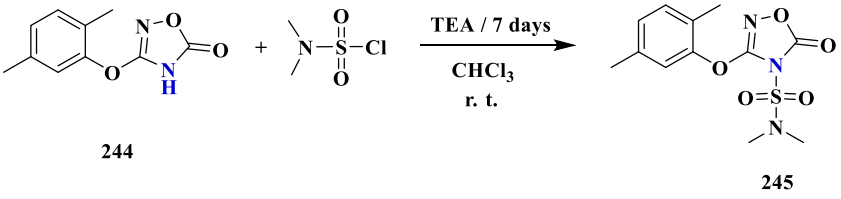
3-(4-Aminophenylsulfonyl)-1,3,4-oxadiazole-2(3*H*)-thione **238** condensed with aromatic aldehydes **239** to yield the corresponding Schiff bases **242** (X = H, 2-HO, 4-HO, 4-MeO, 4-Cl) in good yields.



SCHEME 5.97 Synthesis of 3-chloro-4-substituted phenyl-1-(4-(2-thioxo-1,3,4-oxadiazol-3(2*H*)-ylsulfonyl)phenyl)azetidin-2-one.



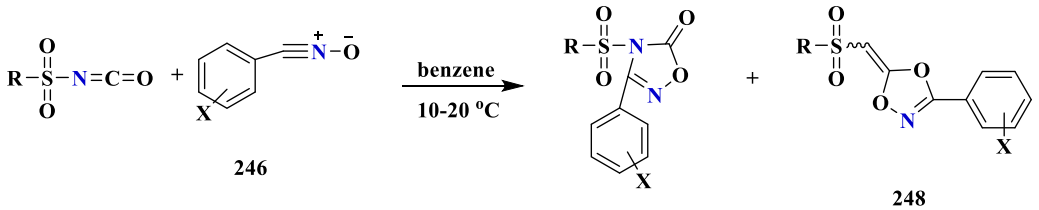
SCHEME 5.98 Synthesis thiazolidin-4-ones **243**.



SCHEME 5.99 Formation of 3-(2,5-dimethylphenoxy)-*N, N*-dimethyl-5-oxo-1,2,4-oxadiazole-4(5*H*)-sulfonamide.

Cyclocondensation of **242** with thioglycolic acid yielded thiazolidin-4-ones **243**, which were evaluated for their antibacterial and antifungal activities (Scheme 5.98) [123].

A mixture of 3-(2,5-dimethylphenoxy)-4*H*[1,2,4] oxadiazol-5-one **244** and *N, N*-dimethylsulfonyl chloride was stirred in chloroform in the presence of trimethylamine at room temperature for 7 days afforded 3-(2,5-dimethylphenoxy)-*N, N*-dimethyl-5-oxo-1,2,4-oxadiazole-4(5*H*)-sulfonamide **245** in 44.73% yield in which at 100 g/ha gave 99% protection of tomato seedlings against phytophthora infestants (Scheme 5.99) [124].



	247	248
R = Pr, X = 2,4,6 $(Me)_3$	42%	12%
R = Ph, X = 2,4,6 $(Me)_3$	80%	14%
R = 4-MeC_6H_4 , X = 2,4,6 $(Me)_3$-3,4-$(Cl)_2$	72%	14%
R = Cl, X = 2,3,5,6 $(Me)_4CH$	0%	89%

SCHEME 5.100 Synthesis of oxadiazolones and dioxazoles.

The reaction of aromatic nitrile oxides **246** with sulfonylisocyanates **247** in benzene at 10°C−20°C afforded a mixture of oxadiazolones **248** and dioxazoles **249**. Whereas, using chlorosulfonylisocyanate instead of alkyl-/arylsulfonylcyanates **246** results in the exclusive formation of dioxazoles **249** (R = Cl) Scheme 5.100 [125].

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Chapter 6

Synthesis, chemistry and uses of *N*-sulfonated *N*-triazoles and *N*-tetrazoles

6.1 Introduction

Triazole is an aromatic heterocyclic ring with a five-membered ring and three nitrogen atoms. These atoms can be arranged in a certain order or not arranged at all to form the common 1,2,3-triazole or 1,2,4-triazole (Fig. 6.1).

Many synthetic biologically active compounds and agrochemicals contain 1,2,3-triazole as a structural component. Substituted 1,2,3-triazoles and analogs are important components commonly used in synthesis, biology, and medicinal chemistry [1−5]. In organic synthesis, arylsulfonyl-1,2,3-triazole compounds are considered to be intermediates of a large number of nitrogen heterocyclic compounds [6−12]. The most important method for synthesizing triazole-containing compounds is the Cu-catalyzed [3 + 2] cycloaddition reaction of azides and alkynes (CuAAC) [13−16]. However, the use of azides with electron-withdrawing groups, such as sulfonyl azides, will lead to the formation of reactive ketene imine intermediates in situ through the ring-opening rearrangement of copper naphthylsulfonyl triazoles [17−20].

6.2 Synthesis of *N*-sulfonyl-1,2,3-triazoles

Fokin et al. [21] have reported that in the presence of 2,6-lutidine and a catalytic amount of CuI, alkynes **1** with sulfonyl azides **2** at low temperature in chloroform, the *N*-sulfonyl-1,2.3-triazoles **3** were obtained regioselectively in good to excellent yields (Scheme 6.1).

The new *N*-sulfonylated triazoles **5** were produced by Shen et al. [22] by reacting ethyl-3-(1-(but-3-yn-1-yl) indolin-2-yl)acrylate **4** with sulfonyl azides **2** in tetrahydrofuran (THF) in the presence of a catalytic amount of CuI at room temperature for 30 min (Scheme 6.2).

1,2,3-triazole 1,2,4-triazole

FIGURE 6.1 The common structures of 1,2,3-triazole and 1,2,4-triazole.

Narsimha et al. [23] developed a one-pot synthesis of novel sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives **7** with good yields (63%-77%) using various sulfonic acids **6** and 4-(prop-2-yn-1-yl)thiomorpholine-1,1-dioxide in the presence of triphenylphosphine (PPh_3), copper iodide (CuI) and trichloroisocyanuric acid at room temperature (Scheme 6.3).

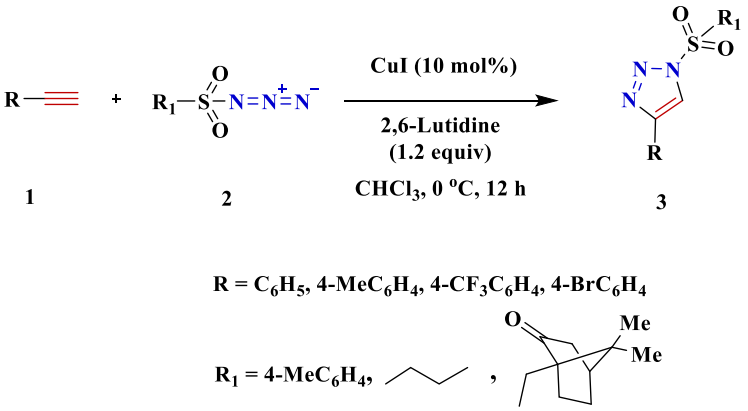
4-(3-Methylthiophen-2-yl)-2-oxo-6-(thiophen-2-yl)-1-((1-tosyl-1*H*-1,2,3-triazol-4-yl)-methyl) 1,2-dihydropyridine-3-carbonitrile **10** was obtained by reacting acetylenic derivative **9** [prepared from the reaction of 4-(3-methylthiophen-2-yl)-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile **8** with propargyl bromide in *N, N*-dimethylformamide (DMF) with a catalytic amount of potassium carbonate at 70°C] with *p*-toluenesulfonyl azide under the catlysis of copper(I)-catalyzed to carry out the azide/alkyne cycloaddition in 65% yield (Scheme 6.4) [24].

Lu et al. [25] reported the synthesis of *N*-sulfonyltriazoles **12** by the reaction of *o*-alkynylanilines **11** with sulfonylazides **2** in the presence of 10% copper chloride ($CuCl_2$) and trimethylamine (2.2 equivalents) in acetonitrile with stirring at room temperature (Scheme 6.5).

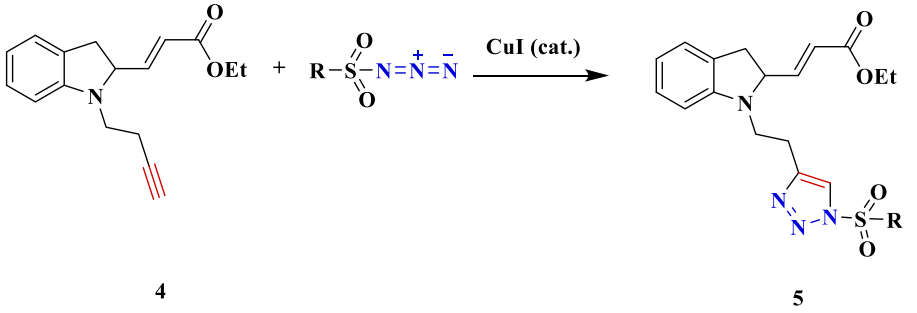
Zhang and co-workers [26] have reported that the (*Z*)-arylvinyl bromides **13** bearing in *para* position both electron-donating methyl group and electron-withdrawing groups like CO_2Me, F, Cl, and Br reacted smoothly with sulfonyl azides **2** using copper bromide and methyl(phenyl) sulfane in water at room temperature to afford *N*-sulfonyl-1,2,3-triazoles **14** in yields range from 81% to 91% (Scheme 6.6).

N-Arylsulfonyl-1,2,3-triazoles **16** were synthesized from 1,1-dibromo-2-arylethylenes **15** through a one-pot reaction, including cesium carbonate (Cs_2CO_3)-mediated dehydrobromination process of the dibromoalkenes to produce alkynes followed by addition of tosyl azide under Cu(I)-catalyzed Huisgen cycloaddition (Scheme 6.7) [27].

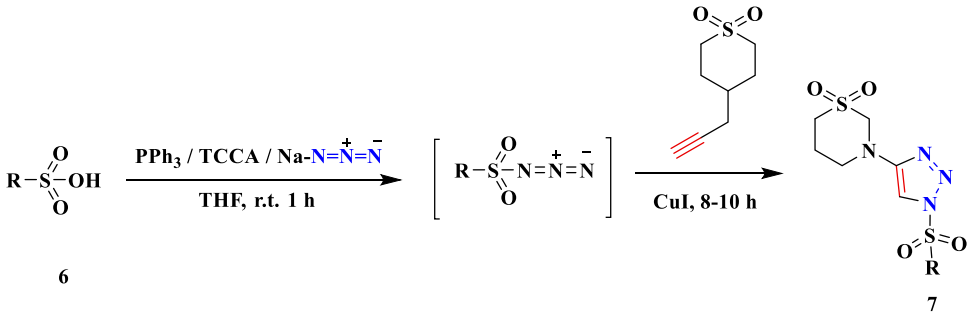
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00005-7



SCHEME 6.1 Synthesis of *N*-sulfonyl-1,2,3-triazoles 3 using 2,6-lutidine and CuI.



SCHEME 6.2 Synthesis of *N*-sulfonyl-1,2,3-triazoles 5.



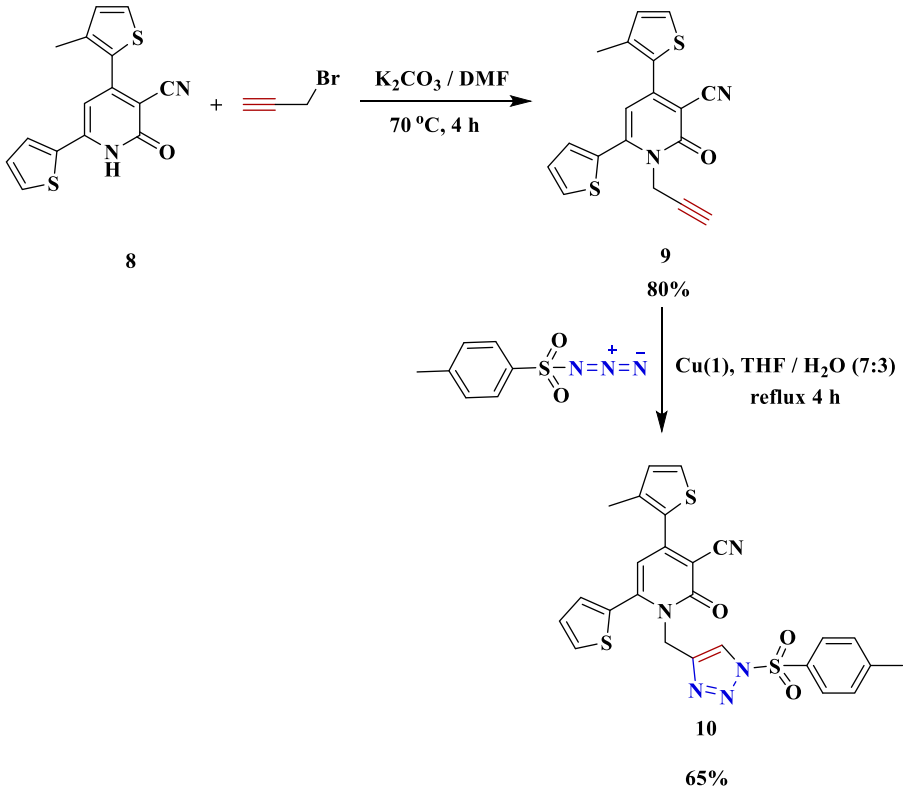
SCHEME 6.3 Synthesis of sulfonyl-1*H*-1,2,3-triazolyl-thiomorpholine 1,1-dioxide derivatives **7.**

Xihe et al. [28] showed that copper oxide (Cu_2O) in water acts as a reliable catalyst for the azide-alkyne cycloaddition reaction (CuAAC) to form a series of *N*-sulfonyl-1,2,3-triazoles **17** without additional stabilizing ligands. Water has been shown to play an important role due to the significant acceleration of the rate compared to pure organic solvent reactions (Scheme 6.8).

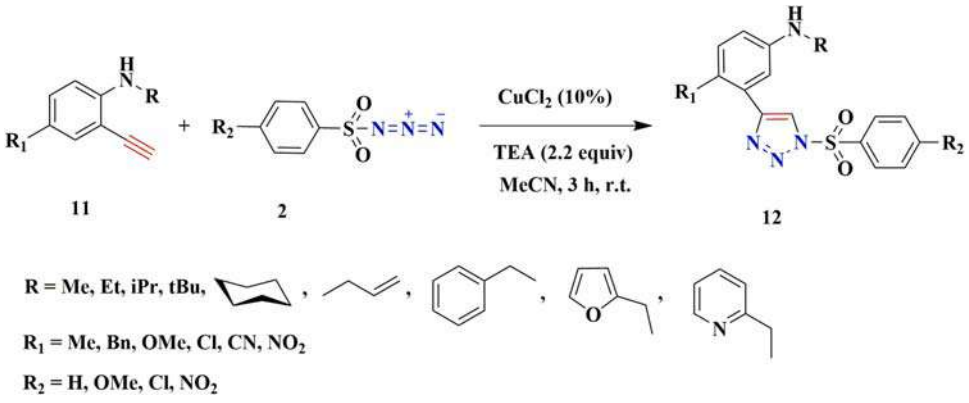
A two-component reaction is used to prepare a series of *p*-acetamidobenzenesulfonyl-1,2 3-triazoles **18** from *p*-acetamidobenzene sulfonyl azide and terminal alkynes **1** in the presence of copper sulfate and sodium ascorbate using *t*-butyl alcohol (*t*-BuOH) as solvent. This procedure provides a powerful click process even more eco-friendly and safe through 1,3-dipolar cycloaddiation (Scheme 6.9) [29].

In another report, some new 1,4-disubstituted-sulfonyl-1,2,3-triazoles **19** were regioselectively synthesized in high yields using a Cu(I) catalyzed 1,3-dipolar cycloaddition reaction of *p*-acetamidobenzenesulfonyl azide with terminal alkynes **1** (Scheme 6.10) [30].

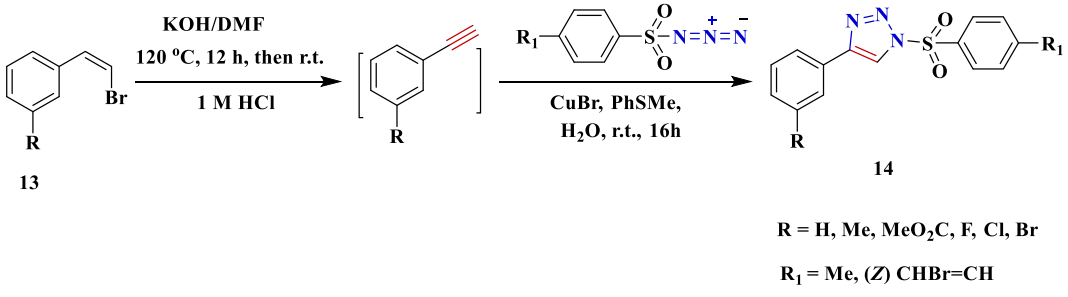
Li and co-workers illustrated the synthesis of 2-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-ethanol **20** and 2-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-propan-2-ol **21** by click chemistry reaction using $CuSO_4{\cdot}5H_2O$ and ascorbic acid in a mixture of *t*-BuOH and H_2O in ratio 1:1 under stirring and investigated



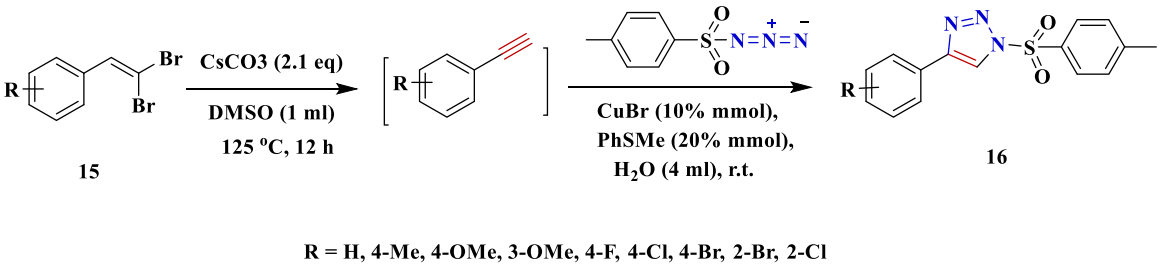
SCHEME 6.4 Azide/alkyne cycloaddition reaction.



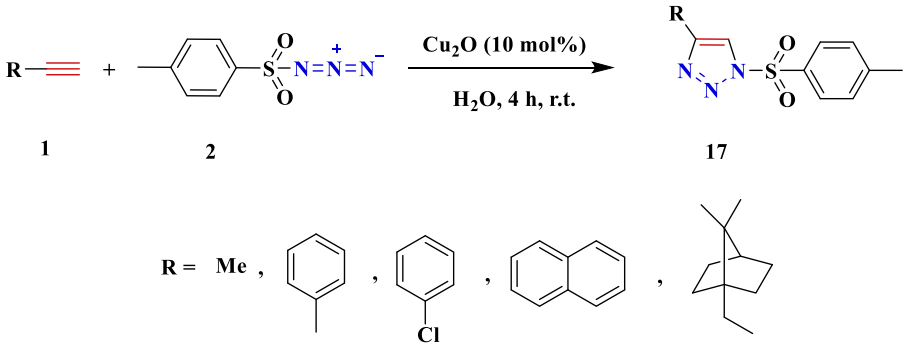
SCHEME 6.5 Synthesis of *N*-sulfonyltriazoles **12** using copper chloride.



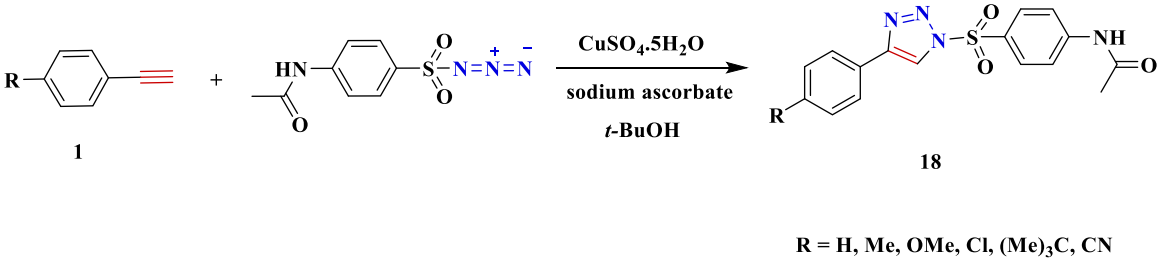
SCHEME 6.6 Synthetic pathways of *N*-sulfonyl-1,2,3-triazoles **14.**



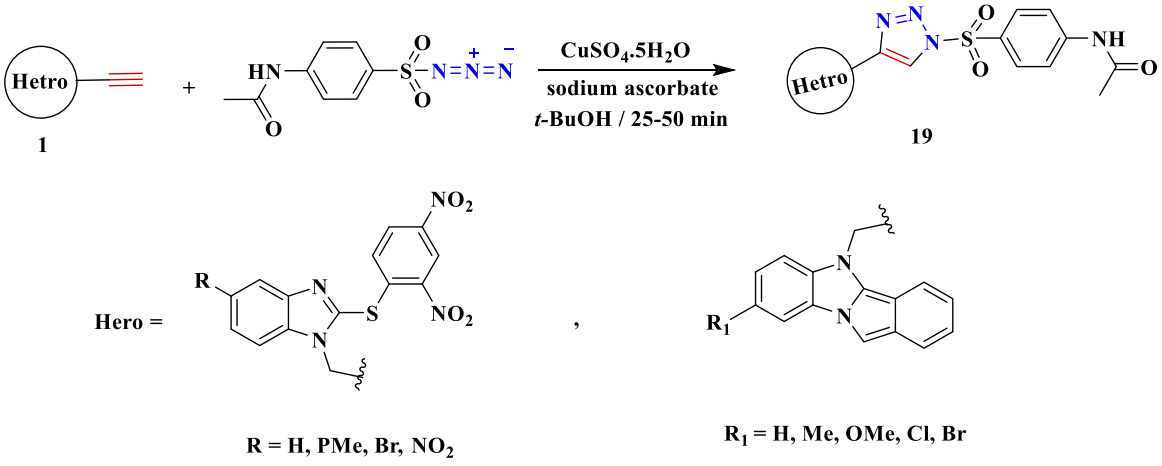
SCHEME 6.7 Synthetic routes of *N*-arylsulfonyl-1,2,3-triazoles **16** *via* Huisgen cycloaddition.



SCHEME 6.8 Synthesis of *N*-sulfonyl-1,2,3-triazoles **17** without additional stabilizing ligands.



SCHEME 6.9 Synthesis of *p*-acetamidobenzenesulfonyl-1,2 3-triazoles **18** through **1,3-dipolar cycloaddiation**.



SCHEME 6.10 Cu(I) catalyzed 1,3-dipolar cycloaddition reaction of 4-acetamidobenzenesulfonyl azide with terminal alkynes.

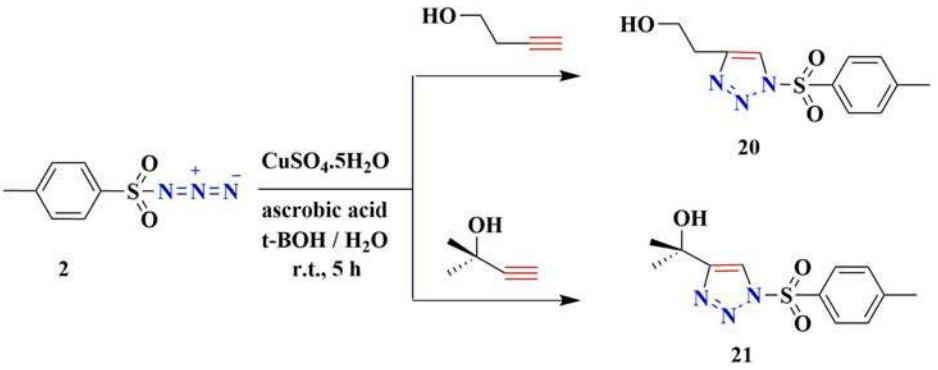
their use to for the preparation of self-assembled membrane against copper corrosion obtaining inhibitory activity of 93.1% and 89.4%, respectively (Scheme 6.11) [31].

It has been reported that reaction of alkynyl esters **22** with tosylazide in a mixture of *t*-BuOH and water (1:1) using $CuSO_4.H_2O$ with sodium ascorbate under stirring at room temperature for 24 h afforded the *N*-sulfonated-1,2,3-triazoles **23** (Scheme 6.12) [32].

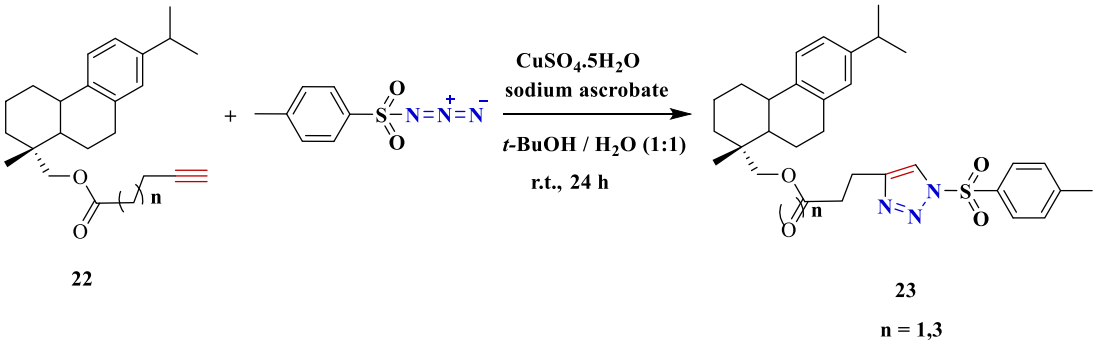
Hu et al. [33] developed a combination of Cu $(OAc)_2.5H_2O$ and 2-aminophenol as a highly efficient and control catalytic system for sulfonyl azides through CuAAC. Thus, normal alkynes **1** or propynoates react with sulfonyl azides **2** to form *N*-sulfonyl-1,2,3-triazoles **3**. This catalytic system is characterized by the use of cheap and chemically stable $Cu(OAc)_2.5H_2O$ as a copper source and all examples were obtained with excellent yields in minutes (Scheme 6.13).

Knoevenagel condensation of alkyne **24** with dimethyl malonate afforded alkyne **25** in 63% yield, which was then deprotected to give alkyne **26** in 67% yield. Eventually, alkyne **26** was converted into triazole **27** in 66% yield by copper-catalyzed triazolation (Scheme 6.14) [34].

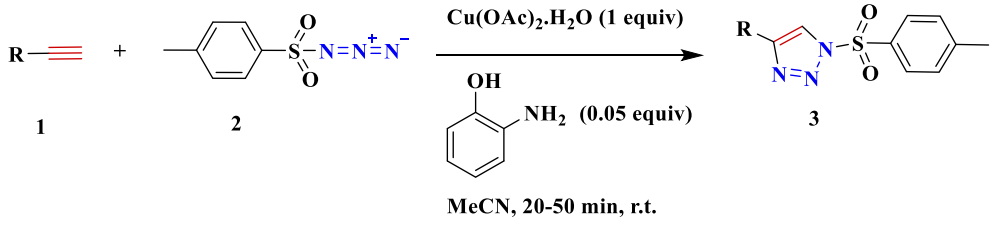
It has been reported that the desilylation of the alkynyl derivative **28** in the presence of potassium fluoride afforded the terminal alkyne **29** in 95% yield with 93% ee, which could be further transformed to 1-sulfonyl-1,2,3-triazole **30** by click reaction in 82% with 93% ee yield without loss of enantioselectivity when using *p*-acetamidobenzene sulfonyl azide and CuTc at room temperature (Scheme 6.15) [35].



SCHEME 6.11 Synthesis of 2-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-ethanol **20** and 2-(1-tosyl-1*H* 1,2,3-triazol-4-yl)-propan-2-ol **21** by click chemistry reaction.

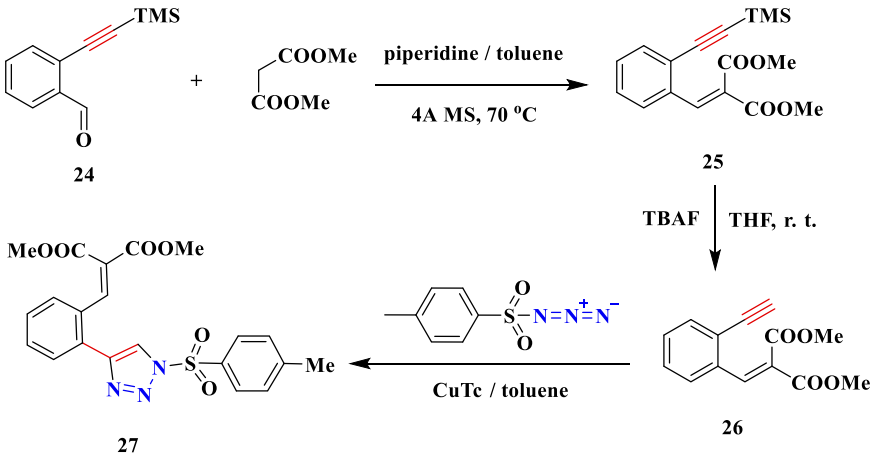


SCHEME 6.12 Synthesis of *N*-sulfonated-1,2,3-triazoles **23**.

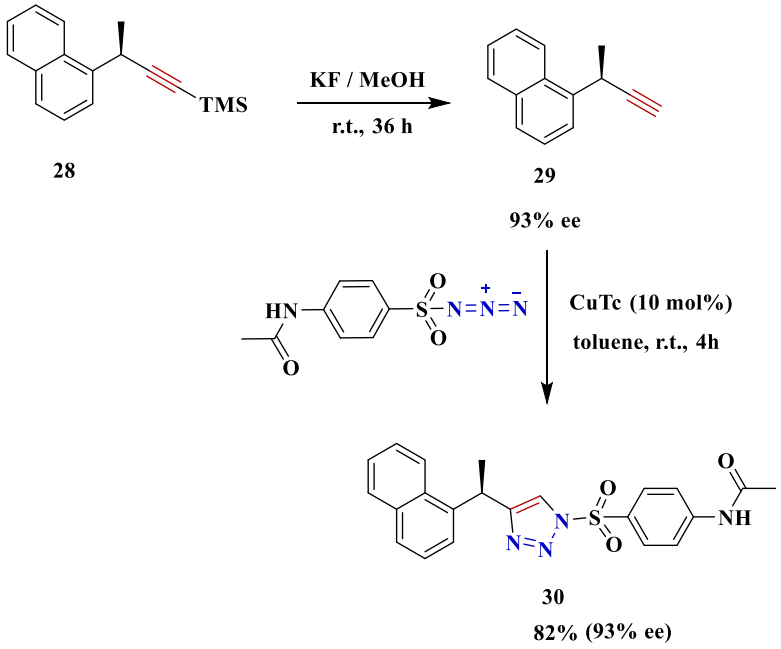


R = *t*Bu (95%); *t*PrOH (92%); $BnOCH_2$ (90%); $BocNHCH_2$ (94%); MeCOO (45%); Ph (95%); 4-MeC_6H_4(96%)

SCHEME 6.13 Use of $Cu(OAc)_2.5H_2O$ as catalyst in *N*-sulfonyl-1,2,3-triazoles **3**.



SCHEME 6.14 Synthesis of *N*-sulfonyl-1,2,3- triazoles **27** by copper-catalyzed triazolation.



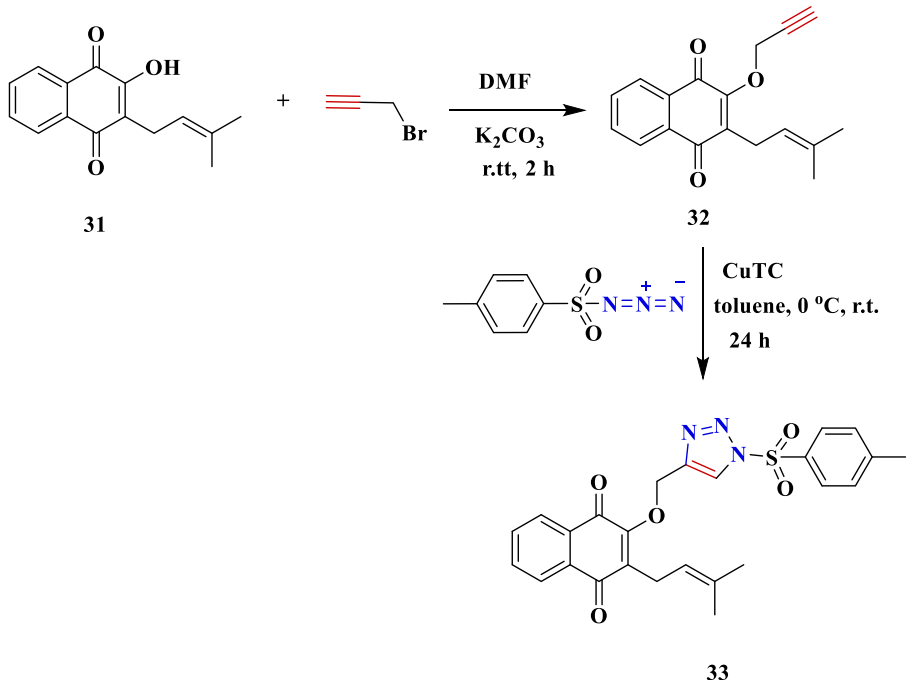
SCHEME 6.15 Possible pathways for 1-sulfonyl-1,2,3-triazole derivative **30**.

Sulfonyl-1,2,3-triazoles **33** were prepared by propargylation of 2-hydroxy-3-(3-methylbut-2-en-1-yl)naphthalene-1,4-dione **31** and propargyl bromide in DMF containing potassium carbonate at room temperature for 2 h, followed by CuAAC with tosyl azide in toluene at 0°C (Scheme 6.16) [36].

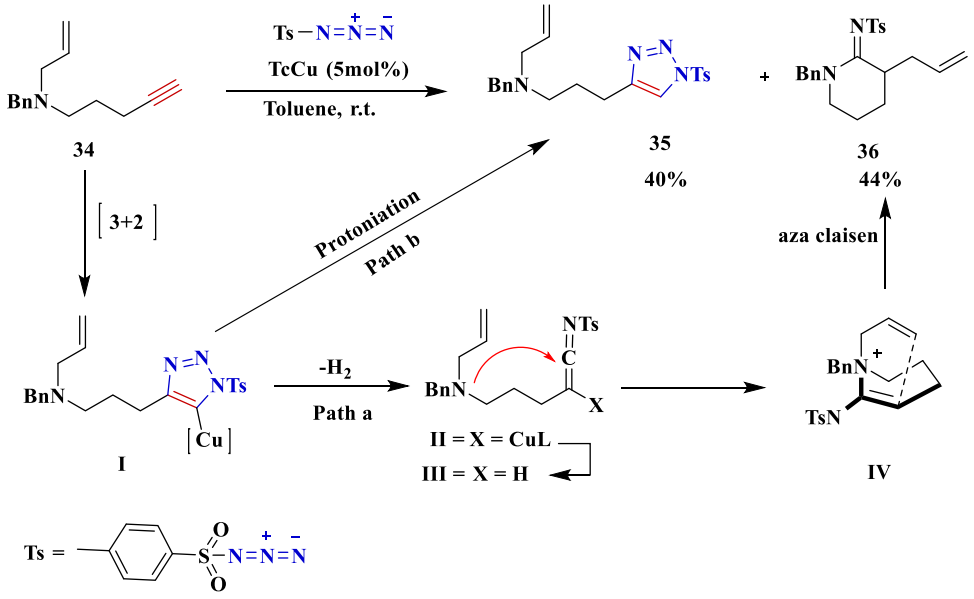
The tertiary amino enyne **34** was reacted with tosyl azide in the presence of a catalytic amount of CuTc in anhydrous toluene at room temperature, to furnish the triazole **35** and amidine **36**, in 40% and 44% yield, respectively. The formation mechanism of **35** and **36** is through the starting [3 + 2] adduct **I**, which is protonated to give triazole **35** (path b). In contrast, **I** can further decompose to the sulfonyl ketenimine **II**, and then cyclize by virtue of a tethered nitrogen nucleophile to generate the cyclic zwitterion **IV**. Finally, sequential aza-Claisen rearrangement gives amidine **36** (path a) (Scheme 6.17) [37].

N-Sulphonyl 1,2,3-triazole derivatives **38** were synthesized by Arthur et al. [38] from compound **37** and sulfonyl azides using CuTC (30 mol%) in toluene at room temperature for 8 h. Deprotection of the carboxylic group of the carbapenem derivative **38** was performed by hydrogenolysis (Pd/C;3.5 bar H_2) under biphasic conditions (THF/triethylammonium-bicarbonate; pH 8.5) to provide carbapenem **39** (Scheme 6.18).

Reaction of 2-[(trimethylsilyl)ethynyl]phenols **40** with thiocarbamoyl chloride in the presence of tetrabutylammonium fluoride (TBAF) and 1,4-diazabicyclo-[2.2.2] octane (DABCO) at 50°C has been reported to give the *O*-(2-ethynylphenyl) dimethylcarbamothioate derivative **41**, which was treated with tosylazide in the presence of



SCHEME 6.16 Synthetic method for the preparation of substituted sulfonyl-1,2,3-triazoles **33**.



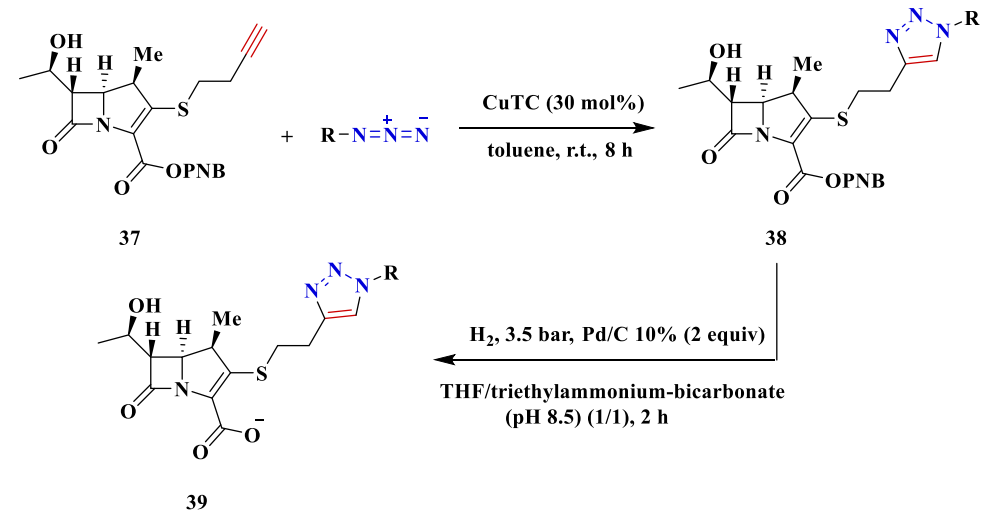
SCHEME 6.17 Proposed reaction pathways for the synthesis of *N*-tosyltriazole derivative **35.**

copper(I)thiophene-2-carboxylate (CuTc) to give the *N*-tosylated 1,2,3-triazole derivatives **42** (Scheme 6.19) [39].

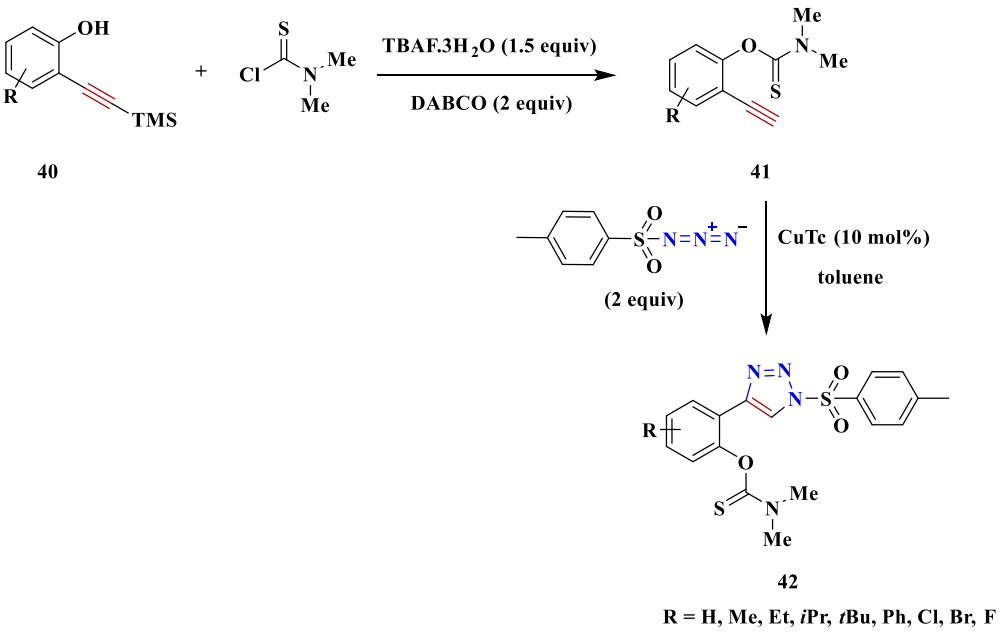
The trimethyl silyl group in the silylated compound **43** can be easily removed by treatment with K_2CO_3 in MeOH to give the ethynylcyclopropane derivative **44**, which reacted with tosyl azide to afford the 1,2,3-triazole substituted cyclopropane **45** in 70% yield with > 20:1 Dr and 94% ee (Scheme 6.20) [40]

Palladium catalyzed ligand has been reported to promote alkynation of unstrained aryl ketones. Thus 4-(acetoxymethyl)-6-(4-acetyl-2-methoxyphenoxy)cyclohexane-1,2,3-triyl triacetate **46** is silylated with 1,2-bis(trimethylsilyl)ethyne in the presence of 2,4-dinitrohydroxylamine, 2% hydrochloric acid, ligand, $Pd(OAc)_2$ and sodium tetrakis[3,5-bis(trifluoromethyl) phenyl]-borate (NaBArF) to afford compound **47** which, upon reaction with tosylazide in the presence of CuTc gave polyfunctional sulfonyltriazole **48** (Scheme 6.21) [41].

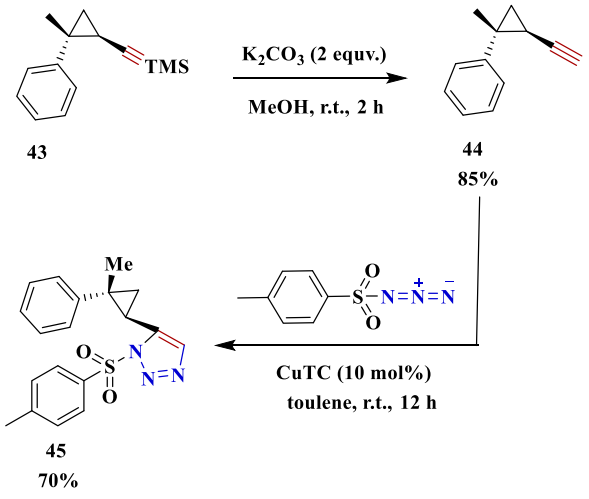
Junior and co-workers [36] described the synthesis of aminonaphthoquinone based triazoles **51** from *N*-propargylated 2-amino-1,4-naphthoquinones **50** (which is prepared



SCHEME 6.18 Synthesis of carbapenem **39**.



SCHEME 6.19 Synthesis of *N*-tosylated 1,2,3-triazoles **42** using TBAF and DABCO.

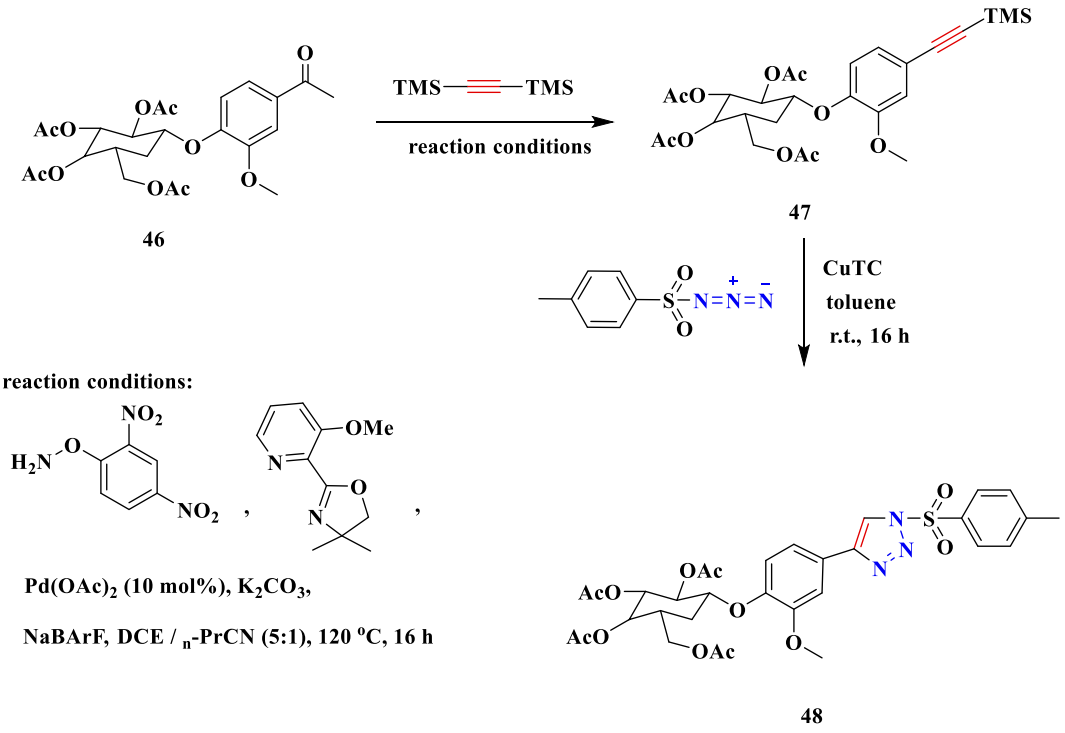


SCHEME 6.20 Synthesis of 1,2,3-triazolesubstitutedcyclopropane 45.

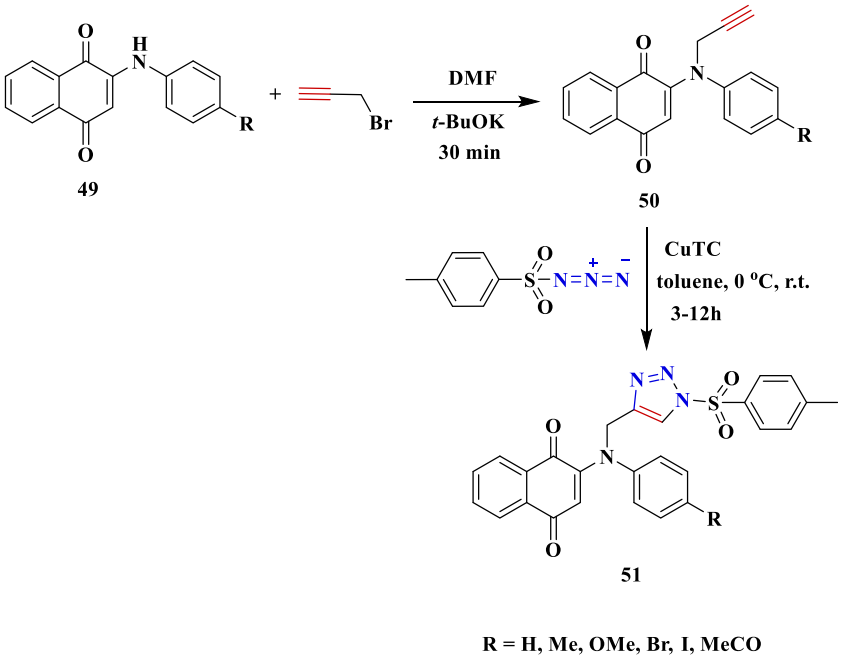
from *t*-BuOK-promoted propargylation of aminonapthoquinones **49** with propargyl bromide in DMF) with alkyne bromide under copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) (Scheme 6.22).

6-(4-(Pro-2-yn-1-yl)piperazin-1-yl)phenanthridine **53** was obtained by heating 6-(piperazin-1-yl)phenanthridine **52** with propargyl bromide (80% in toluene) in the presence of triethylamine (TEA) using DMF as solvent. The 6-(4-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl) phenanthridines **54** were synthesized from compound **53** with tosylazides employing a catalytic amount of CuTC in toluene as solvent (Scheme 6.23) [42].

Jebasingh et al. [43] developed a new tetraaza coordinated copper(II) complexes of 1,10-phenanthroline ($[Cu^{II}(L_1)_2]ClO_4$), 2,2′-bipyridine($[Cu^{II}(L_2)_2]ClO_4$) and 1,4,7,10-tetraazacyclododecane ($[Cu^{II}(L_3)](ClO_4)_2$), is used



SCHEME 6.21 Sequence reaction of polyfuntional sulfonyltriazole **48.**

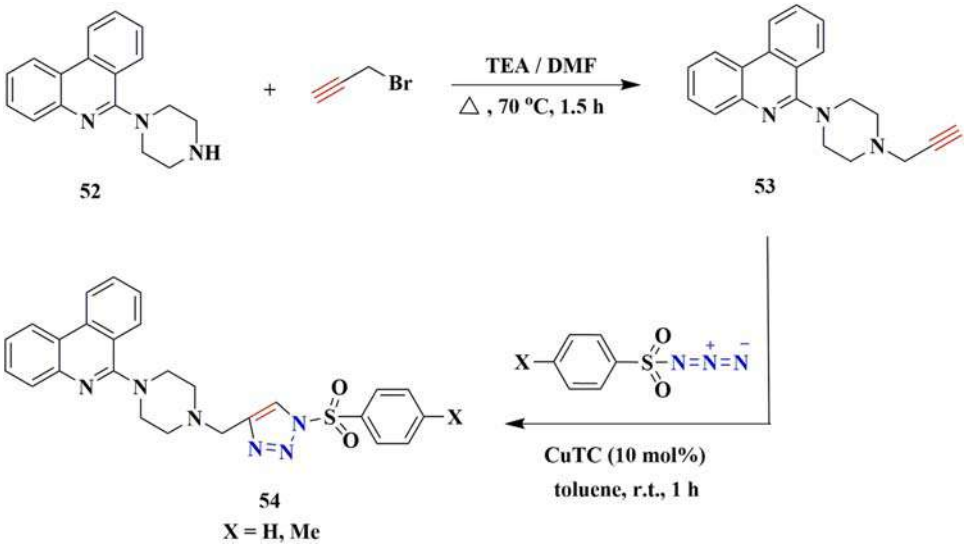


SCHEME 6.22 Synthesis of aminonaphthoquinone based triazoles **51.**

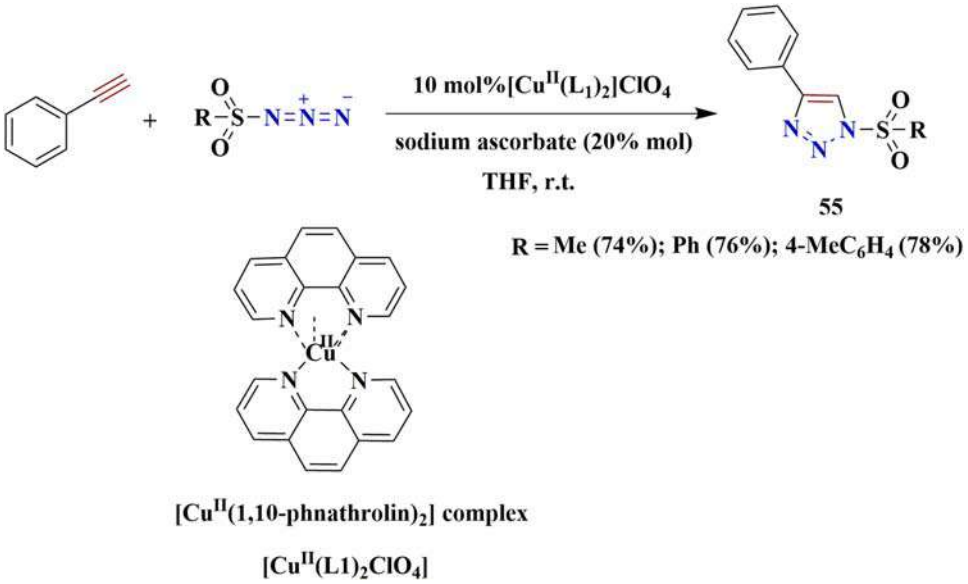
as an effective catalyst for the Cu^{II}AAC reaction. The $[Cu^{II}(L_1)_2]ClO_4$ complex shows high catalytic activity in the formation of 1,4-disubstituted *N*-sulfonyl-1,2,3-triazoles 55 in 78%−97% yields using phenyl acetylene and sulfonyl azides as starting materials (Scheme 6.24).

Cazin et al. [44] have found that the Bis-NHC and a mixture of NHC/PR_3 copper(I) complexes (NHC = *N*-heterocyclic carbene) are efficient catalysts enabling the azide-alkyne cycloaddition reaction leading to the formation of *N*-sulfonyl-1,2,3-triazoles **3** under click conditions with high yields (99%) (Scheme 6.25).

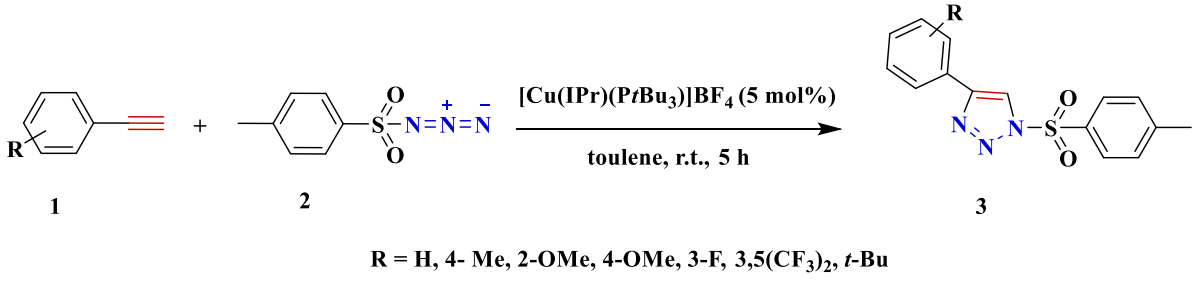
The efficient proline catalyzed synthesis of 4,5-disubstituted-*N*-sulfonyl-1,2,3-triazoles **57** has been accomplished from 1,3-dicarbonyl compounds **56** with sulfonyl azides in



SCHEME 6.23 Synthesis of 6-(4-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)phenanthridines **54.**



SCHEME 6.24 Synthesis of *N*-sulfonyl-1,2,3-triazooles using $[Cu^{II}(L1)_2]ClO_4$ complex in Cu^{II}AAC reaction.



SCHEME 6.25 Bis-NHC and mixed NHC/PR3 copper(I) complexes in the synthesis of *N*-sulfonyl-1,2−3-triazoles 3.

the presence of 20 mol% of proline with excellent regioselectivity. A probable reaction mechanism was proposed when a 1,3-dicarbonyl compound was treated with proline to form the enamine intermediate **I**. The formation of the cyclic intermediate **III** can be explained by the enamine nitrogen initiated by the addition of the electron-rich β-carbon of **I** to terminal nitrogen of sulfonyl azide **2**, followed by ring convergence, formal [3 + 2] annulation.

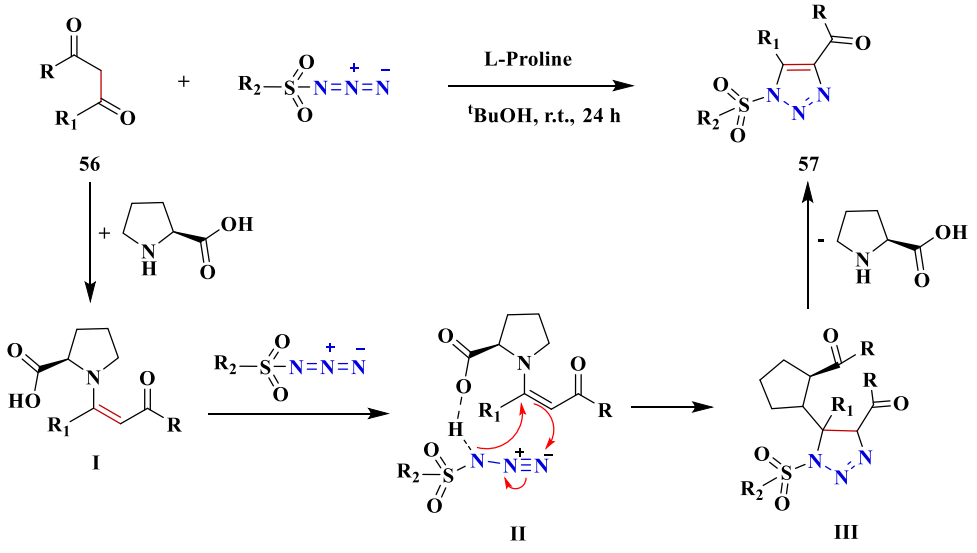
This regioselective addition is further facilitated by the transition state **II** which involves hydrogen-bond interactions. Later, the removal of proline from **III** will lead to the formation of 4,5-disubstituted *N*-sulfonyl-1,2,3-triazoles **57** with high regioselectivity and proline regeneration to continue the catalytic cycle (Scheme 6.26) [45].

Reactions of *N*-unsubstituted triazoles **58** with sulfonyl chlorides **59** in ethyl alcohol containing *N,N*-diisopropylethyl amine (DIPEA) afforded regioisomeric mixtures of 1- and 2-sulfonyl-1,2,3-triazoles **60** and **61**, respectively. The isomer ratio depends on both the nature of the azolyl ring and the size of the substituent in the sulfonyl chlorides (Scheme 6.27) [46].

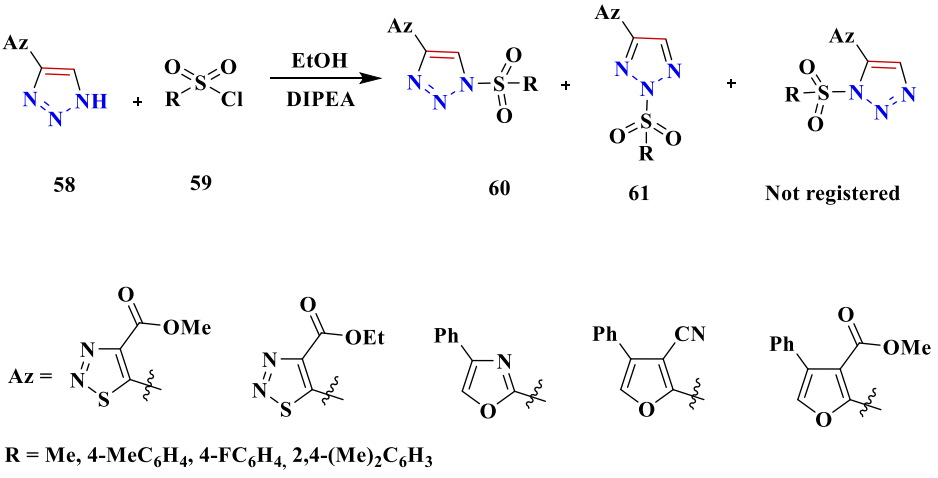
The reaction of the azadienes **62** with 4-toluenesulfonyl azide leads to the formation of *N*-sulfonyl-1,2,3-triazoles **63** in low yield (15%). The formation mechanism of compound **63** is through the reaction of aminobutadiens **62** with 4-toluenesulfonyl azide leading to the formation of intermediate **I**, from which HBr can be easily eliminated from the intermediate creating a stable compound **63** (Scheme 6.28) [47].

The subjection of *tert*-butylacetylene **64** to butyllithium (BuLi) followed by the reaction with trisyl azide at −45°C afforded the *N*-sulfonyl-1,2,3-triazole **65** in 20% yield, trace amounts (0.2%) of the regioisomeric heterocycle **67**, and unexpected product **66** (2%), as well as some reduced starting compounds (Scheme 6.29) [48]

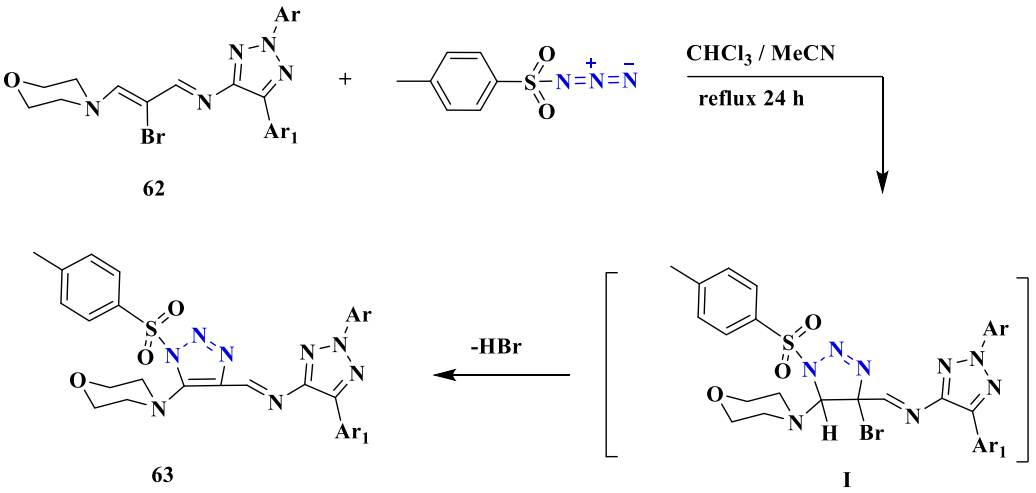
The reaction of phenylacetylene **1** with tosylazide **2** and 3-phenyl-2*H*-azirine **68** in the presence of copper(I) phenylacetlide **69** with *N,N*-diisopropyl ethylamine, and methylene chloride as a solvent gives the *N*-sulfonyl-



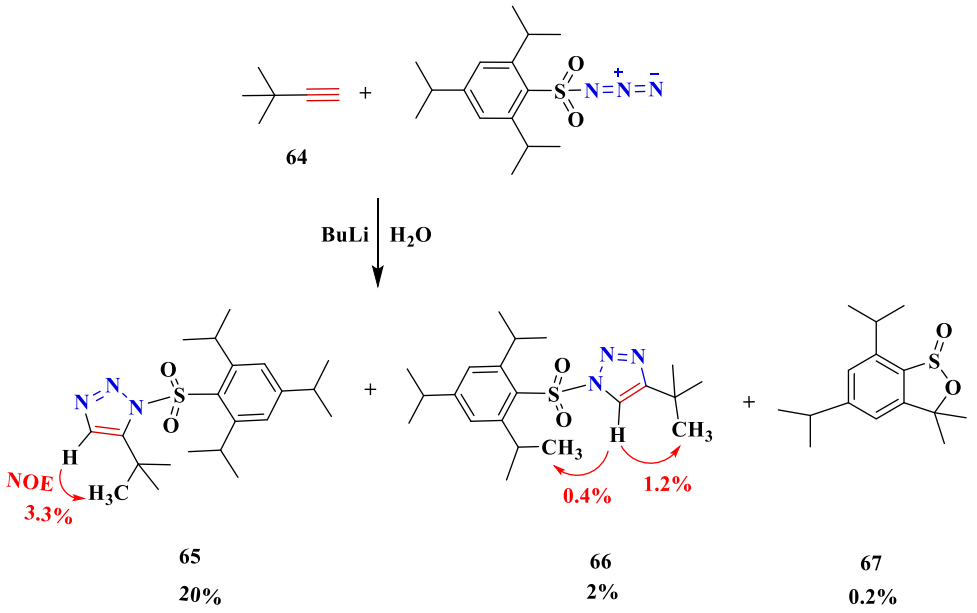
SCHEME 6.26 Proline catalyzed synthesis of 4,5-disubstituted-*N*-sulfonyl-1,2,3-triazoles **57.**



SCHEME 6.27 Synthesis of regioisomeric mixtures of 1- and 2-sulfonyl-1,2,3-triazoles **60** and **61.**



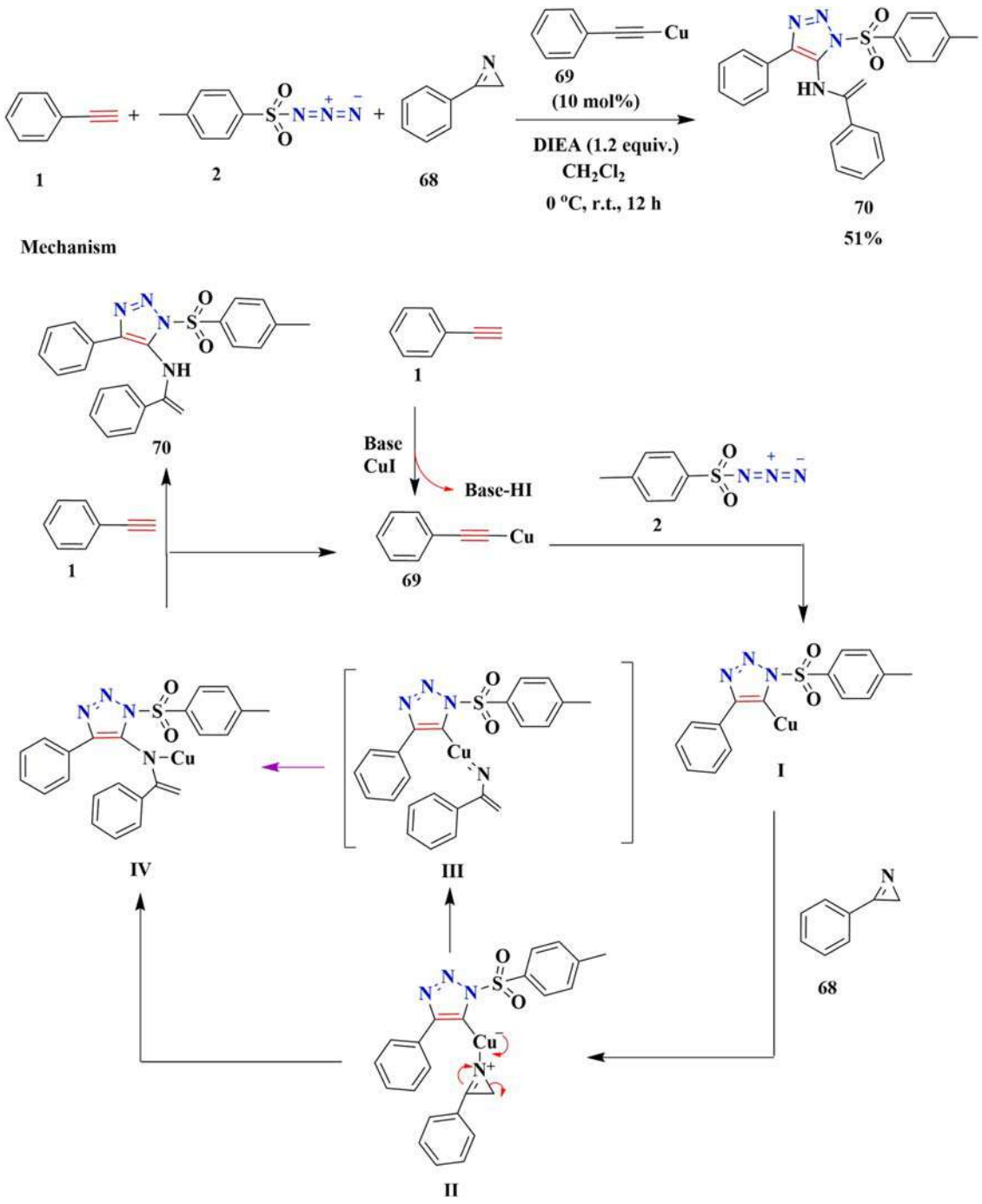
SCHEME 6.28 Synthesis of polyfunctional *N*-sulfonyl-1,2,3-triazoles **63**.



SCHEME 6.29 Synthesis of trisyl-*N*-sulfonyl-1,2,3-triazoles **65** and **66.**

1,2,3-triazole derivative **70**. The proposed mechanism runs through the reaction of alkyne **1** with CuI in the presence of a base-forming copper(I) phenylacetylide species **69**, and then reaction with tosylazide **2** gives intermediate **I** *via* a 1,3-dipolar cycloaddition reaction. The triazolyl-Cu(I) species I is rapidly taken up 2*H*-azirine, to give the triazolyl-Cu (I)/2*H*-azirine complex **II**. The **II** rearrangement will lead to the formation of Cu(III)-vinyl nitrene species **III**. Further insertion of the vinyl nitrene into the C-Cu bond would yield Cu-NR_1R_2 complex **IV**. Finally, protonation of **IV** with alkyne afforded the product **70**, and copper(I)phenylacetylide was regenerated to complete the entire catalytic cycle (Scheme 6.30) [49].

Ramachary and co-workers discovered new a copper-free, novel and green technology for the synthesis of fused *N*-sulfonyl-1,2,3-triazoles such as ethyl 4-methyl-1-tosyl-6,7-dihydro-1*H*-benzo[*d*][1,2,3]triazole-5-carboxylate **73** and ethyl 4-methyl-6,7-dihydro-1*H*-benzo[*d*][1,2,3] triazole-5-carboxylate **74** with using organocatalytic cascade enamine amination/elimination (EA/E) and [3 + 2]-cycloaddition/hydrolysis ([3 + 2]-CA/H) reactions from commercially available ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate **71**, tosylazide and 20 mol% proline (Scheme 6.31) [50]. The mechanism of formation of NH-triazole and *N*-tosyl triazole starting from the reaction of proline with ester **71** generates the dienamine **72**, which on treatment with tosylazide furnish the selectively 7a-(2-carboxy-pyrrolidin-1-yl)-4-methyl-1-(toluene-4-sulfonyl)-3a,6,7,7a-tetrahydro-1*H*-benzotriazole-5-carboxylic acid ethyl ester **I** *via* concerted [3 + 2]-cycloaddition, that



SCHEME 6.30 The reaction sequence for the formation of *N*-sulfonyl-1,2,3-triazole derivative **70**.

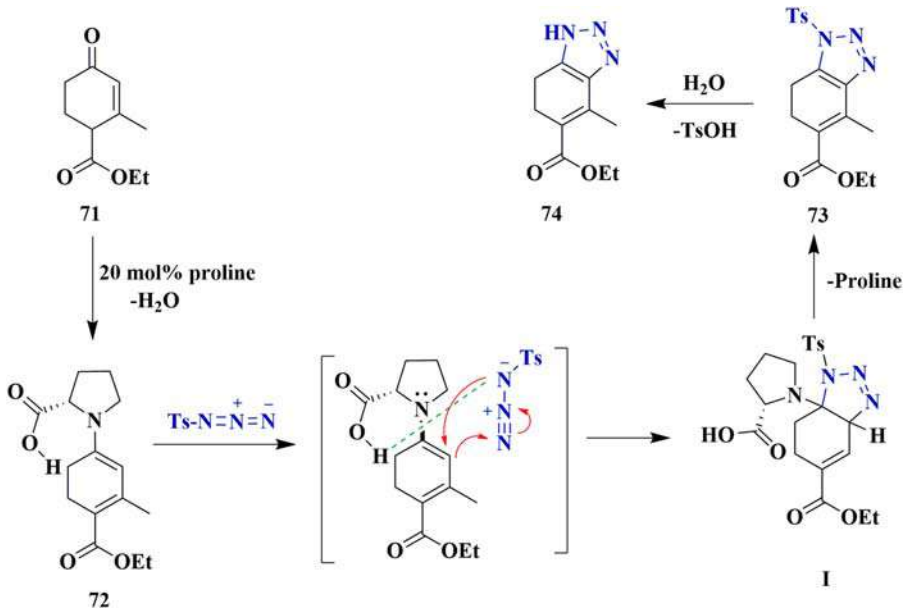
can be converted to product **73** by rapid proline removal. The combination of dimethylsulfoxide (DMSO) and H_2O induced in situ by hydrolysis of the resulting 1,2,3-triazole **73** gives the NH-1,2,3-triazole **74** good yields as shown in Scheme 6.31.

Compound **75** having hemiacetal moiety, is acetylated to afford the diacetyl derivative **76**, which is converted to alkyne **77** by Bingel-Hirsch reaction. Alkyne **77** is highly reactive towards silyazide in a click reaction with the formation of bis-*N*-sulfonyl-1,2,3-triazole **78** (Scheme 6.32) [51].

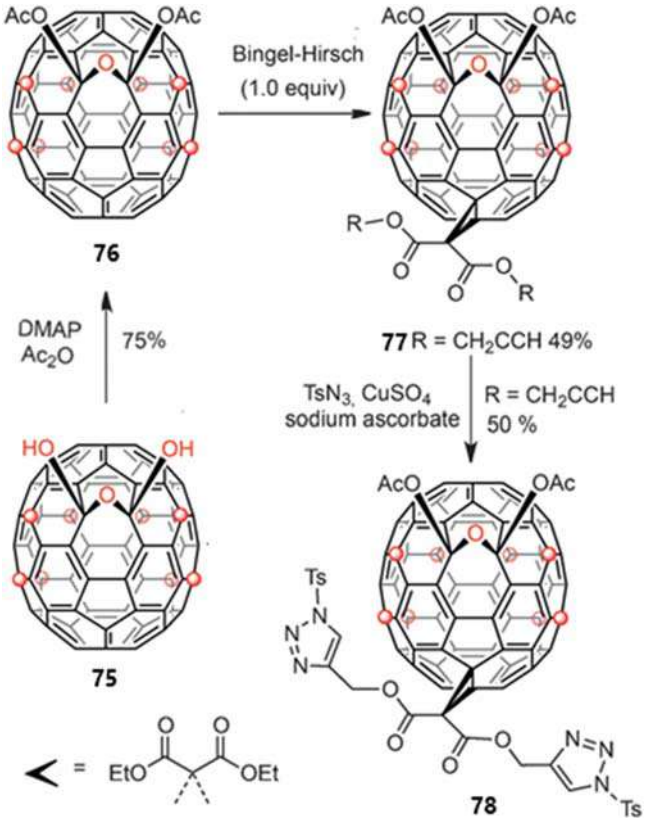
6.3 Reactions of *N*-sulfonyl-1,2,3-triazoles

6.3.1 Reactions with alcoholic compounds

Some reports investigated the reactivity of *N*-sulfonyl-1,2,3-triazoles with respect to various types of alcoholic compounds, therefore Bi et al. [52] were the first to develop Rh(II)-catalyzed tandem cyclization reaction of *N*-sulfonyl-1,2,3-triazoles **79** with alcohols **80**. Both primary and secondary alcohols such as ethanol, phenylethyl



SCHEME 6.31 Green method for synthesis of *N*-sulfonyl-1,2,3-triazoles **73.**

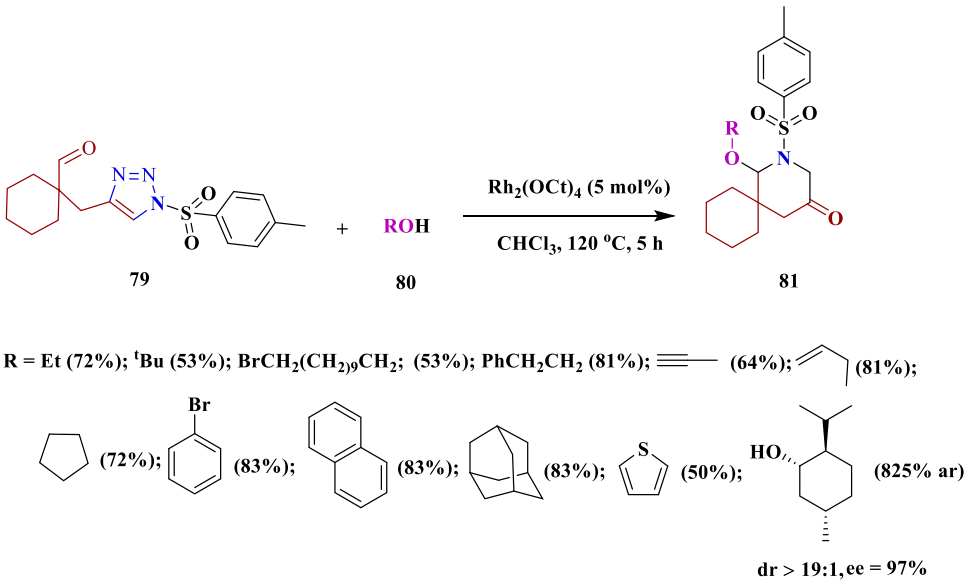


SCHEME 6.32 Synthesis of bis-*N*-sulfonyl-1,2,3-triazole **78**.

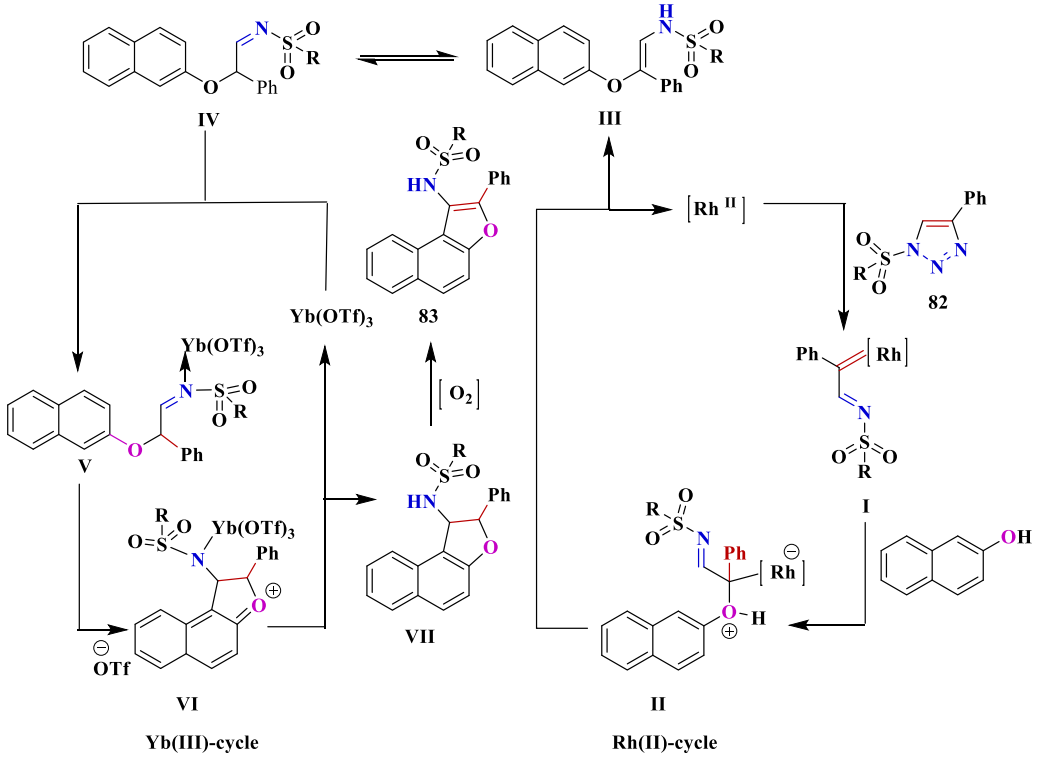
alcohol, cyclopentanol and 2-adamantanol performed well under the optimized conditions yielding alkoxy-2-tosyl-2-azaspiro[5.5]undecan-4-ones **81** in excellent yields. Tertiary alcohols such as *t*-butanol and 2-methyl-2-butanol gave the corresponding compound **81** in moderate yield, possibly due to steric hindrance. Thus, the formation of alkoxy products depends on the nature of the alcohol functional groups (Scheme 6.33).

4-Phenyl-1-tosyl-1*H*-1,2,3-triazole **82** and β-naphthol were treated with rhodium(II)acetate dimer [$Rh_2(OAc)_4$] at 110°C in the absence of additive and oxygen to furnish *N*-(2-phenylnaphtho[2,1-*b*]furan-1-yl)sulfonamides **83**. The formation of O−H insertion product **83** was obtained in 43% yield (Scheme 6.34). The proposed mechanism for the generation of **83** proceeds through the cascade transannulation of **82** by β-naphthol catalyzed by Rh and Yb, which occurs sequentially. The reaction of an active Rh(II) catalyst with **82** will lead to the formation of a rhodium carbenoid **I** as a result of the formation of diazoimine from ring-chain isomerism **82**. Insertion of **I** into O−H bond of β-naphthol would afford the inserted product **III** by forming the ylid **II** with the regeneration of the rhodium catalyst for the next cycle. Then, the formed insertion product **III** enters the Yb catalytic cycle. Tautomerization of enamide **III** gives imine **IV**, which upon activation by $Yb(OTf)_3$ provides intermediate **V**. Intramolecular cyclization in **V** from electron-rich ortho-position can lead to the formation of cation **VI**. The formation of fused-dihydrofuran **VII** and regeneration of Yb-catalyst can be rationalized by aromatizing **VI** due to proton loss and ion exchange. Finally, oxidation of **VII** in the air would furnish the expected fused-furan products **83** [53].

Anbarasan et al. [54] disclosed rhodium-catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles **84** from 2-(hydroxy(phenyl)methyl)phenol to benzopyran derivatives **85** in good yields by the generation of potential reactive intermediates, namely α-imino metal carbenoids and *o*-quinone methides using of 2 mol% of rhodium acetate in toluene at 100°C. The reaction proceeds by involving a nucleophilic attack of *o*-quinone methide (*o*-QM) on



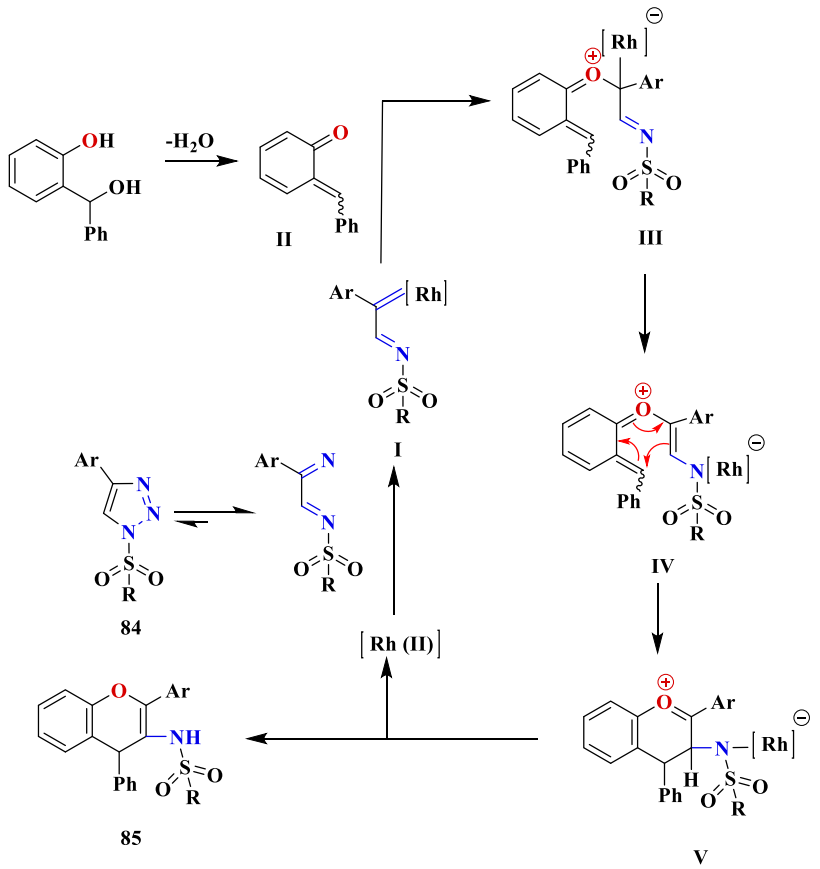
SCHEME 6.33 Synthesis of alkoxy-2-tosyl-2-azaspiro[5.5]undecan-4-ones **81**.



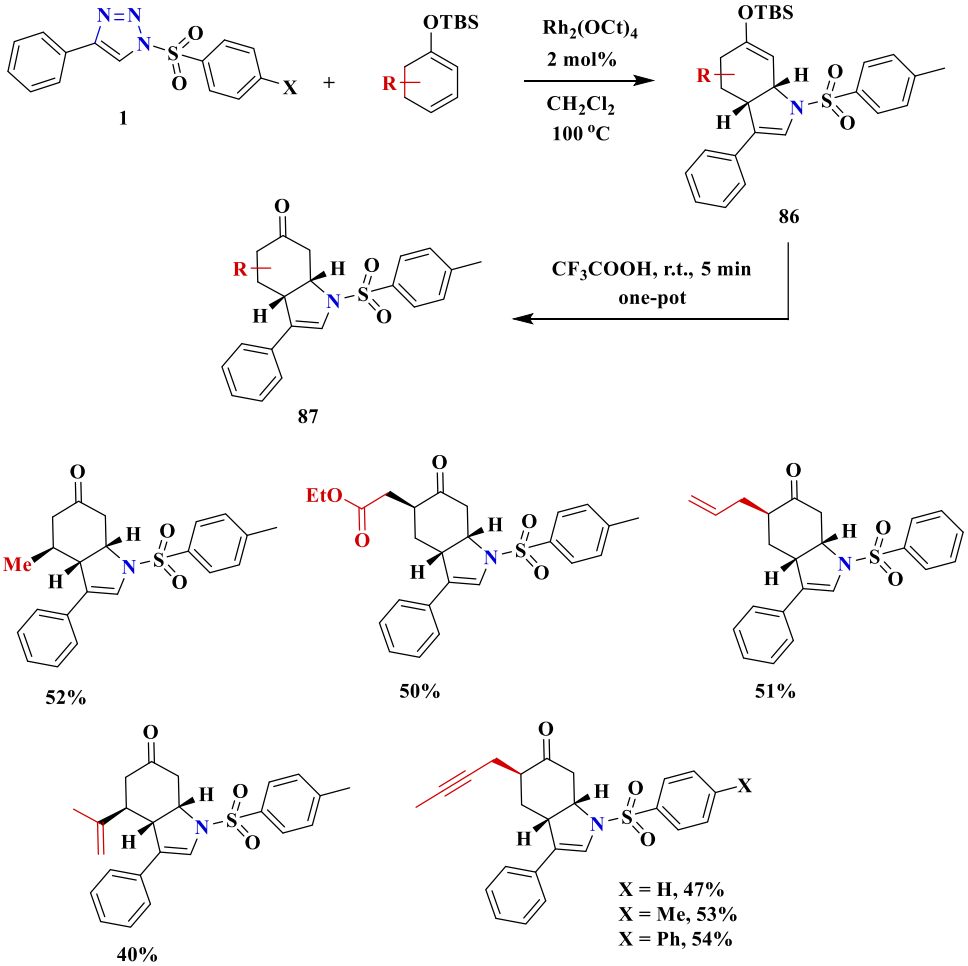
SCHEME 6.34 The formation of *N*-(2-phenylnaphtho[2,1-*b*]furan-1-yl)sulfonamides **83**.

α-imino rhodium carbenoid with the formation of the carbonyl ylide followed by 6π-electrocyclization and isomerization (Scheme 6.35).

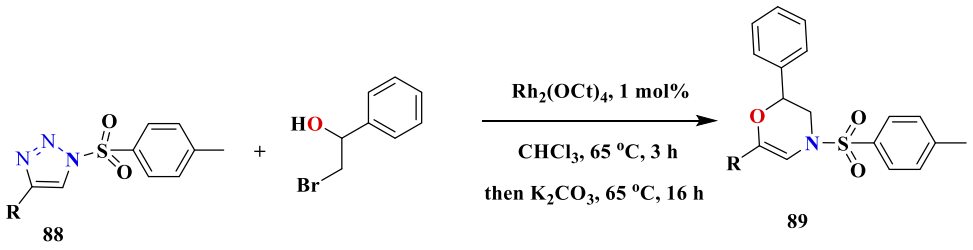
Zhai et al. [55] developed the synthesis of functionalized silyl enol ethers **86**, through rhodium-catalyzed denitrogenation [3 + 2] cycloaddition by the reaction of 4-phenyl-1-tosyl-1,2,3-triazole **1** with tertbutyl(cyclohexa-1,3-dien-1-yloxy)dimethylsilane in the presence of $Rh_2(OAc)_4$ in dichloroethane (DCE) at 110°C, followed by the addition of trifluoroacetic acid which converted the silyl enol ethers **86** to hydroindolones **87**. The method has been employed to construct synthetically valuable bicyclo [3.3.1]alkenone derivatives and pyrrolidine-ring-containing bicyclic indole compounds (Scheme 6.36).



SCHEME 6.35 Synthesis of benzopyran derivatives **85**.

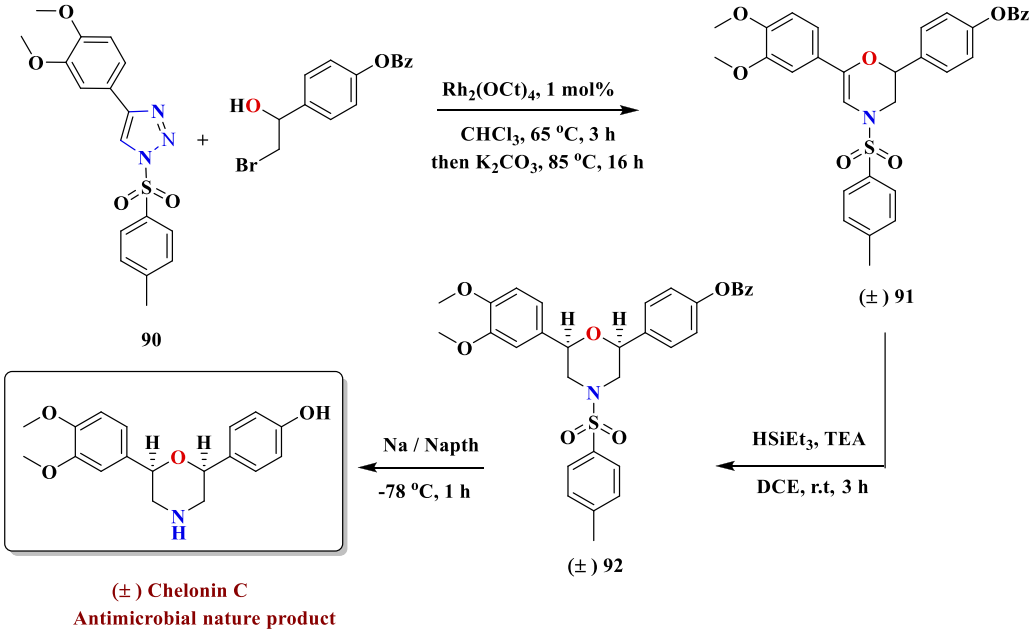


SCHEME 6.36 Synthesis of functionalized silyl enol ethers **86**.



R = Ph (96%); 4-OMeC$_6$H$_4$ (86%); 4-MeCOC$_6$H$_4$ (78%), 3,4-(OMe)$_2$C$_6$H$_3$ (86%); 4-FC$_6$H$_4$ (8162%); 4-CNC$_6$H$_4$ (75%); 4-BzOC$_6$H$_4$ (82%); naphthyl (88%)

SCHEME 6.37 Synthesis of 2,6-substituted 3,4-dihydro-2*H*-1,4-oxazines**89**.



SCHEME 6.38 Synthesis of (±) Chelonin C.

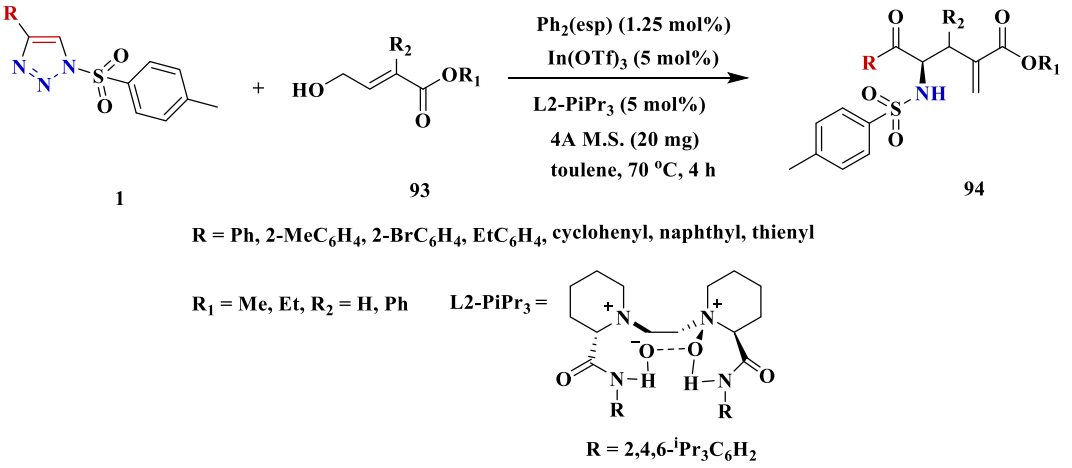
Stewart et al. [56] described the Rh(II)-catalyzed reaction between 1-tosyl-1,2,3-triazoles **88** and 2-bromo-1-phenylethan-1-ol, which produces a 2,6-substituted 3,4-dihydro-2*H*-1,4-oxazines **89** using 1 mol% of $Rh_2(Oct)_4$ in chloroform at 65°C, followed by addition of potassium carbonate. The reaction is assumed to enter rhodium carbenoid 1,3-insertion into O−H followed by an annulation (Scheme 6.37).

Moreover, with this new method the antimicrobial natural product (±)-chelonin C was obtained with 70% yield (Scheme 6.38) [56].

6.3.2 Reactions with ketones

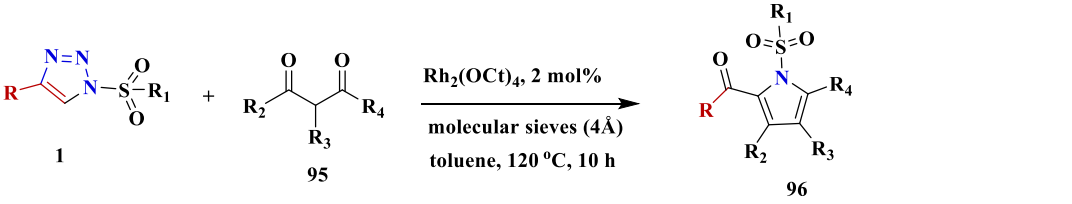
It has been reported that the catalytic insertion/asymmetric Claisen rearrangement tandem reaction of *N*-sulfonyl-1,2,3-triazoles **1** with allyl alcohol esters **93** was achieved by bimetallic relay catalytic systems involving a chiral rhodium salt and chiral *N,N′*-dioxideindium(III) complex. This manifold could overcome the limitation of single RhII catalysis, providing a straight and facile route to the various enantioenriched *β*/*γ*-amino acid derivatives **94** in high yields (up to 99%) with excellent diastereo- and enantioselectivities (up to > 95:5 Dr, 98:2 er) (Scheme 6.39) [57].

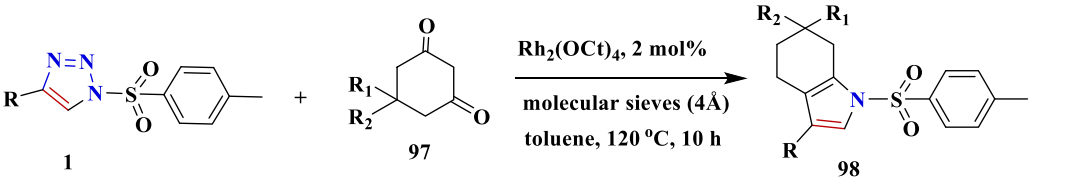
The efficient reaction of 1-sulfonyl-1,2,3-triazoles **1** with 1,3-diketones as atom-economic reaction components was reported by Zhang et al. [58]. This cyclization has been found to be 1,3-diketone dependent, as acyclic 1,3-ketones **95** resulted in 2-acetyl pyrroles **96**, while cyclic 1,3-diketones **97** chemoselectively afforded 2,3-fused pyrroles **98** (Scheme 6.40). Thus this reaction provides a new and powerful method for the synthesis of highly functionalized pyrroles and fused pyrrole derivatives. In order to justify the selectivity of the reaction, the initial selective insertion of OH or CH with Rh-azavinyl carbenes formed in situ was proposed as shown in Scheme 6.40.



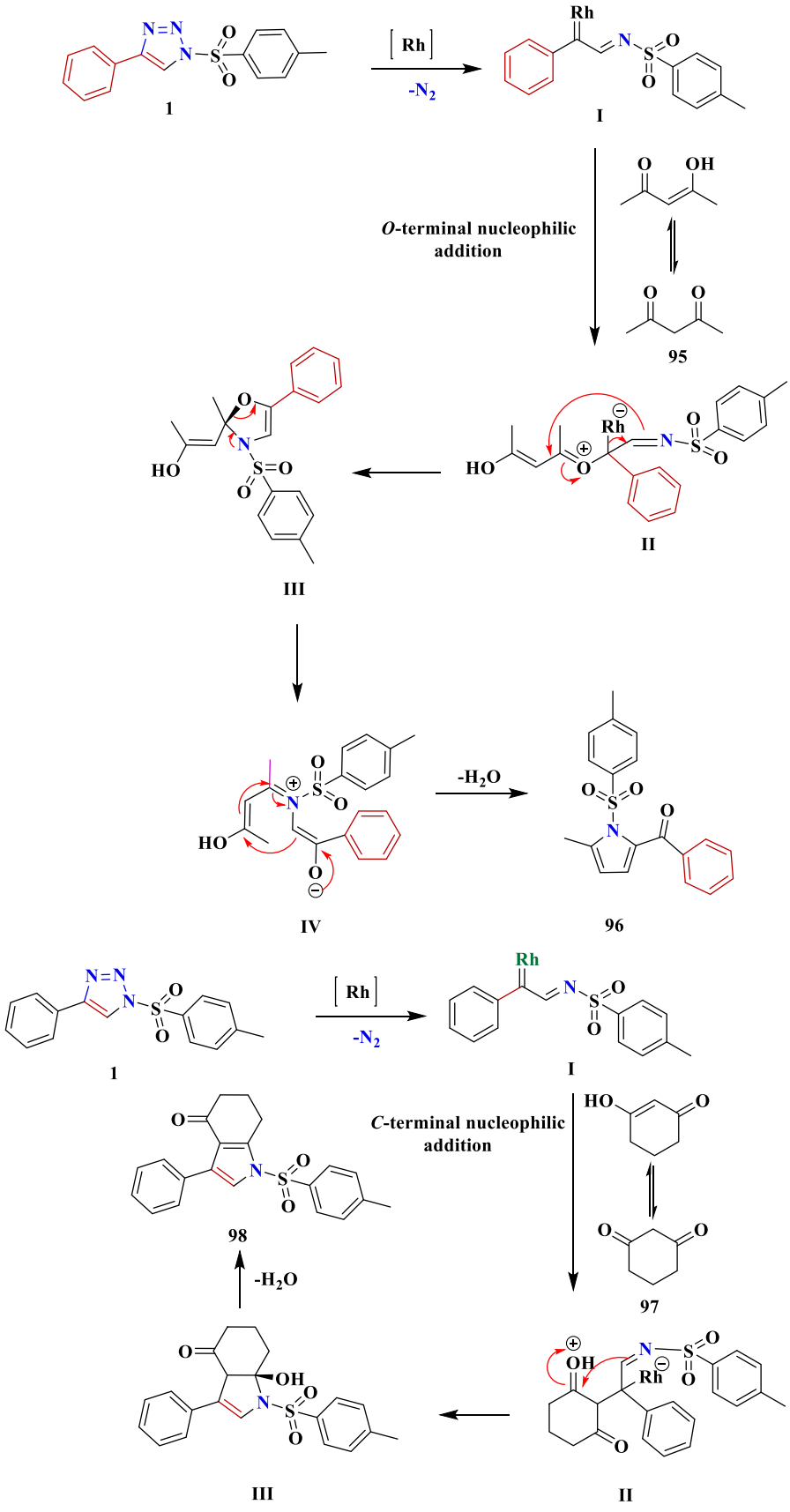
SCHEME 6.39 Chiral rhodium salt and chiral *N*,*N*′-dioxideindium(III) complex to the synthesis of enantioenriched *β*/*γ*-amino acid derivatives **94**.

Initially, *N*-sulfonyl-1,2,3-triazole **1** is converted into *α*-diazo imine intermediate **I**, along with the release of molecular nitrogen. For acetylacetone **95**, the enol isomer is dominant, so the hydroxy group adds to the electrophilic carbene center of **I** to generate zwitterionic intermediate **II**. Anionic rhodium releases an electron pair, which induces an attack of the imino nitrogen atom at the *α*-carbon atom of the oxonium ion to form 4-oxazoline intermediate **III**. C−O bond cleavage subsequently occurs to give zwitterionic intermediate **IV**. Finally, pyrrole **96** is formed by dehydration of intermediate **IV**. Cyclic 1,3-diketones that do not contain a substituent at the 2-position, one possible route could be *C*-nucleophilic addition of cyclohexane-1,3-dione **97** to the electrophilic carbene carbon atom, which forms zwitterionic species **VII**. Following sequential intramolecular





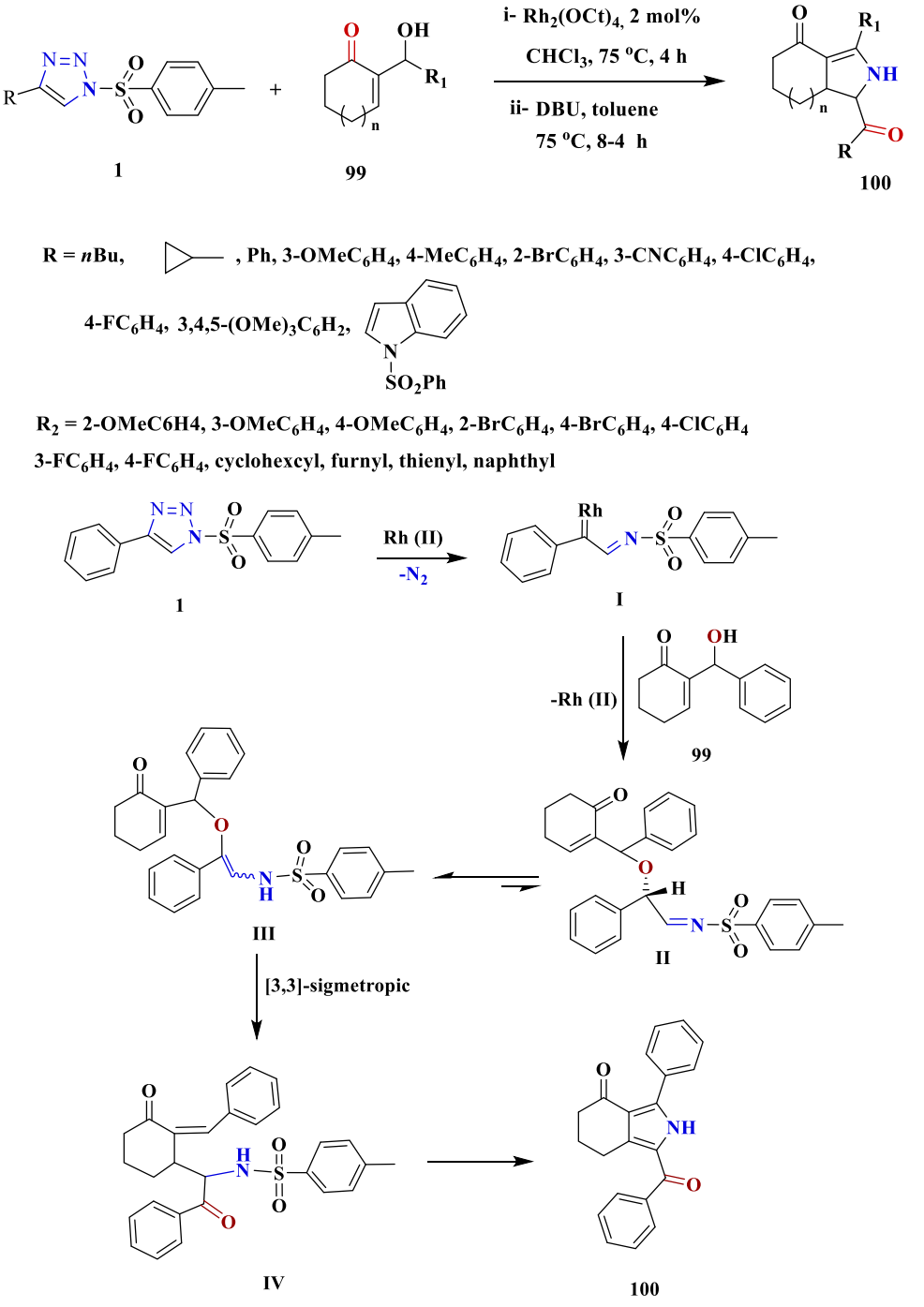
SCHEME 6.40 Proposed reaction pathways of the formation of compounds **96** and **98**.



SCHEME 6.40 (Continued)

cyclization and dehydration processes, 2,3-fused pyrrole **98** is produced.

Yu and co-workers [59] demonstrated the developed a novel and efficient way for the synthesis of potential biological active 3,4-fused pyrroles **100** in good yields by Rh(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles **1** with Morita-Baylis Hillman (MBH) adducts as starting materials derived from α,β-unsaturated cyclic ketones **99** and subsequent rearrangement/aza-Michael addition/oxidative aromatization tandem reactions in chloroform containing 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (Scheme 6.41). The plausible mechanism for the formation of the 3,4-fused pyrrole as shown in Fig. 6.1 illustrated the reaction of *N*-sulfonyl-1,2,3-triazole **1** with Rh(II) catalyst generates a rhodium-stabilized carbene, along with the release of molecular



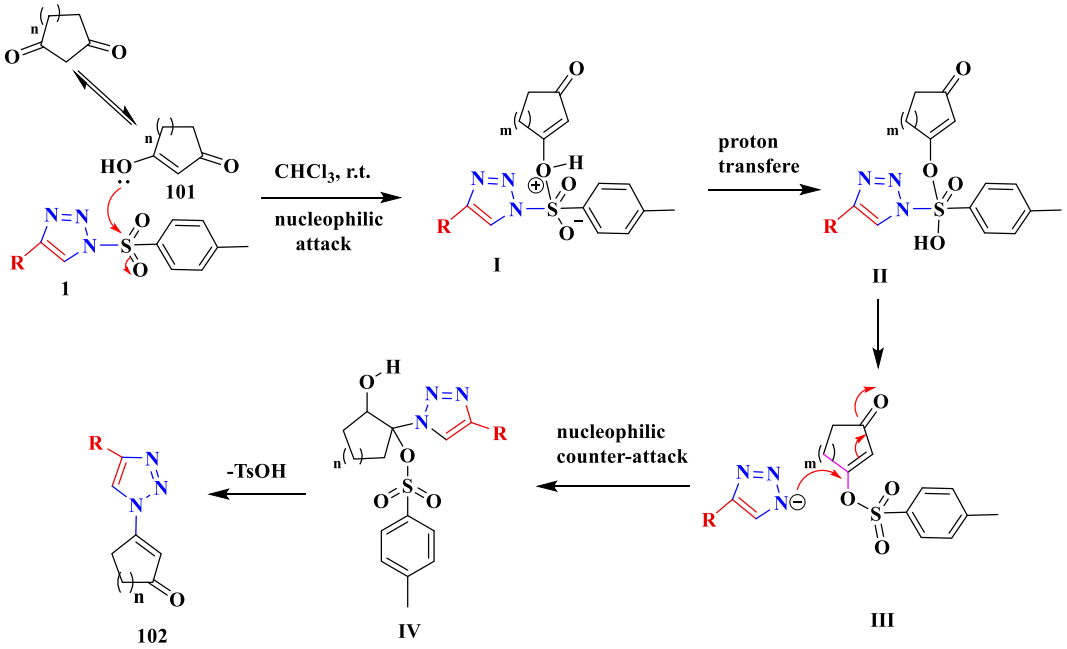
SCHEME 6.41 The mechanism of formation of 3,4-fused pyrrole **100**.

nitrogen. The azavinyl carbene reacts with the α,β-unsaturated cyclic ketones **99** adducts through an O−H 1,1-insertion followed by tautomerization, which could lead to an isomeric mixture of enamide intermediate **III**. Then intermediate **III** undergoes intramolecular [3,3] sigmatropic rearrangement, and subsequent intramolecular cyclization and oxidative aromatization give the desired 3,4-fused pyrrole **100** (Scheme 6.41).

Desulfonylative alkylation of *N*-tosyl-1,2,3-triazoles under metal-free conditions has been reported to lead to β-triazolylenones **102** using 1,3-dicarbonyl compounds as detosylative alkylating agents. Thus, the reaction of cyclic 1,3-dicarbonyl compounds **101** and *N*-tosyltriazoles **1** in chloroform at room temperature gives β-triazolylenones in moderate to high yields. This method provides an efficient, versatile, and straightforward strategy for the synthesis of new functionalized 1,2,3-triazoles. The proposed mechanism proceeds initially, the enol form of 1,3-dicarbonyl **101** attacks the sulfonyl group in **1** to form intermediate **I**, which later undergoes a proton transfer to form intermediate **II**. Cleavage of the N−S bond in intermediate **II** leads to the formation of β-*O*-tosylcycloalkenone **III** and triazolyl anion **IV**. The subsequent counter-attack of the triazolyl anion **IV** on the enone intermediate **III**, followed by elimination of *OTs* affords the corresponding β-triazolylenone **102** (Scheme 6.42) [60].

The efficient synthesis of 2,5-diaryloxazole derivatives **104** by a rhodium-catalyzed annulation of triazoles **1** with aldehydes **103** is described by Li et al. [61]. Various oxazole derivatives can be obtained in good to excellent yields by the reaction of *N*-sulonyl-1,2,3-triazoles **1** with *o*-cyanobenzaldehydes **103** in the presence of 1 mol% of $Rh_2(OAc)_4$ in chloroform at room temperature. Applying this strategy, the antimycobacterial natural products balsoxin and texamine have been synthesized in good yields in one step (Scheme 6.43).

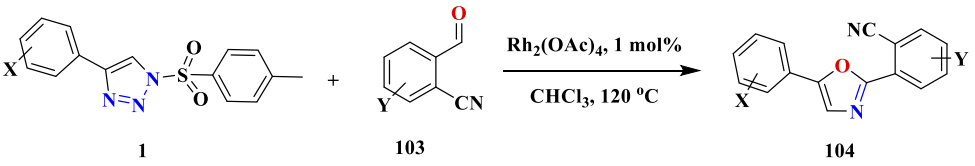
He and co-workers [62] developed a facile and efficient strategy for the synthesis of novel 5-aryl-2-(quinolin-2-yl)oxazoles **106** as a new chemosensor in metal ion recognition *via* rhodium-catalyzed formal [3 + 2] cyclization of 4-aryl-1-tosyl-1*H*-1,2,3-triazoles **1** with quinoline-2-carbaldehydes **105**. The protocol employs mild conditions and gives good yields of 2,5-aryloxazole derivatives. Moreover, this 5-aryl-2-(quinolin-2-yl)oxazole skeleton is indeed a new fluorophore and its use in metal ions probes is also being investigated and shows fluorescent responses to mercury ions such as 5-phenyl-2-(quinolin-3-yl)oxazole highly selective sensing toward Hg^{2+} ion in compared with an ion of another metal examined. This highly efficient protocol constructs two new carbon-heteroatom bonds and one new five-membered ring. The



n = 1, R = Ph (55%); *n*-Pr (52%); *t*-BuC$_6$H$_4$ (53%); 4-MeFC$_6$H$_4$ (67%); 4-ClC$_6$H$_4$ (52%); 4-BrC$_6$H$_4$ (54%); thienyl (75%)

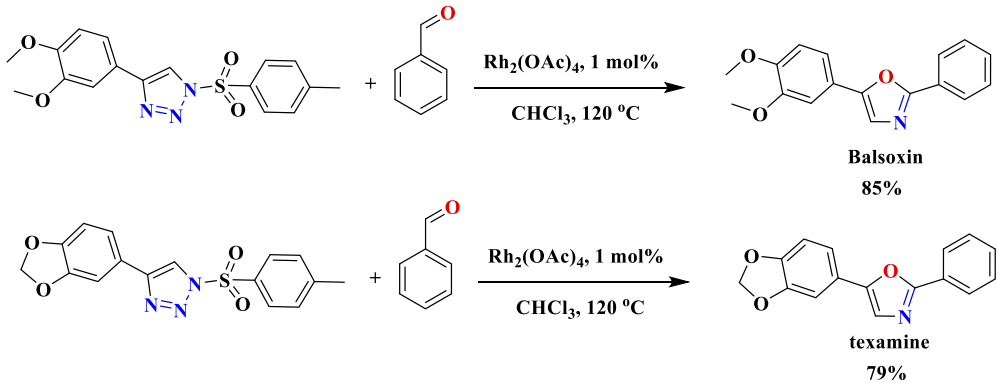
n = 2, R = Ph (78%); t-BuC$_6$H$_4$ (70%)

SCHEME 6.42 Synesis of β-triazolylenones **102**.

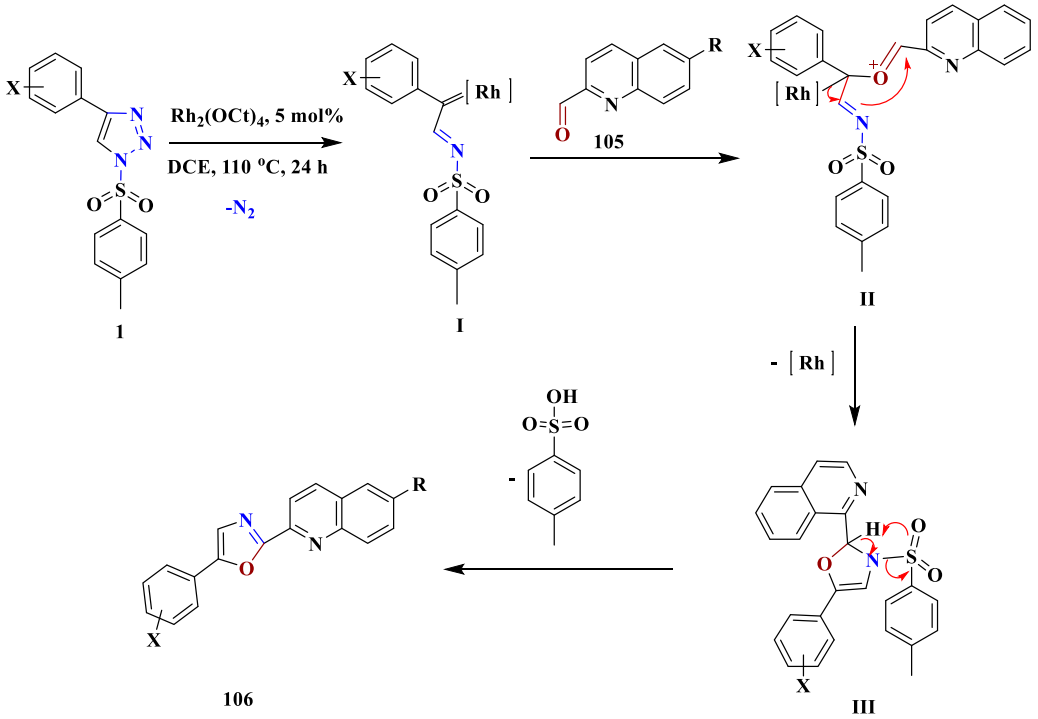


Y = H, X = H (79%); *n*-Bu (85%); 4-OMe (88%); 3-Cl (85%); 4-Cl (85%); 2,4-$(NO_2)_2$ (52%); 3-Br (79%); 4-Br (82%); 2-F (79%); 3-F (84%); 4-F (83%); 4-MeCOO (81%); 4-Ph (86%); phenylactylene (72%)

X = 4-OMe, Y = 4-F (78%); 4-Cl (89%); 4-Br(91%); 4-Ph (79%); 4-OPh (75%); 9-F (76%)



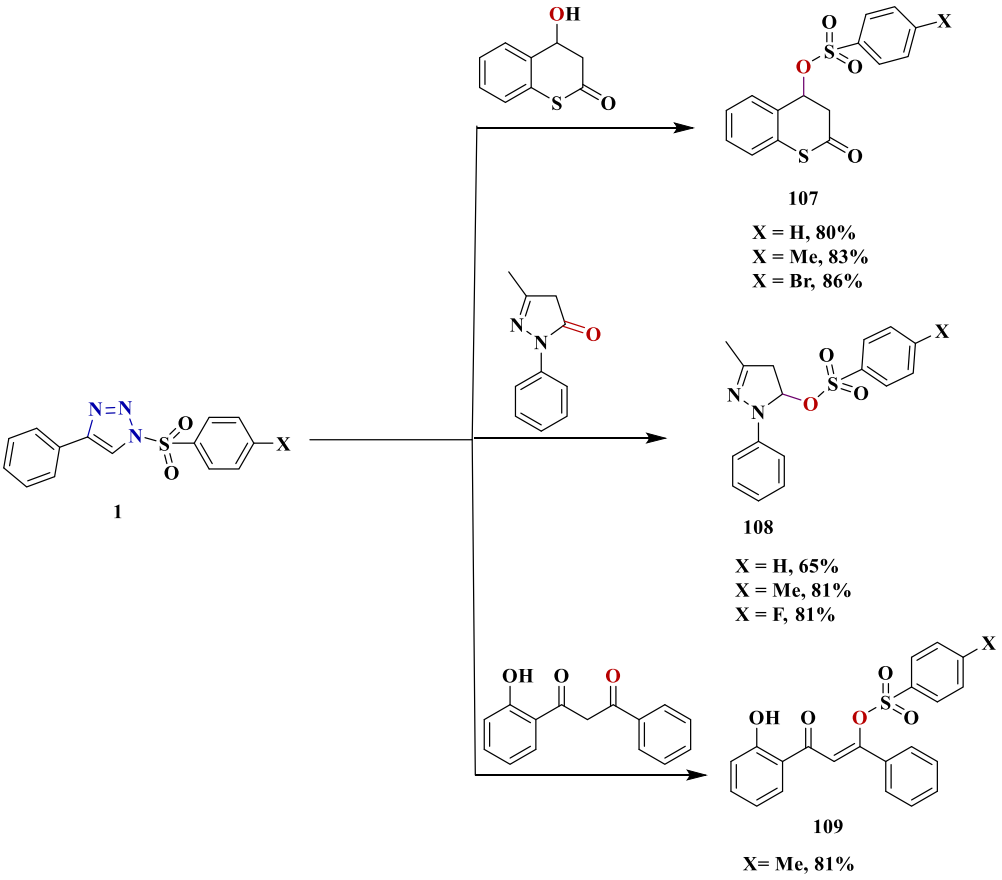
SCHEME 6.43 Synthesis of 2,5-diaryloxazole derivatives **104**, balsoxin, and texamine.



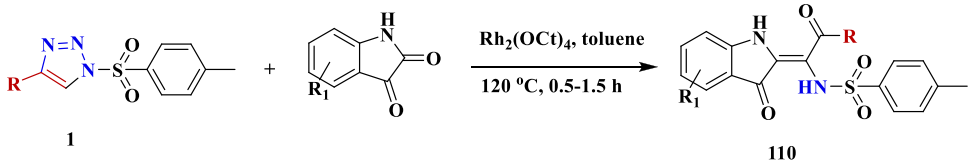
R = H, X = H (75%); 3-Me (70%); 4-Me (85%); 4-$OMeC_6H_4$ (62%); 3-Cl (76%); 3-Br (71%); 4-Br (58%); 2-F (82%); 4-F (54%); 4-CF_3 (76%); 3,5-$(F_3C)_2$ (49%)

X = H, R = Me (78%); F (66%); Br (71%)

SCHEME 6.44 Synthesis of 5-aryl-2-(quinolin-2-yl)oxazoles **106**.



SCHEME 6.45 1,4-diazabicyclo[2.2.2]octane (DABCO) in the synthesis of 2-oxothiochromines **107**, pyrazoles **108** and 2-hydroxy-3-oxo-1-phenyl-propanes **109**.

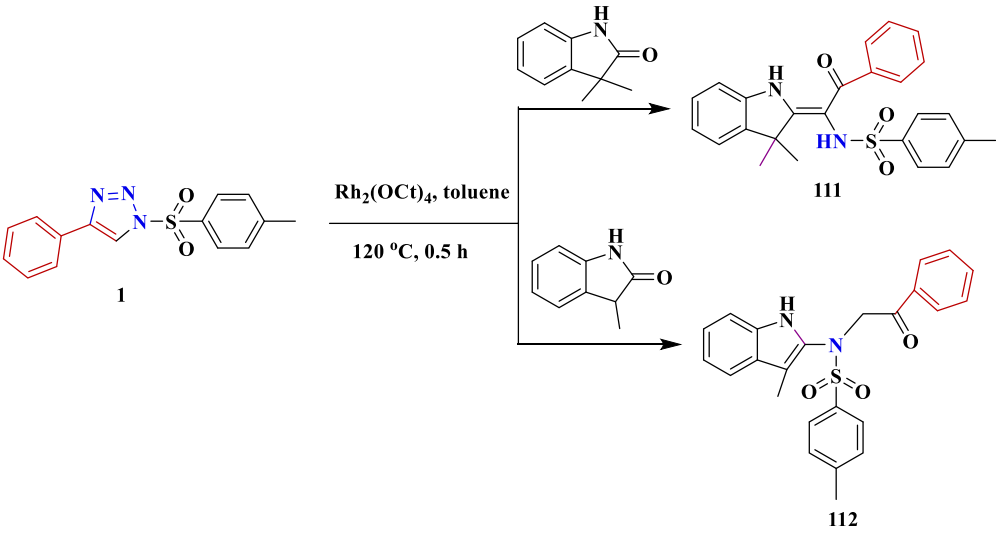


R / R_1	Yield %	R / R_1	Yield %
Ph / H	75	4-MeC_6H_4 / H	74
Ph / 4-Br	73	4-FC_6H_4 / H	75
Ph / 5-Cl	70	4-ClC_6H_4 / H	74
Ph / 5I	61	4-BrC_6H_4 / H	76
Ph / 5-Me	77	3-CNC_6H_4 / H	83
Ph / 5-OCF_3	80	3-thienyl / H	47
Ph / OMe	86	3,4,5 $(MeO)_3C_6H_2$ / H	64
Ph / 7-Cl	82	3-OMeC_6H_4 / H	51

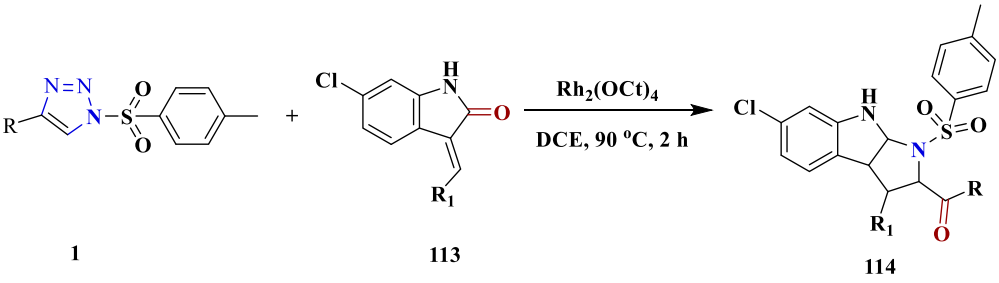
SCHEME 6.46 Synthesis of unsymmetrical indigo-like (*E*)-α-aminoenaminones **110**.

proposed mechanism for the formation is illustrated in Scheme 6.44. Initially, 1,2,3-triazoles **1** reacted with the Rh-catalyst to release nitrogen and formed Rh(II)-azavinyl carbine species **I**. Subsequently, the interaction of the carbene center with the carbonyl group of substrate 2 formed the intermediate ylide **II**, which underwent cyclization, to yield intermediate **III**. Finally, removal of the *p*-toluenesulfonic acid (detected by GC-Ms) to afford 2,5-aryloxazoles **106**.

The reaction of 4-phenyl-1-arylsulfonyl-1*H*-1,2,3-triazoles **1** reacted with 4-hydroxy-2*H*-thiochromen-2-one using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base catalyzed in DCE yields the corresponding products **107a-c** in yield 80%, 83%, and 86%, respectively.



SCHEME 6.47 Synthesis of sulfonamide derivatives **111** and **112**.



R_1 = Ph; R = *n*Bu (73%); 3,5-$(Me)_2C_6H_4$ (83%); 3-$OMeC_6H_4$ (76%); 3-C_6H_4 (84%);

4-FC_6H_4 (88%); *n*-pentylC_6H_4 (82%); thienyl (28%)

R = Ph; R_1 = 4-MeC6H4 (55%); 4-FC6H4 (70%); 2-Mefurnyl (66%); pyridyl (trace)

SCHEME 6.48 Synthetic route of pyrroloindoles **114**.

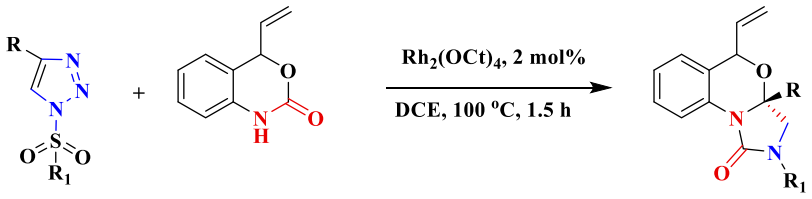
Moreover, compound **1** was reacted with 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one under the same conditions to afford the products **108a-c** in 65% and 81% yields. It is also noted that the reaction of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione with 4-phenyl-1-tosyl-1*H*-1,2,3-triazole **1** produces compound **109** in the presence of DABCO (Scheme 6.45) [63].

Deng et al. [64] described a novel C−C bond-formation of secondary amides and rhodium azavinyl carbenes by the O−H insertion, followed by rearrangement *via* the reaction of 1-tosyl-1,2,3-triazoles **1** with isatin derivatives **110** using of $Rh_2(OCt)_4$ in toluene at 120°C to produce the unsymmetrical indigo-like (*E*)-α-aminoenaminones with moderate to good yields (up to 86%) (Scheme 6.46).

Additionally, the reaction of 1-tosyl-4-pheny-1,2,3-triazole **1** with each of 3,3-dimethylindolin-2-one and 3-methylindolin-2-one as substrates, afforded products **111** and **112**, respectively, which indicates that the keto-carbonyl of isatins are not needed for this transformation, but no α-hydrogen is required (Scheme 6.47) [64].

Wang et al. [65] developed a new route of synthesizing pyrroloindoles **114** through the annulation of 3-benzylidene-indolin-2-ones **113** with *a*-imino rhodium carbenes, which are formed in situ from *N*-sulfonyl-1,2,3-triazoles **1**. The formation mechanism of **114** occurs through the formation of oxonium ylide species, and nucleophilic addition followed by rearrangement. The method provides a simple, straightforward, and practical approach to the synthesis of diverse and structurally complex bioactive compounds (Scheme 6.48).

The efficient, Rh(II)-catalyzed, denitrogenation reaction of 4-vinyl benzoxazinanones with *N*-sulfonyl-1,2,3-triazoles **1** was developed to synthesize various tricyclic 2-imidazolones **115** in moderate to good yields with excellent diastereoselectivity. The reaction proceeds by

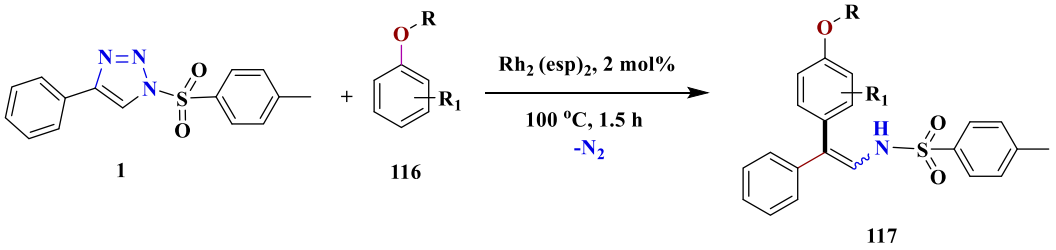


1 115

R_1 = 4-MeC_6H_4, R = Ph (90%); 3-Me C_6H_4 (85%); 4-MeC_6H_4 (93%); *n*-BuC6H4 (60%);
4-^{t}BuC_6H_4 (77%); 4-*n*-pentylC_6H_4 (80%); 4-OMeC_6H_4 (82%); 4-FC_6H_4 (87%);
3-ClC_6H_4 (78%);4-BrC_6H_4 (81%); 3-thienyl (72%); indanyl (72%)

R = Ph, R_1 = Ph (90%); t-BuC_6H_4 (83%); 4-OMeC_6H_4 (82$); 4-Br$C_6H_4$ (89%); PhC_6H_4 (89%)

SCHEME 6.49 Synthesis of tricyclic 2-imidazolones **115**.

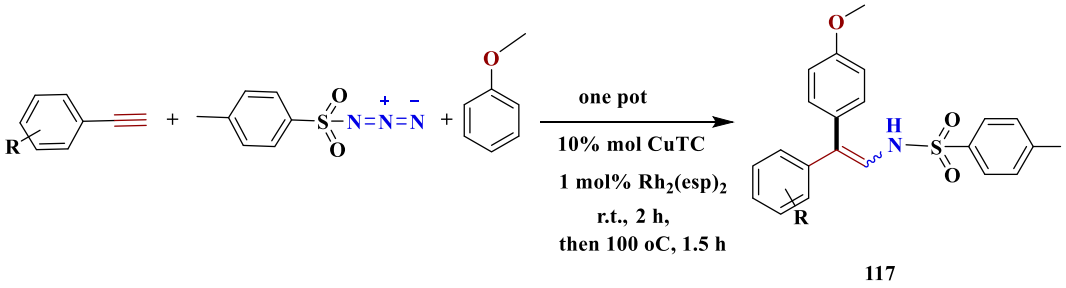


1 116 117

R = H; R_1 = Et (71%); Ph (82%); 3-Me (70%)

R = Me, R_1 = 2-OMe (73%); 3-OMe (77%);2,5-(OMe)$_2$ (71%); 2,5-(OMe)$_2$ (53%), Et (88%)

R = H, R_1 = n-penylbromide (70%)



117

R = H (51%), 3-Me (60%); 4-OMe (67%); 3-Cl (55%); 4-NO_2 (57%)

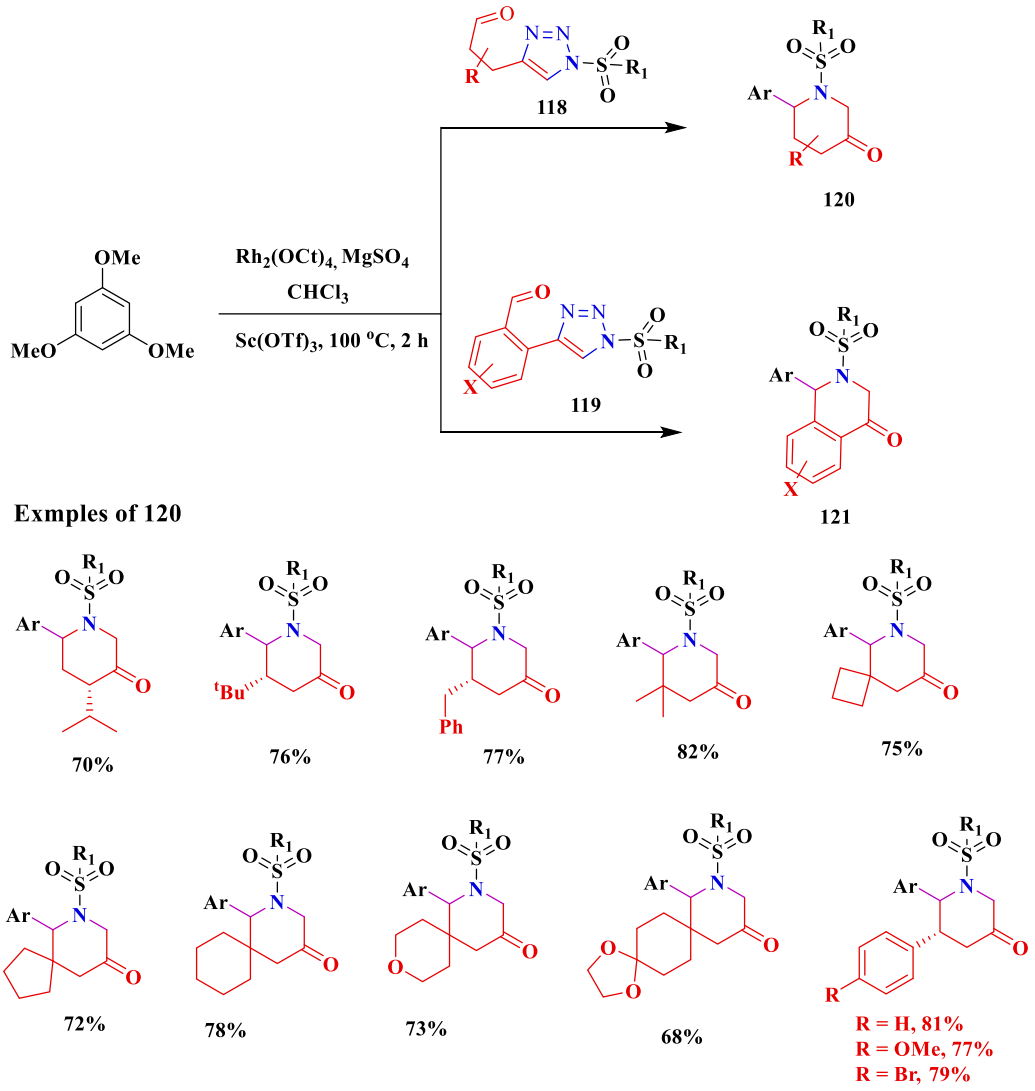
SCHEME 6.50 Alkoxyarylation of *N*-sulfonyl-4-aryl-1,2,3-triazoles.

forming four new bonds formation: two C−N bonds and two C−O bonds in the cascade. It also represents the first catalytic non-decarboxylative cyclization of vinyl benzoxazinanones with triazoles (Scheme 6.49) [66].

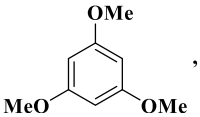
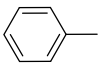
6.3.3 Reactions with substituted ether

A synthetic route for a wide range of 2-alkoxyaryl-2-aryl enamines **117** was developed from Rh-catalyzed alkoxyarylation of *N*-sulfonyl-4-aryl-1,2,3-triazoles **1** with arylethers **116** *via* the elimination of nitrogen molecule. In addition, 2-alkoxyaryl-2-aryl enamines are prepared *via* tandem Cu-catalyzed cycloaddition and Rh-catalyzed alkoxyarylation starting from terminal alkynes, tosyl azide, and aryl ethers in good yields ranging from 50% to 67% (Scheme 6.50) [67].

On the other hand, the synthesis of functionalized 6-substituted piperidin-3-ones **120** and **121**, from *N*-sulfonyl triazoles **118** or **119** and 1,3,5-trimethoxybenzene in chloroform at 120°C in the presence of catalytic $Rh_2(OCt)_4$, which are not easily obtainable by other methods. The mechanism of formation of **120** and **121** includes oxonium ylide formation, Lewis acid-assisted C−O cleavage, C−N recombination, and enol isomerization. The wide variety of substrates for aliphatic and aromatic *N*-sulfonyl triazoles together with the high



X = H (84%); 5-Me (84); 6-OMe (68%); 6-BnO (68%); 5,6-$(OMe)_2$ (82%); 5-Cl (82%); 6-Cl (81%); 7-F (80%)

Ar =  , R_1 = 

SCHEME 6.51 Synthesis of substituted piperidin-3-ones **120** and **121**.

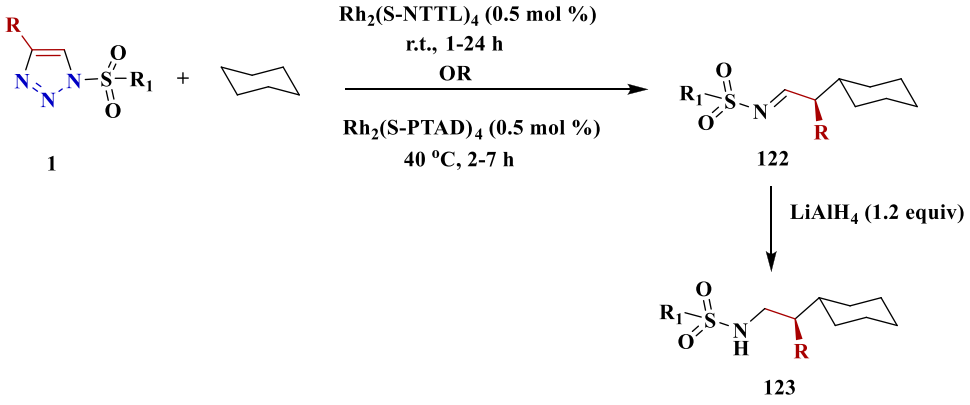
diastereoselectivity make this reaction promising for the creation of useful scaffolds in biomedical research and drug discovery (Scheme 6.51) [68]

6.3.4 Reaction with cyclohexane

The arylsulfonyl substituted triazoles **1** were C−H inserted in the presence of Rh_2 (SNTTL)$_4$ or Rh_2 (SPTAD)$_4$ complexes at 40°C or at room temperature, resulting in the smooth formation of the corresponding arylsulfonyl **123** protected amines (Scheme 6.52) [69].

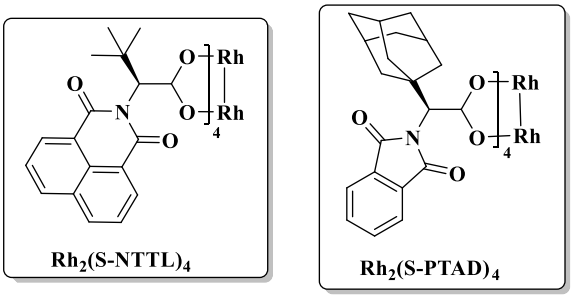
6.3.5 Reactions with different amines

Li et al. [70] described the synthesis of cyclic amidines **126** in good to excellent yields from the reaction of *N*-sulfonyl-1,2,3-triazole **124** with aminobenzenes **125** in chloroform. The higher reactivity was observed with electron-donating groups and the reaction passed

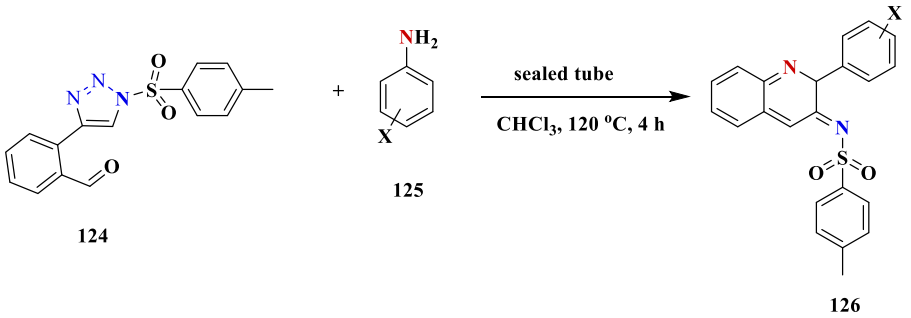


R = Ph, 2-MeC_6H_4, 4-$OMeC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4

R_1 = Me, ^{i}Pr, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, trimethyl(propyl)silane



SCHEME 6.52 Synthesis of arylsulfonyl **123** protected amines.

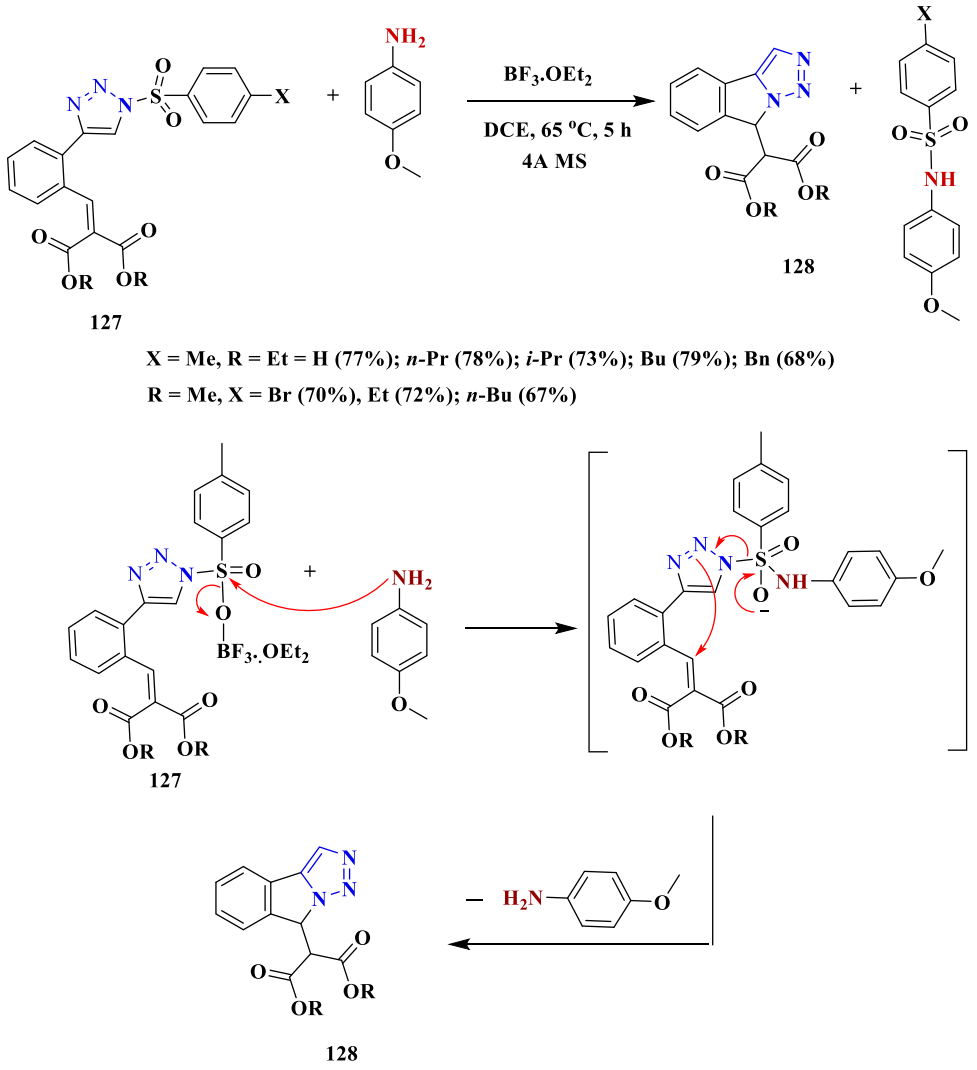


X = H (91%); 2-Me (72%); 4-Me (93%); 3-OBn (86%); 3,5-$(Me)_2$ (83%); 4-Et (84%); 3-SMe (72%); 4-OMe (86%); 2,5-$(OMe)_2$ (85%); 3,4-$(OMe)_2$ (91%); 3-Cl (70%); 4-Cl (66%); 2-Me, 4-Cl (86%); 3-Br (74%); 4-Br (70%); 4-I (75%)

SCHEME 6.53 Synthesis of cyclic amidines **126**.

through 6π electrocyclic ring closure of ketenimine and imine and the method provides expeditious access to a variety of 10π-electron cyclic amidines. From a fluorescence-structure relationship study, it was found that cyclic amidine fluorophores have the advantages of large Stokes shifts, pH insensitivity, low cytotoxicity, and higher photostability. Furthermore, they can be used efficiently in developing new fluorescent probes for imaging in living systems (Scheme 6.53).

An unexpected cyclization reaction of *N*-sulfonyl-1,2,3-triazoles **127** bearing electron-deficient alkenes with amines under Lewis acid catalysis has been reported. This strategy involves the removal of the sulfonyl group and further intramolecular 1,4-addition,



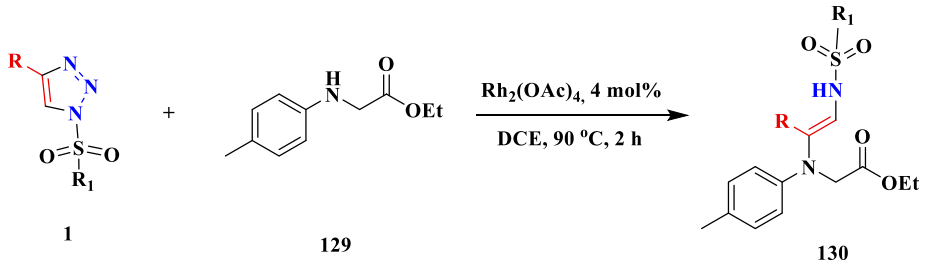
SCHEME 6.54 Synthetic route of 1,2,3-triazole-fused isoindolines **128**.

yielding a series of 1,2,3-triazole-fused isoindolines **128** in good yields under mild conditions (Scheme 6.54) [71]. Proposed mechanism of cyclization reaction for the synthesis of 1,2,3-triazole-fused isoindolines under $BF_3{\cdot}OEt_2$, initially, the methoxyaniline attack on the sulfonyl group on the triazole ring of substrate **127** to afford intermediate **I**. Then sulfamide was removed from intermediate **I** and further intramolecular 1,4-addition between the triazole and the electron-deficient alkene to generate desired products **128** as shown in Scheme 6.54.

He et al. [72] developed a novel and efficient rhodium (II)-catalyzed dehydrogenative coupling of *N*-sulfonyl-1,2,3-triazoles **1** with ethyl *p*-tolylglycinate **129** to afford phenylvinyl-1,2-diamines **130** in good to excellent yields (Scheme 6.55). This method provides a highly regioselective synthesis of a variety of *N*,*N*-disubstituted glycine esters having a *Z*-configuration of the (1-aryl-2-(sulfonamido)vinyl) substituent **130**. This work shows that *N*-sulfonyl-1*H*-1,2,3-triazoles can be used for efficient N−H functionalization for the binding sp^3 N−H bond of substrates containing additional functionality.

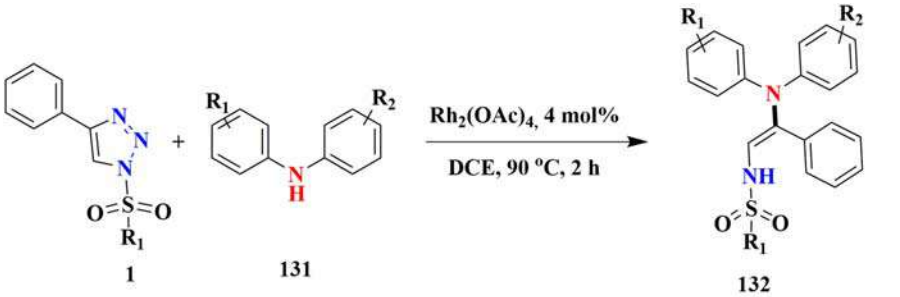
Additionally, under the same conditions, 4-phenyl-1-tosyl-1*H*-1,2,3-triazole **1** reacted with diarylamines **131** to afford the phenylvinyl-1,2-diamines **132** with good to excellent as shown in Scheme 6.56 [72].

Lacour and co-workers [73] described a novel hexahydropyrazinoindoles **134** that was prepared in a single step from *N*-sulfonyl triazoles **1** and imidazolidines **133**. In dirhodium catalysis, α-iminocarbenes were obtained and nitrogen ylide intermediates were formed, after subsequent aminal opening, compounds **134** were formed predominantly by a formal C-reactivity/[1,2]-Stevens pathway and tandem Friedel-Crafts cyclization. Of



R_1 = 4-MeC_6H_4, R = 4-MeC_6H_4 (80%), 4-EtC_6H_4 (83%); 4-OMeC_6H_4 (81%); 4-ClC_6H_4 (85%); 4-FC_6H_4 (83%); 2-FC_6H_4 (80%); 4-BrC_6H_4 (80%); F_3CC$_6H_4$ (traces); *n*-propylphenylC$_6H_4$ (80%)

SCHEME 6.55 Synthesis of phenylvinyl-1,2-diamines **130**.



$R_1 = R_2$ = H (85%)

$R_1 = R_2$ = 4-Me (88%)

R_1 = 4-Me, R_2 = H (86%)

R_1 = 2-Me, 4-Me, R_2 = H (80%)

R_1 = OH, R_2 = H (82%)

R_1 = 4-Me, R_2 = H (82%)

R_1 = 4-OMe, R_2 = H (90%)

$R_1 = R_2$ = 4-OMe (90%)

$R_1 = R_2$ = 3-Me (89%)

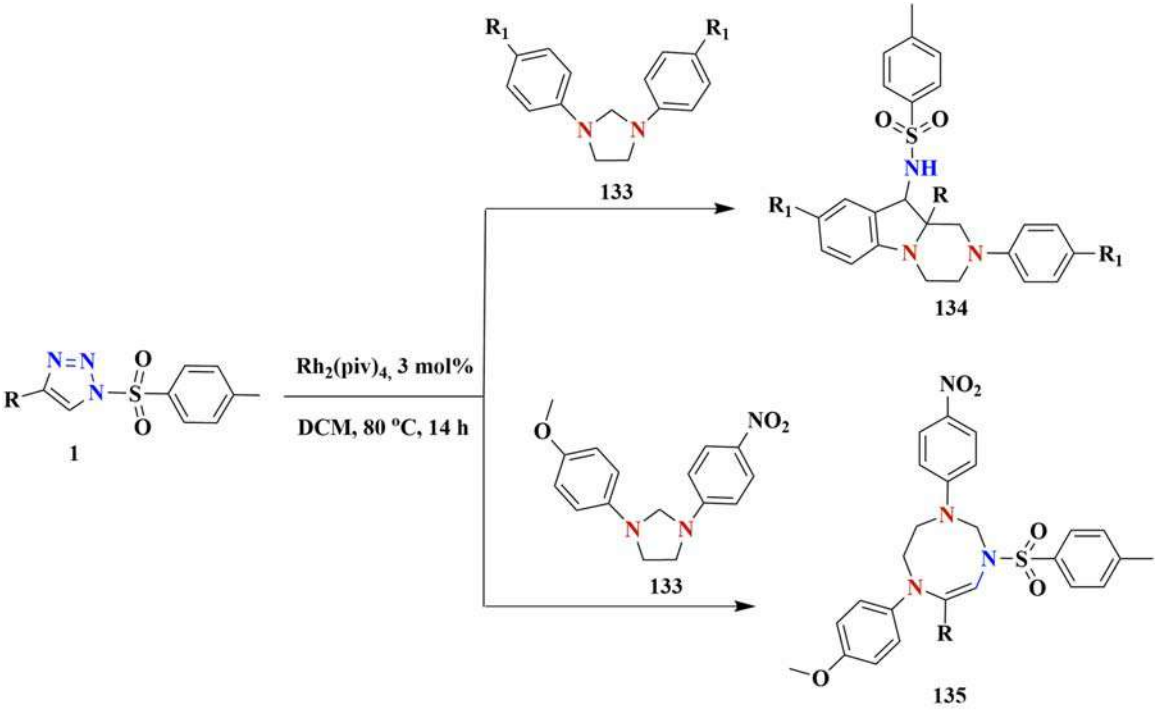
R_1 = naphthyl, R_2 = Ph (80%)

SCHEME 6.56 ynthesis of phenylvinyl-1,2-diamines **132**.

mechanistic importance, a regiodivergent reactivity could be engineered through the use of unsymmetrically substituted imidazolidine substrate **133** that promoted the exclusive formation of 8-membered ring derivative **135**. Compounds of type **135** are formed as kinetic products and reopened reversibly with the aid of the $Rh_2(Piv)_4$ catalyst. Given time and energy, the system evolves towards the formation of the thermodynamically preferred product **134**, after an irreversible Friedel-Crafts alkylation that seals the multi-step pathway. With imidazolidine **133** as a reagent, the formation of **135** becomes irreversible and the unexpected hexahydro1,3,6-triazocines of 8-membered heterocycle is formed preferentially as a unique regioisomer (Scheme 6.57).

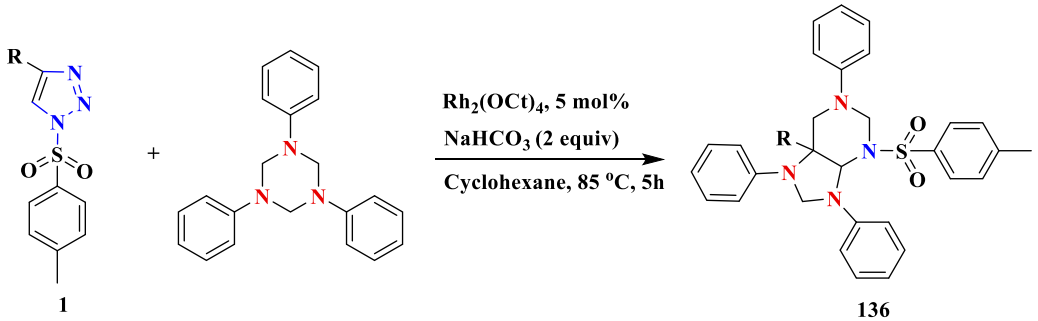
Various aryl substituted *N*-sulfonyl-1,2,3-triazoles **1**, can react with 1,3,5-triazinanes in cyclohexane at 85°C in the air for 5 h, in the presence of $Rh_2(OAc)_4$ (5 mol%) using basic condition such as sodium bicarbonate, to furnish the corresponding octahydro-1*H*-purine derivatives **136** in moderate to good yields (Scheme 6.58) [74].

Davies et al. [75] demonstrated an effective method for aminoacylation of indoles and pyrroles. Thus electron-rich triazoles **137** were subjected to a metal-free thermal denitrogenation reaction with indole of 0.2 mmol scales under microwave irradiation, which was completed in 15 minutes to afford the aminoacylated products **138** in good to excellent yields (Scheme 6.59). Further investigation of the substituted indoles with C(3)-substituents showed that they are also reactive substrates; however, instead of the expected C(2)-acylated product, the dearomatized [3 + 2] annulation products **139** were observed. Moreover, the reaction of 4-phenoxy-1-sulfonyl triazoles **137** with pyrrole derivatives under metal-free thermal conditions yields the corresponding aminoacylated products 140 moderately to excellent yields (Scheme 6.59).



134, R_1 = Me, R = Ph (78%, *dr*, 3.6:1); -2-MeC_6H_4 (58%, *dr*, 1:1); 4-OMeC_6H_4 (88%, *dr*, 4.2:1);
3,4-$(Cl)_2C_6H_3$ (67%, *dr*, 3.2:1), ;thienyl (82%, *dr*, 4.9:1); 4-OMe-naphthylC_6H_4 (71%, *dr*, 3.3:1)
R = Ph, R1 = OMe (90%, *dr*, 3:1); Br (86%, *dr*, 4:1); Cl (74%, *dr*, 3.1:1)
135, R = Ph (57%); 4-OMeC_6H_4 (65%); F_3C-C_6H_4 (36%)

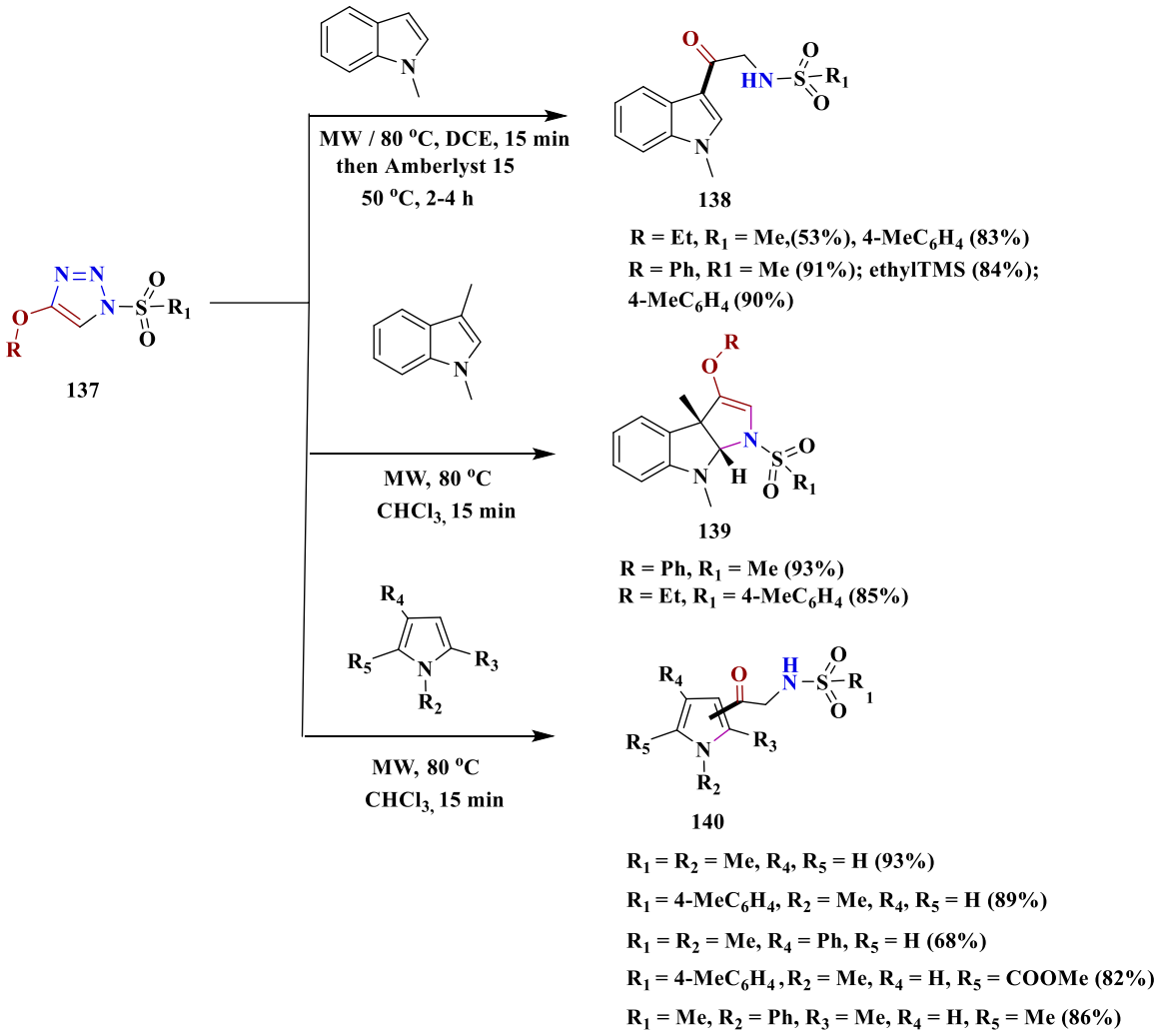
SCHEME 6.57 Synthesis of new hexahydropyrazinoindoles **134**.



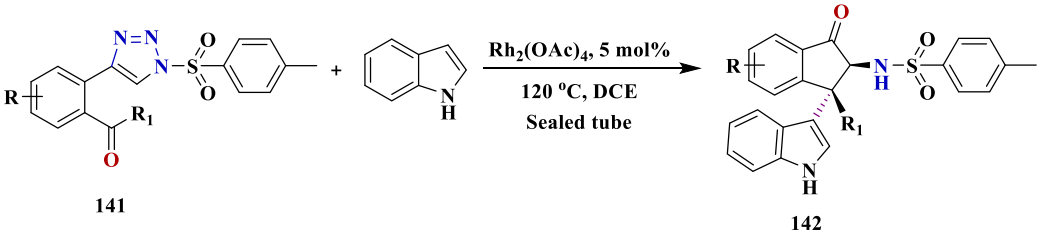
R = Ph (70%); 3-Me C_6H_4 (55%); 4-MeC_6H_4 (73%); 4-EtC_6H_4 (72%); 4-OEtC_6H_4 (50%);
2-OMeC_6H_4 (47%); 4-OMeC_6H_4 (82%); 3-ClC_6H_4 (35%); 3-BrC_6H_4 (28%); 4-BrC_6H_4 (25%)
naphthyl (58%); 2-thienyl (65%); 3-thienyl (58%)

SCHEME 6.58 Synthesis of octahydro-1*H*-purine derivatives **136**.

Gong et al. [76] described an efficient strategy to synthesize structurally different indole-substituted indanones **142** by rhodium(II)-catalyzed tandem reaction of *N*-sulfonyltriazoles **141** with indole. The reaction involves rhodium(II)-catalyzed denitrogenation of the *N*-sulfonyltriazoles to form an oxonium ylide followed by nucleophilic addition of the indoles and subsequent skeletal rearrangement. This strategy provides straightforward



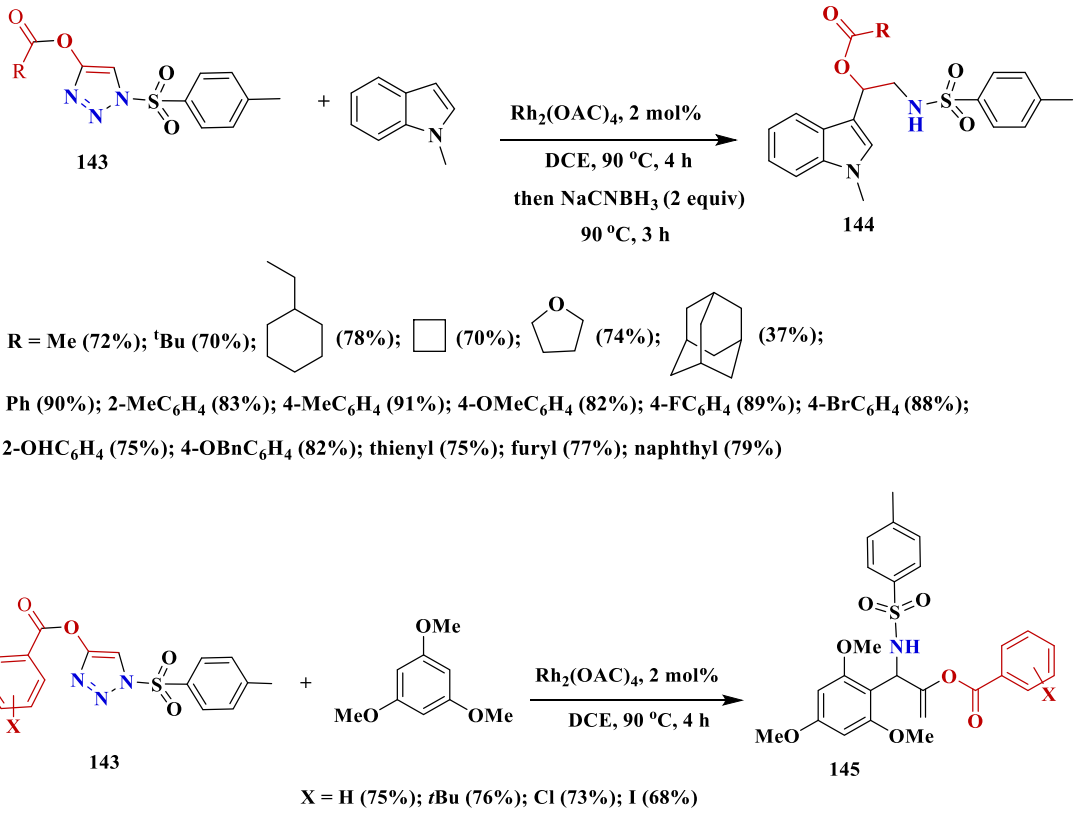
SCHEME 6.59 Aminoacylation of indoles and pyrroles to give compounds **138**, **139**, and **140**.



SCHEME 6.60 Synthesis of indole substituted indanones **142**.

access to indanone scaffolds containing quaternary carbon centers (Scheme 6.60).

In other reports, Volla et al. [77] developed a convenient denitrogenation synthetic methodology for the efficient production of homotryptamines **144** and allyl amines **145** with good to excellent yields from the reaction of *N*-sylfonyl-1,2,3-triazole esters **143** with each of indole and trimethoxybenzene. The reaction



SCHEME 6.61 Synthetic route to the formation of compounds **144** and **145**.

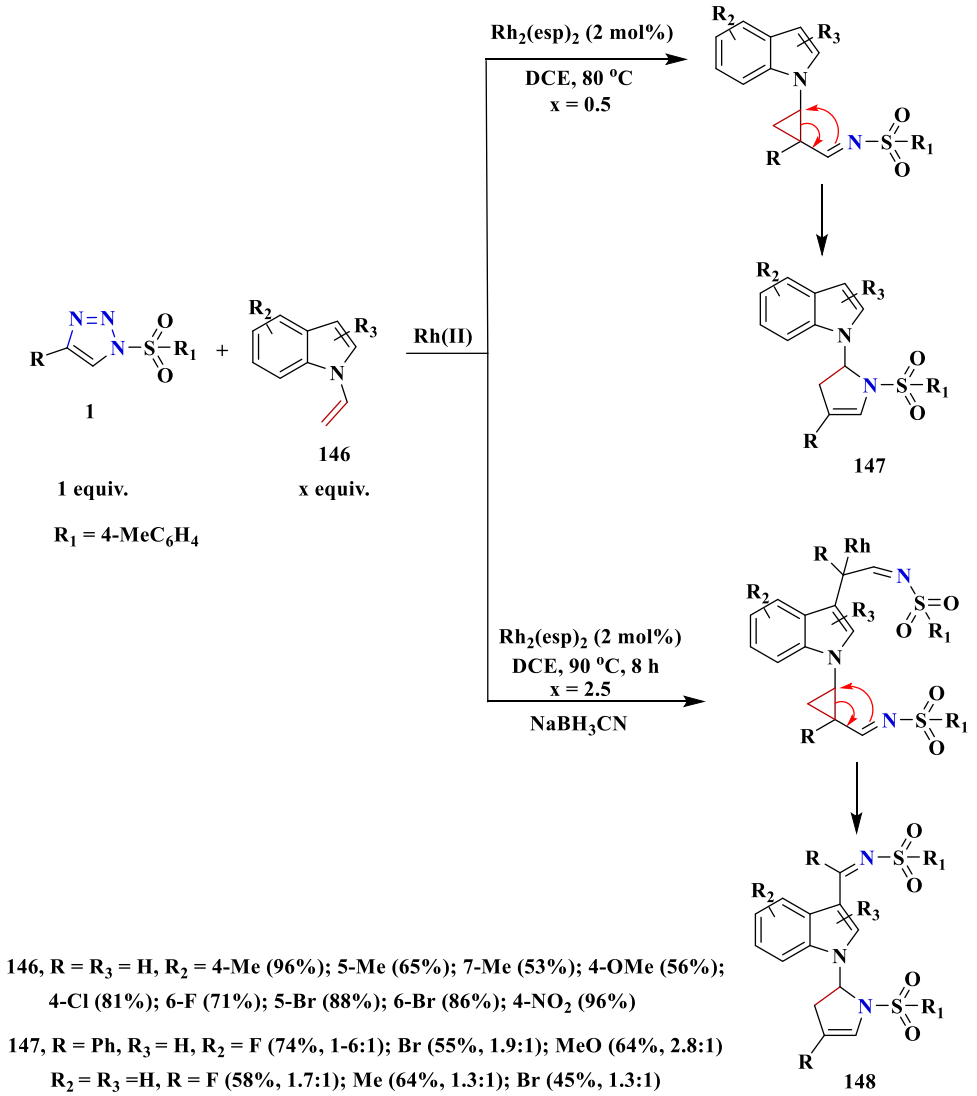
proceeds through Rh(II)-catalyzed intramolecular 1,2-rearrangement of triazoles to 1-azadienes, followed by regioselective intermolecular nucleophilic addition (Scheme 6.61).

The new rhodium(II)-catalyzed annulations of *N*-tosyl-1,2,3-triazoles **1** with *N*-vinyl indole derivatives **146** were reported to obtain indoles **147** containing dihydropyrrole ring in moderate to good yield, along with a wide substrate scope and high reaction compatibility. When testing the reaction conditions, it was found that the reaction of 4-aryl-*N*-sulfonyl-1,2,3-triazoles (2.5 equivalent) and *N*-vinylindoles (1.0 equivalent) can only give C3-functionalized indoles containing *N*-sulfonyl-dihydropyrrole **148** with moderate yields. This discovery opens a new method of constructing functionalized indoles containing dihydropyrrole or Rh(II) pyrrole carbenoid (Scheme 6.62) [78].

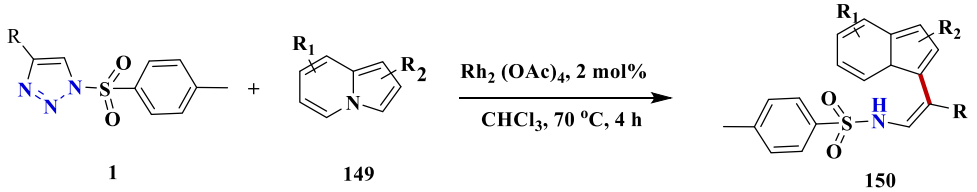
An efficient and highly stereoselective approach for the C-3 functionalization of indolizines has been described *via* rhodium (II)-catalyzed insertion of azavinyl carbenes for the synthesis *N*-sulfonylamine alkenyl derivatives of indolizines **150** from *N*-sulfonyl triazoles **1** with indolizines **149** in moderate to good yields (Scheme 6.63) [79].

Novikov et al. [80] developed a method for the synthesis of 1-alkyl-3-sulfonamido-1*H*-pyrroles **152** by Rh (II)-catalyzed denitrogenation cross-coupling of 1-sulfonyl-1,2,3-triazoles. The reaction proceeds *via* the attack of the Rh-bound azavinyl carbene, derived from the sulfonyl-1,2,3-triazole **1**, at the N2 atom of the 1-alkyl-4-aryl-1,2,3-triazole **151** and the successive formation of the rhodium-bound 1,2,3-triazol-3-ium ylide, metal-free 1,2,3-triazol-3-ium ylide, 1,4,5,8-tetraazaocta-1,3,5,7-tetraene, and 3-(azavinyl)-3,4-dihydro-1,2,4-triazine. The concerted denitrogenative ring contraction of the latter followed by 1,2-prototropic shift affords the 1-alkyl-3-sulfonamido-1*H*-pyrrole **152** (Scheme 6.64). The reaction of 4-(phenoxymethyl)-substituted triazole **153** with sulfonyltriazole **1** under the same reaction conditions afforded 1,2,3-triazol-3-ium ylides **154** in good yields (Scheme 6.64).

Yoo et al. [81] described the efficient synthesis of 1-sulfonyl-1,2,3- triazoles **1** with benzamides as sources of atom economic coupling partners. Thus, the reaction 1-sulfonyl-1,2,3- triazoles **1** with *N*,*N*-dimethyl benzamide in the presence of 1 mol% of $Rh_2(esp)_2$ in toluene at 80°C yields substituted α-amido-enaminones **155**. This method is a new approach for the construction of multi-



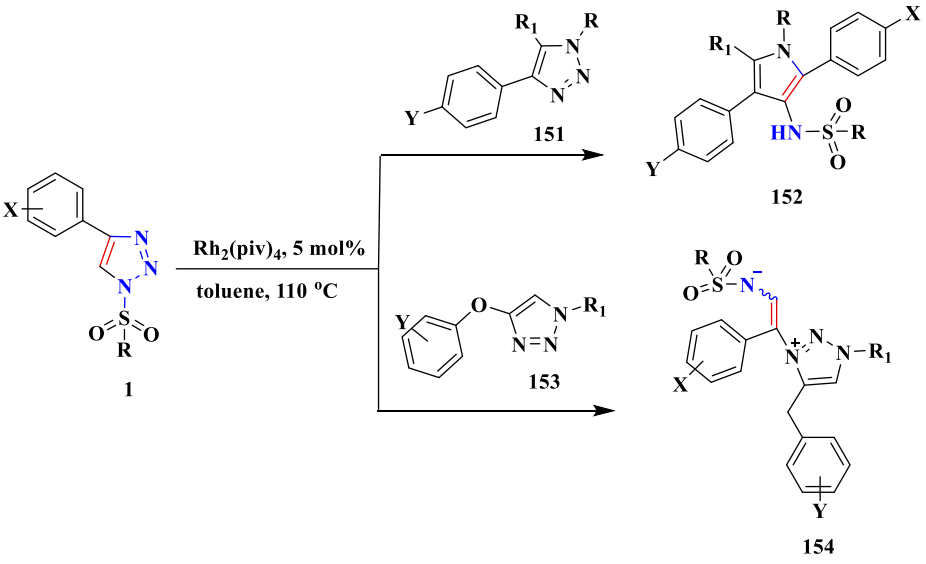
SCHEME 6.62 Synthesis of indoles **147** and *N*-dihydropyrrole **148**.



SCHEME 6.63 Synthesis of *N*-sulfonylamine alkenyl derivatives of indolizines **150**.

functionalized enaminones or enamides **156** in yields ranging from 64% to 92% (Scheme 6.65).

A metal- and additive-free, highly efficient, step-economical deoxygenative C-2-heteroarylation of quinolines and isoquinolines was achieved by Volla et al. [82] from available *N*-oxides and *N*-sulfonyl-1,2,3-triazoles **1** in dichloroehane at room temperature. A variety of α-triazolylquinoline derivatives **157** were synthesized with



152, R_1 = X =Y = H, R = $CH(Me)_2$ (34%); $CH_2CH_2CH_2COOEt$ (50%); CH_2Ph (58%); $CH_2C_6H_4$-4-Me (58%)

R = Me, R_1 = X = H, Y= H (91%); Me (43%); *t*Bu (51%); Br (53%); Cl (64%)

R = Me, R_1 = Y = H, X = *t*Bu (62%); Cl (43%); OMe (70%)

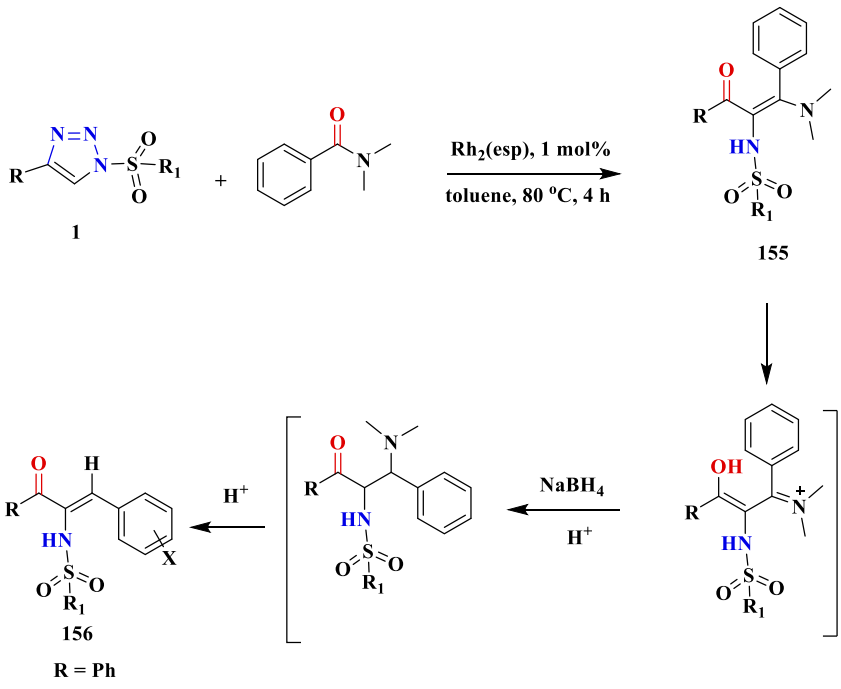
154, R_1 = Me, X = Y = H (89%); Cl (74%)

R_1 = CH_2Ph, X = H, Y = Cl (82%)

R_1 = 4-ClC_6H_4, X = Y = H (84%)

R_1 = Me, X = *t*Bu, Y = Cl (50%)

SCHEME 6.64 Synthetic route for formation of 1-alkyl-3-sulfonamido-1*H*-pyrroles **152** and 1,2,3-triazol-3-ium ylides **154**.

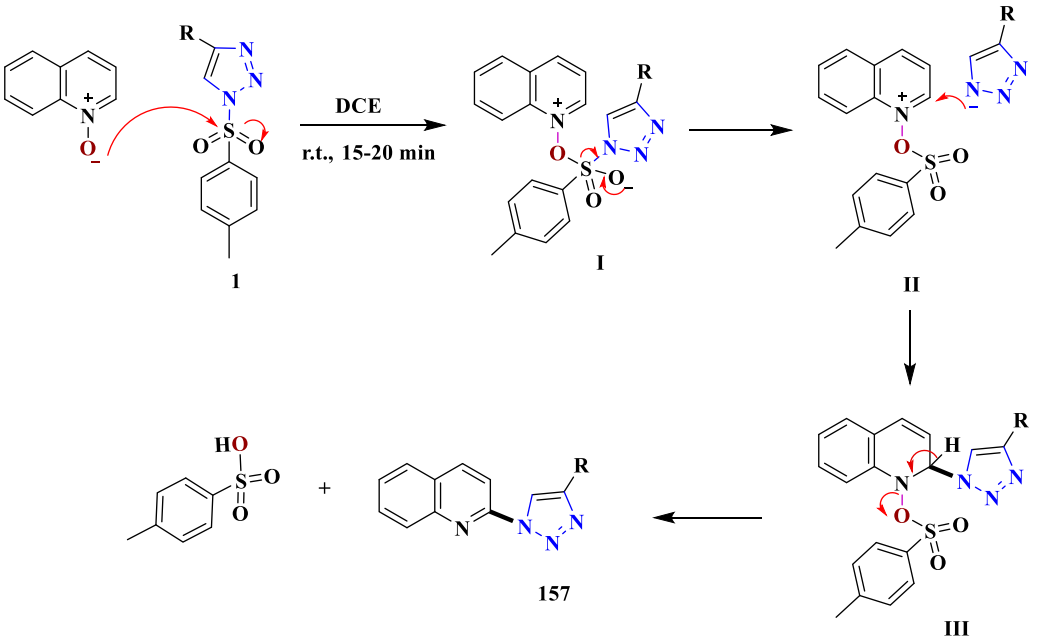


155, R = *t*-Bu, Ph, 3-MeC_6H_4, 4-$OMeC_6H_4$, 3-$CF_3C_6H_4$, 4-BrC_6H_4, 3-thienyl

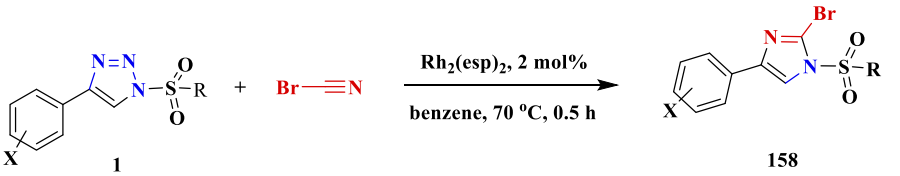
155, R_1= Me, *n*-Bu, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-$CF_3C_6H_4$,

156, X = H (88%); *t*Bu (74%); 3-Cl (81%); 4-F (86%); 4-NO2 (85%)

SCHEME 6.65 Synthesis of substituted α-amido-enaminones **155**.



SCHEME 6.66 Synthetic route of α-triazolylquinoline derivatives **157**.



SCHEME 6.67 Synthesis of 2-bromo-4-substitued-1-tosylimidazoles **158**.

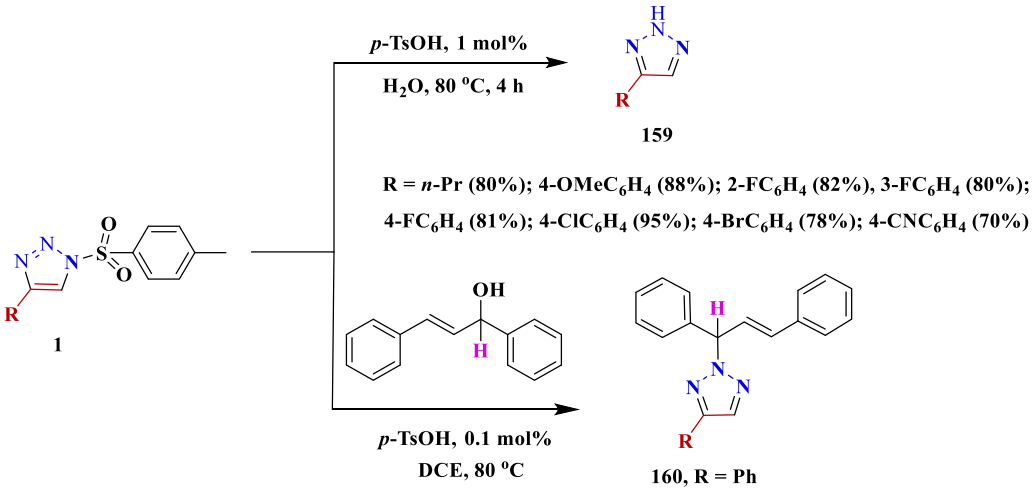
good regioselectivity and with excellent yields under mild reaction conditions (Scheme 6.66). The likely mechanism of the C2-triazolylation of quinoline oxides is presumably due to a reaction initiated by nucleophilic quinoline oxide attack on the sulfonyl group of *N*-sulfonyl-1,2,3-triazole **1**, resulting in the formation of intermediate **I**. The triazolyl anion forms intermediate **II**. In the next step, the triazolyl anion attacks the electrophilic C2 position of the quinoline oxide, yielding intermediate **III** which, upon reomatization, yields the desired 2-triazolylquinoline product **157** along with the transfer of the quinoline oxygen atom to the triazole sulfonyl group with the formation of *p*-toluenesulfonic acid as a by-product

6.3.6 Reaction with bromocyanide

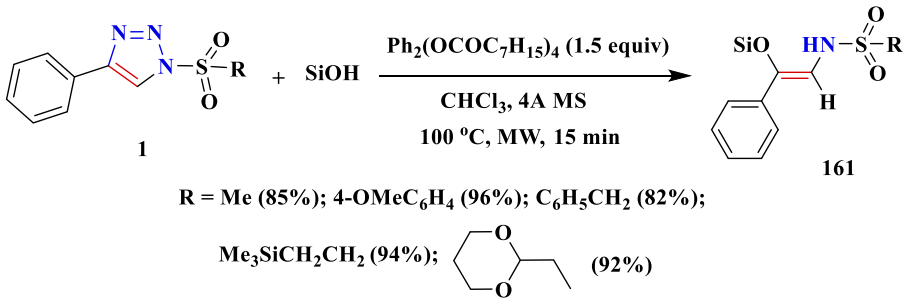
Cyclization of *N*-sulfonyl-1,2,3-triazoles **1** with bromocyanide was studied under different conditions to give 2-bromo-4-substitued-1-tosylimidazoles **158** in moderate to excellent yields (Scheme 6.67) [11,83].

6.3.7 Hydrolysis

Wang et al. [84] investigated the first example of autocatalytic hydrolysis of 4-aryl-1-tosyl-1,2,3-triazoles triggered by *p*-toluenesulfonic acid, providing an effective and metal-free synthetic approach to produce a series of new 4-



SCHEME 6.68 Synthetic route of new 4-aryl-2H-1,2,3-triazoles 159 and 160.



SCHEME 6.69 Synthesis of α-amino silyl enol ethers **161**.

aryl-2*H*-1,2,3-triazoles **159** in good yields. Moreover, by reacting 1-tosyl-1*H*-1,2,3-triazole **1** with 1,3-diphenyl-2-propen-1-ol, the desired N2-allylated 2*H*-1,2,3-triazole **160** was easily obtained in 80% of all cases (Scheme 6.68).

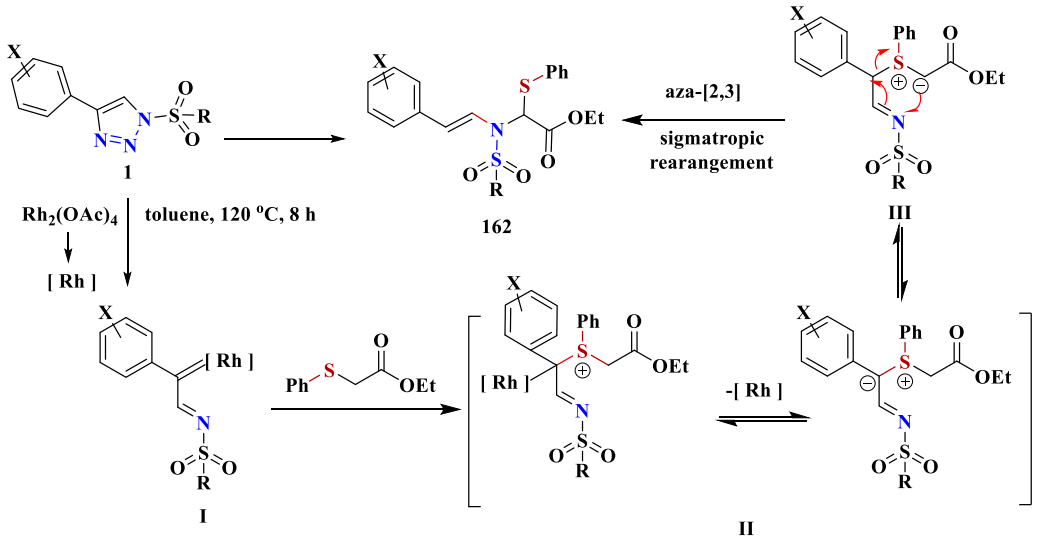
Miura and co-workers [85] synthesized esters of α-amino silyl enol ethers **161** from various 1-tosyl-1,2,3-triazoles **1** by their reaction with silanol in chloroform in the presence of 1.5 equivalents of $Ph_2(OCOC_7H_{15})_4$ with 4 Å molecular sieves (4 A Ms) in good to excellent yields. The carbonyl groups remained intact, indicating the relatively low basicity of the reaction conditions (Scheme 6.69).

For the production of functionalized enamides **162**, Anbarasan et al. [86] demonstrated efficient rhodium-catalyzed Sommelet Hauser type rearrangement of sulfur-ylide generated from α-thioesters and *N*-sulfonyl-1,2,3-triazoles. The plausible mechanism for the formation of **162** is thought to be initiated by the formation of rhodium carbenoid **I**, which is generated from *N*-sulfonyl-1,2,3-triazole **1** and $Rh_2(OCt)_4$, and then followed by in situ the generation of sulfur ylide **II** from rhodium carbenoid with α-thioester. The resulting ylide **II** can not rearrangement, due to the absence suitable bond with the conjugated system. Due to the presence of relatively acidic α-proton in the ester, the proton was then transferred from sulfurilide **II** to form a new sulfurilide III intermediate which, upon another aza [2,3] sigmatropic rearrangement, would yield enamide **162** (Scheme 6.70).

6.3.8 Miscellaneous reactions

In the presence of a Rh(II) catalyst and β-(methylthio)-α,β-unsaturated ketones like 3-oxobis(methylthio)ketene acetal, 1-sulfonyl-1,2,3-triazoles **1**, can be converted into functionalized β-amino-α,β-unsaturated ketones **163** by the formation of α-imino rhodium carbene/sulfur ylide, followed by rearrangement. These products are decomposed into 2-methylthiopyrrole derivatives conveniently in high yields (Scheme 6.71) [87].

Treatment of 4-phenyl-1-tosyl-1,2,3-triazole **1** with 2-methylbenzothiote in the presence of $(t\text{-}BuCO_2)_4Rh_2$ and 4 Å molecular sieves (Ms) in chloroform at 70°C followed by addition of acidic silica gel, where elimination of methyl 4-methylbenzenesulfonate gives 2,5-diphenylthiazole **164** in 87% yield. A plausible mechanism for the preparation of the thiazole derivatives (Scheme 6.72). First, a reversible ring-chain tautomerization of **1** produced α-diazoimine, which reacts with rhodium(II) to form α-imino rhodium carbene complex **I** with extrusion

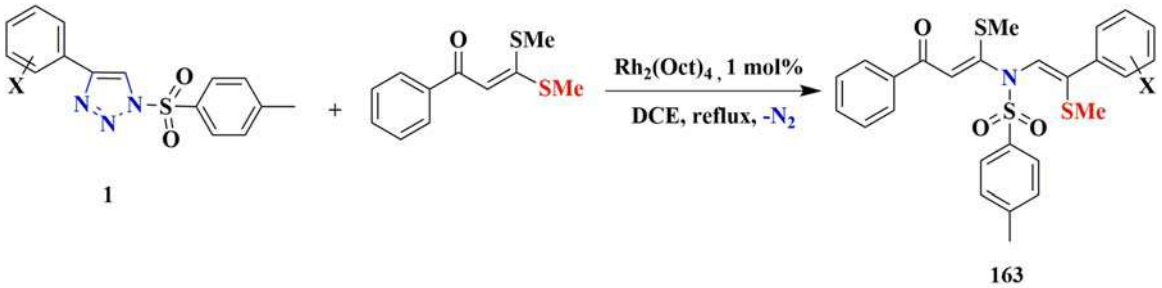


X = H, R = Me (73%); Ph (75%); 4-MeC$_6$H$_4$ (70%)

R = 4-MeC$_6$H$_4$, X = 3-Me (80%); 4-Me (74%), 4-Et (88%); *t*Bu (90%);

4-OMe (79%); 4-Cl (71%); 3-F (79%); 4-F (71%)

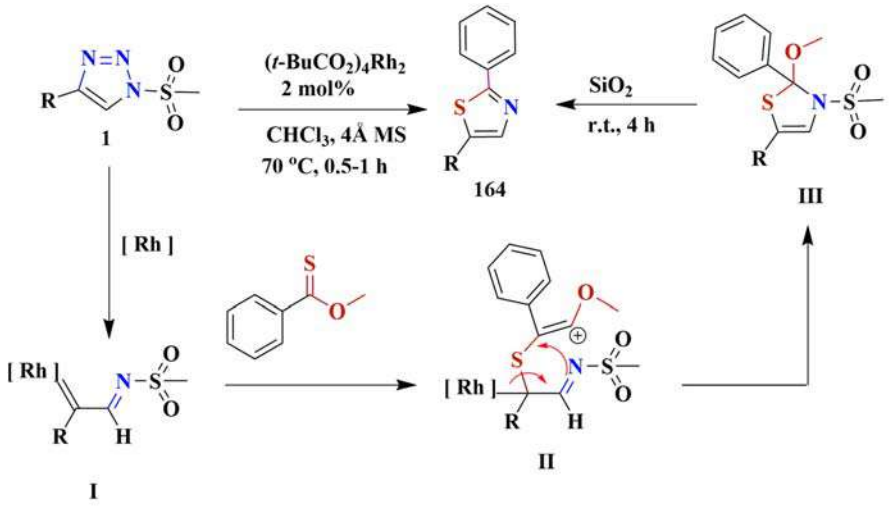
SCHEME 6.70 Formation of enamides **162**.



X = 4-Et (83%); 4-*t*Bu (77%); 4-Me (94%); 2-MeO (76%); 3-MeO (87%); 4-MeO (86%); 4-Cl (85%);

X = 4-Br (88%); 3-F (98%); 4-F (77%); 4-CF$_3$ (72%); 4-CN (53%); 4-MeCOO (72%)

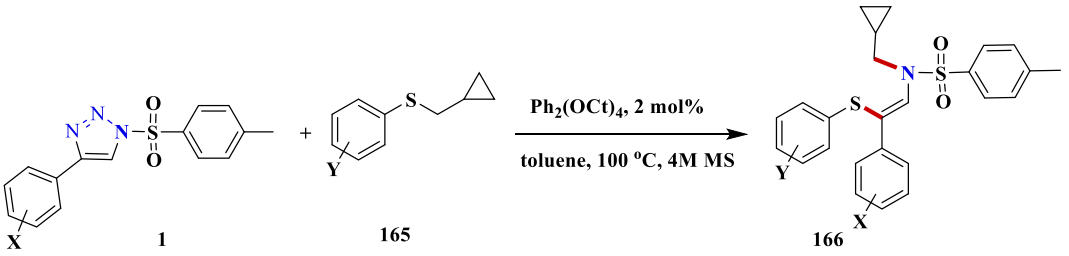
SCHEME 6.71 Synthesis of β-amino-α,β-unsaturated ketones **163**.



R = *n*-propyl (49%); 4-MeC$_6$H$_4$ (90%); 4-OMeC$_6$H$_4$ (84%); 2-BrC$_6$H$_4$ (91%); 4-BrC$_6$H$_4$ (96%)

4-IC$_6$H$_4$ (87%); 4-FC$_6$H$_4$ (90%); 4-(pin)BC$_6$H$_4$ (67%); 3-thienyl (48%); 1-cyclohexenyl (87%)

SCHEME 6.72 Synthetic route for 2,5-disubstituted thiazoles **164**.

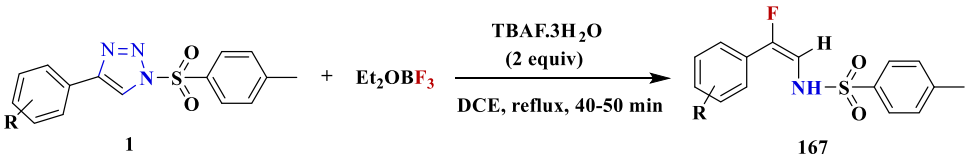


X = H, Y = Me (62%); 2-OMe (60%); 4-OMe (51%); 2,4-$(OMe)_2$ (56%); 4-Cl (48%); 2-F (83%); F_3C (65%)

Y = H, X = 4^tBu (73%); 3-Me (63%); 4-Me (75%); 2-OMe (55%); 4-OMe (54%); 4-Cl (70%);

4-Br (73%); 3-F (66%); 4-F (50%); 4-CF_3 (83%); 4-CN (77%)

SCHEME 6.73 Synthesis of enamines **166**.



R = H

R_1 = Me (70%); ^iPr (68%); 4-MeC_6H_4 (58%); 4-BrC_6H_4 (69%); naphthyl (45%)

R_1 = Me

R = 4-F (66%); 4-Cl (68%); 4-Br (74%); 3-Br (77%); 2-Br-5-Cl (78%); 2-Br-4-F(76%);

4-COOMe (51%); 4-COMe (28%)

SCHEME 6.74 Synthesis of *E*-monofluoroenamine **167**.

of molecular nitrogen. The sulfur of 2-methylbenzothiote attacks the electrophilic carbene center of **I** to furnish zwitterionic intermediate **II**. The anionic rhodium releases an electron pair, that induces the addition of the imino nitrogen to the carbon of the oxonium ion, and forms a five-membered ring. The resulting 3-sulfonyl-4-thiazoline III is readily aromatized after acid silica gel treatment by elimination of the methyl sulfonate to give 2,5-disubstituted thiazoles **164** (Scheme 6.72) [88].

Koenigs et al. [89] studied the Rh(II)-catalyzed enamine homologation reactions of *N*-sulfonyl-1,2,3-triazoles **1** with cyclopropylmethyl sulfides **165**. In this unusual reaction, the imino carbenes can form ylides that do not follow classic rearrangement pathways but preferentially undergo intramolecular alkylation reaction to yield the product of an enamines **166** in good yields (Scheme 6.73).

Li et al. [90] have achieved an unprecedented user-friendly protocol for the synthesis of valuable (*E*)-monofluoroenamine **167** from 1-sulfonyl-1,2,3-triazole **1** and boron trifluoride diethyl ether ($Et_2O \cdot BF_3$) which acted in the form of electrophile and a fluorinated resource in this mild transformation. In this method, the denitrogenative of the conversion 1-sulfonyl-1,2,3-triazole **1** is mediated by $Et_2O \cdot BF_3$, and a transition metal was not required in a stereospecific synthesis with dense products. This method is synthetically attractive for the preparation of fluorine-containing compounds (Scheme 6.74).

New silver-catalyzed complex annulations of the *N*-sulfonyl-4-(2-(ethynyl)aryl)-1,2,3-triazoles **168** with water in the presence of 20 mol% of $AgSbF_6$ to obtain a diverse array of functionalized isoquinolines **169** with good yields and excellent functional group tolerance, which can find significant applications in synthetic and medicinal chemistry. From a mechanistic point of view, the reaction involves the participation of a key intermediate silver carbenoid, which allows the formation of multiple chemical bonds by ring-opening, nitrogen extrusion, silver carbenoid formation, nucleophilic addition, and complex annulations cascades to formation **169** (Scheme 6.75) [91].

Jiang and co-workers [92] established the coupling of *N*-sulfonyl-1,2,3-triazole **1** with *H*-phosphine oxides using a nickel-catalyzed bis(1,5-cyclooctadiene)nickel(0) {[Ni(cod)2]} to the construction of $C(sp^2)$-P bonds. The unexpected reaction proceeds follow the formal nickel-bound ketenimine pathway, representing a which is a previously unknown type of 1,2-azavinyl carbene reaction. The method provides an efficient approach to the stereoselective and site-selective synthesis of α-aminovinylphosphoryl derivatives **170** in moderate to good yields (Scheme 6.76).

Li and co-workers [93] reported a tandem reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazoles **171** involving α-imino rhodium carbene formation, 1,2-migration of an

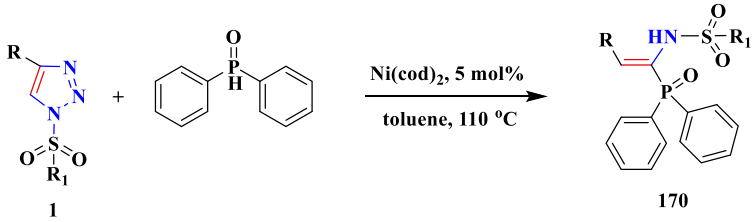
R = 4-MeC$_6$H$_4$, R$_2$ = H, R $_1$= n-pentyl (21%); 2-MeC$_6$H$_4$ (64%); 3-MeC$_6$H$_4$ (69%); 4-MeC$_6$H$_4$ (80%)

4-OMeC$_6$H$_4$ (51%); 2-ClC$_6$H$_4$ (58%); 4-ClC$_6$H$_4$ (72%); 4-FC$_6$H$_4$ (69%); thienyl (69%); cyclopropyl (55%)

R = 4-MeC$_6$H$_4$, R$_1$ = Ph, R$_2$ = 7-Me (72%), 5-Me (70%); 5-F (73%)

R$_1$ = Ph, R$_2$ = H, R = Me (78%); 4-ClC6H4 (69%); naphthyl (71%)

SCHEME 6.75 Synthesis isoquinolines **169**.

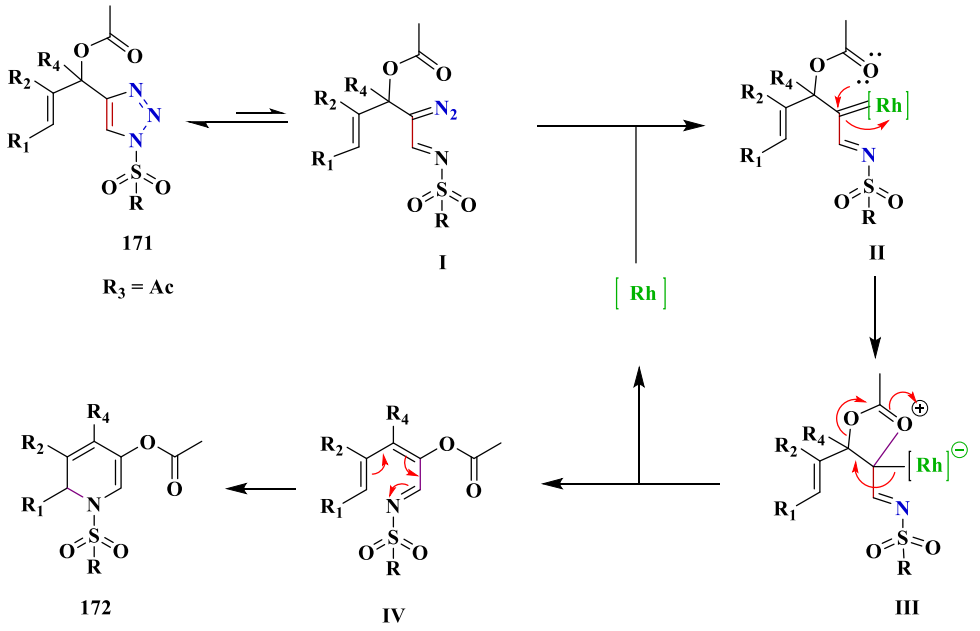


R$_1$ = Me, R = Ph (68%); 4-OMeC$_6$H$_4$ (64%); 4-BrC$_6$H$_4$ (58%); 4-ClC$_6$H4 (51%); 4-FC$_6$H$_4$ (55%)

R = R$_1$= Ph (58%)

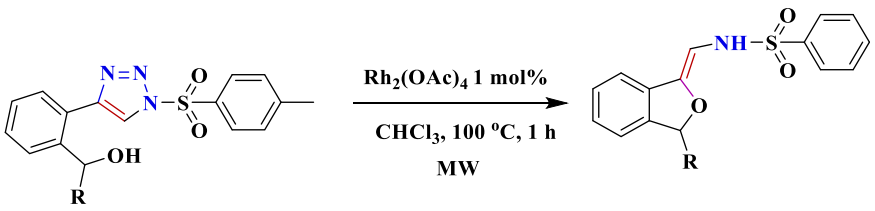
R = 4-MeC$_6$H$_4$, R$_1$ = *i*-Pr (63%); 4-MeC$_6$H$_4$ (60%); 4-OMeC$_6$H$_4$ (63%); 4-BrC$_6$H$_4$ (62%); 4-OCF$_3$C$_6$H$_4$ (68%)

SCHEME 6.76 Synthesis of α-aminovinylphosphoryl derivatives **170**.



SCHEME 6.77 Synthesis of dihydropyridine derivatives **172**.

acetoxy group and six electrons electrocyclic ring closure. Migration of the OAc group with excellent chemoselectivity was the crucial process, leading to the formation of 1,2-dihydropyridines **172** in a particular with a yield of up to 90%. The plausible formation mechanism of **172** was considered as shown in Scheme 6.77.



173

174

R = H 90%
R = Ph 87%
R = *i*-Pr 73%

SCHEME 6.78 Synthesis of phthalanes **174**.

Treatment of triazoles **173** with 1 mol% $Rh_2(OAc)_4$ in chloroform under microwave irradiation provided phthalans **174** in moderate to excellent yield and as a single geometric isomer. The reaction mechanism proposed by the 1-sulfonyl-1,2,3-triazoles undergoes inter- and intramolecular 1,3-OH insertion with the rhodium(II)-azavinyl carbenoids intermediate after treatment with a rhodium (II) catalyst (Scheme 6.78) [94].

Fu et al. [95] performed efficient rhodium-catalyzed hydrosilylation of *N*-sulfonyl-1,2,3-triazoles by reacting *N*-sulfonyl-1,2,3-triazoles **1** with triphenylsilane afforded the 2-(triphenylsilyl)-2-aryl-*N*-(arylsulfonyl)ethanimines, which isomerized into (*E*)-2-(triphenylsilyl)-2-aryl-*N*-(arylsulfonyl)ethenamines **175** in the presence of TEA; whose reduction with $LiAlH_4$ gives 2-(triphenylsilyl)-2-aryl-*N*-(arylsulfonyl)ethanamines **176**. The possible mechanism for rhodium-catalyzed hydrosilylation of *N*-sulfonyl-1,2,3-triazoles **1** with triphenylsilane is suggested by Rhodium-catalyzed denitrogenation of **1**, which produces α-imino Rh(II) carbine **I**, which reacts with triphenysilane to form **II** and releasing the Rh(II) catalyst. Isomerization of **II** in the presence of TEA affords **175**, while reduction of **II** with $LiAlH_4$ in THF gives **176** (Scheme 6.79).

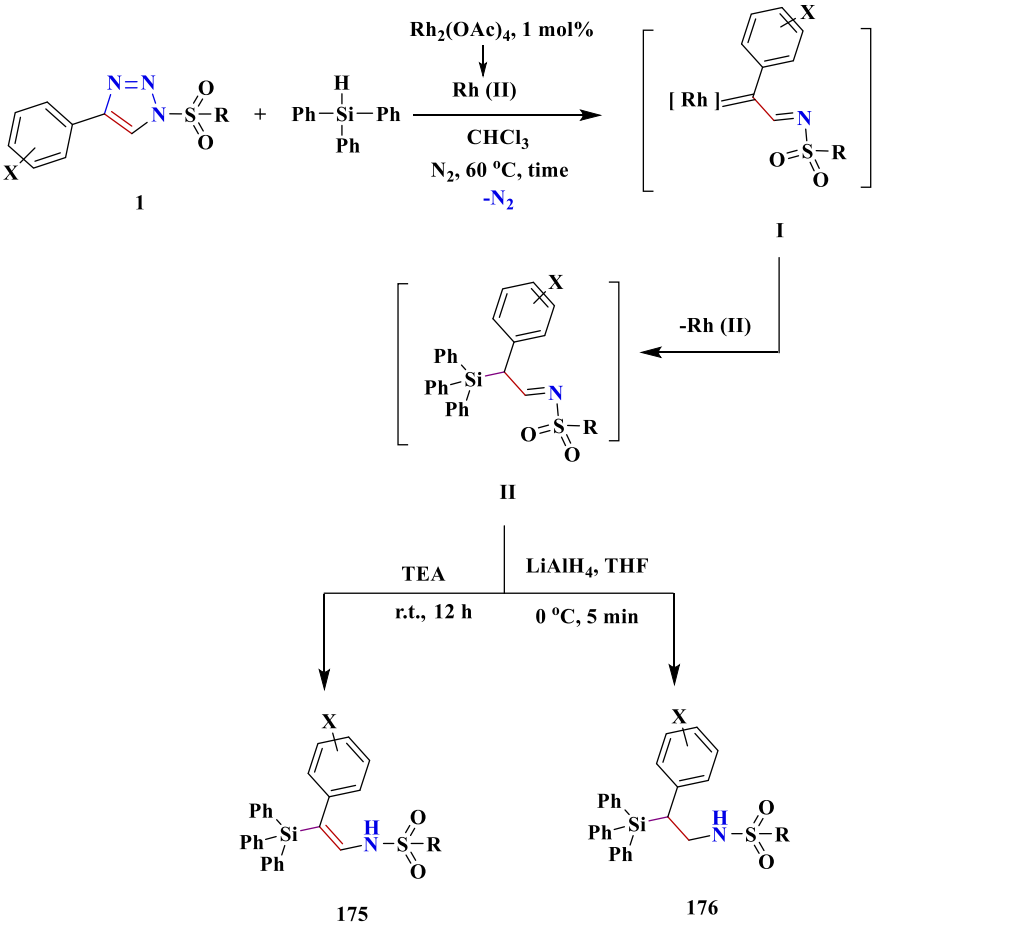
It has been reported that the denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles **177** was converted to 2,3-fused pyrroles **178** and substituted indoles using 2 mol% rhodium(II)octanoate [$Rh_2(OCt)_4$] as a catalyst. The concept is based on the denitrogenative of an *N*-sulfonyl-1,2,3-triazole ring, followed by an opening to form the reactive Rh carbenoid intermediate. The electrophilicity of the resulting Rh carbenoid enables subsequent cyclization, initiated by amino groups, *via* aromatic electrophilic addition (Scheme 6.80) [96].

$\alpha,\beta,\gamma,\delta$-Unsaturated imines are synthesized from *N*-sulfonyl-1,2,3-triazoles **1** and allenes **179**. Monosubstituted allenes containing primary alkyl substituents (CH_2R_2) react readily with the 1-tosyl-substituted triazole **1** to form the corresponding products **180** with yields ranging from 69% to 78% with an *E/Z* ratios of 84:16/88:12. The mechanism of formation of **180** initially allenes cyclopropanated by intermediate α-imino rhodium carbene complexes, and the resulting alkylidenecyclopropyl methanimines subjected to an ring opening thermal rearrangement to afford the corresponding $\alpha,\beta,\gamma,\delta$-unsaturated imines (Scheme 6.81) [97].

Li et al. [98] described, highly efficient gold-catalyzed *N1*-selective alkenylation yielding the desired *N1*-vinyl-1,2,3-trizoles **183** in good yields. The sulfonyl group of 1,2,3-trizole derivatives was converted to alkenyl groups in by a "one-pot two steps" method. The plausible mechanism is illustrated in the catalytic cycle shown in Scheme 6.82. Initially, in the synthesis of *NH*-trizole **181** was prepared from **1** as the starting material in the presence of H_2O, then intermediate **182** of *N1*-vinyl-gold substituted 1,2,3-triazole derivative was obtained by a one-step process involving a nucleophilic attack of **181** on Au(I)-coordinated phenylacetylene. It then undergoes protodemethylation to give the final product **183** as the only sole isomer. The high regioselectivity may be related to the low concentration of *NH*-1,2,3-trizole **181**, which was obtained by the slow hydrolysis of 1-sulfonyl-1,2,3-trizole **1** (Scheme 6.82).

Koenigs et al. [99] studied the reaction of organoselenium compounds **184** with triazoles **1** under thermal conditions with 2 mol% of $Rh_2(OAc)_4$ was dissolved in toluene (1.0 mL) and heated to 100°C for 15 h, dihydropyrroles **185** as the only product with good yields (Scheme 6.83).

Fokin et al. [100] developed a novel and very efficient Rh(II)-catalyzed asymmetric cyclopropanation methodology that uses the stable and available *N*-sulfonyl-1,2,3-triazoles **1** as azavinyl carbine, readily reacting with olefins **186** under thermal conditions to afford cyclopropanecarboxaldehydes **187** and *N*-sulfonyl homoaminocyclopropanes **188** with excellent yields with high enantioselectivity (Scheme 6.84).



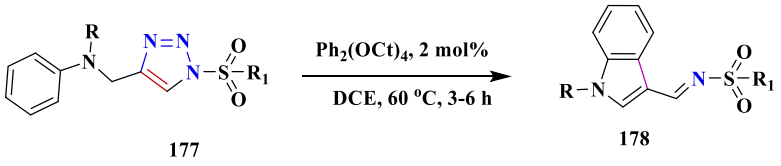
175 / 176, R = Ph, X = H (91%/92%); 4-Et (88%/95%); 4-Me (85%96%)

175 / 176, R = 4-MeC$_6$H$_4$, X = H (89%/97%); 4-Me (93%/98%); 4-Et (93%/94%);

3-OMe (84%/97%); 3,5-(Me)$_2$ (95%/95%); 4-Cl (81%/92%); 4-Br (83%/93%); 4-F (89%/96%)

175 / 176, X = H, R = 4-Me (755/90%); 4-OMe (86%/93%)

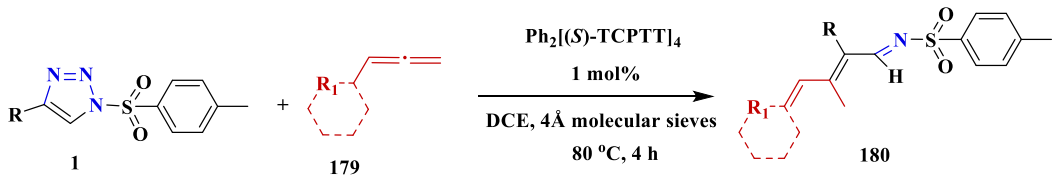
SCHEME 6.79 Reaction sequence for the formation of (*E*)-2-(triphenylsilyl)-2-aryl-*N*-(arylsulfonyl)ethenamines **175** and **176**.



R$_1$ = 4-MeC$_6$H4, R = Et (92%); C$_3$H$_7$ (80%); C$_4$H$_9$ (81%); C$_6$H$_{13}$ (83%); Bn (81%)

R$_1$ = Ph, R = Me (82%); Et (81%)

SCHEME 6.80 Synthesis of 2,3-fused pyrroles **178**.



R = Ph,

R$_1$ = Me, 51% (*E*:*Z* = 82:18)

R$_1$ = PhCH$_2$, 69% (*E*:*Z* = 85:15)

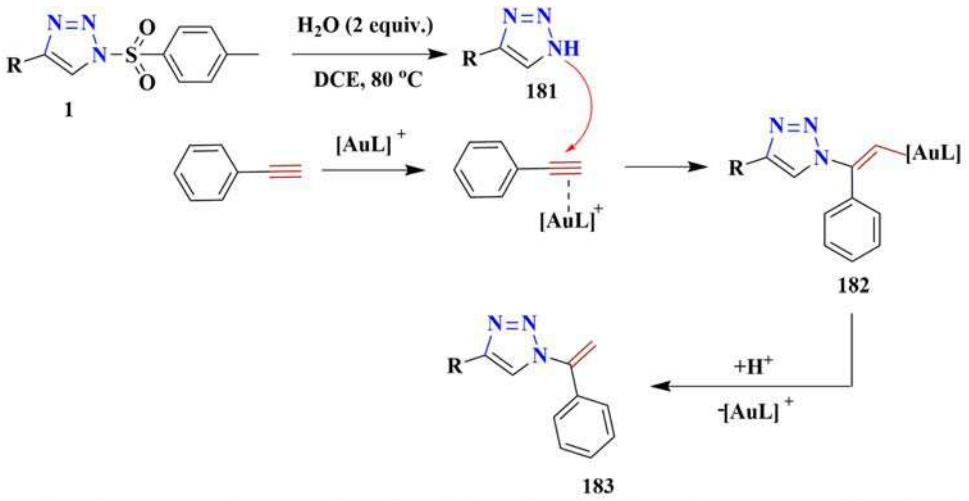
R$_1$ = Hept, 78% (*E*:*Z* = 84:16)

R$_1$ = Cy, 77% (*E*:*Z* = 88:112)

R = 4-MeC$_6$H$_4$, R$_1$ = Hept, 54% (*E*:*Z* = 83:17)

R = 4-F$_3$C-C$_6$H$_4$, R$_1$ = Hept, 83% (*E*:*Z* = 81:19)

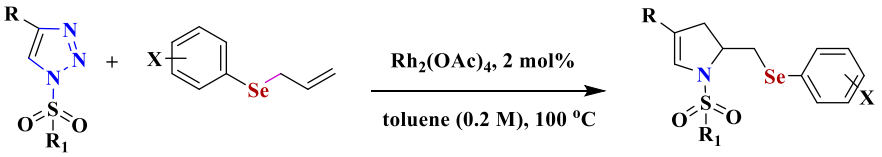
SCHEME 6.81 Synthesis of $\alpha,\beta,\gamma,\delta$-unsaturated imines **180**.



1 181 182 183

R = 4-MeC$_6$H$_4$ (67%); 4- *n*PrC$_6$H$_4$ (84%); tBuC$_6$H$_4$ (75); 2-FC$_6$H$_4$ (62%); 3- FC$_6$H$_4$ (58%); 4-FC$_6$H$_4$ (64%); 4-Cl C$_6$H$_4$ (70%); 2,4-(Cl)$_2$ (64%); 3-CF$_3$C$_6$H$_4$ (41%); 4-OMeC$_6$H$_4$ (47%); 2-thienyl (84%)

SCHEME 6.82 Synthesis of *N1*-vinyl-1,2,3-trizoles **183**.



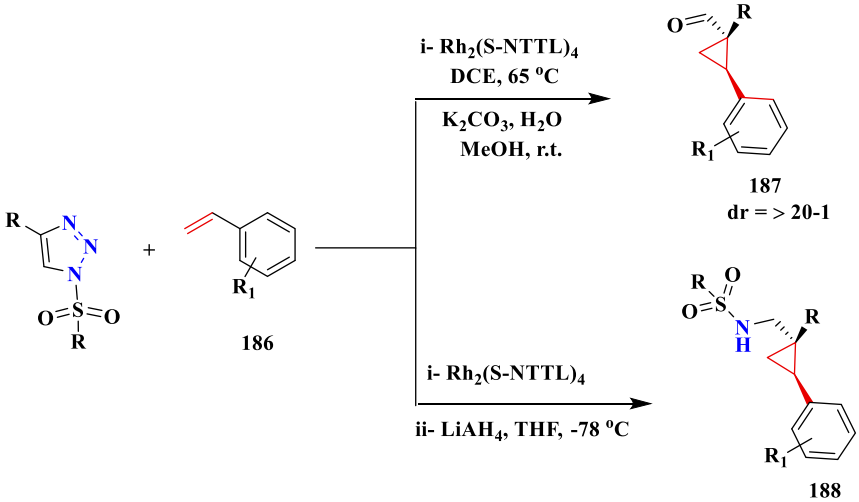
1 184 185

R = Ph, X = H, R$_1$ = *i*-Pr (55%); 4-(i-Pr)$_3$C$_6$H$_2$ (24%); *i*-BuC$_6$H$_4$ (70%); 4-MeC$_6$H$_4$ (86%); 4-F$_3$CC$_6$H$_4$ (52%)

R$_1$ = MeC$_6$H$_4$, X = H, R = 4-MeC$_6$H$_4$ (73%); 4-$_i$-BuC$_6$H$_4$ (82%); 3-MeOC$_6$H$_4$ (69%); 4-MeOC$_6$H$_4$ (43%); 4-ClC$_6$H$_4$ (73%); 4-BrC$_6$H$_4$ (75%); 4-FC$_6$H$_4$ (62%); 2-FC$_6$H$_4$ (75%); 4-CNC$_6$H$_4$ (66%); 4-F$_3$CC$_6$H$_4$ (71%)

R = Ph, X = 4-Me, R$_1$ = Ph (20%); 4-MeC$_6$H$_4$ (62%); 4-OMeC$_6$H$_4$ (58%); 4-ClC$_6$H$_4$ (57%); 4-FC$_6$H$_4$ (70%)

SCHEME 6.83 Synthesis of dihydropyrroles **185**.



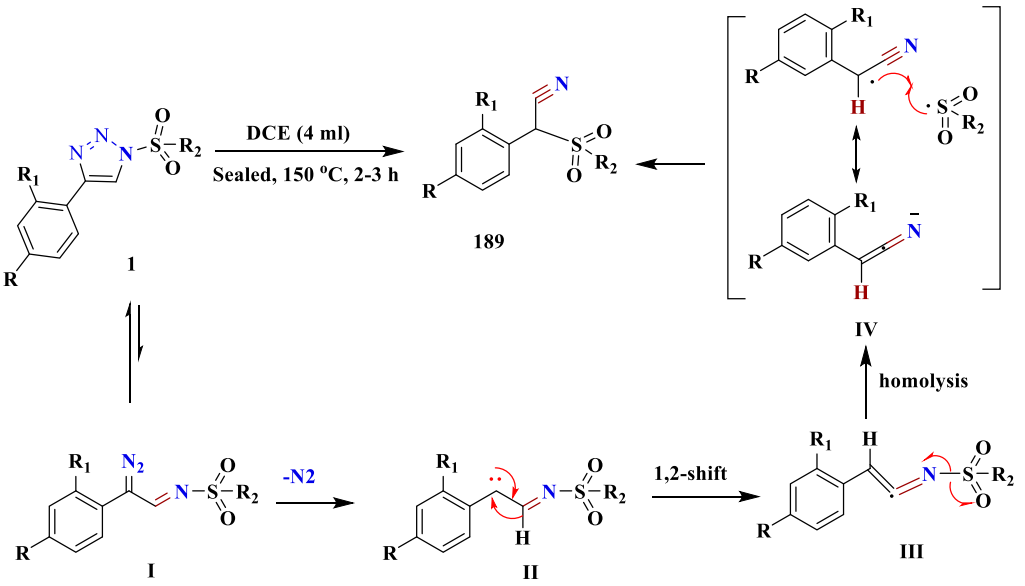
186 187 188

dr = > 20-1

187, R = Ph, R$_1$ = 4-OMeC$_6$H$_4$ (94%, 97%, ee); 4-CF$_3$C$_6$H4 (80%, 97% ee); 4-MeCOC$_6$H$_4$ (59%, 98% ee); thienyl (57%, 93%, ee); cyclohexenyl (57%, 96%, ee)

188, R = Me, R$_1$ = H (89%, 96% ee)
R = *i*Pr, R$_1$ = 4-CF$_3$ (82%, 98% ee)
R = *i*Pr, R$_1$ = 2-Cl (77%, 96% ee)

SCHEME 6.84 Synthesis of cyclopropanecarboxaldehydes **187** and *N*-sulfonyl homoaminocyclopropanes **188**.



R = R_1 = H, R_2 = Ph (57%); 4-MeC_6H_4 (71%);4-$^tBuC_6H_4$ (59%); 4-$OMeC_6H_4$ (62%); 4-$NO_2C_6H_4$ (52%)

R = H, R_2 = Me, R_1 = Me (58%); 4-OMe (51%)Ph (44%); 2-furanyl (37%); hex-1-yn-1-yl (36%); alkoxy (37%)

R_1 = H, R_2 = Me, R = Me (57%); tBu (62%); Ac (56%); OMe (67%); F (54%); CF3 (26%); CN (21%)

SCHEME 6.85 Metal-free rearrangement of 4-substituted 1-sulfonyl-1,2,3-triazoles to α-cyano sulfones **189**.

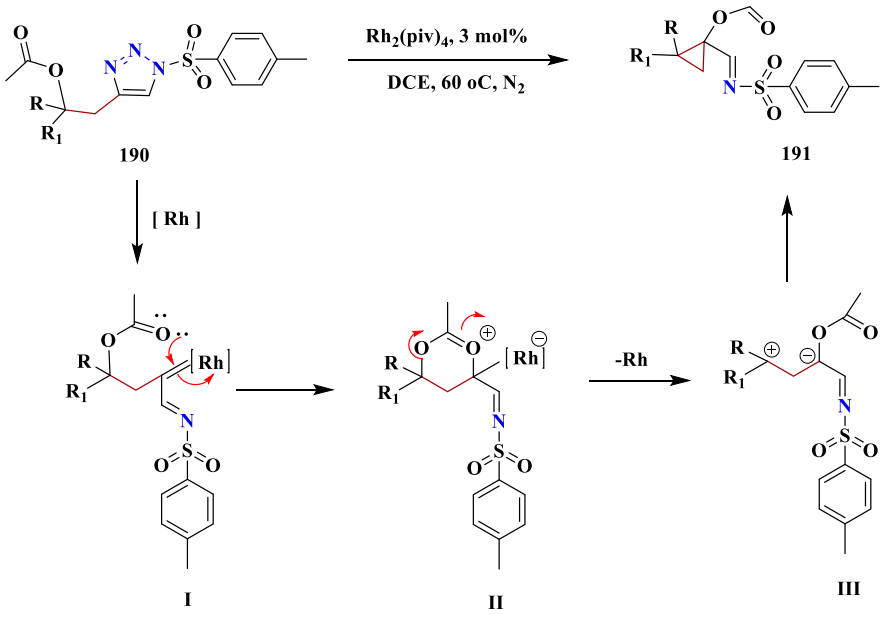
A novel metal-free rearrangement of 4-substituted 1-sulfonyl-1,2,3-triazoles **1** has been disclosed to produce α-cyano sulfones **189** in satisfying good yields. Carbene and the radical were proposed as the key intermediates, while ketenimine was captured in an intramolecular reaction (Scheme 6.86) [101]. The proposed mechanism for the formation of **189** ia *via* ketenimine **III** is formed by tandem ring-chain tautomerization, departure of N_2, and a 1,2-H shift. Then upon homolytic cleavage of N−S bond, a close pair of radicals is formed, bounded by the same solvent cage. Recombination of the two radicals causes migration of 1,3-sulfonyl and thus produces sulfone **189** (Scheme 6.85).

Xu et al. [102] described a novel and highly efficient synthetic approach to multifunctionalized cyclopropanes **191** through 1,3-migration of acyloxy groups of triazoles **190** induced by α-imino rhodium carbenes under mild reaction conditions. The proposed **191** formation mechanism is illustrated in Scheme 6.86.

Xu et al. [103] developed a cascada reaction of acyloxy substituted *N*-sulfonyl-1,2,3-triazoles **190** with 2*H*-azirines **192**, prepared by 1-azadienes, to be used as a 1-aza-[4C] synthon for cyclization with 2*H*-azirines to form fused pyrimidine derivatives **193**. The success of the unusual cyclization of electron-deficient dienes with electron-deficient dienophiles cab be explained by the high reactivity of the strained 2*H*-azirine three-membered ring (Scheme 6.87).

It has been reported that the reaction of *N*-sulfonyl-4-phenyl-1,2,3-triazole **1** with azirine 3-phenylspiro [azirine-2,9′-fluorene] in the presence of dirhodium tetraacetate ($Rh_2(OAc)_4$) after heating in toluene for 1.5 h, a spiro-fused dihydropyrazine **194** formed by 1,6-cyclization of diazatriene **I**. On the other hand, when the reaction was run with a longer heating time for 2.5−3 h until the complete disappearance of starting materials and subsequent chromatographic purification, 3*H*-pyrroles **195** was isolated with good yield (Scheme 6.88) [104].

Novikov et al. [105] developed an effective and simple method for the preparation of 1-(2-(sulfonamido) vinyl)indoles (SAV indoles) 197 *via* the Rh(II)-catalyzed reaction in toluene at a temperature of 110°C starting from 1-sulfonyl-1,2,3-triazoles **1** with 2,2-diaryl-2*H*-azirines **196**. This method provides a stereoselective synthesis of various 1,2,3-trisubstituted indoles having *Z*-configuration of the (1-aryl-2-(sulfonamido)vinyl) substituent. The reaction mechanism, confirmed by density functional theory (DFT) calculations, leads to the formation of 1,4-diazahexa-1,3,5-trienes, which rapidly cyclize to 2,2-diaryl-1-sulfonyl-1,2-dihydropyrazines. These compounds were isolated early in the reaction but were isomerized into 7*aH*-indolium ylides under prolonged heating, followed by a barrierless 1,5-prototropic shift in SAV-indoles (Scheme 6.89).

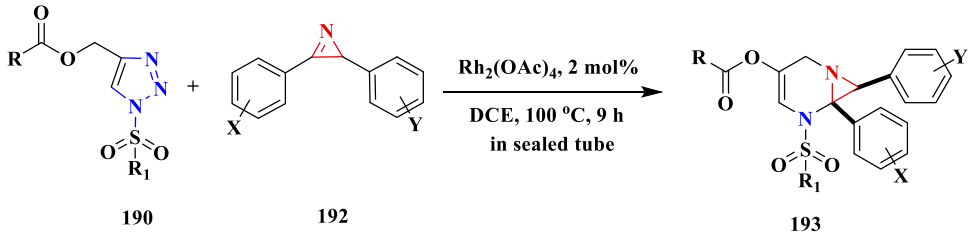


R = MeC_6H_4, R_1 = 4-BrC_6H_4 (98% dr1.7:1); 4-ClC_6H_4 (98% dr1.9:1); 4-FC_6H_4 (96% dr 1.2:1)

R = 4-FC_6H_4, R_1 = 4-*t*-BuC_6H_4 (92% dr 1:1); 4-ClC_6H4 (92% dr 1.2:1); 4-BrC_6H_4 (94% dr 1.5:1); CCPh (98% dr 1.1:1)

R = R_1 = 4-MeC_6H_4 (80%); R = R_1 = 4-FC_6H_4 (80%); R = R_1 = 4-ClC_6H_4 (94%); R = R_1 = 4-BrC_6H_4 (85%)

SCHEME 6.86 Synthesis of multifunctionalized cyclopropanes **191** *via* 1,3-migration of acyloxy groups of triazoles.



R = Me, X = Y = H, R_1= Me (57%); 4-MeC_6H_4 (38%)

R = Ph, X = Y = H, R_1 = Me (83%); *n*-Pr (75%); 4-MeC_6H_4 (51%); 4-BrC_6H_4 (61%); 2-naphthyl (72%)

R_1 = Me, X = Y = H, R = 2-MeC_6H_4 (70%); 4-MeC_6H_4 (63%); 2-IC_6H_4 (65%); 4-ClC_6H_4 (68%)

R = Ph, R_1 = Me, X = 4-Me, Y = H (49%)

R = Ph, R_1 = Me, X = 4-Me, Y = 4-Me (42%)

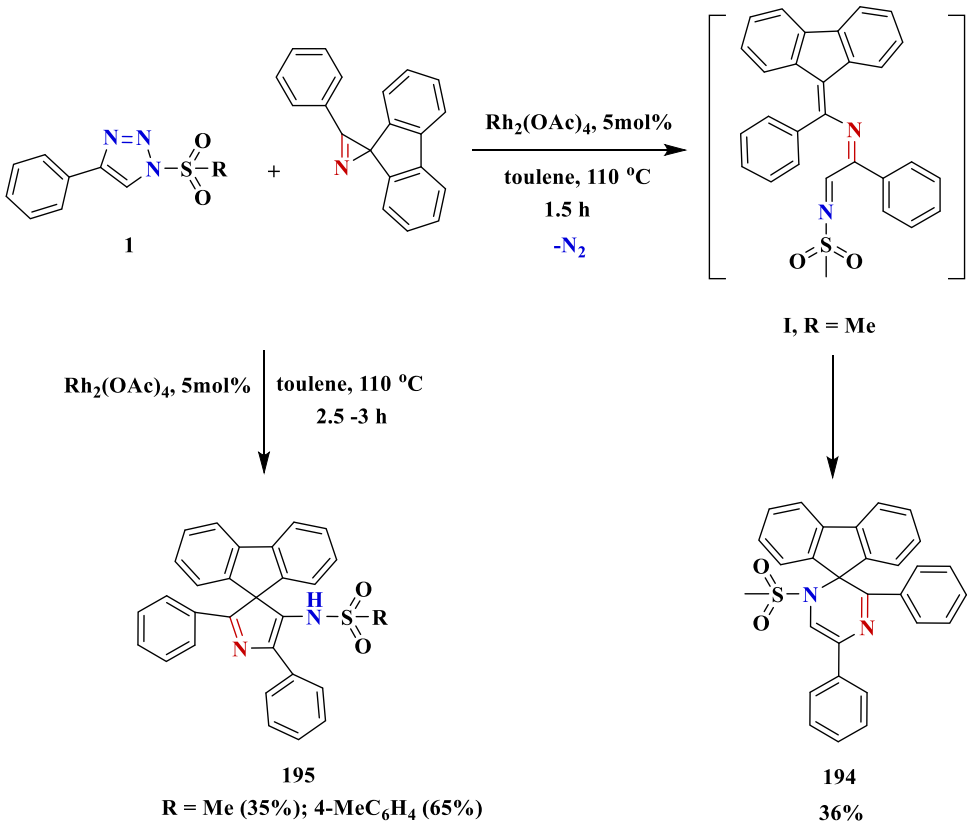
R = Ph, R_1 = Me, X = 4-Cl, Y = H (50%)

R = Ph, R_1 = Me, X = 4-Me, Y = 4-F (45%)

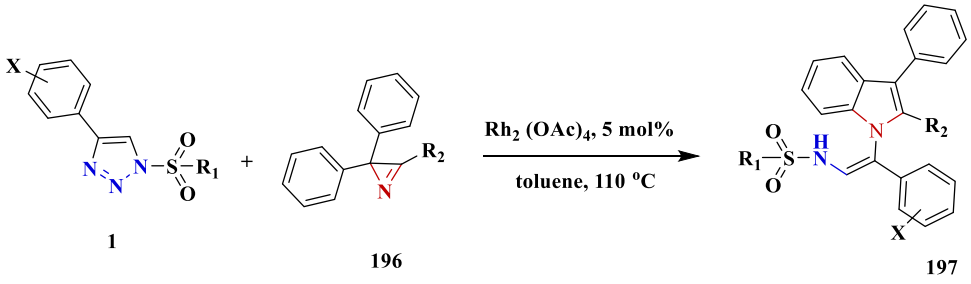
SCHEME 6.87 Synthesis of fused pyrimidine derivatives **193**.

Kang et al. [106] developed a cascade with sequential catalysis for the synthesis of benzofuran derivatives **198** in 88% yield from 1-sulfonyl-1,2,3-triazoles **1** and 1 mol % of $Rh_2(Oct)_4$, 10 mol% of CuTc and 4 Å molecular sieves in toluene. The reaction proceeds *via* rhodium-catalyzed C(sp3)-H insertion and copper-catalyzed aerobic oxidation. The method has become more convenient for the synthesis of benzofurans starting with terminal alkynes through a one-pot sequential copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC)/C−H insertion/dehydrogenation cascade reaction (Scheme 6.90).

A rhodium-catalyzed intramolecular denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazole-tetheredcyclohexadienones **199** was demonstrated by Novikov et al. [107] for the synthesis of benzofurans **200** and cyclopropa[*cd*]indole-carbaldehydes **201** by a simple



SCHEME 6.88 Synthesis of spiro-fused dihydropyrazine **194** and 3*H*-pyrroles **195**.

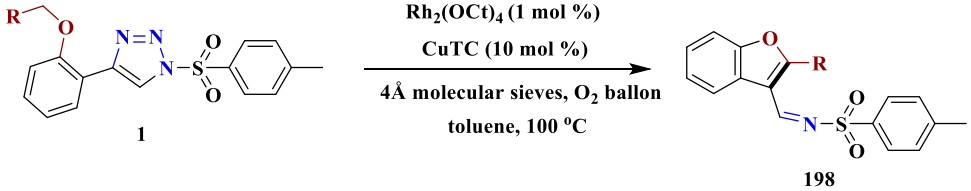


R_2 = Me, X = H, R_1 = Me (37%); 4-MeC_6H_4 (52%)

R_1 = 4-MeC_6H_4, R_2 = Ph, X = 2-F (98%); 4-CF_3 (89%); 2-Br (75%); 4-NO_2 (85%)

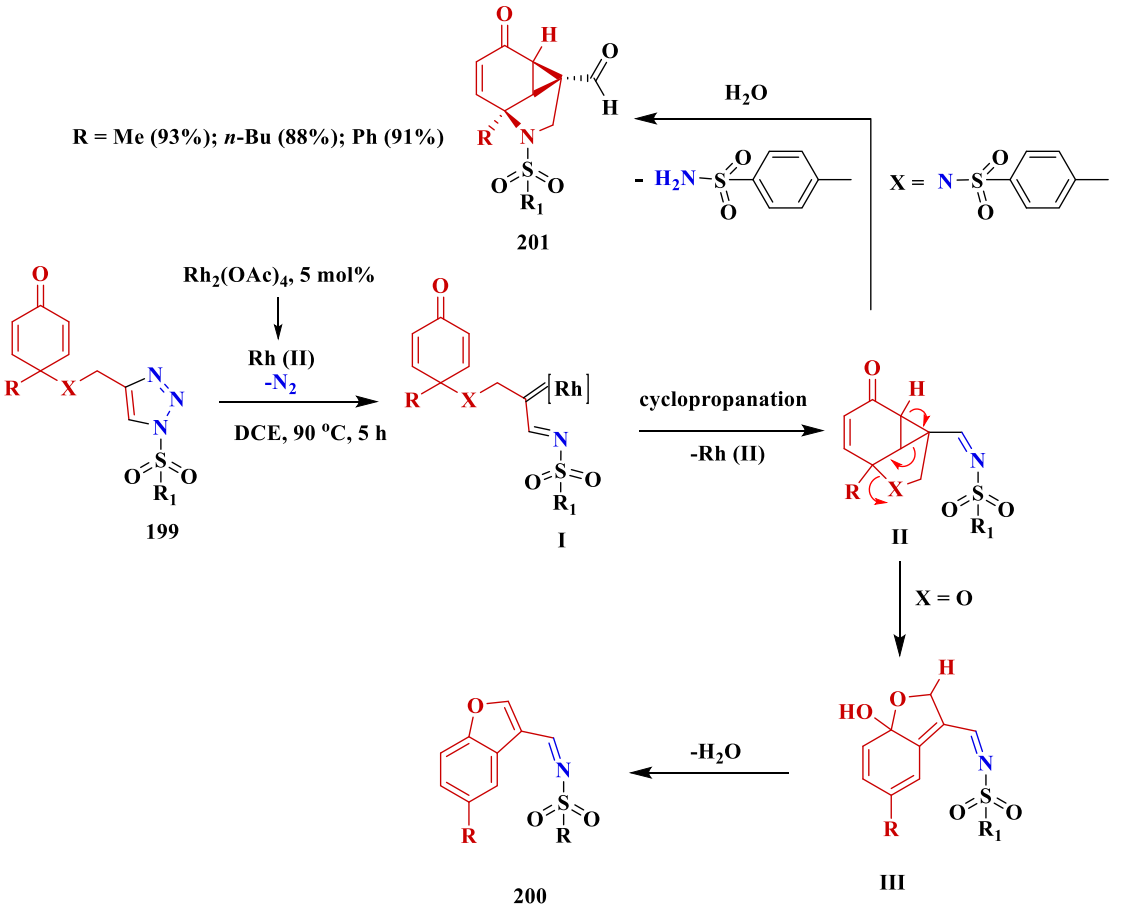
R_2 =Ph, X = H, R_1 = Me (61%); 2,4,6-$(Me)_3C_6H_2$ (41%); 4-$AcNHC_6H_4$ (58%)

SCHEME 6.89 Synthesis of 1-(2-(sulfonamido)vinyl)indoles **197** (SAV indoles).



R = 4-Me (27%); CH_2=CH_2 (0%); 2-MeC_6H_4 (79%); 3-FC_6H_4 (51%); 4-$MeCOOC_6H_4$ (74%); 4-Cl C_6H_4(67%); 2,4-$(Cl)_2$ (64%); 3-$CF_3C_6H_4$ (41%); 4-$OMeC_6H_4$ (84%); cyclohexayl (64%)

SCHEME 6.90 Synthesis of benzofuran derivatives **198**.



R_1 = 4-MeC_6H_4, R = Me (84%); Et (81%); *n*-Pr (82%); *n*-Bu (75%); *i*Pr (68%); *t*Bu (61%); $MeOCH_2CH_2$ (71%);

$TBSOCH_2CH_2$ (75%); $BoNHCH_2CH_2$ (67%); $BrCH_2CH_2$ (75%); ICH_2CH_2 (72%); CH_2Ph (65%); Ph (735)

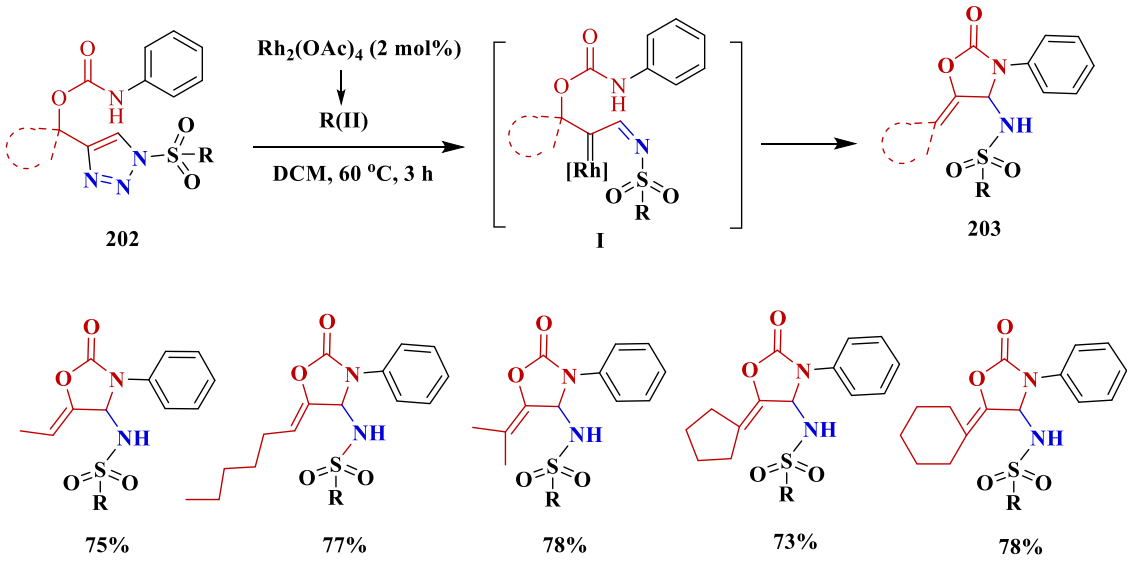
R = Me, R_1 = Ph (82%); 2,4,6-$(Me)_3$ (74%); 4-*t*BuC_6H_4 (80%);4-BrC_6H_4 (75%); 4-$NO_2C_6H_4$ (82%); 4-PhC_6H_4 (78%)

SCHEME 6.91 Reaction sequences for the formation of 3-imino benzofuran **200** and cyclopropane carbaldehydes **201**.

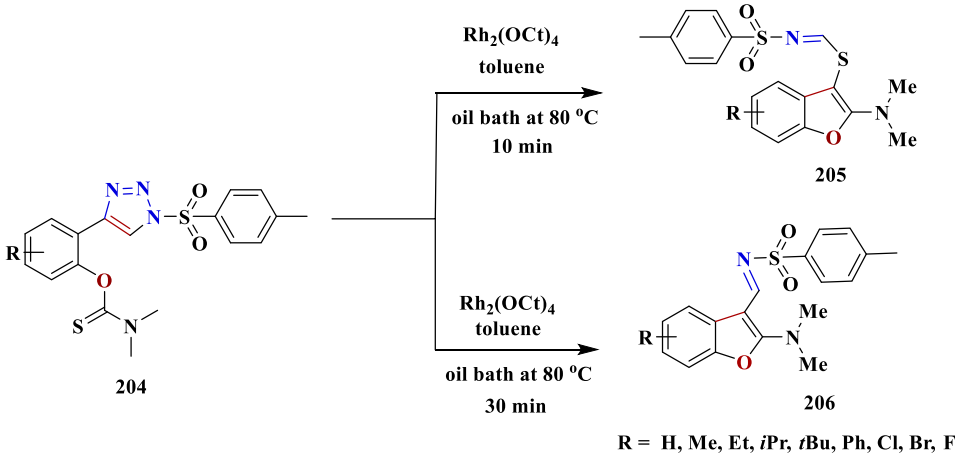
method. Remarkably, the reaction path depends entirely on the linker heteroatom (O or N) present between the cyclohexadienone unit and the triazole group. In the case of O-linked triazoles, there is a cascade sequence consisting of intramolecular cyclopropanation and rearrangement, leading to the formation of benzofurans, while in the case of *N*-linked triazoles, only cyclopropa [*cd*]indole carbaldehydes have been isolated. The mechanism of formation of compounds **200** and **201** is through intramolecular cyclopropanation of Rh-azavinyl carbene intermediate **I** with an olefin, which leads to the formation of fused tricyclic imine intermediate **II**. In the case of O-linker, intermediate **II** undergoes cyclopropane ring-opening and proton transfer to form the alcoholic intermediate **III**. Subsequent intramolecular nucleophilic addition to the carbonyl group followed by water elimination produces 3-imino benzofuran **200**. If the linker was nitrogen, intermediate **II** is hydrolyzed to afford cyclopropane carbaldehydes **201** (Scheme 6.91).

Walla et al. [108] described a new Rh (II) catalyzed intramolecular transannulation of 1,2,3-triazolylcarbamates to obtain functionalized 4-amino-oxazolidinones under the simplest operating conditions with low catalyst loading. Thus heating *N*-sulfonyl-1,2,3-triazoles having substituents at the methylene position **202** with 2 mol% $Rh_2(OAc)_4$ in DCM affords the corresponding 5-alkenyl-4-amino-2-oxazolidinones **203** in good yields (73%–78%). It is noteworthy that the reaction showed high diastereoselectivity, giving the (*E*) alkylidene-3-phenyloxazolidinone as the major isomer, and the conversion proceeded through rhodium (II) catalyzed intramolecular annulations of indolyl-tethered *N*-sulfonyl-1,2,3-triazoles **202** (Scheme 6.92).

Synthesis 2-aminobenzofuran derivatives **205** and **206** from *N*-sulfonyl-1,2,3-triazoles **204** bearing thiocarbamates,



SCHEME 6.92 Some examples of prepared 5-alkenyl-4-amino-2-oxazolidinones **203**.

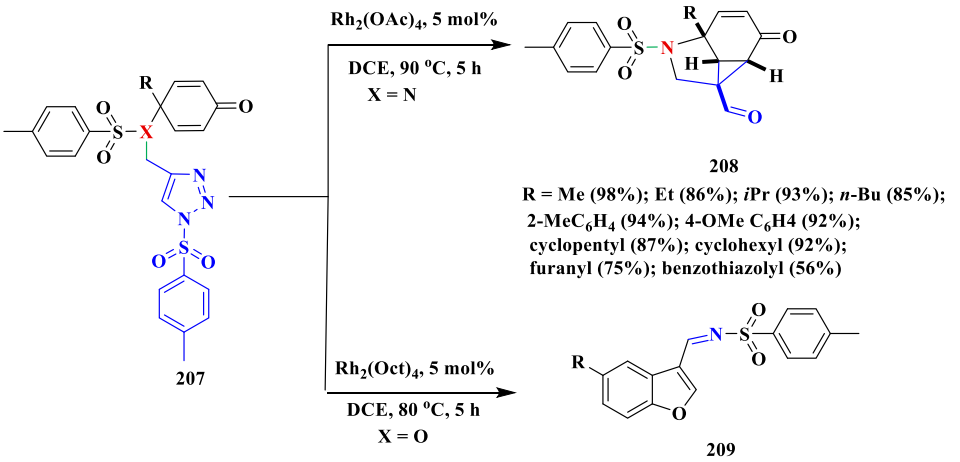


SCHEME 6.93 Synthesis of 2-aminobenzofuran derivatives **205** and **206**.

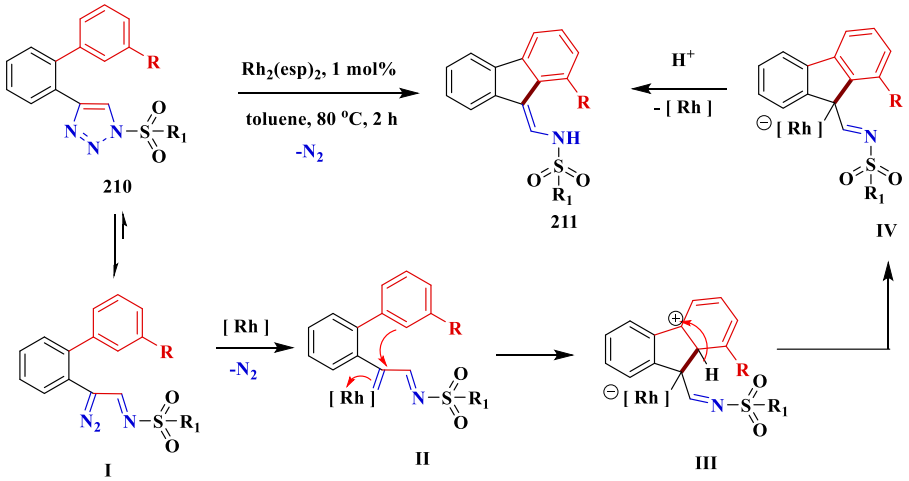
is an unprecedented process of migration of imine derivatives. Moreover, Song et al. [109] initiated Barton-Kellogg type reactions without desulfurization reagents, starting with *N*-sulfonyl-1,2,3-triazoles **204**, and it was confirmed that elemental sulfur was a by-product during this transformation. Experimental data, as well as DFT calculations, elucidated the unique reactivity in detail (Scheme 6.93).

Shi et al. [110] investigated the divergent intramolecular tandem cyclization of *N*- or *O*-tethered cyclohexa-2,5-dienones **207** bearing 1-sulfonyl-1,2,3-triazole by rhodium(II)-catalyzed. When the linking atom between the cyclohexa-2,5-dienone unit and the 1-sulfonyl-1,2,3-triazole moiety is an *N*-sulfonated group, cyclopropanation of the olefinic unit on the cyclohexa-2,5-dienone moiety can give derivatives of cyclopropa[*cd*]indole **208** with yield moderate to good. This is the first example of the cyclopropanation of α-imino rhodium carbenes by electron-deficient intra-annular olefins. If the connecting linker was an oxygen atom, the rearrangement of the oxy-Cope could be induced under similar reaction conditions, providing benzofuran derivatives **209** (Scheme 6.94).

Lee et al. [111] described an efficient method for the synthesis of fluorenes **211** containing an enamine moiety at C-9, methylene bridge prepared from *N*-sulfonyl-4-biaryl-1,2,3- triazole derivatives **210** by Rh-catalyzed denitrogenative cyclization in a *5-exo* mode. The probable mechanism of the formation of fluorene **211** from *N*-sulfonyl-4-(2-biaryl)-1,2,3-triazoles **210** is shown in Scheme 6.96. Initially, the reversible tautomerization of the ring-chain **210** produces α-diazo imine **I**, which when interacting with rhodium(II) catalyst affords α-imino rhodium(II) carbenoid **II** with the evolution of nitrogen gas. The carbenoid carbon of **II** is sufficiently electrophilic to cause



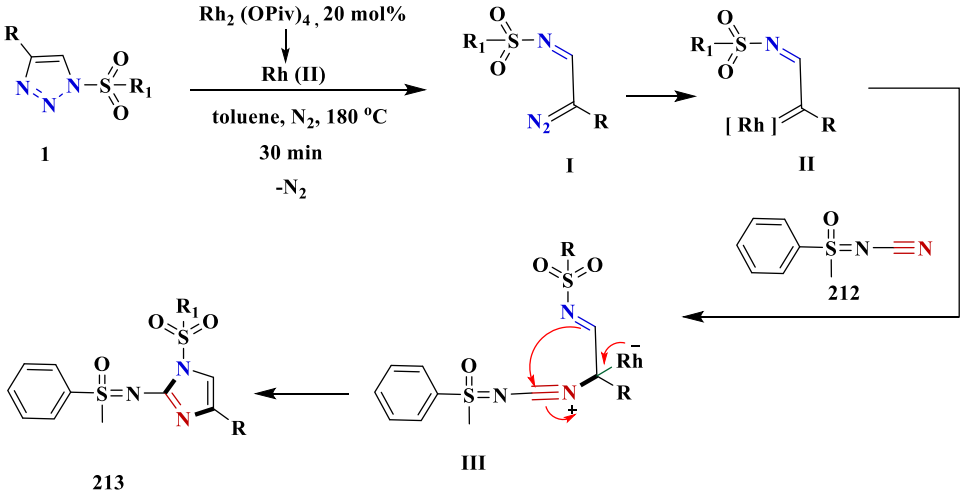
SCHEME 6.94 Synthesis of cyclopropa[*cd*]indole derivatives **208** and benzofuran derivatives **209**.



SCHEME 6.95 Proposed reactions of synthesis of fluorenes **211**.

cyclization by the intramolecular attack of the phenyl ring in a *5*-exo mode to produce the Rh-bound zwitterionic intermediate **III**. Subsequently, rearomatization followed by protoderhodation produces the desired fluorenes **211**. This reaction is in marked contrast to the synthesis of tricyclic 3,4-fused dihydroindoles via a Rh-catalyzed dearomatizing [3 + 2] annulation reaction of 4-(3-arylpropyl)-1,2,3-triazoles in the 6-exo mode (Scheme 6.95).

Lee et al. [112] described the *N*-imidazolylation of *N*-sylfonyl-1,2,3-triazoles **1** with *S*-phenyl-*N*-cyano sulfoximine **212** under optimal reaction conditions using 2.0 mol % of $Rh_2(OPiv)_4$ in toluene at 80°C for 30 min, to obtain the *N*-imidazolyl sulfoximines **213** in good yields. A possible mechanism for the synthesis of *N*-imidazolyl sulfoximines **213** initially proposed a reversible ring tautomerization of *N*-sulfonyltriazole **1** that produces α-diazo imine **I**. Subsequent irreversible treatment of **I** with Rh catalyst yields α-imino Rh-carbenoid **II** with the removal of nitrogen gas. Nucleophilic attack of *N*-cyano sulfoximine **212** to the electrophilic Rh-carbenoid **II** yields Rh-bound zwitterionic intermediate **III**, which is a nitrilium ion. At this point, the anionic rhodium of **III** pushes an electron pair, which displaces the imine moiety, allowing the nitrogen atom to become nucleophilic



R = Ph, R_1 = Me (92%); *i*Pr (87%); *n*Bu (85%); 4-MeC_6H_4 (87%); 4-OMeC_6H_4 (82%); 4-$CF_3C_6H_4$ (82%)

R_1 =Me, R = *n*-hexane (44%); 3-MeC_6H_4 (91%); 4-MeC_6H_4 (99%); 2-OMeC_6H_4 (61%); 3-OMeC_6H_4 (83%); 4-OMeC_6H_4 (80%); 3-ClC_6H_4 (89%); 4-ClC_6H_4 (89%); 2-BrC_6H_4 (90%), 4-C_6H_4 (87%); 4-$CF_3C_6H_4$ (84%); cyclohexenyl (62%); naphthyl (85%); thienyl (65%)

SCHEME 6.96 Synthesis of *N*-imidazolyl sulfoximines **213**.

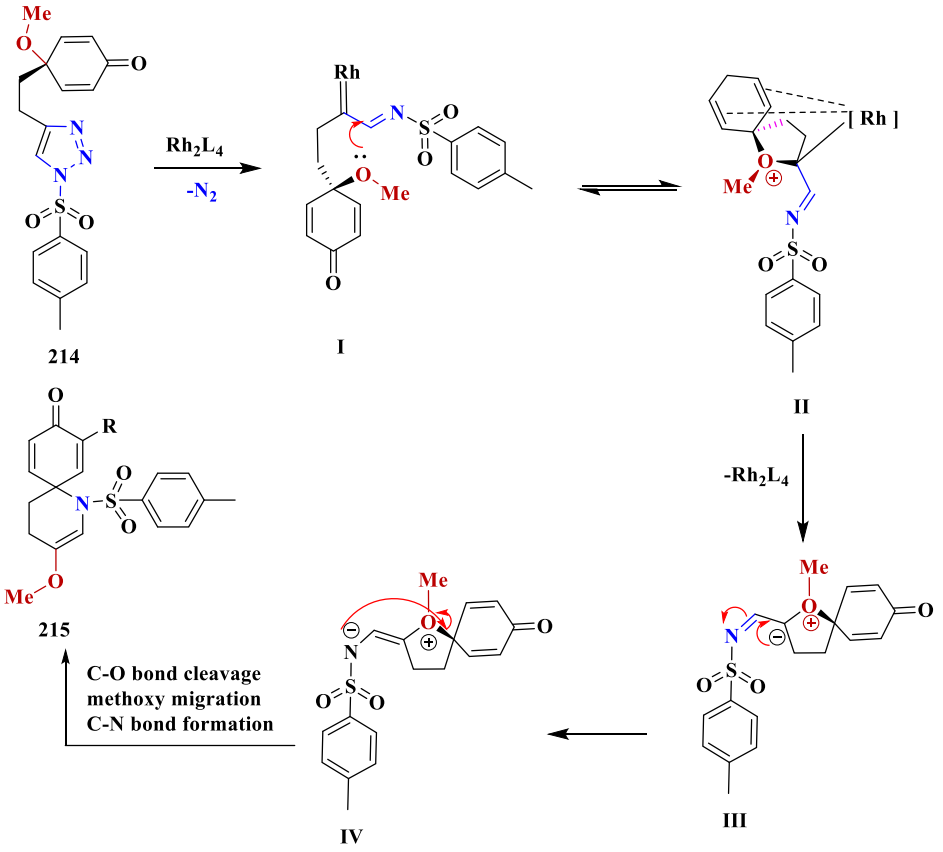
enough to react with nitrilium ion **III** to form *N*-imidazolyl sulfoximines **213** to the regeneration of the Rh catalyst (Scheme 6.96).

4-Methoxycyclohexa-2,5-dienone tethered *N*-sulfonyl-1,2,3-triazoles **214** were treated with 5 mol% $Rh_2(OAc)_4$ in dry DCE at 80°C, to afford 3-methoxy-1-tosyl-1-azaspiro[5.5]undeca-2,7,10-trien-9-one **215** in 70% yield after 2 h (Scheme 6.97) [113]. The predicted formation mechanism of **215** as a result of treatment *N*-sulfonyltriazole **214** by rhodium(II) catalyst underwent a denitrogenation process to produce the corresponding α-imino rhodium carbene **I**, which can additionally be captured by a methoxy group to yield oxoniumylide **II**. Intermediate **III** was formed after the rhodium catalyst was liberated. Intermediate **III** was subjected to intramolecular isomerization to afford intermediate **IV**, which then underwent an intramolecular nucleophilic attack leaving C−O bond, to afford the corresponding 1-azaspiro[5.5]undecane derivative **215**.

Treatment of 1-sulfonyl-1,2,3-triazoles **216** having a sulfinyl ester side chain with a catalytic amount of $Rh_2(OAd)_4$ yields various C, N-disulfonylated unsaturated piperidines **217** with good yields, that should be versatile synthetic intermediates based on their vinyl sulfone and enamide moieties. This reaction most likely proceeds by a new reorganization of the bonds in the same molecule, adding a sulfur atom of the sulfonate ester to the α-(sulfonylimino)carbene moiety formed from sulfonyltriazole, followed by the counter-attack on the sulfonylimino nitrogen to the carbon bearing the oxygen terminus of sulfonate ester. Mechanistically, the new reorganization of the bond between sulfonylotriazole and sulfinate should be of great interest, demonstrating the unique collaboration between modern Rh-catalyzed reactions and traditional organosulfur chemistry (Scheme 6.98) [114].

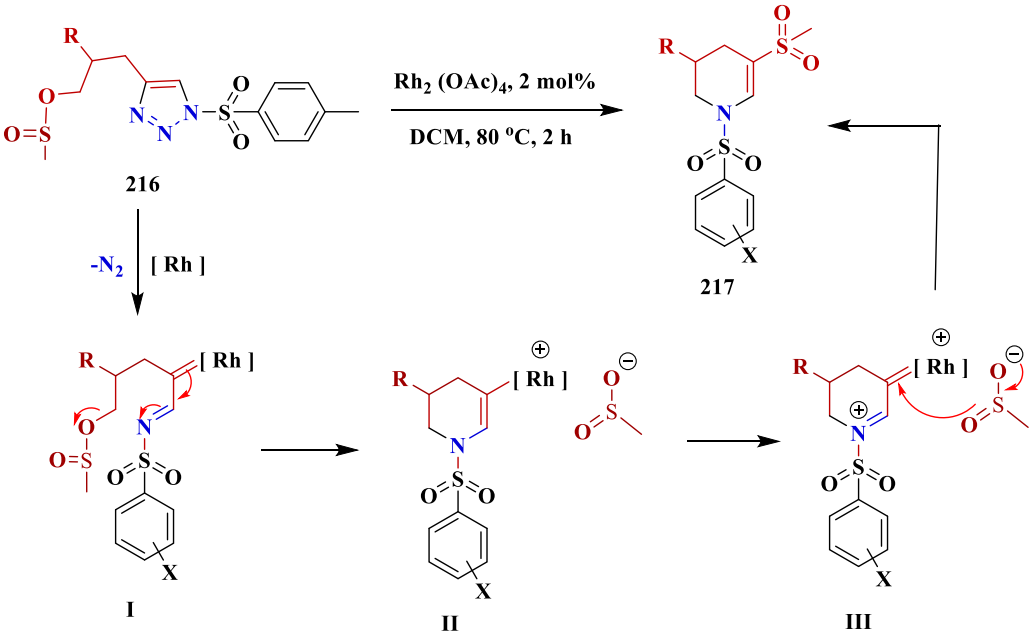
Muthusubramanian et al. [115] described a regioselective α-heteroarylation followed by deoxygenation towards the synthesis of a variety of 2-(4-aryl-1*H*-1,2,3-triazol-1-yl)pyridines **219** from *N*-tosyl-1,2,3-triazoles **1** and simple azine *N*-oxide derivatives **218**. The reaction is metal-free and base free with lesser reaction time, high yields, and broad substrate scope. The proposed mechanism for the formation of product **219** is illustrated as presented in Scheme 6.99.

Anbarasan et al. [116] reported that the efficient rhodium-catalyzed synthesis of substituted tetrahydropyridines **221** and a bicyclic compound, THF fused tetrahydropyridine **222** based on the reaction time gives good to excellent yields from readily available thio-tethered *N*-sulfonyl-1,2,3-triazoles **220**. The formation of **221** and **222** can be explained by previous reports on 1,2-sulfur migration and denitrogenative functionalization of 1,2,3-triazoles **220**, mechanism of tetrahydropyridines synthesis from *N*-sulfonyl-1,2,3-triazoles (Scheme 6.100). First, trapping of α-diazoimines **I**, prepared from 1,2,3-triazole **220**, with a rhodium catalyst yields the reactive rhodium carbenoid **II**. The intramolecular attack on the sulfur atom on the electrophilic carbenoid carbon would lead to the formation of thiiranium intermediate **III**, which upon rearrangement, would furnish 1-azadiene **IV** and active



R_1 = 4-MeC_6H_4, R = Me (79%); Br (75%); Cl (73%); F (72%); Ph (62%); 3-MeC_6H_4 (61%); 4- MeC_6H_4 (67%); 4-$OMeC_6H_4$ (56%); 4-ClC_6H_4 (56%); 4-FC_6H_4 (68%); 4-FC_6H_4 (55%); naphthyl (66%)

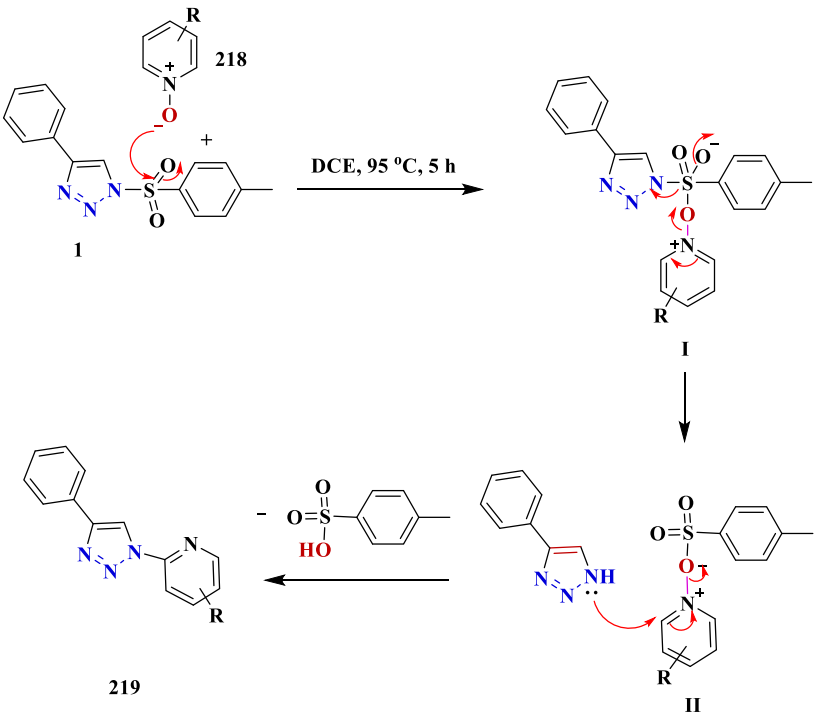
SCHEME 6.97 Synthesis of 3-methoxy-1-tosyl-1-azaspiro[5.5]undeca-2,7,10-trien-9-one **215**.



R = H, X = 4-Me (76%); 4-Et (76%); 4-*i*Pr (73%); 4-OMe (59%); 4-Br (51%); 3-Me (56%)

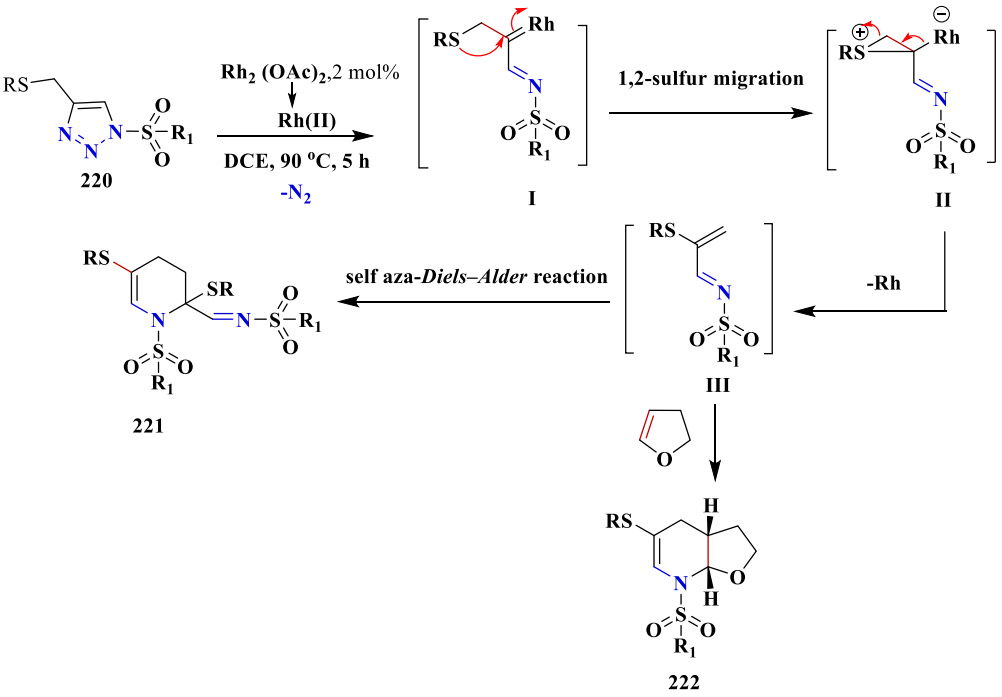
X = Me, R = 4-Me (58%); Et (61%); *n*-Bu (50%); -$CH_2CH_2OC_6H_4$-*t*Bu (76%)

SCHEME 6.98 Synthesis of C, *N*-disulfonylated unsaturated piperidines **217**.



R = H (82%); 2-Me (73%); 3,4-$(Me)_2$ (81%); 4-OMe (78%); 2-Cl (89%); 2-Br (79); 4-Br (75%); 3,5 $(Br)_2$ (69%); 3F-4Cl (38%); 4-Ac (76%); 2-CN (81%)

SCHEME 6.99 Synthesis of 2-(4-aryl-1*H*-1,2,3-triazol-1-yl)pyridines **219**.



221, R_1 = 4-MeC_6H_4 ,R = 4-MeC_6H_4 (87%); 2,4-$(Me)_2C_6H_3$ (89%); 4-$OMeC_6H_4$ (96%); 2-ClC_6H_4 (83%); 2-BrC_6H_4 (77%); 4-BrC_6H_4 (55%); $PhCH_2$ (68%), cyclohexayl (85%); 4-$NO_2C_6H_4$ (44%); 2-FC_6H_4 (82%)

222, R_1 = MeC_6H_4 R = Ph (90%); 4-MeC_6H_4 (84%); 2,4-$(Me)_2C_6H_3$ (61%); 4-$MeOC_6H_4$ (72%); 2-BrC_6H_4 (80%); 4-BrC_6H_4 (78%); 2-F C_6H_4 (76%); benzoxazol-2-yl (91%); cyclohexyl (86%)

SCHEME 6.100 Synthetic route of tetrahydropyridines **221** and tetrahydrofuran fused tetrahydropyridine **222**.

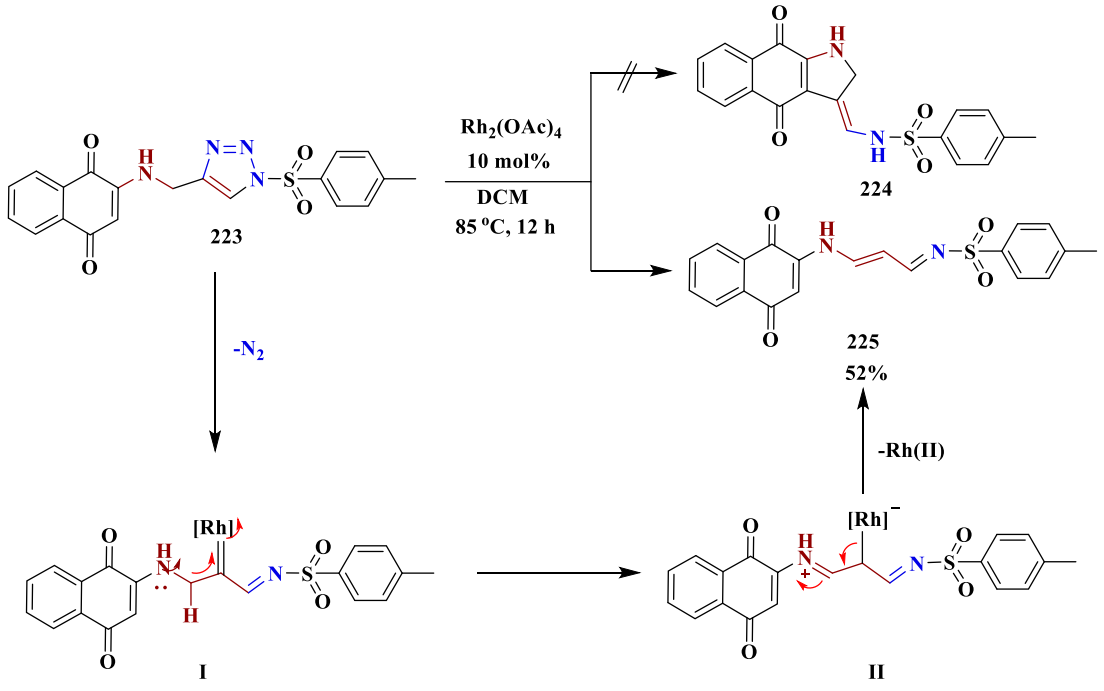
rhodium forms for the next catalytic cycle. Dimerization of the formed 1-azadiene **IV** under the thermal conditions of aza-Diels–Alder provide the expected tetrahydropyridines **221**. On the other hand, the in situ trapping of 1-azadiene **IV** with duhydrofuran produces the corresponding compound **222** (Scheme 6.100).

The reaction of 2-amino-1,4-naphthoquinone-tethered sulfonyltriazole **223** in the presence of 10 mol% $Rh_2(OAc)_4$ catalyst in DCM at 85°C for 12 h afforded aminonaphthoquinone bearing *N*-substituted conjugated tosyl ene-imine **225** in 52% yield, instead of the anticipated dihydropyrrole fused naphthoquinone derivative **224**. The structure of the product was confirmed unambiguously by single-crystal X-ray analysis. The mechanism for the formation of **225** can be reasonably explained by the 1,2-hydride migration to the Rh-center of intermediate imino rhodium(II) carbene complex **I** generate by the extrusion of nitrogen. The electron pushing effect of the lone pair of electrons on the nitrogen atom facilitates the 1,2-hydride migration and generates the zwitterionic intermediate **II**. Elimination of rhodium from intermediate **II** gives the sulfonylimine containing naphthoquinone (Scheme 6.101) [117].

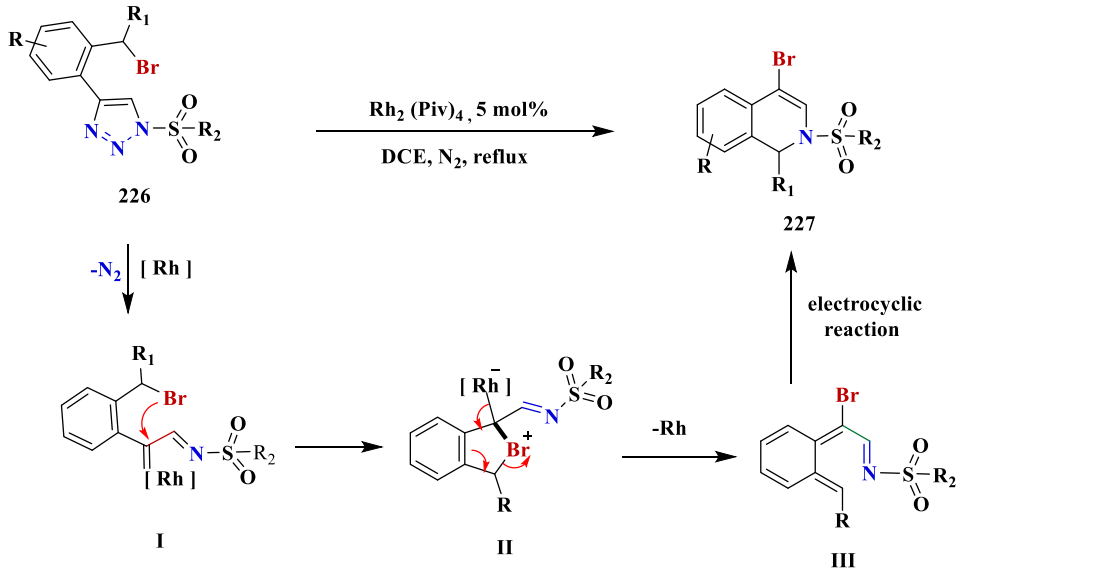
Highly functionalized 4-bromo-1,2-dihydroisoquinolines **227** were synthesized from readily available 4-(2-(bromomethyl)phenyl)-1-sulfonyl-1,2,3-triazoles **226**. A bromonium ylide is proposed as the key intermediate, which can be produced by the intramolecular nucleophilic attack of the benzyl bromide on the α-imino rhodium carbene formed in the presence of the rhodium catalyst. The proposed mechanism for the formation of compounds **227** was illustrated in Scheme 6.102 [118].

Volla et al. [119] demonstrated a convenient and simple, RhII-catalyzed denitrogenative method for the synthesis of biologically interesting 2-amino-benzoxazinones **228** and 5-amino-oxadiazoles **229** from isatoic anhydrides, oxadiazolones and *N*-sylfonyl1,2,3-triazoles **1**. Thus, the mixture of compounds **1** and the isatoic anhydride was heated at 100°C for 1 h in the presence of 2 mL% of $Rh_2(Oct)_4$ in DCE afforded 2-amino-benzoxazinones **228**. The reaction proceeds by introducing O–H onto the α-imino RhII-carbenoid species followed by rearrangement. 5-Amino-oxadiazoles **229** were synthesized from isatoic anhydrides and oxadiazolones in the same manner under the same reaction conditions as shown in Scheme 6.103.

Dehaena et al. [120] described the selective decomposition of bis(1,2,3-triazoles) **230** by rhodium(II)-catalysis. Thus, a mixture of bis(1,2,3-triazole) **230** and complex $Rh_2(esp)_2$ was heated at 80°C in DCE for 4 h to form the dihydroindole, and then MnO_2 was added, which was further stirred at 80°C for 24 h to afford fused indole derivative **231** in good yield. The formation of compound **231** is proceeded by an intramolecular transannulation reaction *via* an azavinylcarbene intermediate, resulting in to form polycyclicdihydroindoles containing a fused triazole ring (Scheme 6.104).



SCHEME 6.101 Synthesis of aminonaphthoquinone bearing *N*-substituted conjugated tosyl ene-imine **225**.



R = R$_1$ = H, R$_2$ = Me (80%); *i*Pr (70%); 4-MeC$_6$H$_4$ (64%); 4-OMeC$_6$H$_4$ (73%); 4-BrC$_6$H$_4$ (50%)

R$_2$ = Me, R$_1$ = H, R = 1-Me (83%); 1-Et (81%); 6-F (52%); 7-F (65%); 7-Cl (56%); 7-F$_3$C (77%); 1-allyl (60%)

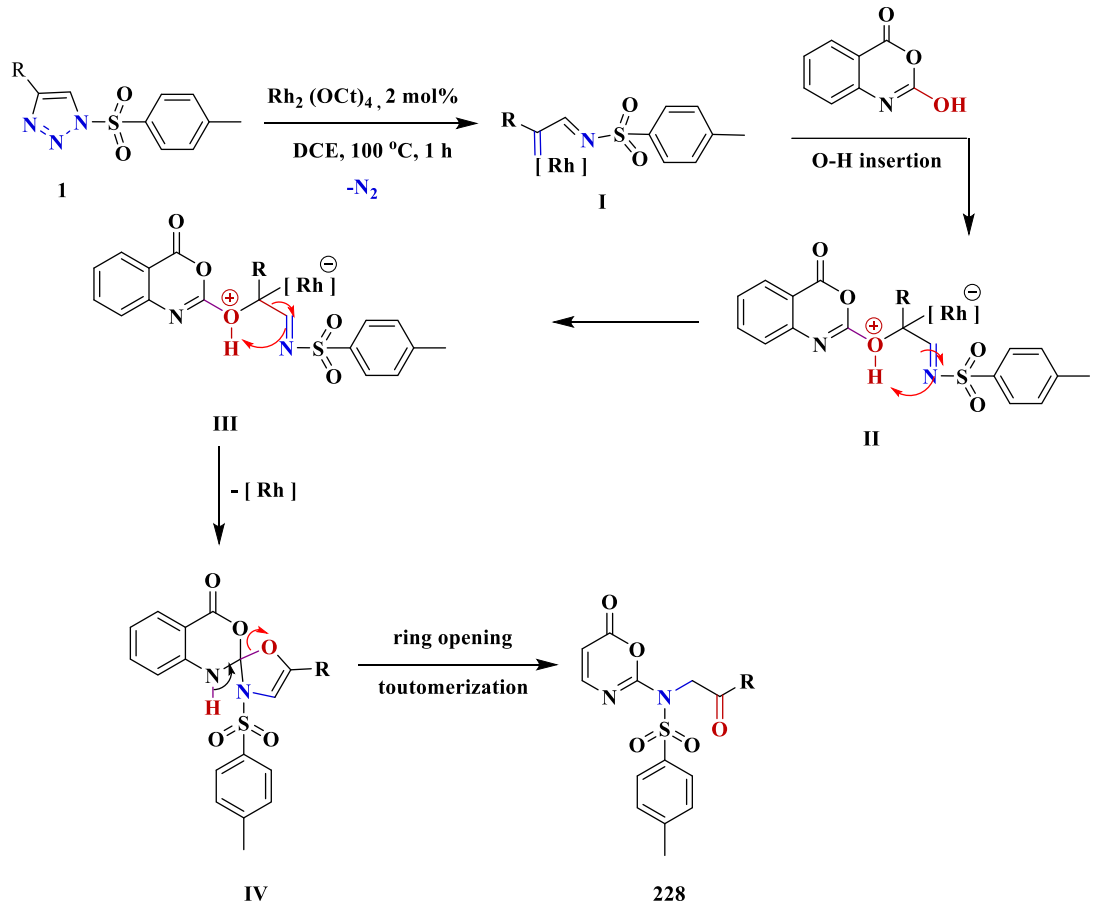
SCHEME 6.102 Synthetic route of Highly functionalized 4-bromo-1,2-dihydroisoquinolines **227**.

Moreover, Dehaena et al. [121] reported the selective decomposition of bis(1,2,3-triazoles) by rhodium(II)-catalysis. Thus, the bis(1,2,3-triazoles) **232** undergo an intramolecular transannulation reaction *via* the azavinylcarbene intermediate, leading to the formation of polycyclicdihydroindoles **233** containing a fused triazole ring. The mechanism is through the intramolecular nucleophilic attack of phenyl on the electrophilic carbene center in the *6-exo* mode with the formation zwitter ionic species. In the last step, anionic rhodium **III** is eliminated, leading to a final cyclization step leading to the end product **233** and regeneration of Rh(II)-catalytic species (Scheme 6.105).

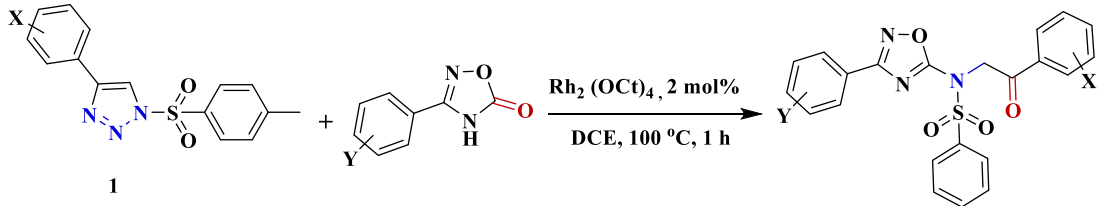
Lee et al. [122] developed a cyclization cascade promoting detosylation of TBAF for the synthesis of [1,2,3] triazolo [5,1-*a*] isoquinoline. Reaction of **234** and one equivalent of TBAF in toluene at 100°C gave cyclized [1,2,3] triazolo[5,1-*a*]isoquinoline **236**. Most of the products were obtained in excellent yields under mild conditions. Therefore, a possible mechanism has been proposed whereby the tosyl group **234** was first removed in the presence of TBAF and H_2O. If the triazole anion **I** were quenched with water at this stage, **235** would be obtained. Meanwhile, **235** may be deprotonated in the presence of TBAF. The cyclization product **236** could be obtained smoothly if the triazole anion **I** attacked the acetylene group and then protonated (Scheme 6.106).

Davis et al. [123] achieved an efficient synthesis of tetrahydrocarboline **238** and polycyclic spiroindolines **239**. The conversion takes place by rhodium(II)-catalyzed intramolecular annulations of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles **237**. The reaction could be tuned toward either the formal [3 + 2] cycloaddition or the C−H functionalization reaction depending on the electronic and structural features of the substrates, leading to the production of a variety of structurally related heterocyclic compounds (Scheme 6.107).

Lacour et al. [124] established the synthesis of polycyclic indoline-benzodiazepines obtained in one step by the reaction of *Tröger* bases ([3.3.1] bicyclic tertiary amines) (TB) with *N*-sulfonyl-1,2,3-triazoles. Thus treatment of enantiopure (*R,R*) or (*S,S*)-TB with *N*-sulfonyl-1,2,3-triazoles **1** in 2 mol% of $Rh_2(Piv)_4$ at 80°C in $CHCl_3$ gives products **240** only in the racemic form. The reaction proceeds after the formation of α-imino carbene, the process includes the cascade of [1,2]-*Stevens* rearrangement, *Friedel-Crafts* reaction, *Grob* fragmentation, and aminal formation reactions. It is highly diastereoselective (*d.r.* >49:1, four stereocenters including two bridgehead *N*-atoms). However and in contrast with other reported carbene additions to these moieties, full racemization occurs when enantiopure *Tröger* bases are used as substrates. To pinpoint the cause of this unexpected behavior, a key elementary step in the mechanism was assessed and tested. Interestingly, this is not only the initial ring-opening, but also the last reversible *Mannich* reaction of the imino-substituted *ethano Tröger* base intermediate that is responsible for the loss of enantiospecificity (Scheme 6.108).

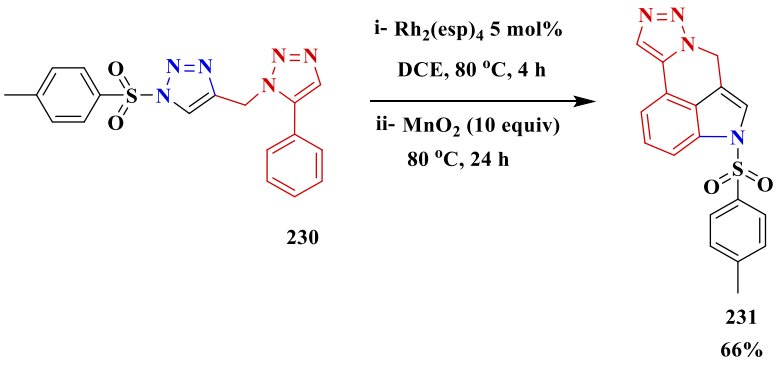


R = *n*-Bu (91%); Ph (89%); 3-MeC$_6$H$_4$ (83%); 4-MeC$_6$H$_4$ (87%); 2,4,6-(Me)$_3$C$_6$H$_2$ (73%);
2-OMe C$_6$H$_4$ (78%); 4-OMeC$_6$H$_4$ (91%); n-pentylC$_6$H$_4$ (75%)



Y = H, X = H (92%); 3-Me (90%); *n*-pentyl (83%); 4-F (87%); OMe-naphthyl (83%);
Y = Me, X = H (86%); 4-OMe (89%);
Y = 4-Cl, X = H (84%); 4-*t*Bu (81%)

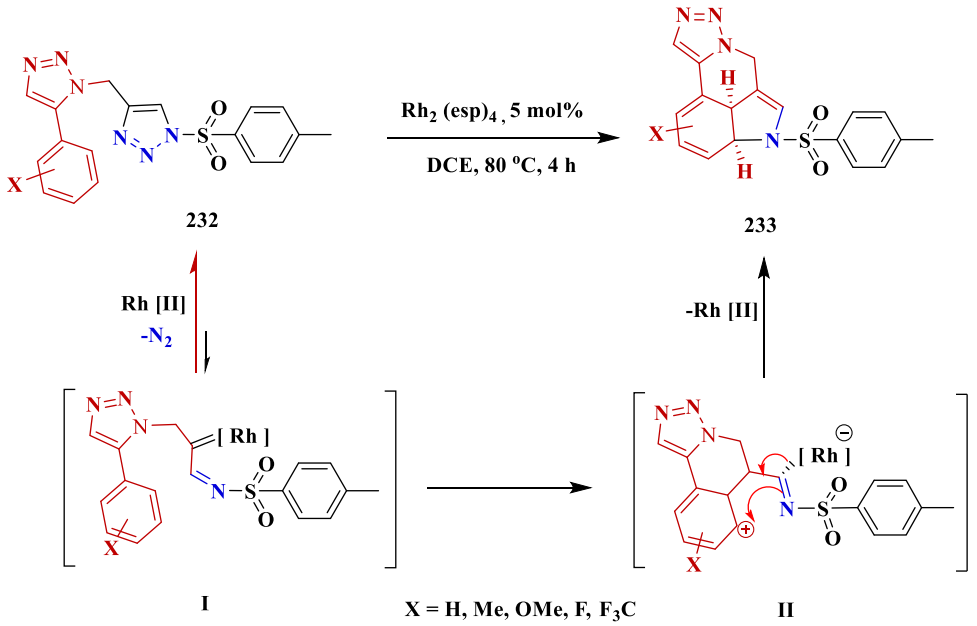
SCHEME 6.103 RhII-catalyzed denitrogenative method for formation of 2-amino-benzoxazinones **228** and 5-amino-oxadiazoles **229**.



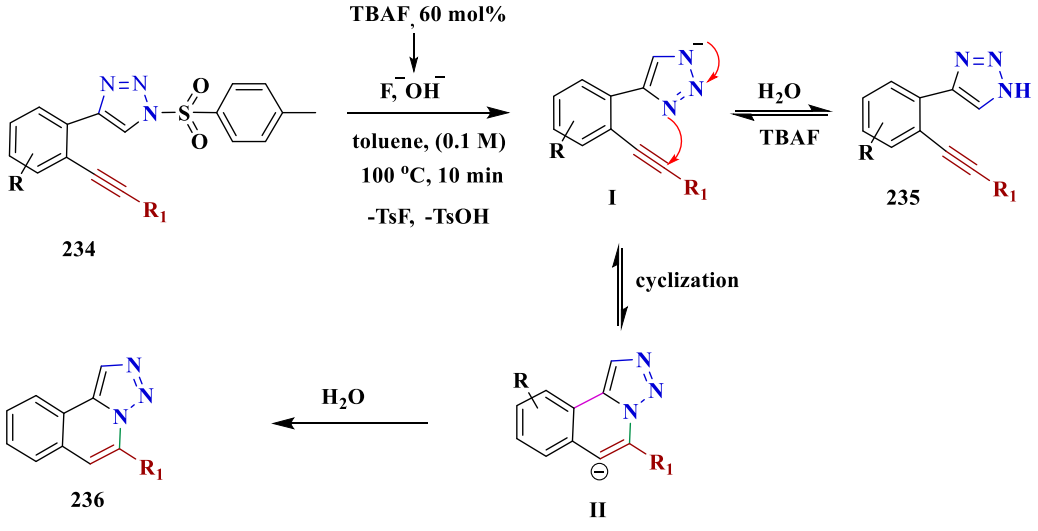
SCHEME 6.104 Synthesis of polycyclicdihydroindoles containing a fused triazole ring **231**.

Lacuor et al. [125] constructed 2-imino-tetrahydrofurans, 13- and 15-membered azamacrocycles. Thus, the reaction of *N*-sulfonyl triazoles **1** with oxetanes **241** under dirhodium catalysis (Rh_2(*S*-TCPTTL)$_4$, 1−2 mol%) at high temperature using regular concentration conditions (0.1 M in CH_2Cl_2), afforded 5-membered 2-iminotetrahydrofurans, **242**, as the major product (Scheme 6.109).

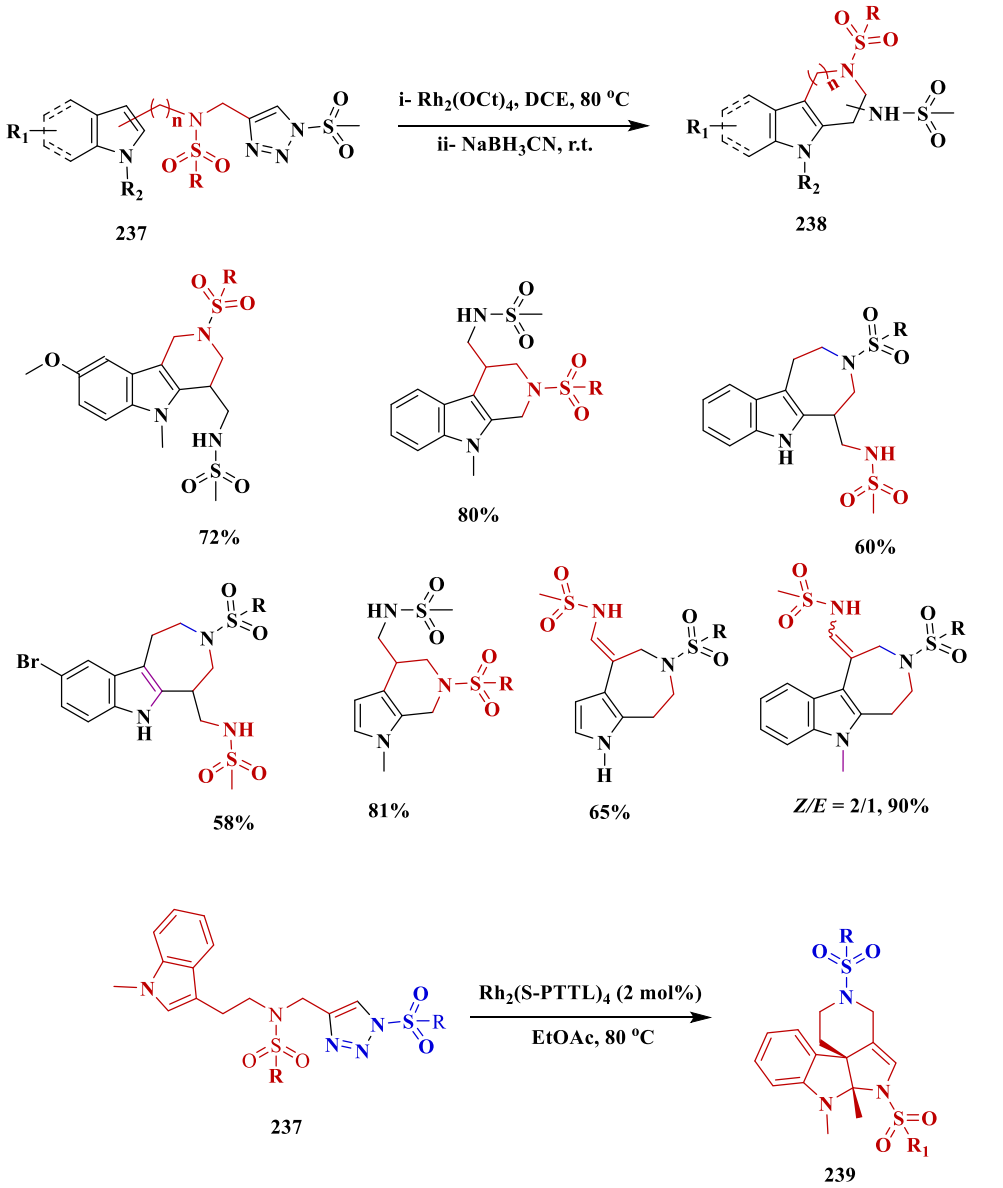
In addition, unsaturated aza-macrocycles (15-membered ring heterocycles) **243** are produced using oxetanes as a solvent with *N*-sulfonyl triazoles **1** with a high concentration (1.0 M). These two sets of conditions favor the condensations of one and three oxetane fragments, respectively, and therefore the formation of compounds **242** and **243** occurs by [1 + 4] and [3 + 4 + 4 + 4] processes respectively, and selectively by formal [1 + 4], [5 + 4 + 4] and [3 + 4 + 4 + 4] condensations of α-imino carbenes and oxetanes under the influence of Rh(II)-catalysis or thermal activation (Scheme 6.110) [125].



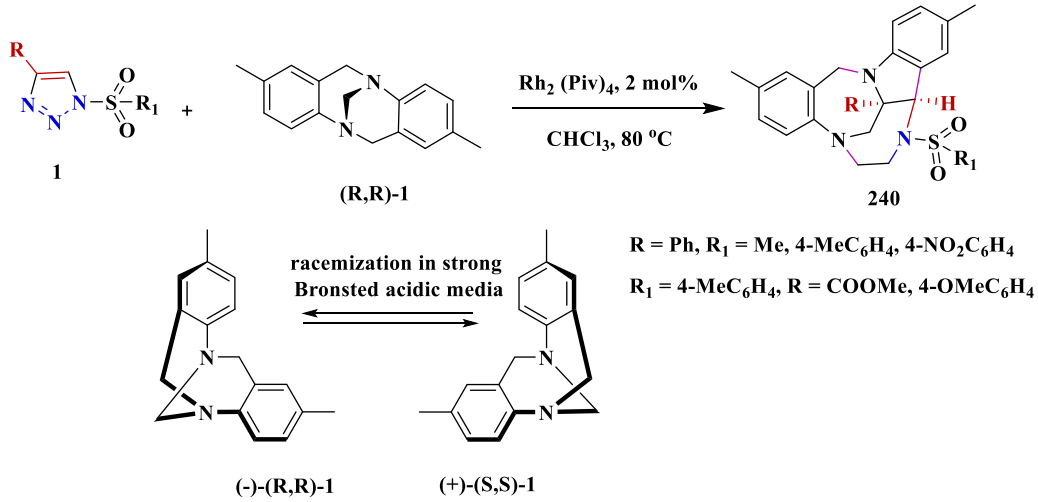
SCHEME 6.105 Synthesis of polycyclicdihydroindoles **233**.



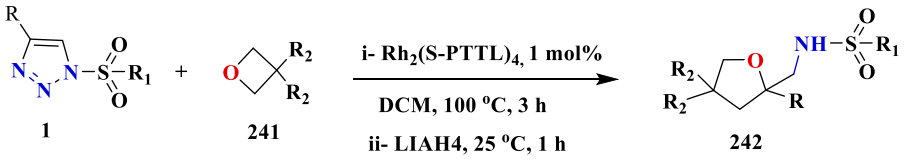
SCHEME 6.106 Synthesis of [1,2,3]-triazolo[5,1-a]-isoquinolines **236**.



SCHEME 6.107 An efficient synthesis of tetrahydrocarboline **238** and polycyclic spiroindolines **239**.



SCHEME 6.108 Synthesis of polycyclic indoline-benzodiazepines are produced in one step by the reaction of *Tröger* bases ([3.3.1] bicyclic tertiary amines) **240**.



1 241 242

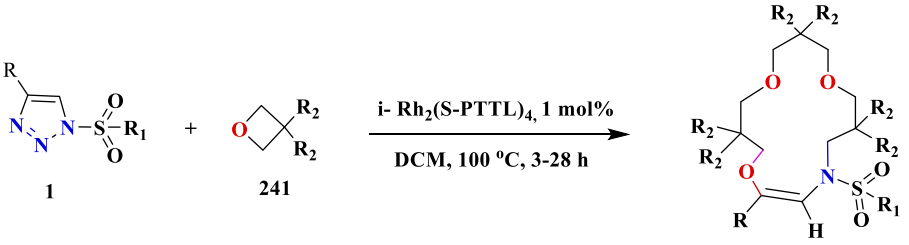
If $R_1 = R_2 = Me$,
R = Ph (80%); 2-BrC_6H_4 (58%); 4-$OMeC_6H_4$ (63%); $CF_3C_6H_4$ (68%); thienyl (75%)

If R_1 = Ph, R_2 = Me,
R = 4-$NO_2C_6H_4$ (56%); 4-MeC_6H_4 (60%)

If R = OEt, R_1 = 4-MeC_6H_4, R_2 = Me (50%)

If R = Ph, R_1 = 4-MeC_6H_4,
R_2 =  (44%);CH_2Cl_2 (75%)

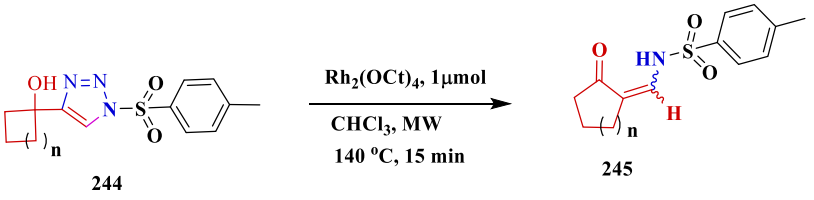
SCHEME 6.109 Synthesis of 5-membered 2-iminotetrahydrofurans **242**.



1 241 243

R = COOMe, Ph, 4-$OMeC_6H_4$, 4-$F_3CC_6H_4$
R_1 = Me, 4-OMe-C_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$
R_2 = H, Me

SCHEME 6.110 Synthesis of unsaturated aza-macrocycles (15-membered ring heterocycles) **243**.



244 245

n = 1 (80%); n = 2 (90%); n = 3 (95%); n = 4 (74%); n = 5 (78%)

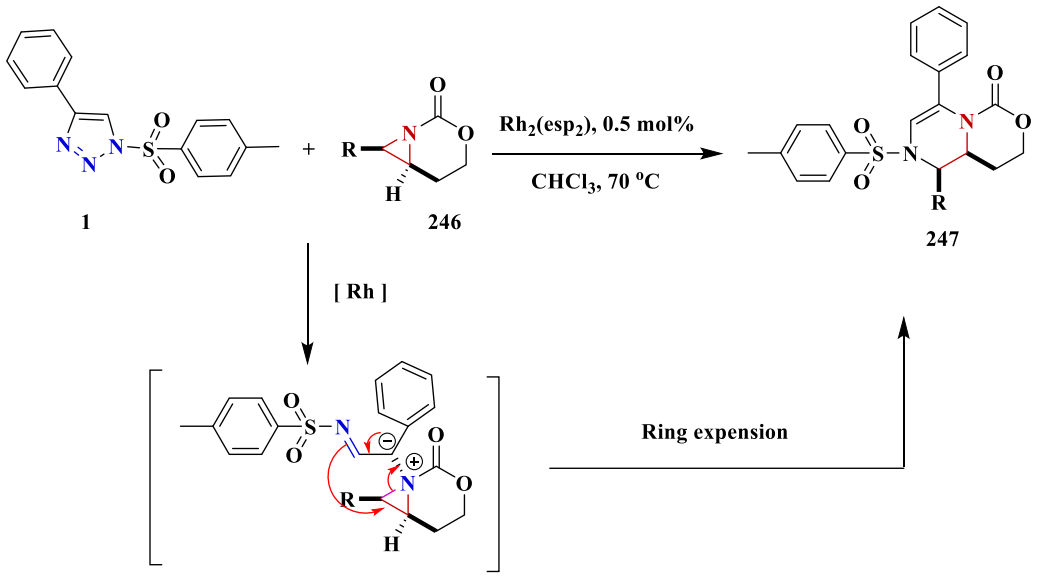
SCHEME 6.111 Synthesis of enaminones **245**.

Enaminones **245** were obtained by rhodium(II)-catalyzed denitrogenative of the rearrangement of the cyclic 1-triazolylalkanols **244**, with ring expansion employed $Rh_2(OCt)_4$ (1 μmol) in chloroform under microwave irradiation at 140°C. Intramolecular migration of 1,2-hydride (or alkyl) occurs with the intermediate α-iminorodium (II) carbenoid resulting in denitrogenation of the 1,2,3-triazol-4-yl moiety. The resulting enaminone is considered as a precursor for various heterocycles with the replacement of the *N*-sulfonyl group (Scheme 6.111) [126].

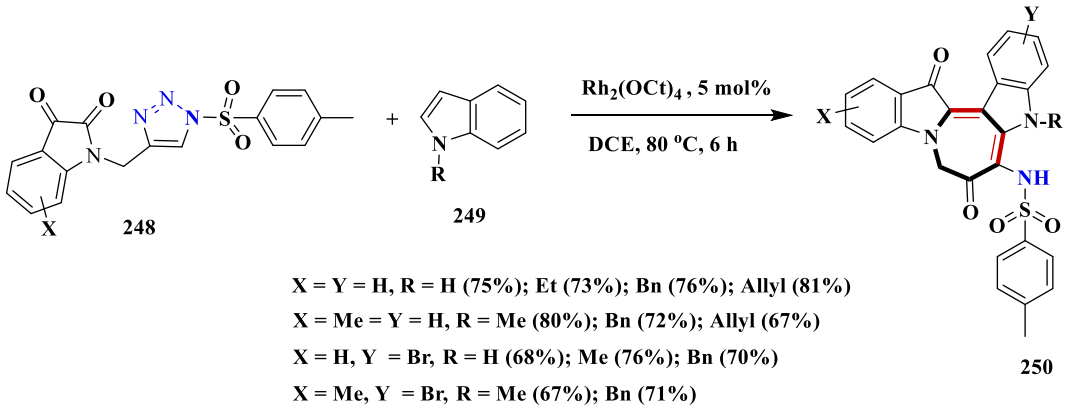
Rh-catalyzed ring expansions of aziridines **246** have been reported to afford dehydropiperazines **247** with excellent diastereocontrol by reacting *N*-sulfonyl-1,2,3-triazoles **1** with aziridines **246**. Productive ring expansion occurs due to pseudo-1,4-sigmatropic rearrangement of aziridinium ylide species (Scheme 6.112) [127].

6.3.9 Ring expansion

Dawande et al. [128] disclosed an efficient and convenient synthesis protocol for a new class of azepino fused diindoles. Thus, the reaction of the substituted isatin triazoles **248** with different indoles **249** in the presence of 5 mol% $[Rh_2(Oct)_4]$ as a catalyst in DCE yields azepino fused diindoles **250**. The reaction proceeds by denitrogenative aza-vinyl rhodium carbene formation to give carbonyl ylide,



SCHEME 6.112 Synthesis of dehydropiperazines **247**.



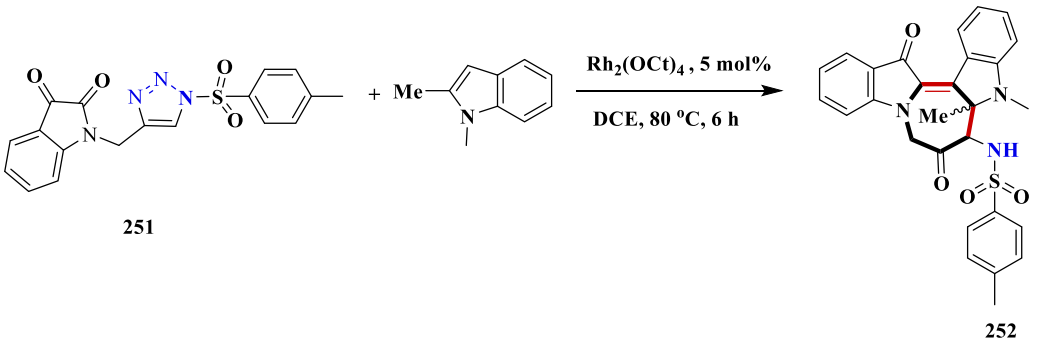
SCHEME 6.113 Synthesis of azepino fused diindoles **250**.

which with indole leads to 1,3-dipolar cycloaddition followed by sequential semipinacol rearrangement/ring expansion/oxidation to produce azepino fused diindoles with a yield of up to 81% (Scheme 6.113).

Additionally, the reaction of triazole **251** with 1,2-dimethyl indole under the same reaction conditions results in 1,3-dipolar cycloaddition/semipinacol rearrangement to produce octahydroazepino diindole **252** with 88% yield as diastereoisomers as shown in Scheme 6.114 [128].

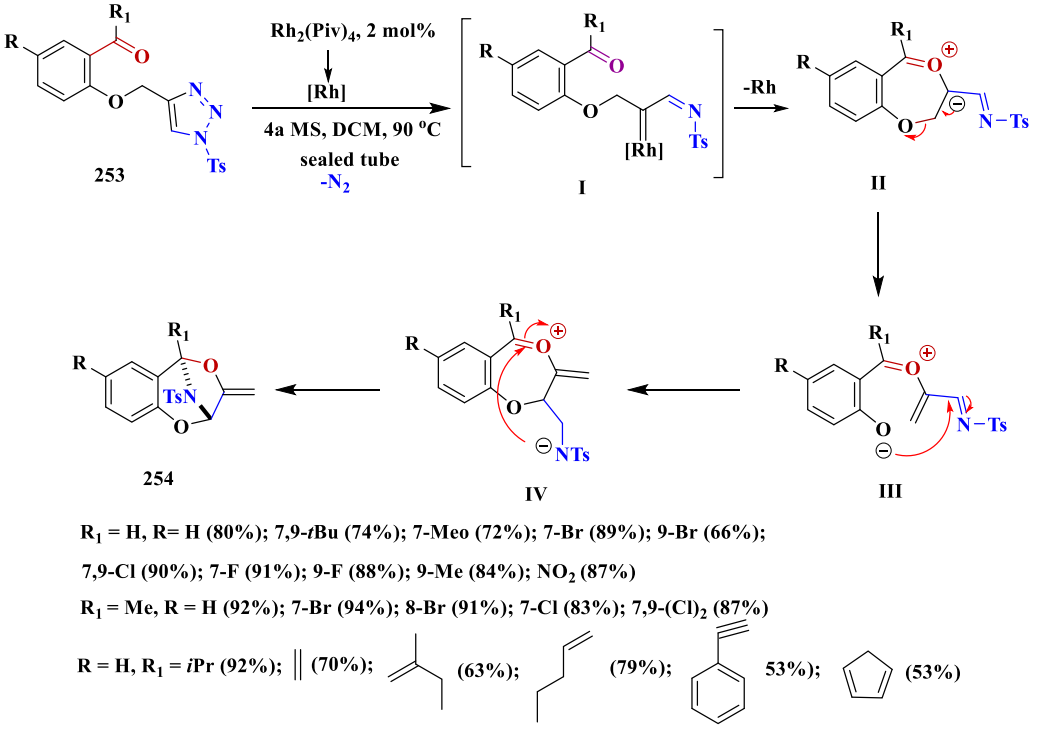
Shi et al. [129] described a novel tandem intramolecular cycloisomerizations of aldehydes or ketones with 1-sulfonyl-1,2,3-triazoles providing a facile protocol to access a series of functionalized aza-bridged benzodioxepine heterocycles **254** using $Rh_2(piv)_4$ as catalyzed in DCM at 90°C in a sealed tube. A plausible mechanism for this reaction is outlined in Scheme 6.115, initially, after treatment of 1-sulfonyl-1,2,3-triazoles **253** with the Rh(II) catalyst, an intermediate of azavinyl carbine **I** am formed, which undergoes intramolecular nucleophilic attack with the carbonyl group to form intermediate **II**. The C−O bond is cleaved to give intermediate **III**, giving another zwitterionic intermediate **IV** through 1,2-addition, followed by recycling to the corresponding product **254**.

Yu et al. [130] reported that 1-sulfonyl-1,2,3-triazoles **1** were converted into α-imino carbenes in the presence of catalytic amounts of rhodium(II) salts. The carbenes underwent a tandem reaction with salicylaldehyde to produce a series of functionalized 2,5-epoxybenzo[*f*][1,4]oxazepines **255** with high yields. The proposed mechanism for the formation of compound **255** is shown in Scheme 6.116.



251 252

SCHEME 6.114 Synthesis of octahydroazepino diindole **252**.



253 I II III IV 254

R_1 = H, R= H (80%); 7,9-*t*Bu (74%); 7-Meo (72%); 7-Br (89%); 9-Br (66%);
7,9-Cl (90%); 7-F (91%); 9-F (88%); 9-Me (84%); NO_2 (87%)
R_1 = Me, R = H (92%); 7-Br (94%); 8-Br (91%); 7-Cl (83%); 7,9-$(Cl)_2$ (87%)
R = H, R_1 = *i*Pr (92%); (70%); (63%); (79%); 53%); (53%)

SCHEME 6.115 Rh(II)-catalyzed tandem intramolecular cycloisomerizations to form functionalized aza-bridged benzodioxepine heterocycles **254**.

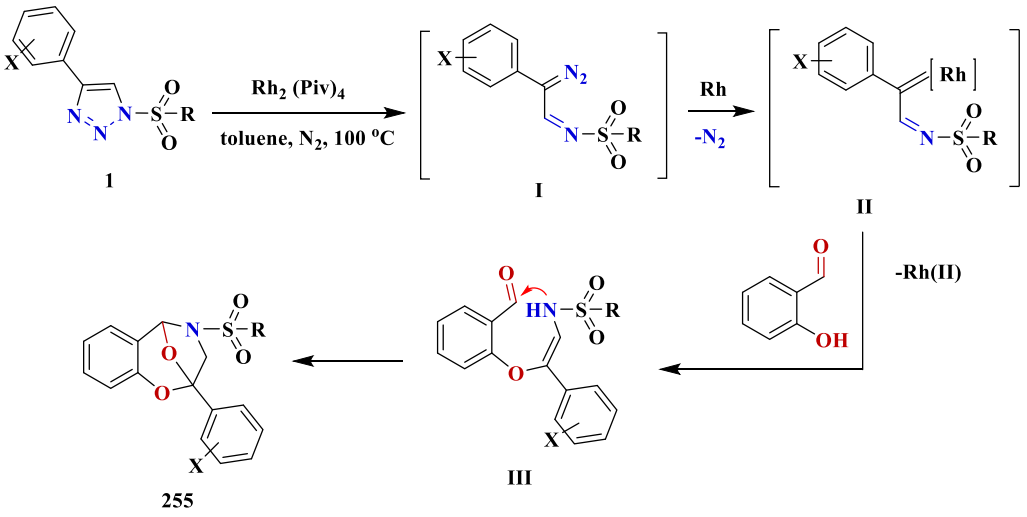
Beller et al. [131] discussed the rhodium(II)-catalyzed denitrogenative coupling of *N*-alkylsulfonyl 1,2,3-triazoles **1** with 1,3,5-trioxane gave nine-membered-ringed trioxazonines **256** in moderate to good yield. 1,3,5-Trioxane, acting as an oxygen nucleophile, reacts with the α-aza-vinylcarbene intermediate, to form an ylide, which is probably the key step in the reaction (Scheme 6.117).

Lee et al. [132] reported a synergistic palladium(0)/rhodium(II) dual catalytic cycloaddition of *N*-sulfonyl-1,2,3-triazoles **1** with vinylpropylene carbonates **257** to afford monocyclic nine-membered *N,O*-heterocycles **258**. The catalytically formed 1,6-dipole-equivalent zwitter ionic π-allyl palladium(II) complex and the 1,3-diple-equivalent α-imino rhodium carbenoid intermediate interact with each in a formal [6 + 3] dipolar cycloaddition to furnish nine-membered Alder oxaznines, that may be transformed into cis-fused[4.3.0]bicyclic compounds **259** by a transannular Alder-ene rearrangement. A tandem sequence of cycloaddition/alderene rearrangement is also possible (Scheme 6.118).

6.4 Chemistry of 1,2,4-triazoles

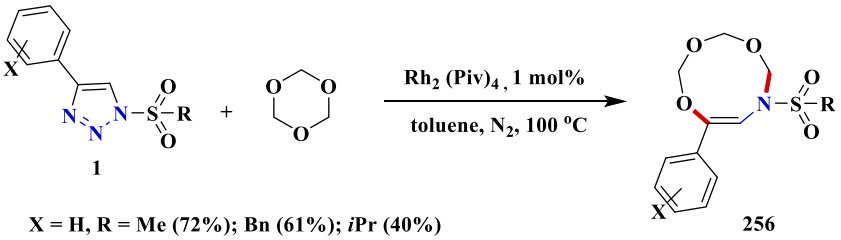
6.4.1 Synthesis of *N*-sulfonylated 1,2,4-triazoles

The substituted 1,2,4-triazoles **261** were obtained by reacting phenylnitrile with hydrazides **260** in *n*-butanol in



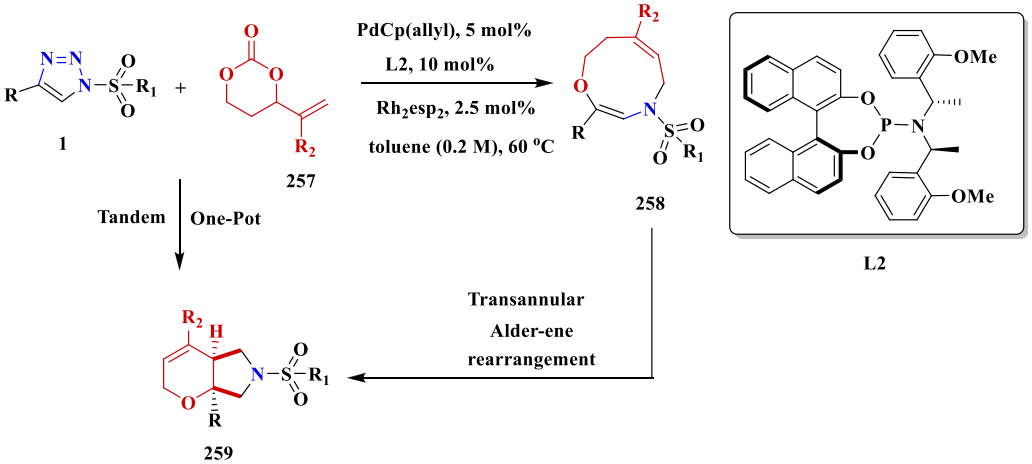
X = H, R = Me (86%); 4-OMeC$_6$H$_4$ (80%); 4-BrC$_6$H$_4$ (70%); TMSCH$_2$CH$_2$ (53%)
R = 4-MeC$_6$H$_4$, X = 4-Me (71%); 4-Et (72%); *t*Bu (70%); 2-MeO (50%), 3-MeO (73%); 4-MeO (70%);
4-Cl (60%); 3-F (60%); 4-F (66%); 4-Br (70%); 3-CF$_3$ (57%); 4-CF$_3$ (83%); 4-CN (62%); 4-MeOCO (52%)

SCHEME 6.116 Synthesis of a series of functionalized 2,5-epoxybenzo[*f*][1,4]oxazepines **255**.



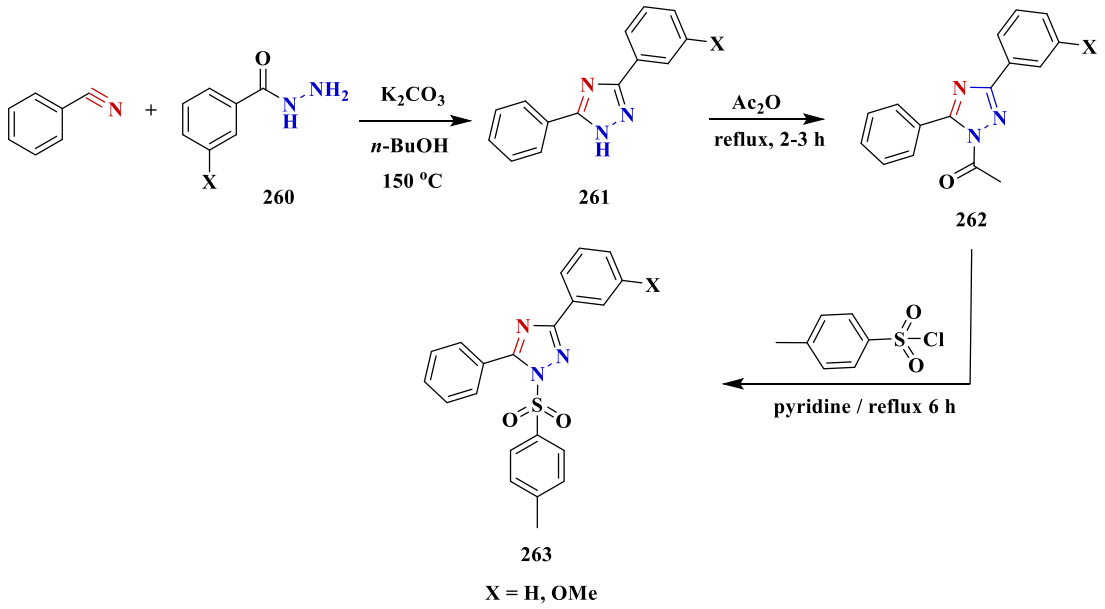
X = H, R = Me (72%); Bn (61%); *i*Pr (40%)
R = Me, X = H (72%); 3-Me (74%); 4-Me (72%); 3,5-(Me)$_2$ (48%); *t*Bu (64%);
3-OMe (60%); 4-MeO (70%); 3-F (80%); 4-Cl (65%); 3,4(Cl) (68%)

SCHEME 6.117 Synthesis of nine-membered-ringed trioxazonines **256**.

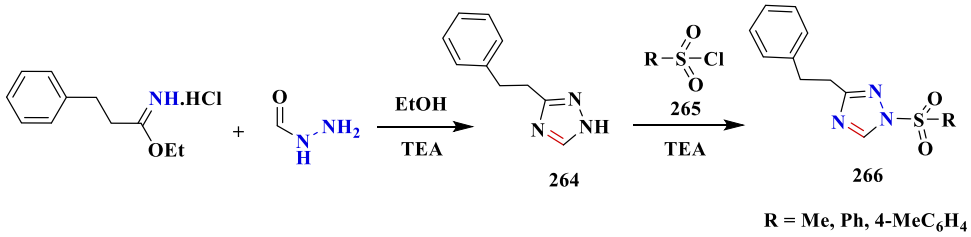


258, R$_1$ = 4-MeC$_6$H$_4$, R = Ph, R$_2$ = Ph (80%); 3-MeC$_6$H$_4$ (59%); 4-MeC$_6$H$_4$ (53%);
3-MeOC$_6$H$_4$ (59%); 4-ClC$_6$H$_4$ (77%); 3-BrC$_6$H$_4$ (59%); 4-BrC$_6$H$_4$ (81%);
4-FC$_6$H$_4$ (81%); PhC$_6$H$_4$ (77%); CF$_{3C6}$H$_4$ (60%); cyclohexayl (60%)
R$_1$ = 4-MeC6H4, R$_2$ = Ph, R = 3-MeC$_6$H$_4$ (81%); 4-MeC$_6$H$_4$ (73%); 4-BrC$_6$H$_4$ (57%); 4-ClC$_6$H$_4$ (76%);
2-FC$_6$H$_4$ (54%); 3-FC$_6$H$_4$ (78%); 4-FC$_6$H$_4$ (76%); 2,4-(F)$_2$C$_6$H$_3$ (36%); 4-CF$_3$C$_6$H$_4$ (27%);
naphthyl (62%); piperonyl (56%); thienyl (20%)

SCHEME 6.118 Synthesis of monocyclic nine-membered *N,O*-heterocycles **258** and cis-fused[4.3.0]bicyclic compounds **259**.



SCHEME 6.119 Synthesis of 1,2,4-triazoles **263**.



SCHEME 6.120 Synthesis of *N*-sulfonyl-3-phenetyl-1,2,4-tiazoles **266**.

the presence of anhydrous potassium carbonate at a temperature of 150°C. The synthesized triazoles **261** are refluxed in acetic anhydride to give the acetyl derivatives **262**. Sulphonyl derivatives **263** were prepared by the reaction of **262**with *p*-toluene sulfonyl chloride in the presence of pyridine (Scheme 6.119). The synthesized compounds showed potent liver X receptor (LXR) modulators and exhibit good isoform selectivity in a cell-based cotransfection assay where they usually behave as agonists. Also, these compounds display "modulator" pharmacology since they function as inverse agonists in terms of fatty acid synthase (FASN) expression and are inactive on sterol regulatory element-binding proteins (SREBP-1c) expression in contrast to the activity observed in cotransfection assays [133].

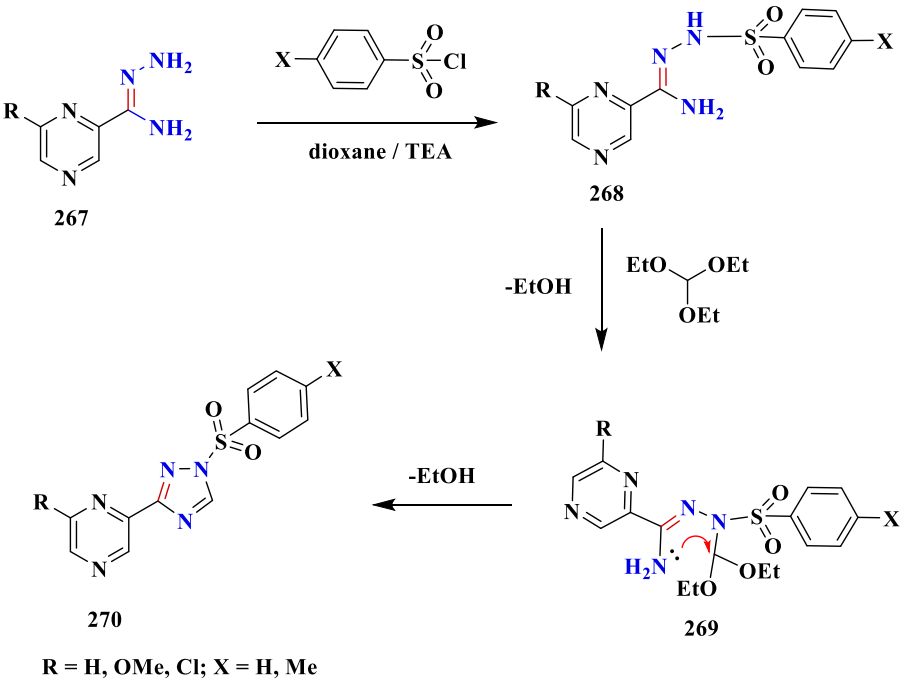
The 3-phenethyl-1*H*-1,2,4-triazole **264** was obtained by reacting ethyl 3-phenylpropionimideate with formylhydrazine in the presence of trimethylamine. The triazole **264** was sulfonylated with sulfonyl chlorides **265** to afford the *N*-sulfonyl-1,2,4-tiazoles **266** (Scheme 6.120) [134].

The 3,5-dipyrazine derivatives of *N*-sulfonyl-1,2,4-triazoles **270** were obtained by reacting pyrazinamidrazones **267** with sulfonyl chlorides to afford the corresponding sulfonyl amidrazones **268**, which were cyclized with triethylorthoformate (Scheme 6.121) [135].

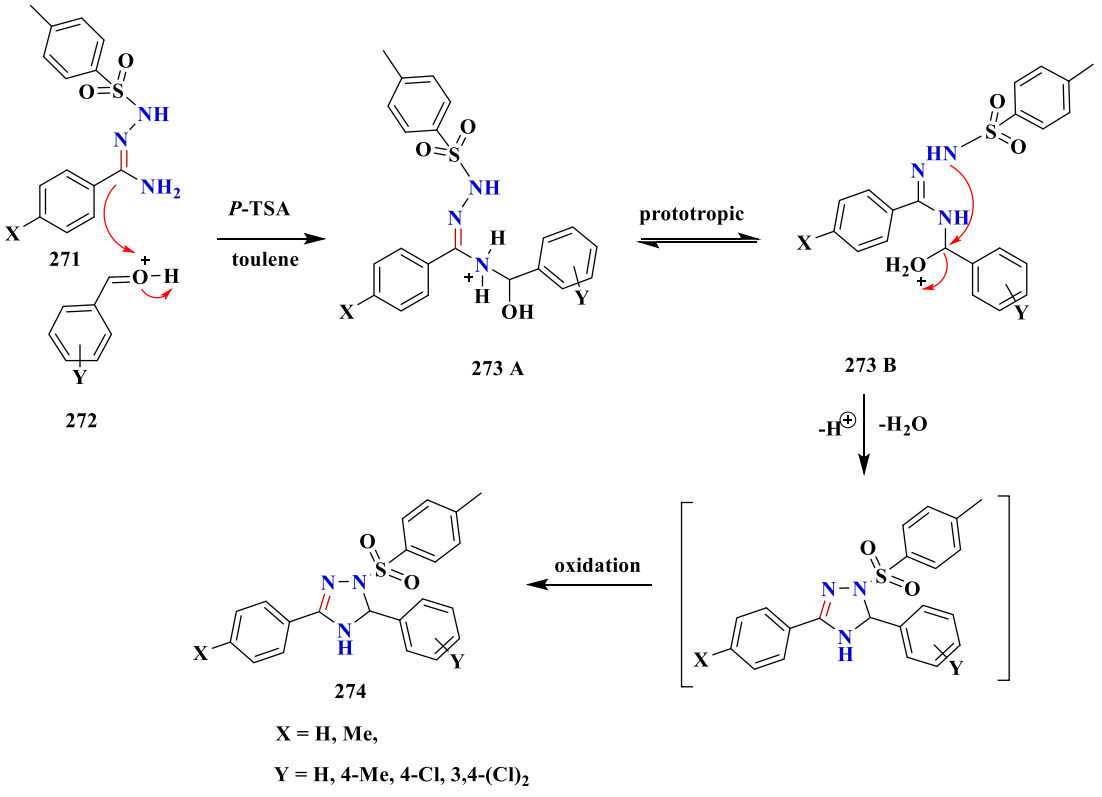
The new *N*-tosyl-1,2,4-triazoles **274**, were synthesized by Allouche et al. [136] through the reaction of *N*-tosyl amidrazones **271** with an aldehyde **272** under reflux in toluene with azeotropic removal of water. Satisfactory results are obtained with the use of a catalytic amount of *p*-toluenesulfonic acid (Scheme 6.122).

The reaction of *N*-tosylhdrazones **275** with potassium cyanate in acetonitrile under stirring at room temperature for 5−18 h afforded the 1,2,4-triazolones **276** as shown in Scheme 6.123 [137].

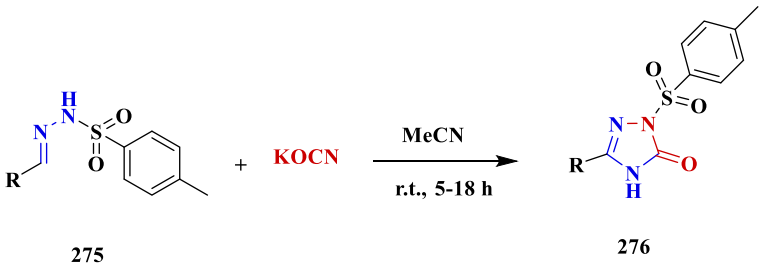
The reaction of tosyl-amidrazone **277** with ethyl chloroformate (ClCOOEt) in dry chloroform and pyridine produces the tosylated triazolone **278** with a yield 70%, which is deprotected according to the Zemplen protocol to give 2-tosyl-trihydroxy-6-(hydroxymethyl)tetrahydro-



SCHEME 6.121 Synthesis of 3,5-dipyrazine derivatives of *N*-sulfonyl-1,2,4-triazoles **270**.



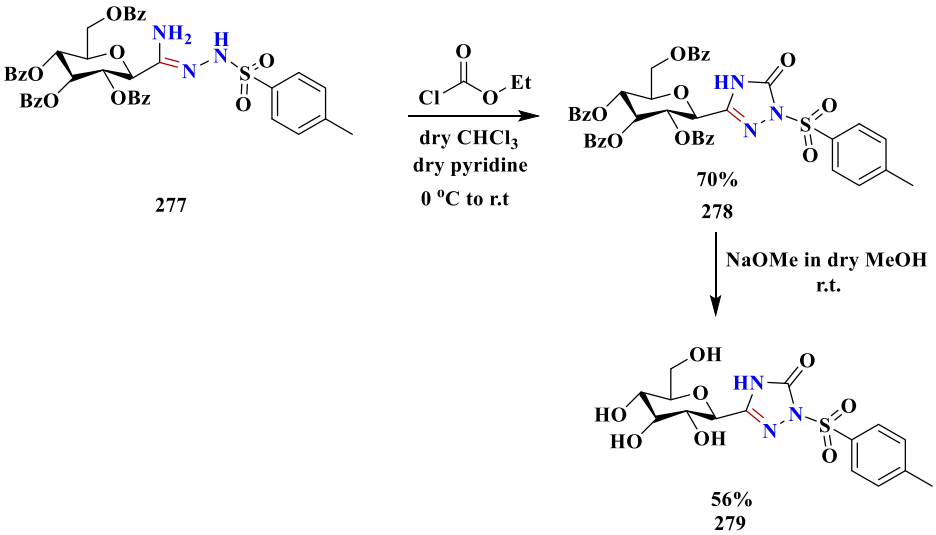
SCHEME 6.122 Possible pathways for the synthesis of substituted *N*-sulfonyl-1,2,4-triazoles **274**.



275 276

R = Ph (69%); 2-Me (54%); 4-OMe (61%); 3-Cl (45%); 2-Br (53%); 4-Cl (43%); PhCH=CH (65%); 2-thienyl (65%); iPr (84%);

SCHEME 6.123 Synthesis of *N*-sulfonyl-1,2,4-triazolones **276**.



277 278 279

SCHEME 6.124 Synthesis of 2-tosyl-5(3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one **279**.

2*H*-pyran-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one **279** (Scheme 6.124) [138].

Reaction of 2-[(5-amino-1*H*-1,2,4-triazol-3-yl)thio]-6-isopropyl-4,4-dimethyl-3,4-dihydronaph-thalen-1(2*H*)-one **280** with substituted sulfonyl chlorides **281** has been reported to give the new 2-[(5-amino-1-(arylsulfonyl)-1*H*-1,2,4-triazol-3-yl)thio]-6-isopropyl-4,4-dimethyl-3,4-dihydrona-phthalen-1(2*H*)-ones **282**. The synthesized compounds were screened for cytotoxic activity against a panel of five human cancer cell lines using the MTT assay. Some compounds exhibited better anticancer activity against the tested cancer cell lines compared to 5-FU positive control (Scheme 6.125) [139].

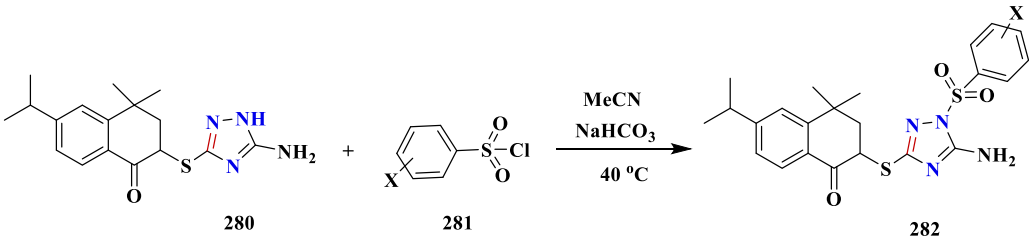
N-Sulfonyl-1,2,4-triazoles **283** were obtained by reacting *N*-fluorobenzenesulfonimide as the sulfonyl source with 1*H*-1,2,4-triazole **1** in the presence of sodium bicarbonate in acetonitrile at 70°C for 12 h (Scheme 6.126) [140].

Diazodisation of 3-amino-1,2,4-triazole **284** with sodium nitrite is reported to afford 3-nitro-1,2,4-triazole **285** with a yield of 68%, which is sulfonylated with mesitylenesulfonyl chloride to give 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole **286** in a yield of 48% (Scheme 6.127) [141].

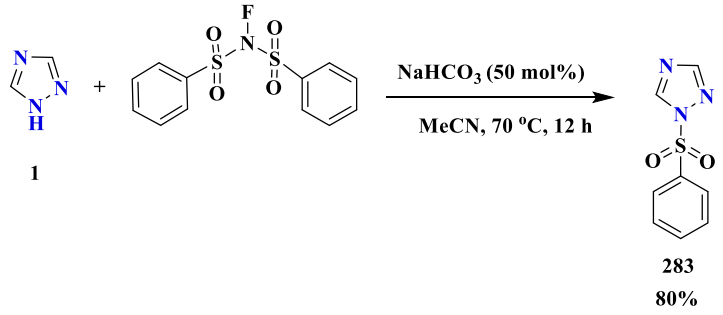
2^1-*O*-*p*-Tolylsulfonylcyclomaltoheptaose **288** was obtained in 42% yield from the reaction of 1-(*p*-tolylsulfonyl)-(1*H*)-1,2,4-triazole **1** with NaH-deprotonated cyclomaltoheptaose **287** in DMF, which converted into the corresponding mono-2^1,3^1 -manno-epoxide **289** (Scheme 6.128) [142].

6.5 Biological activity of some *N*-sulfonyltriazoles

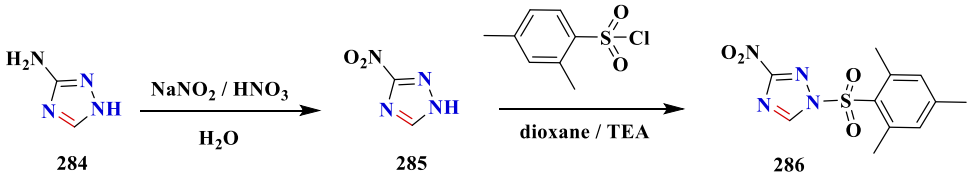
Some new 1,4-disubstituted-sulfonyl-1,2,3-triazoles **290** have been evaluated for in vitro antibacterial activity against a panel of Gram-positive *Bacillus sphericus*, *Staphylococcus epidermidis*, and Gram-negative *Klebsiella pneumonia*, *Escherichia coli* species. Several of these compounds were found to have growth inhibitory activity comparable to commercial standards penicillin G and streptomycin (Fig. 6.2) [30].



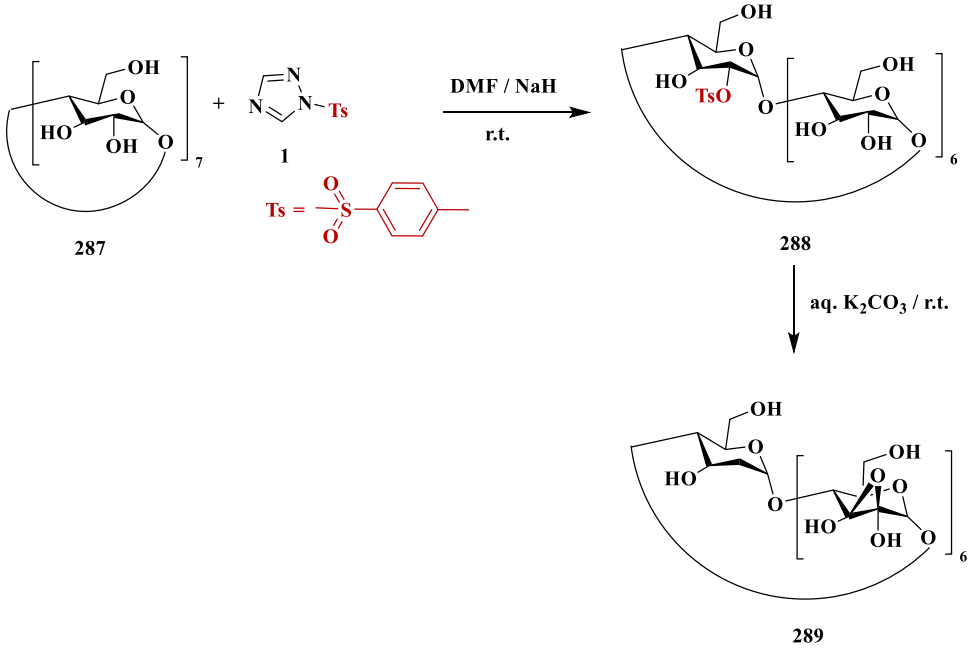
SCHEME 6.125 Synthesis of 5-amino-1-(arylsulfonyl)-1*H*-1,2,4-triazoles **282**.



SCHEME 6.126 Preparation of *N*-sulfonyl-1,2,4-triazole **283**.



SCHEME 6.127 Synthesis of 1-(Mesitylenesulfonyl)-3-nitro-1,2,4-triazole **286**.



SCHEME 6.128 Synthesis of 2^1-*O*-*p*-tolylsulfonylcyclomaltoheptaose **288** and mono-2^1, 3^1 -manno-epoxide **289**.

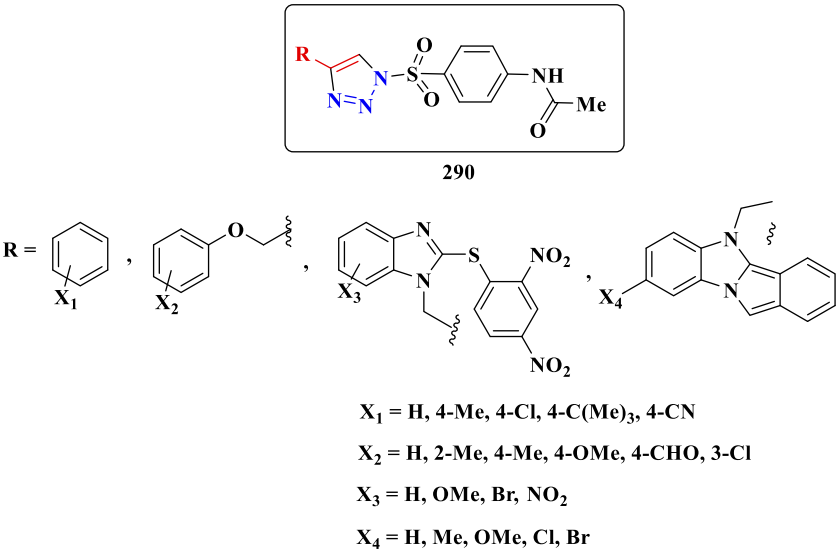


FIGURE 6.2 Antibacterial activity of 1,4-disubstituted-sulfonyl-1,2,3-triazoles **290**.

The reaction of tetrakis(azidosulfonyl)calixarene **291** with *N*-cyclohexylcyanoacetamide in the presence of a catalytic amount of sodium ethoxide, afforded tetrakis(5-amino-1,2,3-triazol-1ylsulfonyl)calixarene **292**, which boils with excess TEA undergoes *Dimroth rearrangement* to form tetrakis[(1*H*-1,2,3-triazol-5-yl)-aminosulfonyl] calixarenes **293**. The synthesized compounds were tested by membrane transport to investigate their chelating properties. The study showed that when was transported across a liquid-impregnated membrane, the initial sodium sulfate flow for **292** was $1.37 \cdot 10{-}6$; for **293**, $6.95 \cdot 10{-}5$; for 5-tosylamino-1,2,3-triazole-4-(*N*-cyclohexyl)-carboxamide, $7.50 \cdot 10{-}10$ mol/s/m^2. The cooperative heteroditopic effect compared to compound **X**, which can only chelate cations, was 1.9 and 95, respectively, for compounds **292** and **293**. Thus, we showed that calixarene **292** (containing a triazole ring with an unsubstituted amino group at the 5-position of the heterocycle) is weak chelates anions, while calixarene **293** (containing an isomeric triazole ring with a sulfamoyl group) exhibits the properties of ditope receptors (Scheme 6.129) [143].

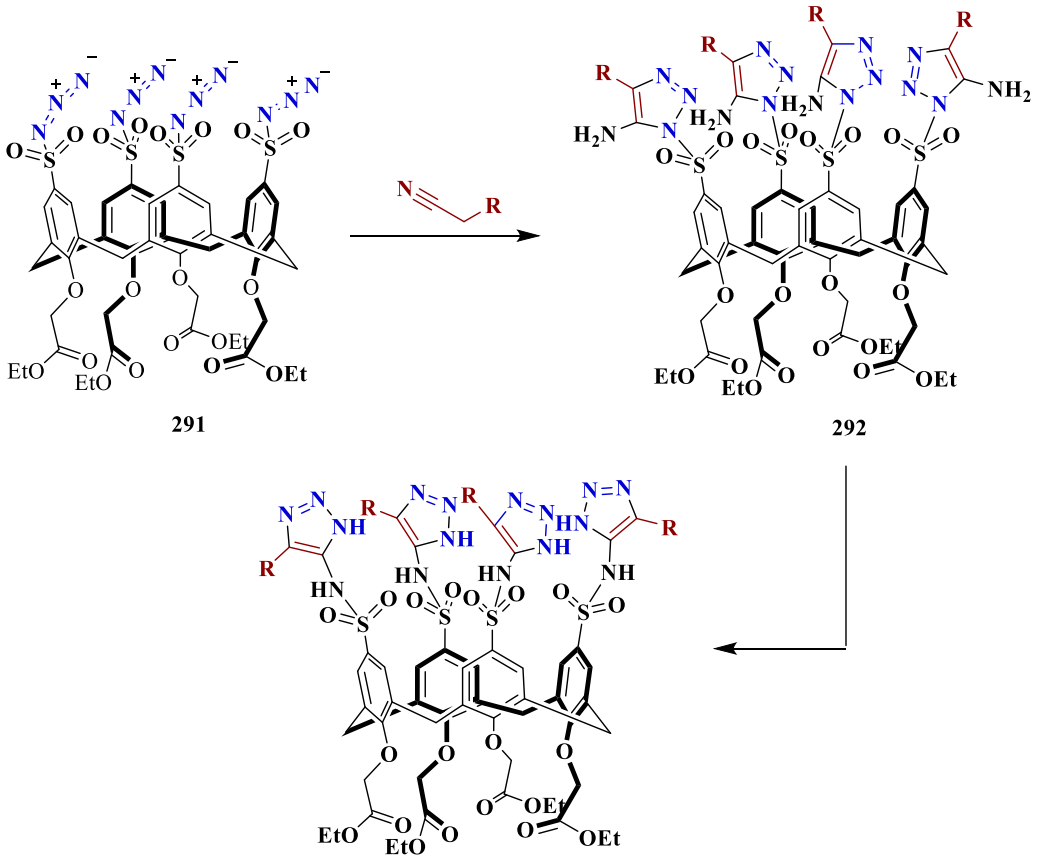
6.6 Chemistry of *N*-sulfonyl-1,2,3,4-tetrazoles

6.6.1 Synthesis of *N*-sulfonyl-1,2,3,4-tetrazoles

A series of compounds bearing a tetrazole ring motif conjugated with a SO_2NH function were synthesized initially from the reaction of 1,3-benzodioxole-5-carbaldehyde with hydroxylamine hydrochloride to form benzo[*d*][1,3] dioxole-5-carbaldehyde oxime **294**, which converted to 1,3-benzodioxole-5-carbonitrile **295** by acetylation. The nitrile group of 1,3-benzodioxole-5-carbonitrile **295** has been cyclized to 5-(1,3-benzodioxol-5-yl)-1*H*-tetrazole **296**. 5-(benzo[*d*][1,3]dioxol-5-yl)-1-(arylsulfonyl)-1*H*-tetrazole **298** was obtained by sulfonylation of compounds **296** with different arylsulfonyl chlorides **297** in the presence of TEA using dry DCM as solvent. The synthesized *N*-sulfonyl-1,2,3,4-tetrazoles were investigated for their antiamoebic activity. The cytotoxicity of the compounds was tested on the human hepatocellular carcinoma cell line (HepG2). The antiamoebic activity of the tested compounds was found to be dependent on the position and substituent. The in vitro cytotoxicity results showed that all the tested compounds were noncytotoxic up to a concentration of 25 mM (Scheme 6.130) [144].

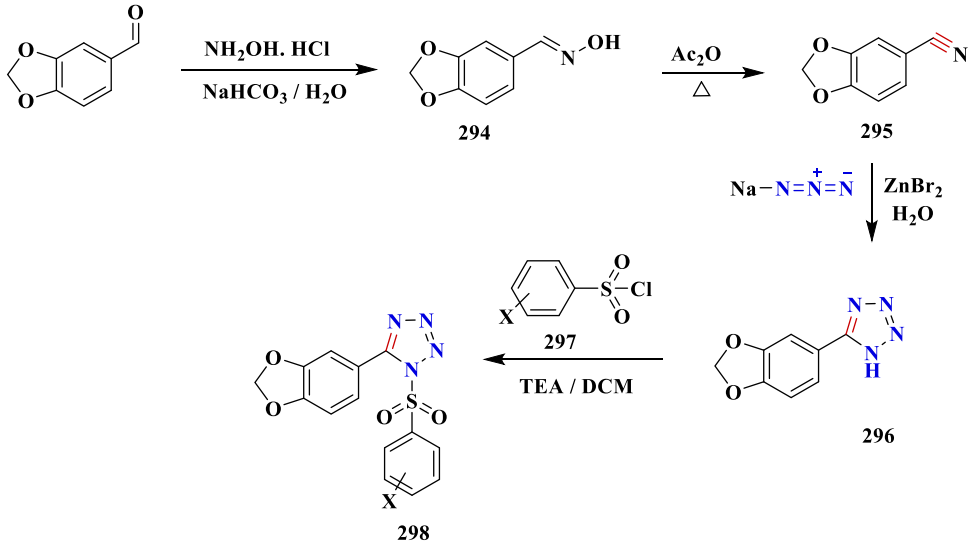
Arshada et al. [145] designed a new series of sulfonynated analogs of bis-tetrazole. The readily synthesized compounds were tested for antimicrobial activity and cytotoxicity. Tests showed that all compounds exhibit significant antimicrobial activity with a low toxicity effect. A four steps synthetic approach to the sulfonynated analogs of bis-tetrazole **300**. Initially, the reaction of terphthaldehyde with hydroxylamine hydrochloride in water gave (*Z,Z*)-benzene-1,4-diylbis(*N*-hydroxymethanimine) **299**. Its subsequent boiling with acetic anhydride led to benzene-1,4-dicarbonitrile **300**, cyclization of which with sodium azide and zinc bromide led to the formation of 5,5′-benzene-1,4-diylbis(1*H*-tetrazole) **301**. Sulfonylation of tetrazoles **301** with different substituted sulfonyl chlorides **302** gave the bis-*N*-sulfonyl-1,2,3,4-tetrazoles **303** (Scheme 6.131).

Sekha et al. [146] described a new class of highly potent anti-tuberculosis substituted sulfonamide tetrazoles. The substituted sulfonamide tetrazoles were prepared by treating epoxide **304** with 4-hydroxy-3-methoxybenzonitrile in the presence K_2CO_3 and



291 **292** **293**

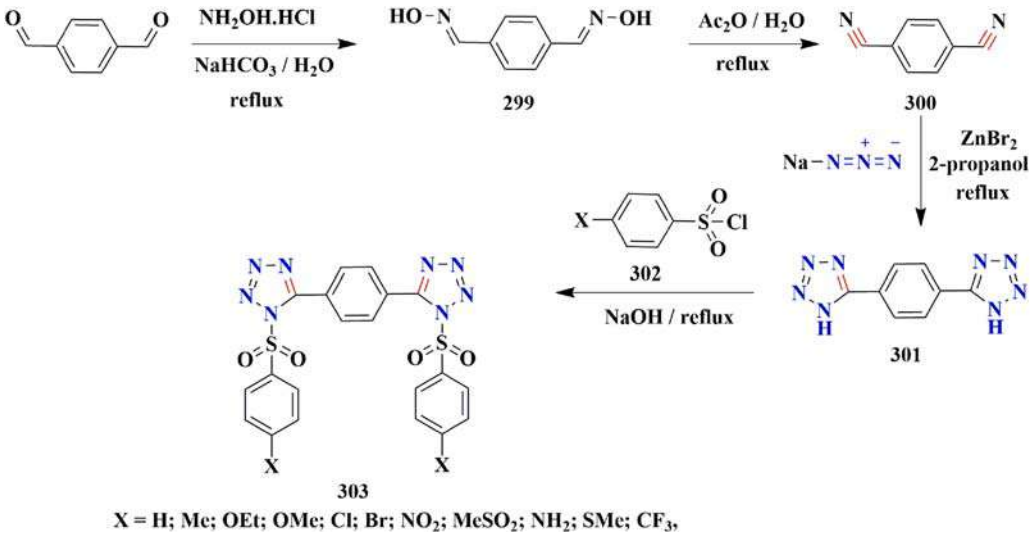
SCHEME 6.129 Chelating properties of tetrakis(5-amino-1,2,3-triazol-1ylsulfonyl)calixarene **292** and tetrakis[(1*H*-1,2,3-triazol-5-yl)-aminosulfonyl] calixarenes **293**.



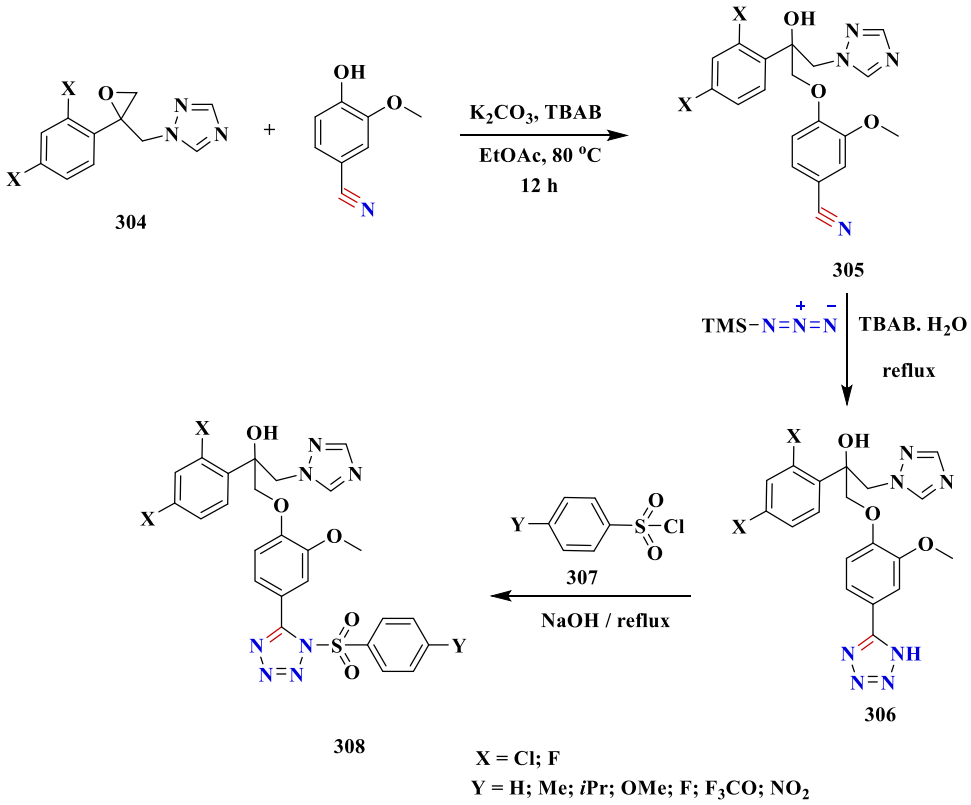
294 **295** **296** **298**

X = H, 4-Me, 4-Cl, 4-NO_2, 2,4-$(Cl)_2$, 4-*i*Pr

SCHEME 6.130 Synthesis of 5-(benzo[*d*][1,3]dioxol-5-yl)-1-(arylsulfonyl)-1*H*-tetrazoles **298**.



SCHEME 6.131 Synthesis of bis-*N*-Sulfonyl-1,2,3,4-tetrazoles **303**.

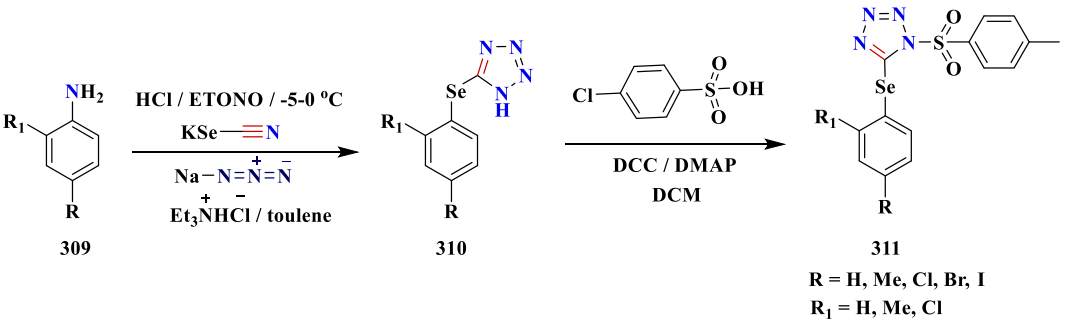


SCHEME 6.132 Synthesis of substituted *N*-sulfonyl-1,2,3, 4-tetrazoles **308**.

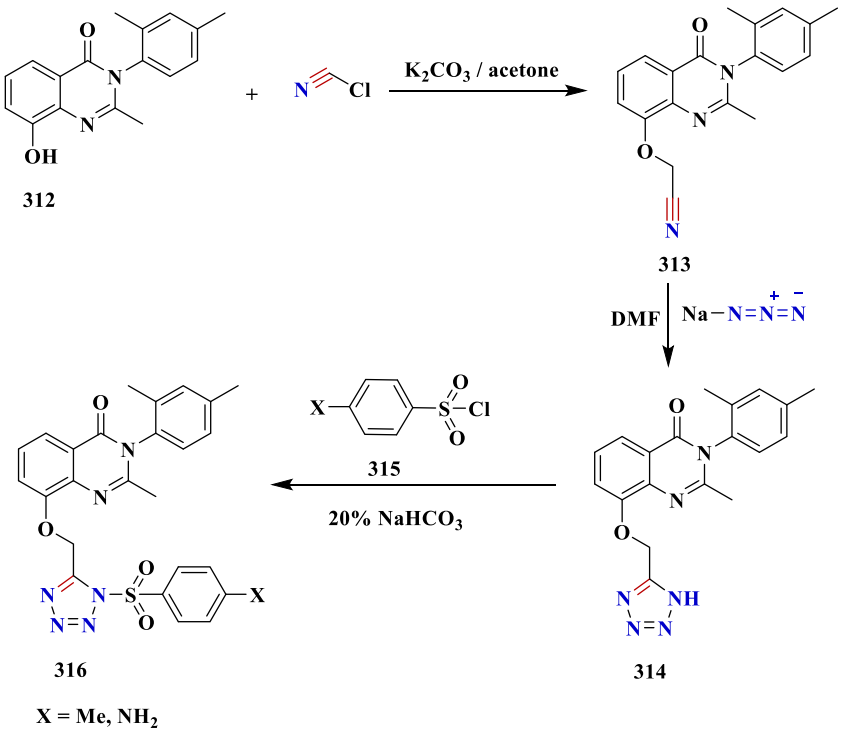
tetrabutylammonium bromide (TBAB) resulting in cyano compound **305**, which was converted to tetrazoles **306** using trimethylsilyl azide and TBAB.3H_2O. The obtained tetrazoles **306** were sulfonylated with aryl sulfonyl chlorides **307** in the presence of TEA in DCM to afford the substituted *N*-sulfonyl-1,2,3,4-tetrazoles **308**. The synthesized compounds were evaluated for their antitubercular activity against the Mycobacterium tuberculosis H37Rv strain. Of the compounds tested, five compounds showed excellent activity (MIC = 1.56 mg/mL) against the growth of Mycobacterium tuberculosis H37Rv (Scheme 6.132).

Some new phenylselanyl-1-(toluene-4-sulfonyl)-1*H*-tetrazole derivatives **311** were obtained starting from substituted anilines **309**, first, converted to their diazonium salts, and then these salts were reacted with KSeCN to form phenylselenocyanates. The tetrazoles **310** were then synthesized by reacting these compounds with sodium azide. The resulting tetrazoles were reacted with *p*-toluenesulfonic acid in the presence of dicyclohexylcarbodiimide/dimethylaminopyridine (DCC/DMAP). In addition, the antimicrobial activity of the synthesized compounds and two antibiotics (sulfamethoxazole and sulfamerazine) were investigated against some microorganisms (Scheme 6.133) [147].

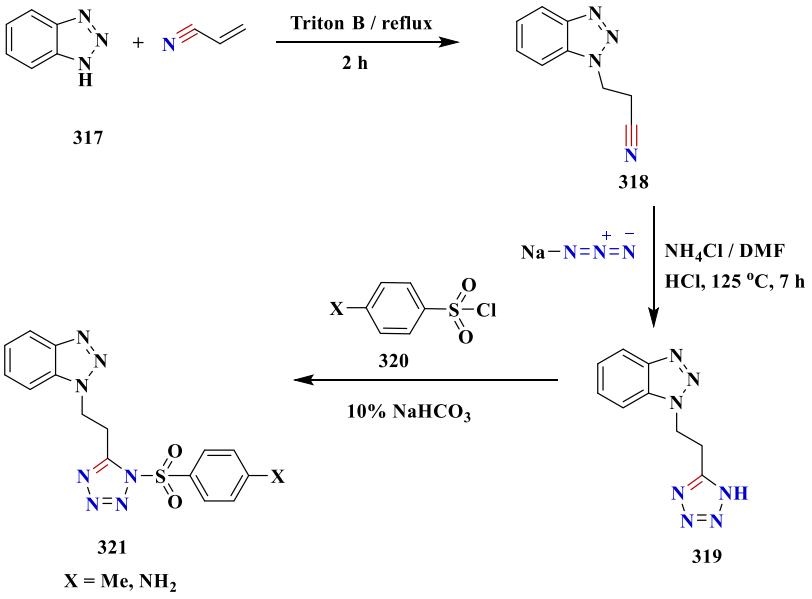
Alkylation of 8-hydroxy-2-methyl-3-*o*-tolylquinazolin4(3*H*)-one **312** with chloroacetonitrile in acetone in the presence of potassium carbonate gives 2-(2-methyl-4-oxo-3-o-tolyl-3,4-dihydroquinazolin-8-yloxy)acetonitrile **313** in good yield. The 8-[(1*H*-tetrazol-5-yl) methoxy]-2-methyl-3-o-tolylquinazolin-4(3*H*)-one **314** was prepared by heating the nitrile derivative **313** with sodium azide in DMF in the presence of triethyl ammonium chloride. The proposed mechanism involves the nucleophilic attack of the azide ion on the carbon of the nitrile group, followed by the ring closure of the imino azide to form the tetrazole ring. The sulfonylation of **314** was performed with benzenesulfonyl chlorides **315** under basic conditions (20% $NaHCO_3$) to afford 2-methyl-8-[(2-(phenyl substituted-sulfonyl)-2*H*-tetrazol-5-yl) methoxy]-3-*o*-tolylquinazolin-4(3*H*)-ones **316**. The presence of a sulphonyl group in tetrazoles is explained by an increase in the anticonvulsant stimulus. Moreover, it seems that the good anticonvulsant activity was limited to compounds containing a free oxygen function (Scheme 6.134) [148].



SCHEME 6.133 Synthesis of phenylselanyl-1-(toluene-4-sulfonyl)-1*H*-tetrazole derivatives **311**.



SCHEME 6.134 Synthesis of 2-methyl-8-[(2-(phenyl substituted-sulfonyl)-2H-tetrazol-5-yl) methoxy]-3-o-tolylquinazolin-4(3H)-ones **316**.



SCHEME 6.135 Synthesis of 1-(2-(1-arylsulfonyl-1*H*-tetrazol-5-yl)ethyl)-1*H*-benzo[*d*][1,2,3]triazole **321**.

1*H*-Benzo[*d*][1,2,3]triazole **317** was reacted with acrylonitrile in the presence of triton B to afford 3-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)propanonitrile **318**, which was reacted with sodium azide and ammonium chloride in the presence of dimethylformamide to give 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[*d*][1,2,3]triazoles **319**. Sulfonylation of compounds **319** with arylsulfonyl chlorides **318** in the presence of 10% sodium bicarbonate produces **321**. The titled compounds were assessed for anti-nociceptive activity by the hot plate method and the writhing response method, and anti-inflammatory activity was evaluated by carragenean induced paw edema method. Compounds 321 have exhibited potential anti-nociceptive and anti-inflammatory activity. In another report, these compounds showed good antibacterial, antifungal, and anticonvulsant activity (Scheme 6.135) [149,150].

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Chapter 7

Synthetic approaches and biological evaluation of *N*-sulfonated *N*-azines

7.1 Introduction

Azine, such as pyridine is a heterocyclic compound that consists of a six-membered aromatic ring that contains one nitrogen atom. Pyridine showed various applications such as being a solvent, reagent, and precursor in agrochemicals and pharmaceuticals. Pyridine ring is a basic component of several important natural products, for example, niconine, nicotine, and nucleic acid. In the field of medicinal chemistry, pyridine derivatives have occupied a unique place because they are important precursors in drug discovery. Various pyridine derivatives have displayed broad biological activities such as antimicrobial [1], antiviral [2,3], anticancer [4], antioxidant [5], antidiabetic [6], antimalarial [7], and anti-inflammatory activities [8]. Their high therapeutic properties have encouraged medicinal chemists to synthesize a large number of novel pyridine scaffolds. Numerous methods have been developed for the synthesis of pyridine derivatives such as condensation reactions of ketones with amines [9,10], multicomponent reactions [11], cycloaddition reactions [12], transition-metal catalyzed C−H bond functionalizations [13], recoverable nano-catalysts [14], and ring-opening method [15].

In this chapter, we classify many *N*-sulfonyl pyridine derivatives based on their structures such as pyrdinone, pyridine, oxazine, and thiazine derivatives. Additionally, we summarize various synthetic methods used for the synthesis of such derivatives and discuss their biological activities.

7.2 Synthesis of *N*-sulfonyl pyridinone derivatives and their biological activities

7.2.1 Synthesis of *N*-sulfonyl 2-pyridinones

Several pathways have been obtained to develop *N*-sulfonyl 2-pyridinones. For example, disubstituted *N*-sulfonyl 2-pyridinones **3** were obtained in practical yields under mild reaction conditions by bifunctional urea-catalyzed, catalyst A, Michael addition/lactamization followed by a $Hg(OAc)_2$ mediated hydrolysis/decarboxylation/dehydrogenation process starting from dithiomalonate and β,γ-unsaturated α-keto esters **1**. The reaction using a range of aryl β,γ-unsaturated α-keto esters **1** bearing a variety of aryl and naphthyl groups which reacted with *p*-toluenesulfonamide ($TsNH_2$) led to the formation of corresponding ketimines **2** *in situ* which directly reacted with dithiomalonate *via* Michael addition, Scheme 7.1. The reaction stopped at the Michael addition step, and the following lactamization did not occur to provide 3,4-dihydro 2-pyridinones 6′ **4**. By using $Hg(OAc)_2$, the Michael adducts **2** converted into 4,6-disubstituted 2-pyridinones **3** in excellent yield (85%−96%) through a lactamization/ hydrolysis/decarboxylation/dehydrogenation sequence [16].

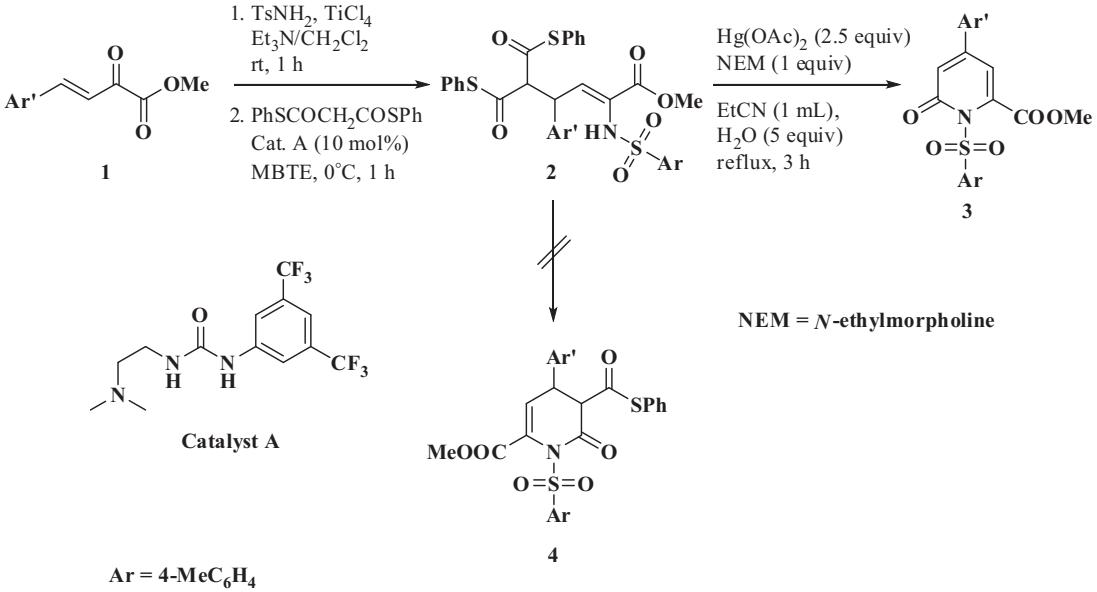
Various *N*-sulfonyl alkenyl carboxamides **5** were found to be efficient substrates to construct *N*-sulfonyl pyridinones **7** through the reaction with allylbenzene derivatives **6** using palladium-catalyzed $C(sp^2) - H$ allylation/aminopalladation/$\beta - H$ elimination/isomerization sequence, Scheme 7.2 [17].

7.2.2 Synthesis of *N*-sulfonyl dihydro 2-pyridinones

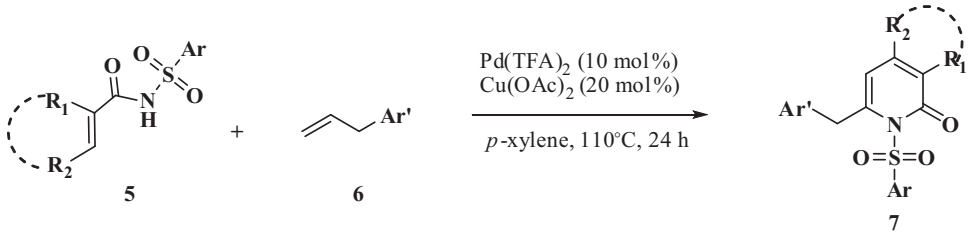
Strained aza rings with π bonds are involved in the cycloaddition reaction to form a large number of *N*-heterocycle compounds through ring expansion methods. A general ring expansion strategy that involves cross-dimerization between three-membered aza heterocycles and three-membered-ring ketones *via* synergistic bimetallic catalysis has been developed and provided *N*-sulfonyl dihydropyridinone derivatives **10** in good yields [18]. After optimization of the condition, the reaction of a large range of *N*-sulfonyl 2-arylaziridines **8** and various diarylcyclopropenones **9** using catalyst B produced with 99% enantiospecificity, Scheme 7.3.

Silyl-substituted aziridines **11** underwent palladium-catalyzed carbonylation under CO pressure forming exclusively δ-lactam **12** [19]. It was observed that the reaction depended on the CO concentration. At higher pressure of CO (50 bar), the reaction produced the β-lactam predominantly as a mixture of diastereomers **13**

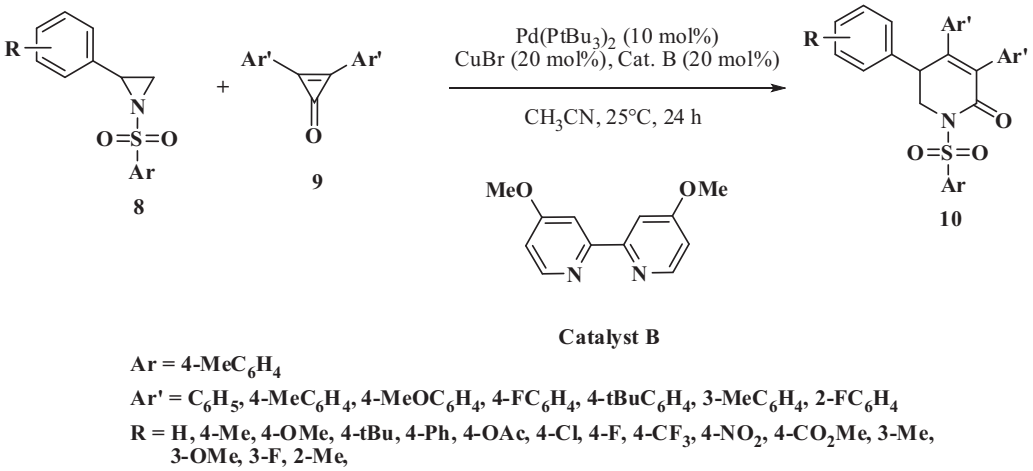
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00009-4



SCHEME 7.1 *N*-Sulfonyl 2-pyridinones **3** by the urea-catalyzed Michael addition/lactamization reaction.



SCHEME 7.2 *N*-Sulfonyl pyridinones **7** by the palladium-catalyzed reaction of *N*-sulfonyl alkenyl carboxamides.

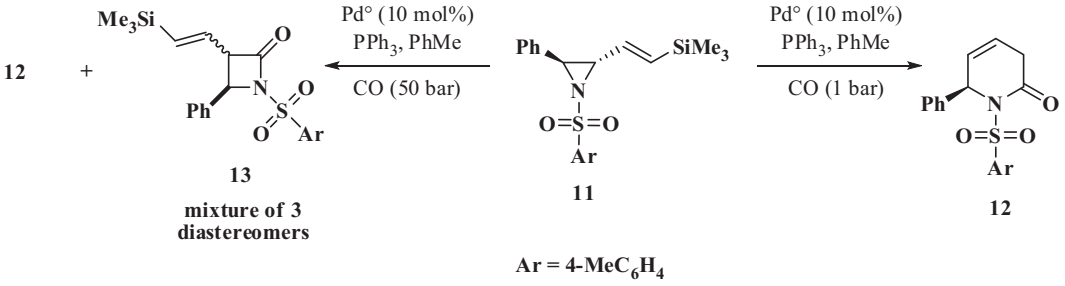


SCHEME 7.3 *N*-Sulfonyl dihydropyridinones **10** through ring expansion methods.

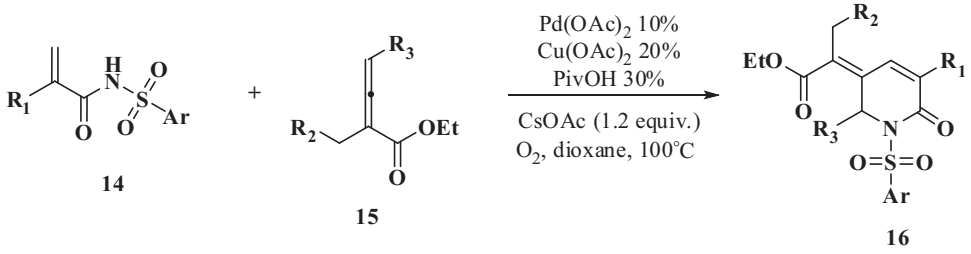
in addition to δ-lactam **12** in 20% yield while at low pressure of CO (1 bar), the reaction underwent fast cyclization to form δ-lactam **12** in 61% yield after protodesilylation, Scheme 7.4.

In 2017, Xia *et al.* reported the palladium(II)-catalyzed direct oxidative C-H olefination of *N*-tosylacrylamides **14** and allenoates **15** for the synthesis of *N*-sulfonyl-1,6-dihydropyridinone **16**. Both amide and ester moieties act as the directing groups for the regio- and the stereo-controlled C−H functionalization/cyclization. Various substituted acrylamides and allenoates were used and the desired products were obtained in moderate to good yields, Scheme 7.5 [20].

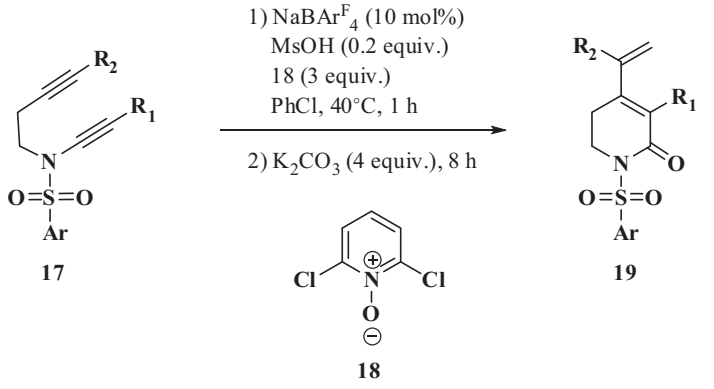
1,6-Diynes **17** were successfully involved in an efficient $NaBAr^F_4$-catalyzed oxidative cyclization to give the desired δ-lactams **19**, Scheme 7.6. This method proceeded *via* a presumable Lewis acid-catalyzed S_N2 pathway and led to the facile and practical construction of a variety of



SCHEME 7.4 δ-Lactam **12** by palladium-catalyzed reaction of silyl-substituted aziridines.



SCHEME 7.5 *N*-Sulfonyl-1,6-dihydropyridinone **16** by the palladium-catalyzed reaction of *N*-tosylacrylamides.



SCHEME 7.6 δ-Lactams **19** through $NaBAr^F_4$-catalyzed oxidative cyclization of 1,6-diynes.

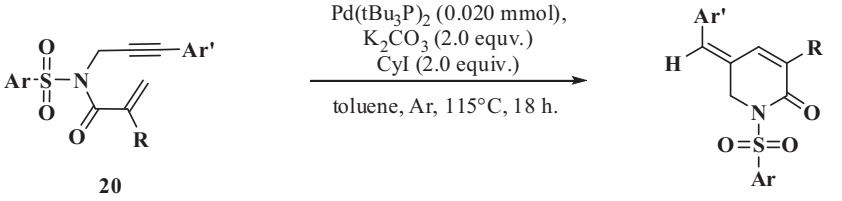
useful δ-lactams. The reaction proceeded well with broad substrate scope of aryl-substituted 1,6-diynes using 2,6-dichloropyridine *N*-oxide **18** to afford the desired **19** in good to excellent yields [21].

Cycloisomerization of 1,6-enynes **20** under the palladium-catalyzed conditions has also been developed. The method gave rise to dihydro 2-pyridinones **21** containing exocyclic double bonds with excellent chemo- and regio-selectivity, Scheme 7.7. Several substrates of 1,6-enynes **20** were screened. Electron-rich aryl substituents on the alkynes were well-tolerated forming the desired products in 70%−88% yields while aryl substituents with electron-withdrawing groups on the alkynes were also suitable and led to the corresponding products in 40%−88% yields [22].

Another way to synthesize *N*-sufonyl pyridinones **24** was through the use of HX **23** surrogates to accomplish a Pd-catalyzed hydrohalogenation of enynes [23]. The optimal condition was tested with various *N*-protecting groups on enynes **22**, Scheme 7.8. *N*-Tosyl pyridinone **24** in 41% yield was prepared under optimal conditions using *N*-tosyl enyne as starting material.

An inverse electron demand aza-Diels-Alder reaction, IED-aza-DA, has become one of the most widely used synthetic strategies for the preparation of *N*-sufonyl azines. IED-aza-DA is an interaction between electron-deficient 1,3-dienes and electron-rich dienophiles. Moreover, there has been a growing interest in the synthesis of heterocyclic azines by chiral *N*-heterocyclic carbenes (NHCs) organocatalysts [24]. In 2006, Bode *et al.*, reported the first example of an enantioselective IED-aza-DA process by using chiral NHC as catalysts, Scheme 7.9. The reaction of DIPEA, triazolium precatalyst, catalyst C, and α,β-unsaturated-δ-dicarbonyl compounds **26** afforded Breslow's intermediate which after addition to 1-azabutadiene **25** yielded the corresponding 3,4-dihydro 2-pyridinones **27**, with complete *endo*-selectivity and excellent enantioselectivities. A wide substrate scope with both aromatic and aliphatic azadienes **25** led to the formation of *N*-heterocyclic carbene-catalyzed smoothly. However, the aldehyde group on the dienophiles **26** was found to be essential for the success of the cycloaddition since the corresponding structures without an aldehyde function did not react [25].

In 2011, Jian *et al.* [26] reported another NHC catalyzed formal IED-aza-DA reaction of 1-azadiene **28** by the reaction with ketenes **29** to afford 3,4-dihydro 2-pyridinones **30** in good yield with high enantioselectivities using the Rovis' tetracyclic NHC, Catalyst D, in benzene, Scheme 7.10. An excess of Cs_2CO_3 was required to facilitate the cycloaddition and formation of corresponding 2-pyridinone compounds.

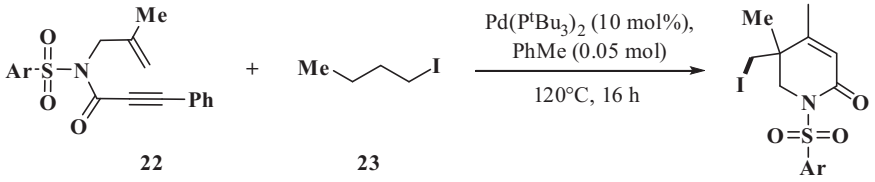


20 **21**

Ar = 4-MeC$_6$H$_4$ **R = Me, C$_6$H$_5$, Bn**

Ar' = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BnOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-CNC$_6$H$_4$, 4-AcC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 2-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 2-thienyl, 2-pyridyl, 3-pyridyl

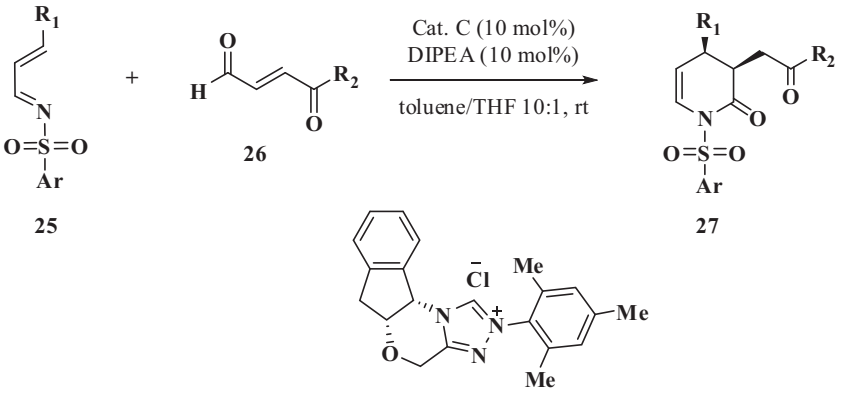
SCHEME 7.7 Dihydro 2-pyridinones **21** *via* cycloisomerization of 1,6-enynes.



22 **23** **24**

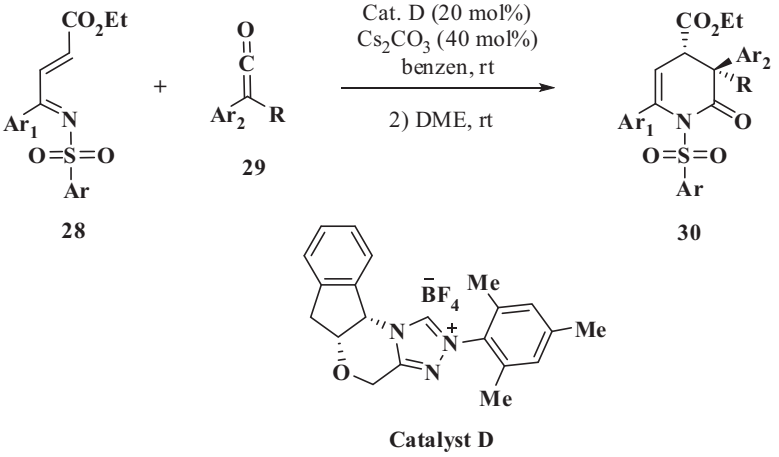
Ar = 4-MeC$_6$H$_4$

SCHEME 7.8 *N*-Sufonyl pyridinones **24** through the Pd-catalyzed hydrohalogenation of enynes.



Ar = 4-MeOC$_6$H$_4$
R$_1$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 2-furyl, *n*-Pr
R$_2$ = C$_6$H$_5$, Me, OEt, O^{t}Bu

SCHEME 7.9 *N*-Tosyl 3,4-dihydro 2-pyridinones **27** through IED-aza-DA catalyzed by chiral *N*-heterocyclic carbenes catalysis.



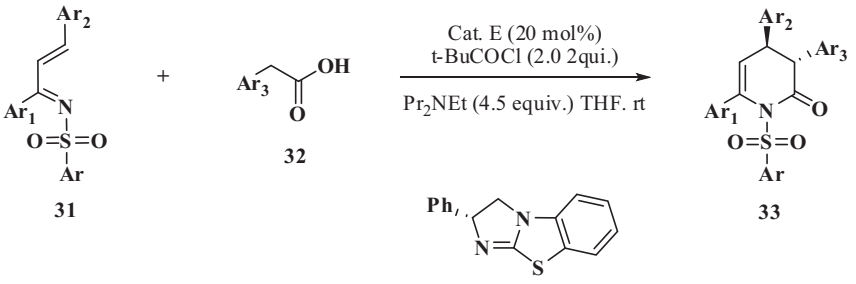
Ar = C$_6$H$_5$, 4-MeC$_6$H$_4$ **R** = Et, *n*-Pr, *n*-Bu
Ar$_1$ = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-furyl
Ar$_2$ = 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$,

SCHEME 7.10 *N*-Sulfonyl 3,4-dihydro 2-pyridinones **30** starting from 1-azadiene using Rovis' tetracyclic *N*-heterocyclic carbenes catalysis.

Under asymmetric NHC-catalysis, of the IED-aza-DA reaction, a range of aryl-acetic acids **32** and *N*-tosyl-α,β-unsaturated imines **31** generated dihydro 2-pyridinones **33** with high diastereo- and enantioselectivities, Scheme 7.11. The synthetic utility of these *N*-tosyl dihydro 2-pyridinone products **33** was demonstrated with various transformation/derivatization such as an *N*- to *C*-sulfonyl photoisomerization using benzotetramisole, catalyst E, as shown in Scheme 7.11 [27]. Hao *et al.* developed a similar reaction using arylacetic esters as a replacement for arylacetic acids [28] forming *N*-tosyl dihydro 2-pyridinones in good yield.

The use of Michael acceptor, ketimines derived from α,β-unsaturated γ-ketoesters **28**, in a Michael addition/lactamisation cascade produced a range of dihydro 2-pyridinones **34** with high enantioselectivity, Scheme 7.12. The nature of the *N*-sulfonyl group present on the ketimine **28** and a wide variety of acetic acid **32** derivatives using catalyst F were extensively investigated [29].

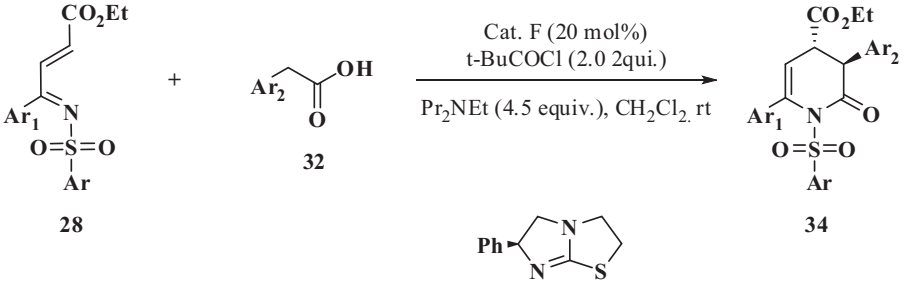
The scope of *N*-tosyl dihydro 2-pyridinone products **36** reachable by isothiourea-catalyzed, catalyst F, processes have been expanded and explored through the use of 2-*N*-tosyliminoacrylates **35** and 2-arylacetic acids **32** in a Michael addition lactonization/lactamization cascade reaction, Scheme 7.13. To



Catalyest E

Ar = 4-MeC$_6$H$_4$ **Ar$_1$ = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl**
Ar$_2$ = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$
Ar$_3$ = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-NMe$_2$C$_6$H$_4$, 2-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-MeC$_6$H$_4$, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl

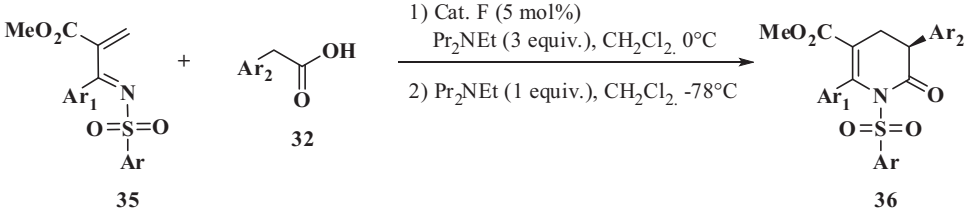
SCHEME 7.11 *N*-Tosyl 3,4-dihydro 2-pyridinones **33** starting from α,β-unsaturated imines under asymmetric *N*-heterocyclic carbenes -catalysis.



Catalyst F

Ar = Me, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$
Ar$_1$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$
Ar$_2$ = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NMe$_2$C$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 1-naphthyl, 2-naphthyl, 3-thienyl

SCHEME 7.12 *N*-Sulfonyl 3,4-dihydro 2-pyridinones by Michael addition/lactamisation reaction.



Ar = 4-MeC$_6$H$_4$
Ar$_1$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-naphthyl
Ar$_2$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NMe$_2$C$_6$H$_4$, 3-thienyl, SPh

SCHEME 7.13 *N*-Tosyl 3,4-dihydro 2-pyridinones **36** starting from *N*-tosyliminoacrylates.

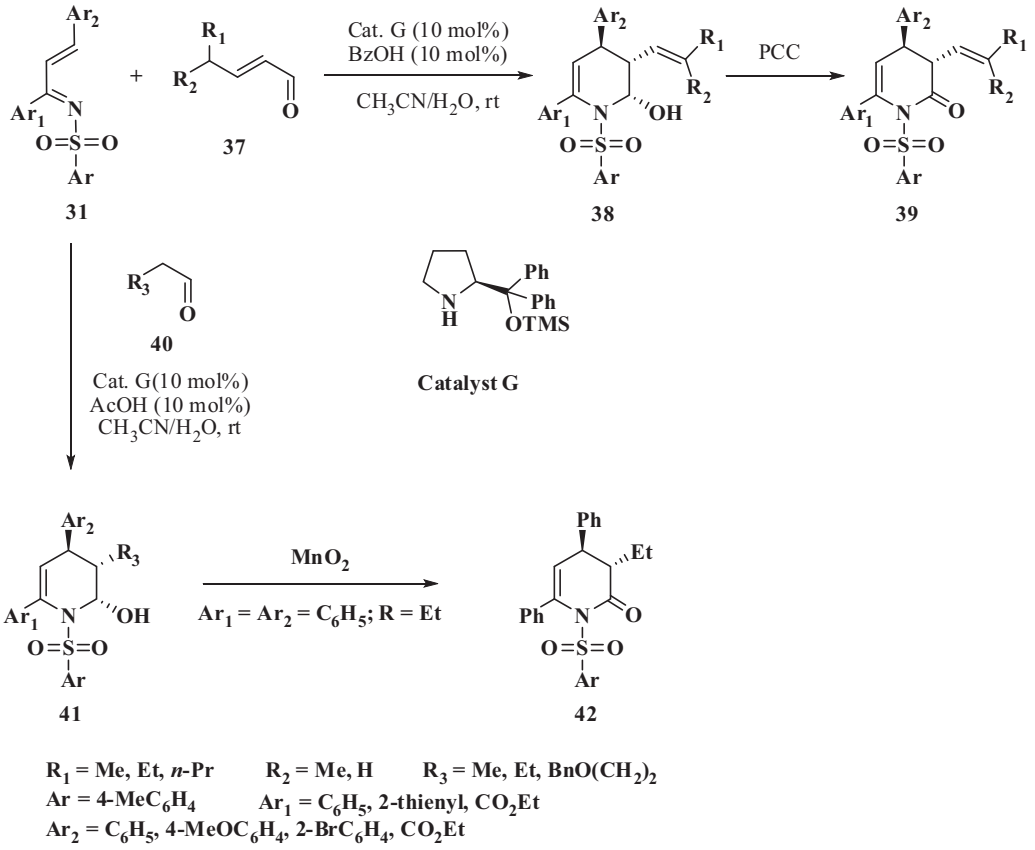
ensure reproducibility, carboxylic acids **32** were used with 2-*N*-tosyliminoacrylates **35** to deliver a range of dihydro 2-pyridinones **36** with high enantioselectivity [30,31].

Chen's group reported the IED-aza-DA transformation of α,β-unsaturated aldehydes **37**, and *N*-tosyl-1-azabutadienes **31** using an (*R*)-diphenylprolinol O-TMS (O-trimethylsilyl), catalyst G, to produce a high functionalized chiral pyridinone compounds **38**. Under catalyst G, the reaction proceeded smoothly with α-regioselectivity to form the hemiaminals in an *E/Z*-mixture, Scheme 7.14 [32]. Oxidation to lactams **39** formed *E*-isomers as major products which separated easily with excellent diastereo- and enantioselectivities. Under the same condition, a wide variety of *N*-tosyl-1-azadienes **31** reacted smoothly with linear aldehydes **40** using catalyst G [33,34]. The reaction proceeded under mild conditions and at room temperature with a wide range of 1-azadienes **31** and with different aldehydes **40** to give the corresponding piperidine compounds **41**. Oxidation of **41** derivatives, containing diphenyl and ethyl substituents, afforded the chiral lactam **42**, Scheme 7.14.

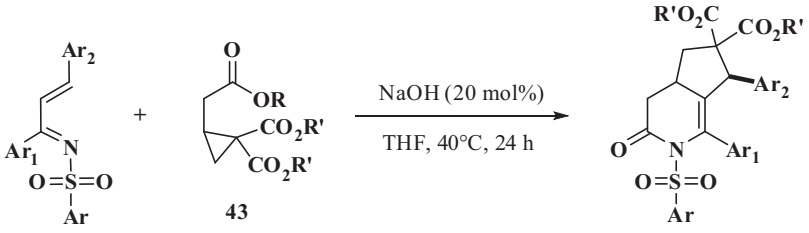
A cascade cycloaddition reaction was developed for efficient access to *N*-tosyl cyclopenta[*c*]pyridinone derivatives **44**. Base, such as NaOH, was used as a catalyst for the reaction of δ-carbon of cyclopropyl ester **43** with α,β-unsaturated imine **31** is highly chemoselective manners, Scheme 7.15. Cyclopenta[*c*]pyridinones **44** bearing various substituents were afforded as the final products in up to quantitative yields [35].

Some of the synthesized compounds showed promising antibacterial activities for potential applications in plant protection. They exhibited superior antibacterial activities against *Xanthomonas axonopodis pv. citri* and *Pseudomonas syringae pv. actinidiae* as compared to the commercially used thiodiazole-copper [35].

In 2012, Wang *et al.* [36], developed an enantioselective IED-aza-DA reaction of cyclic keto/enolate salts **45** with 2-*N*-tosyliminoacrylates **35** using catalyst H, Scheme 7.16. The primary thiourea, catalyst H (10 mol %) with acetic acid (20 mol%) smoothly catalyzed the formal cycloaddition to produce the functionalized aza-spirocyclic products **46** with excellent yields. The reaction displayed broad substrate scope with a diversity of

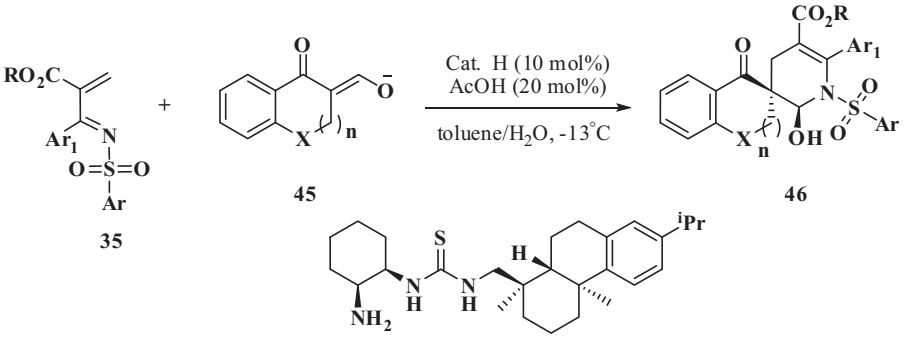


SCHEME 7.14 *N*-Tosyl 3,4-dihydro 2-pyridinone derivatives by IED-aza-DA transformation of *N*-tosyl-1-azabutadienes **31** using an (*R*)-diphenylprolinol O-TMS catalysis.



R = H, Me, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$ R' = Me, Et, i-Pr, Ph
Ar = 4-MeC_6H_4
Ar_1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-ClC_6H_4, 2-thieny
Ar_2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-$MeOC_6H_4$, 3-ClC_6H_4, 3-BrC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 2-thieny

SCHEME 7.15 *N*-Tosyl cyclopenta[*c*]pyridinone derivatives **44** using basic condition.

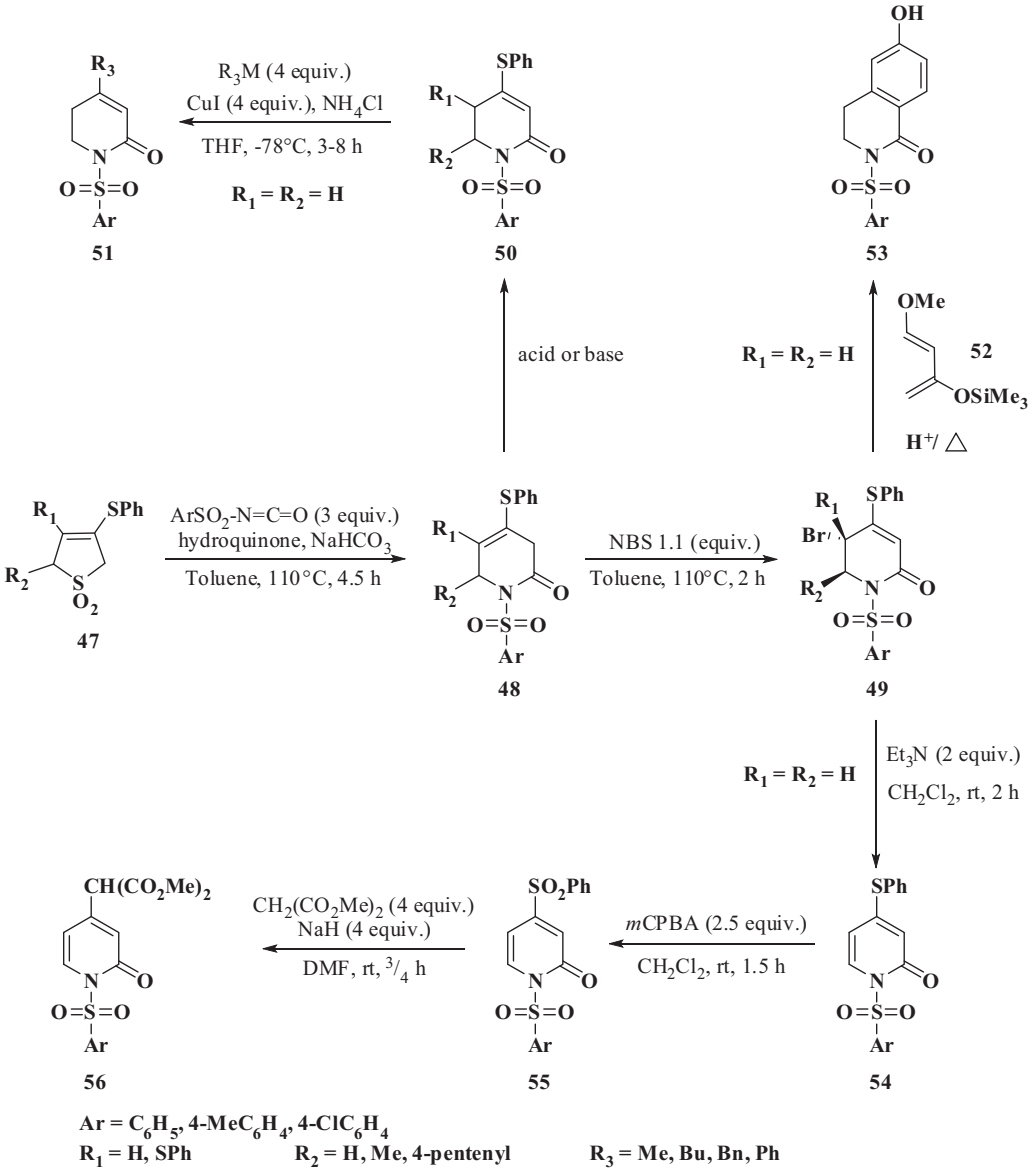


Ar = 4-MeC_6H_4 R = Me, Et X = CH_2, S, O
Ar_1 = C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 2-thienyl, 2-furanyl

SCHEME 7.16 Chiral spirohemiaminals **46** by IED-aza-DA reaction of cyclic keto/enolate salts.

substituted *N*-tosyl-2-methylenebut-3-enoates **35** and cyclic keto/sodium enolates **45** forming chiral spirohemiaminals **46** [37].

A normal electron demand aza-Diels-Alder reaction, NED-aza-DA, is another approach of aza-Diels-Alder which involved the electron-rich 1,3-dienes and electron-deficient dienophiles. Most of the work dealing with synthesizing of *N*-sulfonyl azines has been focused on the reaction of activated imines bearing sulfonamide and electron-rich dienes under catalytic enantioselective reactions. One of the first examples of NED-aza-DA reactions to synthesize dihydro-2-pyridinones **48** was reported by Chou's group [38]. The formation of dihydro-2-pyridinone derivatives **48** was achieved by the reaction of arylsulfonyl isocyanates with thio-substituted 3-sulfolenes **47** as precursors to the dienes. The reaction is performed through *in situ* thermal desulfonylation followed by cycloaddition to produce the cyclized products with complete control of regio- and chemoselectivity. The dihydro-2-pyridinone products **48** were utilized for many useful synthetic transformations. They can be converted to trans-allylic bromides **49** via the direct treatment of compounds **48** with *N*-bromosuccinimide (NBS). They can also undergo further reactions with nucleophiles, bases, and acids to give useful heterocyclic compounds **50** and **51** [39–41]. Upon treatment of allylic bromides **49** with either triethylamine or pyrrolidine, 2-pyridinone **54** formed in good yield [42]. Oxidation of 2-pyridinone **54** substituted with sulfide group with *m*-CPBA afforded the corresponding sulfone **55** in excellent yield. The reaction of later with dimethyl malonate anion led to the formation of 2-pyridinone **56** in 87% yield. Cycloaddition reactions of Danishefsky's diene **52** with allylic bromides **49** led only to the formation of cycloaddition product **53** [42] (Scheme 7.17).



SCHEME 7.17 *N*-Sulfonyl dihydro-2-pyridinone **48** by NED-aza-DA reactions and its transformation to various *N*-sulfonyl 2-pyridinones.

7.2.3 Synthesis of *N*-sulfonyl tetrahydro 2-pyridinones

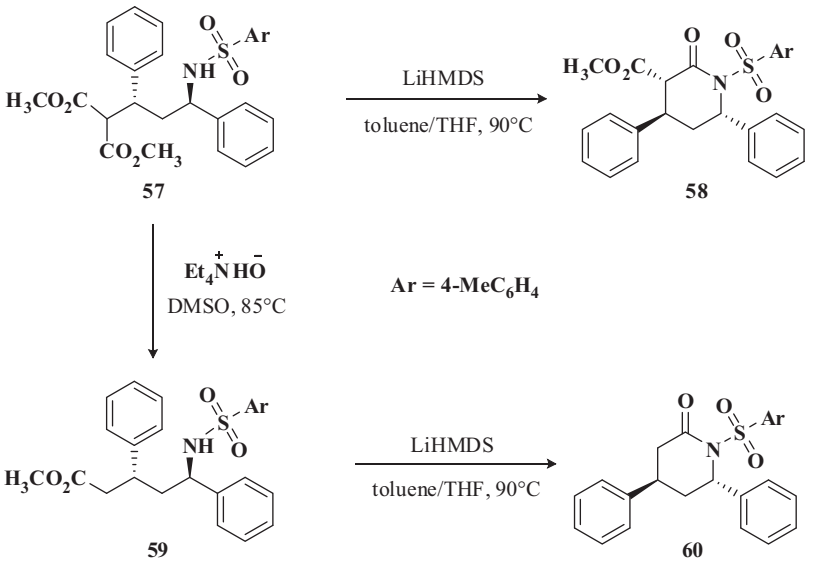
In 2013, Espinosa *et al.* [43], reported the lactamization strategy for chiral *δ*-amindiesters **57** under basic conditions. Chiral *δ*-aminodiesters **57** were subjected to lithium hexamethyl disilazide (LiHMDS) in toluene/THF at 90 °C to produce the chiral 3,4,6-substituted piperidones **58**, Scheme 7.18. For the synthesis of chiral 4,6-substituted piperidones **60**, *δ*-aminodiester **57** was firstly decarboxylated by tetraethylammonium hydroxide and then the resulting monoester **59** was treated with lithium hexamethyl disilazide (LiHMDS).

7.2.4 Synthesis of *N*-sulfonyl 3-pyridinones

The reaction of furanynes **61** in combination with pyridine *N*-oxides **62** in the presence of an Au(I) catalyst afforded *N*-tosyl dihydro 3-pyridinone derivatives **63**, Scheme 7.19. The reactions proceeded smoothly at room temperature and in open air [44].

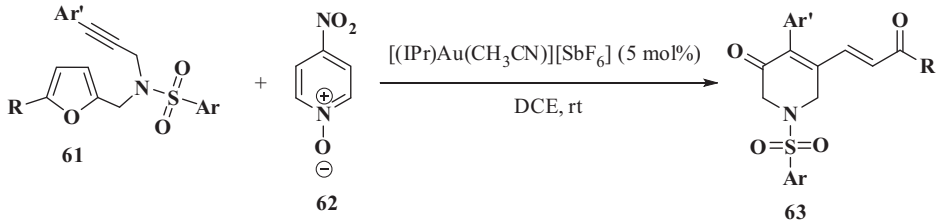
7.2.5 Synthesis of *N*-sulfonyl 4-pyridinones

Generally, the reaction of pyridinones with arylsulfonyl chloride derivatives in the presence of a basic medium afforded the corresponding *N*-arylsulfonyl



57 58 59 60

SCHEME 7.18 Chiral 3,4,6-substituted piperidones **58**, and chiral 4,6-substituted piperidones **60** using lactamization strategy for chiral δ-amindiesters.

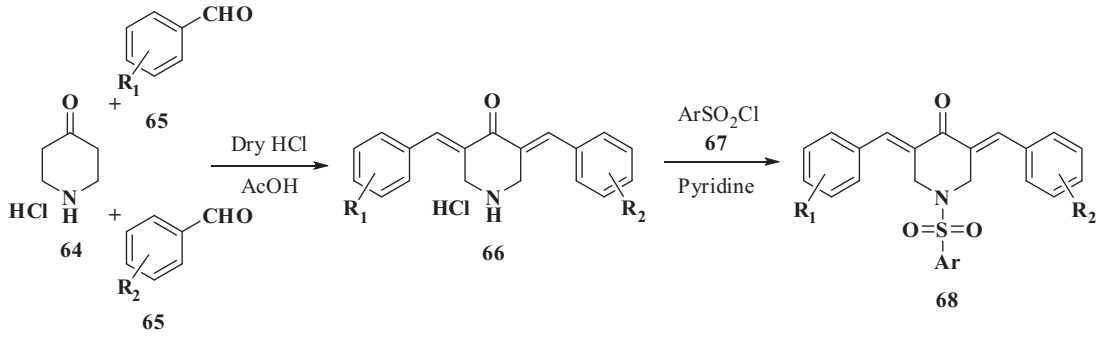


61 62 63

Ar = 4-MeC_6H_4 **R** = Me, Ph, 2-thienyl, 2-furyl

Ar' = Ph, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$MeCO_2C_6H_4$, 4-$MeCOC_6H_4$, 2-thienyl, 1-naphthyl

SCHEME 7.19 Intramolecular cyclization of furanynes **61** by Au(I)-catalyzed reaction.

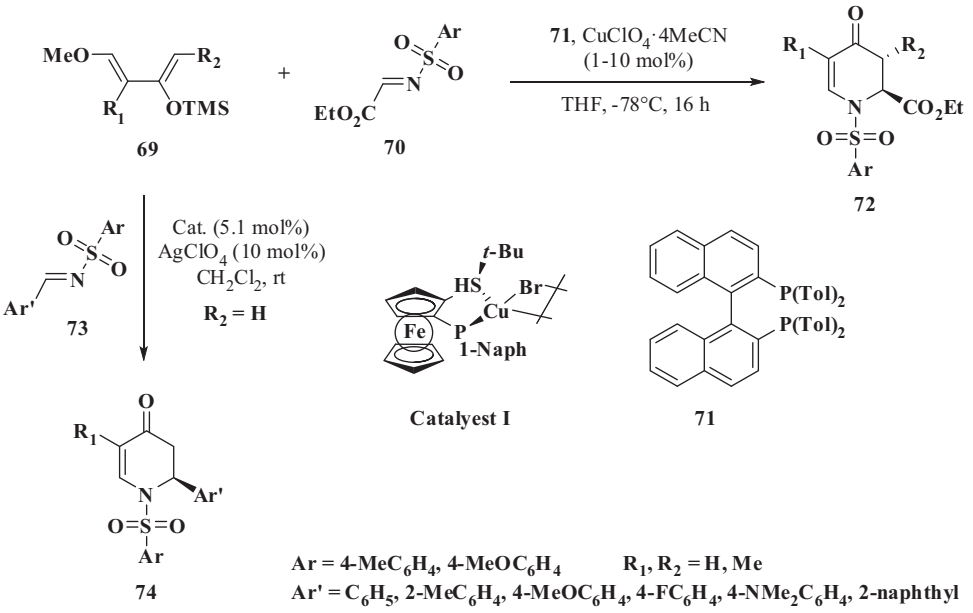


65 64 65 66 68

Ar = 4-$AcNHC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$ **R_1, R_2** = 4-CN, 2-F, 3-NO_2, 3,5-MeO, 3,4,5-MeO

SCHEME 7.20 Symmetric and asymmetric 3,5-bis(arylidene)-4-piperidones **68** by Claisen-Schmidt condensation followed by *N*-sulfonylation.

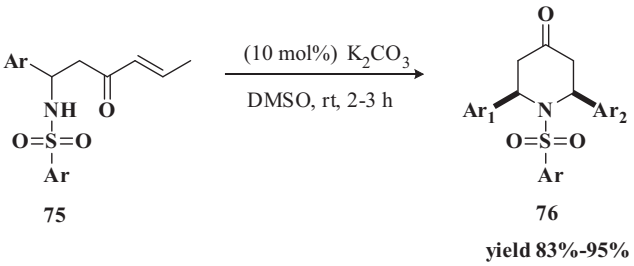
pyridinones [45–49]. For example, symmetric and dissymmetric 3,5-bis(arylidene)-4-piperidone derivatives **68** were synthesized by two steps synthesis protocol, Claisen-Schmidt condensation followed by *N*-sulfonylation. Claisen-Schmidt condensation reaction of morphine **64** with either aromatic aldehyde **65** or pyridine-3-carboxaldehyde derivatives was catalyzed by dry HCl, while *N*-sulfonylation using sulfonyl chloride **67** was carried out in a basic medium, pyridine [50,51], Scheme 7.20.



SCHEME 7.21 *N*-Sulfonyl 4-pyridinones **72** and **74** using NED-aza-DA reaction of Danishefsky's dienes **69** with *N*-tosyl iminoester **70** and aryl imines **73**.

The asymmetric 3,5-bis(arylidene)-4-piperidone derivatives containing electron-donating 3,4,5-triethoxy groups or strong electron-withdrawing, such as 4-CN, 3-NO_2 groups, are recognized as the most potent inhibitors against HepG2, QGY-7703, and SMMC-7721 with lower cytotoxicity toward LO2, HHL-5 cell lines. Some synthesized derivatives significantly reduced the secretion of IL-6 and TNF-α, and their inhibitory effect was better as compared to the positive drug PDTC [50]. Additionally, 4-piperidone derivatives substituted with pyridine ring exhibited potential anti-hepatoma properties against human hepatocellular carcinoma cell lines (HepG2, QGY-7703, SMMC-7721) and hypotonicity for human normal heptical cell line (HHL-5, LO2), and prominently inhibited lipopolysaccharides (LPS) induced IL-6, TNF-a secretion to exert its anti-inflammatory effect [51]. Moreover, some derivatives significantly suppressed the growth and inflammatory response of HepG2 xenografts in nude mice and were relatively nontoxic to mice. These results suggest that such compounds may be effective and hypotoxicity anti-hepatoma agents for the clinical treatment of liver cancers.

The NED-aza-DA reaction of Danishefsky's dienes **69** and *N*-tosyl iminoester **70** in presence of ligand **71** led to the formation of *N*-sulfonyl 4-pyridinone derivatives **72**, Scheme 7.21. A wide range of metal sources such as Cu, Ag, Pd, Ru, and Zn as well as ligands (BINAP, bisoxazoline, diamine) have been investigated [52]. It was found that 2,2′-bis(ditolylphosphanyl)-1,1′-binaphthyl ligand **71** with $CuClO_4 \cdot 4MeCN$ produced the highest enantioselectivity compounds. In 2004, Mancheño *et al.*, [53] reported an enantioselective aza-DA reaction of Danishefsky's diene **69** and *N*-sulfonyl aromatic imines **73** catalyzed by the chiral copper complex, catalyst I, Scheme 7.21. A wide variety of aryl imines **73** with different electronic properties have been used to produce the corresponding *N*-sulfonyl 4-pyridinone derivatives **74**. In this aza-DA reaction, α,β-unsaturated imines have been successfully employed as dienophiles. The authors accomplished later the synthesis of (+)-lasubine employing as a key step the reported enantioselective copper-catalyzed aza-DA reaction [54].



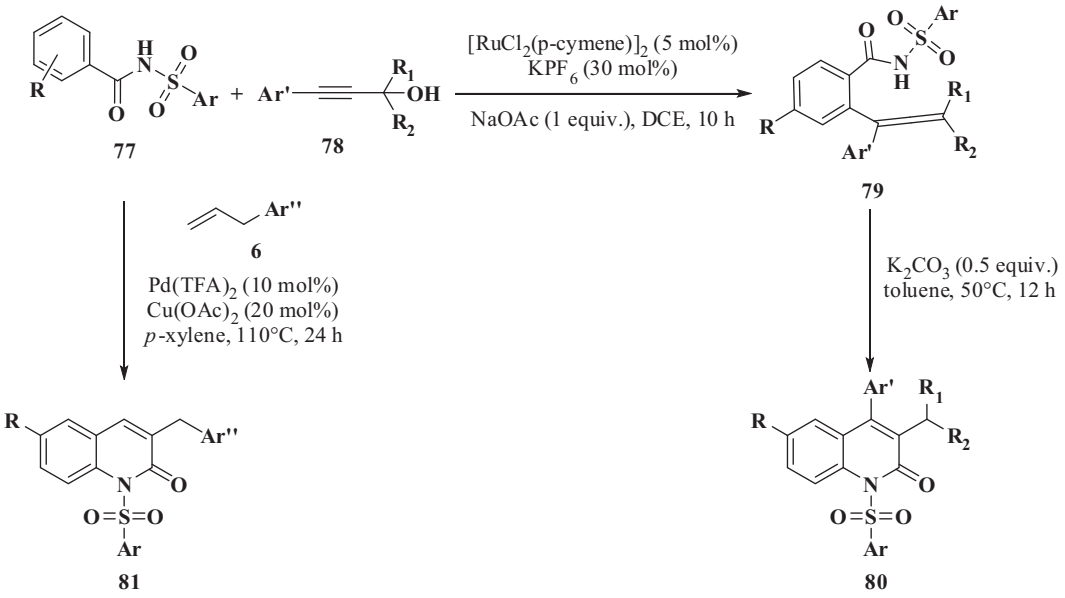
SCHEME 7.22 *N*-Tosyl 2,6-disubstituted 4-piperidinones **76** *via* intramolecular aza-Michael addition of β-amino α,β-unsaturated ketones.

In 2010, Singh *et al.* [55] reported a novel, expeditious, and diastereoselective synthesis of *N*-tosyl 2,6-disubstituted 4-piperidines **76** *via* intramolecular aza-Michael addition of β′-amino α,β-unsaturated ketones **75** in the presence of potassium carbonate, Scheme 7.22. Notably, the corresponding 2,6-disubstituted piperidin-4-ones **76** were formed as cis-diastereomers in excellent yields (83%−95%). A variety of aryl groups on β′-amino ketone **75** were tolerated.

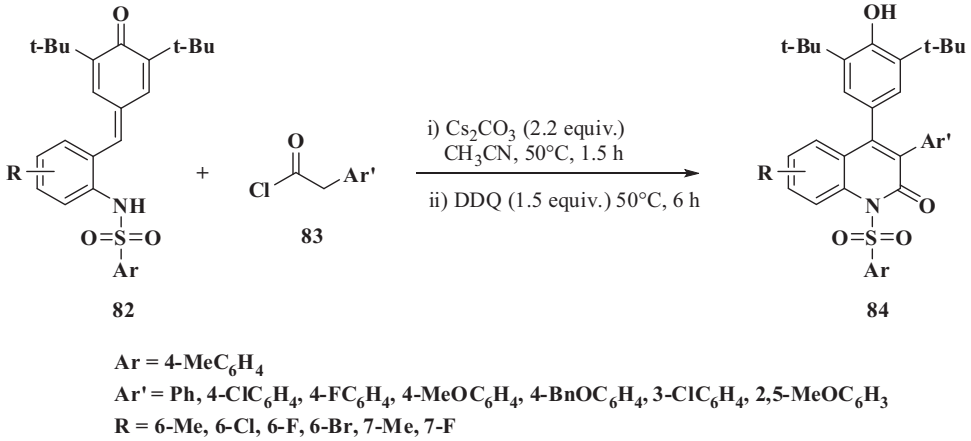
7.2.6 Synthesis of *N*-sulfonyl 2-quinolone and their derivatives

Ru(II)-catalyzed C(sp^2)−H allenylation reaction of *N*-sufonyl benzamides **77** to produce multi-substituted allenylamides **79** was developed. After optimization of the condition, various substituted *N*-tosylbenzamides **77** were studied with alkyne **78**, Scheme 7.23. Attractively, both electron-donating and electron-withdrawing groups were well tolerated at the para position of the benzamide, providing the corresponding allenes **79** in good yields. Moreover, allenes **79** converted smoothly into the corresponding quinolone derivatives **80** *via* base-mediated annulation [56]. A similar reaction of *N*-sulfonyl benzamides **77** and allylbenzenes **6** through a palladium-catalyzed C(sp^2) − H allylation/aminopalladation/β − H elimination/isomerization sequence led to the construct quinolones **81** in up to 96% yield, Scheme 7.23 [17].

A one-pot reaction has been reported for the synthesis of structurally diverse 3,4-diaryl-substituted quinolones **84** through acylation, using acyl chloride **83**, of ortho-tosylaminophenyl **82** substituted with para-quinone methides followed by an intramolecular 1,6-conjugate addition and oxidation sequence, Scheme 7.24 [57].



SCHEME 7.23 *N*-Sulfonyl quinolones **80** and **81** *via* Ru(II)-catalyzed C(sp^2)−H allenylation and Pd(II)-catalyzed C(sp^2) − H allylation reactions, respectively.

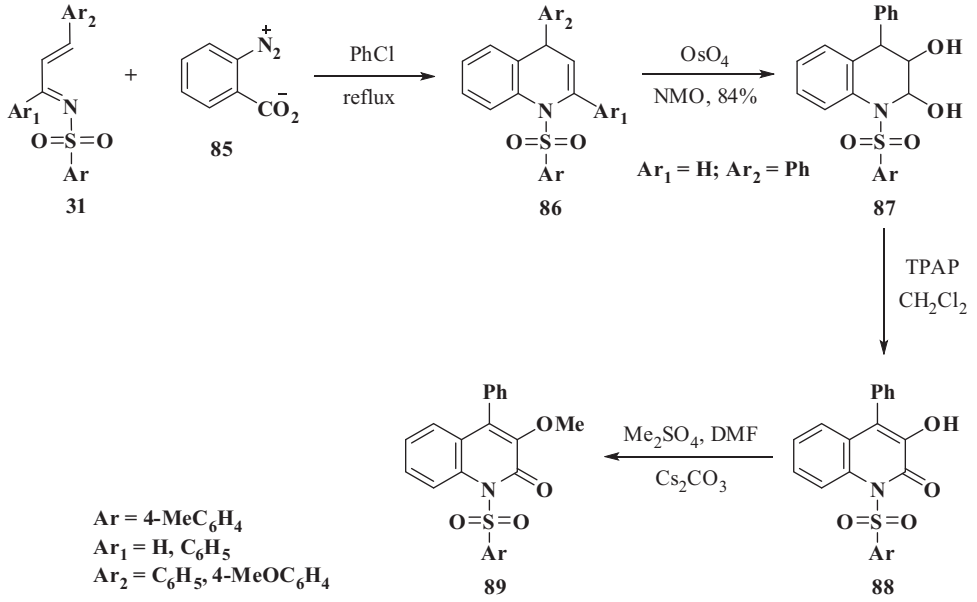


SCHEME 7.24 *N*-Tosyl 3,4-diarylsubstituted quinolones **84** through acylation reaction of ortho-tosylaminophenyl.

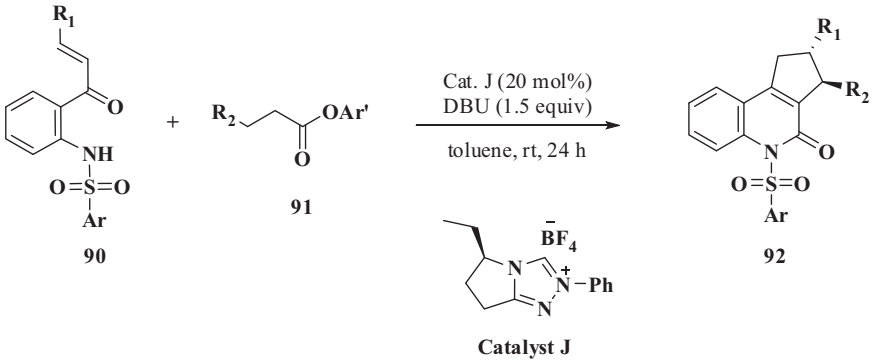
As reported by Stokes *et al.* [58], the synthesis of *N*-tosyl aryl-substituted 1,4-dihydroquinolines **86** was achieved by [4 + 2] cycloaddition between benzyne **85** and various aryl-substituted 1-azadienes **31**. Overall, yields of desirable dihydroquinolines products were good to moderate, and in most cases, a small amount of starting material was recovered. Dihydroquinoline **86** was oxidized to *N*-tosyl diol compound **87** and then to the corresponding *N*-tosyl dione which tautomerized to **88**. The latter was then methylated to form 3-methoxy-*N*-tosyl-4-phenylquinolone **89**, Scheme 7.25.

The achiral triazolium NHC precatalyst, catalyst J, was used for the reaction between amino enones **90** and saturated esters **91** to produce 2-quinolones **92**. Several saturated ester substrates **91** have been evaluated. Using esters with a β-aryl substituent having electron-rich and electron-deficient moieties have led to the formation of *N*-tosyl cyclopenta[*c*]quinolin-4(5*H*)-one **92** in high yield [59] (Scheme 7.26).

Previous research has demonstrated the synthesis of *N*-sulfonyl phenanthridinones **94** by palladium-catalyzed oxidative carbonylation of *N*-sulfonyl-2-aminobiaryls **93**



SCHEME 7.25 *N*-Tosyl aryl-substituted 1,4-dihydroquinolines **86** by [4 + 2] cycloaddition reaction.



SCHEME 7.26 *N*-Tosyl cyclopenta[*c*]quinolin-4(5*H*)-one **92** starting from amino enones using achiral triazolium *N*-heterocyclic carbenes precatalyst.

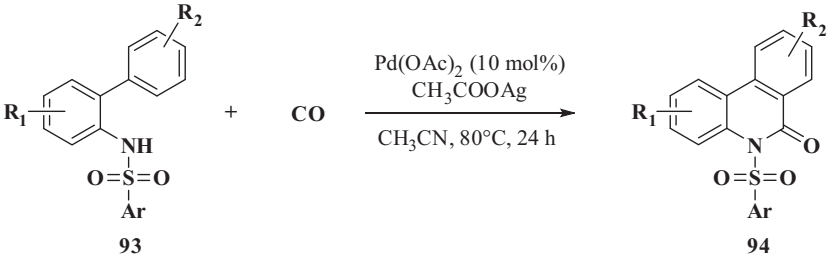
through C−C and C−N bond formation under mild conditions, Scheme 7.27. This carbonylation reaction was considered a straightforward way to form phenanthridinone derivatives **94** [60]. The structure of synthesized phenanthridinone **94** derivatives were existing widely in *amaryllidaceae* alkaloids, various natural products, and bioactive molecules. Under standard reaction conditions, both substrates having no substitutions and substrates bearing an electron-donating group on aryl rings produced the corresponding phenanthridinone derivatives in good to excellent yields.

Synthesis of *N*-tosyl-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinolines **97** was carried out by metal-free protocol under mild reaction conditions with wide functional group compatibility. The reaction between various *N*-tosyl 3-ylideneoxindoles **95** with toluenesulfonylmethyl isocyanide **96** (TosMIC) underwent smoothly to the respective products from good to excellent yields, Scheme 7.28. The crucial steps for the synthesis of *N*-tosyl pyrroloquinolines **97** were the spiro ring expansion of 3-ylideneoxindoles followed by H-shift [61].

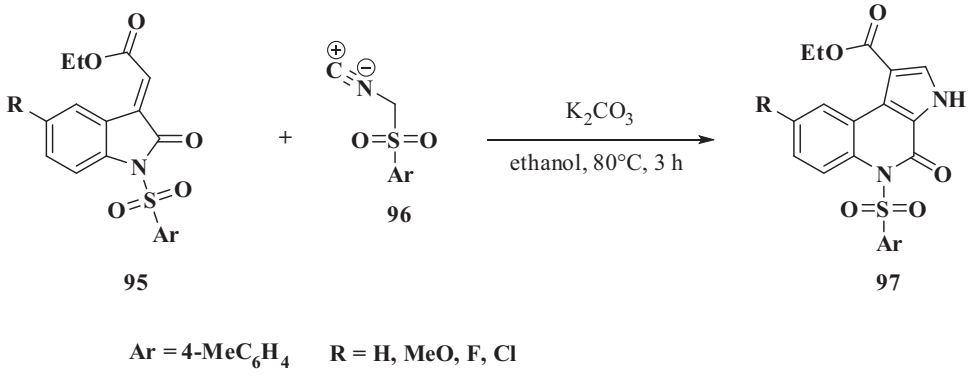
The asymmetric synthesis of functionalized *N*-tosy-4-aryl-3,4-dihydroquinolin-2-ones **99** through an intramolecular vinylogous Rauhut−Currier reaction of paraquinone methides under nucleophilic chiral amine-phosphine catalysis was developed [62]. This intramolecular mode for the catalytic enantioselective 1,6-conjugate addition of amides **98** delivered dihydroquinolinone derivatives **99** in high yields and enantioselectivites. The reaction of amides **98** having the electron-withdrawing *N*-tosyl group has completed in 15 min affording the desired *N*-tosy-4-aryl-3,4-dihydroquinolin-2-ones **99** in excellent enantioselectivities and the yield reached up to 98% yield, Scheme 7.29.

Synthesis of *N*-sulfonyl 3-cyano-2-oxo-1,4-disubstituted-1,2,5,6,7,8-hexahydroquinolines **102** was achieved through the preparation of the key intermediates 3-cyano-8-methyl-2-oxo-4-substituted hexahydrodroquinolines **101**, which have been synthesized *via* one-pot multicomponent reaction of the appropriate aromatic aldehyde **65** and 2 methylcyclohexanone **100** in presence of an excess of ammonium acetate and ethyl cyanoacetate in boiling ethanol, Scheme 7.30. The reaction of the key intermediate **101** with benzenesulfonyl chloride in pyridine resulted in the introduction of a benzenesulfonyl moiety at nitrogen to yield compounds **102** [63,64].

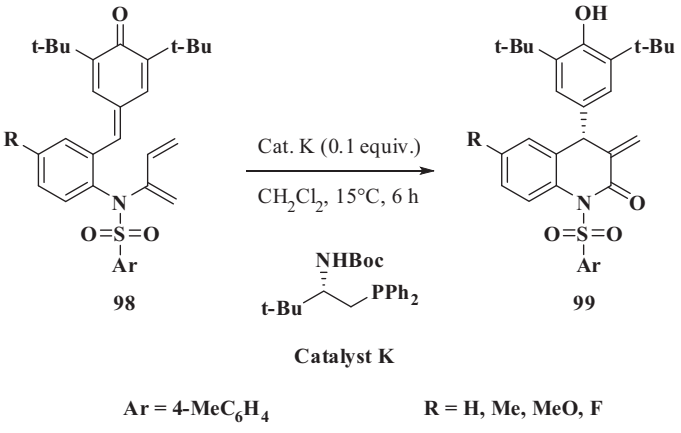
These types of *N*-sulfonyl 2-pyridinone derivatives are considered dual antimicrobial-anticancer candidates.



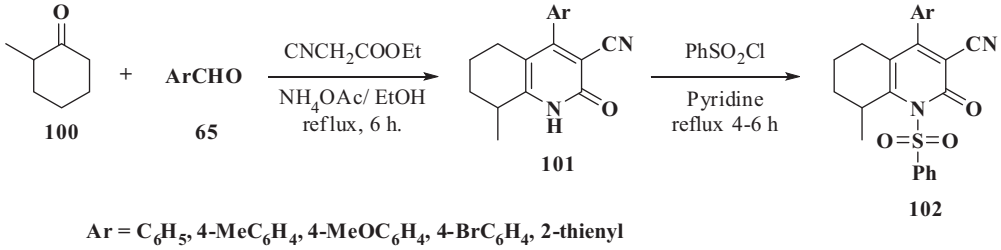
SCHEME 7.27 *N*-Sulfonyl phenanthridinones **94** by palladium-catalyzed oxidative carbonylation reaction of *N*-sulfonyl-2-aminobiaryls.



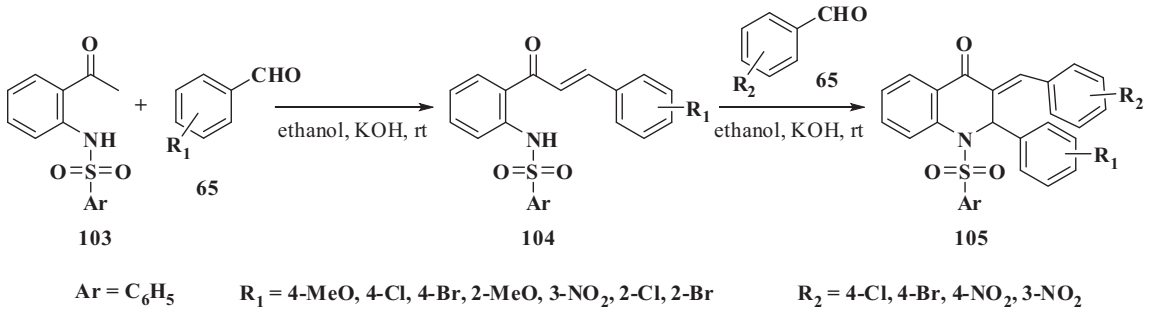
SCHEME 7.28 *N*-Tosyl 3*H*-pyrrolo[2,3-*c*]quinolines **97** by metal-free protocol.



SCHEME 7.29 *N*-Tosy 3,4-dihydroquinolin-2-ones **99** through an intramolecular vinylogous Rauhut − Currier reaction.



SCHEME 7.30 *N*-Sulfonyl 3-cyano-1,4-disubstituted-1,2,5,6,7,8-hexahydroquinolines **102** by sulfonation.



SCHEME 7.31 Chalcone-quinolones **105** through the reaction of 2'*N*-sulfonamide chalcones **104** with arylaldehyde.

They displayed a broad spectrum of cytotoxic activity in HT29, Hep-G2, and MCF7d tumor cell lines. Not only that but also they showed a remarkable cytotoxic potential against the human hepatocellular carcinoma Hep-G2 cell line with high cytotoxicity profiles as compared to doxorubicin. Additionally, *N*-sulfonyl 2-pyridinone derivatives have revealed a broad spectrum of antimicrobial activity [65].

Chalcone-quinolinone hybrid compounds are quite useful as therapeutic agents. Several chalcone-quinolone compounds have been synthesized in a single step starting from 2'*N*-phenylsulfonyl-acetophenone **103** [66]. The latter was synthesized through the reaction of benzenesulfonyl chloride and 2-aminoacetophenone derivatives. 2'*N*-Sulfonamide chalcones **104** were prepared by Claisen-Schmidt condensation between 2'*N*-phenylsulfonyl-acetophenone **103** and arylaldehyde derivatives **65** under basic catalysis in ethanolic medium, Scheme 7.31. The synthesis of chalcone-quinolones **105** was performed by the reaction of 2'*N*-sulfonamide chalcones **104** in a basic medium with various derivatives of arylaldehyde **65**, Scheme 7.31. The products precipitated pure and were isolated by filtration. The yields of such reactions, from 45 to 94%, were promising.

Several *N*-sulfonyl chalcone-quinolone derivatives showed excellent inhibition of cell growth of SF-295, PC-3, and HCT-116 tumor cells [66,67]. Moreover, some derivatives of *N*-sulfonyl chalcone-quinolone showed promising inhibitory activity against trans-sialidase from *Trypanosoma cruzi* (TcTS) but they did not show any significant inhibition against human sialidase Neu2, which increases the chance that they could be useful therapeutically [68].

N-Tosyl 3-methylidene-2,3-dihydroquinolin-4(1*H*)-ones **109** with various substitutes in position 2 have been synthesized. The reaction sequence involved the condensation of diethyl 2-(2-*N*-tosylphenyl)2-oxoethylphosphonate compounds **106** with various alkyl aldehydes **107** and used the resulted 3-diethoxyphosphoryl-1,2-dihydroquinolin-4-ols **108** as Horner-Wadsworth-Emmons reagents for the olefination of formaldehyde, Scheme 7.32 [69].

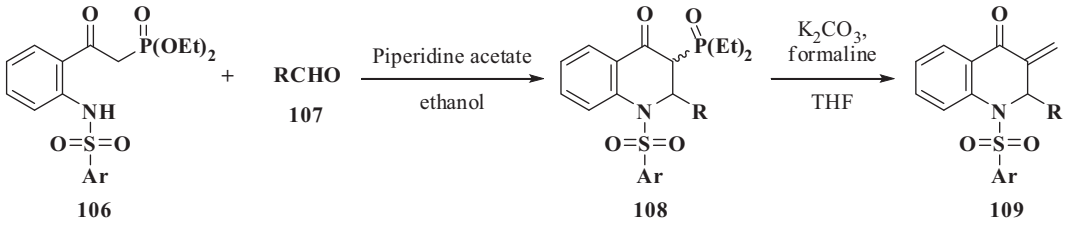
The achieved derivatives of 2,3-dihydroquinolin-4(1*H*)-ones **109** showed very high cytotoxicity with the IC_{50} values below 1 μM in two leukemia cell lines HL-60 and NALM-6 and a breast cancer MCF-7 cell line. Furthermore, the therapeutic index for several synthesized 2,3-dihydroquinolin-4(1*H*)-one derivatives was determined and some of these derivatives showed 10- to 52-fold higher cytotoxicity for leukemia cell line NALM-6 than for normal HUVEC cells. Additionally, some of the obtained derivatives showed to act as ABCB1 transporter inhibitors, which significantly decreased ABCB1 mRNA level and its activity in MCF-7 cells [69].

7.2.7 Synthesis of *N*-sulfonyl isoquinolone and their derivatives

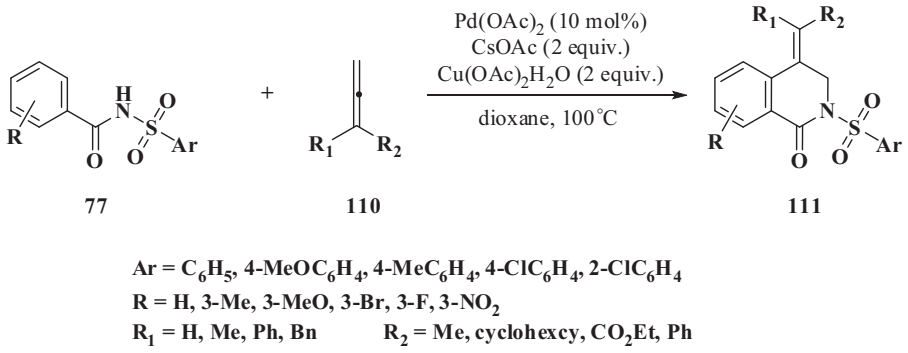
Intermolecular annulation of *N*-benzoylsulfonamide **77** with allenes **110** by PdII-catalyst to synthesize *N*-sufonyl 3,4-dihydroisoquinolin-1(2*H*)-ones **111** was reported by the Xia group [70]. The reaction was applied to both terminal and internal allenes having different functional groups, Scheme 7.33.

N-Sulfonyl 4-diazoisoquinolin-3-ones **113** were prepared *via* tetrabutylammonium bromide (TBAB)-promoted rearrangement of 4-diazoisochroman-3-imines **112** under mild reaction conditions. This resulted in 4-diazoisoquinolin-3-ones **113** which converted to 4-aryltetrahydroisoquinolin-3-ones **114** and dimethylthiophenyl tetrahydroisoquinolin-3-ones **116** using the TfOH-catalyzed reaction with electron-rich arenes and 2,5-dimethylthiophene, respectively [71]. Recently, Doyle−Kirmse reaction of 4-diazoisoquinolin-3-ones **113** with propargyl sulfides was achieved using the visible light to form 4-allenyl-4-(arylthio)-1,4-dihydroisoquinolin-3-ones **115** [72] Scheme 7.34.

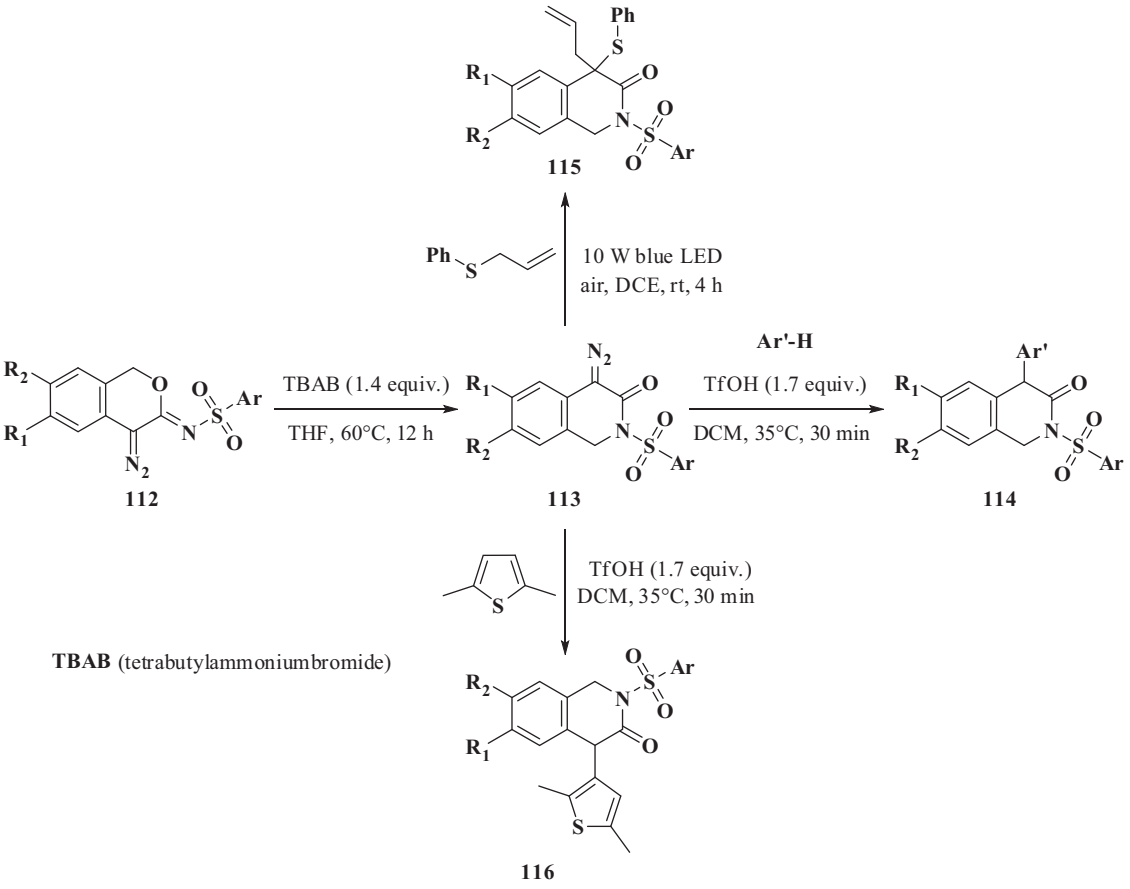
Liu *et al.* [73] reported the synthesis of isoquinolinediones **118** by RhIII-catalyzed C-H activation/annulation/



SCHEME 7.32 *N*-Tosyl 3-methylidene-2,3-dihydroquinolin-4(1*H*)-ones **109** *via* Horner-Wadsworth-Emmons reagents.



SCHEME 7.33 *N*-Sufonyl 3,4-dihydroisoquinolin-1(2*H*)-ones **111** through intermolecular annulation of *N*-benzoylsulfonamide.

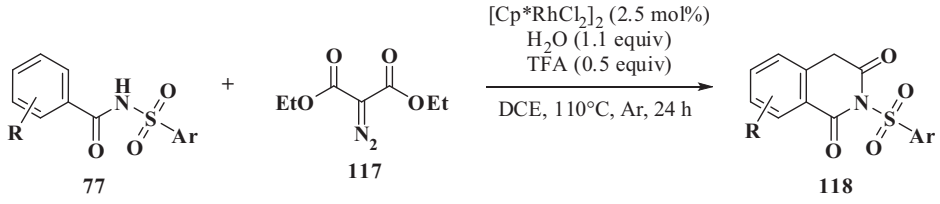


Ar = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-naphthalenyl

Ar' = C_6H_5, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 2-MeC_6H_4, 2-IC_6H_4, 2.5-MeC_6H_3, 3.4-MeC_6H_3, 2.3-MeC_6H_3, 2.4-MeC_6H_3, 2.6-MeC_6H_3

R_1, R_2 = H, 7-MeO, 7-Cl, 7-F, 7-CF_3, 6-MeO, 6-Cl, 6-F,

SCHEME 7.34 *N*-Sulfonyl 4-diazoisoquinolin-3-ones **113** and its conversion to various tetrahydroisoquinolin-3-ones.



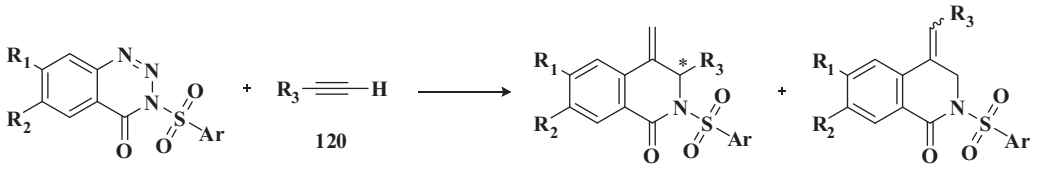
Ar = 4-MeC_6H_4

R = 8-Me, 8-Et, 80MeO, 8-F, 8-Cl, 8-Br, 8-CF_3, 7-Me, 7-Cl, 8-C_6H_5, 7-C_6H_5, 6,8-Me

SCHEME 7.35 Isoquinolinediones **118** by RhIII-catalyzed C−H activation/annulation/decarboxylation of *N*-tosylbenzamides.

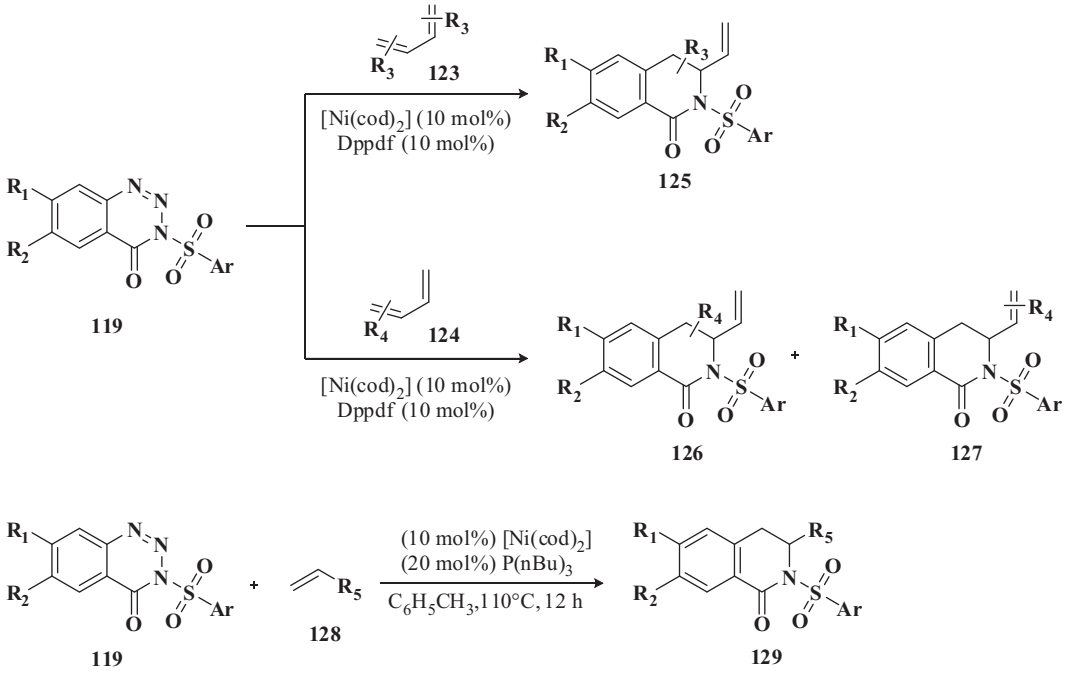
decarboxylation of *N*-tosylbenzamides **77** with diazo compounds **117**, Scheme 7.35. Several *ortho* and *meta*-substituted *N*-tosylbenzamides were employed in the reaction. The efficiency of the reaction was found to be improved with the good tolerance of various functional groups, to produce the corresponding products in moderate to good yields.

1,2,3-Benzotriazinones **119** were good substrates for denitrogenative transannulation reactions. Nickel catalyzed-transannulation reactions of 1,2,3-benzotriazinones **119** with alkynes **120** was a successful approach for the preparation of *N*-sulfonyl-1(2*H*)-isoquinolones, Scheme 7.36. In 2008, Murakami *et al.* [74] confirmed that, in the presence of a nickel(0)/phosphine catalyst,



Ar = 4-MeC$_6$H$_4$
R$_1$, R$_2$ = H, 4-CF$_3$C$_6$H$_4$, CONPh$_2$, (CH$_2$)$_2$N(phth)),
R$_4$= (CH$_2$)$_2$OBn, (CH$_2$)$_2$OSit-Bu(CH$_3$)$_2$, (CH$_2$)$_2$OH, (CH$_2$)$_3$CN, c-Hex

SCHEME 7.36 Isoquinolones **121** and **122** by nickel catalyzed-transannulation reactions of 1,2,3-benzotriazinones.



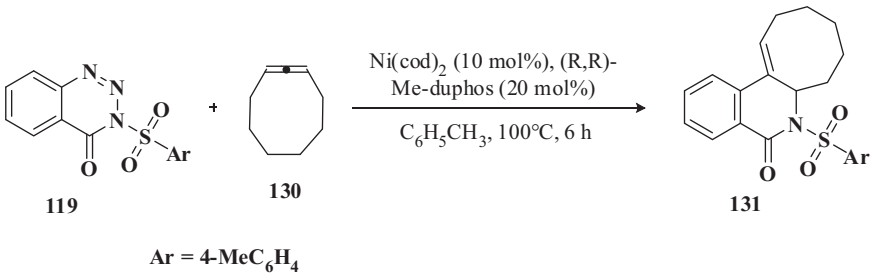
Ar = 4-MeC$_6$H$_4$
R$_1$,R$_2$= H, OCH$_3$, R$_3$ = H, cyclohxane, R$_4$= CH$_3$, C$_6$H$_{11}$, R$_5$ = H,
R$_6$ = C$_6$H$_4$-4-CF$_3$, CN, CON(CH$_3$)$_2$, COC$_2$H$_5$, 2-pyridyl, 4-pyridyl

SCHEME 7.37 Transannulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones to form various *N*-tosyl-3,4-dihydroisoquinolin-1(2*H*)-ones.

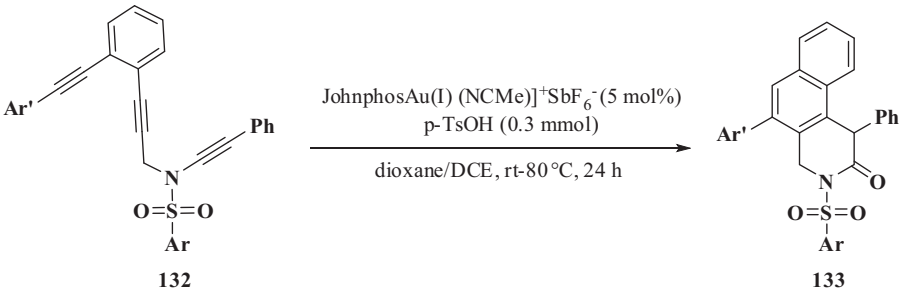
1,2,3-benzotriazinones underwent a facile reaction with terminal alkynes **120** to afford isoquinolones **121** and **122** with very high regioselectivity and in excellent yield, Scheme 7.36. The reaction was initiated by the insertion of Ni^o into the *N-N* linkage forming the aza-nickelacycle after a loss of dinitrogen. Insertion of the alkyne into the Ni-C bond resulted in the formation of a seven-membered nickelacycle intermediate, which after reductive elimination, furnished the major product and regenerated the Ni catalyst.

The same group expanded the above methodology to develop the nickel-catalyzed transannulation of benzotriazinones **119** with 1,3-dienes **123** and **124** and activated alkenes **128**. Different substituted *N*-sulfonyl-1,2,3-benzotriazin-4(3*H*)-ones **119** underwent an efficient transannulation reaction with symmetrical 1,3-dienes **123** in presence of [Ni(cod)$_2$] (10 mol%) and DPPF (10 mol%) at 60°C to produce various 3,4-dihydroisoquinolin-1(2*H*)-ones **125**, Scheme 7.37 [75]. Using the unsymmetrical dienes **124** as substrates resulted in isoquinolones **126** and **127** as major regioisomers, Scheme 7.37. A verity of alkenes **128** such as electron-deficient alkenes and pyridyl-containing alkenes smoothly underwent this transformation but electron-neutral and electron-rich alkenes did not participate in this reaction.

In 2010, Murakami *et al.* [75] also reported an annulation reaction of 1,2,3-benzotriazin-4(3*H*)-ones with



SCHEME 7.38 Transannulation reaction of 1,2,3-benzotriazin-4(3*H*)-one **119** with cyclic 1,3-disubstituted allene **130** using nickel–phosphine complex.



SCHEME 7.39 *N*-Sulfonyl dihydroisoquinolone **133** through cyclization of diyne-tethered ynamides.

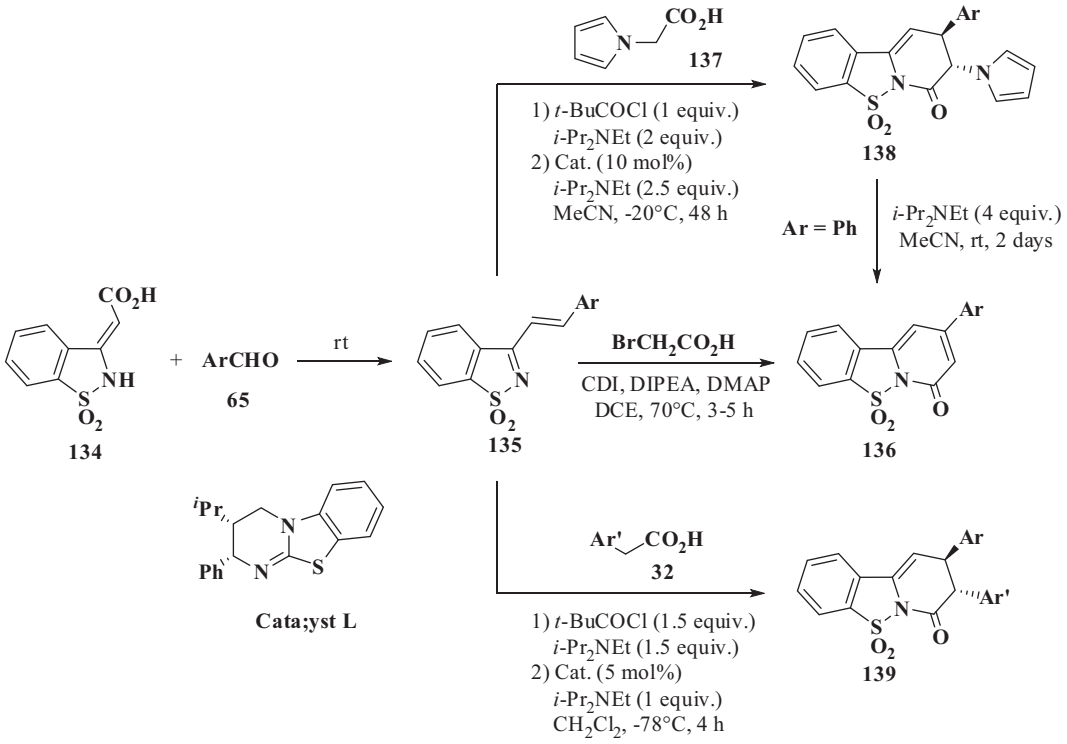
allenes using nickel–phosphine complex to produce a variety of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones. The bidentate phosphine ligand (R,R)-Me-DuPhos was found to be an effective ligand for transannulation reaction of *N*-tosyl-1,2,3-benzotriazin-4(3*H*)-one **119** with cyclic 1,3-disubstituted allene **130** to afford only one product **131** in 99% yield, Scheme 7.38.

Another synthetic route to form dihydroisoquinolone **133** was through a *p*-TsOH promoted cascade cyclization of diyne-tethered ynamides **132** in the presence of an Au (I)-catalyst, Scheme 7.39 [76]. The study showed the effect of substitutions at the *o*-, *m*-, or *p*- position on the aryl moiety at the ynamide terminus in **132** by the Au-catalyzed cascade cyclization. This reaction led to the formation of a wide range of benzo[*f*]dihydroisoquinolones **133** in good yields.

7.2.8 Synthesis of *N*-sulfonyl pyridinone-fused heterocycles

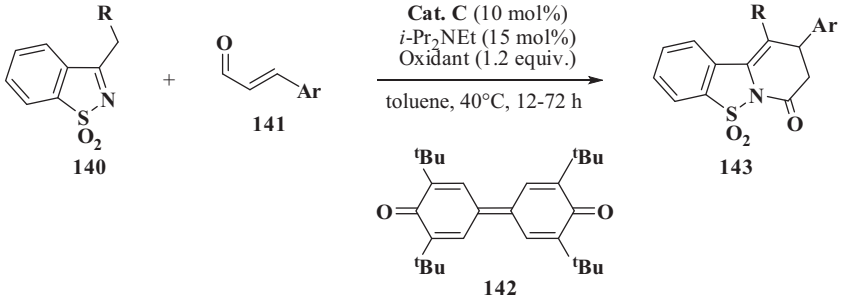
The focus of recent research has been on using chiral isothioureas as effective catalysts for [4 + 2] cycloadditions of carboxylic acids as isothiouronium enolate precursors. By applying this approach, enantioenriched dihydro 2-pyridinones were prepared with a variety of substitutes using either α,β-unsaturated ketimines or α,β-unsaturated sultams based on a saccharin core structure. The saccharin-derived ketimines **135** were first synthesized through the decarboxylation of 3-carboxymethylene-l,2-benzisothiazole-l,l-dioxide **134** by the reaction with arylaldehyde **65** at room temperature [77]. *N*-Sulfonyl fused pyridine-2-ones **136** have been synthesized from bromoacetic acid *via* a DMAP-promoted *in situ* activation strategy, Scheme 7.40. The reaction was fast and produced fused pyridine-2-ones in moderate to high yields [78]. In 2020, the Smith group has developed a protocol for the isothiourea-catalyzed enantioselective functionalization of pyrrolylacetic acids **137** [79]. 2-Pyridinones with pyrrol moiety **138** were obtained in moderate to excellent yield. An unusual elimination of pyrrole from the dihydropyridinone to access achiral pyridinones **136** was achieved and was selectively promoted in Scheme 7.40. Moreover, a range of trans-dihydro 2-pyridinones **139** was also synthesized by catalytic enantioselective synthesis from aryl-, heteroaryl- and alkenylacetic acids **32** and saccharin-derived ketimines **135** in good to excellent stereocontrol using isothiourea catalyst for this transformation at −78°C, Scheme 7.40 [80].

NHC-Catalyzed annulations of cyclic sulfonylimines **140** operating through the catalytic generation of



Ar = C_6H_5, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, 2-BrC_6H_4, 2-naphthyl, 2-thienyl, 2-furyl
Ar' = C_6H_5, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 1-naphthyl, 2-furyl

SCHEME 7.40 Synthesis of various fused pyridine-2-ones starting from saccharin-derived ketimines.



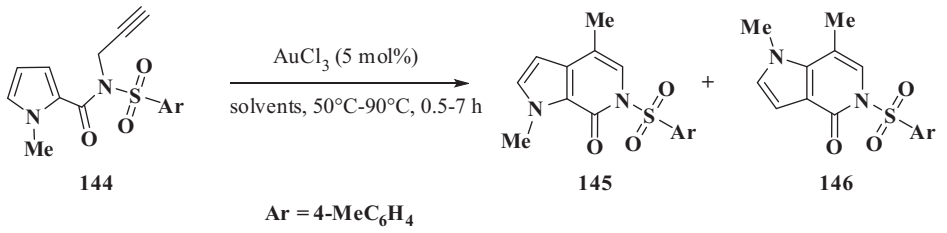
R = H, CH_2CH_2Me
Ar = Me, CH_2CH_2Me, $CH(Me)_2$, C_6H_5, 4-$MeOC_6H_4$, 4-BrC_6H_4, 3,4-BrC_6H_3

SCHEME 7.41 Dihydropyridinones **143** *via* *N*-heterocyclic carbenes-catalyzed annulations of cyclic sulfonylimines.

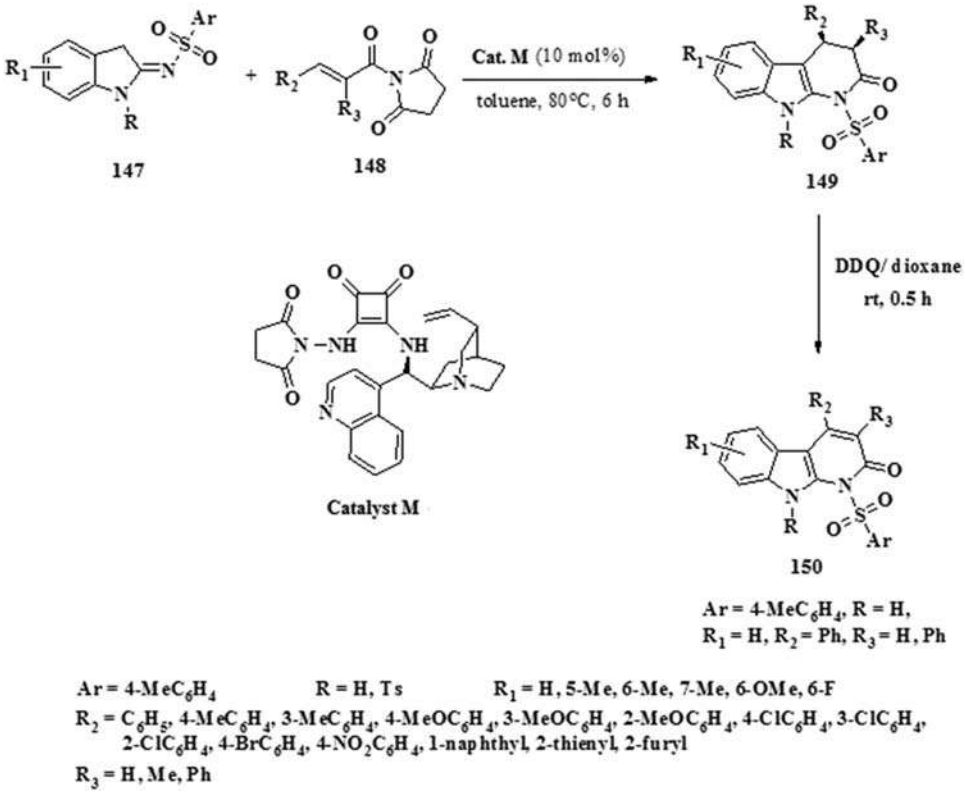
α,β-unsaturated aldehydes **141** have been developed, Scheme 7.41. Chiral *N*-mesityl substituted triazolium salt, catalyst C, used together with oxidant **142** has shown to be an outstanding catalyst for the annulation to afford the desired dihydropyridinone **143** products exclusively [81].

In 2011, Borsini *et al.* reported the intramolecular hydroarylation of *N*-propargyl-pyrrole-2-carboxamides **144** using gold(III) catalysis [82]. The reaction led to the formation of a mixture of substituted pyrrolo[2,3-*c*] pyridinone **145** and pyrrolo[3,2-*c*]pyridinone **146** derivatives through direct cyclization or from a formal rearrangement of the carboxamide group, Scheme 7.42. It was found that terminal alkynes are essential to achieve bicyclic pyrrole-fused pyridinones by a 6-*exo*-dig process. Furthermore, the mechanism of the intramolecular cyclization reactions of terminal alkyne was studied theoretically [83].

A bifunctional Brønsted base-catalyzed asymmetric [3 + 3] cyclization of indolin-2-imines **147** and



SCHEME 7.42 Intramolecular hydroarylation of *N*-propargyl-pyrrole-2-carboxamides.

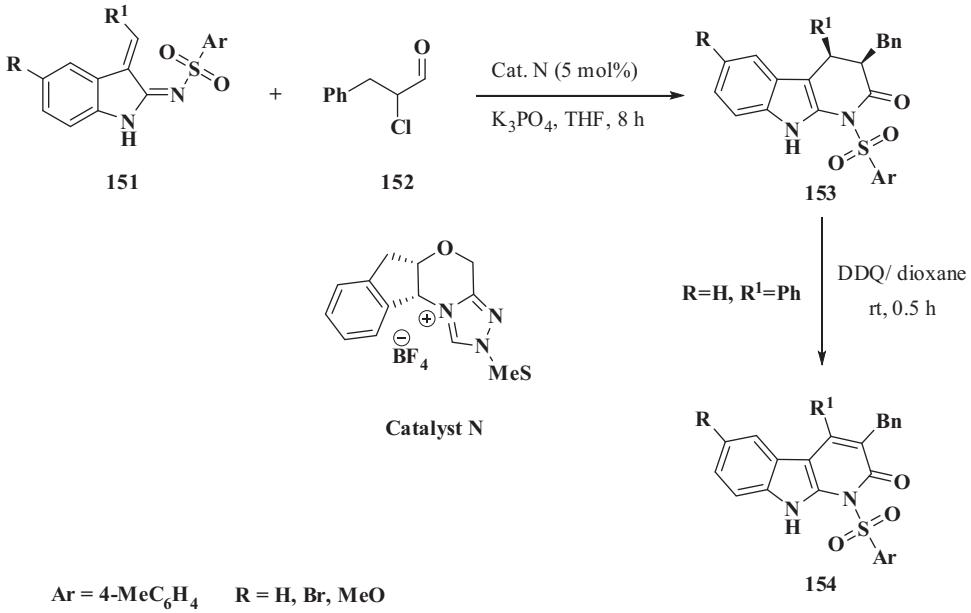


SCHEME 7.43 *N*-Sulfonyl tetrahydro-α-carbolinones **149** by Brønsted base.

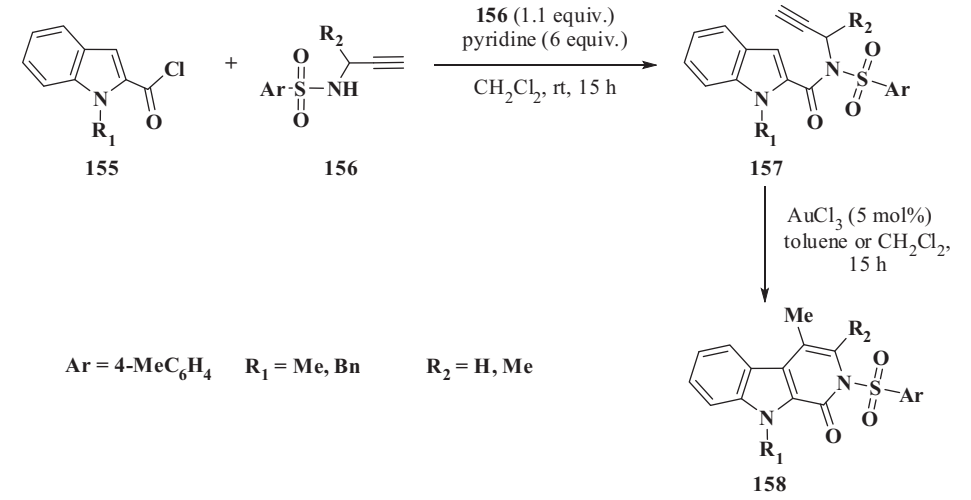
α,β-unsaturated *N*-acylated succinimides **148** by noncovalent bonding catalysis was used to synthesize *N*-sulfonyl tetrahydro-α-carbolinones **149** bearing different substituents with up to 99% yield, Scheme 7.43. Various indolin-2-imines **147** and α,β-unsaturated *N*-acylated succinimides **148** have been tested and all reactions worked smoothly to yield the desired products [84]. Oxidation of **149** using DDQ readily produced α-carbolinone **150** in excellent yield, Scheme 7.43.

A new class of excellent aza-diene electrophiles in NHC-catalyzed asymmetric [4 + 2] cyclizations were used to synthesize *N*-tosyl tetrahydro-α-carbolinones **153** with up to 99% yield from various iminoindoline-derived alkenes **151**. A broad range of iminoindoline **151** with diverse electronic and steric properties readily participated in the [4 + 2] cyclization, forming the desired products tetrahydro-α-carbolinones **153** incorporate various substituents and functionalities, including (hetero)- aryl, (linear or branched)alkyl, alkenyl, alkynyl, and ester groups in excellent yields (up to 99% yield) with excellent stereoselectivity (up to >19:1 Dr and >99% ee), Scheme 7.44. Oxidation of **153** using DDQ readily produced α-carbolinone **154** in 92% yield [85].

It was reported, as well, that indole-substituted *N*-propargylamides **157** underwent a gold(III)-catalyzed cyclization to produce *N*-tosyl β-carbolinones **158**, Scheme 7.45. It was found that 2,9-dihydro-β-carbolin-1-ones **158** synthesized starting from tertiary indole-2-carboxamides



SCHEME 7.44 *N*-Tosyl tetrahydro-α-carbolinones **153** *via* *N*-heterocyclic carbenes-catalyzed asymmetric [4 + 2] cyclizations.

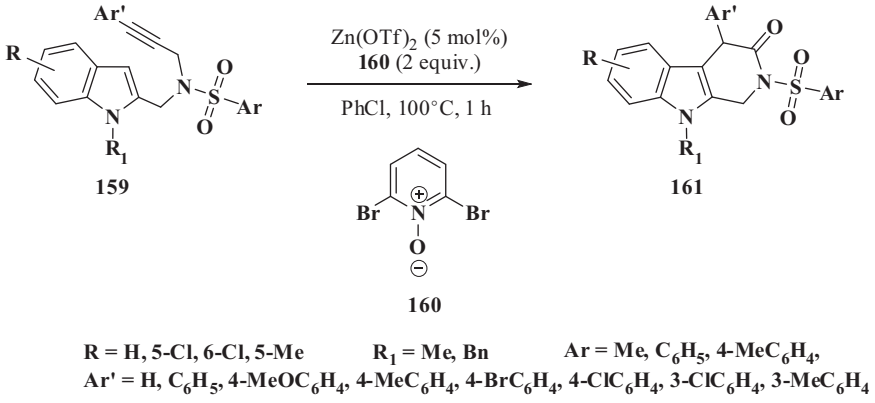


SCHEME 7.45 *N*-Tosyl β-carbolinones **158** through gold(III)-catalyzed cyclization reaction.

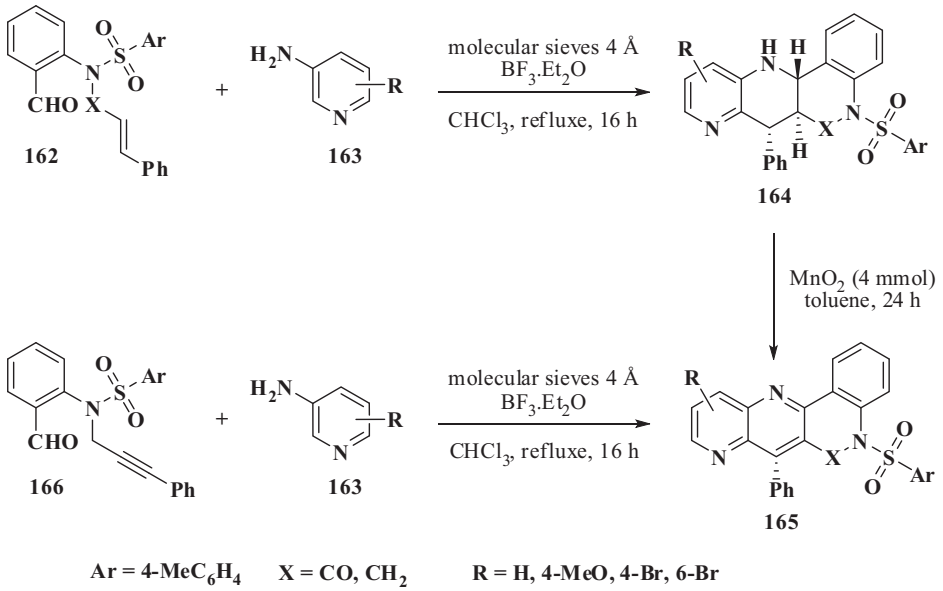
157 which cycloisomerized upon treatment with catalytic amounts of gold(III) chloride. Indole-substituted *N*-propargylamides were prepared *via* the reaction of *N*-benzyl-2-indoloyl chloride **155** with *N*-tosyl-propargylamine **156** [86,87].

Another pathway to develop *N*-sulfonyl β-carbolines was reported by Li *et al.* [88]. A variety of β-carbolines **161** was obtained in a highly site-selective synthesis *via* efficient zinc(II)-catalyzed alkyne oxidation/C-H functionalization sequence, Scheme 7.46. In contrast to the well-established gold-catalyzed intermolecular alkyne oxidation, mechanistic studies and theoretical calculations revealed that the reaction most likely proceeded by a Friedel-Crafts-type pathway.

Synthesis of hybrid quinolino [4,3-*b*] [1,5]naphthyridines and quinolino [4,3-*b*] [1,5]naphthyridin-6(5*H*)-ones in good to high yields was performed by an intramolecular Povarov [4 + 2]-cycloaddition reaction of



SCHEME 7.46 *N*-Sulfonyl *β*-carbolines **161** by zinc(II)-catalyzed alkyne reaction.



SCHEME 7.47 *N*-Tosyl naphthyridin-6(5*H*)-one derivatives **165** by an intramolecular cycloaddition reaction.

functionalized aldimines **162** after the condensation of 3-aminopyridine **163** with aldehyde group, Scheme 7.47. Consequent dehydrogenation of the resulting product **164** led to the corresponding *N*-tosyl naphthyridine and *N*-tosyl naphthyridin-6(5*H*)-one derivatives **165** (X = CH_2, CO). On the other hand, the formation of *N*-tosyl quinolino [4,3-*b*][1,5]naphthyridines **165** (X = CH_2) was achieved through the reaction of aldehyde having a triple bond in their structure with aldimines **166** through an intramolecular cycloaddition in the presence of $BF_3.Et_2O$, Scheme 7.47 [89].

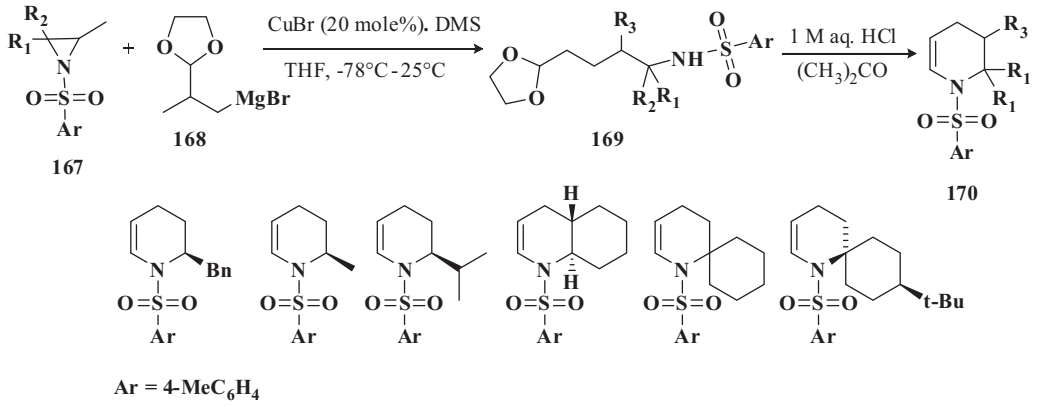
The topoisomerase I (TopI) enzymatic inhibition of the polycyclic products was investigated and the results showed that the synthesized *N*-sulfonyl quiolino derivatives had a high TopI inhibitory activity at short enzymatic reaction time and at longer reaction times as compared to the natural inhibitor CPT [89].

7.3 Synthesis of *N*-sulfonyl pyridine derivatives and their biological activities

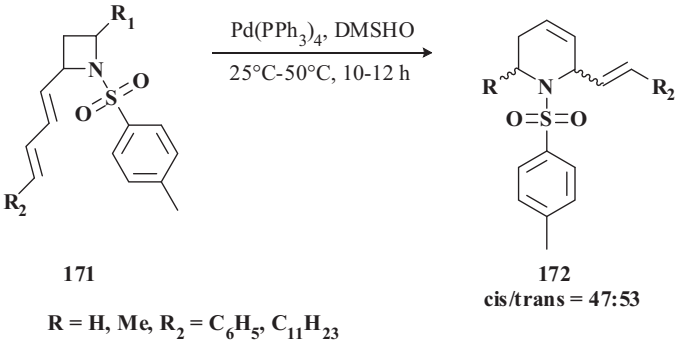
7.3.1 Synthesis of *N*-sulfonyl di- and tetrahydropyridines

In 2006, Pattenden *et al.* reported a stepwise [3 + 3] annelation sequence to tetrahydropyridines from azidirines. In this method, the addition of dioxolane-based Grignard reagent **168** to aziridine derivatives **167** yielded ring-opened products **169**, and subsequent acid-catalyzed deprotection−cyclization produced the desired *N*-tosyl tetrahydropyridine derivatives **170** in high yield [90], Scheme 7.48. Lately, this methodology was applied to the syntheses of (−)-monomorine [91] and quinolizidine (−)-217A [92].

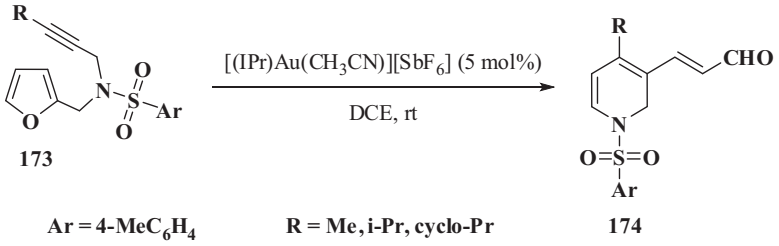
$Pd(PPh_3)_4$ used as effective catalyst for transformation of *N*-tosyl-1,3-butadienyl azetidines **171** to *N*-tosyl



SCHEME 7.48 *N*-Tosyl tetrahydropyridines **170** *via* [3 + 3] annelation sequence from azidirines.



SCHEME 7.49 *N*-Tosyl vinylpiperidines **172** by Pd0)-catalyzed reaction of *N*-tosyl-1,3-butadienyl azetidines.



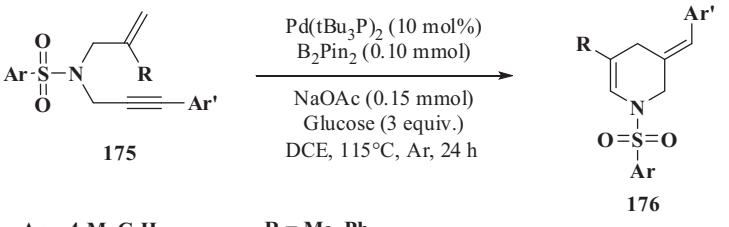
SCHEME 7.50 *N*-Tosyl pyridines **174** *via* gold-catalyzed intramolecular cycloisomerization of α-alkyne-furans.

vinylpiperidines **172** [93], Scheme 7.49. Notably, the occurrence of the *N*-tosyl group which activated the azetidine ring and the dienic moiety was pivotal for the rearrangement.

A gold-catalyzed intramolecular cycloisomerization of alkyl-substituted α-alkyne-furans **173** led to the formation of a variety of cyclic α,β-unsaturated aldehyde derivatives of *N*-tosyl pyridine **174** in moderate yield under mild conditions, Scheme 7.50 [94].

Catalytic divergent cycloisomerization of 1,6-enynes **175** was achieved for the synthesis of *N*-tosyl tetrahydropyridine derivatives **176** using the combination of a palladium catalyst and B_2Pin_2 as the additive in addition to glucose as an H source, Scheme 7.51. A direct hydropalladation of alkyne/6-*endo*-trig cyclization reaction was found to give the tetrahydropyridines using 1,6-enynes with disubstituted terminal alkenes [95].

A palladium-catalyzed iodine atom transfer cycloisomerization of (*Z*)-1-iodo-1,6-diene **177** was a very effective method to construct an *N*-tosyl tetrahydropyridine ring bearing an alkyl iodide group **178**, Scheme 7.52. Both the type and the quantity of ligand execute significant influences on this cycloisomerization, and the combination of 30 mol% 1,10-bis(diphenylphosphino) ferrocene (DPPF) and 10 mol% $Pd(OAc)_2$ was the optimal choice [96].

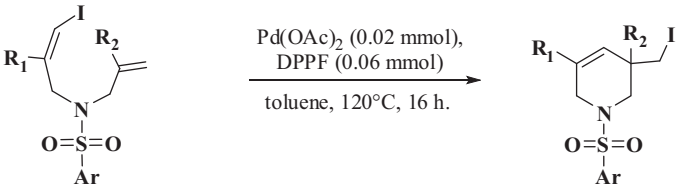


175 **176**

Ar = 4-MeC$_6$H$_4$ **R = Me, Ph**

Ar' = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-t-BuC$_6$H$_4$, 4-BnOC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 2-naphthyl, 2-thienyl

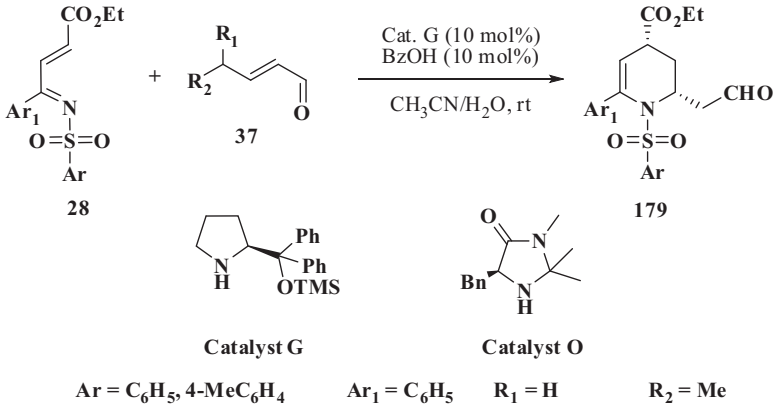
SCHEME 7.51 *N*-Tosyl tetrahydropyridines **176** *via* cycloisomerization of 1,6-enynes.



177 **178**

Ar = 4-MeC$_6$H$_4$ **R$_1$ = Et, Ph** **R$_2$ = Me, *n*-Bu, *t*-Bu**

SCHEME 7.52 *N*-Tosyl tetrahydropyridine **178** *via* cycloisomerization of (*Z*)-1-iodo-1,6-diene.



28 **37** **179**

Catalyst G **Catalyst O**

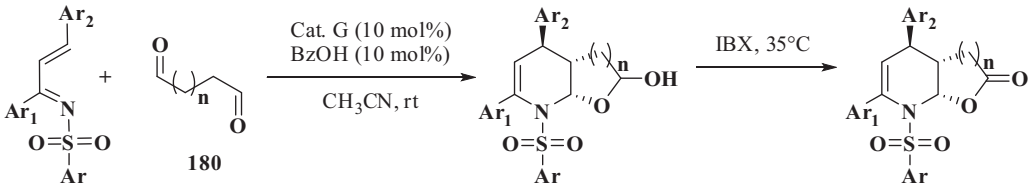
Ar = C$_6$H$_5$, 4-MeC$_6$H$_4$ **Ar$_1$ = C$_6$H$_5$** **R$_1$ = H** **R$_2$ = Me**

SCHEME 7.53 Hemiaminals **179** using an (*R*)-diphenylprolinol O-TMS catalysis.

The unexpected β,γ-regioselectivity when crotonaldehyde **37** was used with a differently substituted *N*-tosyl-1-azadiene **28**, led to the formation of the hemiaminals **179** with low enantioselectivities using an (*R*)-diphenylprolinol O-TMS, catalyst G, Scheme 7.53. A slightly better result is observed when the MacMillan catalyst, catalyst O, was used [32].

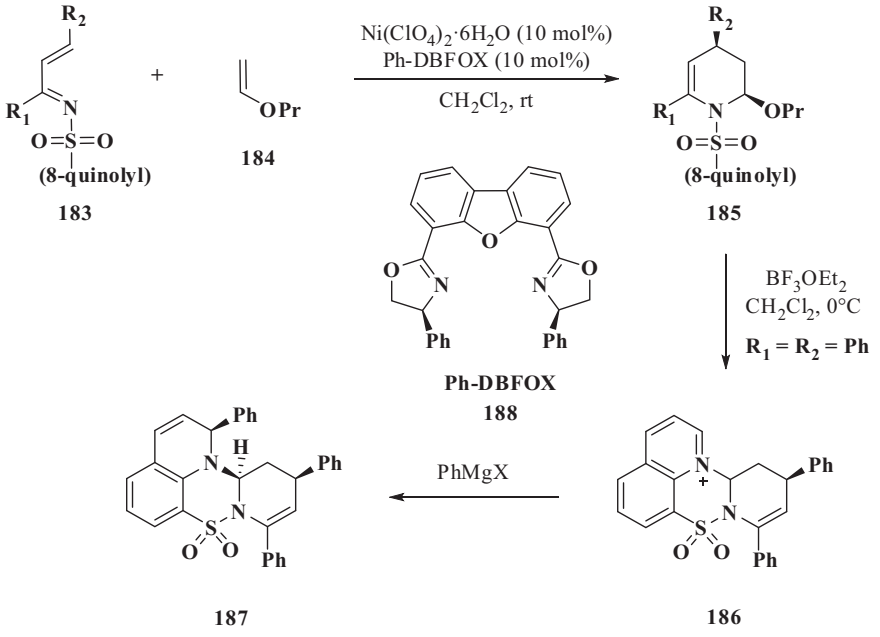
The Chen group reported the use of (*R*)-diphenylprolinol O-TMS, catalyst G, to provide various enantioenriched aza-heterocycles [97]. The IED-aza-DA reaction of glutaraldehyde **180** and *N*-tosyl-1-azadienes **31** followed by oxidation afforded the corresponding chiral *N*-tosyl lactone[2,3-*b*]tetrahydropyridines **182** in moderate yields and with high diastereo- and enantioselectivities, Scheme 7.54.

An effective procedure for the IED-aza-DA of *N*-(heteroaryl)sulfonyl α,β-unsaturated imines with vinyl ethers catalyzed by nickel complex **188** (Kanemasa's Ph-DBFOX ligand) was established. The best results were obtained using *N*-8-quinolyl imine **183** after the screening of many *N*-sulfonyl protecting groups. A wide variety of *N*-8-quinolyl imines underwent the cycloaddition with vinyl ethers **184** to form the functionalized piperidines **185** with high levels of *endo*-selectivity and



Ar = 4-MeC$_6$H$_4$ Ar$_1$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-thienyl, CO$_2$Et
Ar$_2$ = Me, C$_6$H$_5$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, CO$_2$Et

SCHEME 7.54 *N*-Tosyl lactone[2,3-*b*]tetrahydropyridines **182** by IED-aza-DA reaction of glutaraldehyde.



R$_1$ = C$_6$H$_5$, 4-CNC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-CF$_3$C$_6$H$_3$
R$_2$ = C$_6$H$_5$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 2-naphthyl, 2-furyl, *t*-Bu

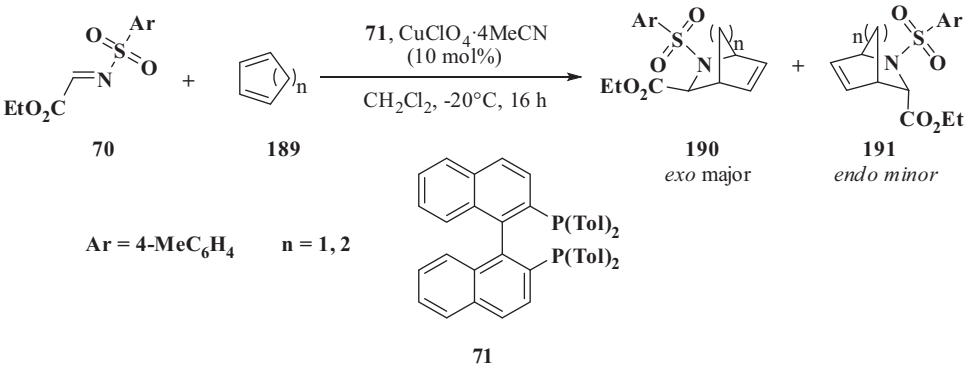
SCHEME 7.55 IED-Aza-DA of *N*-(heteroaryl)sulfonyl α,β-unsaturated imines with vinyl ethers catalyzed by nickel complex.

enantioselectivity, Scheme 7.55. The major isomer was determined as (2*R*,4*S*) by converting the adduct into **187** by a sequence of adding quinoline, forming the product **186**, followed by the Grignard reagent [98].

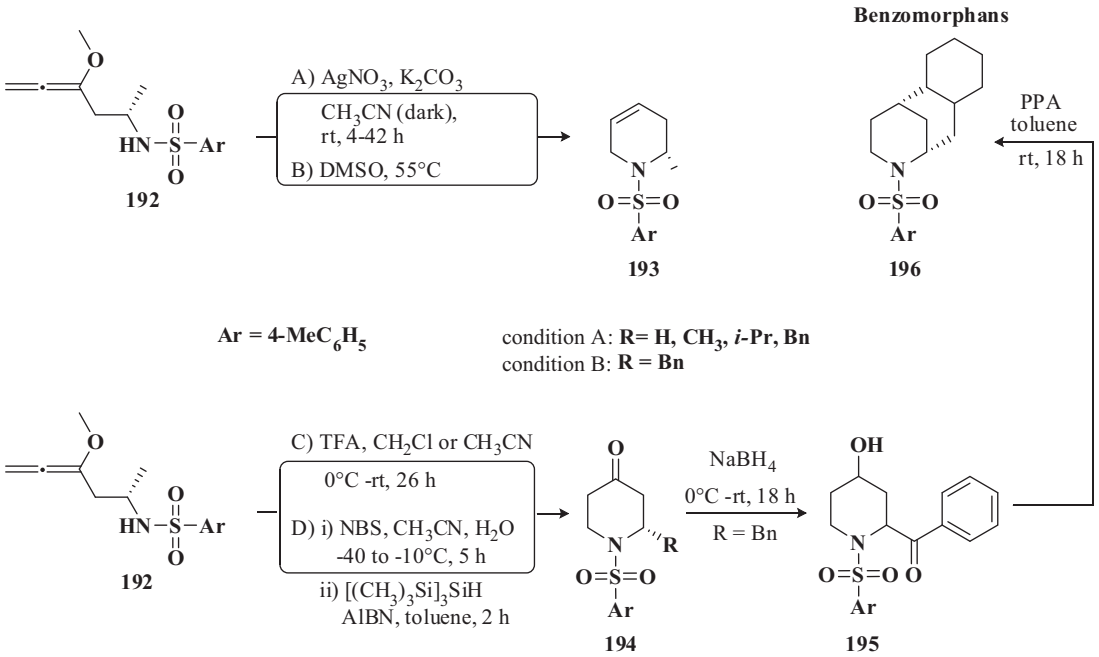
The study of the IED-aza-DA reaction of activated *N*-tosyl imine **70** with unactivated cyclic 1,3-dienes **189**, cyclopentadiene, and 1,3-cyclohexadiene, was expanded. The reaction proceeded well using $CuClO_4$-Tol-Binap and afforded a mixture of *exo*- and *endo*-cycloadducts **190** and **191**, respectively, Scheme 7.56 [99].

7.3.2 Synthesis of *N*-sulfonyl pipyridines

In 2009, Prisyazhnyuk *et al.* [85], reported a silver nitrate-assisted intramolecular cyclization of methoxyallenes **192** under the basic conditions to form *N*-tosyl piperidines **193** in 25% yield only. An alternative method was applied for a better yield *via* heating methoxyallenes **192** to 55°C in dimethylsulfoxidem, Scheme 7.57. In addition to piperidines synthesis, piperidin-4-one **194** was also successfully synthesized by treatment of **192** with either one equivalent of trifluoroacetic acid or bromination with NBS followed by the addition of one equivalent of tris(trimethylsilyl) silane. Additionally, 4-piperidone derivatives were suitable precursors for the synthesis of benzomorphans **196**. Reduction of **194** with sodium borohydride provided secondary alcohol **195** as a mixture of diastereomers. Subsequent treatment of **195** with polyphosphoric acid afforded the desired tricyclic compound, benzomorphans **196**, in excellent yield, Scheme 7.57.



SCHEME 7.56 IED-aza-DA reaction of *N*-tosyl imine with cyclic 1,3-dienes.

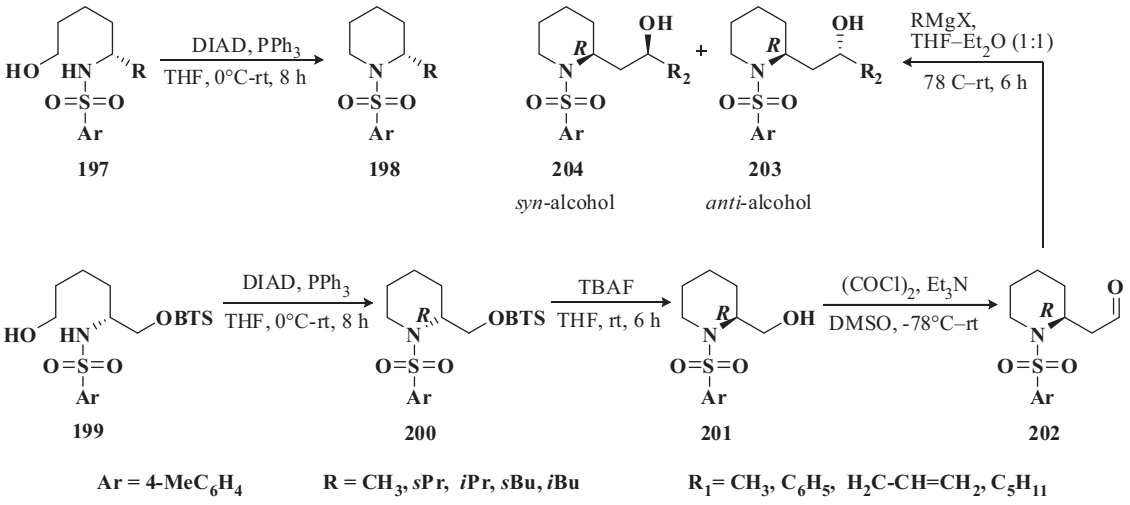


SCHEME 7.57 *N*-Tosyl piperidines **193** *via* silver nitrate-assisted intramolecular cyclization of methoxyallenes.

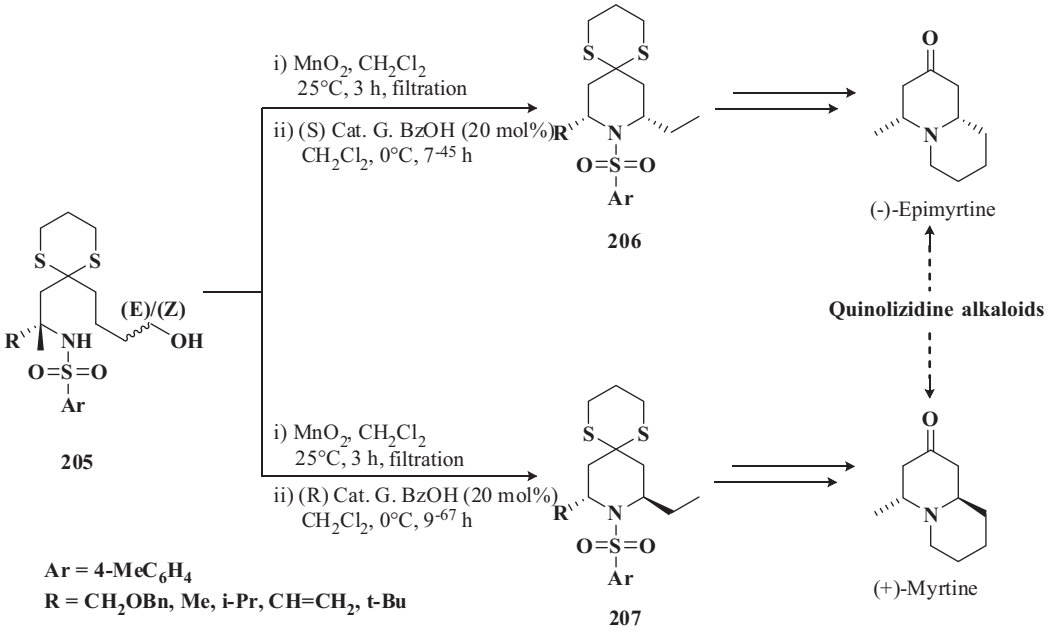
In 2007, Bisai *et al.* [100] explored the exposure of *N*-tosylamino alcohol **197** to diisopropyl azodicarboxylate (DIAD) and n-Bu_3P under Mitsunobu condition resulted in smooth 2-substituted *N*-tosyl piperdine derivatives **198** in excellent yield, Scheme 7.58. Under the same condition, *N*-tosylamino alcohol derivatives **199** converted to *N*-tosyl piperdine **200**. Desilylation of the silyl group using tetrabutylammonium fluoride (TBAF) yielded enantiopure *N*-tosyl-2-piperidinylethanol **201** which was oxidized under Swern conditions to aldehyde **202**. Diastereoselective addition of phenyl or alkyl Grignards to aldehyde **202** afforded a mixture of *anti*-alcohols **203**, as the major product, and *syn* alcohols **204**, Scheme 7.58.

Despite the organocatalytic aza-Michael reaction was rarely used for the stereoselective synthesis of piperidines, Ying *et al.* [101] stereoselectively synthesized both 2,6-*cis*- and 2,6-*trans*-piperidines, compounds **206** and **207**, from germinal substituted 1,3-dithiane **205** through organocatalytic aza-Michael reactions in major amount depending upon the chirality of the organocatalyst employed, Scheme 7.59. Employing the (*S*) catalyst G furnished the *cis*-diastereomer **206** with higher diastereoselectivity while the *trans*-diastereomer **207** afforded in the presence of (*R*) catalyst G.

In 2005, Harrity and co-workers [102] also developed a more efficient alternative method for indirect synthesis of piperidines *via*Grignard addition−cyclization sequence. Double deprotonation of methallyl alcohol **209** followed by addition of the organolithium reagent to *N*-tosyl azidirine **208** furnished **210** which intramolecular cyclized



SCHEME 7.58 *N*-Tosylpiperdines **198** from *N*-tosylamino alcohols.

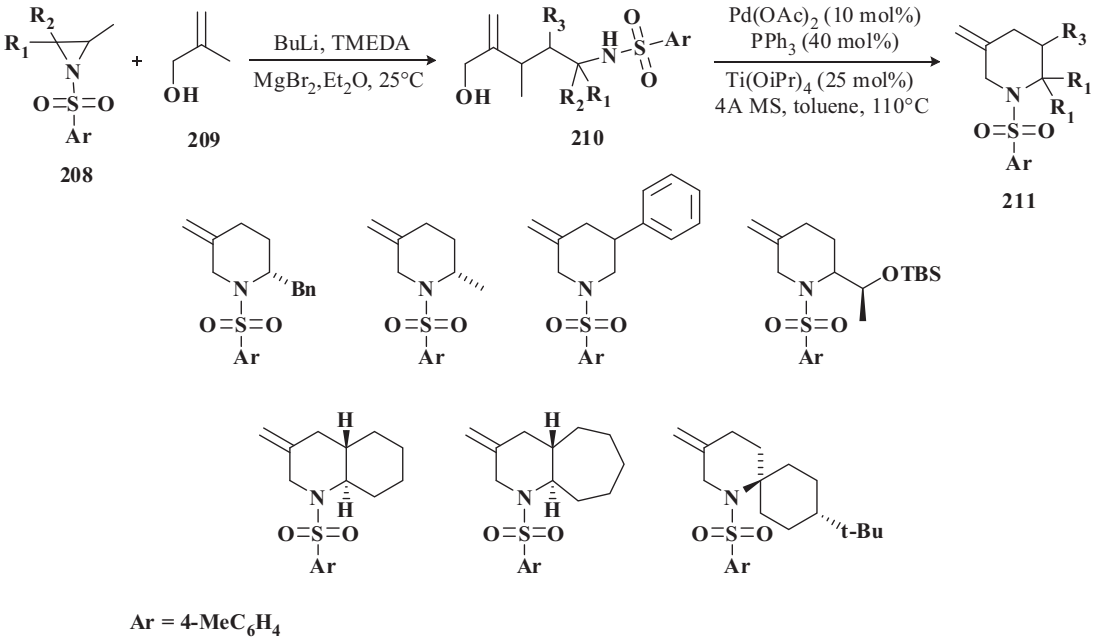


SCHEME 7.59 *N*-Tosyl 2,6-piperidines **206** and **207** through the organocatalytic aza-Michael reaction of 1,3- dithiane.

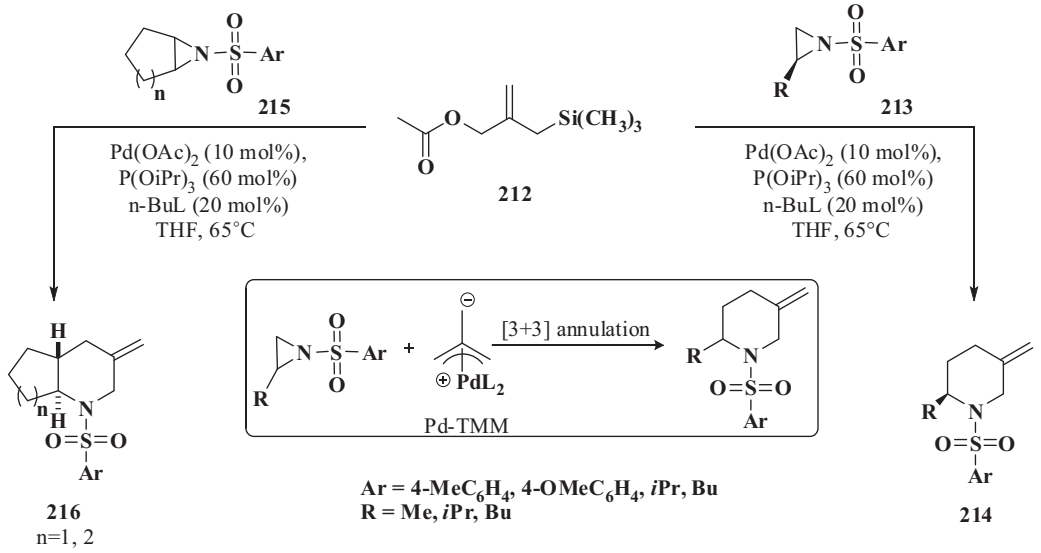
under Pd catalysis to form piperidine derivatives **211** in good yield, Scheme 7.60. The developed strategy was successfully exploited for the formal synthesis of (±)-perhydrohistrionicotoxin [103].

The most interesting approach to directly synthesize different highly functionalized *N*-sulfonyl piperidines **214** and **216** *via* Pd-catalyzed [3 + 3]-cycloaddition reaction of activated 2,2-disubstituted **213**, and 2,3-disubstituted **215** aziridines, respectively, with Pd-trimethylenemethane complexes (Pd-TMM) has been proposed by Harrity and co-workers [104]. In 2001, they explored that the Pd-TMM complex, which *in situ* generated from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **212** in the presence of 10 mol% $Pd(OAc)_2$, 60 mol% $P(OiPr)_3$, and 20 mol% n-BuLi, reacted with diverse 2-alkyl/aryl-*N*-activated aziridines **214** and **216**, Scheme 7.61.

In 2003, the same group [105] extended the substrate scope to various 2,2-substituted aziridines, compounds **217** and **219**, to provide accessing spirocyclic, compounds **218** and **220**, respectively, Scheme 7.62. However, 2,2,3-trisubstituted aziridines failed to participate in such type of transformation. Additionally, the utility of this reaction in the synthesis of *Nuphar* alkaloids from the resulting piperidines was described [106].



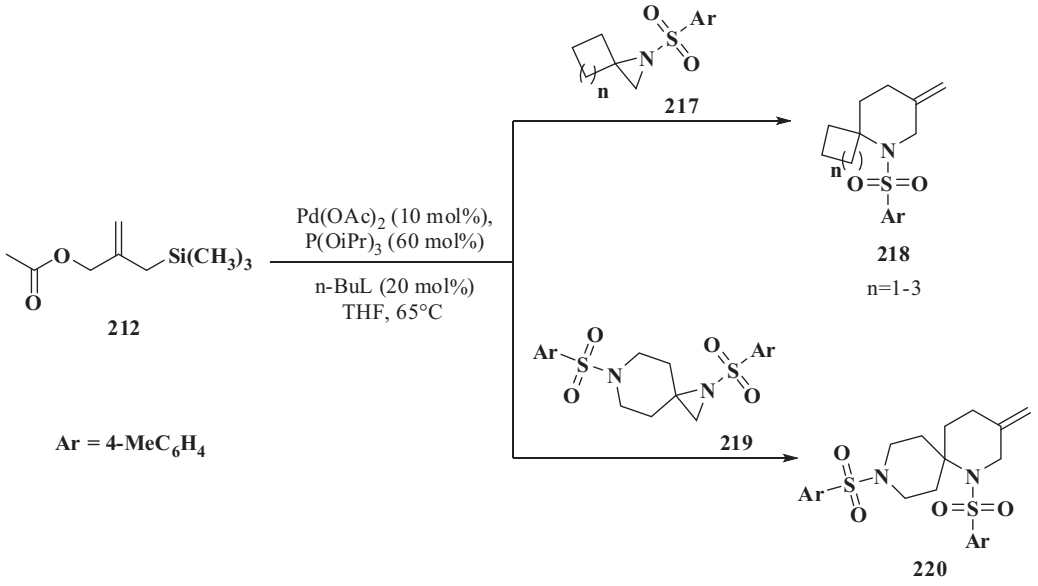
SCHEME 7.60 *N*-Tosyl piperidines **211** *via* intramolecular cyclization under Pd catalysis.



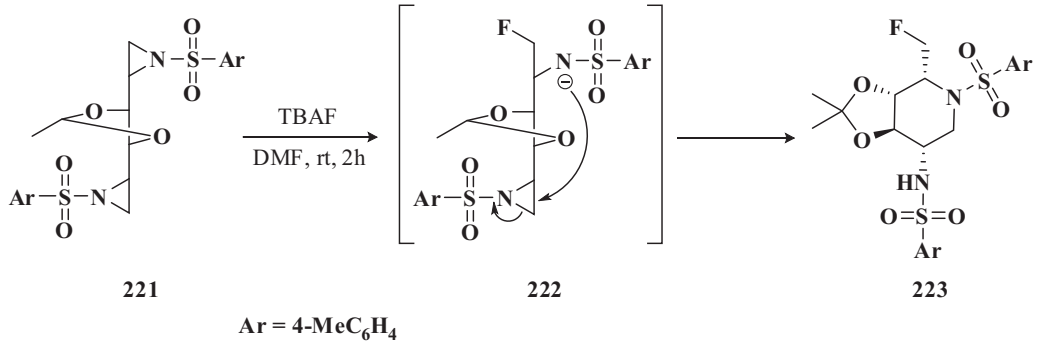
SCHEME 7.61 *N*-Sulfonyl piperidines **214** and **216** *via* Pd-catalyzed [3 + 3]-cycloaddition reaction of disubstituted aziridines.

Previous studies by Dureault *et al.* indicated that a chiral *N*,*N*'-ditosyl bis(aziridine) **221**, which is derived from D-mannitol, transformed to functionalized piperidines **223** in presence of TBAF as a source of fluoride through the ring-opening of one aziridine moiety by fluoride ion followed by the intramolecular opening of the other aziridine moiety with the resulting amide as an intermediate **222**, Scheme 7.63 [107].

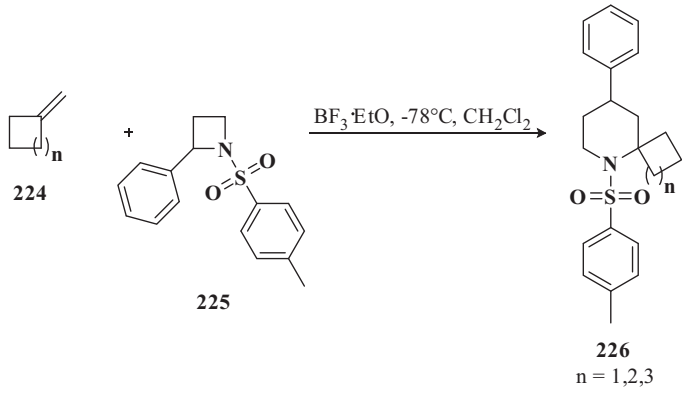
Azetidines in the presence of a suitable Lewis acid behaved as *exo*-stabilized formal 1,4-dipole, which are suitable for [4 + 2] cycloaddition [108]. From this view, Ungureanu *et al.* reported the formal [4 + 2] cycloaddition of azetidine **225** with various unactivated exomethylene cycloalkanes **224** under the catalytic conditions to provide *N*-tosyl spiro-piperidine **226** in good yield, Scheme 7.64 [108].



SCHEME 7.62 Spirocyclic piperidines **218** and **220** *via* Pd-catalyzed reaction of 2,2-substituted aziridines.



SCHEME 7.63 *N*-Tosyl piperidines **223** *via* ring-opening of aziridine by fluoride ion.



SCHEME 7.64 *N*-Tosyl spiro-piperidines **226** through [4 + 2] cycloaddition of azetidines.

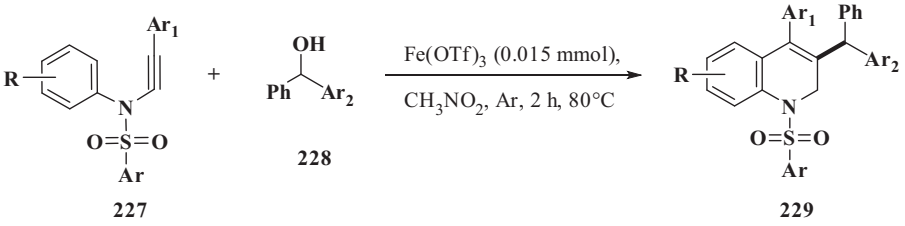
7.3.3 Synthesis of *N*-sulfonyl quinolines

The carbohydroxylation reaction of alkynes with π-activated alcohols was first developed by Jana *et al.* to synthesize various organic molecules *via*the generation of a carbenium ion in the presence of less toxic iron(III) salt [109]. In 2021, synthesis of substituted 1,2-dihydroquinolines **229** from *N*-propargyl anilides **227** and π-activated alcohols **228** was reported using $Fe(OTf)_3$-catalyzed carboarylation of alkynes, Scheme 7.65. The reaction provided a new method for the synthesis of *N*-sulfonyl quinolines by the formation of two carbon−carbon bonds and one ring in a single step [110].

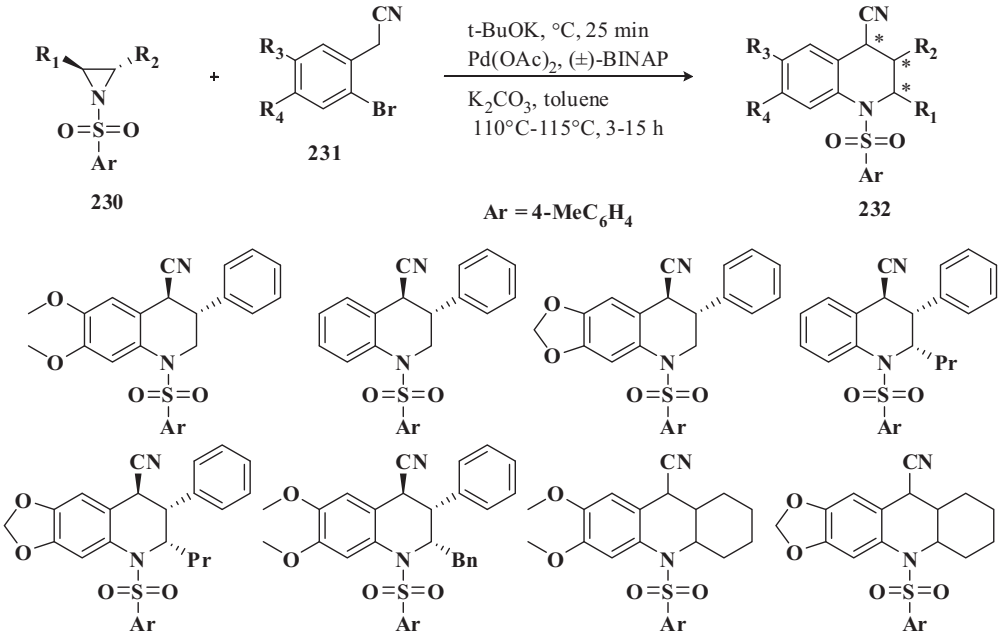
In 2011, Ghorai *et al.* [111] developed a simple and efficient methodology for the construction of substituted *N*-tosyl tetrahydroquinolines **232** through a *t*-BuOK-mediated SN_2-type ring-opening of *N*- tosyl aziridines **230** with arylacetonitriles **231** followed by Pd-catalyzed intramolecular C-N cyclization in excellent yields (up to >99%) and stereoselectivity (ee and de up to >99%) under one-pot reaction conditions, Scheme 7.66. The substrate scope was extended to a variety of aryl and 2,3-disubstituted/bicyclic aziridines.

7.3.4 Synthesis of *N*-sulfonyl isoquinolines and their derivatives

In 2014, Wang *et al.* [112] developed a novel and efficient Lewis acid-catalyzed [3 + 3]-annulation methodology for the construction of tetrahydroisoquinolines **233** from readily available aziridines **8** and benzylic alcohol derivatives in good yield. This reaction, a potential alternative to the classical Pictet−Spengler reaction, began with the nucleophilic ring-opening reaction of the aziridine by the benzylic alcohol to give the intermediate **234** which then underwent an intramolecular amination of the



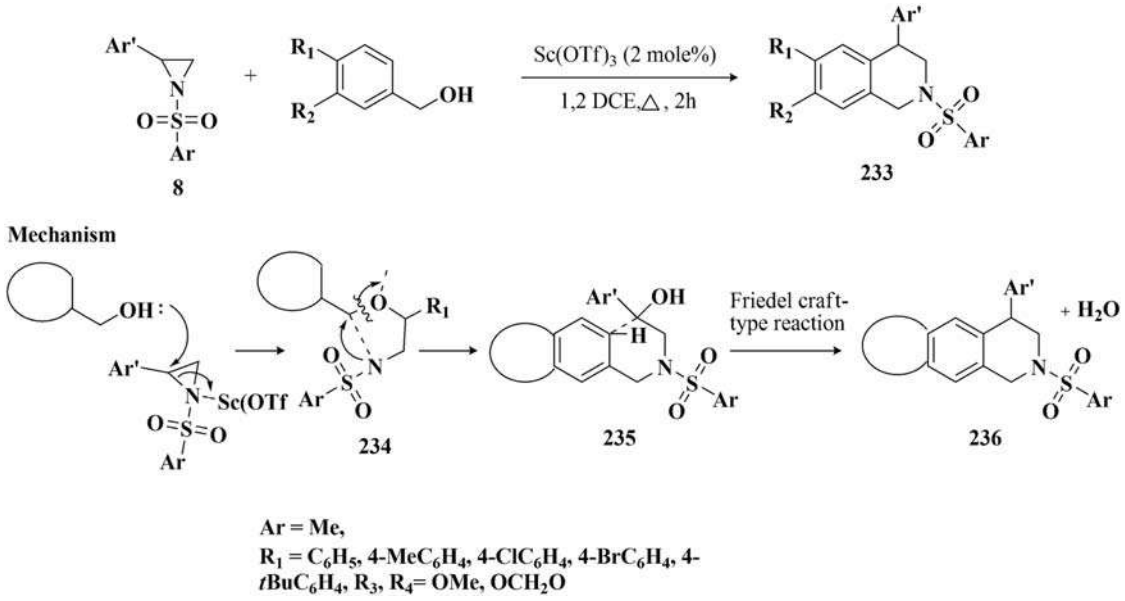
SCHEME 7.65 *N*-Tosyl 1,2-dihydroquinolines **229** through carbohydroxylation reaction of *N*-propargyl anilides.



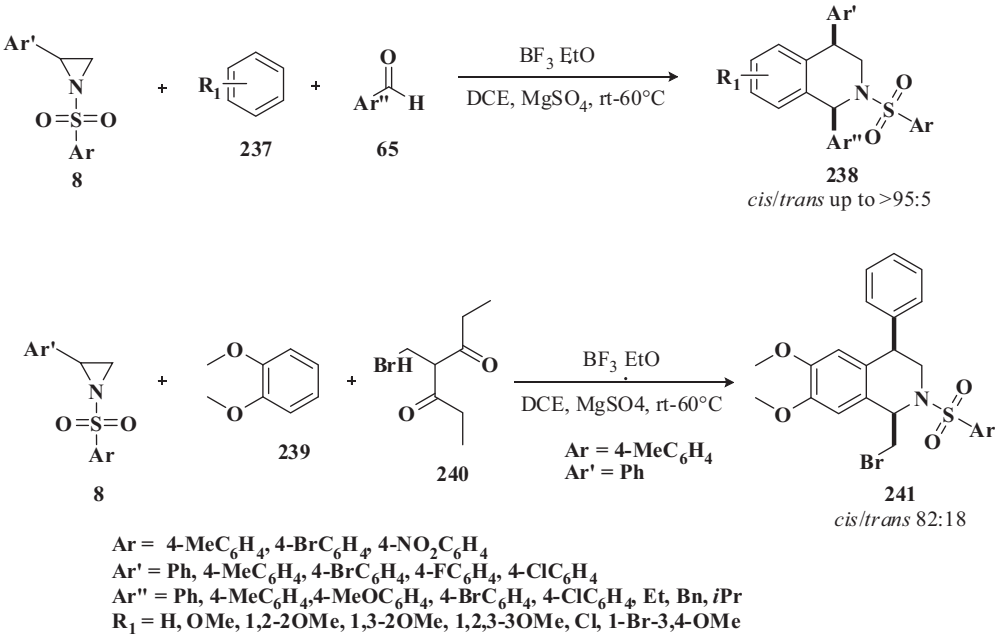
SCHEME 7.66 *N*-Tosyl tetrahydroquinolines **232** through SN_2-type ring-opening of *N*-tosyl aziridines.

benzylic ether to form **235** and sequent an intramolecular Friedel-Crafts-type alkylation to afford the desired products **233**, Scheme 7.67. Notable, this methodology failed to obtain optically pure product from enantiomerically pure aziridine because of racemization of the aziridine in the presence of a Lewis acid.

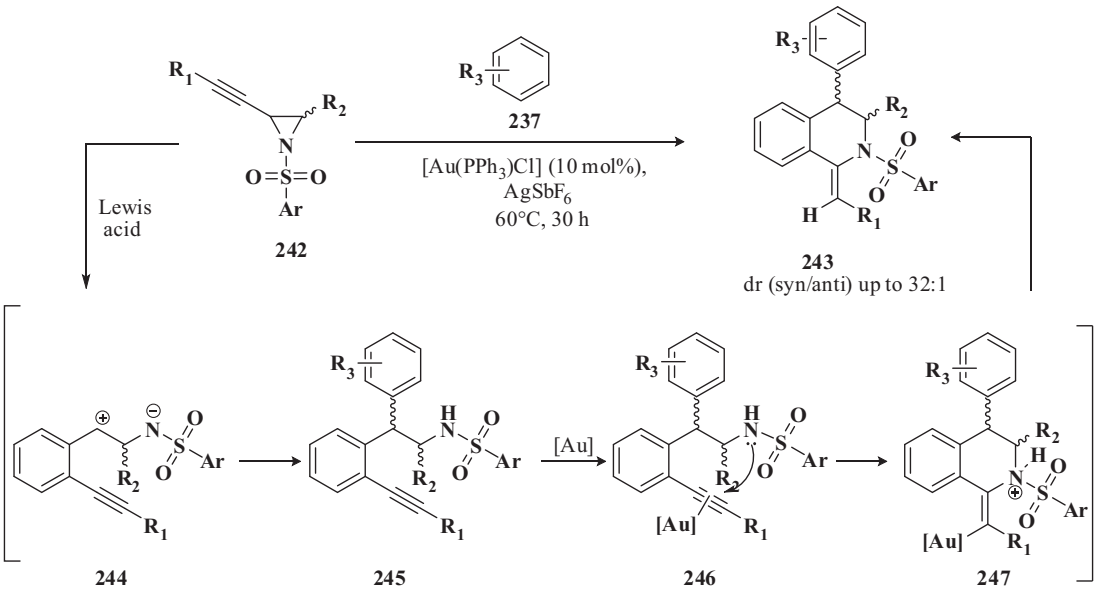
Three-component reactions of aziridines **8**, arenes **237**, and aldehydes **65** catalyzed by Lewis acid BF_3.EtO led to the formation of 1,4-disubstituted tetrahydroisoquinolines **238** [113]. Ring-opening of aziridine followed by pictet-splinger condensation produced abroad range of *cis*-1,4-disubstituted tetrahydroisoquinolines in moderate yield, Scheme 7.68. Abroad ranges of aziridine, arene, and aldehyde substrates were contributed to this reaction. 1,2-Dimethoxybenzen **239** was also a suitable substrate for the three-component reaction, with both of aziridine **8** and 1,3-dicarbonyl derivatives **240**, to produce tetrahydroisoquinoline **241** in 65% yield.



SCHEME 7.67 Tetrahydroisoquinolines **233** *via* Lewis acid-catalyzed [3 + 3]-annulation reaction.



SCHEME 7.68 *N*-Sulfonyl 1,4-disubstituted tetrahydroisoquinolines **238** by ring-opening of azidirines catalyzed by Lewis acid BF_3.EtO.



Ar = 4-MeC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, R_1 = *n*-Bu, Ph, Me, $Si(CH_3)_3$, R_2 = H, Me, OMe, Br, NO_2 *n*-Pr, *n*-Bu, R_3 = H, 1,4-2Me, 1,2-2Me, 1,3,5-3Me,1,4-2Me, 1,2-2OMe

SCHEME 7.69 *N*-Sulfonyl 1,2,3,4-tetrahydroisoquinolines **243** *via* gold-catalyzed domino reaction of aziridinyl alkynes.

In 2010, Zhang *et al.* [114] emerged with an effective protocol for the synthesis of a series of *N*-sulfonyl 1,2,3,4-tetrahydroisoquinolines **243** in excellent yields *via* gold-catalyzed domino reaction of aziridinyl alkynes **242** with several arenes **237**. Mechanistically, it was proposed that zwitterionic species were firstly generated from the aziridine **242** by cleavage of the C−N bond and sequent Friedel−Crafts reaction of the arene with the benzylic cation to produce the intermediate **244** which afforded intermediate **245** by intramolecular proton transfer, Scheme 7.69. Finally, gold-catalyzed intramolecular nucleophilic attack of the nitrogen took place at the alkyne functionality to give **246** and the expulsion of the gold catalyst from intermediate **247** formed tetrahydroisoquinolines **243** within *syn* diastereoselectivity.

Li *et al.* developed an efficient and facile strategy for the preparation of highly substituted *N*-tosyl tetrahydroisoquinolines **250** by unprecedented sequential [3 + 3]/aza-6π-electrocyclization between cross-conjugated *N*-sulfonyl azatrienes **248** and *δ*-sulfonamido-allenoates **249**, under phosphine catalysis [115]. A possible mechanism for this reaction was suggested and the products formed through the addition of phosphine, 1,4-proton shift, isomerization, Michael addition, 1,2-proton transfer, an intramolecular 1,2-addition to the imine, phosphine elimination, and an aza-6π-electrocyclization. Furthermore, the ester group in tetrahydroisoquinolines **250** has been reduced into the hydroxy group in treatment with lithium aluminum hydride forming the corresponding tetrahydroisoquinolines **251**, Scheme 7.70. In addition, isoquinoline derivatives **252** were obtained by the treatment of tetrahydroisoquinolines **250** with 3 equiv of DDQ, Scheme 7.70.

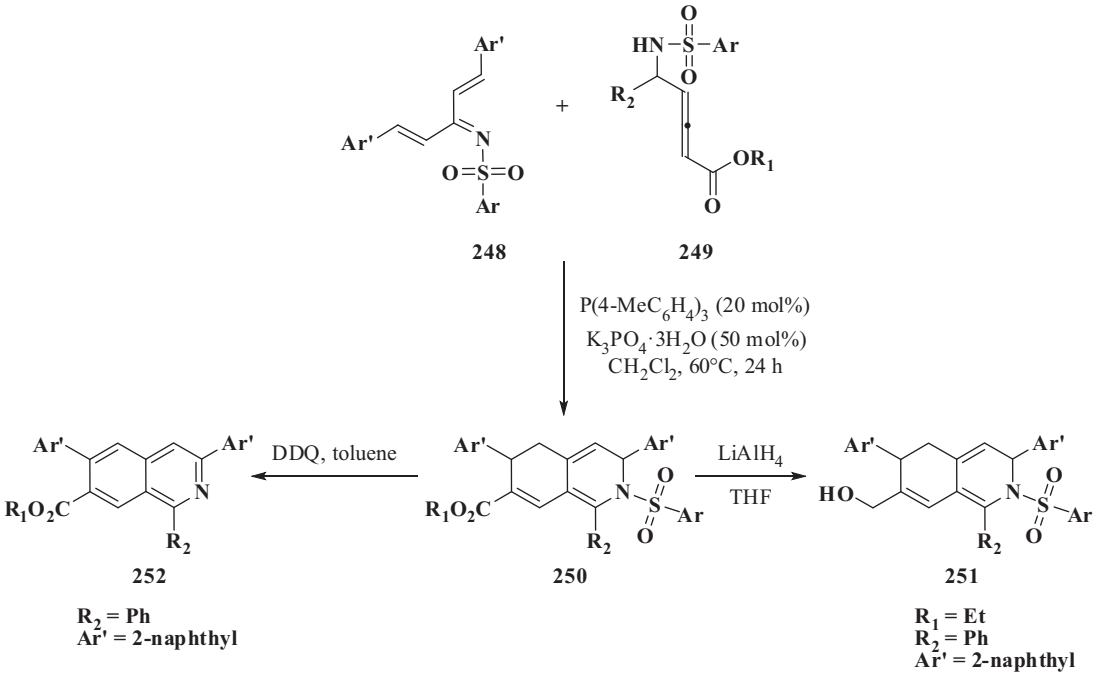
In 2015, Takeda *et al.* [116] reported a synthetic route toward *N*-tosyl hexahydrobenzophenanthridine **254** under mild conditions. Tetralin (*S*,*S*)-trans-**253** underwent facilely Pictet−Spengler reaction providing the desired fused tetracyclic amine (*S*,*R*)-**254** with high regioselectivity and in excellent yield, Scheme 7.71.

7.3.5 Synthesis of *N*-sulfonyl pyridine-fused heterocycles

The methodology of IED-aza-Diels-Alder reaction of *N*-tosyl-1-azadienes derived from 3-argiocarbonylcoumarins **255** and aqueous acetaldehyde has been developed. During this study, it was discovered that the chiral secondary aminocatalysis, catalyst P, gave tricyclic chroman-2-one **256** derivatives in high enantioselectivities, Scheme 7.72 [117].

Using several 2-sulfonamidoindoles **257,** as C/N-donors, and a range of *δ*-acetoxy allenoates **258** as 3C-synthons under phosphine catalysis afforded [3 + 3]-annulations and formation of *N*-tosyl dihydrocarboline **259**, Scheme 7.73. The *N*-tosyl dihydrocarbolines **259** were obtained exclusively at room temperature through Michael addition followed by 1,4-proton shift, isomerization, 1,2-proton transfer, phosphine elimination, and aza-Michael addition [118].

An efficient Lewis acid-catalyzed [3 + 3]-annulation methodology for the construction of tetrahydroisoquinolines



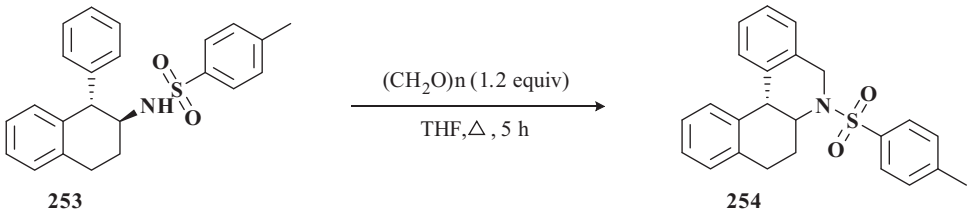
Ar = 4-MeC_6H_4 **R_1** = Et, i-Pr, t-Bu **R_1** = H, 5-Br, 6-Br

R_2 = 1-Pr, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-$MeOC_6H_4$, 2-naphthyl, 2-furyl

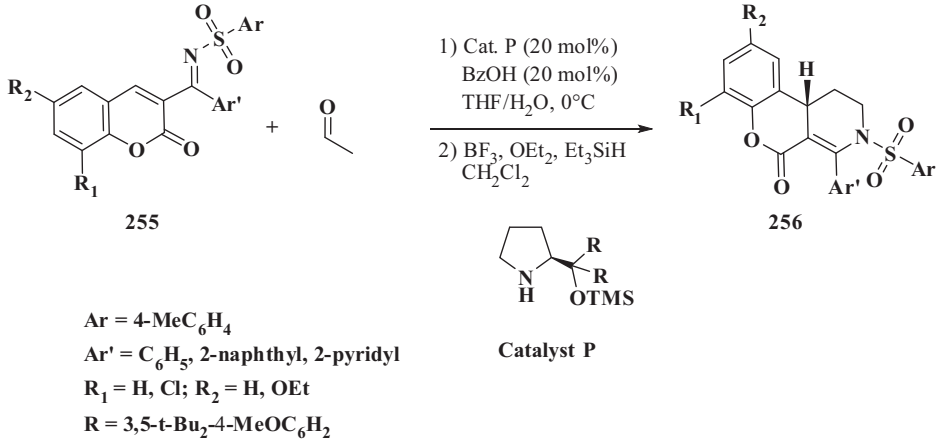
Ar' = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-CNC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4, 4-CNC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2,4-$MeOC_6H_3$, 2,4,6-$MeOC_6H_2$, 3,4,5-$MeOC_6H_2$

6π

SCHEME 7.70 *N*-Tosyl tetrahydroisoquinolines **250** by [3 + 3]/aza-6π-electrocyclization reaction.



SCHEME 7.71 *N*-Tosyl hexahydrobenzophenanthridine **254** through Pictet–Spengler reaction.



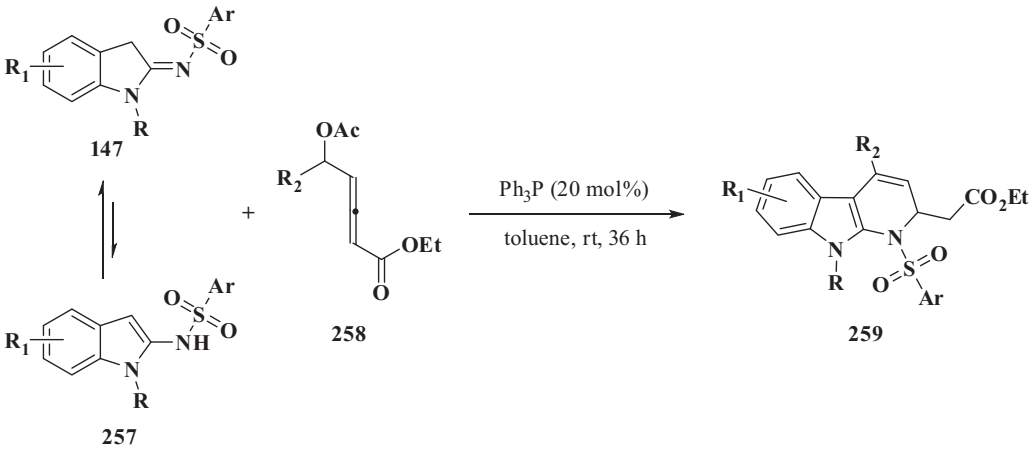
Ar = 4-MeC_6H_4

Ar' = C_6H_5, 2-naphthyl, 2-pyridyl

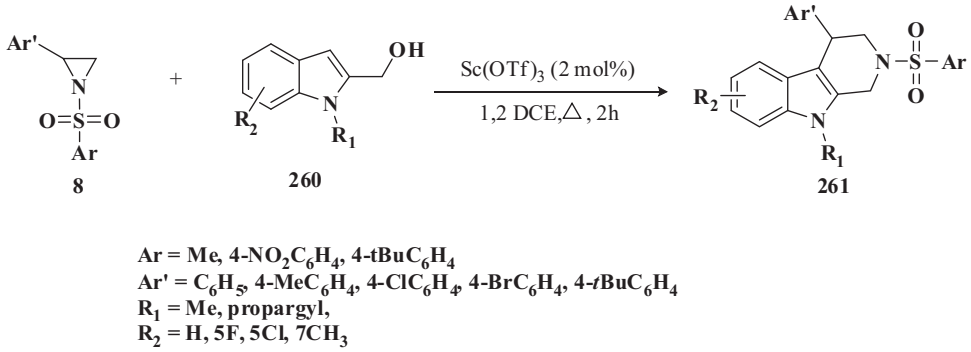
R_1 = H, Cl; **R_2** = H, OEt

R = 3,5-t-Bu_2-4-$MeOC_6H_2$

SCHEME 7.72 IED-Aza-Diels-Alder reaction of 3-argiocarbonylcoumarins **255** and acetaldehyde.



SCHEME 7.73 *N*-Tosyl dihydrocarboline **259** *via* [3 + 3]-annulations catalyzed by phosphine catalysis.



SCHEME 7.74 Tetrahydroisoquinolines **261** by [3 + 3]-annulation catalyzed by Lewis acid.

261 from readily available aziridines **8** and indol derivative **260** in good yield, Scheme 7.74.

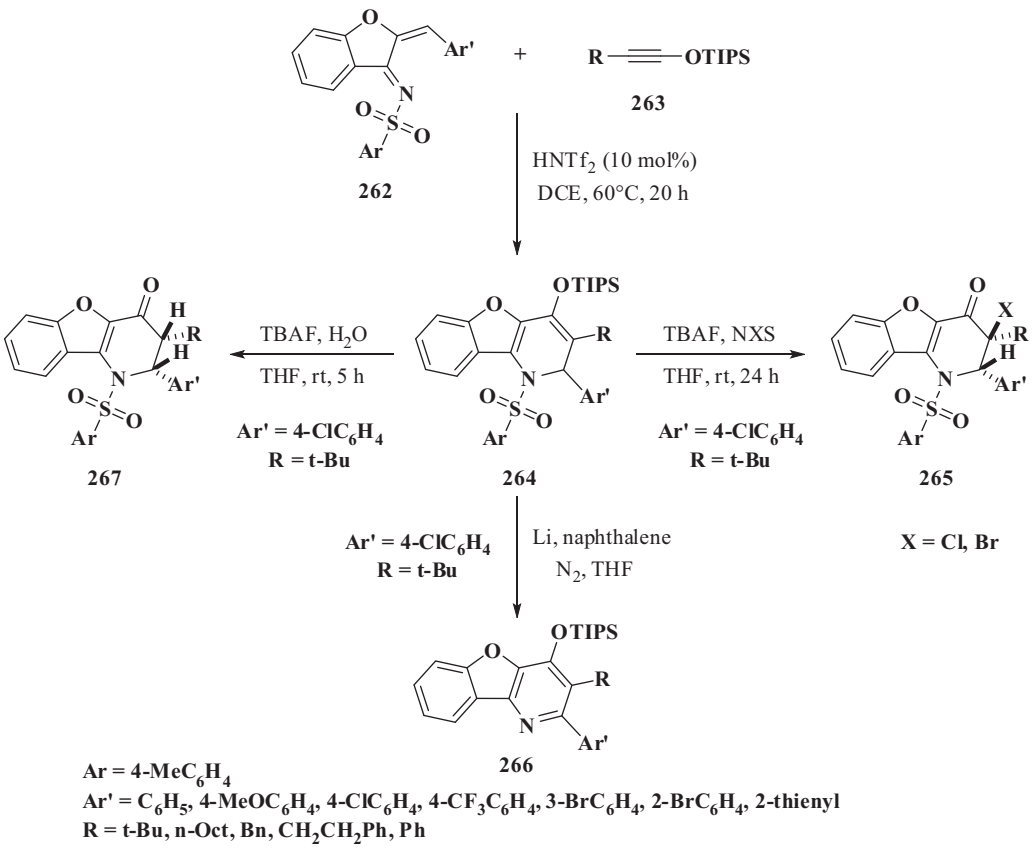
Recently, aurone-derived azadienes, a kind of useful synthon, have been extensively studied [119,120]. They have been used to access various *N*-heterocyclic compounds [121]. Benzofuran-fused *N*-sulfonyl dihydropyridine compounds were formed by an unusual formal migrative cycloaddition of aurone-derived with siloxy alkynes [122]. The reaction proceeded in the presence of a catalytic amount of $HNTf_2$ providing expedient access to a range of useful benzofuran-fused products **264** with unexpected topology, distinct from normal [4 + 2] cycloaddition between aurone-derived azadienes **262** and siloxy alkynes **263**. The process was initiated by less common [2 + 2] cycloaddition followed by 4p and 6p electrocyclic opening and cyclization, Scheme 7.75. The products transformed into other related heterocycles by either deprotection of the silyl group with TBAF in the presence of water to afford benzofuran-fused pyridinone **267** or deprotection **266** of the *N*-tosyl group with Li/naphthalene followed by air oxidation for form benzofuran-fused pyridine. Moreover, the reaction with NBS or NCS led to the formation of the corresponding haloketone **265**, Scheme 7.75.

7.4 Synthesis of *N*-sulfonyl oxazine derivatives and their biological activities

7.4.1 Synthesis of *N*-sulfonyl 1,4-oxazines

7.4.1.1 Synthesis of N*-sulfonyl di- and tetrahydro-1,4-oxazines*

One of the methods used to synthesize *N*-sulfonyl 1,4-benzoxazines and 1,4-benzothiazines was through ring-opening of *N*-sulfonyl aziridine followed by cyclization with a variety of reagents.



SCHEME 7.75 Benzofuran-fused dihydropyridines *via* migrative cycloaddition of aurone-derived with siloxy alkynes.

The unsubstituted and benzyl substituted *N*-tosylaziridines **230** underwent a ring-opening followed by ring-closing reaction with a variety of propargyl alcohols **268** in the presence of potassium *tert*-butoxide and dimethylsulfoxide at 40°C to produce 3,4-dihydro-2*H*-1,4-oxazines **269**, Scheme 7.76. It was observed that substituent on the aryl propargyl alcohols did not affect the yield. The suggested mechanism involves the formation of an oxygen nucleophile of aryl propargyl alcohols that reacts with the *N*-tosylaziridine. Isomerization followed by intramolecular nucleophilic ring-closing reaction led to the formation of dihydroxazine in good yield [123]. The latter compounds are reduced easily to corresponding morpholines **270** using trifluoroacetic acid, Scheme 7.76.

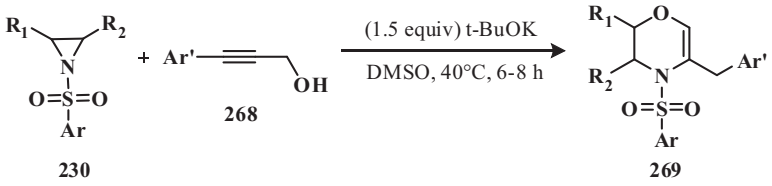
Cyclization/isomerization of aziridines **230** with propargylic alcohols **271** using gold(I)-catalyzed by ring-opening was reported as an efficient method to prepare 3,4-dihydro-2*H*-1,4-oxazine ring system **272** [124]. The formed 1,4-oxazines **272** were synthesized starting from *N*-tosylaziridines **230** with different substituents on C-2 and C-3 positions *via* nucleophilic ring-opening through the S_N1 mechanism followed by cyclization/isomerization cascade, Scheme 7.77. The gold(I) catalyst served as both π acid and σ acid, to activate both the substrates in the reaction.

Stewart *et al.* [125] described the Rh(II)-catalyzed reaction between *N*-tosyl-1,2,3-triazoles **273** and 2-bromo-1-phenylethan-1-ol **274**, which produced enamine **275** in high yields. Treatment of the latter with

K_2CO_3 in acetonitrile allowed cyclization to the oxazine **276**. It has been assumed that rhodium carbenoid enters 1,3-insertion into O—H followed by an annulation, Scheme 7.78. Moreover, with this new method, the antimicrobial natural product (±)-chelonin C with 70% yield was obtained by treating oxazine derivative **276** with a triethylsilane and trifluoroacetic acid mixture resulting in the syn-compound **277** followed by desulfonation using sodium in naphthalene, Scheme 7.78.

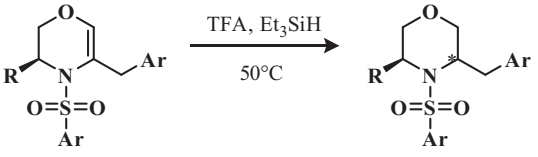
Rh(II)-Catalyzed reaction transannulation of *N*-tosyl-1,2,3-triazoles **273** and ring-opening reactions of epoxides **278** were extended to synthesize some 3,4-dihydro-2*H*-1,4-oxazines **279** in moderate yields through involving of α-imino rhodium(II)carbene species [126], Scheme 7.79.

Another approach to afford 1,4- and 1,3-oxazines was developed by the Kumari group through the cascade cyclization of epoxy ynamides under transition metal-free



230 268 269

Ar = 4-MeC$_6$H$_4$
R$_1$ = H, Me, *i*-Pr, *i*-Bu, Bn, -(CH$_2$)$_4$-
R$_2$ = H, -(CH$_2$)$_4$-
Ar' = Ph, 3-MeC$_6$H$_4$, 3 -CF$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$, 2-thiophenyl, 1-naphthyl

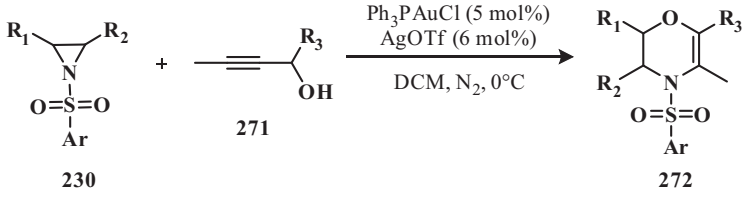


269 270

Ar = 4-MeC$_6$H$_4$

R = Me, Ar = Ph, 3 -CF$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$
R = *i*-Pr, Ar = Ph
R = *i*-Bu, Ar = Ph

SCHEME 7.76 *N*-Tosyl 3,4-dihydro-2*H*-1,4-oxazines **269** *via* ring-opening of aziridines.

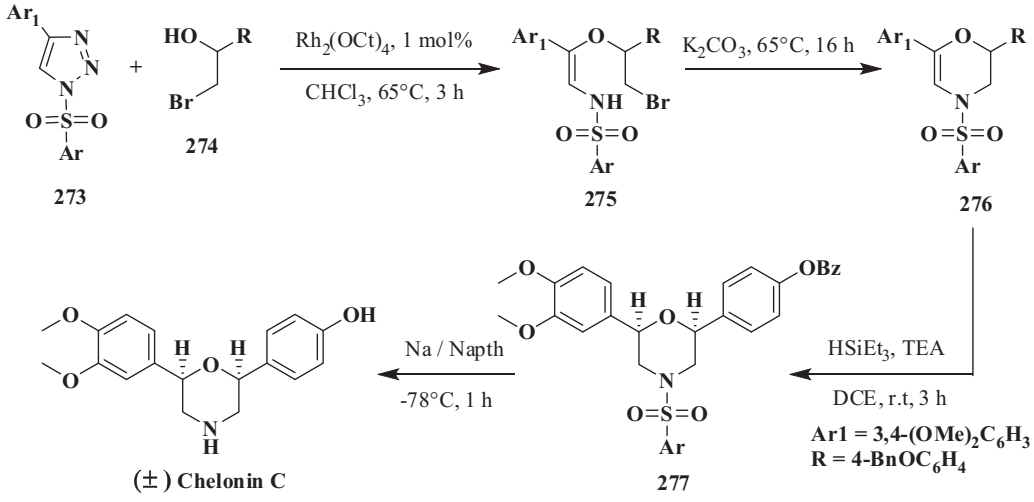


230 271 272

Ar = 4-MeC$_6$H$_4$
R$_2$= aryl, cyclic-pent, cyclic-hex

R$_1$= H, aryl, cyclic-pent, cyclic-hex
R$_3$ = H, alkyl, aryl

SCHEME 7.77 3,4-Dihydro-2*H*-1,4-oxazines **272** *via* cyclization/isomerization of aziridines.



273 274 275 276 277

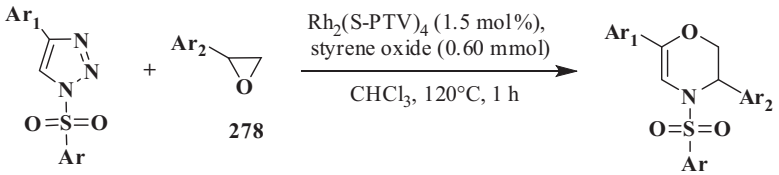
(±) Chelonin C

Ar1 = 3,4-(OMe)$_2$C$_6$H$_3$
R = 4-BnOC$_6$H$_4$

Ar = 4-MeC$_6$H$_4$ **Ar$_1$ = Ph, 4-MeOC$_6$H$_4$, 4-MeCOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 4-FC$_6$H$_4$,4-CNC$_6$H$_4$, 4-BzOC$_6$H$_4$, naphthyl**

R = Ph, 4-AcOC$_6$H$_4$, 4-BnOC$_6$H$_4$, (CH$_2$)$_5$CH$_3$, CH$_2$OBn, CH$_2$OTBS, (CH$_2$)$_3$Br

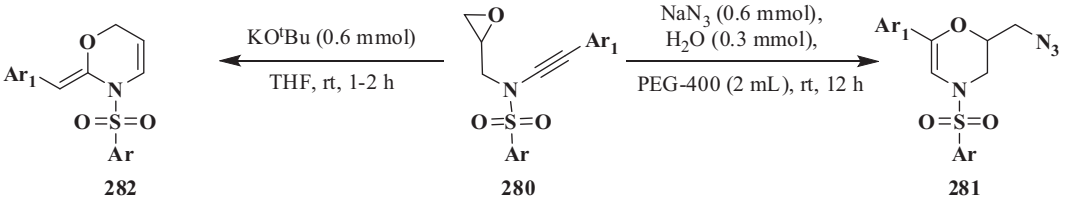
SCHEME 7.78 2,6-Substituted 3,4-dihydro-2*H*-1,4-oxazines **276** through Rh(II)-catalyzed reaction.



Ar = 4-MeC_6H_4 **Ar$_1$** = Ph, 4-$OMeC_6H_4$, 4-$MeCOC_6H_4$, 3,4-$(OMe)_2C_6H_3$, 4-FC_6H_4,4-CNC_6H_4, 4-$BzOC_6H_4$, naphthyl

Ar$_2$ = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, 2-FC_6H_4, 3-BrC_6H_4, 1-naphthyl

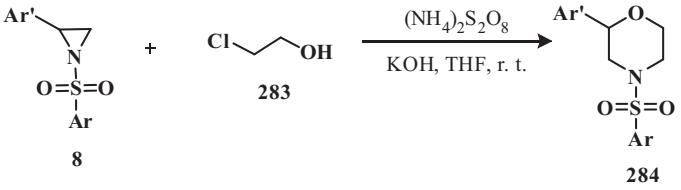
SCHEME 7.79 3,4-Dihydro-2*H*-1,4-oxazines **279** by Rh(II)-catalyzed reaction.



Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-t-BuC_6H_4,1-naphthyl

Ar$_1$ = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 4-BrC_6H_4, 1-naphthyl, 2-pyridyl

SCHEME 7.80 Cyclization of epoxy ynamides **280** to form 1,4- and 1,3-oxazines.



Ar = 4-MeC_6H_4

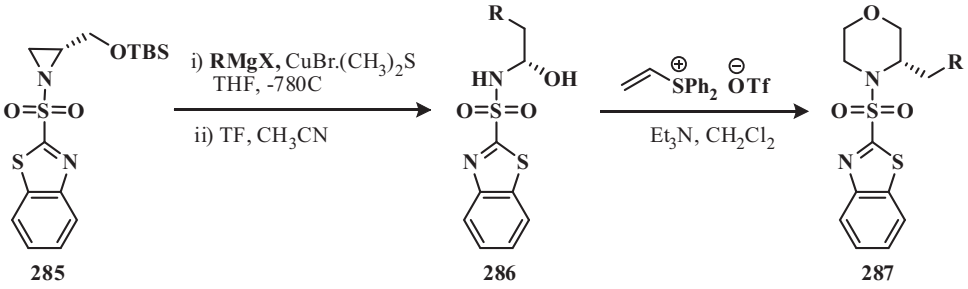
Ar' = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 1-naphthyl, *n*-butyl

SCHEME 7.81 2-Substituted morpholines **284** from 2-arylaziridines.

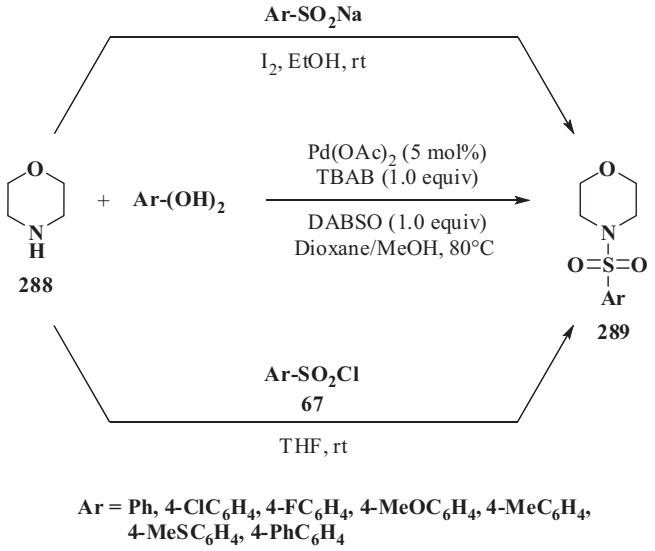
conditions [127], Scheme 7.80. Under the basic condition, 1,3-oxazines **282** were obtained in a regio- and stereoselective manner starting from epoxy ynamides **280**. Cyclization of the latter with sodium azide as a nucleophile resulted in 1,4-oxazines **281**.

2-Substituted morpholines **284** were synthesized by metal-free one-pot synthesis from *N*-tosyl-substituted 2-arylaziridines **8** using an inexpensive reagent, ammonium persulfate, as an oxidant for aziridine ring-opening with 2-haloethanols **283** [128], Scheme 7.81. It was assumed that aziridine participated in single electron transfer with the persulfate anion to generate the radical cation followed by nucleophilic addition of 2-haloethanols to give an amino radical intermediate. After abstraction of a hydrogen atom from alcohol and cyclization in presence of a base, morpholines are isolated in low to moderate yields.

In 2010, Bornholdt *et al.* reported an efficient methodology for facilely accessible a series of novel enantiopure 3-substituted 1,4-benzoxazines **287** from activated (*S*)-2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)aziridin-1-yl)sulfonyl)benzo[*d*]thiazole **285** [129]. Enantiopure 1,4-benzoxazines **287** was efficiently produced by ring-opening of activated aziridine with organocuprates followed by a ring annulation reaction of deprotected 1,3-amino alcohol **286** with a vinylsulfonium salt under basic conditions, Scheme 7.82.



SCHEME 7.82 1,4-Benzoxazines **287** by ring-opening of aziridine.



SCHEME 7.83 *N*-Sulfonyl tetrahydro-1,4-benzoxazines **289** by sulfonation reaction.

A variety of *N*-sulfonyl tetrahydro-1,4-benzoxazines was synthesized by the metal-free method through the reaction of sodium sulfinates and morpholine mediated by I_2 in ethanol and at room temperature [130], Scheme 7.83. The advantages of this method are (1) using cheap and readily available I_2 as an efficient catalyst, (2) the desired sulfonamide compounds were obtained at room temperature and in the open air, (3) the reaction showed broad substrate scopes [131]. The synthesis of *N*-sulfonyl tetrahydro-1,4-benzoxazines **289** could be also synthesized by the reaction of sulphonyl chloride and morpholine **288** at room temperature [132], Scheme 7.83. A straightforward bimetallic Pd/Cu catalytic system has been developed to afford various *N*-sulfonyl tetrahydro-1,4-benzoxazines **289** in one pot from boronic acids, sulfur dioxide surrogate DABSO and *O*-benzoyl hydroxylamines and in high yields [133,134], Scheme 7.83. In the absence of ligands, the catalytic system revealed a broad substrate scope and tolerated a wide range of functional groups even at low catalyst loadings.

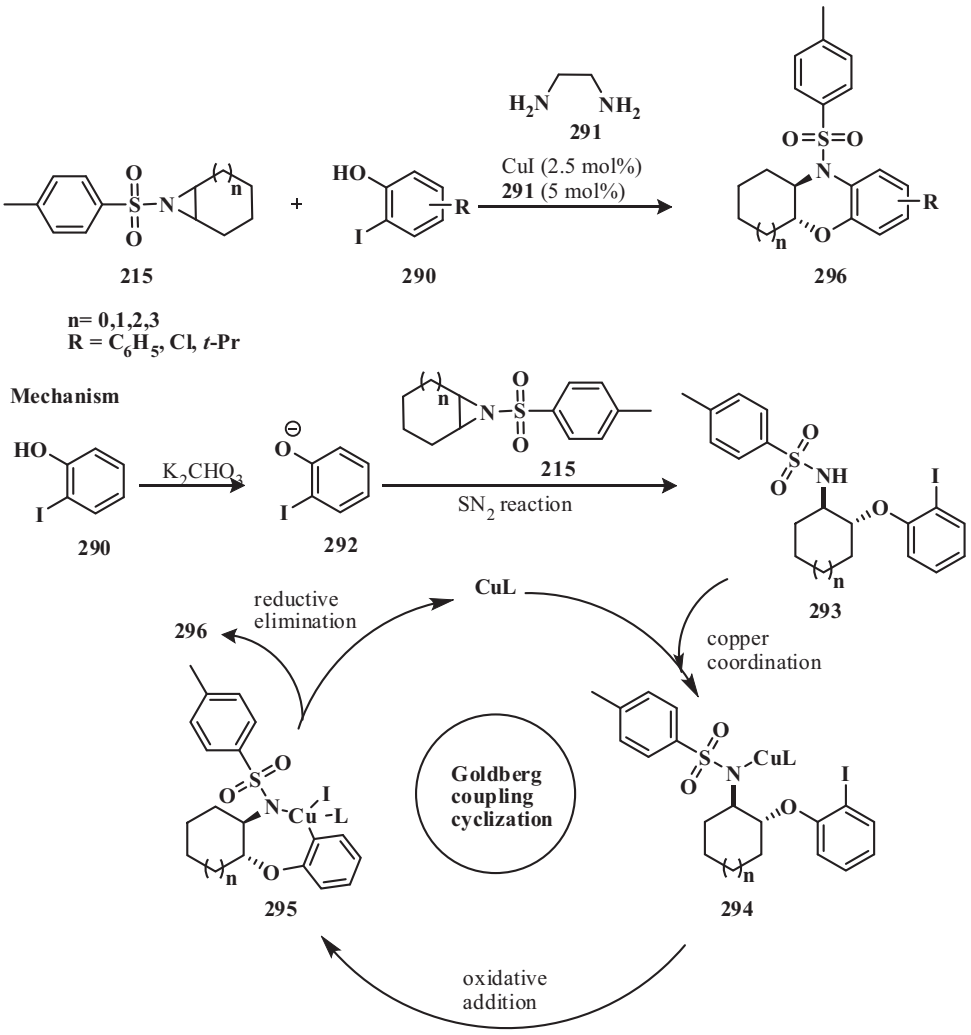
Some compounds containing *N*-sulfonyl tetrahydro-1,4-benzoxazines showed biological activity against Trypanosoma brucei (HAT), T. cruzi (Chagas disease), and Leishmania major (cutaneous leishmaniasis) since they improved drug-like properties [132].

7.4.1.2 Synthesis of N-sulfonyl 1,4-benzoxazines

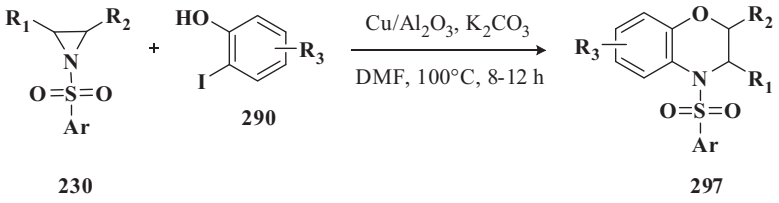
Rao *et al.* [135,136] disclosed a novel protocol for the construction of *trans*-3,4-dihydro-2*H*-1,4-benzoxazine **296** through domino aziridine ring-opening with *ortho*-iodophenols **290** followed by the copper-catalyzed Goldberg coupling cyclization. It is proposed that an initial SN_2-type nucleophilic attack of the phenoxide ion **292**, which is produced from deprotonation of 2-iodophenol **290** under the basic condition form ring-opened product in *trans* form **293**, Scheme 7.84. The nitrogen in **293** then got coordinated with the Cu-complex (CuI-ethylene diamine) followed by oxidative addition to providing the intermediate **295**. The subsequent reductive elimination furnished the final product **296** with the regeneration of the copper catalyst.

In 2010, Bhadra *et al.* [137] utilized an alumina-supported Cu(II) catalyst, an efficient, inexpensive, and environmentally benign stable catalyst system, to facilitate the ring-opening of aziridines **230** with 2-iodophenols **290**. Diverse 2-aryl, 2-alkyl, and cycloalkanefused aziridines were employed as substrates for this one-pot sequential ring-opening cyclization methodology to furnish a variety of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives **297** in high yields, Scheme 7.85.

Methotrexate (MTX) derivatives **303** bearing dihydro-2*H*-1,4-benzothiazine or dihydro-2*H*-1,4-benzoxazine were synthesized by using *N*-sulfonyl dihydro-2*H*-1,4-benzothiazine or *N*-sulfonyl dihydro-2*H*-1,4-benzoxazine **302** as precursors. Sequential



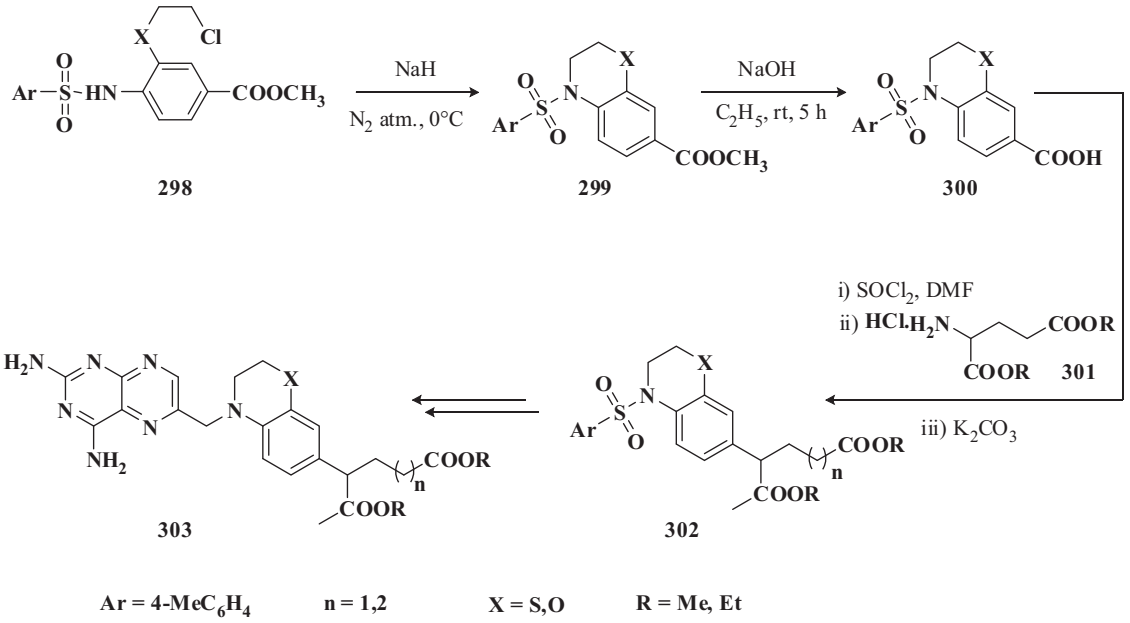
SCHEME 7.84 *trans*-3,4-Dihydro-2*H*-1,4-benzoxazine **296** through ring-opening of aziridines.



Ar = 4-MeC$_6$H$_4$
R$_1$= Ph, n-C$_6$H$_{13}$; R$_2$= H, propyl, R$_1$= R$_2$= propyl, -(CH$_2$)n- (n = 3-6)
R$_3$= 3-Br, 3-I, 2-CHO-5-OMe, 3-Me, 3-C$_5$H$_5$, 4-CO$_2$Et

SCHEME 7.85 3,4-Dihydro-2*H*-1,4-benzoxazine derivatives **297** *via* Cu(II) catalyst.

steps occurred to construct these precursors. Firstly, sulfonyl amides **298** were easily intermolecular cyclized under the strong basic condition to generate the cyclized products **299**, which then hydrolyzed to form the corresponding carboxylic acids **300**, Scheme 7.86. Acylation of **300** with $SOCl_2$, followed by coupling with amino diesters **301** under the Schotten Baumann's condition provided the desired precursors



SCHEME 7.86 Intermolecular cyclized to form dihydro-2*H*-1,4-benzoxa/thiazines.

302 [138]. Antiproliferative activities of synthesized methotrexate (MTX) derivatives **303** were comparable to that of MTX in *in vitro* assays. 3,4-Dihydro-2*H*-1,4-benzothiazincarbonyl-l-glutamic acid **303** exhibited potency as antiproliferative in hSC and hPBMC more than MTX *in vitro*. One of the synthesized 1,4-benzoxazine derivative **303** significantly suppressed the progression of adjuvant arthritis in a dose-dependent manner ranging from 0.5 to 2.5 mg/kg (po) while another synthesized 1,4-benzothiazine derivative completely suppressed this progression at the dose of 2.5 mg/kg (po). *In vivo* antiarthritic activities of methotrexate (MTX) derivatives were evaluated in a rat adjuvant arthritis model, [138].

7.4.2 Synthesis of *N*-sulfonyl 1,3-oxazines

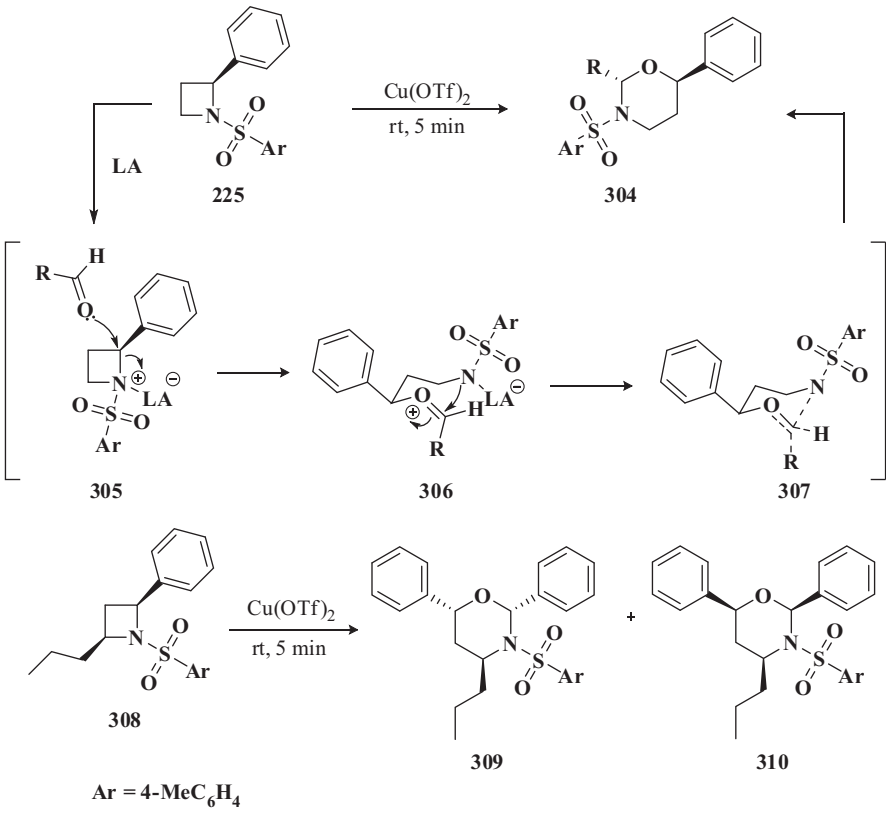
In 2007, Ghorai *et al.* [142] described Lewis acid-mediated S_N2-type nucleophilic ring-opening followed by [4 + 2] cycloaddition reactions of enantiopure 2-phenyl-*N*-tosylazetidines **225** with various aldehydes. Mechanistically, an initial S_N2-type attack of the carbonyl oxygen on the azetidine-Lewis acid adduct/complex **305** furnished the intermediate **306**, and the sequent cyclization from the si-face of the carbonyl functionality **307** afforded the *trans*-substituted 1,3-oxazinanes **304** in excellent yield with moderate enantioselectivity (59%–75% ee). The reduced enantioselectivity in the final products was attributed to the partial racemization of the enantiopure aziridine before the nucleophilic ring-opening step. Additionally, the cycloaddition of *cis*-(2*S*,4*S*)-2-ethyl-4-phenyl-1-tosylazetidine **308** with benzaldehyde was also reported to produce highly substituted oxazinane (2*R*,4*S*,6*R*)-4-ethyl-2,6-diphenyl-3-tosyl-1,3-oxazinane **309** and **310** with 4,6-trans geometry as the major diastereomer **309**, Scheme 7.87.

A synthetic route was developed to propargyl alcohol **315** which was later utilized as a precursor in the synthesis of *ergot* alkaloid. The reductive coupling reaction of chiral 2-ethynylaziridine **311** with aldehyde in the presence of indium(I) and a catalytic amount of Pd(0) produced enantiomerically pure 2-ethynyl-1,3-amino alcohols **312** in a highly stereoselective manner (mostly >99:1), Scheme 7.88. Subsequently, benzylidene acetal protection of the 1,3-amino alcohol afforded the desired alkyne **313** which was added to aldehyde indole derivative **314** in presence of butyllithium (*n*-BuLi) to provide the desired propargyl alcohol **315** in moderate yield [143].

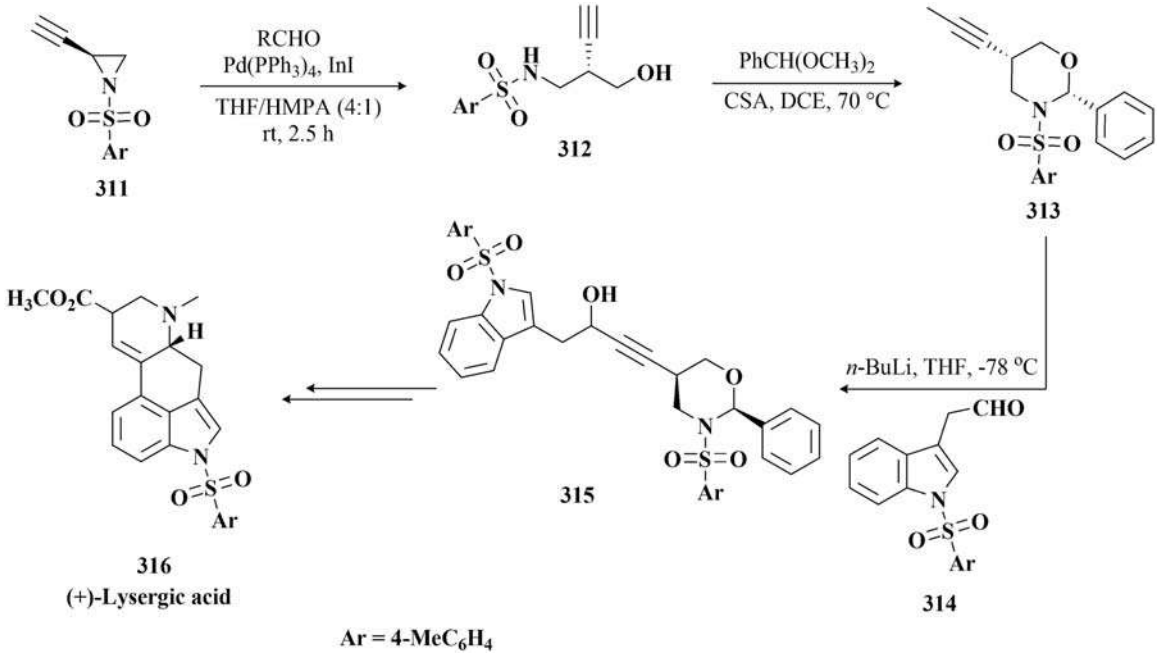
7.5 Synthesis of *N*-sulfonyl thiazine derivatives

7.5.1 Synthesis of *N*-sulfonyl 1,4-thiazines

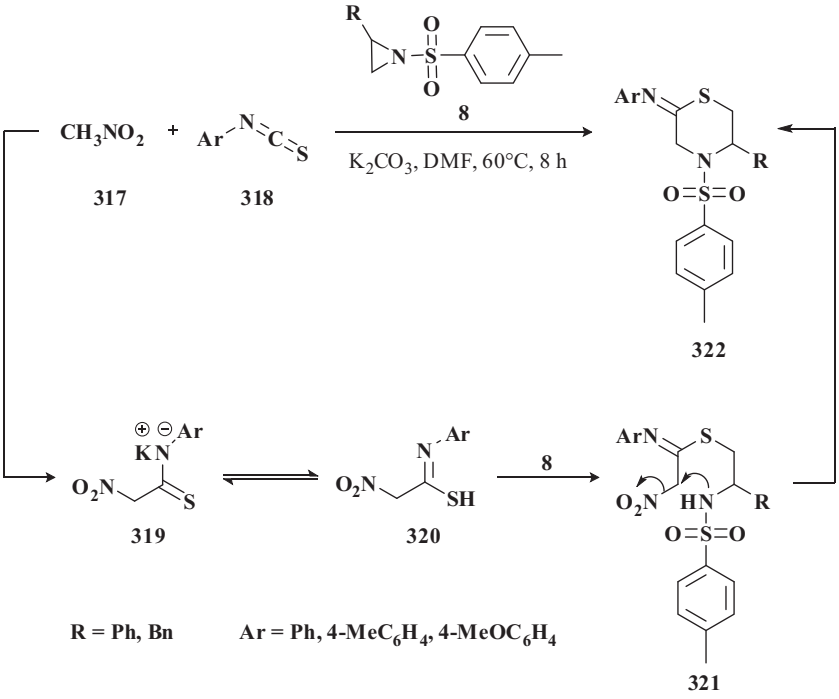
In 2014, Samzadeh-Kermani [139] revealed a one-pot reaction involving nitromethane **317**, isothiocyanate **318**, and *N*-sulfonyl aziridine **8** for the formation of functionalized thiomorpholines **322** under basic conditions,



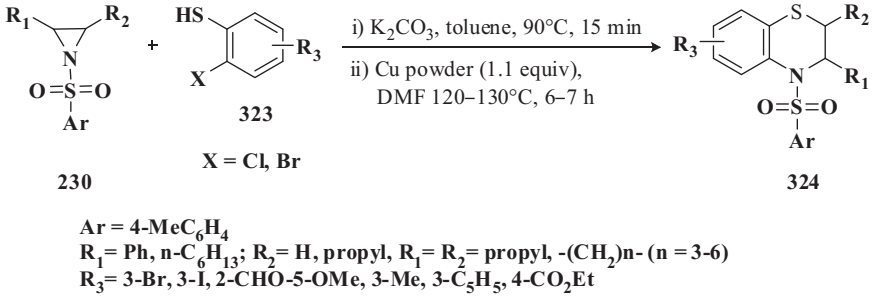
SCHEME 7.87 *trans*-Substituted 1,3-oxazinanes **304** *via* Lewis acid-catalyzed reaction.



SCHEME 7.88 Coupling reaction of chiral 2-ethynylaziridine to form 1,3-oxazinanes **313**.



SCHEME 7.89 *N*-Tosyl 1,4-thiomorpholines **322** ring-opening of aziridines.



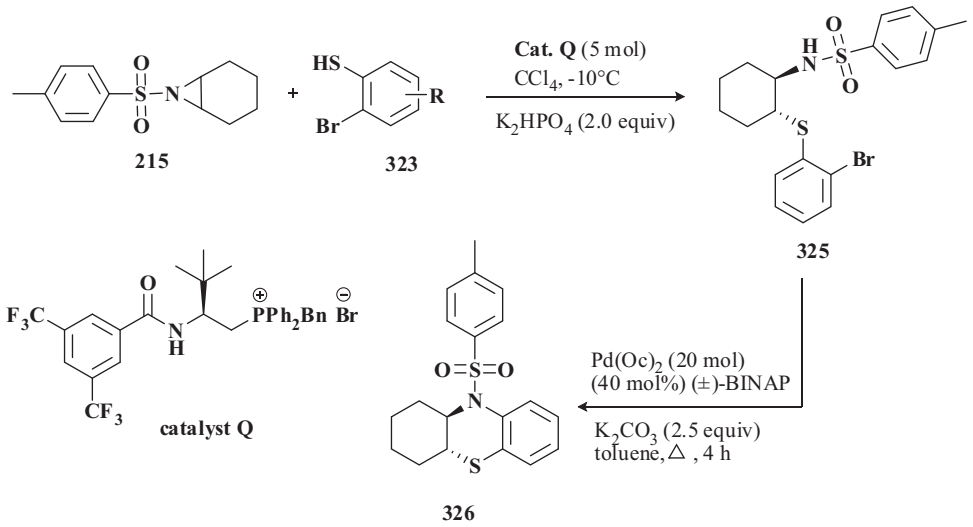
SCHEME 7.90 *N*-Tosyl dihydrobenzothiazines **324** *via* S_N2-type ring-opening of aziridines.

Scheme 7.89. A possible mechanism for this one-pot reaction started with the formation of the intermediate **319** by the coupling of nitromethane with the isothiocyanate group. This intermediate reacted with the aziridine **8** to furnish the ring-opened product **321** followed by an intramolecular cyclization reaction to furnish the desired 1,4-thiomorpholine **322**.

7.5.2 Synthesis of *N*-sulfonyl 1,4-benzothiazines

Ghorai *et al.* developed a simple protocol for the synthesis of *N*-tosyl dihydrobenzothiazines **324** *via* regio- and stereoselective S_N2-type ring-opening of *N*-tosylaziridines **230** with *o*-halosubstituted thiophenol **323** followed by copper-powder-mediated intramolecular C-N cyclization in excellent yields with high diastereo and enantioselectivity [140], Scheme 7.90.

An enantioselective desymmetrization strategy for the ring-opening of activated bicyclic meso-aziridines **215** with *o*-bromosubstituted thiophenol **323** by utilizing chiral α-amino acid-derived bifunctional quaternary phosphonium salt catalyst, catalyst Q, to provide the ring-opened compound **325** in highest enantiomeric excess was reported [141]. The β-amino sulfides product was then subjected to palladium-catalyzed Buchwald–Hartwig-coupling–cyclization for the construction of the phenothiazine derivative **326** in 70% yield without any loss of enantiopurity, Scheme 7.91.



SCHEME 7.91 Phenothiazine derivative **326** *via* palladium-catalyzed Buchwald−Hartwig-coupling−cyclization.

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Chapter 8

Synthesis of *N*-sulfonated *N*-diazines, *N*-triazines and *N*-tetrazines; their uses and biological applications

8.1 Introduction

Nitrogen-containing heterocycles are privileged structural units that are frequently encountered in biologically active natural products as well as in pharmaceuticals and agrochemicals [1]. Also, they are of very considerable significance particularly in medicinal chemistry, for example; analogs of diazines such as pyrazine, pyridazines, and pyrimidine 1,2,4-triazines and triazine analogs as 1,2,3-triazines, 1,2,4-triazines, 1,2,5-triazines, and 1,3,5-triazines to have been identified as pharmacologically important heterocycles with diverse biological activities [2] and applied in organic synthesis [3]. The sulfonyl moieties are pharmacophores responsible for the biological response of several clinically significant drugs. Sulfonamides have relieved an increasing interest from organic chemists due to their diverse biological activities, including carbonic anhydrase inhibition [4,5], antidiabetic [6], anticancer [7–9], antimicrobial [10–12], and antiviral potencies [13]. Moreover, *N*-sulfonated heterocycles possess widespread chemistry and biological activities such as *N*-sulfonated pyridazinone analogs have been reported to be new potent aldose reductase [14] and remarkable antibacterial activity against *Bacillus megaterium*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas fluorescens* and antifungal activity [15]. *N*-sulfonated quinoxaline exhibited high potency in the inhibition of HIV reverse transcriptase and HIV replication in cell culture inhibitor [16] and antitumor [17]. *N*-Sulfonylpyrimidine revealed potent antitumor activity against mammary carcinoma [18]. It has been established that *N*-sulfonylamino azinones are privileged heterocycles possessing diuretic, antihypertensive, anti-inflammatory, and anticancer and other biological activities. In particular, a new generation of competitive AMPA receptor antagonist based on *N*-sulfonylamino 1*H*-quinazoline-2,4-diones is promising useful in the treatment neurological disorders such as epilepsy and schizophrenia [19].

8.2 *N*-Sulfonyldiazines

8.2.1 *N*-Sulfonyl-1,4-diazines (*N*-sulfonyl pyrazines)

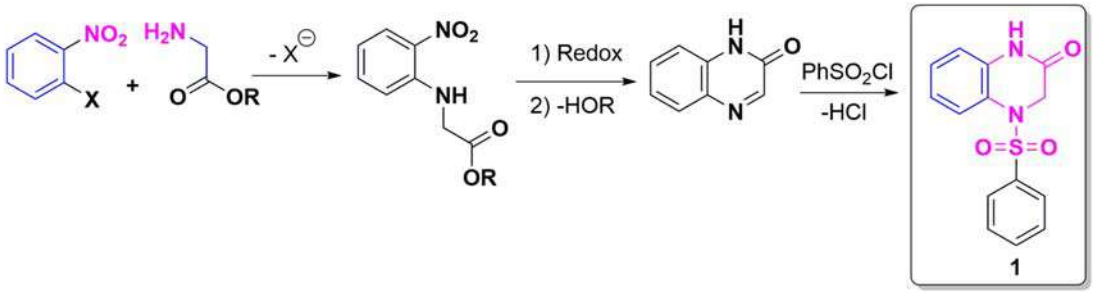
The 1,2,3,4-tetrahydroquinoxalin-2-ones (tQNXs), benzo[*b*]pyrazine **1** [20] (Scheme 8.1) was prepared through aromatic nucleophilic substitution reaction of commercially available *o*-halonitrobenzene with the α-amino acid. Then, by nitro reduction and further cyclization, the acyclic intermediate gave rise to the corresponding heterocyclic secondary amines. Finally, the *N*-phenylsulfonyl tQNXs derivative was prepared by *N*-5 acylation of the heterocyclic amines with phenylsulphonyl chlorides (Scheme 8.1) [16,21]. This type of compound has also shown high potency in the inhibition of HIV reverse transcriptase and HIV replication in cell culture [16].

Zhang et al., reported on the cyclization reaction between vinyl azides and *N*-sulfonyl-1,2,3-triazoles. An Rh/Ag binary metal catalyst system proved to be necessary for successful cyclization. The cyclization reactions feature a broad substrate scope, good functional group tolerance, high reaction efficiency, and good to high product yields (Scheme 8.2) [22].

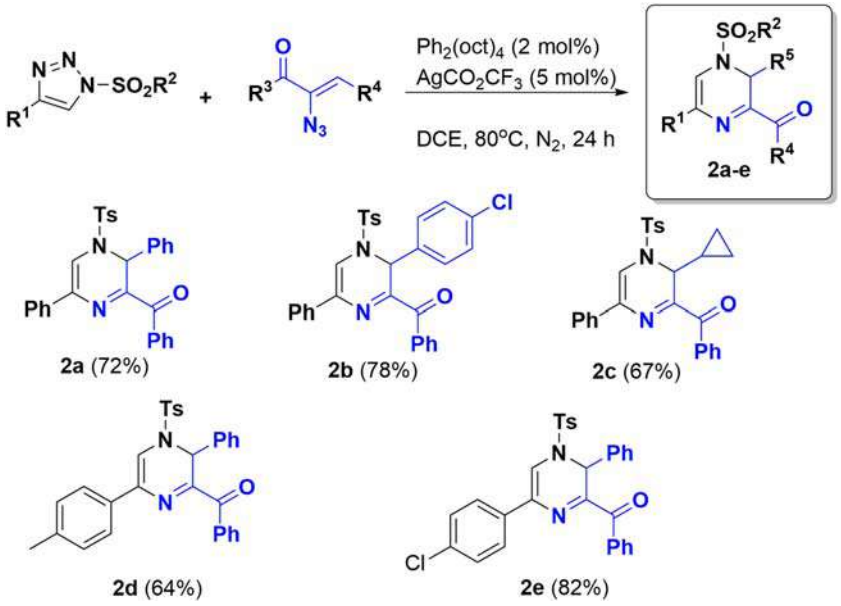
4-Aminopyrrole-3-carboxylates**4** and pyrazine-2-carboxylates **5** were synthesized from 5-alkoxyisoxazoles **3** and 1-sulfonyl-1,2,3-triazoles **4** by tuning the Rh(II) catalyst and the reaction conditions. Treatment of 5-methoxy-3-phenylisoxazole **3a** (1.0 equiv) with 4-phenyl-1-tosyl-1*H*-1,2,3-triazole **3** (2.5 equiv) under $Rh_2(Piv)_4$ catalysis, TFT = α,α,α-trifluorotoluene and reflux gave two products, 3-aminopyrrole **4** and 1,2-dihydropyrazine **5**, in nearly equal amounts and a good overall yield (Scheme 8.3) [20].

Interestingly, it was feasible to unite the two 1,3-dipolarophiles Rh-AVC and 2*H*-azirine in a single transformation to realize a formal aza-[3 + 3] cycloaddition, which would afford an efficient method for the synthesis

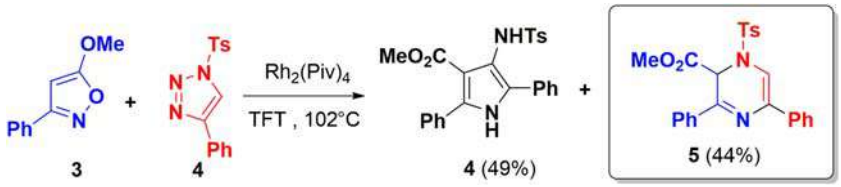
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00011-2



SCHEME 8.1 Synthesis of *N*-sulfonyl benzo[b]pyrazine 1.



SCHEME 8.2 Synthesis of *N*-tosylpyrazine **2a-e** through cyclization reaction between vinyl azides and *N*-sulfonyl-1,2,3-triazoles.

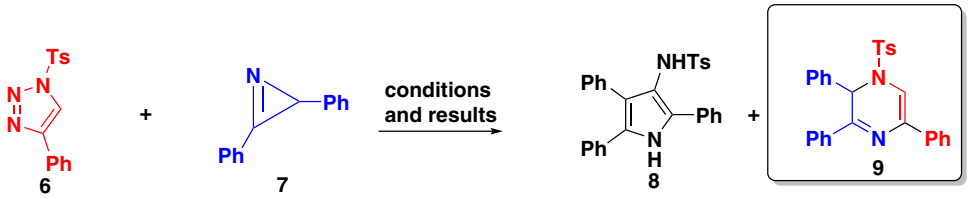


SCHEME 8.3 Synthesis of pyrazine-2-carboxylates 5.

of 1,2-dihydropyrazines **9** (Scheme 8.4) [23]. Although a particular interest in the development of Rh-AVC promoted transformations [24,25], the successful implementation of this design leads to the development of unprecedented Rh(II)-catalyzed formal [3 + 2] and [3 + 3] cycloadditions of 1,2,3-triazoles **6** with 2*H*-azirines **7** (Scheme 8.4). It was found that when triazole **6** was subjected to 2,3-diphenyl-2*H*-azirine **7** under the condition mentioned in Scheme 8.3, a mixture of tetrasubstituted 3-amino-pyrrole **8** and 2,3,5-trisubstituted-1,2-dihydropyrazine **9** was obtained in 36% and 48% yields, respectively (entry 1, Scheme 8.4).

It was established that the synthesized 4-(9-oxofluoren-2-sulfonyl)-2,6-piperazinedione (**10**) (Fig. 8.1) showed medium cytotoxicity of median tolerable dose 2000 mg/kg upon studying the antitumor activity in vivo and in vitro on different cancer cell lines. Compound **10** decreased the rate of ascite liquid formation in the Ehrlich tumor. At the same time, it weakly affected the survival life of experimental mice [17].

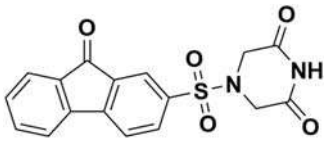
Regarding 1-arenesulfonyl-2-quinoxalinones, they have biological activities whereas sulfonation on 1-position of the corresponding compounds is relatively easy. Arenesulfonyl-2-quinoxalinones **15a**–**h** and their 3-methyl derivatives **16a**–**h**. Two methods to synthesize them were applied. The one



Entry	Condition	Yield
1	$Rh_2(esp)_2$(1.5mol%), 1,2-DCE, 160°C, 1 h	8: 36%; 9: 48%
2	$Rh_2(esp)_2$(1.5mol%), toluene, 160°C, 1 h	8: 13%; 9: 82%
3	$Rh_2(esp)_2$(1.5mol%), $ClCH_2CO_2H$ (50 mol%), 1,2-DCE, 160°C, 0.5 h	8: 86%; 9: 11%

Reaction conditions: 5 (0.30 mmol), 6 (0.60 mmol) and the Rh(II)-catalyst (0.0045 mmol) in the solvent (0.8 mL)

SCHEME 8.4 Condition screening of cycloaddition of 6 with 7.



10

FIGURE 8.1 Structure of 4-(9-oxofluoren-2-sulfonyl)-2,6-piperazinedione (10) as antitumor agent.

(**Method A**) was by the electrophilic substitution of arenesulfonyl chlorides ($ArSO_2Cl$) to the compounds **11** and **9** respectively, and the other (**Method B**) was by the nucleophilic substitution of sodium arenesulfinates (NaOS(=O)Ar) to the compounds **10** and **11** (Scheme 8.5). respectively. The yields of products **12a–h** prepared by **Method A** were in the range of 61%–74% and by **Method B** 49%–69% respectively, and the yields of products **13a–h** prepared by **Method A** were in the range of 58%–76% and by **Method B** 32%–75%. The one-step reactions from the quinoxalinones **8** and **9** (**method A**) gave rather good yields than the two-step reactions *via* 1-chloro derivatives **10** and **11** (**method B**) did (Scheme 8.5) [26].

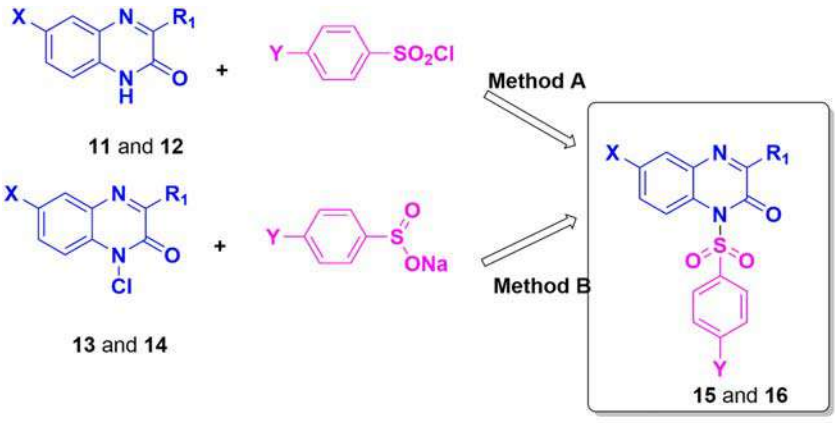
The stereoselective synthesis of 1,2,11,11a-tetrahydrobenzo[*e*]pyrazino[1,2-*b*][1,2,4]thiadiazin-3(4*H*)-one 6,6-dioxides **24** on a solid support *via* tandem *N*-sulfonyl iminium ion cyclization, followed by nucleophilic addition is reported. The synthesis proceeded with full control of stereoselectivity at the formed asymmetric carbon, under mild conditions, and using commercially available building blocks. The synthetic route provided high-purity crude products **24** (Scheme 8.6) [27].

The key intermediates, *N*-acyl-*N*-(2,2-dimethoxyethyl) amines **19** (Scheme 8.6), were prepared according to two different (Scheme 8.16). Briefly, route I started with Rink-supported bromoacetic acid **17** ($R^1 = -CH_2-$; X = −Br). The bromine was substituted with aminoacetaldehyde dimethyl acetal in the presence of DIEA in DMF to yield the resin-bound *N*-((2,2-dimethoxyethyl)amino)amine **18**. Acylation of this intermediate with various Fmoc-amino acids afforded the key intermediates, *N*-acyl-*N*-(2,2-dimethoxyethyl) amines **19** (Scheme 8.6). The second route, route II, enabled access to a greater diversity of compounds; the side chain R^1 represents amides **18** or amines (**19**) (Scheme 8.6) to afford the corresponding 4-nitro-benzenesulfonamides **20**. These intermediates, each bearing an activated nitrogen atom, underwent Mitsunobu alkylation and yielded alkylated sulfonamides **21**. The target compounds **24** were obtained from resin-bound intermediates **23** by acid-mediated deprotection of acetal with concurrent TFA cleavage from the acid-labile linkers.

8.2.2 *N*-Sulfonyl-1,2-diazines (*N*-sulfonyl pyridazines)

The increasing occurrence of antibiotic-resistant human pathogenic microorganisms and infections caused by these microorganisms pose a serious challenge to the medical community and there is a need for an effective therapy, which has led to a search for novel antimicrobial agents

Recently some pyridazinone derivatives **25** and **26** have been reported as potent antibacterial and antifungal agents [28]. A series of 2-arylsulpho-6-substituted-3(2*H*)-pyridazinones were tested for antimicrobial activity to exhibit



15	R1	X	Y
a	Me	H	Me
b	Me	Me	Me
c	Me	NO_2	Me
d	Me	Cl	Me
e	Me	H	H
f	Me	Me	H
g	Me	NO_2	H
h	Me	Cl	H

16	R1	X	Y
a	H	H	Me
b	H	Me	Me
c	H	NO_2	Me
d	H	Cl	Me
e	H	H	H
f	H	Me	H
g	H	NO_2	H
h	H	Cl	H

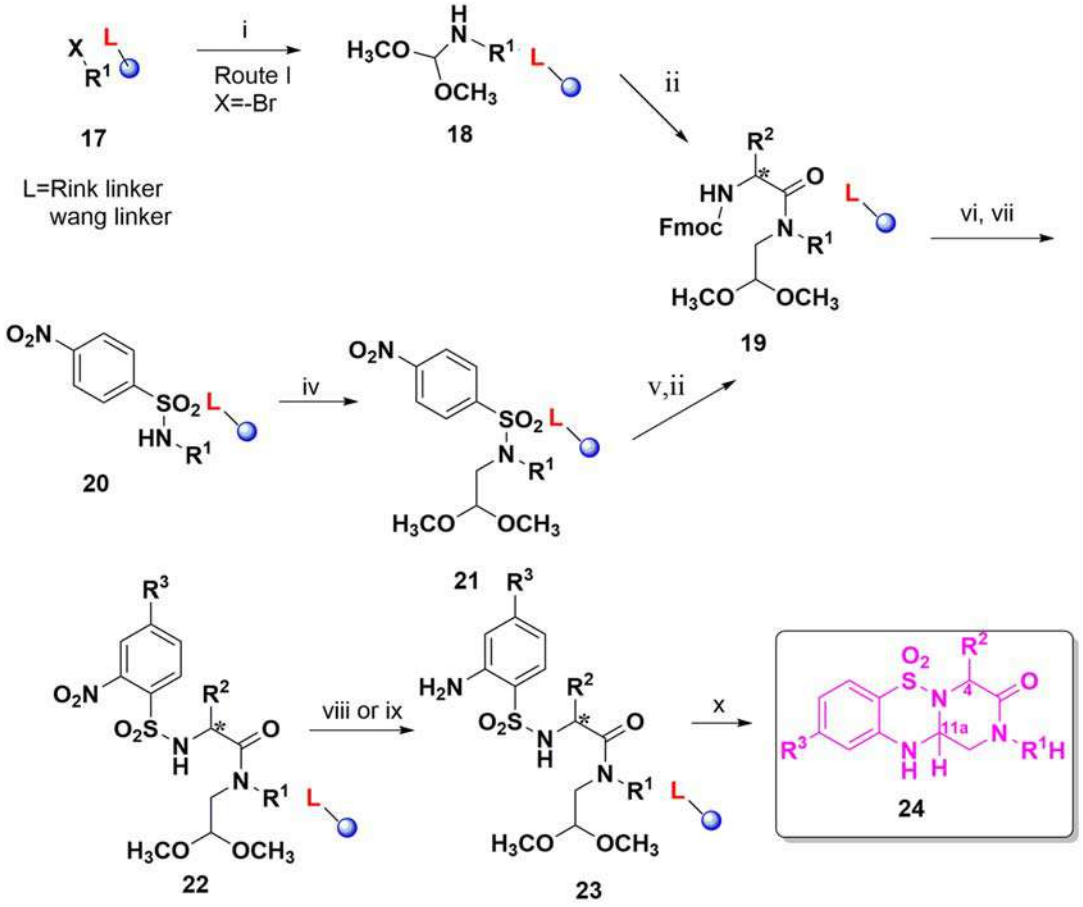
SCHEME 8.5 Synthesis of arenesulfonyl-2-quinoxalinones 15a–h and their 3-methyl derivatives 16a–h.

moderate to good antimicrobial activity against bacteria and fungi [29]. Compounds **25** and **26** (Fig. 8.2) displayed remarkable antibacterial activity against *B. megaterium*, *B. subtilis*, *E. coli*, and *P. fluorescens* and antifungal activity against *Aspergillus awamori* in comparison with those of standard drugs at the same concentration [15].

The direct sulfonylation of 4,5-dichloropyridazin-3-ones with some benzenesulfonyl chlorides in the presence of a base in tetrahydrofuran gave only the corresponding *N*-sulfonylated product. The reaction of compound **27** with substituted benzenesulfonyl chloride in the presence of various bases in tetrahydrofuran gave unexpectedly only 2-(substituted benzenesulfonyl)-4,5 dichloropyridazin-3-one as *N*-sulfonylation product **28** (Scheme 8.7). *O*-Sulfonylation product was not detected by TLC monitoring during the reaction. The rates of sulfonylation for 4,5-dichloropyridazin-3-one **27** were base dependent, whereas the base effect on the regioselectivity was not observed [30].

The reactivity of the exocyclic double bond of the 6-methylidene-1,4,5,6-tetrahydropyridazine **29** was recently evidenced by a quantitative conversion to the 1,4-dihydropyridazine isomer **30** upon dissolution of **29** in chloroform at room temperature (Scheme 8.8) [31]. This observation suggests that the exo/endo migration of the C=C bond is catalyzed by traces of acid in the $CHCl_3$ solvent used. In support of this, using $CHCl_3$ stored over 4 Å molecular sieves (Ms), no isomerization was observed and the 1,4,5,6-tetrahydropyridazine **29** was found stable under such conditions. Related tautomerization processes have been evidenced in general heterocyclic chemistry [32], in particular for the preparation of pyrazole and pyrazoline derivatives [33].

In addition to the electron-rich alkenes, the electron-neutral alkenes are also suitable dienophiles in the inverse electron-demand aza-Diels–Alder reaction due to the high reactivity of azoalkene [34]. In 2015, Luo et al. reported a catalyst-free [4 + 2] cycloaddition of in situ generated azoalkenes and simple olefins [35]. The reaction proceeds smoothly under basic conditions in the absence of any catalysts. Various olefins, such as ethylene, styrene, norbornene, and cyclic diene are also tolerated in this protocol, giving the desired product **31** in good yields (Scheme 8.9) [36].



Reagents and conditions: (i) aminoacetaldehyde dimethylacetal, DIEA, DMF, rt, 2h; (ii) Fmoc-α-amino acid (1 equiv), HOBt (1 equiv), DIC (1 equiv), DCM/DMF (1:1), rt, 16h; (iii) 4-Nos-Cl, 2,6-lutidine, DCM, rt, 4 h; (iv) glycolaldehyde dimethyl acetal, PPh_3, diisopropyl azodicarboxylate (DIAD), anhydrous THF, 0-50°C, 16 h, repetition; (v) 2-mercaptoethanol, DBU, DMF, rt, 5 min; (vi) 50% piperidine in DMF, rt, 15 min; (vii) unsubstituted/ 4-substituted 2-Nos-Cl, 2,6-lutidine, DCM, rt, 4h; (viii) $SnCl_2.2H_2O$, DIEA, DMF (saturated with N_2), 50°C; (ix) $Na_2S_2O_4$ tetrabutylammonium hydrogen sulfate (TBAHS), K_2CO_3, DCM/ water (1:1), rt, 2h; (x) 50% TFA in DCM, rt, 90 min.

SCHEME 8.6 Solid-phase stereoselective synthesis of tetrahydrobenzopyrazinothiadiazinone dioxides 24.

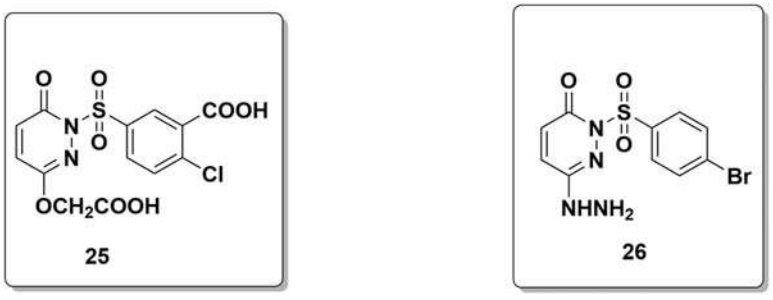
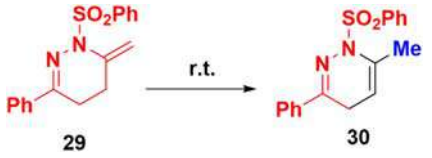


FIGURE 8.2 Structures of pyridazinone derivatives 25 and 26 as antimicrobial activity against bacteria and fungi.

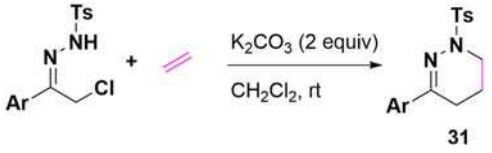
8.2.3 *N*-Sulfonyl-1,3-diazines (*N*-sulfonyl pyrimidines)

The pyrimidine moiety is very widespread in biologically occurring compounds such as nucleic acids and vitamin B1 and, consequently, the synthesis of pyrimidine derivatives has attracted considerable attention. The present synthetic approach is concise, general, highly selective, and efficient. The substrates are readily available and the broader application of this new methodology for pyrimidines is anticipated A one-pot synthesis of *N*-sulfonyl-2-alkylidene-1,2,3,4-tetrahydropyrimidines **32** *via* Cu-catalyzed three-component reaction of sulfonyl azides, terminal alkynes, and α,β-unsaturated imines has been developed. The α and β-unsaturated imines could also be generated from amines and the corresponding unsaturated aldehydes in a sequential one-pot process. The substrate scope was extensively studied and the yields generally range from good to excellent. Only for R^1 = py, a poorer yield of product (43%) was observed (Scheme 8.10) [37].

SCHEME 8.7 Synthesis of *N*-sulfonyl-2-dichloropyridazin-3-one 28.



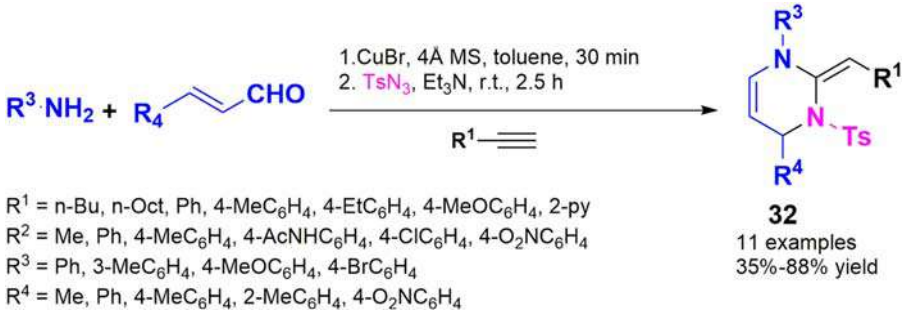
SCHEME 8.8 The exocyclic/endocyclic migration of the C=C bond of *N*-sulfonyl-6-methylidene-1,4,5,6-tetrahydropyridazine 30 to the isomeric 1,4-dihydropyridazine.



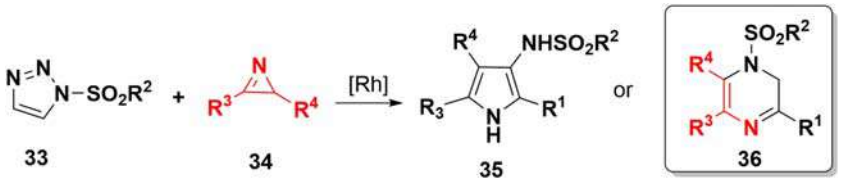
SCHEME 8.9 Base-promoted inverse electron-demand aza-Diels–Alder reaction of azoalkenes with simple olefins.

Consequently, a cascade reaction of acyloxy substituted *N*-sulfonyl-1,2,3-triazole **33** with 2*H*-azirine **34** was designed. The rhodium-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles **33** with 2*H*-azirines **34** could produce 3-amino-pyrrole derivatives **35** or 1,2-dihydropyrazines **36** with the triazole acting as a [2C] synthon or 1-aza-[3C] synthon, respectively (Scheme 8.11) [38].

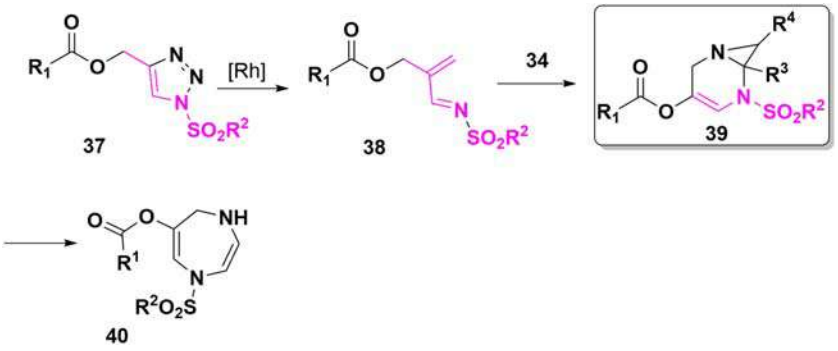
Another synthetic application of *N*-sulfonyl-1,2,3-triazoles **37** acting as a 1-aza-[4C] synthon *via* the 1,2-shift reaction of an a-imine rhodium carbene was developed for the synthesis of fused pyrimidine derivatives **39**. The high reactivity of the strained three-membered 2*H*-azirine ring facilitated the unusual cyclization of electron-deficient dienes with electron-deficient dienophiles. The compatibility was good with common functionalities tolerated. Excellent chemoselectivity was observed, and no reactions occurred between the rhodium carbene and 2*H*-azirine **34**. The products could be converted into seven-membered multi-functionalized 1*H*-1,4-diazepine derivatives **40** (Scheme 8.12). under rhodium catalysis, acyloxy substituted triazoles **37** could be converted to 1-azadienes first **38**, which would be employed as a 1-aza-[4C] synthon **39** to cyclize with 2*H*-azirines **34** producing fused pyrimidine



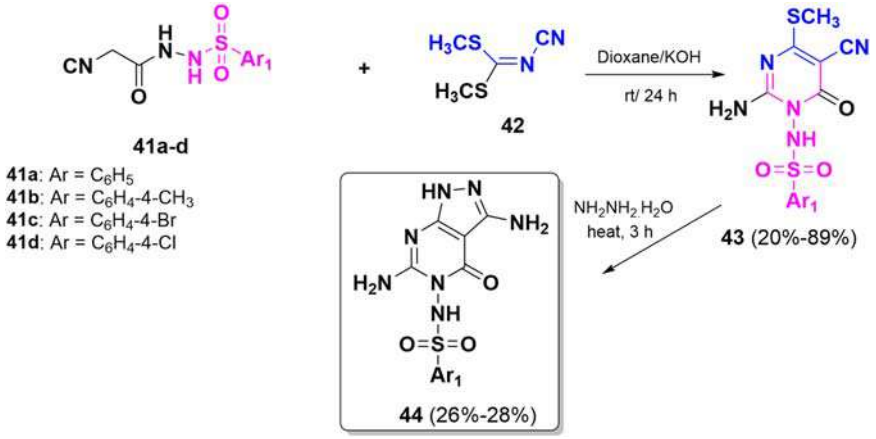
SCHEME 8.10 Cu-Catalyzed multicomponent synthesis of 1,2,3,4-tetrahydropyrimidines 32.



SCHEME 8.11 Synthesis of pyrazines 36 from Rhodium-Catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles 33 with 2H-azirines 34.



SCHEME 8.12 Rhodium-catalyzed synthesis of fused pyrimidine derivatives 39 employing *N*-sulfonyl-1,2,3-triazoles 37 as a 1-aza-[4C] synthon 34.



SCHEME 8.13 Synthetic approaches for *N*-sulfonylamino methylthiopyrimidin-2-ones 43 and 1H-pyrazolo[3,4-d] pyrimidines 44.

skeleton **38** [39]. Pyrimidine derivatives are well-known motifs in bioactive molecules exhibiting antiviral, anticonvulsant, antioxidant, anticancer, and anti-inflammatory activities; [40] Furthermore, the bridging C−N bond could be cleaved to give an interesting medium-sized 1*H*-1,4-diazepine derivative, which is also widespread in bioactive molecules (Scheme 8.12) [41].

Synthesis of *N*-sulfonylamino methylthiopyrimidin-2-ones **43** as non-nucleoside analogs was reported by Elgemeie et al. [42], Elgemeie and Sood [43], Azzam et al. [44], who represented the reaction of *N*-cyanoactoarylsulfonylhydrazides **41a−d** with dimethyl *N*-cyanodithioimino-carbonate (**42**)in the presence of potassium carbonate to provide easy access of *N*-sulfonylamino methylthiopyrimidin-2-ones **43** in low to excellent yield (Scheme 8.13). 1*H*-Pyrazolo[3,4-*d*]pyrimidines **44** were also prepared *via* the treatment of pyrimidin-2-ones **43** with hydrazine hydrate (Scheme 8.13). In comparison with standard drugs, compound **44c** exhibited high potency against all tested bacterial and fungal strains except Aspergillus flavus fungus. In contrast, compound **44d** showed no activity against all aforementioned strains. These findings indicated the effect of bromo substituent on the benzene ring of sulfonamide moiety on antibacterial potency [19].

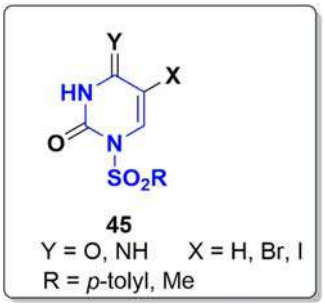
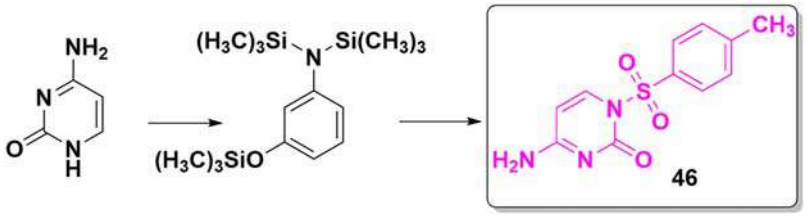


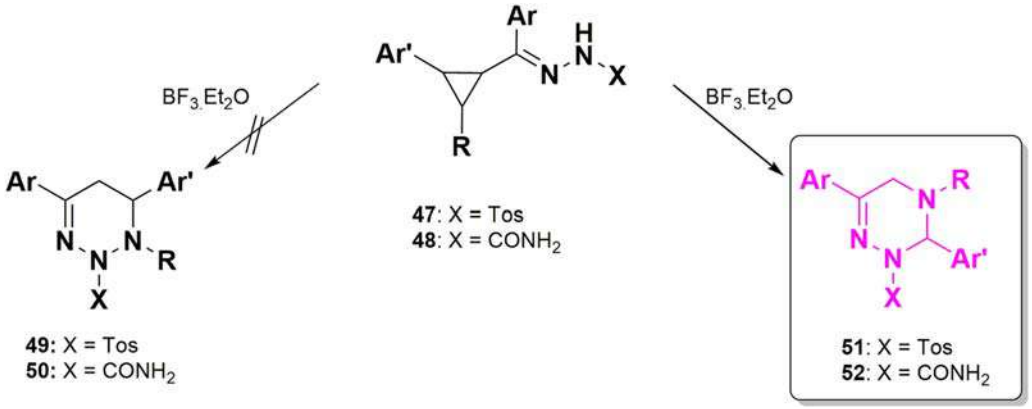
FIGURE 8.3 Structure of *N*-sulfonated pyrimidines 45 as antitumor agents.

It was reported the synthesis of a series of pyrimidine nucleic base derivatives **45** (Fig. 8.3) possessing a sulfonamide pharmacophore [45], and showed that these types of nucleic base derivatives exhibit strong in vitro antitumor activity [46].

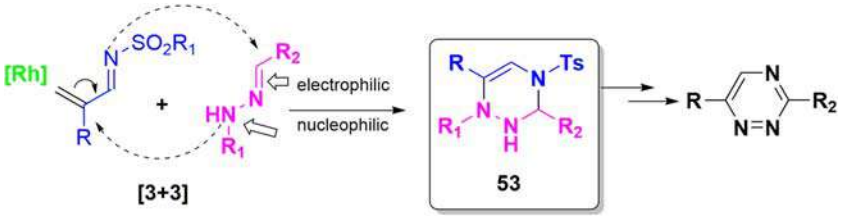
The sulfonamide group $^{1}-SO_2-NH-R^2$ is a common pharmacophore found in various biologically active molecules, enzyme inhibitors, and receptor antagonists [47]. Also, *N*-1-sulfonylpyrimidine derivatives showed potent



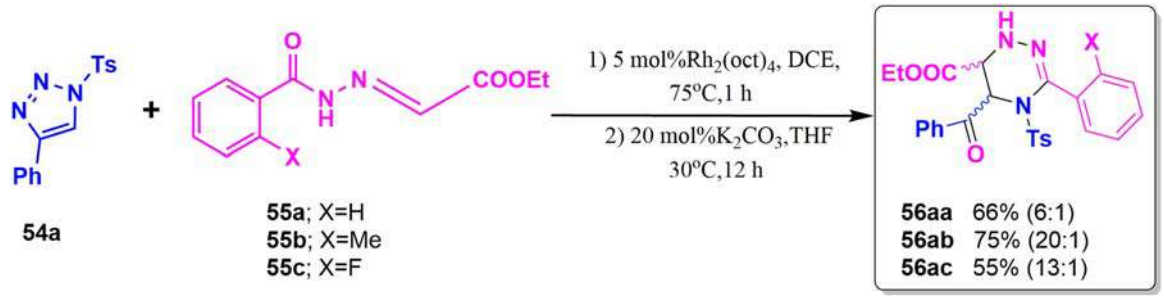
SCHEME 8.14 N-Sulfonylpyrimidine derivatives 46 of antitumor activity on anaplastic mammary carcinoma in vivo.



SCHEME 8.15 Synthesis of 2,3,4,5-tetrahydro-1,2,4-triazines 51 and 52.



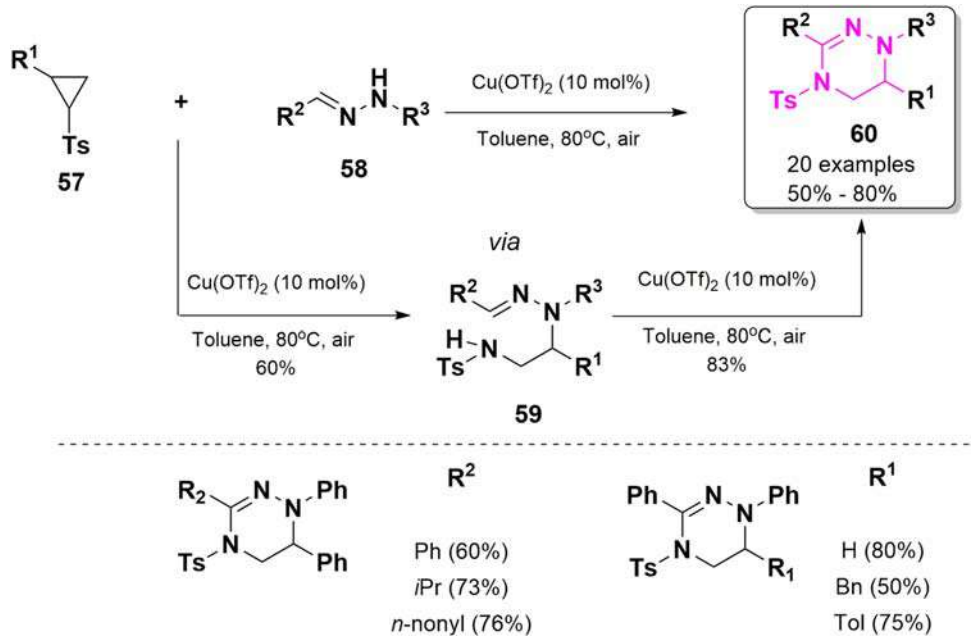
SCHEME 8.16 Rhodium-catalyzed synthesis of 1,2,4-triazine 53.



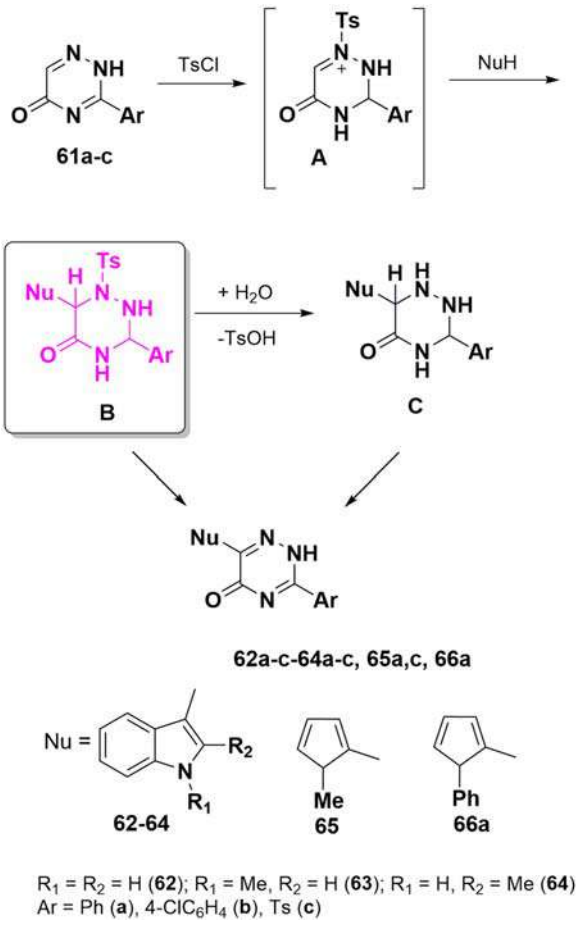
SCHEME 8.17 Synthesis of 1,4,5,6-tetrahydro-1,2,4-triazines 56.

growth inhibitory activity against human tumor cell lines in vitro [48]. In comparison with 5-FU, some *N*-sulfonylpyrimidine derivatives showed ten times stronger inhibitory effects while the effects on normal human cell lines were much lower. 5-FU was used for comparison to *N*-1-sulfonylpyrimidine derivatives because it is a standard chemotherapeutic agent with a pyrimidine structure. It was found that these compounds inhibit DNA, RNA, and protein synthesis. Some of them showed the ability to induce apoptosis in treated tumor cells [48].

Upon in vivo investigation of antitumor activity of the synthesized *N*-sulfonylpyrimidine derivatives 1-(*p*-toluenesulfonyl) cytosine (4*H*) **46**, it has been found that *N*-1-sulfonylcytosine derivatives of **46** have strong antitumor activity against mouse mammary carcinoma which is a good reason (Scheme 8.14) [45,49].



SCHEME 8.18 Cu(OTf)2 catalyzed reaction of N-tosylaziridine 57 with hydrazones 58.



SCHEME 8.19 Synthesis of substituted triazinones 62–66.

8.3 *N*-Sulfonyl-triazines

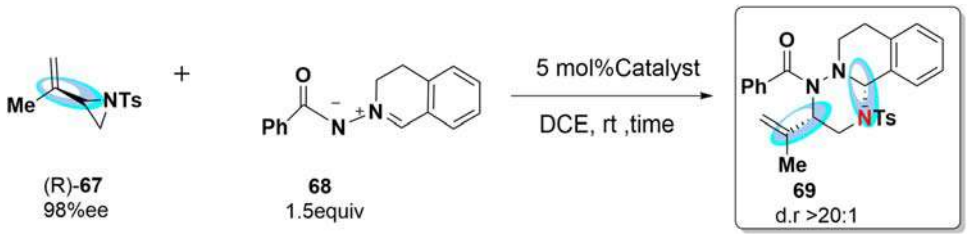
8.3.1 *N*-Sulfonyl-1,2,4-triazines

The reported triazines (1-alkyl-3-arylaziridin-2-yl)-aryl-methanone tosylhydrazones **47** [50] and semicarbazones **48** [51], respectively, by treatment with boron trifluoride etherate are not tetrahydro-1,2,3-triazines **49** and **50** but 2,3,4,5-tetrahydro-1,2,4-triazines **51** and **52**, as proven by a single crystal X-ray structural analysis for **51** (R¼c-C_6H_{11}, Ar¼Ar9¼Ph) (Scheme 8.15) [52].

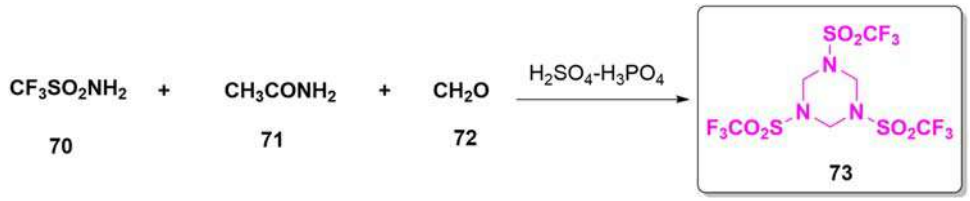
Inspiringly, there was, to the best of our knowledge, a rare method developed for the synthesis of important heterocycles containing more than two heteroatoms in rhodium-aza vinylcarbene chemistry owing to the challenge of choosing an appropriate substrate hydrazone may be the possible substrate for the construction of 1,2,4-triazine **53** *via* a formal [3 + 3] cycloaddition owing to its feature containing two nitrogen atoms (Scheme 8.16) [53].

It was found that inorganic bases could not catalyze the cyclization reaction since the blocking of byproduct formed in rhodium-catalyzed step in a one-pot manner. Moreover, bases like K_2CO_3 catalyzed the cyclization reaction smoothly in a two-step process affording 1,4,5,6-tetrahydro-1,2,4-triazines **56** in good yields and diastereoselectivities as outlined in Scheme 8.17 [53].

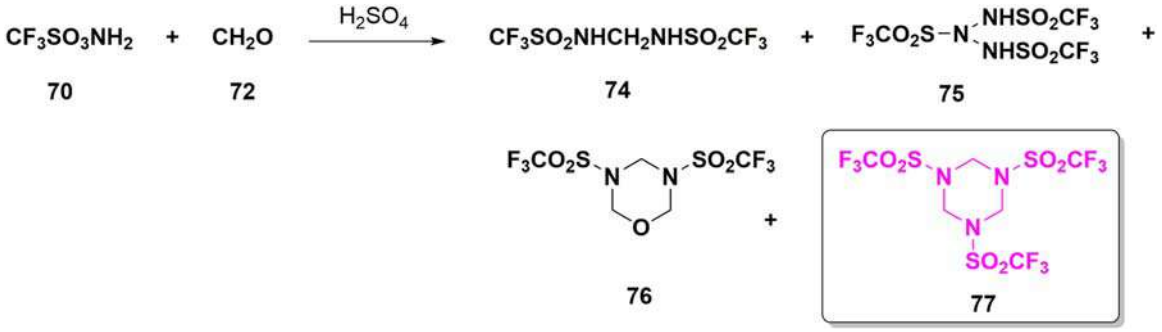
Fatykhov et al. reported the synthesis of 1,4,5,6-tetrahydro-1,2,4-triazines **60** *via* a tandem reaction involving a nucleophilic ring-opening and an intramolecular oxidative amidation of *N*-tosylaziridines **57** and hydrazones **58** and under aerobic conditions [54].



SCHEME 8.20 [3 + 3]Cycloadditions of C,N-cyclic azomethine imines, and cycloaddition chemistry of vinylaziridines.



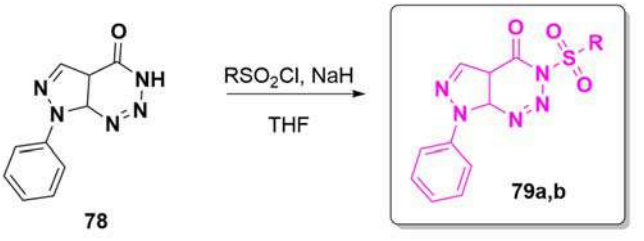
SCHEME 8.21 Reactions of trifluoromethanesulfonamide with amides to synthesize *N*-sulfonated -1,3,5-triazine 73.



SCHEME 8.22 Synthesize *N*-sulfonated -1,3,5-triazine 77.

$Cu(OTf)_2$ was used as a catalyst in toluene at 80°C to produce a series of 1,2,4-triazines in moderate to good yields (Scheme 8.18). Decreasing temperature to room temperature in the presence of $Cu(OTf)_2$ led to product **59**, which then underwent intramolecular cyclization at high temperature (Scheme 8.18). Other catalysts such as AgOTf and $Yb(OTf)_3$ exclusively provided the nucleophilic ring-opening product of the aziridine **58** (Scheme 8.18).

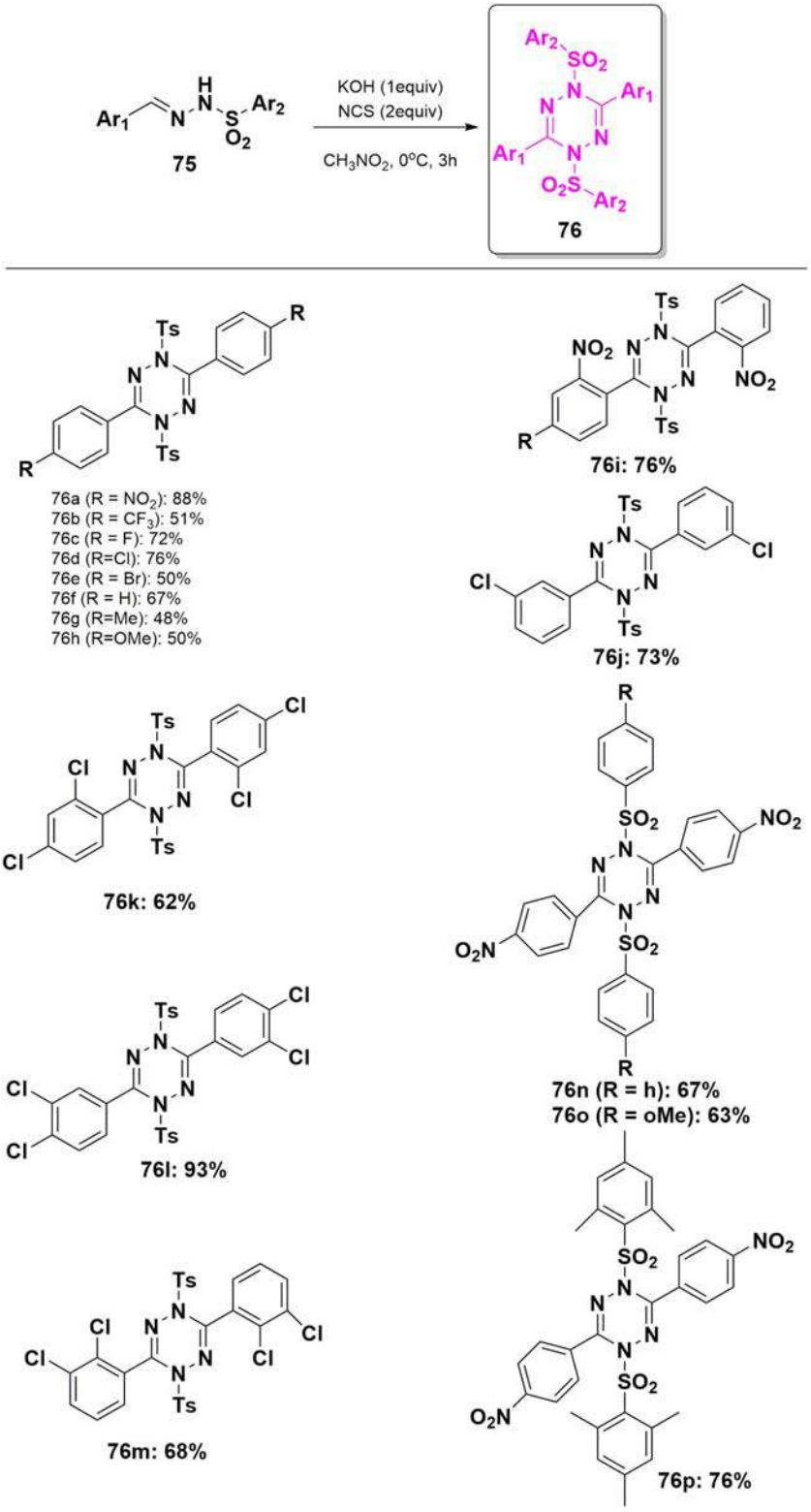
It was documented that the reactions of compounds **61** with indoles, *N*-methylpyrrole, and *N*-phenylpyrrole using chlorides of aromatic sulfonic acids as acylating agents gave rise to the corresponding 3-aryl-6-heteryl-1,2,4-triazin-5(2*H*)-ones **62**–**64**, which are products of the nucleophilic displacement of hydrogen (Scheme 8.19). For example, storage of solutions of 1,2,4-triazin-5(2*H*)-ones **61** and the corresponding π-excessive heterocycles in chloroform in the presence of *p*-toluenesulfonyl chloride at room temperature for 24h afforded compounds **62**–**66** in 80%–90% yields. The spectroscopic characteristics of substituted triazinones **62**–**66** thus obtained correspond to the assumed structures and are consistent with the published data [55]. The following reaction



R = Ph (**79a**), 4-ClC_6H_4 (**79b**)

SCHEME 8.23 Acylation of pyrazolo[3,4-d][1,2,3]triazin-4-ones 79a,b.

pathway can be suggested. Activation of 1,2,4-triazin-5(2*H*)-ones **1** through the formation of acylazinium salts **A** is followed by the addition of a nucleophile to give adducts **B**. The reactions of 3-methylthio-1,2,4-triazin-5-one with water and methanol proceeded analogously to give products of the addition at the C(6) atom of the heterocycle even at below zero temperatures [56]. Compounds **B** can undergo subsequent transformations into the corresponding S_NH products either directly with elimination of the sulfinic acid molecule (path



SCHEME 8.24 Synthesis of 1,2,4,5-tetrazines 76a–p. General conditions: 75 (0.2 mmol), NCS (0.4 mmol), KOH (0.2 mmol), CH3NO2 (1.0 mL), 0°C, 3 h.

a) or in two steps (path *b*). In the latter case, 6-hetaryl-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**C**) are initially generated through hydrolysis with water, which is present in the solvent, followed by oxidation of compounds **C** to produce 3-aryl-6-hetaryl-1,2,4-triazin-5(2*H*)-ones **62**−**66** [56].

The reaction of (*R*)-**67** (98% *ee*) with the *C*,*N*-cyclic *N*'-acyl azomethine imine **68** to test the hypothesis on the cross-1,3-dipolar cycloaddition revealed that the use of 5 mol% of $[Rh(CO)_2Cl]_2$ in DCE for 3 h at80°C provided a 46% NMR yield of **69** as a single diastereomer. However, **69** obtained by such catalyst is in racemic form (Scheme 8.20). Next, other commonly used rhodium catalysts were tested but failed to improve the process. In contrast, treatment of (*R*)-**67** and **68** with commercially available $[Rh(NBD)_2]BF_4$ in DCE for 1 h at room temperature gave [3 + 3] cycloadduct **69** in 77% NMRyield with 57% [57].

8.3.2 *N*-Sulfonyl-1,3,5-triazines

It was documented that the reaction of trifluoromethanesulfonamide **70** with a mixture of amide **71** and paraformaldehyde **72** is very sensitive to the temperature, reaction time, and reactant ratio. Likewise, the results of three-component condensation of **70**, amide **72** (or acetonitrile) with paraformaldehyde **72** strongly depended on the conditions. In 96% H_2SO_4 (acetamide) or 85% H_3PO_4 (acetonitrile) mixed condensation product **73** was obtained [58]. When the reaction of **70** with acetamide **71** and paraformaldehyde **72** was performed in 92% sulfuric acid in the presence of P_2O_5 (the amount of the latter corresponded to complete binding of water present in 92% sulfuric acid; that is the reaction occurred in a mixture of anhydrous sulfuric and phosphoric acids), the major product was previously described 1,3,5-tris(trifluoromethylsulfonyl)hexahydro-1,3,5-triazine **73** (Scheme 8.21) [59].

Orazi and Corral [59] reported on the for *N*-sulfonyl-substituted dihydro-1,3,5-dioxazines, tetrahydro-1,3,5-oxadiazines, and hexahydro-1,3,5-triazines in reactions of 1,3,5-trioxane (as a source of formaldehyde) with alkane- and arenesulfonamide **70**. It was found that trifluoromethanesulfonamide **70** reacted with paraformaldehyde **72** in sulfuric acid at various temperatures and reactant ratios to produce several open-chain and cyclic condensation products. In particular, it was isolated and identified bis(trifluoromethylsulfonylamino) methane **74**, *N*,*N*-bis (trifluoromethylsulfonylaminomethyl)trifluoromethanesulfonamide **75**, 3,5-bis(trifluoromethylsulfonyl)tetrahydro-1,3,5-oxadiazine **76**, and 1,3,5-tris(trifluoromethyl-sulfonyl)hexahydro-1,3,5-triazine **77** (Scheme 8.22) [60].

8.3.3 *N*-Sulfonyl-1,2,3-triazines

The sulfonylation of pyrazolotriazinones **78**, which had not previously been studied, also proceeded regioselectively at the N3 site with the formation of derivatives **79a** and **79b** (Scheme 8.23). The reaction proceeded in THF solution with cooling in the presence of sodium hydride [61].

8.4 *N*-Sulfonated tetrazines

Recently, 1,2,4,5-tetrazines have also attracted a fair amount of attention in life sciences, with applications in cell imaging, DNA labeling, etc [62−66]. In general, 1,2,4,5-tetrazines are synthesized predominantly by the reaction of hydrazine with aromatic nitriles, followed by oxidation of the generated 1,2-dihydrotetrazines [67−69]. In addition, further modification of 1,2,4,5-tetrazines has also emerged as a useful tool [70,71]. On the other hand, arylsulfonylhydrazones are key building blocks in synthetic chemistry [72−76], especially for the synthesis of nitrogen-containing heterocycles [77−79].

In 2015, Prabhu and Ojha [80] reported an elegant synthesis of vinyl halides from arylketone-derived *N*-tosylhydrazones using NXS/(*n*Bu)4NX, in which dihalides were the proposed reaction intermediates (Scheme 8.24). Herein, we report a facile synthesis of 1,2,4,5-tetrazine derivatives from arylaldehyde- derived arylsulfonylhydrazones in the presence of NCS and KOH under metal-free conditions (Scheme 8.24). The discovery of this 1,2,4,5-tetrazine synthetic protocol was somewhat unexpected. It began with our attempts to synthesize dichlorides from arylaldehyde-derived aryl sulfonylhydrazones using Prabhu's conditions. Regrettably, the chlorination reaction did not afford the desired dichlorides; instead, 1,2,4,5-tetrazines were unexpectedly obtained. Considering the importance of 1,2,4,5-tetrazine derivatives in chemical, biological, and environmental sciences [81−83]. Having optimized the reaction conditions, the scope of the reaction with arylaldehyde-derived arylsulfonylhydrazones was subsequently explored and the results are compiled in Scheme 8.24. A wide range of *N*-tosylhydrazones, with either hydrogen atoms, electron-withdrawing groups, or electron-donating groups at the *ortho*, *meta*, or *para* positions of their aromatic rings, reacted smoothly in the presence of NCS (2.0 equiv) and KOH (1.0 equiv) at 0°C to afford 1,2,4,5-tetrazines **76a**−**m** in moderate to excellent yields within 3 h. Aryl sulfonylhydrazones derived from methoxy- and methyl-substituted benzenesulfonyl hydrazides reacted under the optimized conditions to generate 1,2,4,5-tetrazines **76n**−**p** in good yields [67].

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Chapter 9

Synthesis of *N*-sulfonated *N*-azepines

9.1 Introduction

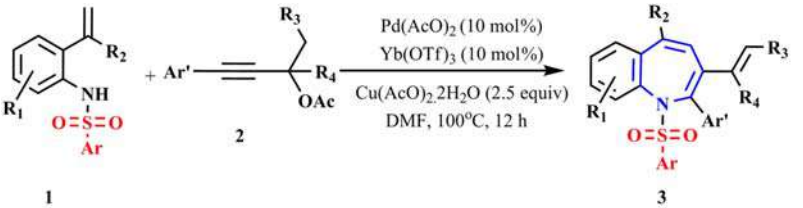
Seven-membered heterocycle compounds abound in natural products, providing optimal properties in various applications such as ligands for PET and MRI imaging, structural cores or side chains in medicinal chemistry, and reagents for native peptide ligation, electroactive materials, and polymers for biomedical applications [1]. Azepines, a seven-membered heterocyclic compound with one nitrogen atom, are existing in four tautomeric forms, 1*H*-, 2*H*-, 3*H*-, and 4*H*-azepines. The most accessible and important tautomeric forms are 1*H*- and 3*H*-azepines. It was noted that the 1*H*-azepine is an unstable compound while the presence of the electron-withdrawing group at the nitrogen atom enhances the stability of its structure, probably, due to the unrolling of lone pair of electrons inside the ring. It was found that some azepine derivatives have great pharmacological and therapeutic effects. A well-known drug, Carbamazepine, is a dibenzoazepine that is 5*H*-dibenzo[*b,f*]azepine carrying a carbamoyl substituent at the azepine nitrogen, used as an anticonvulsant and in the treatment of seizure disorders, neuropathic pain, deficit hyperactivity disorder, schizophrenia, phantom limb syndrome, complex regional pain syndrome, borderline personality disorder, and posttraumatic stress disorder [2]. Eslicarbazepine acetate is a prodrug of eslicarbazepine and was approved as a new antiepileptic drug [3]. Several fused azepine derivatives such as dihydropyrazolo[1,4]oxazepinone and azepino[4,5-*b*]indole have been advanced to clinical trials for the treatment of obesity and as selective farnesoid X receptor FXR agonists, respectively. Azepine sulfonamide derivatives revealed some potency as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors of interest for various metabolic disorders such as hypertension, obesity, and diabetes [4]. Therefore, several methodologies have been developed for the synthesis of *N*-sulfonyl azepine derivatives [5,6]. Most of the mechanisms involved inter- and intramolecular cyclization using metal-catalyzed reactions of various precursors using different transition metal catalyzes such as Pallidum [7], Gold [8], Silver [9], Rhodium [10], and Ruthenium [11]. However, there is much work yet to be done in the biological section, as it is not explored and reported in the literature; therefore, *N*-sulfonyl azepines heterocycles still have much scope for the researchers.

9.2 *N*-Sulfonyl azepines

9.2.1 Metal-catalyzed intermolecular cyclization

9.2.1.1 Palladium-catalyzed reactions

One of the attractive approaches used for the synthesis of *N*-sulfonyl azepines is palladium-catalyzed reactions. This method was used to synthesize benzo[*b*]azepines by applying palladium(II)/Lewis acid cocatalyzed oxidative [5 + 2] annulation of various *N*-tosyl 2-vinylaniline **1** and propargylic esters **2**. The reaction proceeded under mild conditions producing an array of benzo[*b*]azepines **3** in a yield range of 30% to 75% [12] (Scheme 9.1).



SCHEME 9.1 Oxidative annulation of *N*-toyl 2-alkenylaniline with propargylic esters.

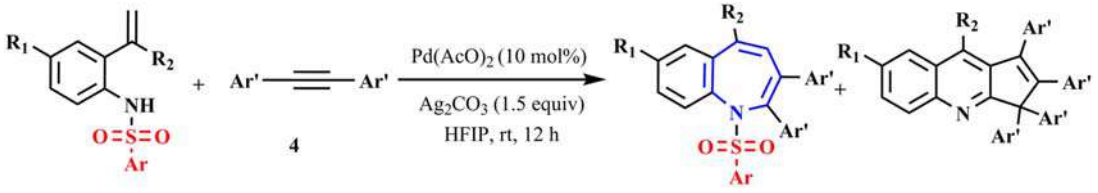
N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00007-0

A similar approach using *N*-tosyl 2-vinylanilines **1** with symmetrically alkynes **4** instead of propargylic esters **2** under palladium-catalyzed reaction ($Pd(OAc)_2$-Ag_2CO_3-HFIP) delivered benzazepine **5** as the main product in addition to a trace of cyclopentaquinoline derivatives **6** (Scheme 9.2) [13].

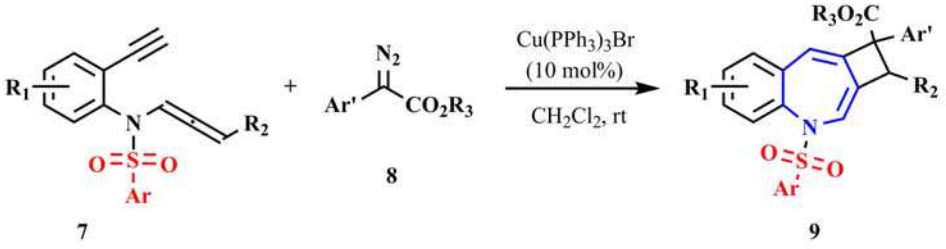
9.2.1.2 Copper-catalyzed reactions

A copper-catalyzed cross-coupling/[2 + 2] cycloaddition of 1,6-allenynes **7** with aryl diazoacetates **8** bearing electron-donating or electron-withdrawing substituents at the aryl moiety was reported by He [14] to provide 3-aza-bicyclo[5.2.0] **9** frameworks in moderate to excellent yields under mild reaction conditions (Scheme 9.3).

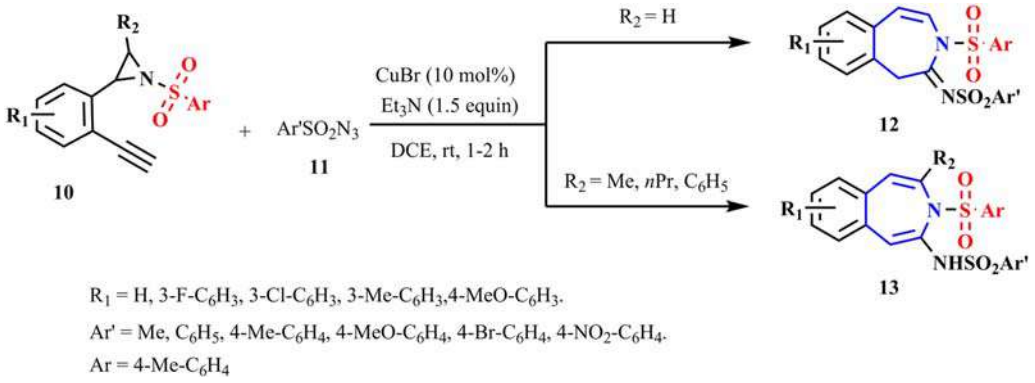
3-Tosyl-1*H*-benzo[*d*]azepin-ylidene **12** derivatives were synthesized by a copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **10** with sulfonyl azides **11** through the formation of a ketenimine as a key intermediate during the reaction process (Scheme 9.4). The expected benzazepine derivatives were isolated in good yields. Different substituents including electron-



SCHEME 9.2 Oxidative annulation of *N*-tosyl 2-alkenylaniline with internal alkynes.



SCHEME 9.3 [2 + 2] Cycloaddition of 1,6-allenynes with aryl diazoacetates.



SCHEME 9.4 Copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine with sulfonyl azide.

withdrawing/donating such as fluoro, chloro, methyl, methoxy, bromo, and nitro groups were compatible under the standard reaction conditions. Interestingly, when R_2 was changed to an alkyl or aryl group, isomerized products of *N*-tosyl azepine **13** were isolated in moderate yields [15].

9.2.1.3 Silver catalyzed reactions

The intermolecular silver-mediated Kondakov–Darzens acylation reaction of *N*-tosyl allylic aniline **14** with acyl chloride **15** would enable the rapid construction of benzazepinone **16** in 50% yield at 0°C (Scheme 9.5) [16].

9.2.2 Metal-catalyzed intramolecular cyclization

9.2.2.1 Palladium-catalyzed reactions

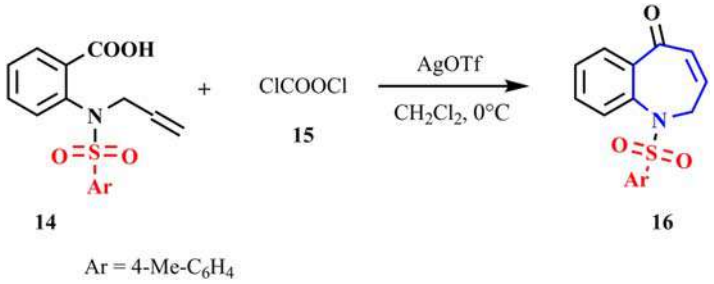
The intramolecular cyclization method has been used widely in the synthesis of azepines derivatives. *N*-Tosyl benzo[*d*]azepin-2(3*H*)-one **18** has been prepared efficiently through the intramolecular cyclization of *N*-tosyl alkynylamides **17**, using Pd complex (Catalyst A), in good yield (Scheme 9.6) [17].

9.2.2.2 Gold catalyzed reactions

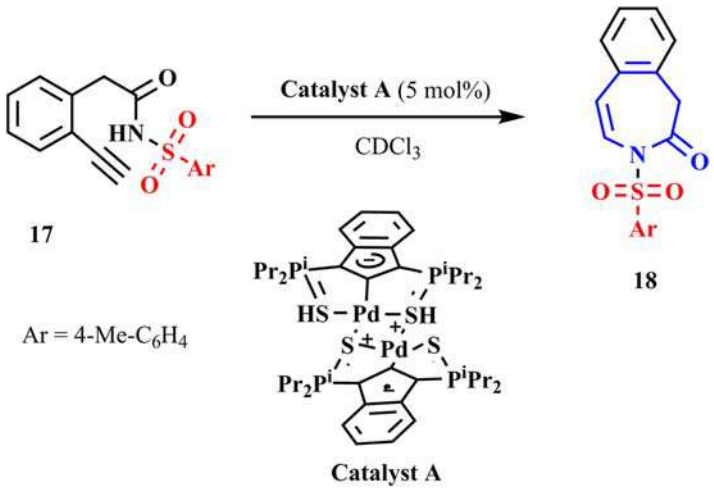
The 7-*exo*-*dig*-selective gold-catalyzed cycloisomerizations of 2-propargylamino biphenyl **19** derivatives produced *N*-tosyl dibenzo[*b*,*d*]azepines **20**. After acidic treatment, all derivatives of dibenzo[*b*,*d*]azepines with either electron-donating and −withdrawing substituents, even the sterically hindered 4-Me-substituted substrate, were isolated as *endo* olefins in high yield (Scheme 9.7). The electron-withdrawing effect of a tosyl group and the nucleophilicity at the reaction site were important for selective transformation [18].

In 2011, Borsini et al. [8] reported that the substituent on alkyne of alkyne-tethered pyrroles **21** determined the regioselectivity of intramolecular cyclization catalyzed by Gold(III), $AuCl_3$. The presence of phenyl-substituted alkynes **21** formed two isomeric products of pyrroloazepines. The major isomer was **22** (68%) in which the carbonyl moiety remains bonded to the pyrrole's α-carbon while the minor isomer was **23** (7%) in which the carbonyl moiety migrates from the pyrrole's α-carbon to the pyrrole's β-carbon (Scheme 9.8).

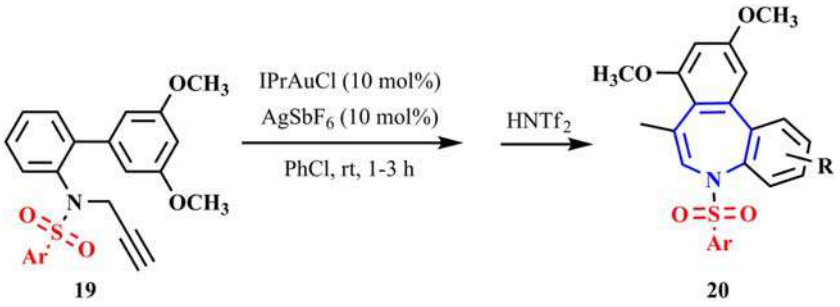
A two-step, one-pot synthetic method, provided a synthetic route for the synthesis of *N*-tosyl benzo[*b*]azepin-3-ones **26** using gold(I)-catalyzed and Brønsted acid. The reactions proceed under mild conditions for a variety of 2-(*N*-



SCHEME 9.5 Acylation reaction of *N*-tosyl allylic aniline with acyl chloride.

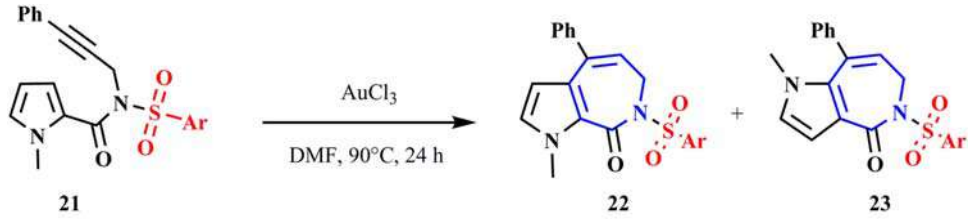


SCHEME 9.6 Intramolecular cyclization of *N*-tosyl alkynylamides.



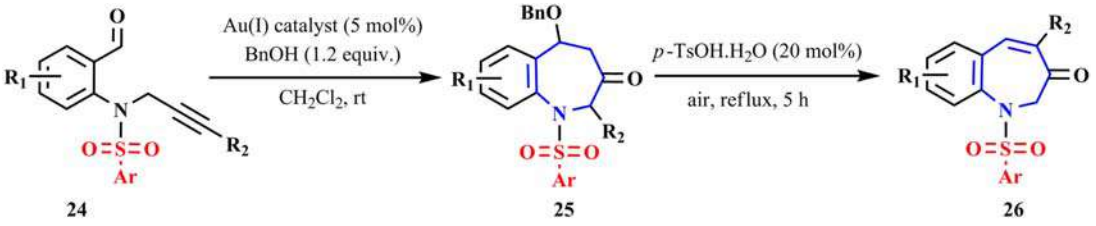
R = 1-F, 2-Me, 2-Cl, 2-CF_3, 3-Me, 3-CF_3, 4-Me
Ar = 4-Me-C_6H_4

SCHEME 9.7 Cycloisomerizations of 2-propargylamino biphenyl derivatives.



Ar = 4-Me-C_6H_4

SCHEME 9.8 Intramolecular cyclization of alkyne-tethered pyrroles.



R_1 = H, 3-Me, 3-Cl, 4,6-Me, 4,5-MeO, 4-Me, 4-Cl, 4-Br, 5-MeO, 5-CF_3, 6-Cl, 6-MeO
R_2 = Me, C_6H_5
Ar = Me, 4-Me-C_6H_4 4-NO_2-C_6H_4

SCHEME 9.9 Gold(I)-catalyzed synthesis of *N*-tosyl benzo[*b*]azepin-3-ones.

(prop-2-ynyl)-*N*-tosylamino)benzaldehyde substrates **24** containing electron-withdrawing, electron-donating, and sterically functional groups and afforded the corresponding benzo-fused aza heterocyclic products in 34%−87% yield through the debenzoxylation of the intermediate **25** (Scheme 9.9) [19].

9.2.2.3 Iridium catalyzed reactions

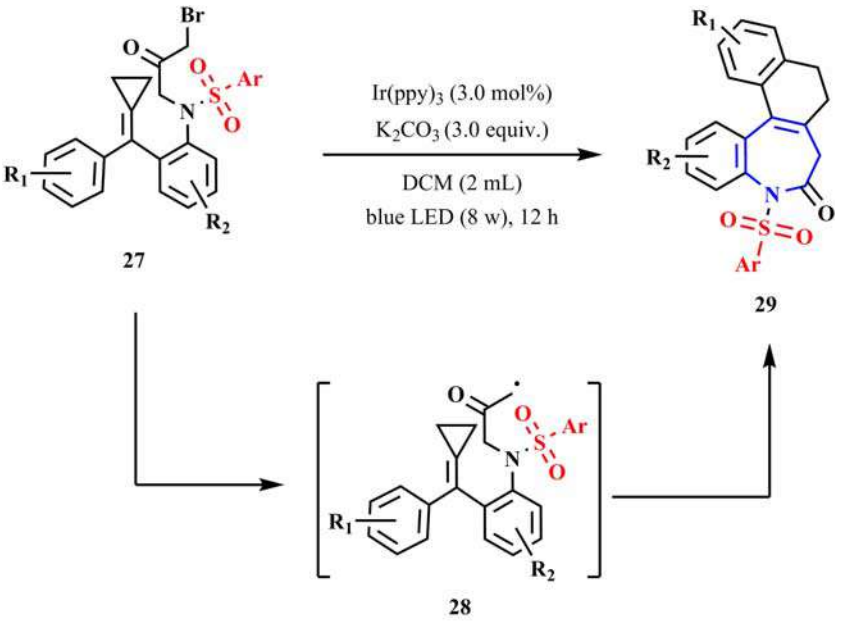
Compounds having alkylidene cyclopropanes moiety **27** under visible light photocatalysis produced a radical intermediate **28** by the cleavage of the C−Br bond at the α-position of the carbonyl group followed by cascade cyclization using $Ir(ppy)_3$ (3 mol%) and K_2CO_3 to afford *N*-tosyl azepine ring-containing polycyclic compounds **29** which their structure confirmed by X-ray crystal diffraction (Scheme 9.10) [20].

9.2.3 Other synthetic pathways

The bridging unit of the biaryl aniline **30** to form *N*-sulfonyl 5*H*-dibenzo[*b,d*]azepin-7(6*H*)-ones **33** required a multi-step synthesis through the formation of *N*-sulfonyl biaryl aniline derivatives **31** (Scheme 9.11). The sequence involved an intramolecular Friedel−Crafts acylation of benzoyl chloride **32** as a crucial step [21].

N-Sulfonyl azepines **37** were synthesized in one step and isolated in moderate yields. The reaction was carried out using benzene and sulfonylnitrene **36**, which were generated in situ from sulfonamide tetrabutylammonium salts **34** and xenon difluoride **35** (Scheme 9.12) [22].

More derivatives of *N*-sulfonyl azepine **37** were produced starting from sulphonyl azide derivatives **11** [23−25] which can be formed from corresponding arylsulfonyl

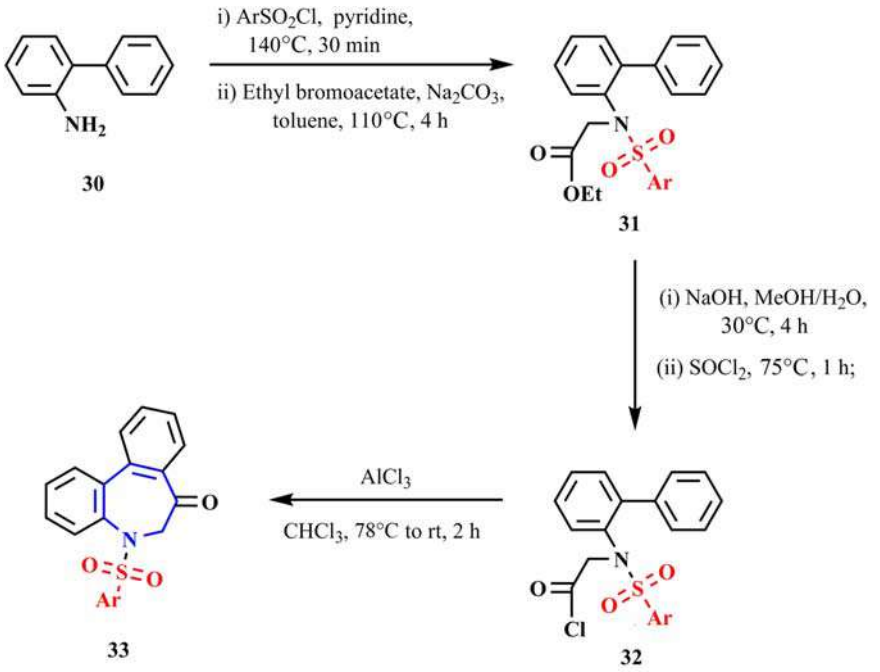


R_1 = H, 4-Cl, 4-Br, 4-F,4-MeO, 4-Me, 2-Me, 2-MeO.

R_2 = H, 4-Cl, 4-Br.

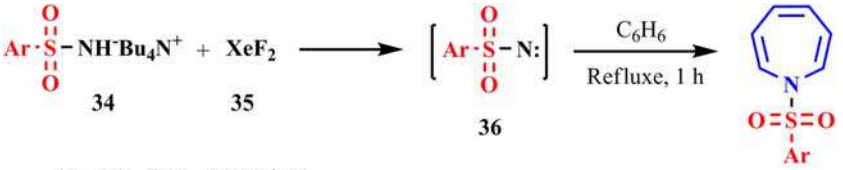
Ar = 4-Me-C_6H_4

SCHEME 9.10 Cascade cyclization of alkylidenecyclopropanes.



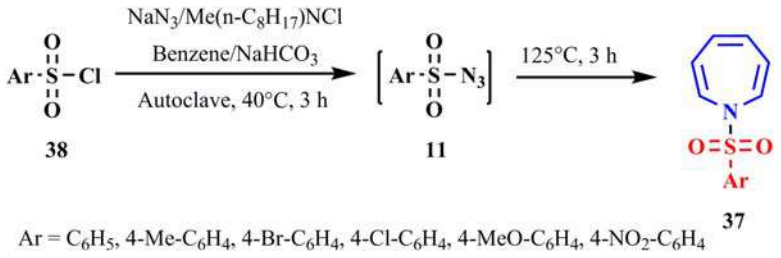
Ar = 4-Me-C_6H_4, 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 2-thionyl

SCHEME 9.11 Synthesis of *N*-sulfonyl 5*H*-dibenzo[*b*,*d*]azepin-7(6*H*)-ones starting from biaryl aniline.

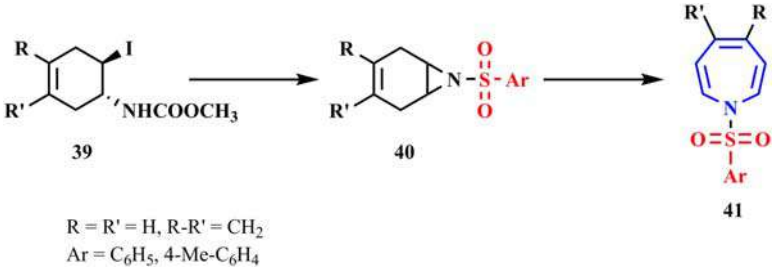


Ar = Me, C_6H_5, 4-Me-C_6H_4

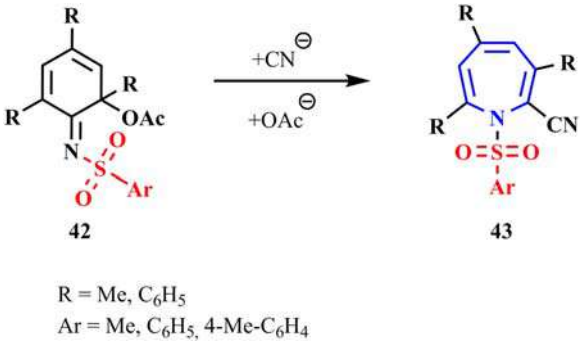
SCHEME 9.12 Reaction of benzene with sulfonylnitrene.



SCHEME 9.13 Synthesis of *N*-sulfonyl azepines from sulphonyl azides.



SCHEME 9.14 Synthesis of *N*-sulfonyl azepines from unsaturated *N*-sulfonyl aziridines.



SCHEME 9.15 Synthesis of *N*-sulfonyl azepine-2-carbonitrile derivatives.

chloride **38** in a one-pot reaction using solid-liquid phase-transfer catalysis technique, benzene/sodium bicarbonate (Scheme 9.13) [26].

General synthesis of substituted *N*-sulfonyl azepine derivatives **41** has been developed using the nitrogen functionalization method through the formation of unsaturated *N*-sulfonyl aziridines **40**, which are formed by cyclization of iodoisocarbamates **39** with various bases (Scheme 9.14) [27].

The reaction of triethylammonium cyanide with conjugated 6-benzensulfonyliminocyclohexadienyl acetate derivatives **42** led to the formation of corresponding *N*-sulfonyl azepine-2-carbonitrile derivatives **43** (Scheme 9.15). The mechanism involved the attack of cyanide at the imine carbon atom of **42** followed by nitrogen participation with loss of acetate residue producing the 1*H*-azepine derivatives [28].

9.3 *N*-Sulfonyl dihydroazepines

9.3.1 Metal-catalyzed intermolecular cyclization

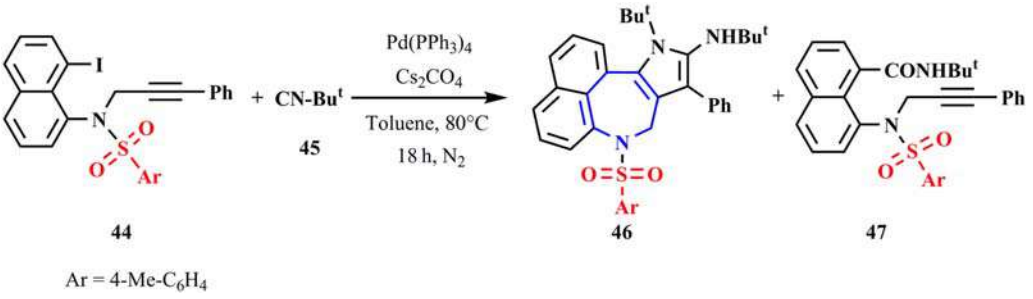
9.3.1.1 Palladium-catalyzed reactions

A palladium-catalyzed [2 + 2 + 1] cyclization of internal alkynes with double isocyanides was used for synthesizing 7*H*-naphtho[1,8-*bc*]pyrrolo[2,3-*e*]azepine **46**. The reaction of *N*-(8-iodonaphthalen-1-yl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)-benzenesulfonamide **44** with double isocyanides **45** proceeded smoothly to provide **46** in 29% yield in addition to a byproduct **47** in 37% yield (Scheme 9.16). The sequential double isocyanide insertion, 6-*exo*-dig cyclization of alkyne, and addition of an imino group were involved [29].

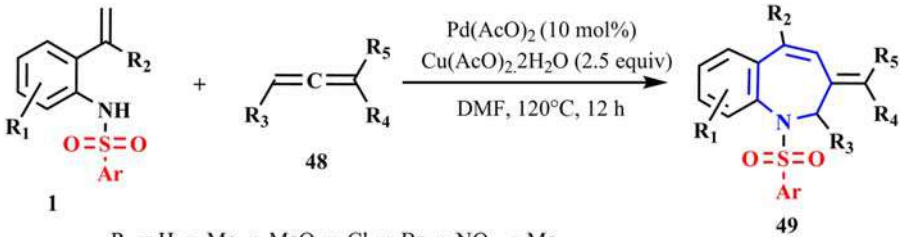
Benzo[*b*]azepines have been developed based on the palladium-catalyzed oxidative annulation of *N*-tosyl 2-alkenylanilines **1** with allenes **48**. The procedure represented a straightforward and efficient approach to *N*-tosyl 2-ylidene 2,3-dihydro-1*H*-benzo[*b*]azepine derivatives **49** and involved the cleavage of the terminal $C(sp^2) - H$ bond of the *N*-tosyl 2-alkenylanilines **1** and the participation of allenes **48** as two-carbon cycloaddition partner (Scheme 9.17). The synthesis was carried out under mild reaction conditions and resulted in a variety of benzo[*b*]azepines in good to excellent yields [30].

9.3.1.2 Silver catalyzed reactions

Silver-catalyzed tandem [5 + 2] cycloaddition reaction of *N*-tosyl γ-amino ketones **50** with diverse terminal alkynes

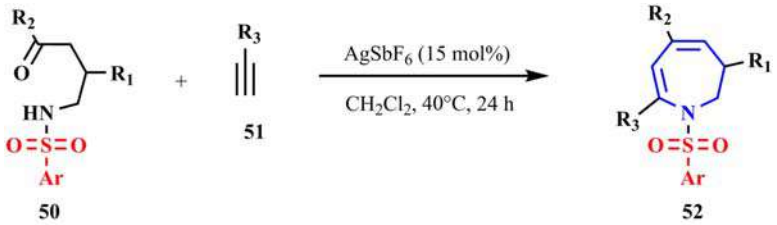


SCHEME 9.16 Palladium-catalyzed double isocyanides insertion.



R_1 = H, *p*-Me, *p*-MeO, *p*-Cl, *p*-Br, *p*-NO_2, *o*-Me
R_2 = C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-Cl-C_6H_4, Me,
R_3 = H. Me. Bn
R_4 = H, Me, C_6H_5, 4-CH_3-C_6H_4
R_5 = H, Me, C_6H_5, 4-CH_3-C_6H_4, 4-CH_3-C_6H_4, COOEt, Bn
Ar = 4-CH_3-C_6H_4

SCHEME 9.17 Oxidative annulation of *N*-tosyl 2-alkenylanilines with allenes.



R_1 = H, C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 3-Cl-C_6H_4,
R_2 = Me, C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4
R_3 = C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4
Ar = 4-Me-C_6H_4

SCHEME 9.18 Intermolecular cycloaddition reaction of *N*-tosyl γ-amino ketones with terminal alkynes.

51 was excellent access to synthesize 2,3-dihydro-1*H*-azepines **52** [9]. This intermolecular [5 + 2] cycloaddition reaction had a broad substrate scope and allowed the formation of four new chemical bonds in one step, creating seven-membered ring systems through the release of H_2O as a by-product (Scheme 9.18). It was found that both functionalized aryl and alkyl groups of *N*-tosyl γ-amino ketones **50** were compatible with the optimized conditions. It was found that the presence of electron-deficient aryl groups, such as 4-NO_2-C_6H_4, had a lower reactivity than electron-rich aryl groups, such as a 4-Me-C_6H_4 [31].

9.3.1.3 Rhodium-catalyzed reactions

Several strategies based on the rhodium(II)-catalyzed intermolecular cycloadditions of *N*-sulfonyl-1,2,3-triazoles were used to produce dihydro azepine derivatives. Employing various (*Z*)-1-aryl-1,3-dienes **54** and 4-aryl-1-

sulfonyl-1,2,3-triazoles **53** using $Rh_2(oct)_4$ furnished 2,5-dihydroazepines **55** in good to excellent yields. Under a similar condition, the reaction of 4-aryl-1-sulfonyl-1,2,3-triazoles **53** with (*Z*)-3-aryl-1,3-dienes **56** afforded the corresponding [4 + 3] cycloadducts, 2,5-dihydroazepines **57**, with a small amount of the [4 + 2] adducts **58** in some cases (Scheme 9.19). It was noted that the 2,5-dihydroazepines **57**, which were generated from 2-aryl-dienes **56**, were rather stable and did not transform to the corresponding 2,3-dihydropyrroles **58**, even with long reaction times [32].

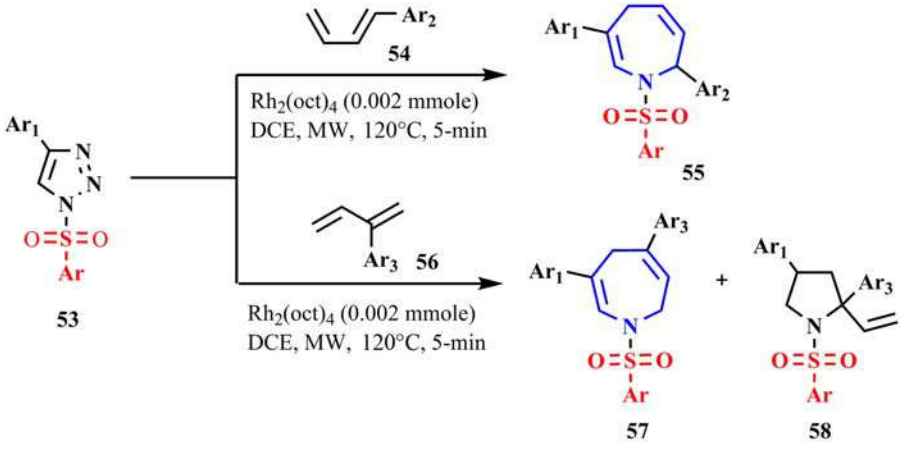
Another approach for the synthesis of 2,5-dihydroazepine derivatives **61** using a rhodium-catalyzed [5 + 2] cycloaddition strategy was achieved by the reaction of *N*-sulfonyl aziridines **59** with unsymmetrical terminal alkyne **60** (Scheme 9.20) [33].

9.3.2 Metal-catalyzed intramolecular cyclization

9.3.2.1 Palladium-catalyzed reactions

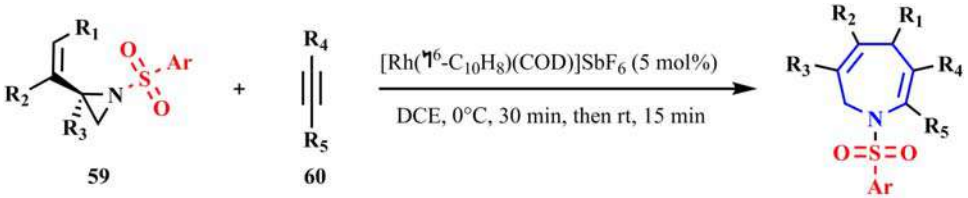
An efficient Pd(II)-catalyzed ($PdCl_2$, 10 mol%) intramolecular cyclization approach was established for the synthesis of *N*-sulfonyl 1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones **63** starting from *N*-propargyl arylamine bearing an α,β-unsaturated ester scaffold **62** (Scheme 9.21). A series of electron-donating and -withdrawing substituents were introduced at the aryl group and the desired products of 1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones derivatives were obtained in high yields of 84 − 88% [34].

The unique palladium-catalyzed cascade cyclization of allylamine-tethered alkylidene cyclopropanes **64** with commercially available reagent ethyl difluoroiodo acetate, as the difluoromethyl source, or perfluoroalkylated was developed.



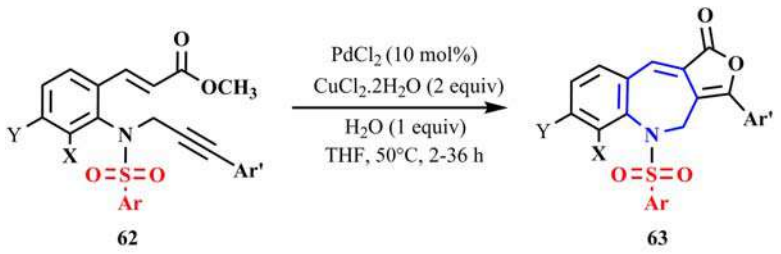
Ar_1 = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-^{t}Bu-C_6H_4, 4-CF_3-C_6H_4, 4-F-C_6H_4
Ar_2 = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 4-F-C_6H_4, 2-Cl-C_6H_4
Ar_3 = C_6H_5, 4-Br-C_6H_4, 4-^{t}Bu-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 2-F-C_6H_4,
Ar = 4-Me-C_6H_4

SCHEME 9.19 Intermolecular cycloadditions of *N*-sulfonyl-1,2,3-triazoles with aryl-1,3-dienes.

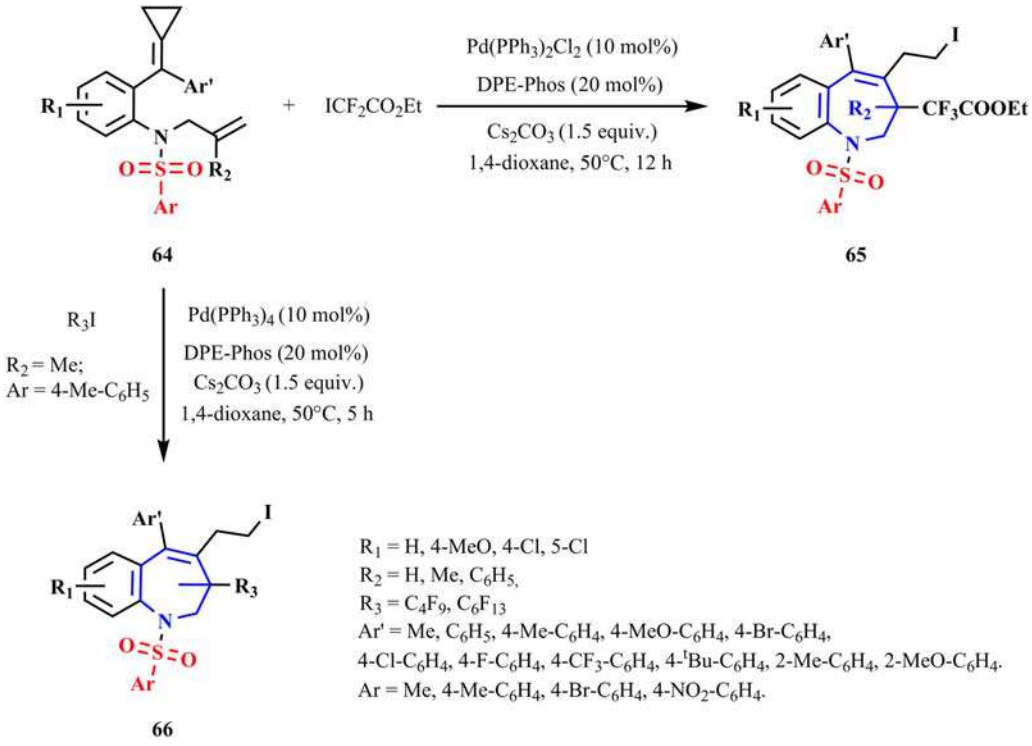


R_1= H, C_6H_5,
R_2 = C_6H_5, *i*-Pr, *n*-Bu, OTBS, OTES,
R_3 = Me, *i*-Pr,
R_4 = H, Me, Et CH_2OMe,
R_5 = C_6H_5, 4-Me-C_6H_4, 4-*t*-Bu-C_6H_4, 4-EtO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Ac-C_6H_4, 4-$MeCO_2$-C_6H_4
Ar = Me, 4-Me-C_6H_4, 4-NO_2-C_6H_4

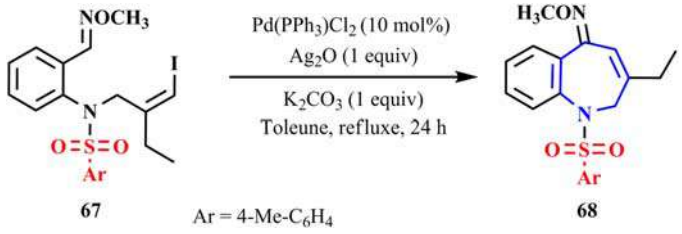
SCHEME 9.20 Rhodium-catalyzed cycloaddition of *N*-sulfonyl aziridines with an unsymmetrical alkyne.



SCHEME 9.21 Intramolecular cycloadditions of *N*-propargyl arylamine derivatives.



SCHEME 9.22 Cascade cyclization of allylamine-tethered alkylidenecyclopropanes.



SCHEME 9.23 Intramolecular Heck-type reaction of (*Z*)-vinyl halide oxime ethers.

As a result, a variety of synthetically and medicinally valuable iodine/difluoromethylene- and perfluoroalkyl-containing benzo[*b*]azepine derivatives, **65** and **66**, respectively, were produced in 61%–85% yield (Scheme 9.22) [35].

A Pd(0)-catalyzed intramolecular Heck-type reaction of (*Z*)-vinyl halide oxime ethers **67** with nitrogen functionalized has been developed, providing a 7-membered cyclic oxime **68** (Scheme 9.23) [36]

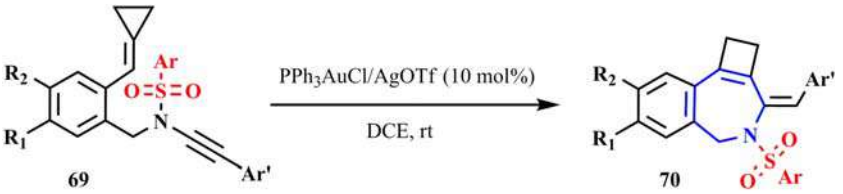
9.3.2.2 Gold catalyzed reactions

Alkynylamide tethered alkylidenecyclopropanes **69** underwent gold(I) catalyzed, $PPh_3AuCl/AgOTf$, ring expansion to yield sequential heterocyclic polycyclic derivatives **70** in a yield range of 56% to 78% (Scheme 9.24) [37].

A wide range of cyclobutene fused azepine heterocycles **74** were synthesized through the gold-catalyzed intramolecular cycloisomerization of ketene *N*,*N*-acetals **73** which were prepared, in moderate to good yields, through the reaction of *N*-sulfonyl propargyl amines **71** with 3-bromopropiolate **72** in presence of K_3PO_4 as a base (Scheme 9.25) [38].

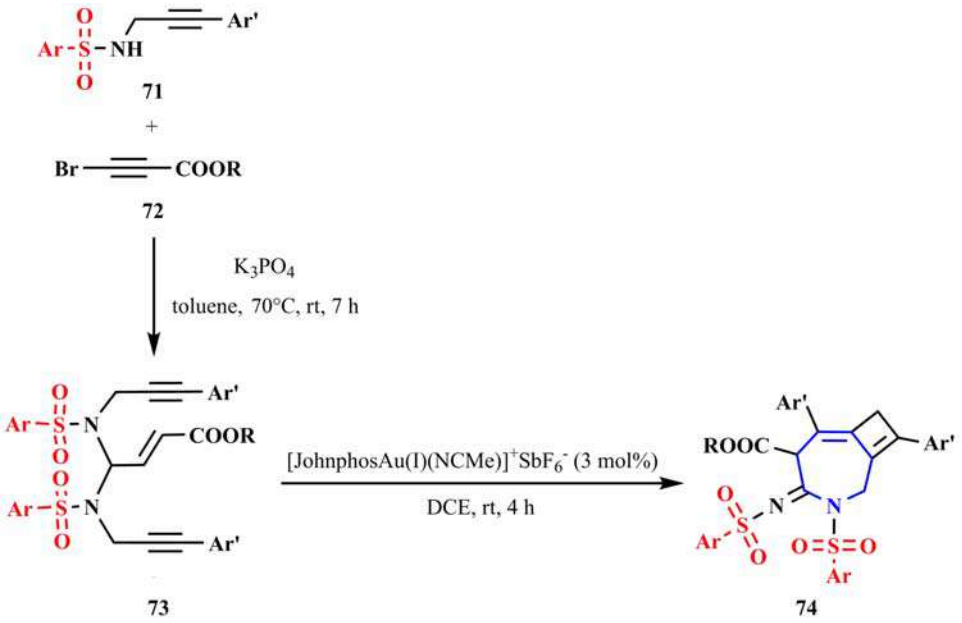
9.3.2.3 Silver catalyzed reactions

Substituted cyclobutene-fused azepines **74** had also been synthesized via silver-catalyzed cyclization reaction, AgOTf (15 mol%), at room temperature. For ketene *N*,*N*-acetals **73** having *p*-F, *p*-Br and *p*-I substituted arenes in the alkyne-terminus successfully underwent the cycloisomerization to produce the corresponding products in a yield range from 66%−78%. Substrates having electron-withdrawing groups such as CF_3, $COCH_3$, and CO_2CH_3 in the *para*-position led to the formation of the corresponding products with yields 57%−76% (Scheme 9.26). Having an electron-rich methyl group at the *para*-position of ketene aminals readily provided



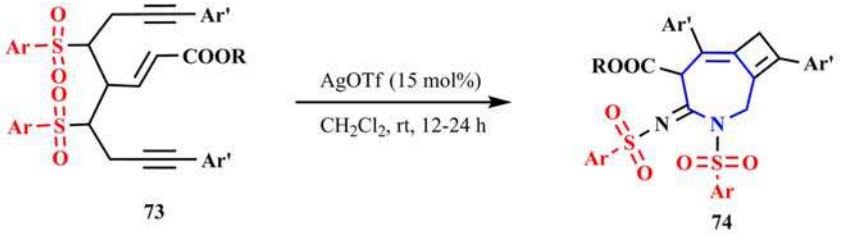
R_1, R_2 = H, MeO
Ar' = C_6H_5, 4-Et-C_6H_4, 4-^{n}Pr-C_6H_4, 4-^{n}Bu-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4.2-Br-C_6H_4
Ar = 4-Me-C_6H_4

SCHEME 9.24 Ring expansion of alkynylamide tethered alkylidenecyclopropanes.



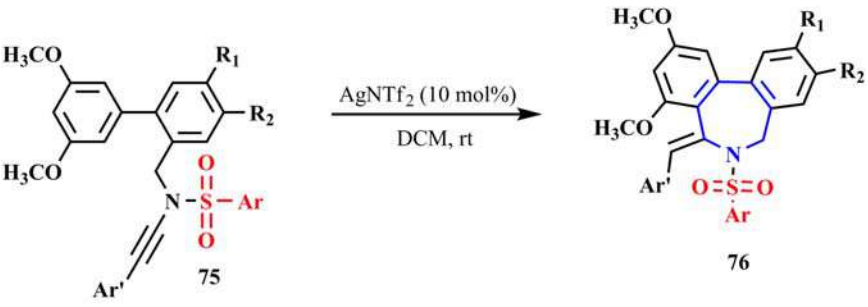
Ar' = C_6H_5, 4-F-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 4-CF_3-C_6H_4, 4-COMe-C_6H_4, 4-COOMe-C_6H_4, 4-Me-C_6H_4
3-Me-C_6H_4, 3-CF_3-C_6H_4, 3-NO_2-C_6H_4
R = Et, Me, Bn
Ar = CH_3, 4-Me-C_6H_4, 4-NO_2-C_6H_4

SCHEME 9.25 Gold-catalyzed cycloisomerization of ketene *N*,*N*-acetals.



Ar' = C_6H_5, 4-F-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 4-CF_3-C_6H_4, 4-COMe-C_6H_4, 4-COOMe-C_6H_4, 4-Me-C_6H_4
R = Et, Me, Bn
Ar = 4-Me-C_6H_4

SCHEME 9.26 Silver-catalyzed cycloisomerizations of ketene *N,N*-acetals.



R_1 = Me, MeO; R_2 = MeO
Ar = 4-Me-C_6H_4
Ar' = C_6H_5, 2-F-C_6H_4, 2-Cl-C_6H_4, 2-CF_3, 3-F-C_6H_4, 3-Cl-C_6H_4, 3-NO_2-C_6H_4, 4-Me-C_6H_4

SCHEME 9.27 Silver-catalyzed cyclization of 2-propargylamino biphenyl substrates.

the desired product of cyclobutene-fused azepines in a 61% yield. Products bearing ester CO_2Me/CO_2Bn were also prepared with a good yield [38,39].

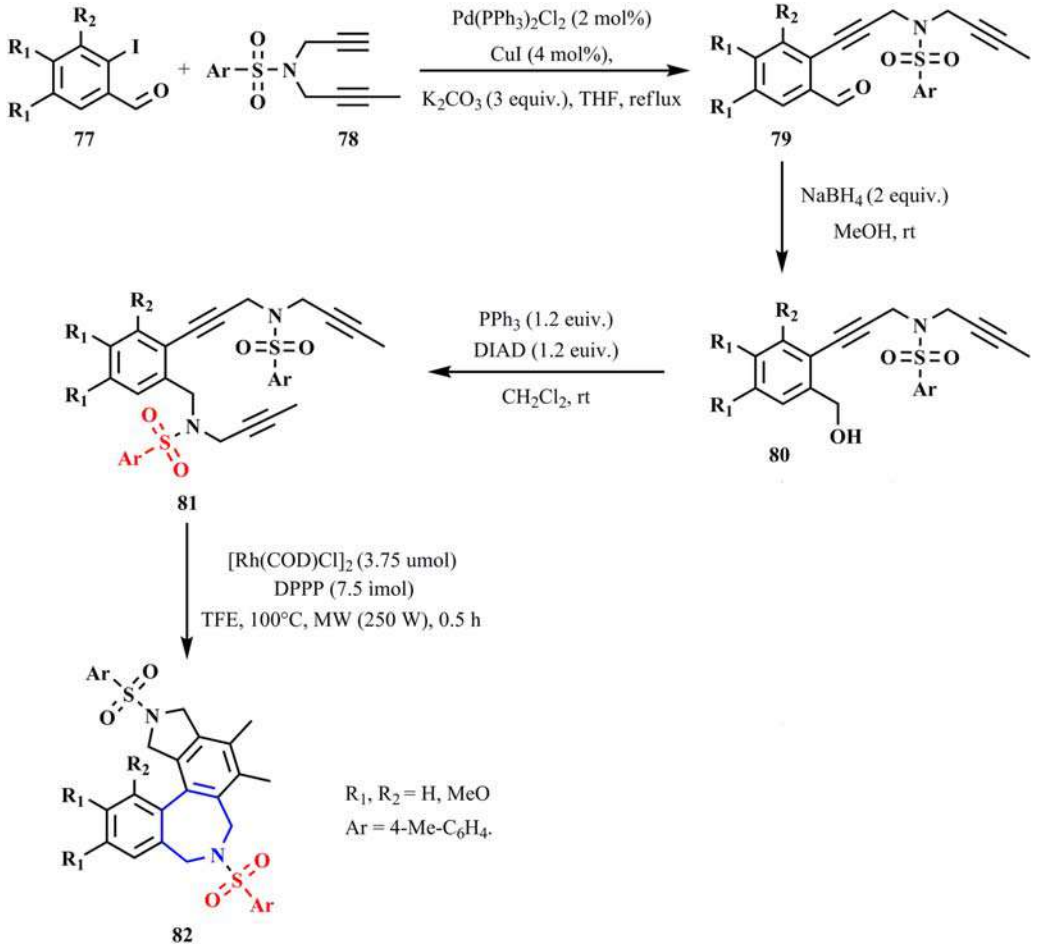
The silver-catalyzed intramolecular cyclization of 2-propargylamino biphenyl substrates **75** formed 7-*exo-dig* products, *N*-tosyl 6,7-dihydro-5*H*-dibenzo[*c,e*]azepine **76**, selectively (Scheme 9.27). The hydroarylation proceeded in *Z* selectivity with the use of silver catalysts, $AgNTf_2$ [18].

9.3.2.4 Rhodium-catalyzed reactions

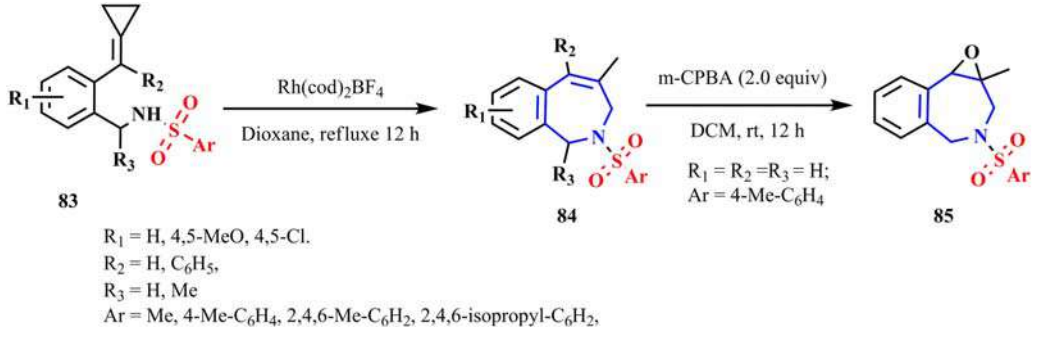
Rh-catalyzed carbonylative [2 + 2 + 2] cycloaddition of *N*-tosyl *o*-phenylenetriynes **81** led to the formation of allocolchicinoids **82** bearing the 6−7−6−5 fused tetracyclic system, in one-step. *o*-Phenylenetriynes bearing *N*-tosyl groups on both side chains were synthesized from diynebenzyl alcohols **80** which was prepared by Sonogashira coupling of iodobenzaldehydes **77** with diethyl malonate derivatives **78**, forming compounds **79**, followed by a reduction reaction with $NaBH_4$ (Scheme 9.28). Mitsunobu reaction of **80** with *N*-tosylbut-2-yn-1-amine gave *o*-phenylenetriynes in good yields. Rh-catalyzed [2 + 2 + 2] cycloaddition was well-tolerated under microwave irradiation conditions to produce the corresponding allocolchicinoids **82**, in high to excellent yields [40].

Benzyl sulfonamide/alcohol-tethered alkylidenecyclopropanes **83** could undergo intramolecular cyclization by rhodium complexes, such as $Rh(cod)_2BF_4$ and Rh(cod)OH_2, producing three types of common organic structural units: benzo[*c*]azepine/oxepines; dihydronaphthalen-1-amines and conjugated dienes. It was noted when $Rh(cod)_2BF_4$ was used as a catalyst, benzo[*c*]azepine **84** was isolated in high yield as the sole product. Upon treating benzo[*c*]azepine **84** with 3-chloroperbenzoic acid (*m*-CPBA) in DCM at room temperature for 12 h, the epoxy product **85** was obtained in 81% yield (Scheme 9.29) [41].

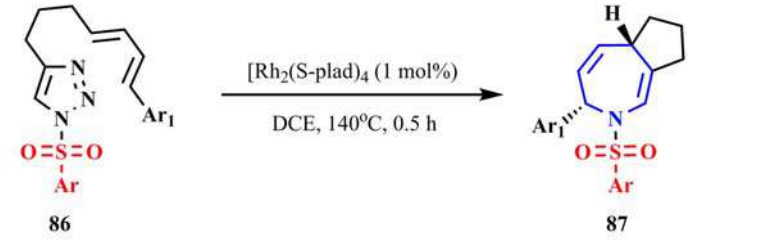
Synthesis of fused dihydroazepines, hexahydrocyclopenta[*c*]azepine **87**, was achieved from *N*-sulfonyl-1,2,3-triazoles bearing a tethered diene **86** *via* intramolecular cyclopropanation of ∝-imino rhodium(II) carbenoid, leading to a transient 1-imino-2-vinylcyclopropane intermediate which rapidly undergoes a 1-aza-Cope rearrangement (Scheme 9.30) [42]. A similar transformation was achieved using diverse dienyltriazoles as substrates [43].



SCHEME 9.28 Rh-catalyzed carbonylative cycloaddition of *N*-tosyl *o*-phenylenetriynes.



SCHEME 9.29 Intramolecular cyclization of benzyl sulfonamide-tethered alkylidenecyclopropanes.



Ar1 = C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 4-F-C_6H_4

Ar = 4-Me-C_6H_4

SCHEME 9.30 Intramolecular rhodium(II)-catalyzed dihydroazepine formation.

In contrast to the intermolecular version [33], the intramolecular formal hetero-[5 + 2] cycloaddition reactions of aziridine-alkyne substrates **88** were found to be a highly efficient method for the synthesis of fused 2,5-dihydroazepines derivatives **89** (Scheme 9.31) [44].

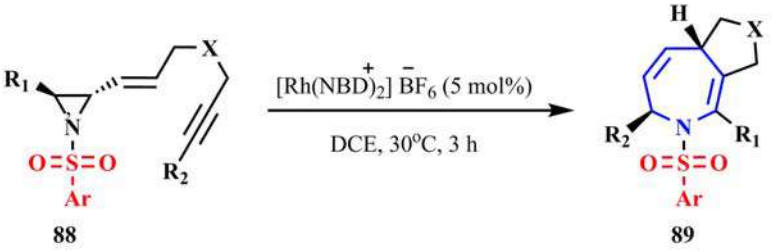
9.3.2.5 Ruthenium catalyzed reactions

Substituted *N*-sulfonyl-2,3-dihydro-1*H*-2-benzazepines **93** were synthesized by an isomerization-ring-closing metathesis (RCM) approach of *N*-sulfonyl *N*-{2-[(1*E*)-prop-1-en-1-yl]benzyl}prop-2-en-1-amine **92**. The latter was synthesized by the reaction of benzaldehyde **90** with allylamine, followed by a sodium borohydride reduction to afford amine **91** in good yield, 89% over two steps, which was then protected with sulfonyl group (Scheme 9.32). Treatment of compound having a tosyl group with 5% Grubbs second-generation catalyst **B** afforded the corresponding *N*-tosyl 2,3-dihydro-1*H*-2-benzazepine in good yield (82%), while treatment of the compound having a benzenesulfonyl gave the desired benzazepine in poor yield (39%) [45].

N-Tosyl 2,5-dihydro-1*H*-benzo[*c*]azepine derivatives **95** were also synthesized via RCM of terminal alkyne of the eneynamide **94** using Grubbs second-generation catalyst **B** under an argon atmosphere (Scheme 9.33) [46].

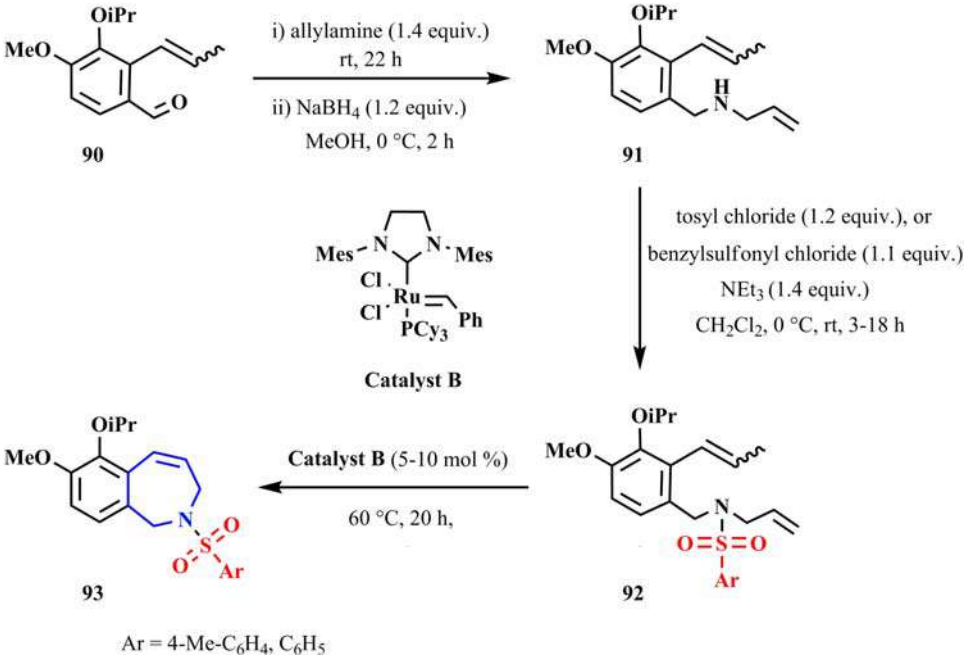
9.3.2.6 Platinum-catalyzed reactions

Platinum-catalyzed cyclization of *N*-sulfonyl 1,5-bisallenes **96** in the presence of oxygen nucleophile formed 6- or 7-membered rings based on the nucleophile and the



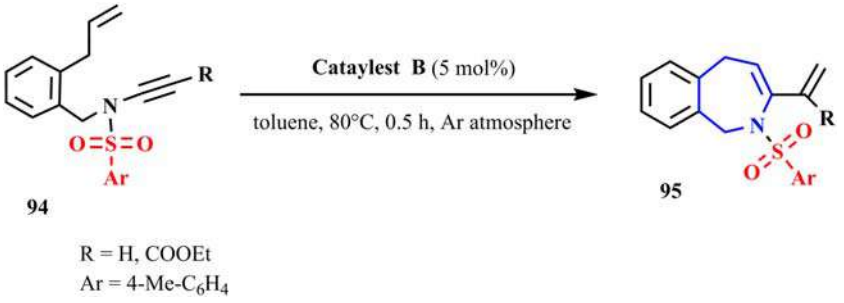
R_1 = H, C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4, Me, *n*-Bu, $(CH_2)_3$OTBS, $(CH_2)_3$OH,
R_2 = H, Me, *n*-Pr, *i*-Pr
X = NTs, O. $C(CO_2Me)_2$
Ar = 4-Me-C_6H_4

SCHEME 9.31 Intramolecular formal hetero-[5 + 2] cycloaddition reactions of aziridine-alkynes.

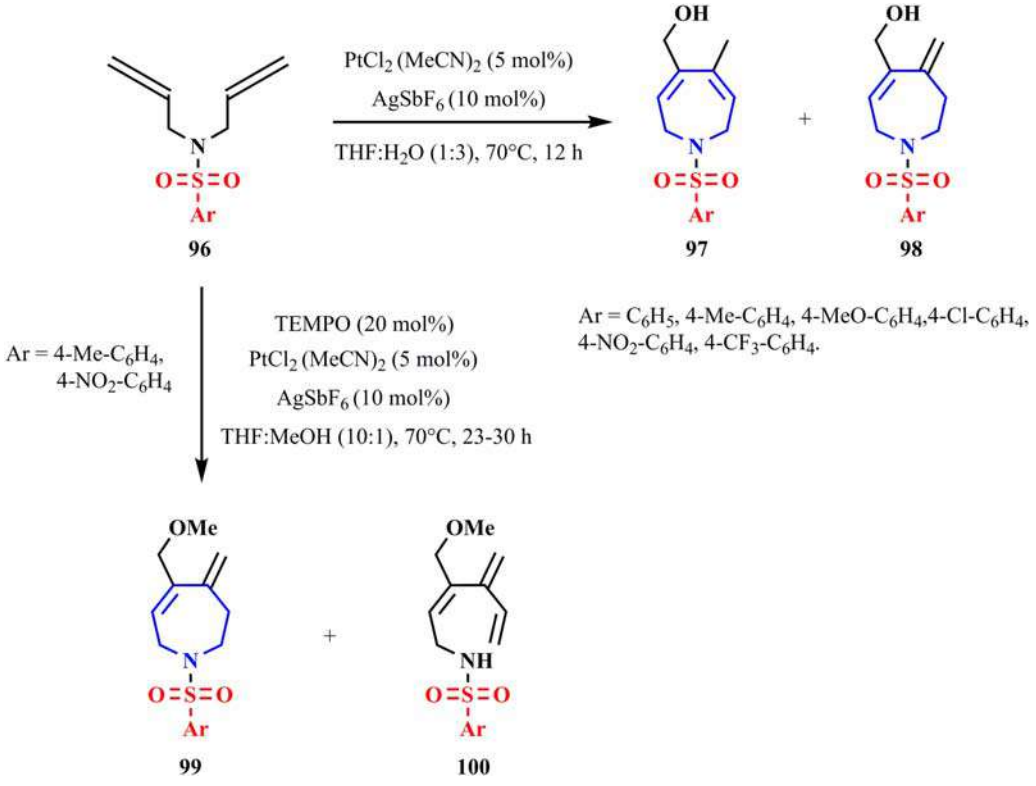


Ar = 4-Me-C_6H_4, C_6H_5

SCHEME 9.32 Ring-closing metathesis of *N*-sulfonyl *N*-(2-propenyl)benzyl 2-propen-1-amine.



SCHEME 9.33 Synthesis of *N*-tosyl 2,5-dihydro-1*H*-benzo[*c*]azepine ring.



SCHEME 9.34 Platinum-catalyzed cyclization of *N*-sulfonyl 1,5-bisallenes.

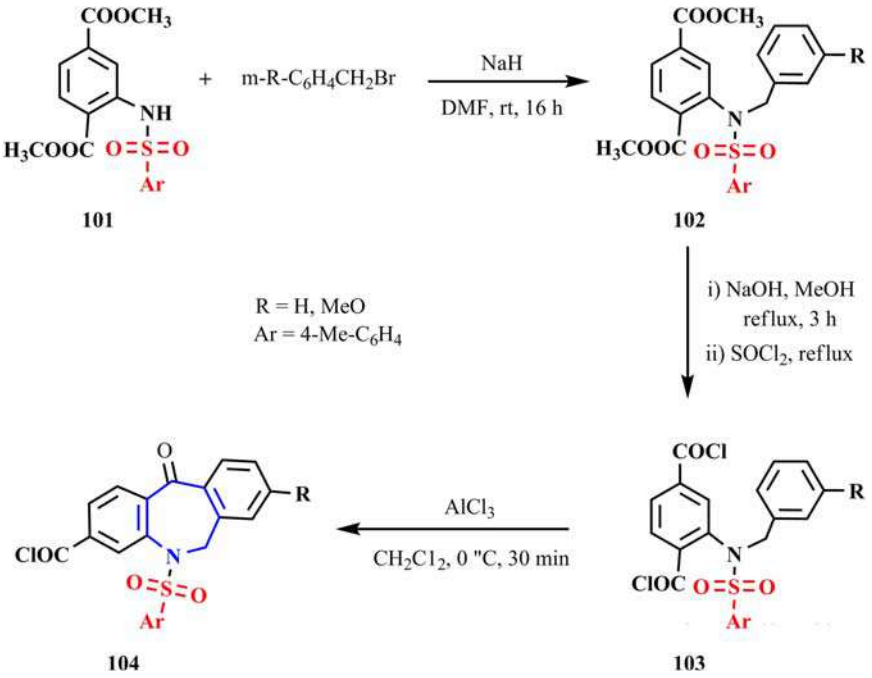
electronic properties of the bisallene. When water was used as a nucleophile in presence of 5 mol% of $PtCl_2(MeCN)_2$ and $AgSbF_6$, both di- **97** and tetrahydro-1*H*-azepines **98** with an extra hydroxyl group were formed *via* nucleophilic attack/carbocyclization as the favored pathway (Scheme 9.34). However, using methyl alcohol and TEMPO under similar conditions produced a mixture of tetrahydro-*1H*-azepines **99** and trienes **100** with an extra methoxy group [47].

9.3.3 Other synthetic pathways

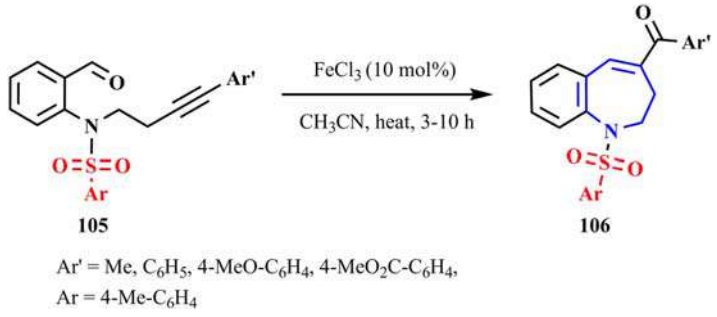
Many *N*-tosyl 5,6-dihydro-dibenzo[*b,e*]azepines **104** were synthesized in three steps. Base-catalyzed alkylation of dimethyl 2-(*p*-toluenesulfonamido) terephthalate **101** with benzyl bromide or 3-methoxybenzyl bromide produced compound **102**. The latter is converted to acid by base hydrolysis and then to acid chloride by thionyl chloride to form compound **103**. Cyclization of acid chlorides could be achieved in the presence of aluminum chloride or stannic chloride (Scheme 9.35) [48].

Synthesis of 2,3-dihydro-1*H*-benzo[*b*]azepine derivatives **106** was achieved by intramolecular alkyne−carbonyl metathesis reaction using the iron(III) chloride, $FeCl_3$ (10 mol%) (Scheme 9.36). Various functionalized dihydrobenzo[*b*]azepines were prepared in good yield from *N*-tosyl-2-aminobenzaldehyde **105** [49].

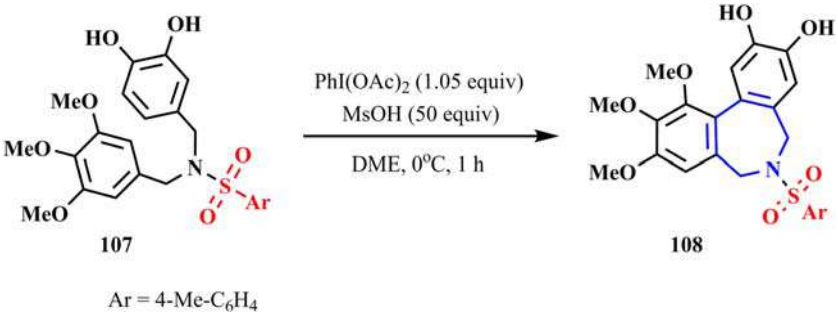
Oxidative cyclization of catechol derivative **107** with $PhI(OAc)_2$ (1.05 equiv) in the presence of methanesulfonic acid and 1,2-dimethoxyethane was found to be a successful method to synthesize *N*-sulfonyl-6,7-dihydrodibenzo[*c,e*]azepine **108** (Scheme 9.37) [50].



SCHEME 9.35 Platinum-catalyzed cyclization of *N*-sulfonyl 1,5-bislenes.

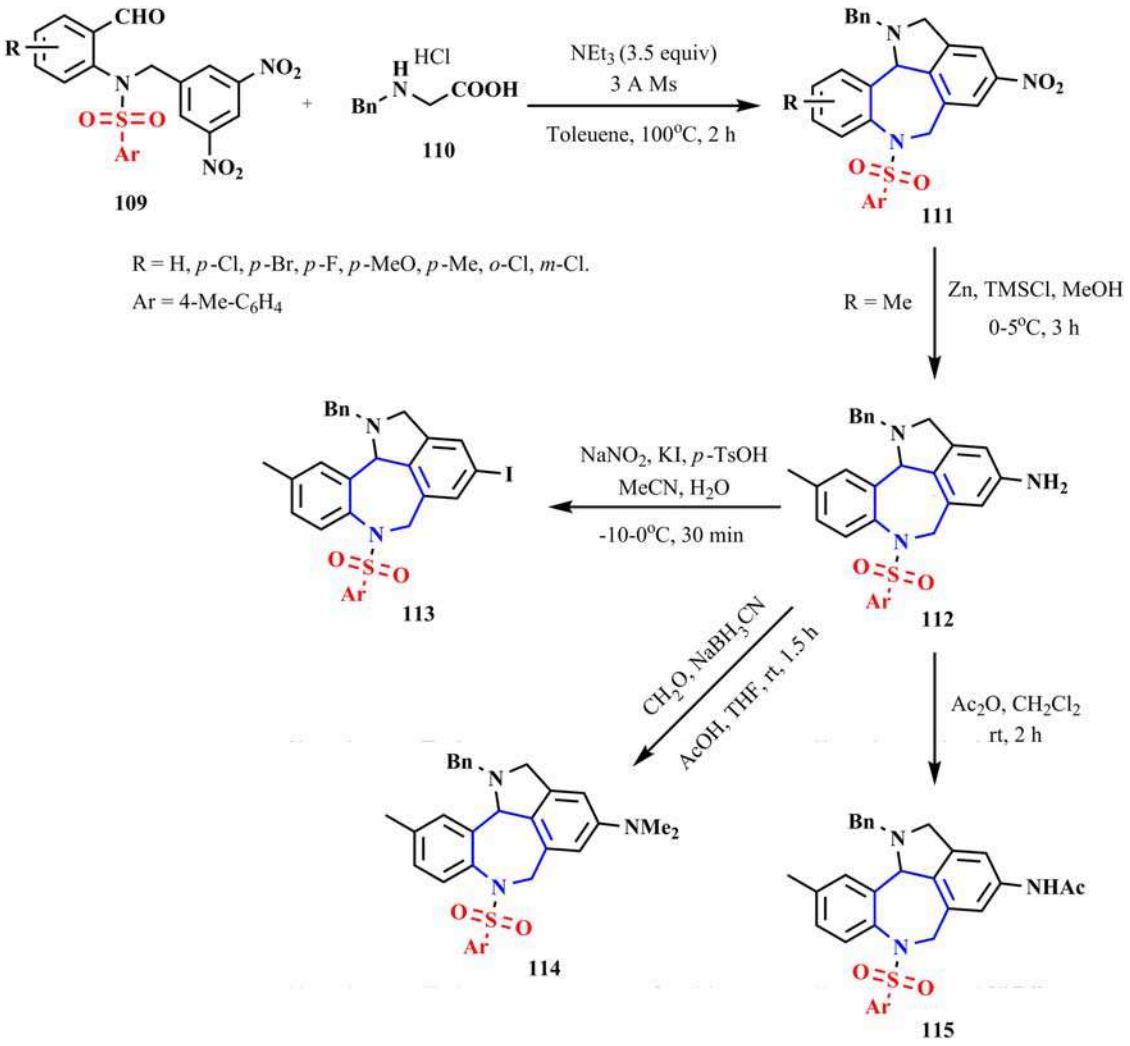


SCHEME 9.36 Intramolecular alkyne−carbonyl metathesis of *N*-tosyl-2-aminobenzaldehyde.



SCHEME 9.37 Oxidative cyclization of catechol derivatives.

A series of *N*-tosyl-2-aminobenzaldehydes tethered to 3,5-dinitrobenzene **109** were reacted thermally with *N*-substituted α-amino acids **110** by intramolecular cyclization in presence of trimethylamine to form *N*-tosyl benzoazepine-fused isoindolines **111**. Various glycine derivatives, as well as branched substrates based on cyclic, were tolerated. Reduction of *N*-tosyl benzoazepine having Me on aryl ring with zinc produced the corresponding aniline derivative **112**, which provided a small set of derivatives **113**−**115** using conventional *N*-acetylation, iodination, and *N*-dimethylation methods (Scheme 9.38) [51].



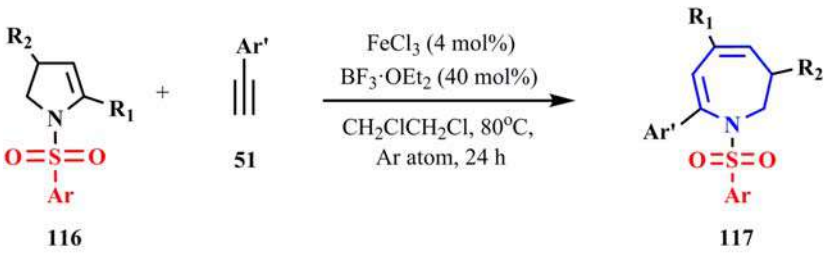
SCHEME 9.38 Synthesis of benzoazepine-fused isoindolines via intramolecular cycloadditions.

The first example of Lewis acid-catalyzed [5 + 2] cycloaddition of *N*-tosyl-2,3-dihydro-1*H*-pyrroles **116** with terminal alkynes **51** was reported by Zhou et al. The reaction proceeded via ring-opening of *N*-tosyl-2,3-dihydro-1*H*-pyrroles, by employing a $FeCl_3$ and BF_3_OEt_2 co-catalytic strategy, through the selective cleavage of the C (sp^2)−N bond and followed by [5 + 2] cycloaddition with terminal alkynes to access *N*-tosyl-2,3-dihydro-1*H*-azepines **117** with excellent region selectivity (Scheme 9.39) [52]. Similar products were achieved by involving the use of hexafluoroantimonic acid to catalyze a formal [3 + 2 + 2] cycloaddition of *N*-tosyl-aziridines with two alkynes [53].

Diverse 2,3-dihydro-1*H*-azepines **119** were simply produced through the ring-opening of 2-(2-aminoethyl) oxiranes **118** by [5 + 2] intermolecular cycloaddition with alkynes **60**. The $FeCl_3$ and $BF_3 \cdot OEt_2$ co-catalysis was found the most effective condition for the synthesis of the desired compounds in good yield (Scheme 9.40). This condition promoted the ring-opening process in this tandem cycloaddition and a stoichiometric amount of $BF_3 \cdot OEt_2$ could support the final dehydroxylation process and make the reaction faster [54].

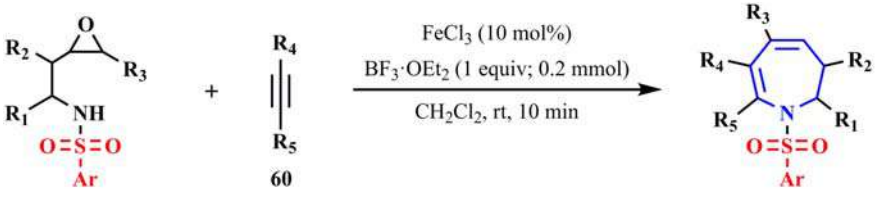
An *ortho*-selective of iodo-Friedel−Crafts reaction occurred under the iodocyclization conditions to provide chiral *N*-tosyl 2-benzazepines **122** with high enantioselectivity using racemic Morita−Baylis−Hillman (MBH) carbonates. The use of diverse *N*-propargylsulfonamides **121** was explored with allylic alkylation product from MBH carbonate **120** of piperonal to produce the alkylated compounds which were subsequently treated with iodine monochloride (Scheme 9.41). Moderate yields were obtained for 3-aryl-*N*-tosylpropargylamines containing electron-withdrawing groups [55].

In 1987, Hegedus et al. firstly reported the synthesis of *N*-tosyl azepino[5,4,3-*cd*]indole **125** through the condensation reaction of compound **123** with *p*-toluenesulfonamide **124** in the presence of 10% *p*-toluenesulfonic acid (Scheme 9.42) [56].



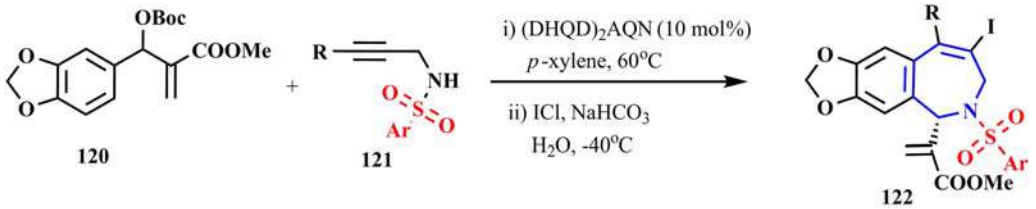
R_1= Me, *i*-Pr, C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Me-C_6H_4,
R_2 = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_4,
Ar' = 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-^{i}Bu-C_6H_4, 4-CO_2Me-C_6H_4, 4-CO_2Et-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 2-Cl-C_6H_4.
Ar = 4-Me-C_6H_4

SCHEME 9.39 Intermolecular cycloadditions of *N*-tosyl-2,3-dihydro-1*H*-pyrroles with terminal alkynes.



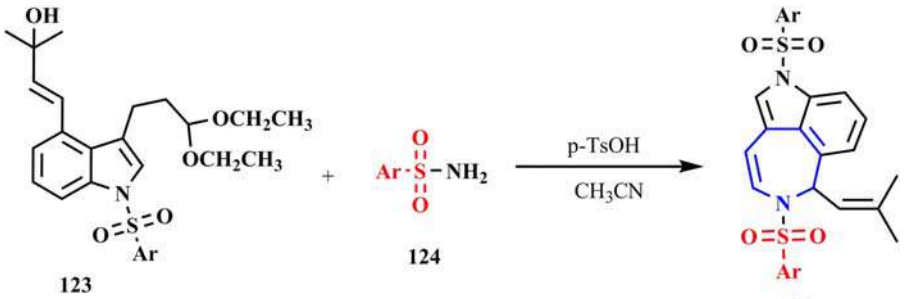
R_1 = H, Me, $CH_2CH_2C_6H_5$, $CH_2CH(Me)_2$, *n*-hex, Bn,
R_2 = H, C_6H_5
R_3 = H, Et, *n*-Bu
R_4 = H, Me, *n*-Bu, C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4
R_5 = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-MeO-C_6H_4, 3-Me-C_6H_4, 3-Me-C_6H_4, 2-Cl-C_6H_4
Ar = 4-Me-C_6H_4

SCHEME 9.40 Intermolecular cycloadditions of 2-(2-aminoethyl)oxiranes with terminal alkynes.



R = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Br-C_6H_4, 4-EtOOC-C_6H_4, 2-Br-C_6H_4, 3-Br-C_6H_4, 1-cyclohexanyl
Ar = 4-Me-C_6H_4

SCHEME 9.41 Intermolecular cycloadditions of piperonal derivatives with *N*-propargylsulfonamides.



Ar = 4-Me-C_6H_4

SCHEME 9.42 Intermolecular cycloadditions of piperonal derivatives with *N*-propargylsulfonamides.

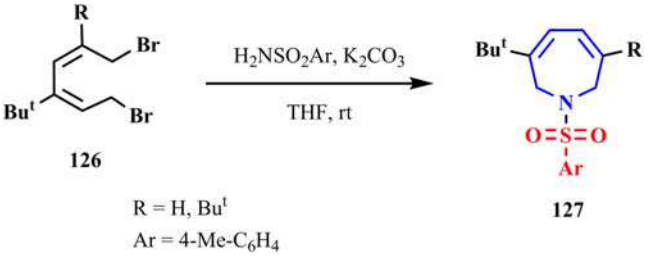
2,7-Dihydro-1*H*-azepines **126** synthesized by the reaction of substituted (*Z*,*Z*)-l,6-dibromohexa-2,4-dienes **127** with *p*-toluenesulfonamide (Scheme 9.43) [57].

9.4 *N*-Sulfonyl tetrahydroazepines

9.4.1 Metal-catalyzed intermolecular cyclization

9.4.1.1 Rhodium-catalyzed reactions

It was also found that vinyl aziridines **128** could serve as new aza-3C synthons in aza-[4 + 3] cycloaddition reactions with silyl dienol ethers **129** in presence of rhodium complex [[{Rh(NBD)Cl}$_2$]/$AgClO_4$ as combined catalyst (Scheme 9.44). Enantiomerically enriched functionalized 2,3,4,7-tetrahydro-1*H*-azepine derivatives **130** were obtained with net inversion of the absolute configuration in good to excellent yield [58].



SCHEME 9.43 Synthesis of 2,7-dihydro-1*H*-azepines.

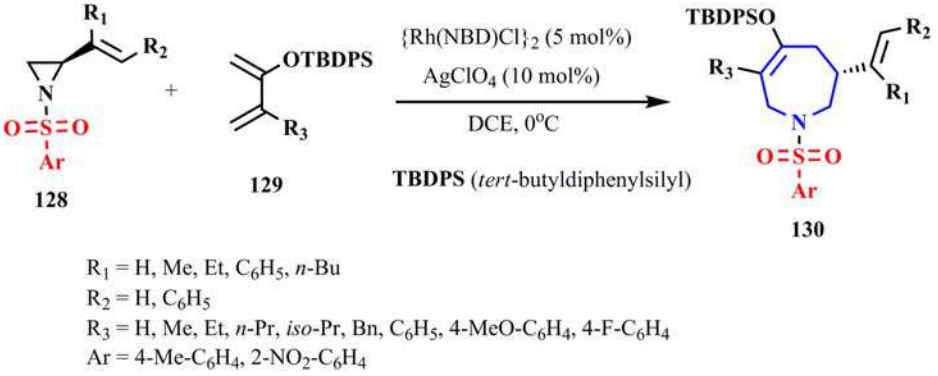
9.4.2 Metal-catalyzed intramolecular cyclization

9.4.2.1 Pallidum catalyzed reactions

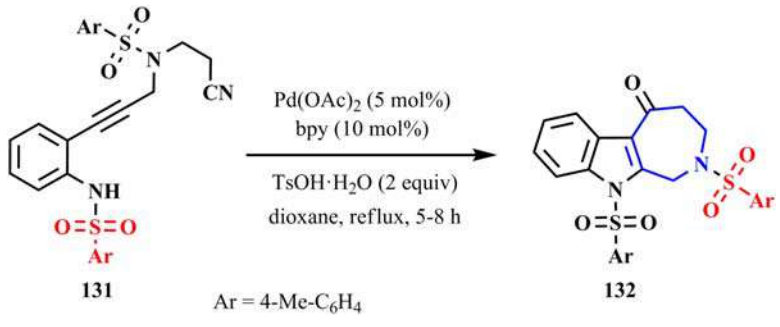
Cyclization reaction initiated by intramolecular aminopalladation of alkynes using redox-free Pd(II)-catalyzed tandem followed by nucleophilic addition to nitriles was a versatile approach for the synthesis of six- to eight-membered ring fused indoles in one step. Alkyne substrate **131**, containing *p*-toluenesulfonamide, formed an excellent yield, 96%, of 1,2,3,4-tetrahydroazepino[3,4-*b*] indol-5(10*H*)-one **132** (Scheme 9.45) [59].

Pd(II)-catalyzed intramolecular aerobic oxidative allylic C−H amination of olefins **133** in presence of Brønsted base has favored the formation of 7-membered rings **134** over the 5-membered rings **135** (Scheme 9.46) [60].

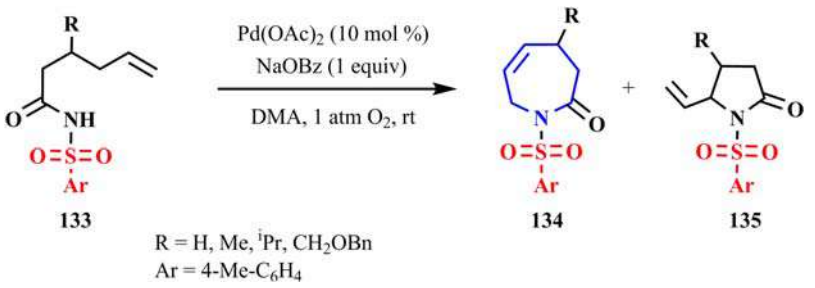
An efficient $Yb(OTf)_3$ promoted palladium-catalyzed oxidative cyclization of γ-heteroalkenyl β-keto amides under simple aerobic conditions has led to the formation of a variety of six-, seven-, and eight-membered-ring *N*- and *O*-heterocycles in excellent yield. *N*-Sulfonyl tetrahydro-1*H*-azepine-4-carboxamide **137** was prepared in 91% by oxidative cyclization of *N*-tosyl β -keto amide **136** using 1 equivalent of $Yb(OTf)_3$ and 20 mol% of $PdCl_2(MeCN)_2$ (Scheme 9.47) [61].



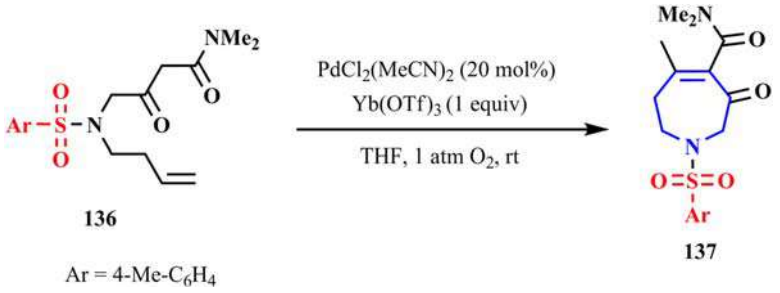
SCHEME 9.44 Rhodium [4 + 3] cycloaddition for the synthesis of 2,3,4,7-tetrahydro-1*H*-azepines.



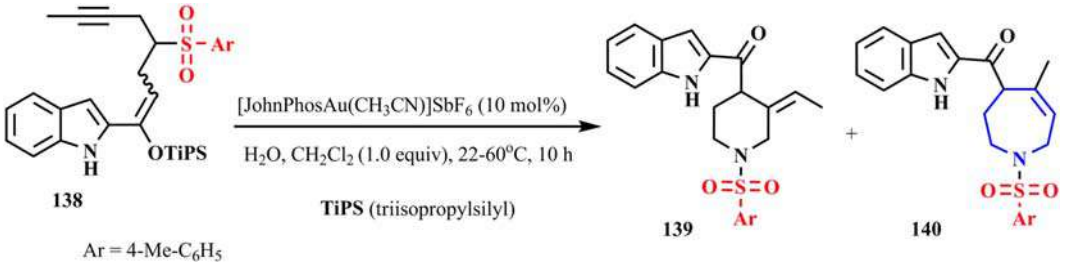
SCHEME 9.45 Pd(II)-catalyzed cycloaddition reaction for the synthesis of 1,2,3,4-tetrahydroazepino[3,4-*b*]indol-5(10*H*)-one.



SCHEME 9.46 Pd(II)-catalyzed intramolecular oxidative cyclization of allylic C−H amination **133**.



SCHEME 9.47 Pd(II)-catalyzed intramolecular oxidative *N*-tosyl *β*-keto amide **136**.



SCHEME 9.48 Gold(I)-catalyzed reaction of 1*H*-indolyl *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide.

9.4.2.2 Gold catalyzed reactions

A gold(I)-catalyzed Conia-ene reaction (Toste cyclization) and a Pictet−Spengler reaction served as key transformations for the synthesis of the 6-*exo*-dig **139** and 7-*endo*-dig products **140** in 29% and 49% yields, respectively, starting from 1*H*-indolyl *N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide **138** (Scheme 9.48) [62].

9.4.2.3 Rhodium-catalyzed reactions

The cycloisomerization of allenene bearing the tosylamide group **141** catalyzed by rhodium(I) complex, $[RhCl(CO)_2]_2$, was found to produce the unexpected seven-membered-ring **142**, cyclic enamide, as the major product in 82% yield (Scheme 9.49) [63,64].

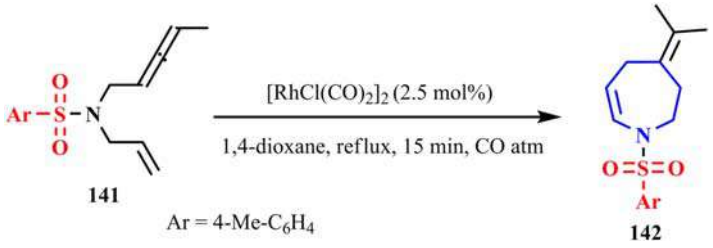
9.4.2.4 Ruthenium catalyzed reactions

Ring-closing metathesis involving dienes or conjugated enynes bearing tosylamides and catalyzed by Rutheniumcomplexesto produced *N*-sulfonyltetrahydro-1*H*-azepines was examined [65−71]. For example, RCM of *N*-allyl-4-methyl-*N*-(pent-4-en-1-yl)tosylamide **143** catalyzed by Ru-catalyst C was accompanied by significant double bond migration to produce a mixture of tetrahydro-1*H*-azepine symmetric **144** (58%), asymmetric **145** (8%), and **146** (34%) (Scheme 9.50) [72−75].

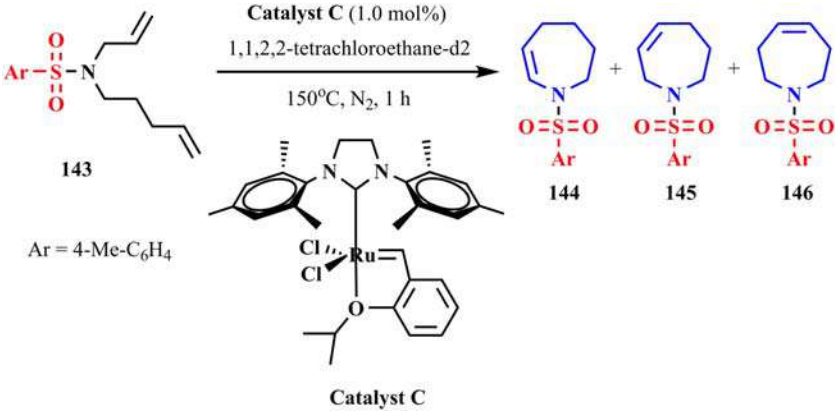
Synthesis of *N*-sulfonyl-2,3,4,7-tetrahydro-1*H*-azepin-3-ol **148** can be demonstrated from homoallyl alcohols **147** using Hoveyda−Grubbs catalyst (Catalyst D). This RCM reaction led to the formation stereo defined azepines (Scheme 9.51) [71,76−80].

9.4.2.5 Molybdenum catalyzed reactions

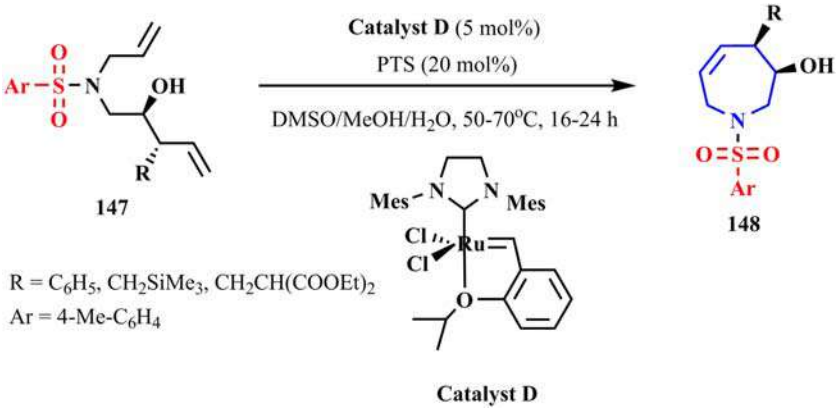
Mo-catalyzed reactions improved significantly the RCM reactions of *N*-substituted 1,7-enyne substrates [81]. Using 5 mol% of Mo catalyst E with aryl-substituted enyne **149**, converted within 30 min to seven-membered *endo* diene **150** in >98% selectivity (<2% *exo* product **151**) (Scheme 9.52) [82].



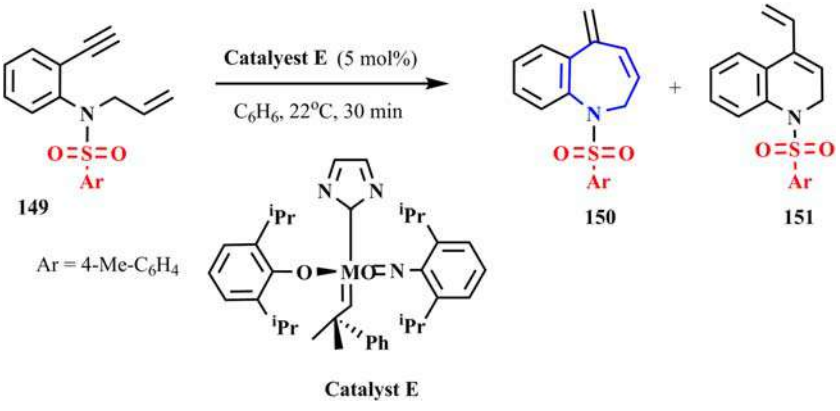
SCHEME 9.49 Rhodium(I) catalyzed reaction of allenene bearing the tosylamide group.



SCHEME 9.50 Ring-closing metathesis of *N*-allyl-4-methyl-*N*-(pent-4-en-1-yl)tosylamide.



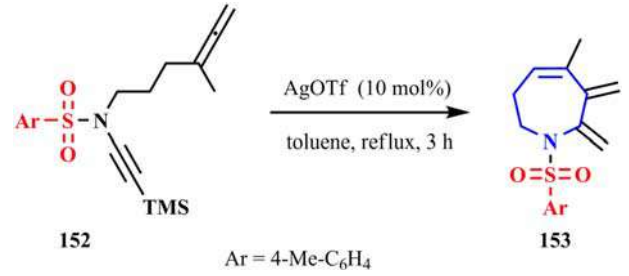
SCHEME 9.51 Synthesis of *N*-sulfonyl-2,3,4,7-tetrahydro-1*H*-azepin-3-ol by ring-closing metathesis.



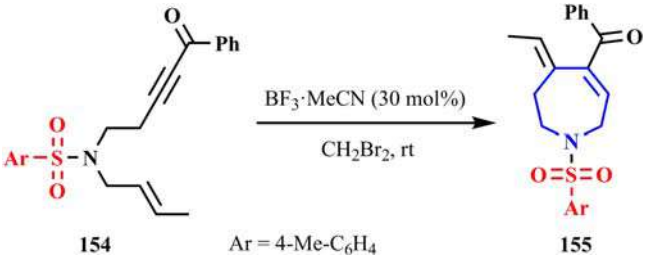
SCHEME 9.52 Mo-catalyzed reactions of *N*-sufonyl 1,7-enyne substrates.

9.4.2.6 Silver catalyzed reactions

Cycloisomerization reactions of allenynamides in the presence of silver triflate led to the formation of *N*-containing heterocycles incorporating cross-conjugated trienes. Cycloisomerization process of 1,7-allenynamide **152** provided *N*-sulfonyl tetrahydro-1*H*-azepine **153** in 58% yield when the reaction was carried out in toluene at reflux for 3 h (Scheme 9.53) [83].



SCHEME 9.53 Cycloisomerization reactions of 1,7-allenynamide **152**.



SCHEME 9.54 BF3 · MeCN-catalyzed reaction of 7-en-2-ynones **154**.

9.4.3 Other synthetic pathways

$BF_3 \cdot MeCN$-catalyzed reaction of 7-en-2-ynones **154** to provide tetrahydro-1*H*-azepine **155**, representing the first nonmetal-catalyzed intramolecular Diels – Alder reaction, of 1,7-enynes to *endo*-type cyclic dienes (Scheme 9.54) [84].

A series of tetrahydro-1*H*-azepinein sulfonamides were synthesized and tested as potent inhibitors of 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1). The synthesis of this series started from the reaction of 4-phenylazepan-4-ol **156** with concentrated HCl and glacial acetic acid under reflux conditions to provide an inseparable mixture of tetrahydro-1*H*-azepines **157** (major isomer) and **158** (minor isomer). This mixture of tetrahydro-1*H*-azepines was taken directly and treated with various para-substituted aryl sulfonamide chloride to produce a mixture of *N*-sulfonyl tetrahydro-1*H*-azepine **159** and **160** (Scheme 9.55) [4].

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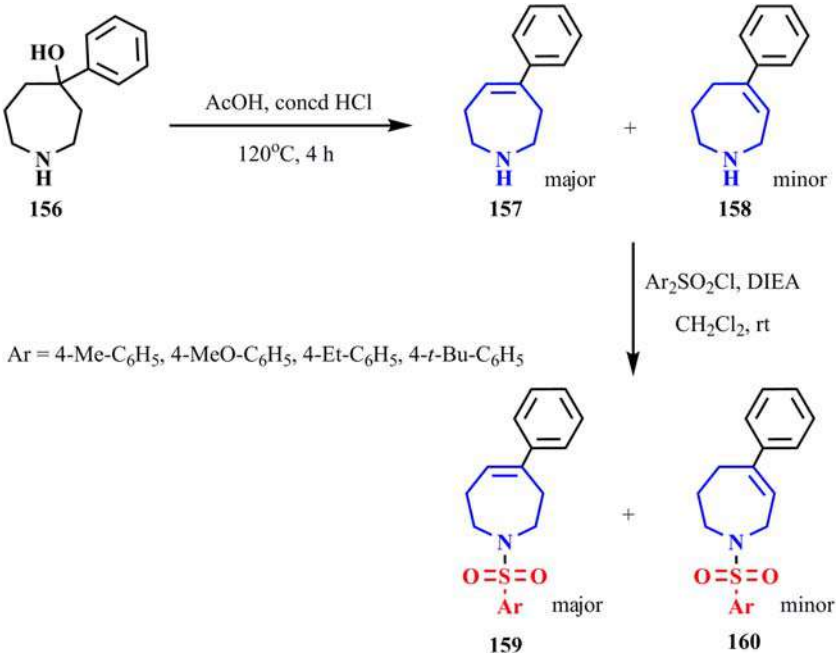

SCHEME 9.55 Synthesis of *N*-sulfonyl tetrahydro-1*H*-azepines.

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Chapter 10

Synthesis of *N*-sulfonated *N*-benzoazoles and their use in medicinal chemistry

10.1 Introduction

Nitrogen-containing heterocycles as privileged structural motifs are widely found in natural products and small molecule pharmaceuticals [1]. In particular, indoles are of great significance in drug discovery because of their diverse biological activities [2]. For example, indometacin (I), a synthetic indole acetic acid derivative, is an effective non-steroidal anti-inflammatory drug [2].

Benzoazoles such as indoles, benzoxazoles, and benzothiazoles has been of considerable interest because of their profound biological activities [2].

The protection and deprotection of nitrogen-containing compounds such as different benzoazoles categories are very important topics in synthetic organic chemistry. Among various protecting groups for amines, sulfonyl plays a vital role due to the advantages of being stable to many reaction conditions as well as easy preparation and isolation [3].

Sulfonylation of heteroatoms is a valuable transformation that resulted in the imide, sulfonimide, amide, sulfonamide, ester, and sulfonate ester moieties as building blocks of important biologically active and polyfunctional molecules [4,5]. Sulfonate esters are well-known alkylating agents and cell proliferation inhibitors [6], while sulfonamide derivatives are clinically used as antibacterial and antibiotic medicines [7]. Additionally, a number of enzyme inhibitors [8], new therapeutic agents for Alzheimer's disease [9], and hepatitis C virus NS protease inhibitors [10] are derived from *N*-acylsulfonamides.

Moreover, the sulfonamide moiety is a robust constituent of numerous pharmaceutical molecules [11,12]. Sulfonamides have drawn enormous attention in exploring new synthetic methodologies for peptidomimetics that represent a broad array of sulfa-antibiotics [13]. Recent trends show that their cyclic counterparts (sultams) have gained prominence in medicinal chemistry [14]. Compounds affluent with benzosultam core manifest diverse biological activities like antimalarial [15], anti-inflammatory (e.g., Ampiroxicam, Calpain I inhibitor) [16], and enzyme inhibition such as brinzolamide, trichloromethiazide. In addition to these, fused benzosultams can be used as protecting groups, chiral auxiliaries, and directed metallation groups [17]. Among the fused benzosultams, benzodithiazine-1,1-dioxide shows inhibitory properties against HIV [18], and hypoglycemia [19]. Thus, their syntheses have attracted the attention of many organic and medicinal chemists for decades.

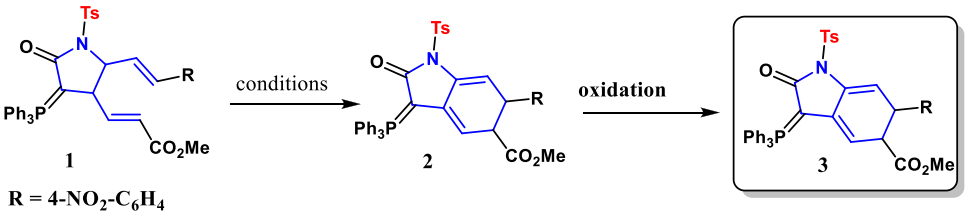
10.2 Chemistry of *N*-sulfonyl indoles

Several studies reported the optimal conditions for the transformation of lactam **1** to **3** through 6π electrocyclization in a freshly prepared solution containing both **1** and 2%−16% of **3** (Scheme 10.1) [20].

Lactam **1** (0.25 mM in solvents) was chosen as the model substrate for optimization of the conditions of the 6π electrocyclization under aerobic and thermal conditions. Although lactam **1** was easily converted to **3** during column chromatography, it was found that its transformation to **3** was sluggish in ethyl acetate (14% and 26% yields, entries 1 and 2) and moderate in acetonitrile (46%, entry 3), this finding indicated that such a cyclization may be promoted by slightly acidic silica gel. It was further noted that reactions in chlorinated solvents, such as 1,2-dichloroethane (DCE), $CHCl_3$, dichloromethane (DCM), *o*-dichlorobenzene (*o*-DCB), and chlorobenzene, gave promising outcomes (entries 4−8; 70%, 62%, 45%, 57%, and 52%, respectively); but that in the non-chlorinated aromatic solvent, toluene, did not. Furthermore, the reaction rate of the 6π electrocyclization can be accelerated under photochemical conditions with halogen lamp irradiation, providing good yields of **3** (entries 10 and 11). Doubly reducing or increasing the solution concentration also gave comparable yields under photochemical conditions (entries 12 and 13).

It was found that the reaction rate of 6π electrocyclization was accelerated evidently by the addition of acetic acid (entries 14 and 15), however, 92% yield was obtained with 3 equiv. of acetic acid as an additive under photochemical conditions for 1 h. A control experiment displayed that the use of bases as additives such as Cs_2CO_3 impeded the

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00013-6



R = 4-NO_2-C_6H_4

Entry	Solvent	Temp. [°C]	Time [h]	Conc. [mM]	Yield [%][b]
1	EA	r.t.	24	0.25	14
2	EA	77	24	0.25	26
3	ACN	83	24	0.25	46
4	DCE	84	24	0.25	70
5	$CHCl_3$	62	24	0.25	62
6	DCM	40	24	0.25	45
7	*o*-DCB	84	24	0.25	57
8	PhCl	84	24	0.25	52
9	toluene	111	24	0.25	21
10[c]	DCE	84	24	0.25	41
11[c]	DCE	84	3	0.25	79
12[c]	DCE	84	3	0.13	79
13[c]	DCE	84	3	0.50	75
14[c,d]	DCE	84	3	0.50	63
15[c,d]	DCE	84	1	0.50	92
16[e]	DCE	84	24	0.50	3

[a] Reactions were carried out with 1 (0.010 mmol) in denoted solvents under aerobic conditions unless otherwise noted.
[b] Yields were determined by ^{1}HNMR spectroscopy with mesitylene as an internal standard.
[c] Irradiated by a 500W halogen lamp at a distance of 25 cm.
[d] 3 equiv. of acetic acid were added as an additive.
[e] 3 equiv. of Cs_2CO_3 were added as an additive and the mixture was bubbled with O_2.

SCHEME 10.1 Optimization of the reaction conditions for the synthesis of *N*-tosyl-indole derivatives **3**.

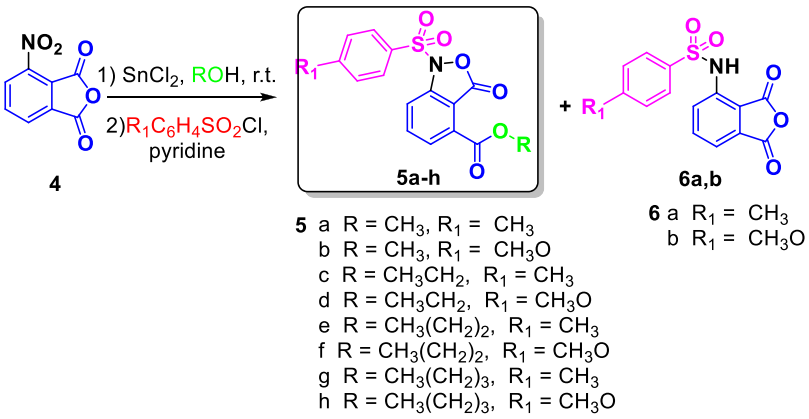
performance of the 6π electrocyclization, resulting in a poor yield (3%, entry 16). In contrast, Srinivasan and coworkers reported the oxidation of cyclohexadienyl to the benzene moiety with a catalytic amount of Pd/C [21].

Also, cyclohexadienyl fused γ-lactam intermediate **2** can be readily oxidized to **3** in the air without additional Pd/C. In short, this 6π cyclization was accelerated by thermal and photochemical conditions as it was as by using acid additives [22].

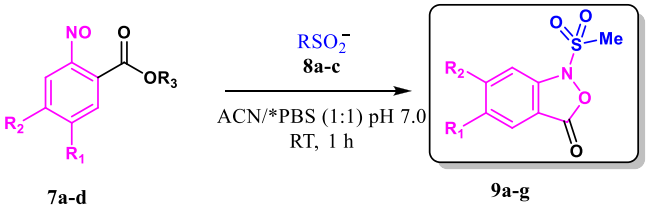
1,2-Benzisoxazoles and their derivatives show interesting pharmacological and biological activities [23–25]. One such example bearing a sulfonamide functionality is Zonisamide (benzo[d]isoxazol-3-ylmethanesulfonamide) which is used as an antiepileptic drug [26].

Along these lines, and searching for the synthesis of new 1-arylsulfonyl-1,3-dihydro-3-oxo-2,1-benzisoxazoles, which are useful for biological screening, the reduction of 3-nitrophthalic anhydride (4) with $SnCl_2$ in different alcohols was examined, followed by coupling of the obtained amines with various arylsulfonyl chlorides in pyridine [27]. However, in all cases, a mixture of the two sulfonamides **5a–h** and **6a,b** were isolated in good to excellent combined yields (57%–84%; Scheme 10.2).

When ortho-nitroso benzoic esters (**7a–b**) were synthesized and tested their reactivity with methane sulfinic acid (**8b**) in a solvent system containing pH 7.0 PBS buffer (50%; PBS = phosphate buffered saline) and CH_3CN (50%; Scheme 10.3). Interestingly, the methyl ester **7a** reacted with **8b**, but the intermediate species was not converted into the *N*-sulfonylbenzisoxazolone **9a** (Scheme 10.3, entry 1). Considering that the analogous result was obtained with ethyl ester **7b** (Scheme 10.3, entry 2), it was speculated that low conversion reflects the relatively weak acidity of the sulfonyl hydroxylamine **11** (Scheme 10.4). Thus, to increase the acidity of this group, a nitro substituent was introduced on the phenyl ring (**7c**).



SCHEME 10.2 Reduction of **4** in different alcohols and protection with arylsulfonyl chlorides in pyridine.



Entry	Compound #	R_1	R_2	R_3	RSO_2^-	Yield [%][a]
1	7a	H	H	Me	8b	- (9a)
2	7b	H	H	Et	8b	- (9b)
3	7c	NO_2	H	Me	8b	84 (9c)
4	7c	NO_2	H	Me	8a	88 (9d)
5	7d	H	CO_2H	Me	8b	84 (9e)
6	7d	H	CO_2H	Me	8a	89 (9f)
7	7d	H	CO_2H	Me	8c	81 (9g)

[a] Yields of isolated products after purification by silica gel chromatography.
*PBS (phosphate buffered saline)

SCHEME 10.3 Reactivity of 2-nitroso benzoic acid derivatives towards sulfinic acids.

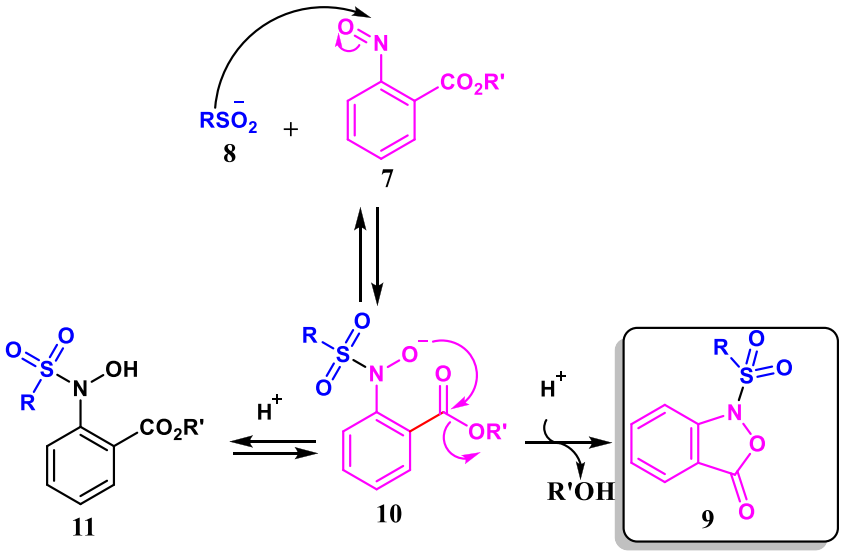
Compound **7c** was converted in good yield into the sulfonyl adducts (Scheme 10.3, entries 3 and 4), consistent with the hypothesis. To improve solubility in water, while preserving reactivity, was then synthesized 2-nitroso terephthalic acid methyl ester (**7d**), in which the scaffold is elaborated with a carboxylic acid group. Compound **7d** showed excellent solubility under neutral pH conditions and robust reactivity toward a variety of sulfinic acids (Scheme 10.3, entries 5–7), as envisioned [28]. Importantly, the nitroso **7d** proved stable in neutral aqueous conditions ($t_{1/2} \geq 24$ h). Together, these studies highlight the potential compatibility of this reaction with biological systems [28].

Moinet et al. have described the intramolecular cyclization reaction of *N*-sulfonyl aromatic hydroxylamines with an ester group in the ortho position (e.g., **10**; Scheme 10.4) [29]. Since cyclization proceeds through acid-catalyzed transesterification, long reaction times (24 h) are required to obtain moderate yields. However, it was reasoned that the reaction kinetics could be improved by performing the ligation in neutral or slightly basic conditions.

Recently, Wang and coworkers [30] reported a reaction to be carried out in an undivided cell under constant current electrolysis (CCE) with $Pd(OAc)_2$(5 mol.%) as the catalyst [31] and $LiClO_4$ as the supporting electrolyte [32] (Scheme 10.5). The substrate scope of this method was evaluated as shown in Scheme 10.5. The methyl-substituted substrates such as **10b** and **10c** could afford the desired products **11b** and **11c** in the yields of 71% and 61%, respectively. For the C3′-substituted substrates such as **10d** and **10e**, there are two potential reactive sites (C2′ and C6′), therefore, a total yield of 60% for **11e** plus **11e′** was obtained. However, **11d** was formed in 50% with high regioselectivity. For the C4-substituted substrates with methyl and halide substituents (**10f–10i**), moderate to good yields were achieved. C4′-substituted substrates with electron-donating groups (**10j–10m**) performed better than those with electron-withdrawing groups (**10n, 10o**). The halogenated carbazoles (**11g–11i, 11n, 11o**) could be used as potential candidates for further functionalization. Remarkably, except for the phenyl substituted *N*-sulfonylanilines, other arenes such as naphthyl, thienyl, etc. (**10p–10s**) delivered in moderate to good yields.

At the same time, the substrates with electron-withdrawing groups (e.g., CF_3) could not be compatible with this method and only trace amounts of product could be monitored (Scheme 10.5).

In continuation of Das work [33] on palladium-catalyzed reactions, it was anticipated that a general synthesis of fused 2,4,6-cyclooctatrien-1-ols **13** could be achieved in one pot. from acetylenic substrates **12**, respectively, employing an appropriate catalyst (Scheme 10.6) [34].



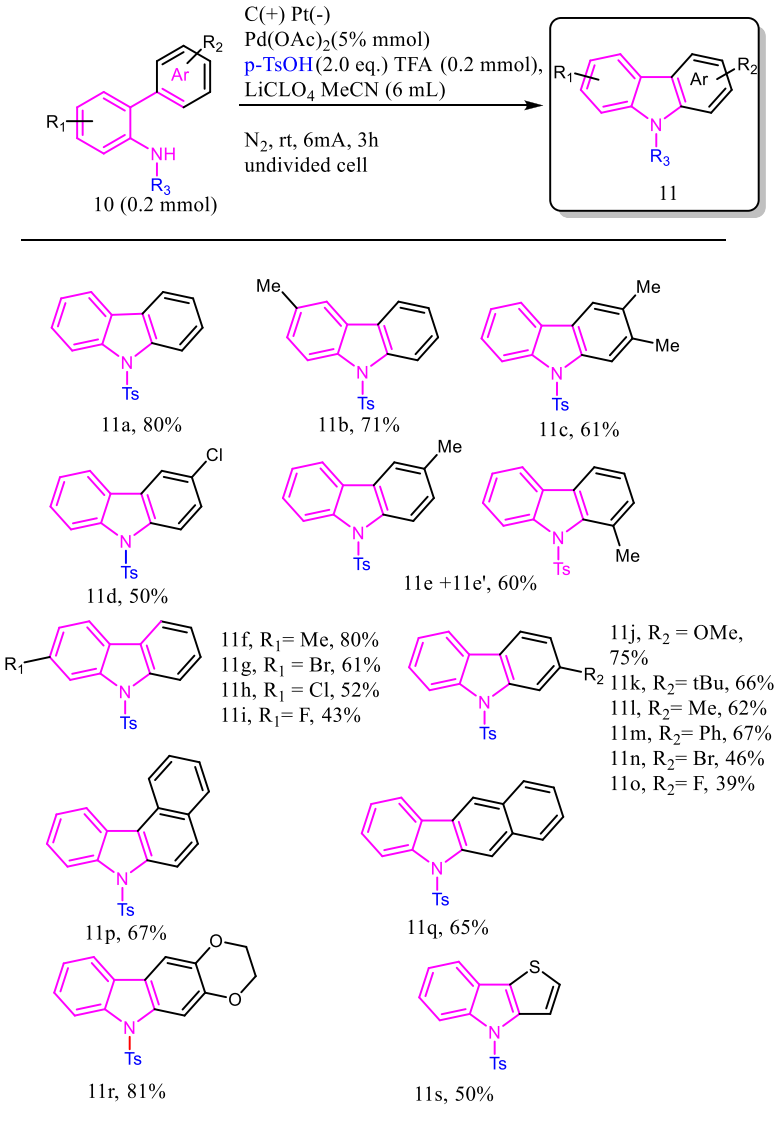
SCHEME 10.4 Proposed mechanism of *N*-sulfonylbenzisoxazolone formation.

Despite the importance of this field, only a few reports [35], on the synthesis of some specific examples of 2,4,6-cyclooctatrien-1-ones fused with arenes or other rings are known; this clearly indicates the requirement of a reliable method for their general synthesis [36].

With the optimized reaction conditions in hand, the generality of the reaction protocol was explored by carrying out the reactions of acetylenic substrates **12a−q** (Scheme 10.6). Interestingly, when the nosyl group (−Ns) was used as an *N*-protecting group instead of tosyl (-Ts) as in **12b**, the reaction required a longer reaction time (i.e., 5.5 h) and the yield of the product **13b** decreased (Scheme 10.6, product **13a** vs **13b**) underlining the importance of the *N*-tosyl group. Thereafter, it was studied the effects of different functional groups at the meta and para positions (with respect to the acetylenic group) in ring A of substrate **12**. For the meta position, both moderate electron-withdrawing (i.e., R_1 = F/Cl/CF_3) and -donating (R_1 = Me) groups performed it as well, resulting in the formation of products **13c-e** and **13f**, respectively, within 4.5−5.5 h in 72%−81% yields. But a strong EWG (R1 = CO_2Me) or EDG (R_1 = OMe) did not favor this reaction resulting in lighter yields [i.e., **13g** (64%), **13h** (66%)]. For the para position, incorporation of a moderate EWG (viz., R_1 = F; substrate **13i**) facilitated the reaction affording **13i** in 81% yield, compared to an EDG (viz., R_1 = Me) as in **12j** which furnished **13j** in a lighter yield (68%). These substituent effects are perhaps predictable keeping in view the importance of electrophilicity of the b-carbon (of the triple bond of **12**) for the cyclization to proceed smoothly. To the surprise, a strong EWG (viz., R_1 = CO_2Me) or EDG (viz., R_1 = OMe) placed at the same position in the substrates (**12k** or **12l**) delivered the product **13k** or **13l** to an extent of 60%−70%. The reason behind these results is not very clear at this moment [34].

Interestingly, when a strong EWG (viz., R_1 = CO_2Me) in ring A and EDG (viz., R_2 = OMe) in ring B are simultaneously placed para to the acetylenic group, product **13m** (94%) was formed within 3 h. When the ester group was absent (as in **12n**), 6n was furnished in a somewhat lighter yield (81%), while removing the methoxy group from 4n and incorporating a moderate EDG (R**2** = Me) as in substrate **12o** led to the formation of **13o** in 59% yield. Furthermore, the incorporation of an additional EWG (R**1** = CO_2Me) in ring A (**12p**) benefited the reaction by producing product **13p** (78%) within 3 h. Surprisingly, the reaction of substrate **12q** having an EDG (R_3 = OMe) at the para position of the C ring was somewhat sluggish to furnish the product **13q** in 61% yield [34].

The protection of nitrogen-containing compounds is a very important topic in synthetic organic chemistry. Among various protecting groups for amines, sulfonyl plays a vital role due to the advantages of being stable to many reaction conditions as it was as easy preparation and isolation. To date, a lot of methods have been developed to remove the sulfonyl groups, and some representative ones are as follows: (1) reductive cleavages of NAS bond with alkaline metals [37,38], Mg [39,40], Al [41], SmI_2 [42,43], Red-Al [44], low valent titanium [45], organic electron donors [46,47], (2) basic conditions such as Grignard reagent [48], MOH [49], M_2CO_3 [50], NaOMe [51], NaOt-Bu [52], $KPPh_2$ [53], $LiSiMe_2Ph$ [54], TBAF [55], (3) acidic conditions such as HBr [56], HF [57], H_2SO_4 [58], (4) other approaches including electrochemistry [59], photoinduced electron transfer [60] et al. However, many of these strategies suffer from harsh reaction conditions and low functional group tolerance. Therefore, the development of mild and efficient deprotection protocols for sulfonyl groups (especially the most

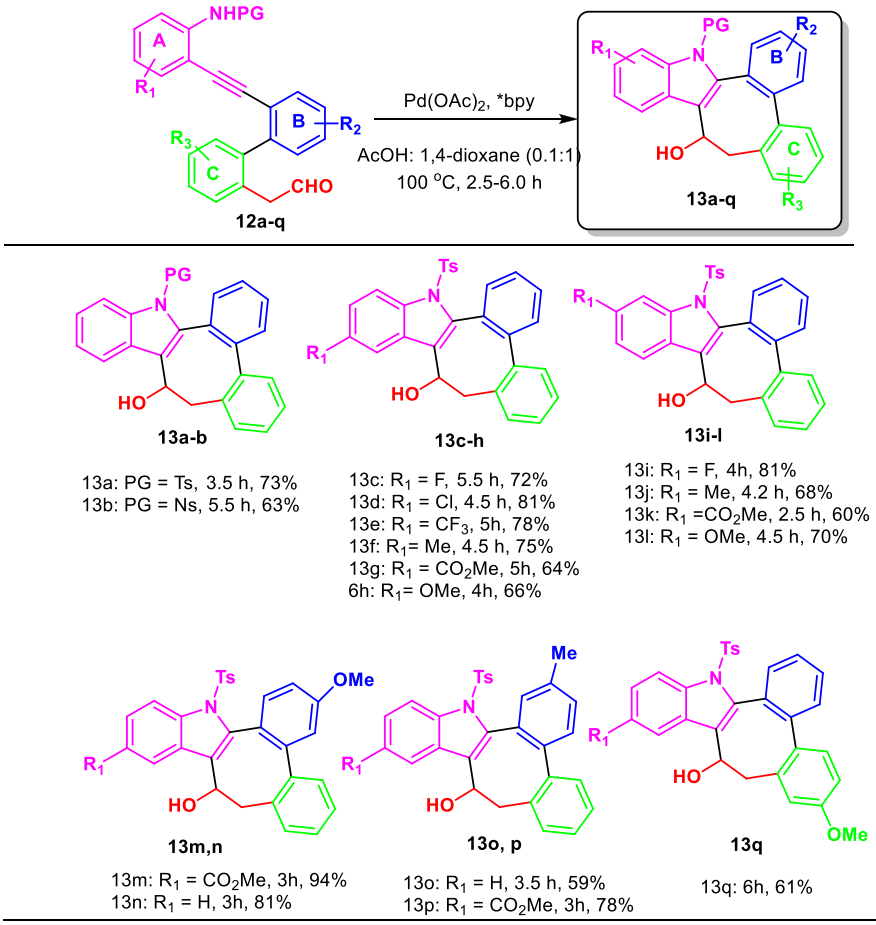


Reaction conditions: 1 (0.2 mmol), $Pd(OAc)_2$ (5 mol%), *p*-TsOH (0.4 mmol), TFA (0.2 mmol) in undivided cell with graphite rod anode (15 mm × 15 mm × 0.36 mm) and Pt plate cathode (15 mm × 15 mm × 0.3 mm), $LiClO_4$ (0.1 mmol) as the supporting electrolyte, MeCN (6 mL), rt, 3 h, constant current = 6.0 mA (janode = 2.6 mA/cm_2), nitrogen. Isolated yields are shown.

SCHEME 10.5 Electrochemical Palladium-Catalyzed synthesis of *N*-tosylcarbazole.

commonly used tosyl group) is urgently required. In the continuous explorations in the field, it was occasionally found that a detosylation reaction took place when treating *N*-tosyl-indole with NaH in DMF (Scheme 10.7). It was found that the tosylation of indole **14** to **15** also frequently applied NaH as a base in the same solvent [50,55]. The discovery means excessive NaH is actually detrimental to the tosylation reaction [61].

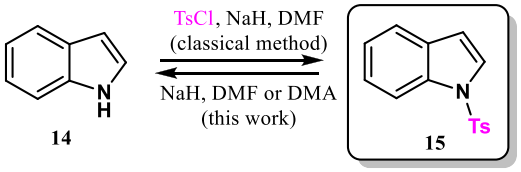
Recently, para-quinone methides (*p*-QMs) have emerged as versatile building blocks due to their intrinsic reactivities. A large number of transformations based on *p*-QMs have been achieved since the seminal reports by Fan [62] and Jørgensen [63]. For example, annulation reactions based on simple *p*-QMs and vinyl *p*-QMs have been reported by Yao, Fan, Zhao, and Waser groups [64–66]. Although great progress has been made in the synthesis of oxygen-containing heterocyclic frameworks, the application of *p*-QMs in the construction of nitrogen-containing heterocyclic frameworks remains underdeveloped. Cyclizations using ortho tosylaminophenyl-substituted *p*-QMs as building blocks are still rather limited. Inspired by this work, it was wondered whether this strategy could be extended to ortho-tosylaminophenyl-substituted *p*-QMs. It was hypothesized that assembly of 2,3-dihydroindoles could be realized



*(bpy) = bipyridine

Reaction conditions: a mixture of 4 (0.086 mmol) and $Pd(OAc)_2$bpy (6 mol%) in a solution (1.1 mL) containing AcOH: 1,4-dioxane (0.1 : 1, v/v) was heated at 100 °C under argon.

SCHEME 10.6 Palladium-catalyzed synthesis of dibenzo [5−8] cycloocta[1,2-b] indol-10-ols **13a−q**.

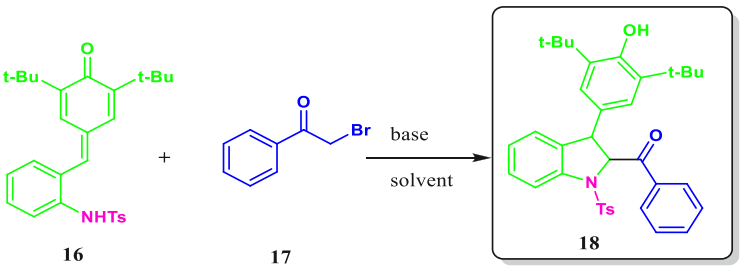


SCHEME 10.7 The NaH-mediated "reversible" reactions.

through the union of ortho-tosylaminophenyl substituted *p*-QMs and α-halo ketones via *N*-alkylation followed by intramolecular cyclization. Then, a suitable oxidant can promote the in situ generation of indoles. Although it was have reported the synthesis of 2,3-dihydroindoles through a formal [4 + 1] annulation of ortho-tosylaminophenyl-substituted *p*-QMs with sulfur ylides [67], the direct one-pot synthesis of 2,3-disubstituted indoles and 3,4-diaryl-substituted quinolinone derivatives from ortho-tosylaminophenyl-substituted *p*-QMs through *N*-alkylation/acylation followed by intramolecular 1,6-conjugate addition and oxidation strategy has not been reported yet (Scheme 10.8) [62].

Several methods including intramolecular cyclization of indole derivatives [68], 2 tandem reaction [68], Fischer indolization [69], [3 + 2] [69,70], [4 + 2] [71] and formal [3 + 3] [72] cycloaddition reactions have been developed for the synthesis of various hydrocarbazoles. Among them, some methods have been successfully applied to the total synthesis of natural alkaloids [73−75]. Crotonate-derived sulfur ylides as the of C1, C2 or C3 synthons in various annulation for the synthesis of diverse cyclic compounds have received great attention and contributed tremendously to progress [76−81]. The tandem annulations involving sulfur ylides are efficient protocols to construct polycyclic systems. Herein, it was reported the first base-promoted [3 + 3]/[1 + 4] tandem reaction of tosyl protected *o*-amino α,β-unsaturated ketones and crotonate-derived sulfonium salt for the efficiently diastereoselective synthesis of functionalized hydrocarbazoles (Scheme 10.9) [82].

Enantioenriched, vicinal diamines are frequently encountered across the many disciplines of chemistry [83].



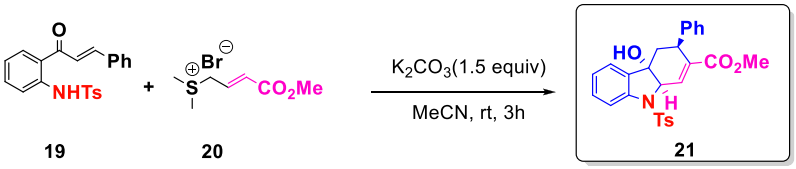
Entry	Base	T (°C)	Solvent	Yield[b] (%)
1	Et_3N	20	CH_3CN	54
2	DBU	20	CH_3CN	38
3	$^{i}Pr_2NH$	20	CH_3CN	7
4	Na_2CO_3	20	CH_3CN	4
5	K_2CO_3	20	CH_3CN	5
6	Cs_2CO_3	20	CH_3CN	82
7	Cs_2CO_3	20	CH_2Cl_2	60
8	Cs_2CO_3	20	$CHCl_3$	57
9	Cs_2CO_3	20	Acetone	80
10	Cs_2CO_3	20	Toluene	53
11	Cs_2CO_3	20	DCE	50
12[c]	Cs_2CO_3	20	CH_3CN	80
13[d]	Cs_2CO_3	20	CH_3CN	76
14[e]	Cs_2CO_3	20	CH_3CN	83
15	Cs_2CO_3	35	CH_3CN	85
16	Cs_2CO_3	50	CH_3CN	92

[a] All reactions were conducted with 16 (0.11 mmol), 17 (0.10 mmol), base (1.5 equiv.), solvent (1.5 mL), 1.5 h. [b] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; dr > 20 : 1.[c] 1.0 equiv. of base was used. [d] 2.0 equiv. of base was used. [e] t ¼ 3 h.

SCHEME 10.8 Divergent synthesis of indoles from *o*-tosylaminophenyl-substituted para-quinone methides (*p*-QMs).

Furthermore, many different chiral, enantioenriched auxiliaries, ligands, and catalysts for organic synthesis are derived from vicinal diamines [84,85], including Noyori enantioselective hydrogenation catalysts [85], *N*- heterocyclic carbenes [86], and various ligands for asymmetric additions of organometallic reagents [85,87]. Many of these chiral diamines are still most frequently obtained in enantioenriched form by classical resolution [88,89], stereocontrolled transformations of enantioenriched starting materials [90,91], or functional group interconversion of amino acids and other chiral pool materials [83,92,93]. It was found early on that use of 1 equiv of sodium fluoride was sufficient and led to improved reaction homogeneity. The diamination reaction of **22** in presence of **24** as a catalyst is general across a wide variety of *trans*-1,2-disubstituted alkenes bearing many kinds of substituents, to afford *syn*-difunctionalized products (Scheme 10.10), however, unsymmetrical diaryl olefins afforded products with significantly higher selectivities for the imidazolidinone product **25** in good yields and enantioselectivities [94].

In the last decade, the concept of carbon−carbon bond formation by the direct substitution of π-activated alcohols (R-OH) in the presence of catalytic Lewis- or Brønsted acids with various nucleophiles such as aromatic rings, alkenes and alkynes (R′−H) has generated



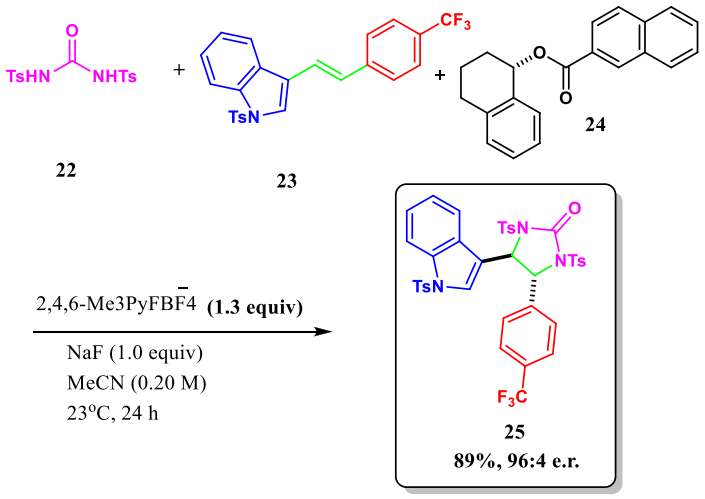
19 20 21

compound #	R_1, R_2	dr[a]	yield[b] (%)
21a	Ph, H	> 20:1	92
21b	4-MeOC_6H_4, H	> 20:1	86
21c	4-MeOC_6H_4, H	> 20:1	84
21d	4-FC_6H_4, H	> 20:1	89
20e	4-ClC_6H_4, H	> 20:1	80
21f	4-BrC_6H_4, H	> 20:1	93
21g	4-NO_2OC_6H_4, H	> 20:1	82
21h	4-CNOC_6H_4, H	> 20:1	81
21i	2-FC_6H_4, H	> 20:1	90
21j	3-FC_6H_4, H	> 20:1	96
21k	3,4-$F_2C_6H_3$, H	> 20:1	95
21l	3-$CF_3C_6H_4$, H	> 20:1	93
21m	2-naphthyl, H	> 20:1	95
21n	2-furyl, H	> 20:1	93
21o	2-thienyl, H	> 20:1	94
21p	*t*-Bu, H	≥ 20:1	nr
21q	Ph, 4-Me	> 20:1	91
21r	Ph, 6-Me	> 20:1	90
21s	Ph, 4-F	> 20:1	86
21t	Ph, 4-Cl	> 20:1	89
21u	Ph, 4-Br	> 20:1	80

Reaction conditions: **19** (0.10 mmol), **20** (0.15 mmol, 1.5 equiv), K_2CO_3 (0.15 mmol, 1.5 equiv), CH_3CN (1 mL). [a]Determined by ^{1}H-NMR (400 MHz) of the crude product. [b]Isolated yields.

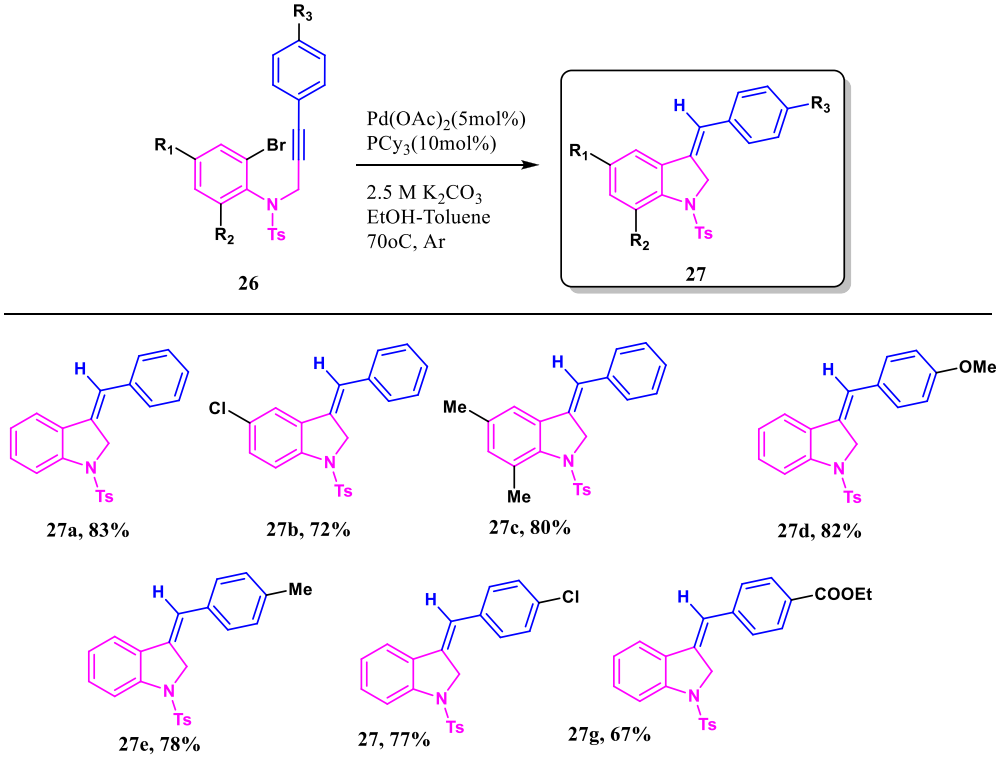
SCHEME 10.9 Base-promoted tandem annulation.

considerable interest in the area of green chemistry, as the process is catalytic and water is the only byproduct [95–98]. The required starting materials, 3-benzylidene-1-tosylindoline derivatives **27**, were prepared by Heck coupling of substituted 2-bromo-*N*-propargylanilidines **26**, using 5 mol.% $Pd(OAc)_2$, 10 mol.% tricyclohexylphosphine (PCy_3), 2.5 M aqueous K_2CO_3 in a mixed solvent of toluene and ethanol (1:1) at 70°C within 4 h (Scheme 10.11) [99,100]. The reaction proceeded in a stereoselective manner via 5-*exo-dig* cyclization to obtain the 3-benzylidene-1-tosylindoline derivatives in moderate to good yields. 2-bromoaniline derivatives possessing electron withdrawing group like −Cl, and electron donating group like 2,4-dimethyl underwent a smooth transformation under the aforesaid condition with 72% and 80% yields, respectively (Scheme 10.11, entries **27b** and **27c**)



The reaction was performed on 1.00 mmol scale. Enantiomeric ratios was determined after chromatographic purification by chiral stationary phase HPLC. Yields are of isolated, analytically pure material.

SCHEME 10.10 Metal-catalyzed, catalytic, *syn*-diamination of alkenes.

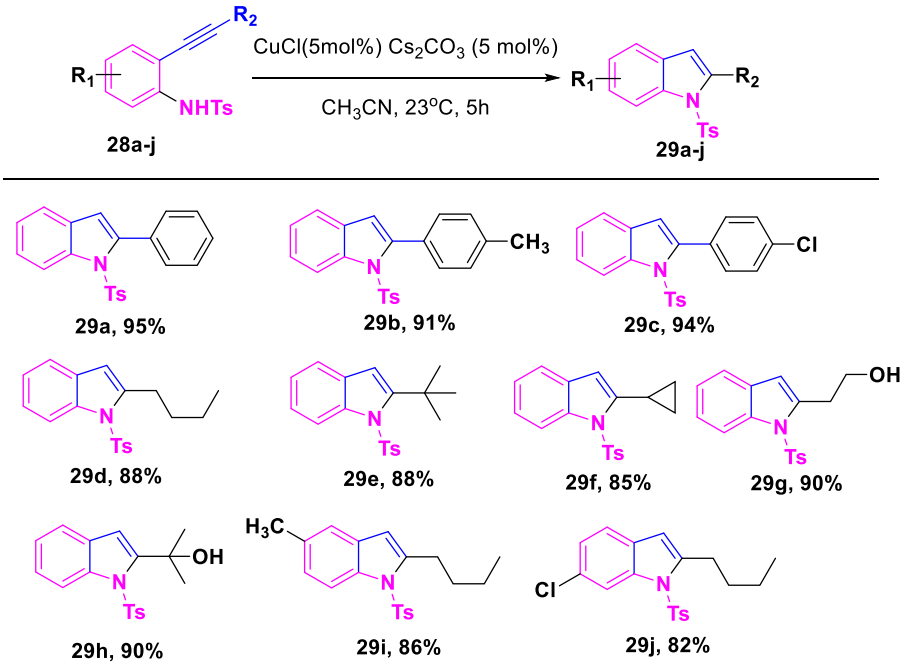


Reaction conditions: 0.05 mmol of $Pd(OAc)_2$, 0.10 mmol of PCy_3, 2.5 M K_2CO_3 (2 mL of H_2O), 2 mL of EtOH and 2 mL of toluene at 70 °C under Ar.

SCHEME 10.11 Preparation of 3-benzylidene-1-tosylindoline substrates by Pd catalyzed Heck coupling reaction.

[101]. Moreover, alkyne units bearing a number of functional groups were also well-tolerated, giving 67%–82% yields (Scheme 10.11, **27d–27g**) [101].

Some one-pot cascades have also been developed according to this strategy (Scheme 10.12) [102–105]. However, these transformations usually require the participation of noble metals, ligands, or harsh conditions to complete the cyclizations. Copper, in the merit of cost, is a superior choice in organic catalysis [106–108]. It has also been used in the construction of benzo[b]furan and



All reactions were performed with 28 (0.5 mmol), CuCl (0.025 mmol), Cs_2CO_3 (0.025 mmol) in CH_3CN (2 mL) at 23 °C for 5 h. Isolated yields of 29 were listed

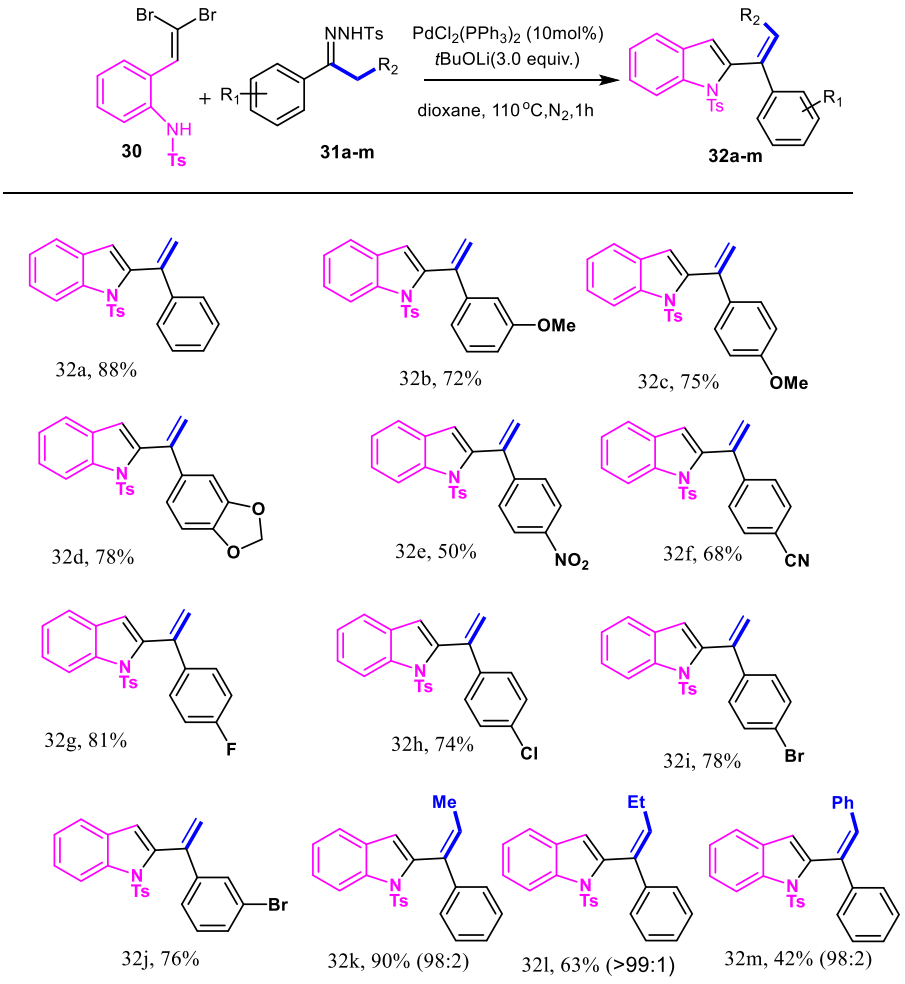
SCHEME 10.12 Copper-catalyzed *N*-tosyl-indole synthesis.

indole rings [109]. Hence, 2-(phenylethynyl) tosylaniline **28a** was submitted to the standard conditions and the reaction proceeded smoothly to afford *N*-tosyl-2-phenyl indole **29a** in 95% yield. Then various 2-alkynyl tosylanilines were tested under the standard conditions. It was found that in all cases, 2-arylethynyl tosylanilines gave the desired products (**29a**−**c**) in excellent yields. Similar results were obtained when different 2-alkylethynyl tosylanilines (**28d**−**f**) were used as the substrates. Hydroxyl group was still tolerated in this transformation and tosylanilines with Me or Cl substitutes remained active to give the corresponding tosylindoles **29i** and **29j** in 86% and 82% yield, respectively [110].

Arrayás's group reported a palladium (II)-catalyzed alkenylation of indoles at the C2-position by using an excess of alkenes with *N*-pyridylsulfonyl as a directing group [111]. Recently, Punji and coworkers described a Ni-catalyzed regioselective C2 alkenylation of indoles through utilizing alkenyl bromides, directed by a *N*-2-pyrimidinyl group under relatively mild conditions [112]. Schipper and other groups successively achieved Co or Ru catalyzed intermolecular C2-alkenylation of indoles by using alkynes instead of alkenes, in which *N,N*-dimethylcarbonyl or pyrimidyl group was employed as a directing group Moreover, some examples without *N*-directing groups were developed. In 2006, Nakao, Hiyama and coworkers described a C2-addition to internal alkynes under mild nickel catalysis [113].

With the optimized conditions in hand, the substrate scope of *N*-tosylhydrazones was investigated with 2-*gem*-dibromovinylanilines, and the results were illustrated in Scheme 10.13 [114]. The substitutions on phenyl group of *N*-tosylhydrazones exhibited quite good tolerance. Both electron donating groups (*m*-OMe, *p*-OMe and -OCH_2O-) and electron-withdrawing groups (NO_2 and CN) could give the corresponding products in moderate to good yields (**32b**−**32f**). Not only fluro and chloro substituted *N*-tosylhydrazones performed smoothly, but also the substrates bearing *m*- and *p*-Br substitutions could survive well under the standard conditions, which could be readily transformed to more valuable molecules *via* cross-coupling reactions (**32a**−**32j**). Furthermore, the tri-substituted alkenes were synthesized from the corresponding *N*-tosylhydrazones, which exhibited high *Z*-selectivity determined by NOE (**32a**−**32m**) [114].

Multicomponent polymerizations (MCPs), as a burgeoning field in polymer chemistry, have gained wide popularity recently among polymer scientists [115−118]. Besides the advantages inherited from small molecular multicomponent reactions, such as high atom/step economy, simple and inexpensive reactants, environmental benefits, synthetic efficiency, and operational simplicity [119−121], the unique feature of MCPs compared with other polymerizations is the great structural diversity of the polymer products that could be achieved through various combinations of multiple monomers [122−131].



Reaction conditions: **30** (0.3 mmol), **31a-m** (0.6 mmol), $PdCl_2(PPh_3)_2$ (10 mol %), *t*BuOLi (0.9 mmol), dioxane (4 mL), N_2, 1 h, 110 °C.

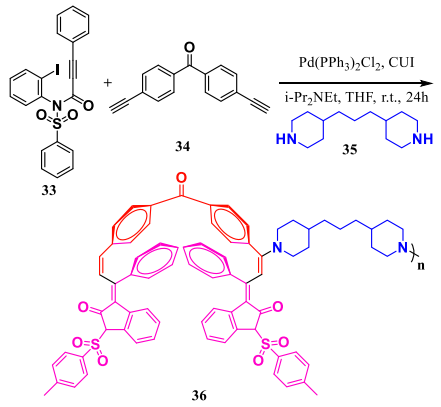
SCHEME 10.13 Scope of *N*-Tosylhydrazones in the construction of tandem reaction.

To develop one-pot two-step three-component tandem polymerization for the preparation of poly(indolone)s, monomer **33** was synthesized (Scheme 10.14) [132], electron-deficient aromatic diyne **34** was designed concerning its high reactivity, and secondary diamine **35** was chosen as a reactive nucleophile. The polymerizations of **33, 34**, and **35** were carried out in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and *i*-Pr_2NEt in THF under nitrogen. In the first step, monomer **33** was reacted with **34** for 24 h at room temperature, and **35** was then added in the second step to proceed with the Michael addition at 60°C for 12 h to afford polymer **36** (Scheme 10.14). The reaction conditions of the MCTP such as monomer concentration, reaction temperature, and time were optimized. When the concentration of **33** was increased from 0.025 to 0.2 M, while keeping the monomer loading ratio [**33**]:[**34**]:[**35**] = 2:1:1, the polymerization yields were generally high, but significant influence on the Mws of the products was observed and the best result was obtained with an Mw of 27,700 g/mol and a yield of 90% from the monomer concentration of 0.1 M (Scheme 10.14, entries 1 − 4) [132]. The reaction temperature of the second step after the addition of **35** was then investigated from room temperature to 70°C (Scheme 10.14, entries 3 and 5 − 9). A gradual increase of both yield and Mw was observed and a product with a Mw of 28,500 g/mol was obtained in 86% yield at 60°C.

When the second step was reacted for 6 h, a polymer with a Mw of 29300 g/mol was already produced in 84% yield, indicating the high efficiency of the MCTP. Further increasing the reaction time did not show a significant influence on the polymerization result (Scheme 10.14, entries 9 − 11). In addition, the MCTPs of **33, 34**, and **35** were conducted in the air to learn the influence of air conditions on each step [132].

Reported is a modular one-step three-component synthesis of ditosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole **40** via a Catellani strategy. This process exploits aziridines as the alkylating reagents through palladium/norbornene cooperative catalysis to enable a Catellani/Heck/aza-Michael addition cascade. The development of general and efficient approaches for the direct synthesis of ditosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole **40** from readily available starting materials would be a highly desirable yet challenging subject [133]. The Catellani reaction, firstly introduced by Prof. Catellani [134], utilizes the palladium/norbornene (NBE) cooperative catalysis to facilitate sequential ortho C−H bond activation and ipso coupling of aryl iodide, thereby allowing the precise functionalization of ortho and ipso positions simultaneously [135−141]. Notably, Lautens, Catellani, and others have developed a gamut of elegant Catellanitype annulations to access diversified benzo-fused rings [139,142−150]. Recently, it was identified that epoxides could act as alkylating reagents for the Catellani reaction, providing an efficient strategy for the synthesis of isochromans [149]. Inspired by this discovery, we envisaged that the readily available aziridines [151−153] might also act as alkylating reagents to enable a Catellani/Heck/aza-Michael addition cascade [154] for the direct synthesis of **40** the aryl iodides was examined with aziridine **38** and olefin **39** as the reaction partners (Scheme 10.15) [155]. Gratifyingly, aryl iodides containing electron-donating and electron-withdrawing groups all proved to be competent substrates, providing the desired products **40** [155].

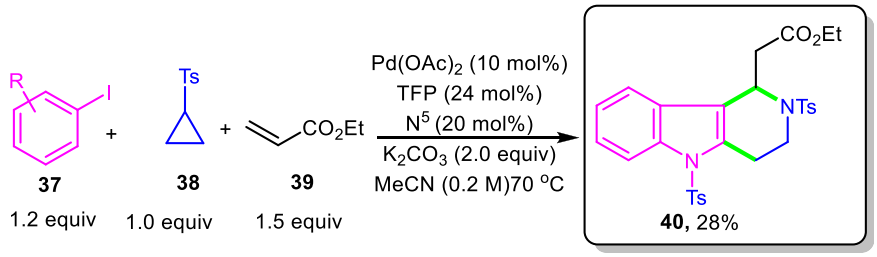
The 11a-*N*-tosyl-5-carbapterocarpan LQB-2223 (**41a**) was previously designed and prepared as a racemate, as part of research aiming to the synthesis of new antineoplastic and antiparasitic drug candidates (Fig. 10.1). This compound presented antineoplastic activity towards multidrug-resistant (MDR) leukemias and breast cancer cells [156−158], leishmanicidal properties in vitro [156], as well as in vitro and in vivo antimalarial activities [159]. The potential of **41a** as an antineoplastic prompted us to prepare derivatives for these studies. Recently, it is reported the synthesis of compound **41a**, the effect of substitutions at A and D-rings on the cytotoxicity against models of human leukemias (K562, Lucena-1, and FEPS) and breast cancers (MCF-7 and MDA-MB-231) presenting diverse phenotypes of drug resistance. Additionally, ADMET properties were predicted in silico. The exchange



Entry	[33] (M)	T2 (°C)	t (h)	yield (%)	M (g/mol)[b]	Mw/Mn[b]
1	0.025	70	24	98	9400	1.21
2	0.05	70	24	91	16100	1.44
3	0.1	70	24	90	27700	1.82
4	0.2	70	24	91	15400	1.47
5	0.1	rt	24	87	19600	1.71
6	0.1	40	24	84	24500	2.01
7	0.1	50	24	84	25000	1.90
8	0.1	55	24	84	27200	1.94
9	0.1	60	24	86	28500	1.96
10	0.1	60	12	83	30400	1.99
11	0.1	60	6	84	29300	1.96

[a]Monomer 33 was reacted with 34 at room temperature in THF solution under nitrogen in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and i-Pr_2NEt for 24h. 35 was then added to react at different temperatures (T2) with different times (t2). The polymerization was carried out with 0.2 mmol of 33, [33] =[34] = [35], $[Pd(PPh_3)_2Cl_2]$ = 0.05 [33], [CuI] = 0.1 [33], and [i-Pr_2NEt] = 10 [33]. bDetermined by GPC in THF on the basis of a polystyrene calibration.

SCHEME 10.14 Optimization of the Multicomponent Tandem Polymerization of **33, 34**, and **35**.



The reaction was performed on a 0.2 mmol scale.

SCHEME 10.15 Modular one-step three-component synthesis of 2,5-ditosyl-2,3,4,5-tetrahydro-1*H*-pyrido [4,3-b]indole **40**.

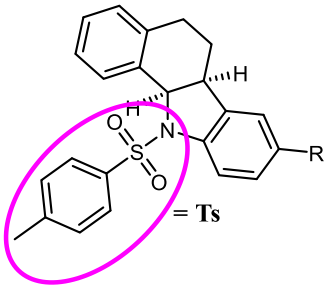
of the *N*-tosyl group for mesyl or benzoyl groups led to a drastic reduction in cytotoxic effect [157].

The fluoro- (**41b**) or iodo-(**41c**) substitution of D ring did not improve the antileukemic activity. Due to increased levels of antioxidants, resistant cells usually have lower reactive oxygen species (ROS) levels compared to their sensitive counterparts [160].

Chronic myeloid leukemias such as K562 are tolerant to oxidative stress, and the MDR counterpart Lucena-1 is described as even more resistant due to overexpression of catalase and glutathione [160–164]. ROS levels are reported to be lower in MDA-MB-231 than in MCF-7 [165], and since glutathione is also present in high levels in the latter [166], Compound **41a** was previously demonstrated to be selective to leukemia cells, not affecting normal proliferating murine lymphocytes [157].

It was further investigated the role of tosyl group for the toxicity exerted by the aza-carbapterocarpan derivatives Aza-carbapterocarpan **44** was synthesized in moderate yields (56%) by palladium-catalyzed Aza-Heck arylation in PEG 400 between dihydronaphthalene and *N*-tosyl-4-fluoro-o-iodoaniline (**43**), previously prepared in good yield (86%) by reaction of tosyl chloride and 4-fluoro-o-iodoaniline employing similar conditions as to obtain **43** [167] (Scheme 10.16).

The most studied approach to the synthesis of alkoxylated cycloalka[*b*]indoles is the Fischer synthesis from

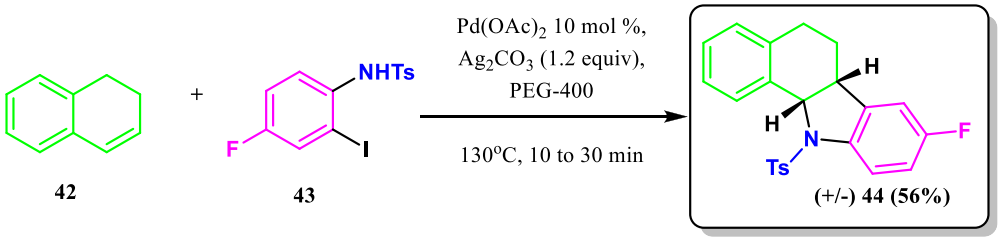


11a-aza-carbapterocarpan
(+/-)-LQB-2233 **(41a)**

41a, R= H
41b, R= F
41c, R=I

FIGURE 10.1 Structure of 11a-*N*-tosyl-5-carbapterocarpan LQB-2223 (**41a**).

cycloalkane (alkoxyphenyl)-hydrazones [168]. This method is convenient and widely used in the synthesis of heterocycles with the alkoxy group in the aromatic ring [169]. When preparing cycloalka[*b*]indoles with hydroxy, alkoxy, or acyloxy groups as substituents in the cycloalkane ring, depending on the goal of the synthesis [170], the oxy function can be attached to various carbon atoms of the carbocycle [171,172]. The reaction of 3-carboxyindoles with (1*Z*)-1-methoxy-3-(trimethylsilyl)-1,3-butadiene (the Danishefskydiene) proceeds as the Diels–Alder reaction with the formation of *cis*- and *trans*-4-methoxyhexahydrocarbazoles [173]. Recently, *N*-tosylate of 4-methoxy-1,2,3,4-tetrahydrocarbazole **50** was synthesized and tested its cytotoxic activity. For preparation of heterocycle **50** we have used the readily accessible from 2-(1-cyclohexen-1-yl)aniline [24] tosylamide **45a** [174,175], which was earlier used in the synthesis of *N*-tosylates of 1,2,3,4-tetrahydro- **46a** [175,176] or 1,2,3,9a-tetrahydrocarbazole **48** [177]. During the synthesis of the latter via the stage of bromination of tosylate **45a** halogenide **47** [174] is formed, which, upon the treatment of the reaction mixture with aqueous ammonia, enters the reaction of intramolecular condensation resulting in tetrahydrocarbazole **48** [174]. This approach to the synthesis of heterocycle **48** is more effective than the cyclization reaction initiated by metal complexes. An attempt to prepare compound **48** by oxidative cyclization of sulfonylamide **45a** by the action of palladium acetate led to the formation of the recently described *N*-tosylate of tetrahydrocarbazole **46a** [175,176,178]. When heated in the presence of $Cu(OAc)_2$, sulfonylamide **45a** under the same conditions affords isomers **46a** and **48** in about equal ratio. The C4a = C4 double bond in the formed *N*-tosyl-1,2,3,9a-tetrahydrocarbazole **48** turned out to be more stable to further migration into the heterocyclic ring than in 2-ethyl-3-methylideneindole [30,179]. The tosyl group stabilizes the double bond as indicated by the fact that on heating the *N*-mesyl analog **46b** in the same conditions in the presence of $Cu(OAc)_2$ only tetrahydrocarbazole **46b** is formed, which was earlier synthesized by the reaction of radical cyclization of *N*-mesyl-*N*-(2-bromo-2-cyclohexen-1-yl)-2-iodoaniline [180] in moderate yield or by keeping *N*-mesyl-2-(6-bromo-1-cyclohexen-1-yl)aniline [181] at room temperature in high yield. The methoxy substituent was introduced to atom C4



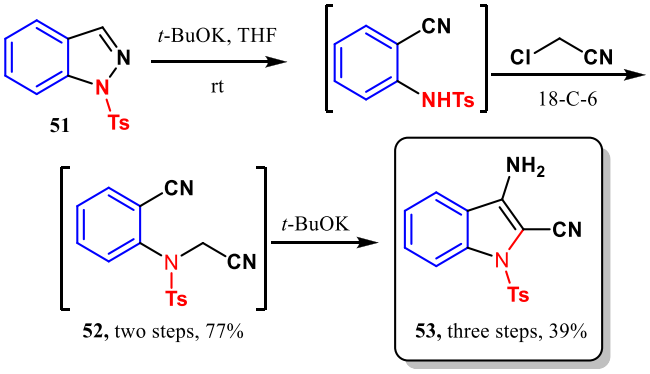
42 43

SCHEME 10.16 Synthesis of compounds **44**.

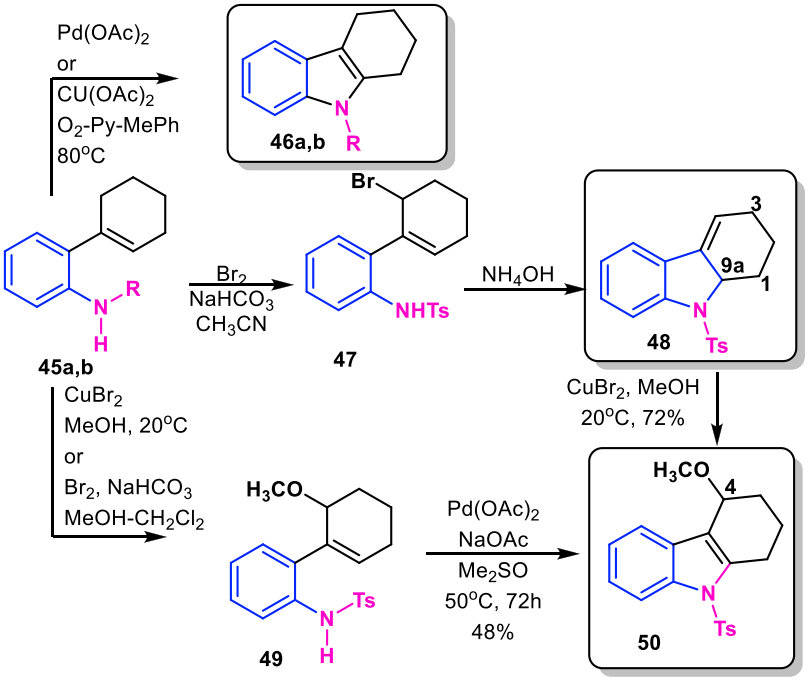
of heterocycle **48** using the reagent prepared by dissolution of copper dibromide in methanol, which was used earlier [182] for the synthesis of ethers from the conjugated diene. The methoxy substituted compound **50** is formed by stirring heterocycle **48** in excess methanol in the presence of 2 equiv. of $CuBr_2$ under mild conditions (Scheme 10.17) [169].

It was developed an efficient synthesis of 1-tosyl-1*H*-indazoles from readily accessible *o*-haloaryl *N*-tosylhydrazones. A series of valuable derivatives were prepared in good yields, and this method was successfully applied to the synthesis of bioactive compounds [183]. With the 1-tosyl-1*H*-indazole derivatives in hand, we attempted their detosylation, with the goal of further functionalizing the indazoles. Although this reaction occurred smoothly in the presence of both magnesium in MeOH and TBAF in THF, as described by Inamoto et al. [184,185] more than 10 equivalents of magnesium were required, whilst TBAF was unsuitable in some cases. Therefore, we wanted to develop a more satisfactory method for this detosylation reaction. The products of the Kemp elimination reaction are useful building blocks in organic chemistry [186–188]. To demonstrate their utility, it was investigated the further elaboration of these products, with the aim of transforming them into a diverse range of derivatives in a one-pot reaction [189]. First, we considered a Thorpe–Ziegler cyclization reaction of the cyano group. Thus, 2-chloroacetonitrile and 18-crown-6 were added to compound **51** as a model substrate after the Kemp elimination reaction, which led to the formation of compound **52** in 77% yield. Furthermore, the addition of a second equivalent of *t*BuOK caused the Thorpe–Ziegler cyclization reaction to occur smoothly, thereby affording compound **53** in 39% yield (Scheme 10.18) [189].

In view of the impressive biological activities of 3,4-fused pyrroles, several strategies for the synthesis of this skeleton have been developed [190–192]0.6 However, to the best of our knowledge, the efficient method for the construction of 3,4-fused cycloalkanopyrroles is rarely achieved up to now. Generally, the way to synthesize 3,4-fused cycloalkanopyrroles is the 1,3-dipolar cycloaddition of Michael acceptors and isonitrile anions [193]. Recently,



SCHEME 10.18 Preparation of compound **53** from compound **51** in a one-pot reaction. 18-C-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6).

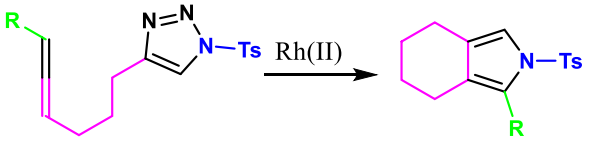


R = Ts (45a, 46a), Ms (45b, 46b).

SCHEME 10.17 Synthesis of *N*-tosylates of 4-methoxy-1,2,3,4-tetrahydrocarbazole.

Sarpong and coworkers [194] reported an elegant method for the synthesis of 3,4-fused partially unsaturated indole **55** using in situ generated Rh-bound trimethylenemethane variants **54** (Scheme 10.19) [195].

Reports on Fischer indole synthesis [196,197] as well as other cyclization methods [198–206] using CF_3-containing building blocks are known, though the synthetic sequences were usually tedious due to the preparation of trifluoromethylated precursors. The majority of current methods are based on trifluoromethylation of existing indole cores [207–218]. Transition-metal-catalyzed cross-coupling of indoles containing boron [207–211,219], halide [220–222], and silicon [213] functional groups have been successfully developed without the need of fluorinated building blocks. We have previously reported an efficient trifluoromethylation method of terminal alkynes using Grushin's fluoroform-derived $CuCF_3$ and TMEDA (tetramethylethylenediamine) [223]. This reaction can potentially be applied to the synthesis of 2-(trifluoromethyl) indoles from readily accessible 2-alknylanilines. In a domino fashion [224], the strategy relies on the trifluoromethylation of terminal alkyne, followed by 5-*endo*-dig cyclization, initiated by the ortho nitrogen nucleophilic attack to the triple bond, to construct the indole core. Such a convenient approach has surprisingly not been reported, despite the fact that the synthesis of functionalized indoles via cyclization of 2-alkynylanilines is well-documented [225–227]. The scope of 2-(trifluoromethyl)indoles **57** was subsequently investigated (Scheme 10.20) [228]. Indoles [229–233] were prepared from **56** at nitrile (**57f**), and ester (**57j**), were obtained in lower yields, compared to those with electron-donating groups (**57b, g**), which was mainly due to the formation of desulfonylated side products. In particular, the nitrile-containing N-H indole product **57f** was isolated as the major product from the reaction [228].



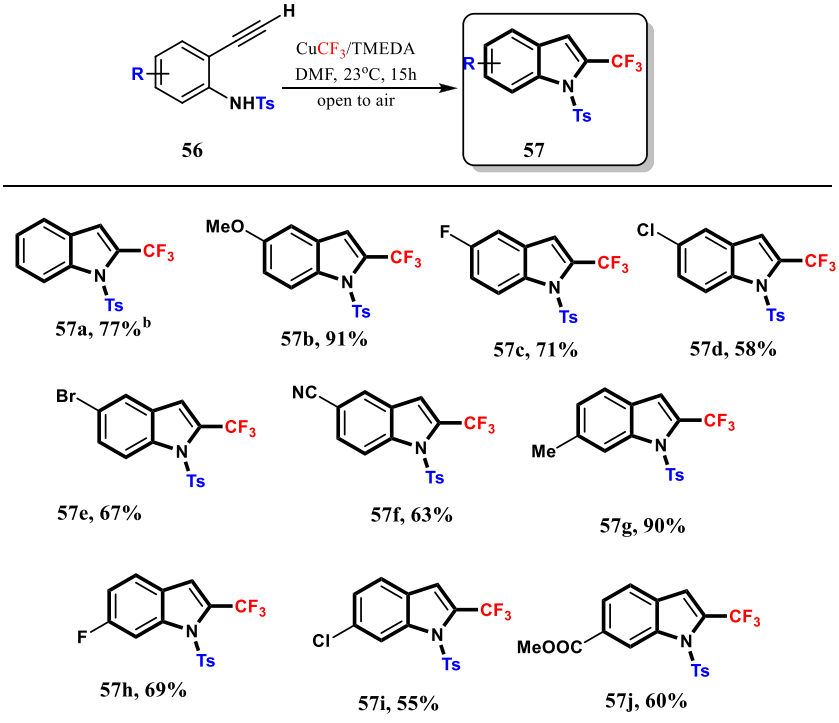
54 55

SCHEME 10.19 Rh (II) catalyzed reaction for the construction of 3,4-fused pyrroles.

10.2.1 Biological activities of *N*-sulfonated indoles

10.2.1.1 Antiparasitic effect

Table 10.1 illustrates the activity of *N*-sulfonated indole derivatives with a percentage growth inhibition above



[a]General conditions:**56** (0.2 mmol, 0.13 M in DMF), fluoroform-derived $CuCF_3$ (3.0 equiv), TMEDA (3.0 equiv), isolated yields. [b]1 mmol scale.

SCHEME 10.20 Synthesis of 2-(trifluoromethyl)-*N*-tosylindoles.

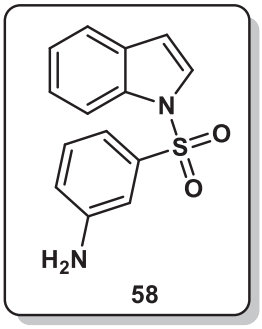


FIGURE 10.2 Structure of the antiparasitic *N*-sulfonated indole derivative **58**.

miscellaneous core structures that have an arylsulfonyl motif as a common structural feature [237]. All these reported antagonists share common pharmacophore features consisting of basic ionizable amine functionality, a sulfonamide or sulfone moiety as a hydrogen bond acceptor group connected to a hydrophobic site, and a *p*-electron donor aromatic or heterocyclic ring [238]. Examples of ligands matching this pharmacophore are Ms-245 (**59**) in addition to compound **60** which exhibit ($IC_{50} = 32$ nM) that was disclosed as a highly potent antagonist in a functional assay of calcium mobilization (Fig. 10.3) [239].

TABLE 10.1 Antiparasitic effect of compound 58.

Compound #	*L. donovani*		*T. cruzi*		*P. falciparum*		*T. b. rhodesiense*	
	0.8 μg/mL	4.8 μg/mL	0.8 μg/mL	4.8 μg/mL	0.8 μg/mL	4.8 μg/mL	0.8 μg/mL	4.8 μg/mL
58	15.9	95.4	36.4	100.0	14.7	79.2	0.0	4.3

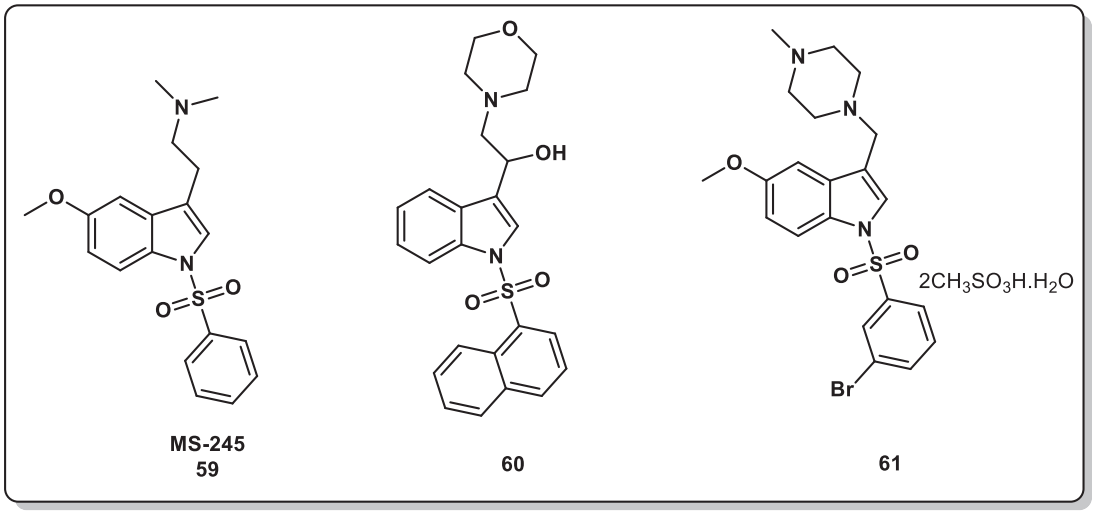


FIGURE 10.3 Structure of *N*-sulfonated indole derivatives **59**–**61** as potent 5-HT6-antagonist.

40% at 4.8 μg/mL. The antiparasitic potential of compound **58** was analyzed according to the hits-activity criteria outlined by WHO/TDR for each parasite (Fig. 10.2) [234]. 20 Based on the in vitro activity results, we observed that the presence of benzenesulfonyl moiety improves the antiparasitic profile against *Plasmodium falciparum*, *Trypanosoma cruzi* and *Leishmania donovani* [235].

10.2.1.2 5-HT6-antagonism

Among the most important structural classes of 5-HT6 receptor antagonists discovered a group comprises the indole and indole-like subclasses derived from the endogenous ligand 5-HT [236]. Other antagonists comprise

Optimization of a novel series of 3-(piperazinylmethyl) indole derivatives as 5-hydroxytryptamine-6 receptor ($5\text{-}HT_6R$) antagonists resulted in the identification of 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1*H*-indole dimesylate monohydrate (**61**, SUVN-502) as a clinical candidate for the potential treatment of cognitive disorders. It has high affinity at human $5\text{-}HT_6R$ ($K_i = 2.04$ nM) and selectivity over 100 target sites which include receptors, enzymes, peptides, growth factors, ion channels, steroids, immunological factors, second messengers, and prostaglandins. It has high selectivity over $5\text{-}HT_{2A}$ receptor. It is orally bioavailable and brain penetrant with robust preclinical efficacy. The combination of **61**, donepezil, and memantine (triple

combination) produces synergistic effects in extracellular levels of acetylcholine in the ventral hippocampus. Preclinical efficacy in triple combination and high selectivity over 5-HT_{2A} receptors are the differentiating features that culminated in the selection of **61** for further development [240].

10.2.1.3 Anti-apoptotic effect

Recently,1H-indole-2-carboxylic acid from the parental molecule was designed and synthesized, a benzenesulfonyl was substituted at the 1-position to adopt a geometry preferred for accessing the p1 pocket according to the binding mode of the parental molecule identified by X-ray crystallography. A linear relationship between the free energy of ligand binding (DG) and the count of non-hydrogen heavy atoms (HAC) was maintained during the molecular growing to occupy the p1 pocket. Finally, we not only obtained compound **62** with a 7.5-fold selectivity to Mcl-1 (Ki = 0.48 mM by fluorescence polarization) over Bcl-2 (Ki = 3.6 mM), but also provided evidence that additional occupation of the p1 pocket is more favorable for Mcl-1 than for Bcl-2 binding, and contributes more to Mcl-1 inhibition than the occupation of the p2 pocket (Fig. 10.4). Compound **62** exhibited a selective killing ability on Mcl-1-dependent cancer cells [241].

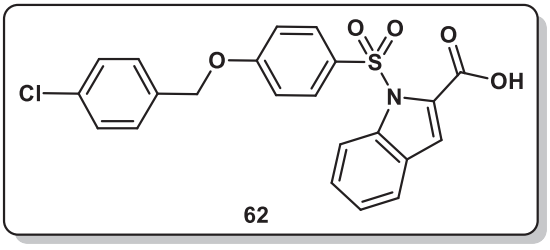


FIGURE 10.4 Structure of anti-apoptotic *N*-sulfonated indole derivative **62**.

10.2.1.4 Retinoic acid receptor-related orphan receptor γ (ROR γ) agonists

The nuclear retinoic acid receptor-related orphan receptor γ (ROR γ; NR1F3) is a key regulator of inflammatory gene programs involved in T helper 17 (TH17) cell proliferation. As such, synthetic small-molecule repressors (inverse agonists) targeting ROR γ have been extensively studied for their potential as therapeutic agents for various autoimmune diseases. Alternatively, enhancing TH17 cell proliferation through activation (agonism) of ROR γ may boost immune response, thereby offering a potential new approach in cancer immunotherapy. *N*-arylsulfonyl indolines such as **63** were developed as ROR γ agonists (Fig. 10.5). Structure-activity studies reveal a critical linker region in these molecules as the major determinant for agonism. Hydrogen/deuterium exchange coupled to mass spectrometry (HDX-Ms) analysis of ROR γ−ligand complexes help rationalize the observed results [242].

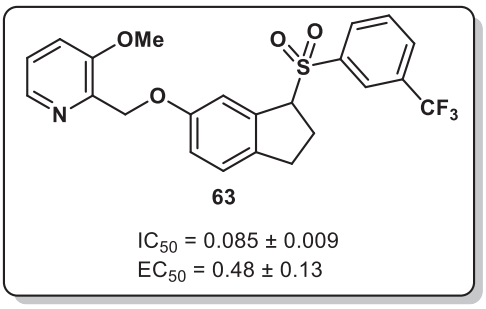


FIGURE 10.5 Structure of *N*-arylsulfonyl indoline **63** as ROR **y** agonists.

10.2.1.5 Antipsychotics activity

All clinically-used antipsychotics display a similar affinity for both D2 (D2R) and D3 (D3R) receptors, and they likewise act as 5-HT2AR antagonists. They provide therapeutic benefit for positive symptoms, but no marked or consistent improvement in neurocognitive, social cognitive, or negative symptoms. Since blockade of D3 and 5HT6 receptors enhance neurocognition and social cognition, and potentially improves negative symptoms, a promising approach for improved treatment for schizophrenia would be to develop drugs that preferentially act at D3R versus D2R and likewise recognize 5HT6R. Starting from the high affinity 5HT6R ligands **64**, compounds **65a** and **65b** that behave as 5HT6R ligands with significant selectivity for D3R over D2R (Fig. 10.6) [243].

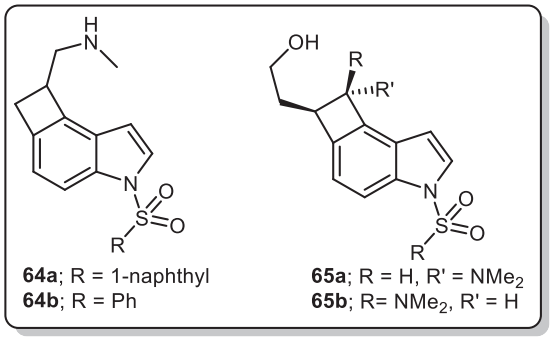


FIGURE 10.6 Structure of antipsychotic *N*-sulfonated indole derivative **64,65a,b**.

10.2.1.6 anti-HIV-1 activity

N-arylsulfonyl-3-propionylindoles **66a−c** were prepared and preliminarily evaluated as *in vitro* inhibitors of human immunodeficiency virus type-1 (HIV-1). These compounds exhibited potent anti-HIV-1 activity with effective concentration (EC_{50}) values of 0.8, 4.0, and 1.2 μg/mL, and therapeutic index (TI) values of 11.7, 16.6, and 84.1, respectively. *N*-(*m*-Nitro)phenylsulfonyl-3-propionyl-6-methylindole (**66c**) exhibited the most promising and best activity against HIV-1 replication (Fig. 10.7). The cytotoxicity of these compounds was assessed as well [244].

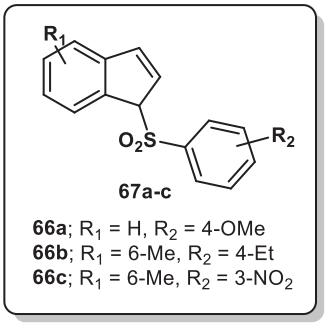


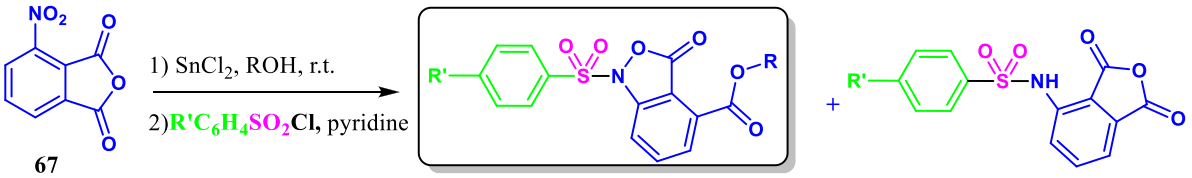
FIGURE 10.7 *N*-arylsulfonyl-3-propionylindoles **66a–c** as HIV-1 inhibitors.

10.3 Synthesis of *N*-sulfonyl benzoxazole

10.3.1 Synthesis of *N*-sulfonyl-1,2-benzoxazole

1,2-Benzisoxazoles and their derivatives show interesting pharmacological and biological activities [23–25]. One such example bearing a sulfonamide functionality is Zonisamide (benzo[d]isoxazol-3-ylmethanesulfonamide) which is used as an antiepileptic drug [26]. Along these lines, and searching for the synthesis of new 1-arylsulfonyl-1,3-dihydro-3-oxo-2,1-benzisoxazoles, which are useful for biological screening, we examined the reduction of 3-nitrophthalic anhydride **67** with $SnCl_2$ in different alcohols, followed by coupling of the obtained amines with various arylsulfonyl chlorides in pyridine [27]. However, in all cases, we isolated a mixture of the two sulfonamides **68** and **69** in good to excellent combined yields (57%–84%; Scheme 10.21). We are now investigating the experimental conditions in order to address the course of the reaction, essentially towards the form [25] ation of the most interesting compounds **68a–h** [27]. The structures of products **68** and **69** were determined from their ^{1}H NMR and ^{13}C NMR spectra and by Ms. The structure of **59d** was further confirmed by X-ray diffraction analysis [27].

A distinguished approach to 3-phosphorus oxindoles was successfully developed. The C = P bond of 3-phosphorus ylide oxindoles can be oxidized to a carbonyl group to provide isoxazolinones with excess *m*CPBA by overoxidation



Entry	R	R'	Yield of 68[a] (%)	Mp (°C)	Yield of 69[a] (%)	Mp (°C)
1	CH_3	CH_3	42 (68a)	75-77	38 (69a)	96-98
2	CH_3	CH_3O	46 (68b)	129-131	35 (69b)	114-116
3	CH_3CH_2	CH_3	40 (68c)	93-95	32 (69a)	96-98
4	CH_3CH_2	CH_3O	48 (68d)	122-124	36 (69b)	114-116
5	$CH_3(CH_2)_2$	CH_3	36 (68e)	44-46	26 (69a)	96-98
6	$CH_3(CH_2)_2$	CH_3O	50 (68f)	58-60	31 (69b)	114-116
7	$CH_3(CH_2)_3$	CH_3	38 (68g)	59-61	19 (69a)	96-98
8	$CH_3(CH_2)_3$	CH_3O	46 (68h)	80-82	30 (69b)	114-116

[a] Isolated yields over the two steps after separation by flash chromatography

SCHEME 10.21 Reduction of **67** in different alcohols and protection with arylsulfonyl chlorides in pyridine.

[20]. This methodology provides a distinguished protocol to the 3-phosphorus oxindole derivatives, isatins, and isoxazolinones through α(δ')-Michael addition and 6Π electrocyclization as key steps. Furthermore, overoxidation of oxindoles **61a–c** with excess *m*CPBA (10 equiv.) at −25°C gave isoxazolinones **71a–c** as the major products (50%–64%), respectively (Scheme 10.22). Compound **71a** was unambiguously characterized by its single crystal structure [20]. Isoxazolinones, normally synthesized by reduction of methyl ortho-nitrobenzoate with zinc and NH_4Cl [245] or photolysis of ortho-azidobenzoic acid [246], possess anticonvulsant, antimicrobial, and antileukemic activities [247].

Since cyclization proceeds through acid-catalyzed transesterification, long reaction times (24 h) are required to obtain moderate yields. However, we reasoned that the reaction kinetics could be improved by performing the ligation in neutral or slightly basic conditions. To evaluate this hypothesis, we synthesized ortho-nitroso benzoic esters (**72a–b**) and tested their reactivity with methane sulfinic acid (**73b**) in a solvent system containing pH 7.0 PBS buffer (50%; PBS = phosphate buffered saline) and CH_3CN (50%; Scheme 10.23) [28]. Interestingly, the methyl ester **72a** reacted with **73b**, but the intermediate species was not converted into the *N*-sulfonylbenzisoxazolone **74a** (Scheme 10.23, entry 1). Considering that the analogous result was obtained with ethyl ester **72b** (Scheme 10.23, entry 2), we speculated that low conversion reflects the relatively weak acidity of the sulfonyl hydroxylamine **78** (see Scheme 10.24). Thus, to increase the acidity of this group, a nitro substitutent was introduced on the phenyl ring (**72c**) [28]. Compound **72c** was converted in good yield into the sulfonyl adducts (Scheme 10.23, entries 3 and 4), consistent with our hypothesis. To improve solubility in water, while preserving reactivity, we then synthesized 2-nitroso terephthalic acid methyl ester (**72d**), in which the scaffold is elaborated with a carboxylic acid group. Compound **72d** showed excellent solubility under neutral pH conditions and robust reactivity toward a variety of sulfinic acids (Scheme 10.23, entries 5–7), as envisioned [28].

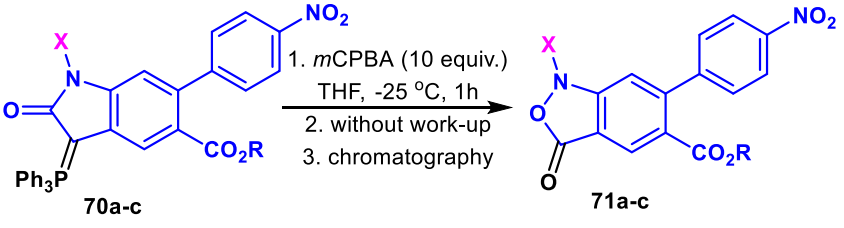
In order to explain the mechanism of Scheme 10.23, it was hypothesized that the deprotonated form of *N*-sulfonyl hydroxylamine is a potential nucleophile, which in the presence of an electrophilic center on the aromatic group could trap the oxyanion by intramolecular rearrangement. In support of this proposal, Moinet et al. [29,248] have described the intramolecular cyclization reaction of *N*-sulfonyl aromatic hydroxylamines with an ester group in the ortho position (e.g., **79**; Scheme 10.24) [29].

A simple and efficient method for the synthesis of benzoxazolidines from the reaction of sulfonamidoalcohol and vinyl acetate was reported. The Ni-catalyzed deacylation of vinyl acetate results in O-alkenylated intermediate, which subsequently undergoes intramolecular annulation to afford C2-alkylated benzoxazolidines [249].

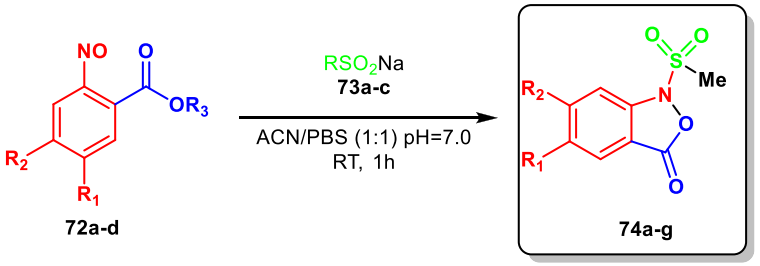
The work illustrates the condensation of 2-(tosylamino)phenol (**80a**) with acetaldehyde to form 2-methylbenzoxazolidine (**82a**) in the presence of PTSA (*p*toluenesulfonic acid) in toluene following a similar procedure reported by Waldvoge [250] for the preparation of acetal. Suitability of the optimized reaction condition was checked with the synthesis of varieties of 2-methylbenzoxazolidines. Notably, when differently substituted sulfamidophenols, including both electron-donating and -withdrawing groups were treated with vinyl acetate, substituted benzoxazolidines were produced in good yield. Functional groups such as Cl, Br, F, OMe, COMe, etc., to the aromatic ring of sulfonamide are compatible with the reaction conditions, and the desired 2-methylbenzoxazolidines (**82a–82q**) were obtained in appreciable yield (Scheme 10.25) [249].

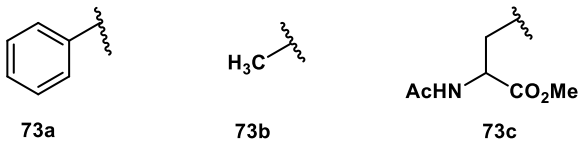
10.3.2 Synthesis of *N*-sulfonyl-1,3-benzoxazole

With the discovery and development of natural products-based agrochemicals, two series of 8/8′-alkylthiol-benzoxazole and *N*-alkyl/sulfonyl-benzoxazolone derivatives of honokiol were designed and synthesized (Scheme 10.26) [251]. Additionally, the pesticide activities of these compounds against *Mythimna separata* and *Plutella xylostella* (Diamondback moth) were investigated in vivo and structure-activity relationships (SARs) were also discussed. The growth inhibitory effects of the prepared compounds against pre-third-larvae of *M. separata* were preliminarily investigated using the leaf-dipping method at a concentration of 1 mg/mL [252,253]. Compounds **84a–e**, when the phenyl was



SCHEME 10.22 Synthesis of isoxazolinones **71a–c** from oxindoles **70a–c**.



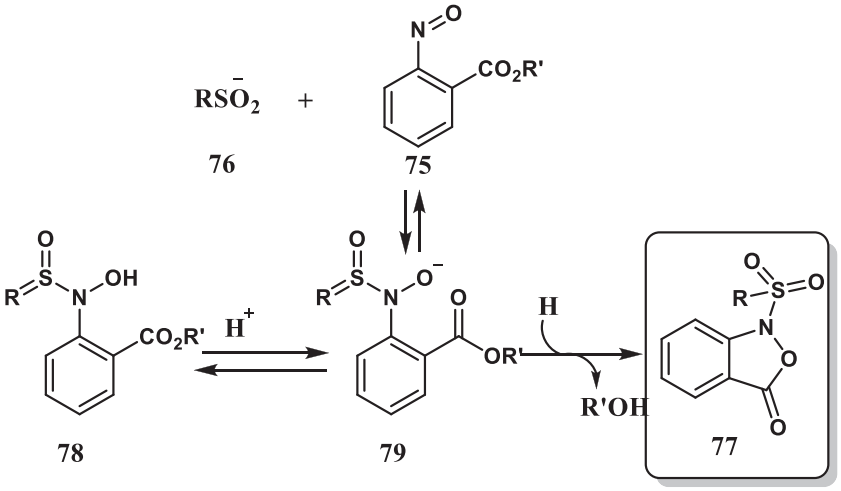


73a 73b 73c

Entry	compound #	R_1	R_2	R_3	RSO_2^-	Yield [%][a]
1	72a	H	H	Me	64b	- (74a)
2	72b	H	H	Et	64b	- (74b)
3	72c	NO_2	H	Me	64b	84 (74c)
4	72c	NO_2	CO_2H	Me	64a	88 (74d)
5	72d	H	CO_2H	Me	64b	84 (74e)
6	72d	H	CO_2H	Me	64a	89 (74f)
7	72d	H	CO_2H	Me	64c	81 (74g)

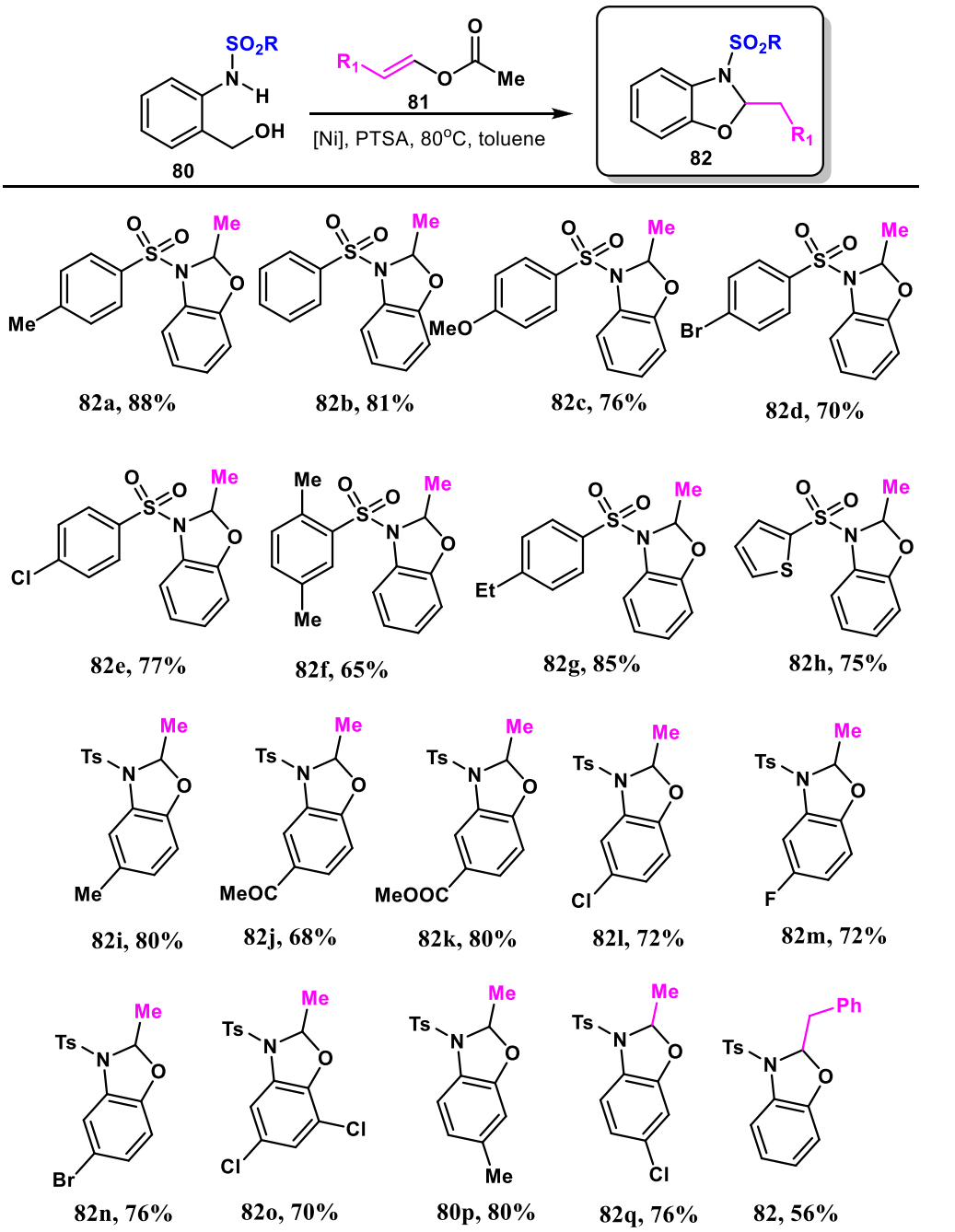
[a] Yields of isolated products after purification by silica gel chromatography.

SCHEME 10.23 Reactivity of 2-nitroso benzoic acid derivatives towards sulfinic acids.



SCHEME 10.24 Proposed mechanism of *N*-sulfonylbenzisoxazolone formation.

introduced in the *N*-position of compound **83**, the corresponding active compound **84** was obtained. In general, it can be found that the introduction of benzoxazole moiety would produce active compounds more likely than the introduction of benzoxazolone moiety in the honokiol, which was proved in this study [251].

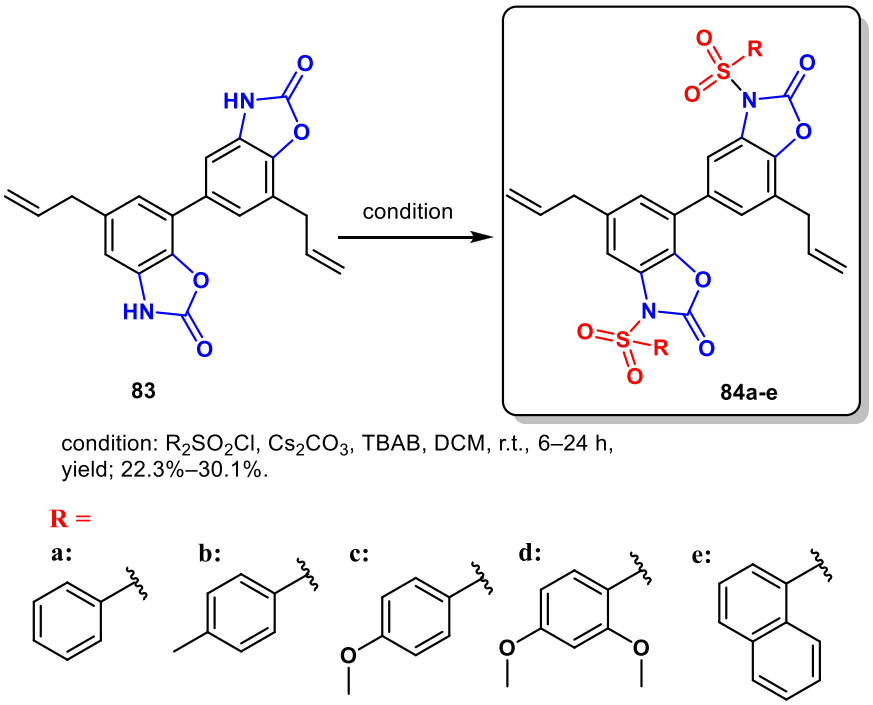


[a]Reaction conditions: 68 (0.38 mmol), 69 (1.14 mmol), $Ni(OAc)_2$ (30 mol%), PTSA (1.14 mmol), toluene (3 ml), 80°C, 5h.

SCHEME 10.25 Synthesis of 2-methyl-*N*-sulfonyl benzoxazolidines.

In addition, the larvicidal activity of the target compounds **84a–e** against third-instar larvae of *P. xylostella* was assessed according to a described method [254].

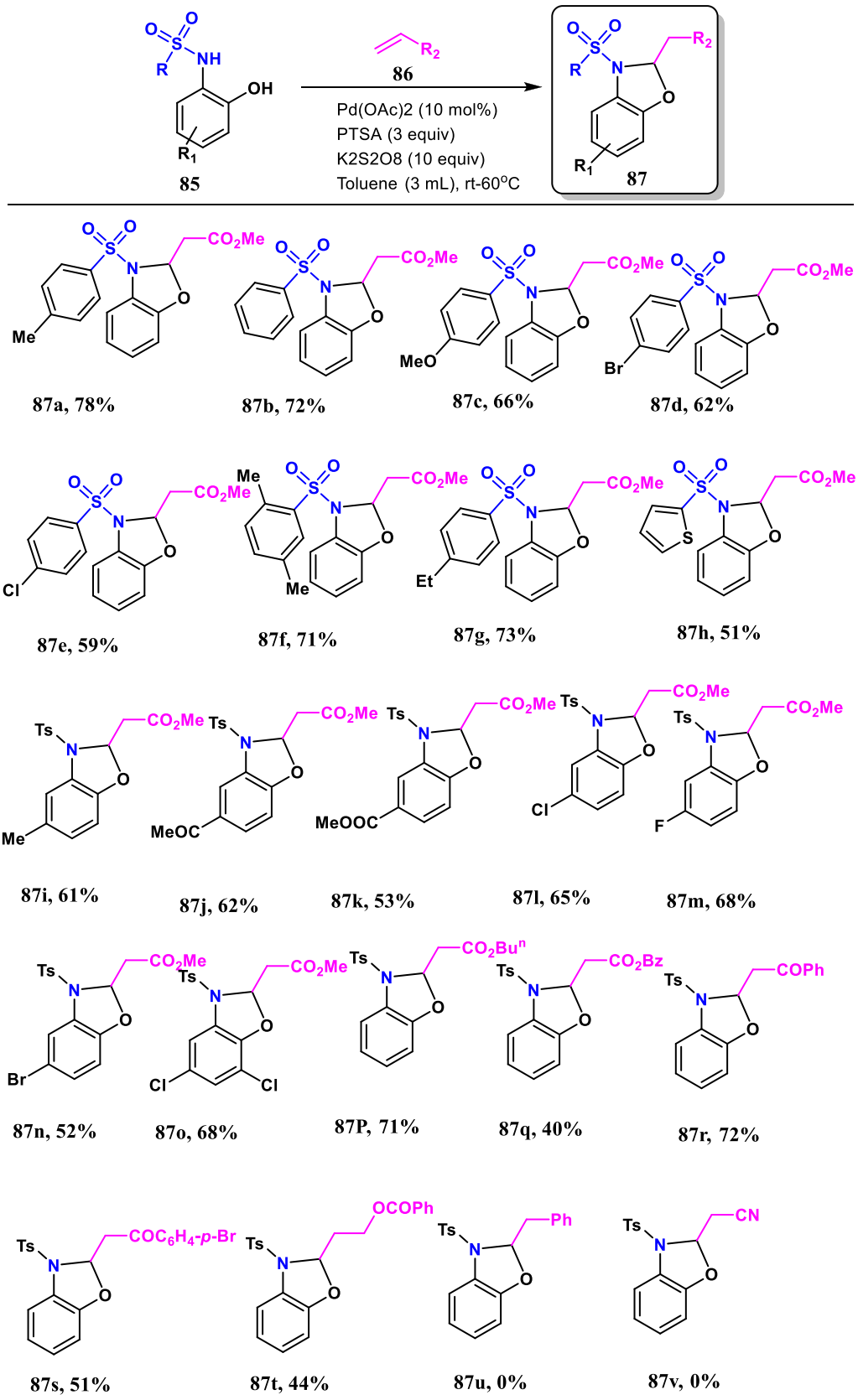
A novel palladium-catalyzed protocol for the synthesis of benzoxazolidine by the reaction sulfamidophenol and terminal alkene was developed [255]. This oxamidation process is simple and does not require any ligand, base, or inert atmosphere for the overall transformation [255]. From control experiments, it is apparent that the cross-coupling reaction proceeds with the initial formation of



SCHEME 10.26 Synthesis of substituted *N*-sulfonyl benzoxazolone derivatives **84a**−**e**.

enesulfonamide which undergoes nucleopalladation by the intramolecular annulation and subsequent protodepalladation by TsOH to afford the benzoxazolidine the oxamidation of an electron deficient olefin i.e., methyl acrylate (**86**) by sulfamidophenol (**85**) in the presence of $Pd(CH_3CN)Cl_2$ catalyst by following a similar procedure reported by Lloyd-Jones and Booker-Milburn [256] for the synthesis of oxazolidine. It examined the generality of the protocol for the synthesis of varieties of benzoxazolidines (Scheme 10.27). Thus, when differently substituted sulfonamides including both donating and withdrawing groups were treated with methyl acrylate, the functional groups were well tolerated and the substituted benzoxazolidines were produced in good yield. Noteworthy that the sulfonamides with halogen substituents, such as chloride, bromide, and fluoride are suitable substrates to produce the corresponding benzoxazolidines in appreciable yields, enabling them as potential substrates for further functionalization (**87d, 87e, 87l, 87m, 87n** and **87o**). Sulfonamides with electron-withdrawing groups having a carbonyl group such as −COMe, $-CO_2Me$ were compatible to produce benzoxazolidines in competent yield. It may be noted that when *N*-(2-hydroxyphenyl) benzamide was treated with **86**, the corresponding benzoxazolidine was not detected; a rather 2-phenyl benzoxazole was produced. The suitability of this protocol with various olefins was also tested. For instance, when terminal olefins with electron-withdrawing groups ($R_2 = CO_2Me$, CO_2Bu, CO_2CH_2Ph, COAr) were employed to react with the sulfonamide **85**, the desired oxazolidines (**87a**−**87s**) were obtained in appreciable yield. Allyl benzoates were also produced the corresponding benzoxazolidine (**87t**) in 44% yield, whereas a similar reaction with styrene failed. This may be due to polymerization of styrene [257] in the presence of persulfate. Acrylonitrile was found to be unreactive, probably due to poor coordination of Pd-catalyst with acrylonitrile. Internal olefins were also observed to be inert to this reaction condition with the recovery of 1aa. Notably, this oxamidation method to access benzoxazolidine in gram scale (3.8 mmol) was found to be successful to afford **87a** in 77% yield; which is consistent yield with the small-scale trial. This effort, in turn, establishes the preparative utility of this method.

An unprecedented simple pyrrolidine catalyzed [4 + 1] annulation reaction of ynals with *N* protected-2-aminophenols is reported. The utilization of the unique property and reactivity of the C≡C triple bond in ynals leads to two consecutive conjugate addition reactions at the same β position with pyrrolidine via iminium activation [258]. The powerful cascade process affords a new alternative approach to biologically and synthetically important benzoxazoles in high yields (83%−95%). capitalizing on reversible iminium-enamine catalysis, many synthetically efficient catalytic cascade processes have been developed for the facile construction of complex molecular architectures [259]. Notably, various cyclic ring structures ranging from 3 to 7 membered sizes have been constructed [260]. Despite these impressive achievements, to the best of our knowledge, there currently exists no amine catalyzed [4 + 1] annulation reaction to produce



SCHEME 10.27 Oxamidation of alkene. [a]Reaction condition: sulfonamide **85** (0.19 mmol), alkene **86** (0.57 mmol.), $Pd(OAc)_2$(10 mol.%), $K_2S_2O_8$, TsOH (0.57 mmol), toluene (3 mL), 60°C, 16 h. [b]Reaction was carried out at rt for 16 h.

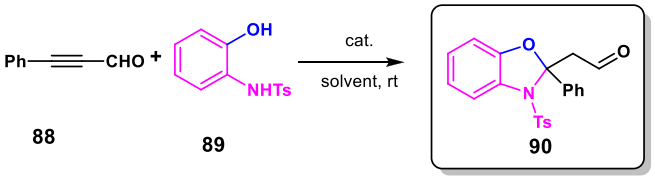
five-membered rings [261–263]. Thus, the identification of an amine catalyzed [4 + 1] annulation that is general and operationally simple remains a prominent and challenging goal. Toward this end, herein we wish to report a catalytic platform for [4 + 1] annulation. Notably, the process involving an unprecedented conjugate addition_protonation_conjugate addition cascade sequence is catalyzed by simple pyrrolidine using readily available *N*-tosyl-2-aminophenols and ynals as reactants under mild reaction conditions to give synthetically and biologically valuable benzoxazoles in high yield.

Amine catalyzed 1,3-dipolar cycloaddition reactions for the formation of five-membered rings have been subjected to intensive studies [264]. In these approaches, R,β-unsaturated aldehydes are generally used as essential substrates through iminium activation with an amine promoter to react with 1,3-dipolar components such as nitrones [265] and azomethine ylides [266] in a concerted or iminium-enamine stepwise process. In contrast, the otherwise inaccessible modality, [4 + 1] annulation, offers an alternative versatile route to five-membered scaffolds because of their ready availability of starting materials. Nevertheless, a survey of the literature reveals that only a handful of organocatalyzed [4 + 1] annulation reactions are reported. Elegant examples include Kwon's phosphine promoted6 and Xiao's sulfur ylide [262] [4 + 1] annulations. proposed a new amine catalyzed [4 + 1] cyclization reaction (Scheme 10.28). Given the importance of benzoxazoles in synthesis and pharmaceuticals. It was devised the binucleophilic *N*-tosyl-2-aminophenol substrates (2) for the proposed [4 + 1] annulation reaction with ynals **88**. To test the validity of the proposed organocatalytic [4 + 1] annulation process, we probed a model reaction of ynal **88** with *N*-tosyl-2-aminophenol (**89**) in the presence of simple pyrrolidine (20 mol.%) as a promoter, which can readily engage in iminium formation with aldehyde functionality in ynal **88** (Scheme 10.28). For a more delightful illustration, pyrrolidine readily affects the [4 + 1] annulation reaction. The reaction proceeded smoothly to afford the desired benzoxazole **90** in 5 min in good yield (75%, entry 1). Furthermore, under the reaction conditions, we did not observe the condensation product between aldehyde **88** and *N*-tosyl-2-aminophenol (**89**). It is believed that under mild nonacidic conditions it is difficult to form the product, whose formation requires an acid promoter. In addition, it appears that the second conjugate addition reaction went smoothly. This may be due to the intramolecular process. With pyrrolidine as the catalyst, we examined the solvent effect on the process (entries 2–5). Dichloroethane (DCE) was identified as the optimal reaction medium for the reaction (entry 5). In this instance, the reaction was accomplished in 5 min to produce product **90** in 84% yield. Furthermore, notably, lowering the catalyst loading to 5 mol.% gave an even higher yield (93%) despite prolonging the reaction time (15 h) (entry 6). The increase in the yield could be explained by the minimization of the undesired aldol reaction between product **90** and reactant **88**, which was observed with a 20 mol.% catalyst loading. Importantly, no product was observed when a background reaction was carried out without any catalyst (entry 7) [258].

10.4 Synthesis of *N*-sulfonyl benzothiazoles

10.4.1 Synthesis of *N*-sulfonyl-1,2-benzothiazoles

1,8-Saphthosultam, the nitrogen analog of *N*-phenylsulfonyl-1,8-naphthosultam, and its *N*-methyl derivative condense with acyl-, aroyl- and arylsulfonyl chlorides in the presence of



entry	cat. (mol%)	solvent	*t*	% yield[b]
1	pyrrolidine (20)	CH_2Cl_2	5 min	75
2	pyrrolidine (20)	$CHCl_3$	5 min	73
3	pyrrolidine (20)	CH_3CN	5 min	69
4	pyrrolidine (20)	toluene	5 min	61
5	pyrrolidine (20)	$Cl(CH_2)_2Cl$	5 min	84
6	pyrrolidine (20)	$Cl(CH_2)_2Cl$	15h	93
7	none	CH_2Cl_2	1h	0
8	TEA	CH_2Cl_2	1h	0

[a]Reactions were carried out with **88** (0.1 mmol) and **89** (0.11 mmol) at rt in 0.2 mL of solvent. [b] Isolated yields

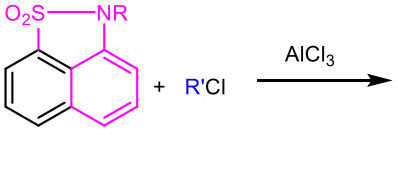
SCHEME 10.28 Optimization of Amine Catalyzed [4 + 1] Annulations.

aluminum chloride to give good yields of 4-acylated products. *N*-Acylated 1,8-naphthosultam derivatives (**91c,d**) undergo migration of the acyl group under the influence of aluminum chloride to give the corresponding 4-acyl derivatives (**92a,b**) [267]. Similar migrations of the arylsulfonyl groups also have been observed with *N,N*-di-(*p*-toluenesulfonyl)-aniline and N-arylsulfonyl-1,8-naphthosultam derivatives (**91e,f**). *N*-Phenylsulfonyl-1,8-naphthosultam (**91e**) undergoes thermal migration of the phenylsulfonyl group when refluxed with nitrobenzene or aniline. When **91e** is refluxed with aniline, **91a** and benzenesulfonanilide are isolated besides **80d** (Scheme 10.29) have investigated the behavior of 1,8-naphthosultam (**91a**). Thus, when **91a** is treated with acetyl, benzoyl, p-nitrobenzoyl, benzenesulfonyl, and *p*-toluenesulfonyl chlorides under the same experimental conditions described for the acylation of 1-naphthol-8-sulfonic acid sultone, the corresponding 4-acyl-, 4-aroyl- and 4-arylsulfonyl derivatives of 1,s-naphthosultam (**92a−e**) are obtained in good yields. Similarly, *N*-methyl-1,8-naphthosultam (**91b**) leads to the formation of the corresponding 4-acylated products (**92f−l**). Although substitution may occur in more than one way, only one product was isolated. Fractional crystallization of the crude reaction product failed to reveal the presence of any other isomer. The structure of the reaction products was not rigorously proved. It seemed probable, by analogy with the behavior of 1-naphthol-8-sulfonic acid sultone and a-naphthyl ethers [268], that the acyl group in **92** occupied the 4-position of the nucleus more preferably than the 2-position. When *N*-phenylsulfonyl-1,8-naphthosultam (**91e**) is allowed to undergo the Friedel-Crafts acylation reaction, the phenylsulfonyl group is eliminated and the corresponding 4-acyl derivatives are obtained. The production of 4-acyl derivatives, not contaminated with 4-phenylsulfonyl-1,8-naphthosultam (**92d**), is unusual in that **91e** is isomerized into **92d** by treatment with aluminum chloride. Thus, when **91e** is allowed to react with acetyl, benzoyl and *p*-toluenesulfonyl chlorides, **92a**, **92b**, and **92e** are obtained, respectively. The formation of **92d**, on the treatment of **91e** with benzenesulfonyl chloride in presence of aluminum chloride, also may be attributed to the isomerization of the phenylsulfonyl group [267].

Chloromethylation.-Recently, it has been shown [269] 2 that 1,8-naphthosultone condenses with paraformaldehyde and hydrogen chloride in the presence of anhydrous zinc chloride to form 4-chloromethyl-1-naphthol-8-sulfonic acid sultone *N*-Arylsulfonyl derivatives of 1,8-naphthosultam (**93a,b**) undergo chloromethylation to yield the corresponding 4-chloromethyl derivatives (**94a,b**), together with **95** in the case of **94a**. **94a** is readily reduced to 4-methyl-*N*-phenylsulfonyl-l,8- naphthosultam [270].

When an acetic acid solution of *N*-phenylsulfonyl-l,8-naphthosultam (**93a**) is treated with paraformaldehyde, hydrogen chloride and zinc chloride under the same experimental conditions for the chloromethylation of 1,8-naphthosultone, 4-chloromethyl-*N*-phenylsulfonyl-1,8-naphthosultam (**94a**), is obtained together with a high melting substance which analyzes correctly for a compound like **95**. Similarly, 4-chloromethyl-*N*-(*p*-tolylsulfonyl)-l,8-naphthosultam (**94b**) is obtained from *N*-(*p*-tolylsulfonyl)-1,8-naphthosultam (**94b**) (Scheme 10.30). Although substitution may occur in more than one way, only one product was isolated. Fractional crystallization of the crude reaction product failed to reveal the presence of any other isomer [270].

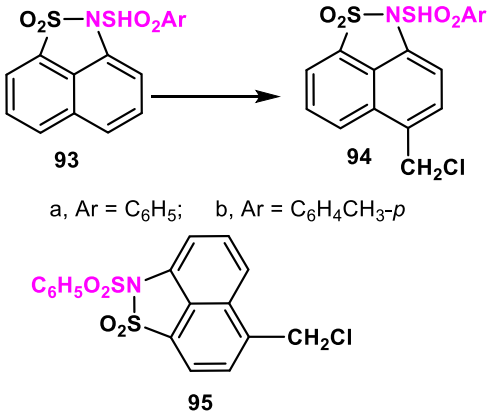
It seemed probable, by analogy with the behavior of 1,8-naphthosultone and with α-naphthyl ether [271] 3,5 that the chloromethyl group in **94** occupied the 4-position of the nucleus in preference to the %position. **94a,b** are valuable intermediates for the production of 4-substituted derivatives of 1,8-naphthosultam. Thus, when **94a** is treated with zinc dust and acetic acid, it is reduced readily to 4-methyl-*N*-phenylsulfonyl-1,8-naphthosultam [270].



91 a, R = H
b, R = CH_3
c, R = $COCH_3$
d, R = COC_6H_5
e, R = $SO_2C_6H_5$
f, R = $SO_2C_6H_4CH_3$-*p*
g, R = $COC_6H_4NO_2$-*p*

92 a, R = H, R' = $COCH_3$
b, R = H, R' = COC_6H_5
c, R = H, R' = $COC_6H_4NO_2$-*p*
d, R = H , R' = $SO_2C_6H_5$
e, R = H , R' = $SO_2C_6H_4CH_3$-*p*
f, R = CH_3, R' = $COCH_3$
g, R = CH_3, R' = COC_6H_5
h, R = CH_3 , R' = $COC_6H_4NO_2$-*p*
i, R = CH_3 , R' = COC_6H_4Cl-*p*
j, R = CH_3 , R' = $SO_2C_6H_5$
k, R = CH_3 , R' = $SO_2C_6H_4CH_3$-*p*
l, R = CH_3, R' = $COCH_2CH_2COOH$

SCHEME 10.29 Friedel-crafts reactions of 1,8-naphthosultam and its derivatives.



SCHEME 10.30 Synthesis of *N*-arylsulfonyl-l,8-naphthosultam derivatives **94a,b** and **95**.

10.4.2 Synthesis of *N*-sulfonyl-1,3-benzothiazoles

Commercially available and preparative ZnO nanoparticles are reported as efficient and reusable catalysts for the chemoselective synthesis of *N*-acylsulfonamides and sulfonate esters. A one-pot sequential sulfonylation and acylation of amines took place to afford the *N*-acylsulfonamides in excellent yields under solvent-free conditions. The ZnO catalyst can be reused without significant loss of catalytic activity [272].

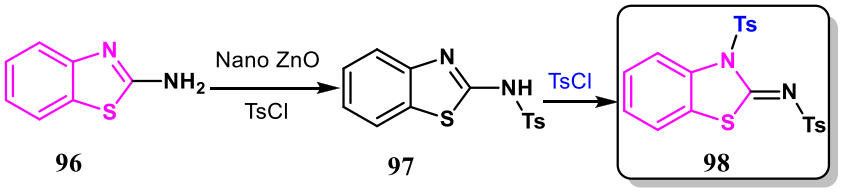
Sulfonylation and acylation of heteroatoms are valuable transformations that resulted in the imide, sulfonimide, amide, sulfonamide, ester, and sulfonate ester moieties as building blocks of important biologically active and polyfunctional molecules [4]. Sulfonate esters are well-known alkylating agents and cell proliferation inhibitors [6], while sulfonamide derivatives are clinically used as antibacterial and antibiotic medicines [7]. Moreover, a number of enzyme inhibitors [8], new therapeutic agents for Alzheimer's disease [9], and hepatitis C virus NS protease inhibitors [10] are derived from *N*-acylsulfonamides.

As a result of the wide range of activity and importance, there are several available procedures for the preparation of these compounds. *N*-acylsulfonamides can be prepared by either base-catalyzed acylation of sulfonamides [8] or sulfonylation of amides [273]. Due to the less nucleophilicity of amide nitrogen and sensitivity of imide bond, acylation of sulfonamides is often preferred to sulfonylation of amides. Similarly, sulfonate esters and sulfonamides have been prepared through the sulfonylation of alcohols and amines [274] in the presence of basic catalysts like pyridine, triethylamine, and aqueous metal hydroxides. Some of these reactions are together with the formation of undesired side products, use of toxic or corrosive reagents, and tedious processes for purification of products. A good option of catalyst is able to enhance the rate of sulfonylation and acylation reactions via dual activation of S = O, C = O and NH groups. Therefore, searching for one-pot catalytic procedures with fewer reaction steps is still of interest.

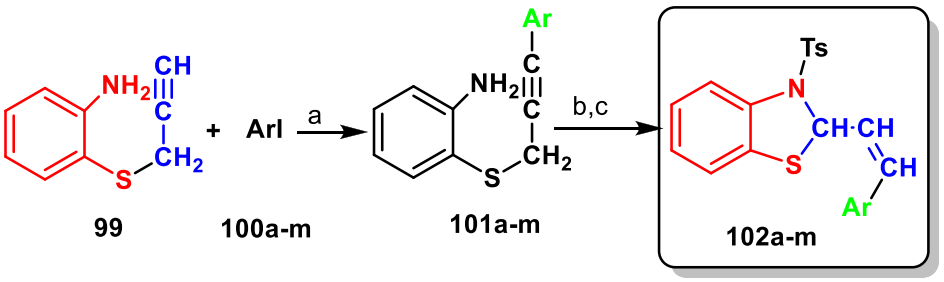
In order to test two consequent sulfonylation of amines. Thus, tosylation of 2-amino-benzothiazol **96** and subsequent tosylation of the product at the optimized reaction conditions were attempted in the presence of nano ZnO **97** and (*E*)-,3-ditosylbenzo[*d*]thiazol-2(3*H*)-imine **98** was obtained in excellent yield (Scheme 10.31).

A highly novel, general, and convenient palladium and the copper-catalyzed procedure has been developed for the synthesis of (*E*)-2-(2-arylvinyl)-3-tosyl-2,3-dihydro-1,3-benzothiazoles **102a**−**m**. 3-(2-Aminophenylthio)prop-1-yne **99** reacts with aryl iodides **100a**−**m** under palladium-copper catalysis to yield the disubstituted alkynes **101a**−**m** which after tosylation undergo a novel cyclization with CuI in the presence of triethylamine in THF to (*E*)-2-(2-arylvinyl)-3-tosyl-2,3-dihydro-1,3-benzothiazoles **102a**−**m** [275]. The reaction is highly regio- and stereoselective. recently it has adopted palladium-catalyzed reactions of terminal alkynes and aryl halides [276] with a nucleophilic group in the ortho position for the syntheses of a number of benzo fused heterocyclic structures with one heteroatom only, for example, benzofurans [277], phthalides [278], quinolines and quinolones [279], isoindolinones [280], and flavones and flavanones [281]. In an alternative strategy, it has utilized the reactions of mono-prop-2-ynyloxy or mono-prop-2-ynylamino aromatic compounds with a nucleophilic group (OH, NH-Ts, CO2H) in the ortho-position and aryl halides under palladium copper-catalyzed conditions for the synthesis of benzofused heterocyclic structures with two heteroatoms, for example, 1,4-benzodioxans [282], 1,4-benzoxazines [283], 1,4-benzodioxepinones, and 4,1-benzoxazepinones. [284]. In an extension of this reaction, it was recently reacted 3-(2-aminophenylthio)- prop-1-yne **99** with aryl iodides **100a**−**m** under palladium copper catalysis to get the disubstituted alkynes **101a**−**m** which, after tosylation, surprisingly cyclized to 2-substituted benzothiazolines **102a**−**m** (Scheme 10.32) [285].

Mechanistically, the formation of benzothiazolines involves the following steps (as shown in Scheme 10.33) [285]: (1) formation of ArPdX [B] through oxidative



SCHEME 10.31 Tosylation of 2-amino-benzothiazol and further tosylation of the product.

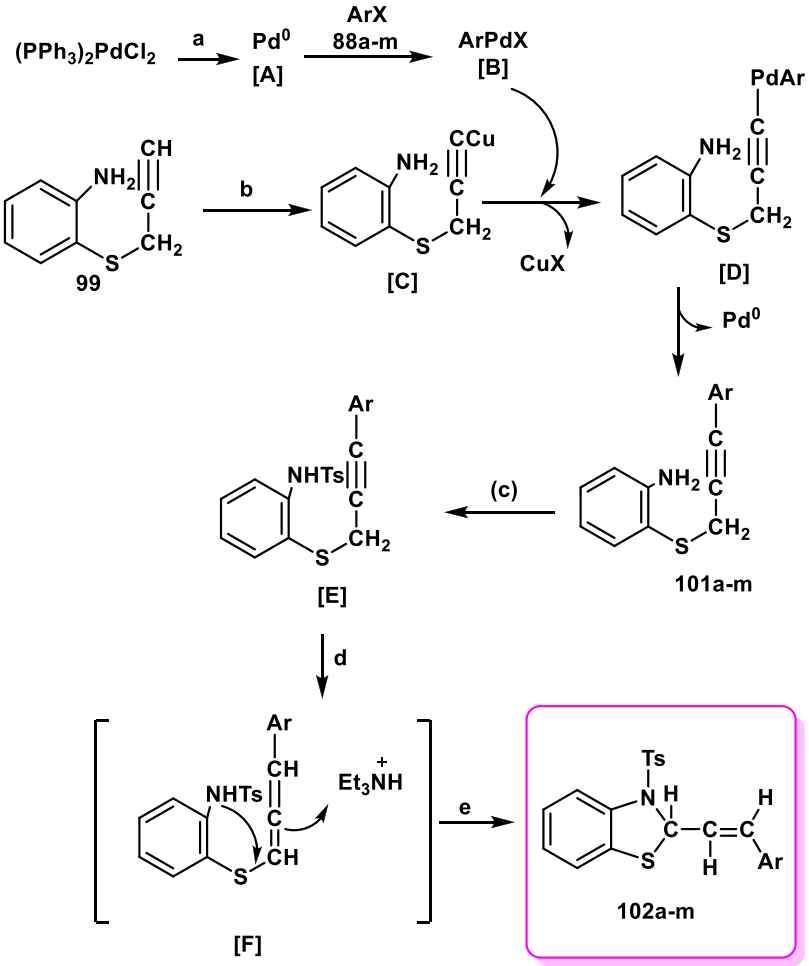


[a] Reaction conditions: (a) $(PPh_3)_2PdCl_2$ (3 mol %), CuI (6 mol %), Et_3N, CH_3CN, rt, 24 h; (b) p-TsCl, py, CH_2Cl_2, rt, 10 h; (c) CuI (40 mol %), Et_3N, THF, reflux, 36 h.

entry	100a-m	101a-m (yield%)*b*	102a-m (yield%)[c]
1	88a (C_6H_5)	89a (73)	90a (67)
2	88b (1-napphthyl)	89b (68)	90b (63)
3	88c (2-naphthyl)	89c (76)	90c (74)
4	88d (3-ClC_6H_4)	89d (78)	90d (76)
5	88e (2-MeC_6H_4)	89e (77)	90e (69)
6	88f (4-MeC_6H_4)	89f (76)	90f (80)
7	88g (4-MeOC_6H_4)	89g (69)	90g (66)
8	88h (2-MeOCOC_6H_4)	89h (80)	90h (70)
9	88i (2-thienyl)	89i (71)	90i (75)
10	88j(2,4-dimethoxy-pyrimidin-5-yl)	89j (73)	90j (80)
11	88k (5-iodo-2-thienyl)	89k (59)	90k (76)
12	88l (3-iodophenyl)	89l (57)	90l (63)
13	88m (4-iodophenyl)	89m (56)	90m (77)

[a] In all cases, $(PPh_3)_2PdCl_2$ (3 mol %) and CuI (6 mol %) were used. [b] Yields are based on 1. [c] Yields are based on tosylates of the disubstituted alkynes.

SCHEME 10.32 Synthesis of (*E*)-2-(2-Arylvinyl)-3-tosyl-2,3-dihydro-1,3-benzothiazoles[a].



a Reagents and conditions: (a) reduction of PdII to Pd_0 with alkynes and Et_3N; (b) CuI, Et_3N; (c) tosylation with p-TsCl-py; (d) isomerization to an allene with CuI, Et_3N; (e) nucleophilic attack on the allene (F) to generate the *N*-tosyl-2-styrylbenzothiazolines (90a-m).

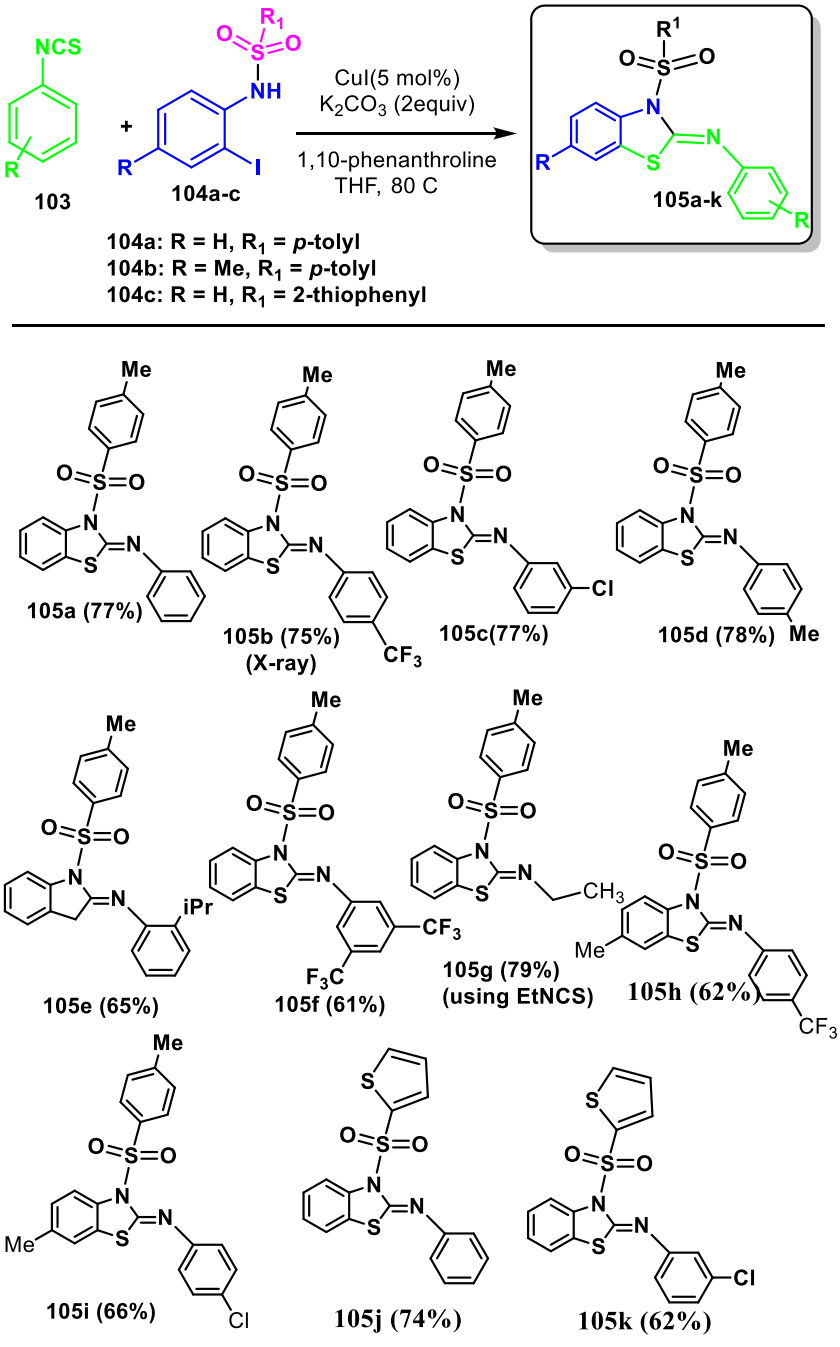
SCHEME 10.33 Plausible mechanism for the formation of 2-styrylbenzothiazolines[a].

addition of Pd^0 [A] (generated from Pd^{II}) to ArX,14 (2) transmetalation of ArPdX with the Cu salt of **99** generating the alkynyl palladium species [D], (3) extrusion of Pd^0 to yield the disubstituted alkynes **101a−m**, (4) tosylation of the free amine to [E], and (5) isomerization to the allenic intermediates [286] [F] which then cyclize to the (*E*)-2-styrylbenzothiazolines **102a−m**. In conclusion, it has been described as a palladium-copper catalyzed reaction of 3-(2-aminophenylthio)prop-1-yne with a terminal acetylenic moiety with readily available aryl iodides. This has resulted in the formation of a number of disubstituted alkynes which under copper catalysis underwent an interesting rearrangement and subsequent cyclization to (*E*)-2-substituted benzothiazolines.

Only five-membered heteroannulation took place when the styryl group at *C*-2 was in the *E*-configuration. No six-membered heteroannulated compounds were observed. It was believed this is the first reported palladium-copper-catalyzed general procedure for the synthesis of various 2-substituted benzothiazolines. Also since benzothiazolines have profound biological activities [287], it was believed that this method will be of interest to many synthetic organic and medicinal chemists as a new general method for the synthesis of 2-substituted benzothiazolines.

The use of heterocumulenes is known to generate many useful heterocycles that are relevant to this study. Thus for the synthesis of pyrimido[1,2-*c*][1,3]benzothiazin-6-imines [288], Ohno's group utilized a base-catalyzed

reaction of 2-(2-haloaryl)tetrahydropyrimidines with heterocumulenes such as access to functionalized benzosultams by copper-catalyzed one pot cyclization of substituted sulfonamides Specifically, it is better to highlight the following: (1) While the $C = S$ moiety forms a part of the sultam ring in the reaction with isothiocyanates, the $N = C$ moiety becomes a part of the sultam ring in the case of isocyanates, reflecting the differing nucleophilicity of the N, S and O centers [288]. Although earlier reports have mentioned the differences between isothio2cyanates/isocyanates [289,290], this method offers two types of cyclization under the same conditions yielding different types of products. (2) The reaction can be extended to 2-iodo-benzyl sulfonamides and *N*-tosyl-2-iodo-anilines leading to six- and five-membered ring sultams. It applied the above annulation approach to 2-iodo-*N*-tosyl system and to this delight, obtained benzo[d]thiazol-2(3*H*)-ylidene-anilines in good to excellent yields. As illustrated in Scheme 10.34, all the reactions tested worked smoothly and the annulation products (**105a–k**) were obtained in moderate to good yields (up to 79%). Aryl isothiocyanates bearing electron-donating (Me, isopropyl; cf. **105d–e**) as



SCHEME 10.34 Substrate scope for [Cu]-catalyzed annulation reaction of *N*-(2-iodophenyl)-4-methylbenzene sulfonamide with isothiocyanates.

well as electron-withdrawing (CF_3, Cl) (**105b,c, 105f**) substituents showed good compatibility. An alkyl isothiocyanate also worked well (e.g., **105g**). Electron donating (methyl) group on sulfonamides also worked well to yield annulated products (**105h−i**) in good yield. Even heterocyclic sulfonyl moiety in place of tosyl furnished the desired products (**105j−k**) in good yields. The reaction using isocyanates, though, did not work. The structure of **105b** was further confirmed by single-crystal X-ray analysis [288].

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Chapter 11

N-Sulfonated *N*-benzodiazoles and *N*-benzotriazoles: Synthesis and medicinal activity

11.1 Introduction

Benzimidazoles containing sulfonamide moieties have been shown to display significant biological properties such as antibacterial [1], antifungal [2], antitubercular [2], antiinflammatory [3], and analgesic activities [4] Therefore, we decided to devote our further attention to the exploration of their sulfonylating transformation [5].

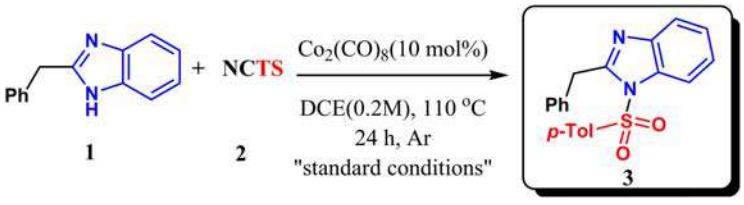
Owing to their diverse biological activity and clinical applications [6,7], benzimidazole derivatives are the potential candidates for a diverse set of biological activities including antiamoebic [8], anti-HIV [6] antiulcer [8,9], and antihypertensive [10,11]. One subset of such compounds is 1,2-disubstituted benzimidazole derivatives, such as 5-nitrobenzimidazoles [12] that exhibit antitumor activity against melanoma and breast cancer [10], telmisartan that acts as AT1 receptor antagonists and tentative angiotensin receptor blocker therapeutic for COVID-19 [13], and bendamustine that acts as an antileukemia agent [14]. The observed activity depends upon the functional group attached to the moiety. To obtain novel effective chemotherapeutic agents, more synthetic methods and routes have been required.

Moreover, *N*-sulfonylbenzotriazoles are important intermediates in organic synthesis. As advantageous sulfonylation reagents, they can react smoothly with amines and phenols to afford the corresponding sulfonamides and sulfonates, respectively [15]. They also easily convert carboxylic acids into *N*-acylbenzotriazoles, which are especially useful when the corresponding acid chlorides are difficult to obtain [15–17]. They have wide applicability in *C*-sulfonylation and a series of -cyanoalkyl sulfones, sulfonylheteroaromatics, -(sulfonylalkyl)heterocycles, -sulfonylalkyl sulfones, and esters of -sulfonyl acids have been prepared in excellent yields [18]. As stabilizers, *N*-sulfonylbenzotriazoles are often used in manufacturing photosensitive materials [19]. They are also useful as herbicides, mutagens, insecticides, fungicides, and antibacterials [5,20].

11.2 *N*-Sulfonyl benzimidazole

11.2.1 Synthesis of *N*- sulfonyl benzimidazole

Air- and bench-stable *N*-cyano-*N*-phenyl arenesulfonamides (NCASs) have been demonstrated to be sulfonylating agents for the synthesis of *N*-arylsulfonyl benzimidazoles catalyzed by dicobalt octacarbony, $Co_2(CO)_8$, without any bases. This protocol undergoes an intermolecular *N*- to *N*-arylsulfonyl transfer process involving the S–N bond cleavage of NCASs instead of normal CN group migration *via* the C–N bond scission. Investigation of the directed C–H cyanation of 2-benzylbenzimidazoles using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as an electrophilic $^{+}$CN source, accessing a diverse range of 2-((benzimidazole-2-yl)methyl)-benzonitriles. Thus, the typical combination of Cp*Rh (5 mol%), NaOAc (30 mol%), and $AgSbF_6$ (20 mol%) was tried to attempt this reaction (Scheme 11.1, entry 1). However, only 15% of a new product was isolated without other by-products being detected. The NMR and HRMS spectra clarified that this new



SCHEME 11.1 Optimization of the sulfonyl transfer from *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide **2** to benzimidazole **1**.

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00003-3

product did not contain a cyano moiety but probably a tosyl fragment. This result indicated that NCTS serves as a sulfonylating reagent *via* the S-N bond cleavage to enable the *N*-sulfonylation of benzimidazoles, which involves an intermolecular *N*- to *N*-sulfonyl transfer process instead of the cyano migration. When the Cp*Rh (5 mol%) system was used in the absence of either NaOAc or $AgSbF_6$, the product yield was improved to 21% and 28%, respectively (Scheme 11.1, entries 4 & 5). The use of Cp*Rh (5 mol%) without both the additive and the base generated product **3** in 37% yield (Scheme 11.1, entry 2). Other metal catalysts including Rh, Co, Cu, and Fe salts were screened. It was found that the catalysts $RhCl_3.H_2O$, $CoCl_2{\cdot}6H_2O$, $CoCO_3$, and $Co_2(CO)_8$ afforded the desired compound in a range of 13% to 51% yields, whereas the Cu or Fe salts tested were ineffective for this transformation, with all starting materials recovered (Scheme 11.1, entries 3–5 vs 6). $Co_2(CO)_8$ was the catalyst of choice for such a sulfonyl transfer reaction [21]. Other solvents such as MeOH, acetone, and toluene were attempted, but no desired reaction occurred (Scheme 11.1, entry 7). Noteworthy, the concentration dependence on 1,2-dichloroethane (DCE) was observed, thus the concentration of 0.2 M brought about the highest efficacy (Scheme 11.1, entry 8). The reaction could happen at 90°C, albeit at a very low yield, whereas the yield of 51% was offered at 130 °C, comparable with that at 110°C (Scheme 11.1, entry 9). With the prolonging of the reaction time, the reaction yield substantially climbed up to 54% (Scheme 11.1, entry 10). Furthermore, the loading amount of $Co_2(CO)_8$ was also tested. The loading amount (10 mol%) gave rise to better transfer efficiency (Table 11.1, entry 11), while the more cobalt catalyst (20 mol%) diminished the reaction yield due to the difficulty of electromagnetic stirring. Besides, the reaction performed better under argon than under air, providing product **3** in 70% yield (Scheme 11.1, entry 1). The addition of bases was reported to help facilitate the CN group transfer of NCTS to anilines [22]. However, the attempts of the bases such as NaO*t*-Bu, NaH, and NaOH failed to promote the reaction [23].

N-Substituted benzimidazoles were prepared by simply stirring a mixture of copper catalysts, *N*-substituted 1,2-phenylenediamines, sulfonyl azides, and terminal alkynes. In particular, the intermediate *N*-sulfonyl ketenimine occurred with two nucleophilic additions, and the sulfonyl group was eliminated *via* cyclization. In a way, sulfonyl azides and copper catalysts activate the terminal alkynes to synthesize benzimidazoles [10].

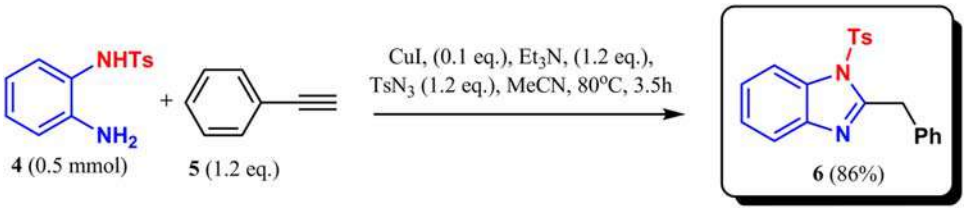
Synthesis of *N*-tosyl substituted benzimidazole **6** *via* *N*-tosyl benzamine **4**, tosylazide and ethynylbenzene **5** was carried out in the presence of CuI and Et_3N in $CHCl_3$ at 80°C for 3.5 h, and compound **6** was isolated in 86% yield (Scheme 11.2) [10].

A Beckmann-type rearrangement of *o*-hydroxy and *o*-aminoaryl N–H ketimines has been developed to prepare benzoxazoles and N-Ts benzimidazoles, respectively. The ketimine derivatives were easily prepared by condensation of ammonia with the corresponding ketones and (diacetoxyiodo)benzene was found to act as an efficient oxidant to trigger the aryl migration [24] toward the formation of the desired heterocycles [25]. Depending on the substitution pattern, the results revealed another mechanistic pathway through which benzisoxazoles or 1*H*-indazoles could be formed. The Beckmann-type rearrangement strategy was

TABLE 11.1 Sulfonation of benzimidazole under various conditions with CuBr, $CuBr_2$, $FeCl_2$ (5 mol%).

Entry	Deviation from standard conditions	Yield [%][b]
1	None	70
2	With Cp*Rh (5 mol%)	37
3	With $RhCl_3.H_2O$ (5 mol%)	36
4	With $CoCl_2.6H_2O$ (5 mol%)	13
5	With $CoCO_3$(5 mol%)	33
6	With CuBr, $CuBr_2$, $FeCl_2$ (5 mol%)	0
7	In MeOH, Acetone or Toluene	0
8	In 0.4 mL or 1.6 mL of DCE[a]	42, 45
9	At 90°C, 130°C	10, 51
10	For 5 h, 10 h, 15 h, 20 h, 24 h, 48 h	41,54
11[c]	With $Co(CO)_8$ (10 mol%), (20 mol%)	66, 31

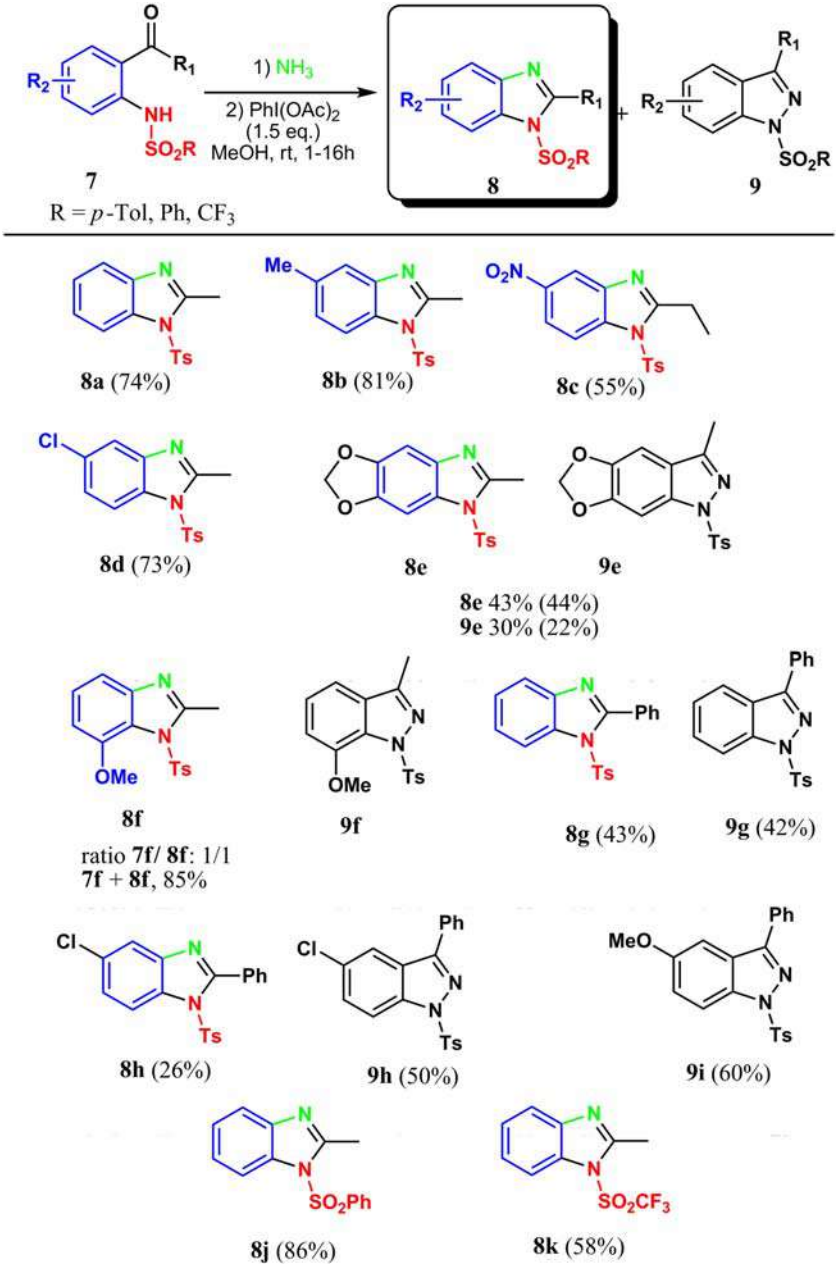
[a]*Reaction conditions: 1 (0.2 mmol), 2 (1.2 equiv), $Co_2(CO)_8$ (5 mol%), air, DCE (1.0 mL) at 110°C for 20 h, sealed tube unless otherwise stated.*
[b]*Yield of isolated product.*
[c]*For 24 h. DCE = 1,2-dichloroethane, Cp*Rh = $[RhCp^*Cl_2]_2$. (Cp* = pentamethylcyclopentadienyl).*



SCHEME 11.2 Copper-catalyzed three-component coupling reaction for the synthesis of *N*-tosyl benzimidazole **6**.

applied to the synthesis of benzimidazole-containing biorelevant targets such as chlormidazole and clemizole [26].

Preliminary results showed that the *o*-aminoaryl *N*–H ketimines could be obtained in quantitative yields from the corresponding ketones **7** without any further purification. These results prompted us to consider a synthetic strategy whereby benzimidazoles **8** would be prepared over two steps from **7** by just removing the solvent after the imine formation. Imines derived from **7** underwent cyclization in the presence of 1.5 equiv of $PhI(OAc)_2$ in MeOH (Scheme 11.3). A screening of the nitrogen protecting group borne by **7** suggested that sulfonamide derivatives are the most suitable substrates to give the corresponding benzimidazole **8** [27]. Treatment of **7a** with ammonia followed by the reaction in the presence of $PhI(OAc)_2$ in MeOH gave rise to **8a** at a 74% overall yield. The heterocyclic structures **8b** and **8d** were obtained at good yields while a decrease in yield was noted when **7c** was subjected to the reaction conditions. The results obtained with substrates bearing electron-donating groups stand in striking contrast to those obtained previously and a modification of the protocol was required to enable the reactions. Both increasing the temperature and reaction time for the first step while conducting the $PhI(OAc)_2$-mediated transformation for 16 h



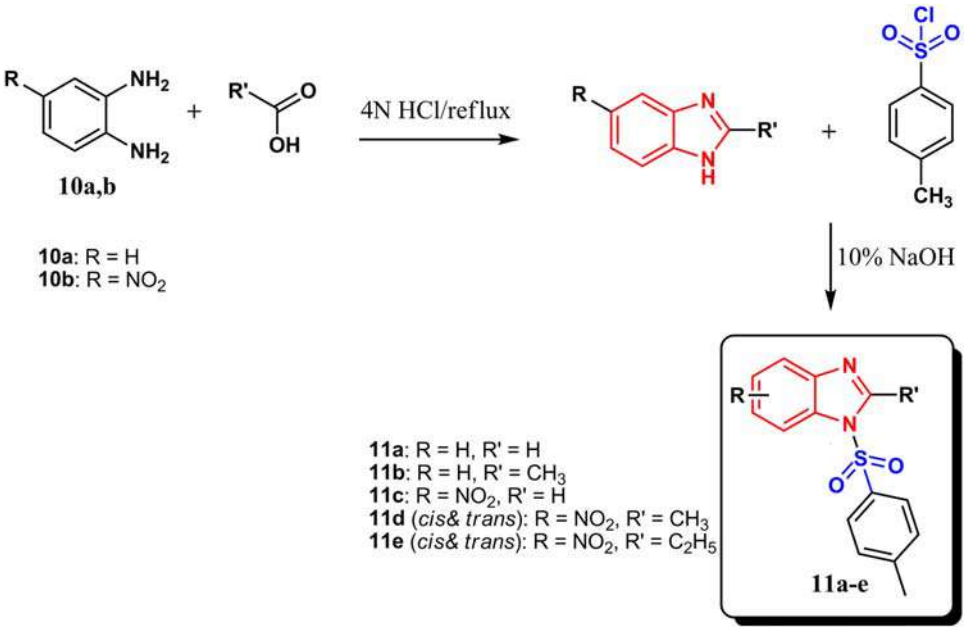
SCHEME 11.3 Heterocyclic synthesis from **7**.

produced ratios of products **7** and **8** depending on the nature of the substrates. While a mixture of the two regioisomers **8e/9e**, **8f/9f** was obtained, the indazole **9i** was selectively formed at 60% yield. Similar to the benzoxazole series, a separable mixture of **8g/9g** and **8h/9h** was obtained starting from the imine **7g** and **7h** bearing a phenyl group. Different sulfonyl groups can be introduced in the heterocyclic framework and compounds **8j** and **8k** were obtained at 86% and 58%, respectively (Scheme 11.3) [26].

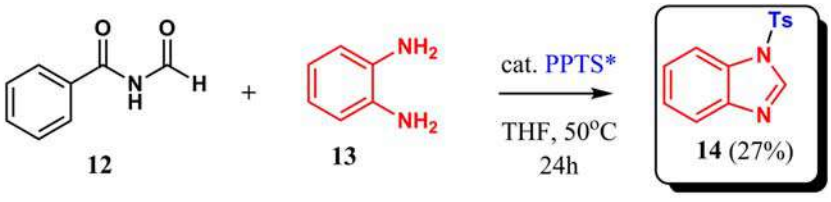
Substituted *N*-tosyl benzimidazoles **11a–e** were synthesized by following the already reported method [28] with slight modifications. 1,2-Phenylenediamines **10a,b** were reacted with monobasic acids in the presence of 4N HCl to obtain substituted benzimidazoles Scheme 11.4 [29]. *N*-Tosyl benzimidazoles **11a–e** were synthesized by reacting 2-alkyl substituted-benzimidazoles with tosyl chloride in 10% sodium hydroxide and acetone solution according to the methods reported earlier [30], Scheme 11.4.

N-Formamide synthesis using *N*-formyl imide with primary and secondary amines with catalytic amounts of *p*-toluenesulfonic acid monohydrate ($TsOH.H_2O$) is described. This reaction is done in water without surfactant use. Moreover, *N*-formyl imide is efficiently synthesized using acylamidines with $TsOH.H_2O$ in water. Additionally, *N*-formyl imide was successfully used as a carbonyl source in the synthesis of benzimidazole and quinazolinone derivatives. Notable features of *N*-formylation of amines using *N*-formyl imide include operational simplicity, oxidant- and metal-free conditions, structurally diverse products, and easy applicability to gram-scale operation. After careful screening of acid catalysts, solvents, and temperature, the pyridinium *p*-toluenesulfonate (PPTS, 20 mol%) under THF system at mild heating conditions (50°C) was selected as the optimized conditions, which resulted in 27% yield of the corresponding benzimidazole **14** (Scheme 11.5) [31].

N-Iodosuccinimide (NIS) which mediated an intramolecular dehydrogenative C(sp^2)-H amidation was reported



SCHEME 11.4 Synthesis of *N*-tosyl benzimidazoles **11a–e**.

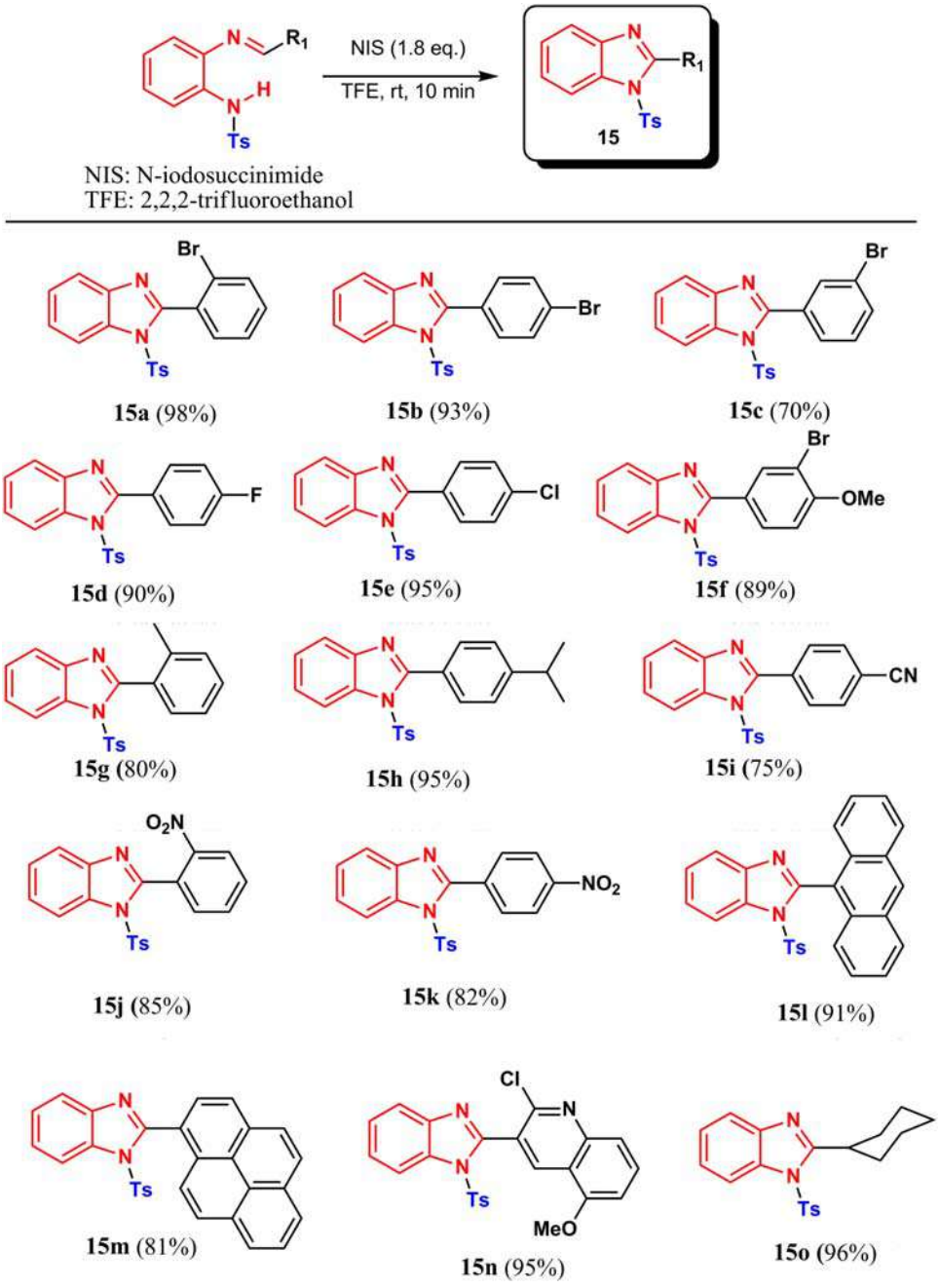


*PPTS: pyridinium *p*-toluenesulfonate

Reaction conditions: **12** (1 equiv), **13** (1 equiv), PPTS (0.2 equiv) in THF (0.3 M) were reacted under nitrogen atmosphere; Reflux conditions.

SCHEME 11.5 Synthesis of 1*H*-benzimidazole derivative **14**.

for easy and convenient access to 1,2-disubstituted benzimidazoles. The non-prefunctionalized C(sp^2)-H and N(sp^3)-H bonds were directly coupled using the NIS in trifluoroethanol and proved to be a mild alternative to strong oxidative iodine(III) reagents. The reaction worked at room temperature, under an open atmosphere, and under any additive (base) free condition [32]. Scheme 11.6 illustrates the substrate's scope for this C–H amination protocol was explored for the synthesis of 1,2-disubstituted benzimidazoles (Scheme 11.6). *N*-Tosyl substituted benzimidazoles containing a differently substituted aryl group at 2-position were isolated in excellent yield within a relatively shorter reaction time (ca. 10 min). Multi-substituted benzimidazole derivatives bearing electron-withdrawing halogen groups **15a–f**, -NO_2 **15j–k**, –CN **15i** groups on aryl rings were isolated in excellent yields. Likewise, electron-donating alkyl **15g–h** or alkoxy **15f** groups containing benzimidazole products were also synthesized with high efficiency. Synthesis of benzimidazole derivatives with fused aromatics such as anthracenyl **15l**, pyrenyl **15m**, and



SCHEME 11.6 C–H amidation reaction for the synthesis of *N*-tosyl benzimidazoles **15a-o**.

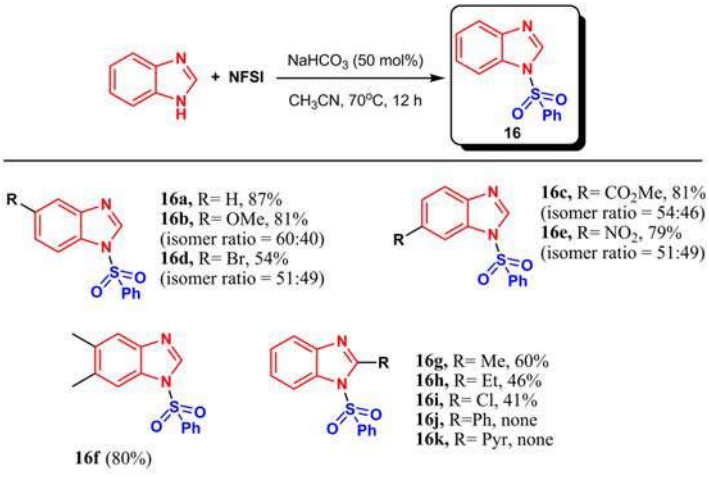
heteroaromatic **15n** at 2-position was also found to be successful. Cyclohexyl substituted benzimidazole derivative **15o** was isolated with a 96% yield [32].

Recently, it was reported the synthesis of *N*-sulfonyl imidazoles has been achieved using *N*-Fluorobenzenesulfonimide (NFSI) as a sulfonyl source [33,34]. This reaction proceeded well in the absence of strong bases and catalysts, providing a convenient alternative method for the preparation of *N*-sulfonyl imidazoles. With the optimal conditions, the generality of this method was explored, and the results are summarized in Scheme 11.7. 5-Methoxybenzimidazole gave the corresponding product at 81% yield with a regioisomeric ratio of 60:40 (**16b**). The regioisomer phenomenon of the product originates from the isomerization of the C = N double bond of benzimidazole. Methyl 3*H*-benzoimidazole-5-carboxylate led to the corresponding product in 81% yield with an isomeric ratio of 54:46 (**16c**). The electron-withdraw groups such as nitro- and bromo in the aromatic ring would pull down the activity of benzimidazoles, which afforded the desired product in moderate yields with an isomeric ratio of 51:49 (**16d**). 6-Nitro benzimidazole at the corresponding product in 79% yield with an isomeric ratio of 51:49 (**16e**). When 5,6-dimethyl benzimidazole was treated in the reaction, the product was afforded at 80% (**16f**). The substituted group in the C-2 position had a lot of influence on the reaction. For instance, 2-methyl, 2-ethyl, and 2-chloro benzimidazole delivered the desired products at moderate yields of 16g–16i because of the steric hindrance, which prohibited the attack of benzimidazole on the NFSI. To verify our assumption, substrates with larger steric hindrance groups such as phenyl and pyridyl at the C-2 position were employed in the reactions, and no products were found **16j, 16k** as illustrated in Scheme 11.7 [35].

Multifunctional 2-aminobenzimidazoles were directly synthesized through sequential addition of *N*-substituted *o*-diaminoarenes to isothiocyanates, formation of carbodiimides *via* I_2-mediated oxidative desulfurization, and intramolecular cycloaddition [36]. This efficient and eco-friendly synthetic process provides facile access to diverse 2-aminobenzimidazole derivatives from readily accessible substrates under mild reaction conditions in a scalable fashion. Upon investigating the annulation reaction of *N*-tosyl-1,2-phenylenediamine (**17**) and phenyl isothiocyanate. Then, a range of aryl isothiocyanates was subjected to the above optimal reaction conditions to probe the scope and generality of this synthetic approach. All these substrates were smoothly converted into the corresponding 2-aminobenzimidazoles **18a–k** (Scheme 11.8) through the addition reaction with **17** followed by I_2-mediated oxidative cyclization. This method is compatible with phenyl isothiocyanates bearing both electron-donating and electron-withdrawing groups (EDGs and EWGs) at the *para*-, *meta*-, and *ortho*-positions [36].

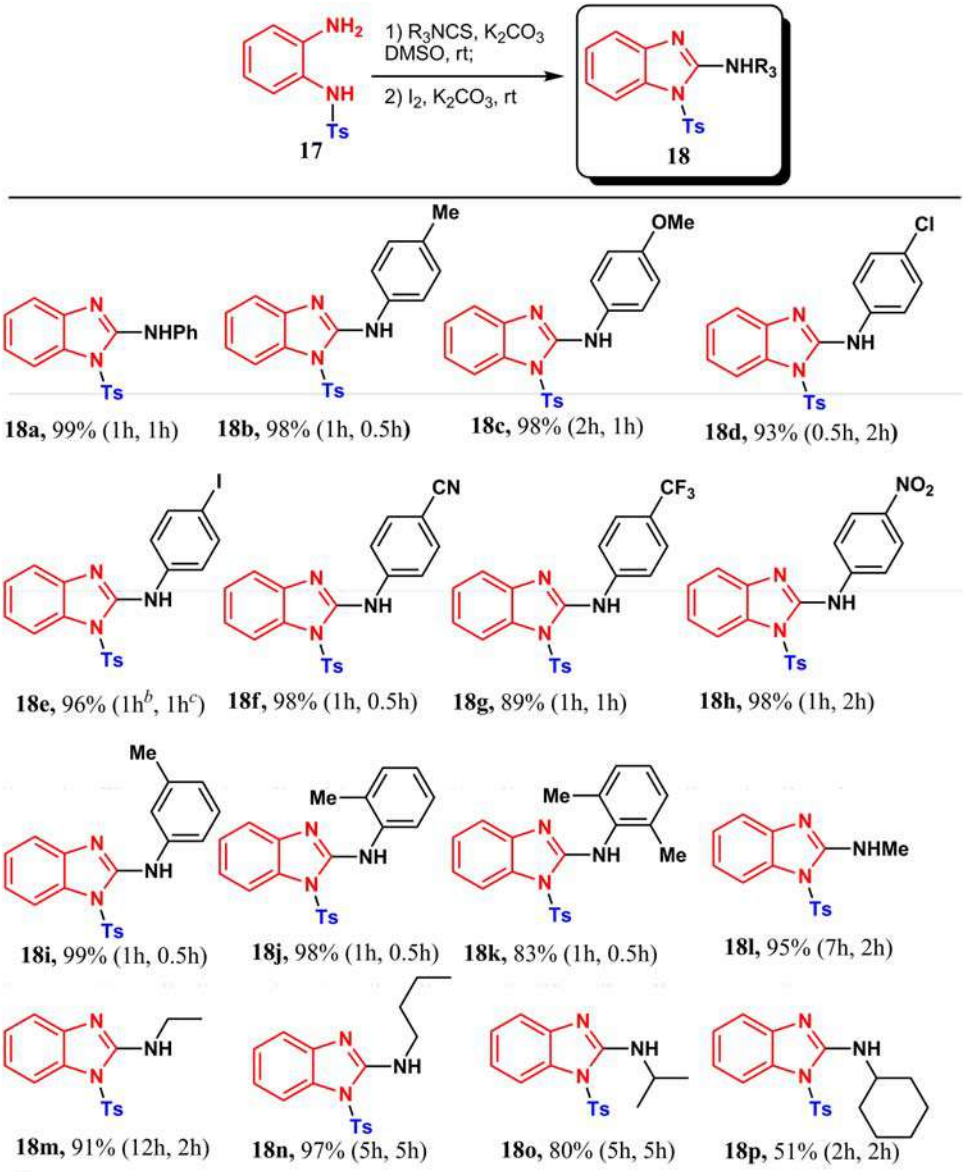
A practical intramolecular C–H amidation methodology has been developed using molecular iodine under basic conditions [37]. The required imine substrates are readily obtained by condensation of simple *o*-phenylenediamine derivatives and aldehydes. The transition metal-free cyclization reaction described here works well with crude imines, and allows for the sequential synthesis of *N*-protected benzimidazoles without purification of the less stable condensation intermediates. This operationally simple synthetic approach is broadly applicable to a variety of aromatic, aliphatic, and cinnamic aldehydes to produce diverse 1,2-disubstituted benzimidazole derivatives in an efficient and scalable fashion.

The imine intermediate **20** necessary for benzimidazole synthesis can be readily prepared by the condensation of



Notes: Reaction conditions: 1 (0.3 mmol), NFSI (0.45 mmol), $NaHCO_3$ (50 mol %), and CH_3CN (2 mL) at 70°C under air for 12 h.
Yields refer to the isolated yields. A mixture of N_1- and N_3-sulfonylated products.

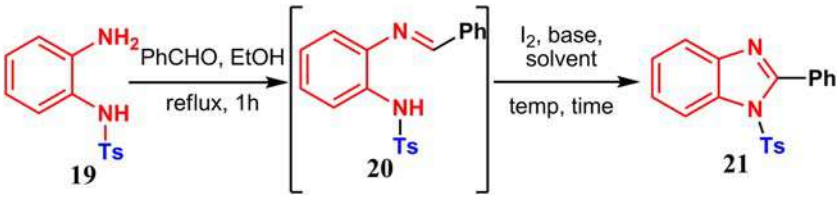
SCHEME 11.7 The sulfonylation of benzimidazoles **16**.



[a]Optimal reaction conditions: (1) **17** (0.5 mmol), R_3NCS (0.55 mmol), K_2CO_3 (0.5 mmol), DMSO (5 mL), rt; (2) K_2CO_3 (0.6 mmol), I_2 (0.5 mmol), rt (isolated yields are given).
[b]Time for the first step. *c*Time for the second step

SCHEME 11.8 Synthesis of 2-aminobenzimidazole **18a–p** using isothiocyanates.

N-tosyl-1,2-phenylenediamine (**19**) with benzaldehyde in EtOH at the reflux temperature (Scheme 11.9). Given the poor stability of imines, we initially investigated the I_2-mediated one-pot synthesis without isolation of **20** in the absence of base, which only resulted in a trace amount of benzimidazole **21** (Table 11.1 entry 1). Upon completion of the first-step condensation, the reaction mixture was treated directly with molecular iodine and K_2CO_3 in sequence, which gave the desired product at a 7% yield (entry 2). To optimize the reaction conditions using the crude imine **20** obtained by removing the EtOH under reduced pressure. Screening demonstrated that CH_2Cl_2 is the optimal solvent for the second annulation step and 1.2 equiv. of the oxidant is sufficient for the transformation. In the presence of K_2CO_3, the I_2-promoted oxidative cyclization of crude **20** at room temperature was completed within 1 h, affording a product with **21** a 90% overall yield (entry 7). With weaker (entry 9) or organic bases (Table 11.2, entry 10), yields of the expected benzimidazole were significantly reduced. Moreover, the one-pot



SCHEME 11.9 Reaction conditions optimization for the synthesis of 1-tosyl benzimidazole **21**.

TABLE 11.2 Synthesis of 1-tosyl benzimidazole 21 under different conditions.

Entry	I_2 (equiv.)	base	solvent	Temp.	Time (h) [a]	Yield (%)[d]
1[b]	1.2	–	EtOH	reflux	6 h	Trace
2	1.2	K_2CO_3	EtOH	reflux	1.5	7
3	1.2	K_2CO_3	MeCN	rt	2	63
4	1.2	K_2CO_3	1,4-dioxane	60°C	1	51
5	1.2	K_2CO_3	Toluene	rt	2	78
6	1.0	K_2CO_3	CH_2Cl_2	rt	2	86
7 [c]	1.2	K_2CO_3	CH_2Cl_2	rt	1	90
8	1.4	K_2CO_3	CH_2Cl_2	rt	1	90
9	1.2	$NaHCO_3$	CH_2Cl_2	rt	1	49
10	1.2	DBU	CH_2Cl_2	rt	1	43
11[b]	1.2	K_2CO_3	CH_2Cl_2	rt	4	38
12[b]	1.2	K_2CO_3	CH_2Cl_2	rt	1	82

[a] *Reaction time for the cyclization step.*
[b] *The reaction mixture was directly treated with iodine and then heated to reflux.*
[c] *Optimal reaction conditions: 1) 19 (0.5 mmol), PhCHO (0.55 mmol), EtOH, reflux; 2), iodine (0.6 mmol), K_2CO_3 (1.5 mmol), CH_2Cl_2, rt.*
[d] *Isolated yields are given.*

reaction of **19** and benzaldehyde in either EtOH or CH_2Cl_2 also formed the expected product **21**, but in lower yields (Table 11.2, entry 1112) [37].

11.2.2 Biological activities of *N*-sulfonyl benzimidazole derivatives

11.2.2.1 Antiinflammatory activity

The discovery of a 2-aminobenzimidazole-based reported series of potent and highly selective p38a inhibitors exhibiting antiinflammatory activity [38]. Awareness of potential CYP activity associated with the imidazole central core [39] led to a SAR around the imidazole C-2, and recognition that sterically bulky groups such as *tert*-butyl, 2,6-dichlorophenyl, or 2,6-difluorophenyl resulted in decreased inhibition of CyP3A4. The lead compound **22** (Fig. 11.1) had low nanomolar activity in both ATP competitive enzyme binding and inhibition of TNF release in macrophages. Expansion of the SAR identified **23** which showed excellent in vivo activity in the rat collagen-induced arthritis model (CIA) as compared to the p38 reference compounds BIRB-796, SB242235, and RWJ-67657 [38].

11.2.2.2 Antitumor activity

The tubulin-targeting drugs category is considered one of the most common anticancer drugs research [40,41]. Benzimidazole grafted benzsulfamide-containing pyrazole ring derivatives were synthesized and evaluated for bioactivity as potential tubulin polymerization inhibitors. Among them, compound **24** (Fig. 11.2) showed excellent inhibition against tubulin assembly ($IC_{50} = 1.52$ M) and in vitro growth inhibitory activity against a panel of four human cancer cell lines ($IC_{50} = 0.15$, 0.21, 0.33, and 0.17 M, respectively for A549, Hela, HepG2 and MCF-7). It could also validly induce A549 cell apoptosis, cause

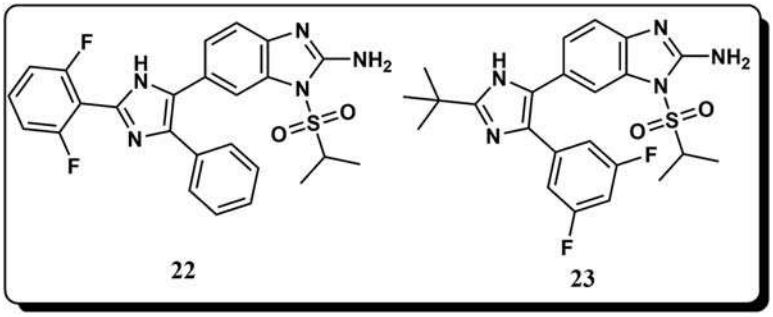


FIGURE 11.1 Structures of the antiinflammatory *N*-sulfonated benzoimidazoles **22** and **23**.

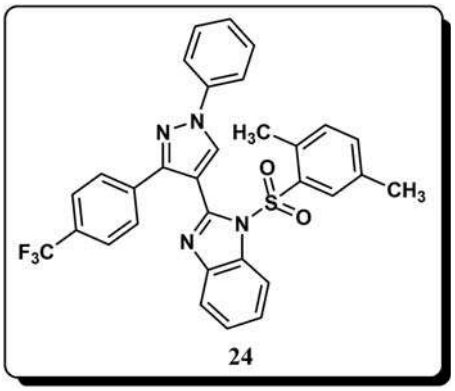
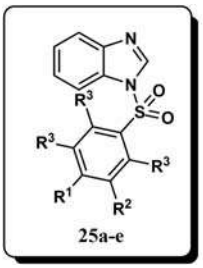


FIGURE 11.2 Structures of the anti-tumor *N*-sulfonated benzoimidazole **24**.



	R^1	R^2	R^3
25a	H	H	H
25b	$NHCOCH_3$	H	H
25c	H	NO_2	H
25d	CF_3	H	H
25e	H	CH_3	CH_3

FIGURE 11.3 structure of antitrypanosoma cruzi benzoimidazole **25a-e**.

cell cycle arrest in the G2/M phase and disrupt the cellular microtubule network. These results provided an important basis for further optimization of compound **24** as a potential anticancer agent [42].

11.2.2.3 Antitrypanosoma cruzi activity

It was reported that only two drugs (i.e. benznidazole (BZN) and nifurtimox (NFX)) have been approved for the treatment of Trypanosoma cruzi (*Tc*) infection, the etiological agent causing Chagas disease [43,44]. Since both drugs exhibit severe side effects, patients frequently abandon therapy, resulting in inefficient pharmacotherapeutic treatment. It was reported that the synthesis and biological activity of *N*-arylsulfonyl-benzimidazole derivatives were tested as potential anti-*Tc* compounds [45]. These compounds were designed as part of a library of synthetic arylsulfonyl heterocycle derivatives constructed from privileged structures exhibiting drug-like properties. Based on bioactivity assays against *Tc*, (in both the extracellular and intracellular forms), some derivatives exhibited bioactivity against the epimastigote form, while others showed activity against the amastigote counterpart. Also, the compounds showed less cytotoxicity compared to the reference drug BZN as measured with Vero cell culture. Consistency it was observed that metabolic profiles of compounds **25a–e** (Fig. 11.3) interfered with the normal glycolysis cycle of *Tc*, while molecular modeling studies were able to establish a solid structure-activity relationship toward the inhibition of 6-phospho-1-fructokinase, a key enzyme involved in the parasite glycolytic cascade [45].

11.2.2.4 Antiviral activity

Enviroxime 26, as a benzimidazole derivative with strong in vitro antirhinoviral activity, is one of the more extensively studied synthetic agents [46]. Enviroxime and related benzimidazoles [47] showed potent broad-spectrum antiviral activity against a range of both rhinoviruses and enteroviruses. Non-cytotoxic concentrations of **26** are associated with complete inhibition of replication of 81 rhinovirus stereotypes. The 50% inhibitory concentration (IC_{50}) ranges from 0.05 to 0.12 g/mL for different serotypes. Although the mechanism of action of **26** is not completely understood, it was believed that the drug inhibits the formation of the viral RNA polymerase replication complex [48]. The major handicaps of Enviroxime are poor oral bioavailability and undesirable side effects. Studies of oral **26** showed low levels in the blood and nasal secretions and an unacceptably high frequency of nausea and vomiting [49]. Thus, despite its potent in vitro antirhinovirus activity, a significant therapeutic benefit was not found with

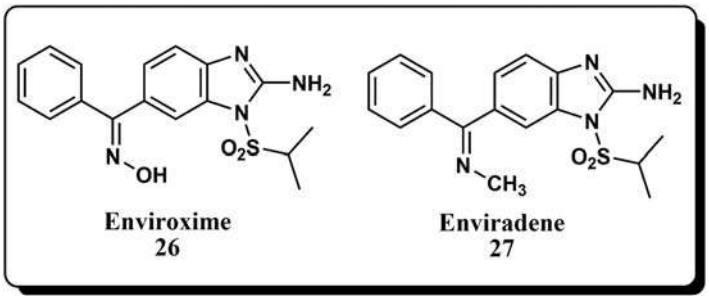
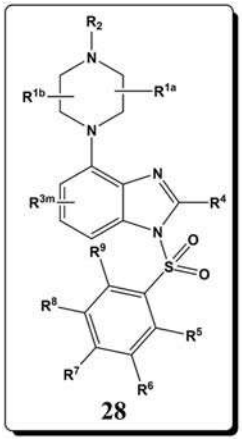


FIGURE 11.4 Structures of antiviral benzoimidazoles **26** and **27**.



R^{1a} and R^{1b} are independently H, (un)substituted C_1-C_4 alkyl, (un)substituted C_2-C_6 alkenyl and (un)substituted C_2-C_6 alkynyl; $R^{1a}R^{1b}$ taken together to form $(CH_2)_{1-2}$; R^2 is H, C_1-C_4 alkyl, CHO and COC_1-C_4 alkyl; R^3 is halogen, NO_2, CN, OH, (un)substituted C_1-C_6 alkyl, (un)substituted C_2-C_6 alkenyl, (un)substituted C_2-C_6 alkynyl, etc; R^4 is H, CN, (un)substituted C_1-C_6 alkyl, (un)substituted C_2-C_6 alkenyl, (un)substituted C_2-C_6 alkynyl, etc; R^5, R^6, R^7, R^8, R^9 are independently H, halo, NO_2, CN, OH, (un)substituted C_1-C_6 alkyl, (un)substituted C_1-C_6 acyl, (un)substituted C_1-C_6 alkoxy, etc; R^5R^6 and R^6R^7 taken together to form (un)substituted aryl, (un)substituted C_3-C_6 cycloalkyl, (un)substituted C_3-C_6 cycloalkenyl; m is 0, 1 or 2

FIGURE 11.5 Structure of 5HT6 receptor antagonists **28**.

either oral or intranasal administration, and Enviroxime clinical studies were terminated.

Enviradene **27**, as a related benzimidazole, showed improved pharmacokinetics in dogs and caused no emesis [50]. However, the peak plasma levels did not surpass the antiviral IC_{50} value, and the studies on **27** (Fig. 11.4) were also discontinued. Although the origins of the poor oral bioavailability and emetic side effects found in this class of antirhinoviral agents are not completely understood, considerable efforts are still devoted to this family of benzimidazoles to find an analog with improved oral plasma levels and a better safety profile [51].

11.2.2.5 5HT6 receptor antagonists

Among a variety of proteins included in a relatively wide GPCR family, serotonin 5HT receptors ($5HT_6Rs$) are highly attractive as important biological targets with enormous clinical importance. Among this subclass, $5HT_6R$ is the most recently discovered group. Available biological data indicate that $5HT_6R$ antagonists can be used as effective regulators in a variety of contexts, including memory formation, age-related cognitive impairments, and memory deficits associated with conditions such as schizophrenia, Parkinson's disease, and Alzheimer's disease. Therefore, this receptor has already attracted considerable attention within the scientific community, due to its versatile therapeutic potential.

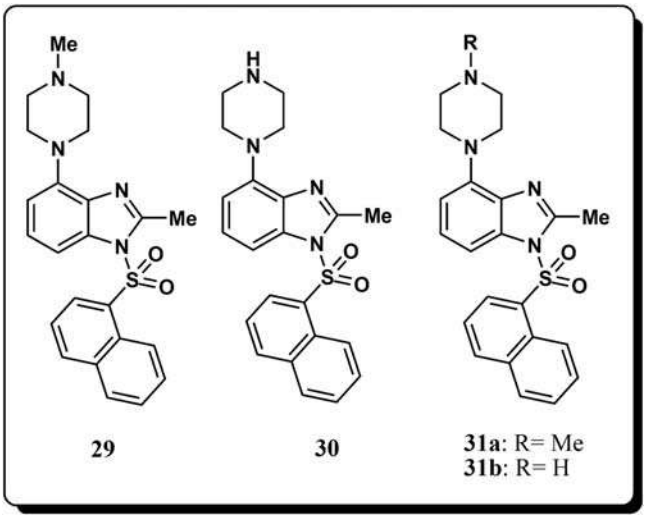


FIGURE 11.6 Structure of 5HT6 receptor antagonists **29**, **30** and **31**.

Substituted 1-(arylsulfonyl)-4-(piperazin-1-yl)-1*H*-benzimidazoles **28** [52] (Fig. 11.5) were found to be highly potent $5HT_6R$ ligands with a Ki value in the nanomolar range. For example, the binding assay ligand of compound **29** (Fig. 11.6) showed a Ki value of 0.004 nM. In general, more than 20 compounds from this series showed a binding affinity between 0.2 and 1.0 nM, including compounds **30** and **31a,b** [52].

11.2.2.6 Antibacterial and urease inhibitory activity

A series of *N*-tosyl benzimidazoles have been bioevaluated to develop compounds with improved antibacterial and urease inhibitory activity, as it was reported that benzimidazole derivatives bearing sulfonamide moiety possess carbonic anhydrase inhibitory activity [53–55]. Antibacterial activity results revealed that compounds **32a** and **32b** having methyl and ethyl substitution respectively in the imidazole ring showed excellent zone inhibition against both gram-positive and gram-negative strains.

The compound **32b** (Fig. 11.7) exhibited 80% growth inhibition against *Bacillus subtilis* and 78% inhibition against *Escherichia coli* compared to the standard drug. Antibacterial activity results revealed that the presence of polar and nonpolar substituents in the synthesized derivatives had a significant influence on their activities. The urease inhibitory activity results showed that derivative **32b** exhibited the highest potential to inhibit the urease enzyme [29].

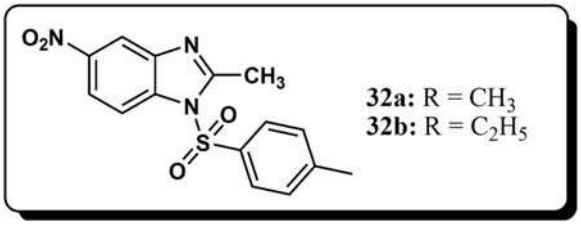


FIGURE 11.7 Structure of anti-bacterial and urease inhibitors **32a,b**.

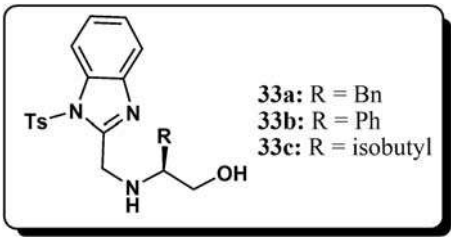


FIGURE 11.8 Structure of Anti-mycobacterium benzimidazole **33a-c**.

Chiral aminoalcohol-benzimidazole hybrids have been synthesized from commercially available aminoalcohols [*S*(+)-Phenylglycinol, *S*(+)- Phenylalaninol, and *S*(+)-Leuicinol] and 2-(chloromethyl)-*N*-tosyl-1-*H*-benzimidazole. The antibacterial properties of amino alcohol-benzimidazole hybrid molecules **33a-c** (Fig. 11.8) were investigated against both gram (+ve) and gram (-ve) bacterial pathogens by the well-diffusion method using several standards. All three chiral molecules showed good activity against tested pathogens [56].

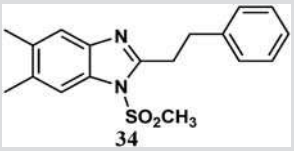
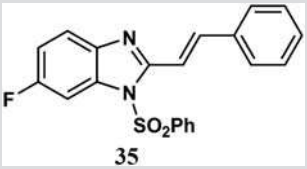
11.2.2.7 Antimycobacterium activity

Extensive screening of a library of benzimidazole derivatives that were previously shown to be active against Mycobacterium tuberculosis. Designated compounds **34** and **35** exerted very strong activity against intramacrophage-residing Mycobacterium *abscessus* [57] (Table 11.3). Insights into the mechanism of action were inferred from the generation of spontaneous benzimidazole-resistant strains and the identification of a large set of missense mutations in MmpL3, the mycolic acid transporter in mycobacteria. Overexpression of the mutated mmpL3 alleles in a susceptible *M. abscessus* strain was associated with high resistance levels to EJMCh-6 and other known MmpL3 inhibitors [57].

11.2.2.8 Anti-HIV mutant strains

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are recommended components of preferred combination antiretroviral therapies used for the treatment of human immunodeficiency virus (HIV) infection [58]. These

TABLE 11.3 Minimum inhibitory concentration (MIC) of compounds 34 and 35.

Compound	MIC (g/mL) M. tuberculosis		MIC (g/mL) *M. abscessus*
	$H_{37}Rv$	Spec.210	CIP104536 (S)
 34	25	25	>128
 35	50	100	>128

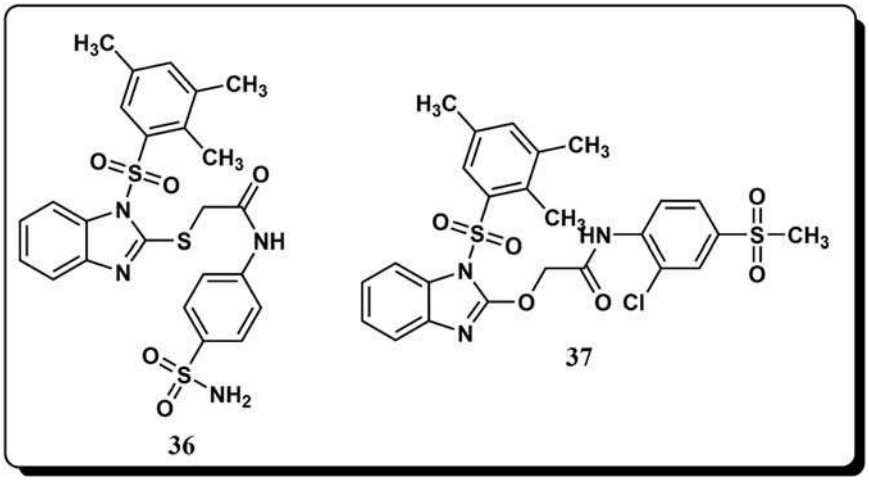


FIGURE 11.9 Structure of Anti- HIV *N*-sulfonated benzimidazole **36** and **37**.

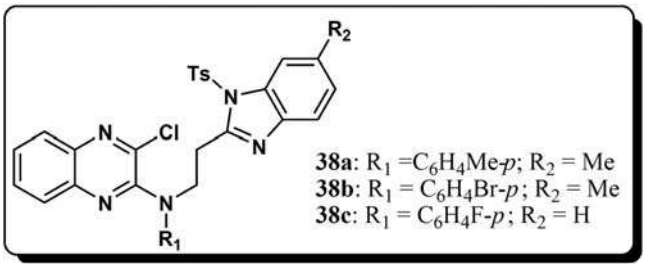


FIGURE 11.10 Structure of apoptosis enhancer **38a-c**.

regimens are extremely effective in suppressing virus replication. Recently, our research group identified some *N* [1]-aryl-2-arylthioacetamidobenzimidazoles as a novel class of NNRTIs. Synthesized compounds were investigated for their effects on reverse transcriptase (RT) inhibition and to better define the features needed to increase the antiviral activity. Most of the new compounds proved to be highly effective in inhibiting both RT enzyme at nanomolar concentrations and HIV-1 replication in MT4 cells with minimal cytotoxicity. Among them, the most promising *N* [1]-aryl-2-arylthioacetamido-benzimidazoles and *N* [1]-aryl-2-aryloxyacetamido-benzimidazoles were also tested on a panel of single- and double-mutant strains responsible for resistance to NNRTIs, showing in vitro antiviral activity toward single mutants L100I, K103N, Y181C, Y188L, and E138K. The best results were observed for derivatives **36** and **37** (Fig. 11.9) active also against the double mutants F227L and V106A [59].

11.2.2.9 Apoptosis enhancement activity

Various hybrid molecules were reported as potential inducers of apoptosis. To assess their potential to induce apoptosis, these compounds were tested in Zebrafish embryos [60,61] along with the known drug methotrexate [62] at 30 M. Based on their considerable effects in the present assay of apoptosis compounds **38a–c** were further tested at 1, 3, 10, and 30 M along with methotrexate. While the compound **38c** showed an increase in its apoptotic activities up to 3 M, a decrease in activity was observed at 10 and 30 M. The embryos were found to be safe at all concentrations. In the case of compound **38a**, the increase in apoptotic activities was observed with the increase of concentration from 1 to 10 M, but the activity was decreased at 30 M. Compound **38b** showed significant apoptotic activity at 10 M; however, the embryos were dead when the concentration was increased to 30 M [63].

These compounds were also evaluated for their potential toxicities e.g., teratogenicity in the zebrafish embryo at a range of 1.0–30 M. The toxicological evaluation was carried out blindly. All the embryos in the control group were found to be normal. Phenobarbital (3 mM) was used as a positive control in this assay. The compound **38c** was found to be non-toxic in all the tested concentrations (Fig. 11.10). While compound **38a** showed mild toxicity at 30 M, it was found to be safe at lower concentrations e.g., 1, 3, and 10 M. Compound **38b** was found to be safe at 1 and 3 M but showed toxicity at 10 and 30 M [63].

11.2.2.10 Inhibitors of NOD1-induced nuclear factor-jB activation

The chemical synthesis of development and structure were documented, downstream counter screens, secondary assay data, and pharmacological profiling of the 2-aminobenzimidazole lead (compound **39**, ML130) as a potent and selective inhibitor of NOD1-induced NF-kB activation [64] (Fig. 11.11). NOD1 (nucleotide-binding oligomerization domain 1) protein is a member of the NLR (NACHT and leucine-rich repeat domain-containing proteins) protein family, which plays a key role in innate immunity as a sensor of specific microbial components

derived from bacterial peptidoglycans and induction of inflammatory responses [65–67]. Mutations in NOD proteins have been associated with various inflammatory diseases that affect NF-kB (nuclear factor kB) activity, a major signaling pathway involved in apoptosis, inflammation, and immune response. A luciferase-based reporter gene assay was utilized in a high-throughput screening program conducted under the NIH-sponsored Molecular Libraries Probe Production Center Network program to identify the active scaffolds [64].

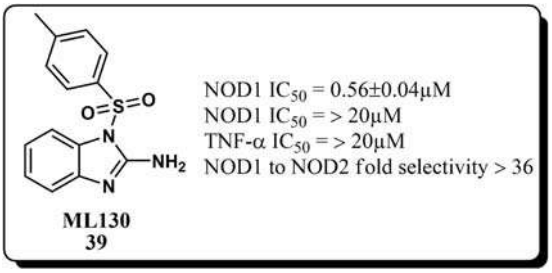


FIGURE 11.11 Structure of inhibitors of NOD1-Induced Nuclear Factor-jB activation **39**.

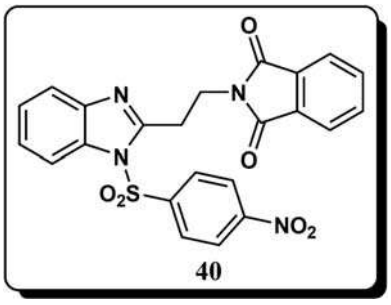


FIGURE 11.12 Structure of anti-Hepatitis B Virus agent **40**.

11.2.2.11 Anti-hepatitis B virus activity

Upon screening the anti-HBV activity of compound 2-{2-[1-(4-nitro-benzenesulfonyl)-1*H*-benzoimidazol-2-yl-ethyl}-isoindole-1,3-dione (**40**), it was identified as a modest inhibitor of HBV, with an IC_{50} of 14.2 M in inhibiting HBV DNA replication and low cytotoxicity (CC_{50} = 200 M) in vitro. Compound **40** (Fig. 11.12) was used as the starting point for developing a series of benzimidazole derivatives and investigated their biological activities as potential HBV inhibitors [68].

Table 11.4, illustrates the subseries of compounds **41a-k** has different patterns of substitution on the fused phenyl ring of the benzimidazole pharmacophore. These compounds generally exhibited good antiviral potency, with IC_{50}s of less than 4 M, except compounds **41c** and **41k**, which had only moderate activities (IC_{50} = 30 and 50 M, respectively) [68]. This result indicates that a range of substituents with different lipophilic, electronic, and steric characters is tolerated in the benzenesulfonyl group at the N-1 position of the benzimidazole core. The three tosylates **41b**, **41g**, and **41h** showed similar antiviral

TABLE 11.4

Compound	R	X	Y	Z	IC_{50} [a] (M)	CC_{50} [b] (M)	SI [c]
41a	H	H	H	H	2.2	28	13
41b	H	H	H	CH_3	2.2	164	75
41c	H	H	CF_3	H	30.4	10	0.3
41d	F	H	NO_2	H	0.14	10	71
41e	F	NO_2	H	H	0.64	77	120
41f	F	H	H	CF_3	3.2	11	3
41g	F	H	H	CH_3	1.2	31	26
41h	Cl	H	H	CH_3	2.9	867	299
41i	Cl	H	H	OCH_3	7.2	189	26
41j	Cl	H	H	*i*-Pr	0.7	17	24
41k	Cl	H	H	NO_2	50.2	181	4
41l	Cl	–	–	–	NA [d]	175	–
lamivudin	–	–	–	–	0.38	>1000	>2632
Adefovir	–	–	–	–	1.3	2.03	156

[a] *Concentrations of compounds achieving 50% inhibition of cytoplasmic HBV-DNA synthesis.*
[b] *Concentrations of compounds required for 50% extinction of HepG 2.2.15 cells.*
[c] *Selectivity index (SI) was determined as the CC_{50}/IC_{50} value.*
[d] *Not active.*

activities (IC_{50} = 1.2–2.9 M), but the Cl analog **41h** appeared to be less toxic than the corresponding H (**41b**) and F (**41g**) analogs. The most potent compound in this subseries was compound **41d** (IC_{50} = 0.14 M), which was nearly three times more potent than the reference drug lamivudine (IC_{50} = 0.38 M) and nine times more potent than adefovir (IC_{50} = 1.3 M). However, it had pronounced cytotoxicity (CC50 = 10 M), resulting in a relatively small selectivity index (SI = 71). Compounds **41e** and **41j** demonstrated similar antiviral potency, with IC_{50}s of less than 0.75 M. Of these, **41e** had higher selectivity (SI = 120) compared to that of adefovir (SI = 156). The introduction of a methanesulfonyl moiety to the N-1 position of the benzimidazole core produced an inactive compound (**41l**). It is noteworthy that compound **41h** showed potent antiviral activity (IC_{50} = 2.9 M) and the highest (SI = 299). Thus, compound **41h** could be considered the benchmark compound for subsequent optimization [68] (Fig. 11.13).

11.3 *N*-Sulfonyl indazoles

11.3.1 Chemistry of *N*-sulfonyl indazoles

Several publications are dedicated to the development or improvement of synthetic approaches to 3-aminoindazoles, exhibiting a high biological activity [69]. In that plan, convenient synthesis of *N*-tosyl-6-fluoro-3-(1-piperazinyl)-1*H*-indazole derivatives **45a–d** (Scheme 11.10), as a potential antipsychotic agent, proceeding preclinical studies, has been described [70]. The original synthesis of **45a–d** involves seven steps, starting from 2-chloro-4-fluorobenzoic (the

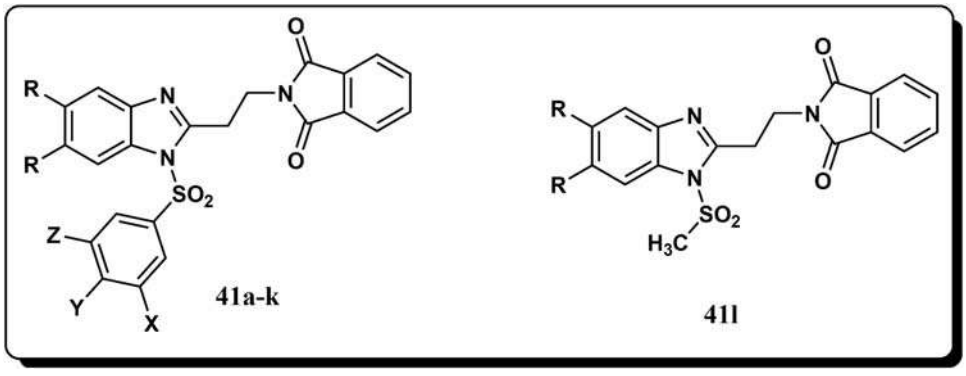
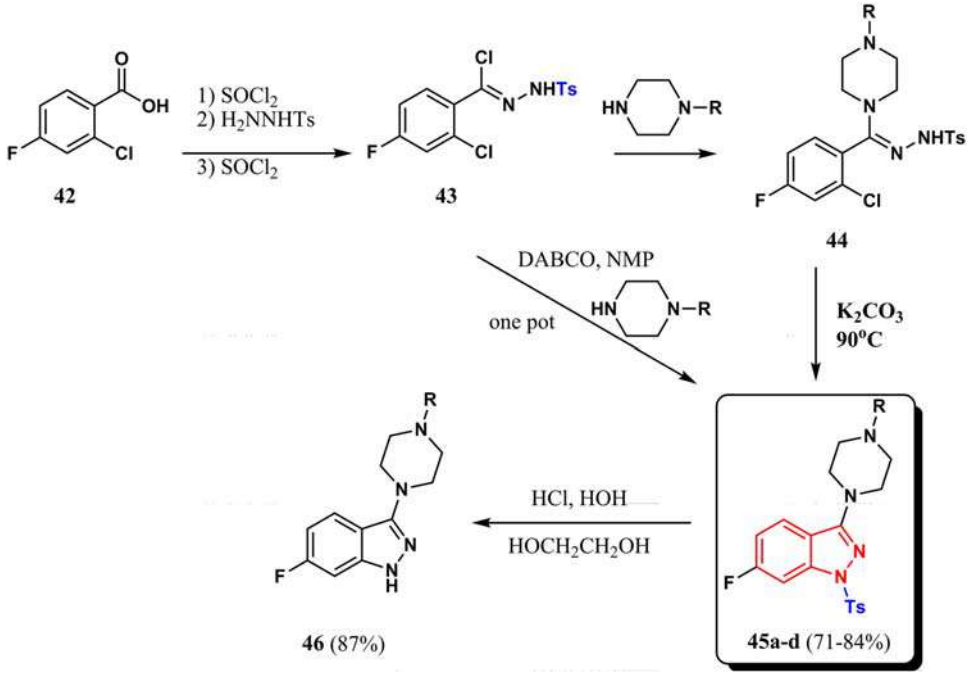


FIGURE 11.13 Structure of anti-Hepatitis B Virus compounds **41a-k** and **41l**.



SCHEME 11.10 Synthesis of *N*-tosyl-6-fluoro-3-(piperazin-1-yl)indazole derivatives **45a–d**.

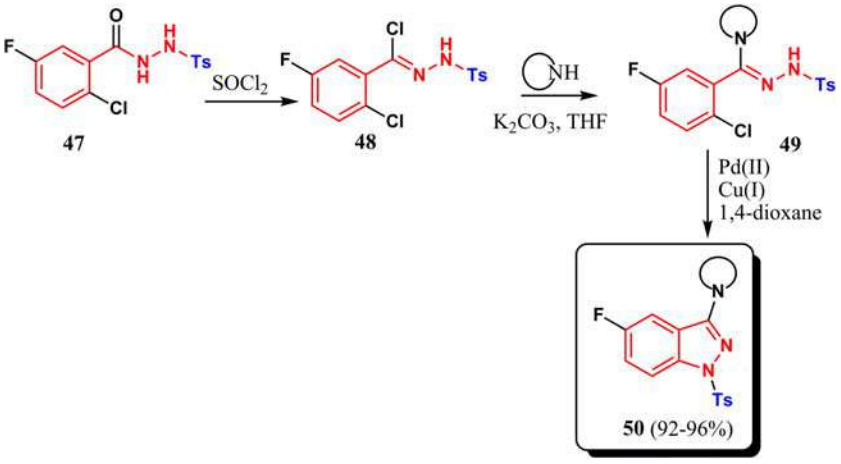
overall yield of 18.4%) [69]. The method for preparation of this compound has been improved: the number of steps and intermediates have been reduced, thus enabling one to avoid chromatographic purification of the final product [69]. 2-Chloro-4-fluorobenzoic acid (**42**) was used as the starting material; compound **42** was converted into the corresponding benzoyl chloride, and, consequently, to tosyl hydrazide and imidoyl chloride **43**. The formation of indazoles **45a–d** was realized in two steps (through cyclization of imidates **44**), or as a one-pot process. Moreover, optimal conditions to obtain 44 candidates have been found. Preparation of indazole **46** requires the removal of the *N*-tosyl group. It has been found that using HCl, H_2O, and ethylene glycol, as a solvent, allows one to obtain **46** from **45d** (R = CO_2Et) [69].

An improved route involves an efficient synthesis of *N*-tosyl-3-amino-5-fluoro-*N*-alkylindazoles **50** *via* the palladium (II)-catalyzed intramolecular *N*-arylation of hydrazines (Scheme 11.11) has been reported [71]. 3-Amino substituted ortho-chloroaryl tosyl hydrazines **49** have been prepared from the corresponding tosyl hydrazone **47**. Cyclization of **49** proceeds at 60°C in 1,4-dioxane by the action of palladium(II) acetate (3 mol%) and copper (I) iodide (1 mol%) in the presence of K_2CO_3 (2 equiv.), thus yielding 3-aminosubstituted indazoles **50**; the reaction conditions have been optimized. (Scheme 11.11) [69].

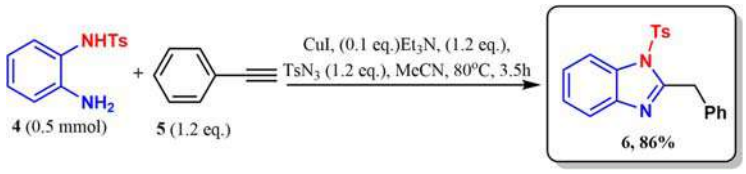
Fused 1*H* and 2*H*-indazoles are well recognized for their antihypertensive and anticancer properties. The transition-metal free method is reported for the synthesis of indazoles, which involves an inexpensive catalytic system composed of a diamine and K_2CO_3. In this method, isomerization with UV light is done when *E*/*Z* isomeric mixtures of the starting material are used (Scheme 11.12) [72].

The 3-aminomethyl-*N*-tosyl-indazoles **52** or **53** are synthesized by reacting amines with vinyl azines (Scheme 11.13) [73]. Thus, by the reaction of 1,3-dinitrobenzene with 4-nitrobenzaldehyde hydrazone, cyclocondensation occurs.

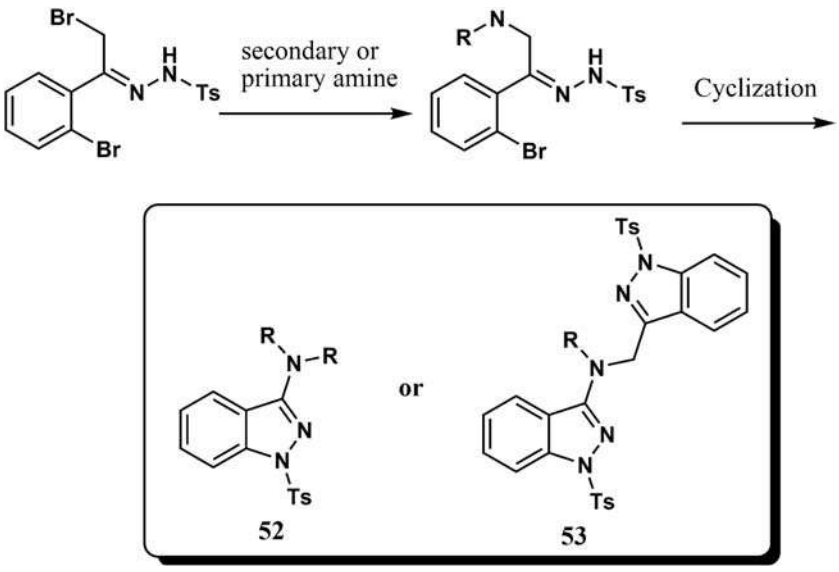
It was reported the reactivity of the isomeric (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles **54** (Scheme 11.14) as dienes under similar MW irradiation conditions. However, the reaction of (*E*)-1-acetyl-3-(2-acetyloxyphenyl)-5-styryl-1*H*-pyrazole with *N*-methylmaleimide under MW irradiation conditions [74,75] was unsuccessful, even after 100 min reaction time in the presence of 9 equivalents of *N*-methylmaleimide. Upon studying the reactivity of these pyrazoles by replacing the acetyl groups with tosyl protecting groups. The reaction of pyrazoles **54a–d** with *p*-toluenesulfonyl chloride in anhydrous pyridine at room temperature for 28–120 h [76] gave (*E*)-5-styryl-1-tosyl-3-(2-tosyloxyphenyl)-1*H*-pyrazoles **56a–d** in good isolated yields together with the corresponding mono-tosylated derivatives **55a–d** as by-products (Scheme 11.14) [76]. The tosylation of pyrazoles bearing strong EWGs (nitro group **54d**) was difficult and led to substantial degradation; in this case, **56d** was obtained at a very low yield. A mixture of (*E*)-5-styryl-1-tosyl-3-(2-tosyloxyphenyl)-1*H*-pyrazole (**56a**), *N*-methylmaleimide (6 equiv) and a few drops of 1,2,4-trichlorobenzene (1,2,4-TCB) was irradiated with MW at 800 W for 1 h (Scheme 11.1). Thin-layer chromatography revealed the presence of the starting material together with a new product; therefore, three additional equivalents of *N*-methylmaleimide were added and the mixture was irradiated for a



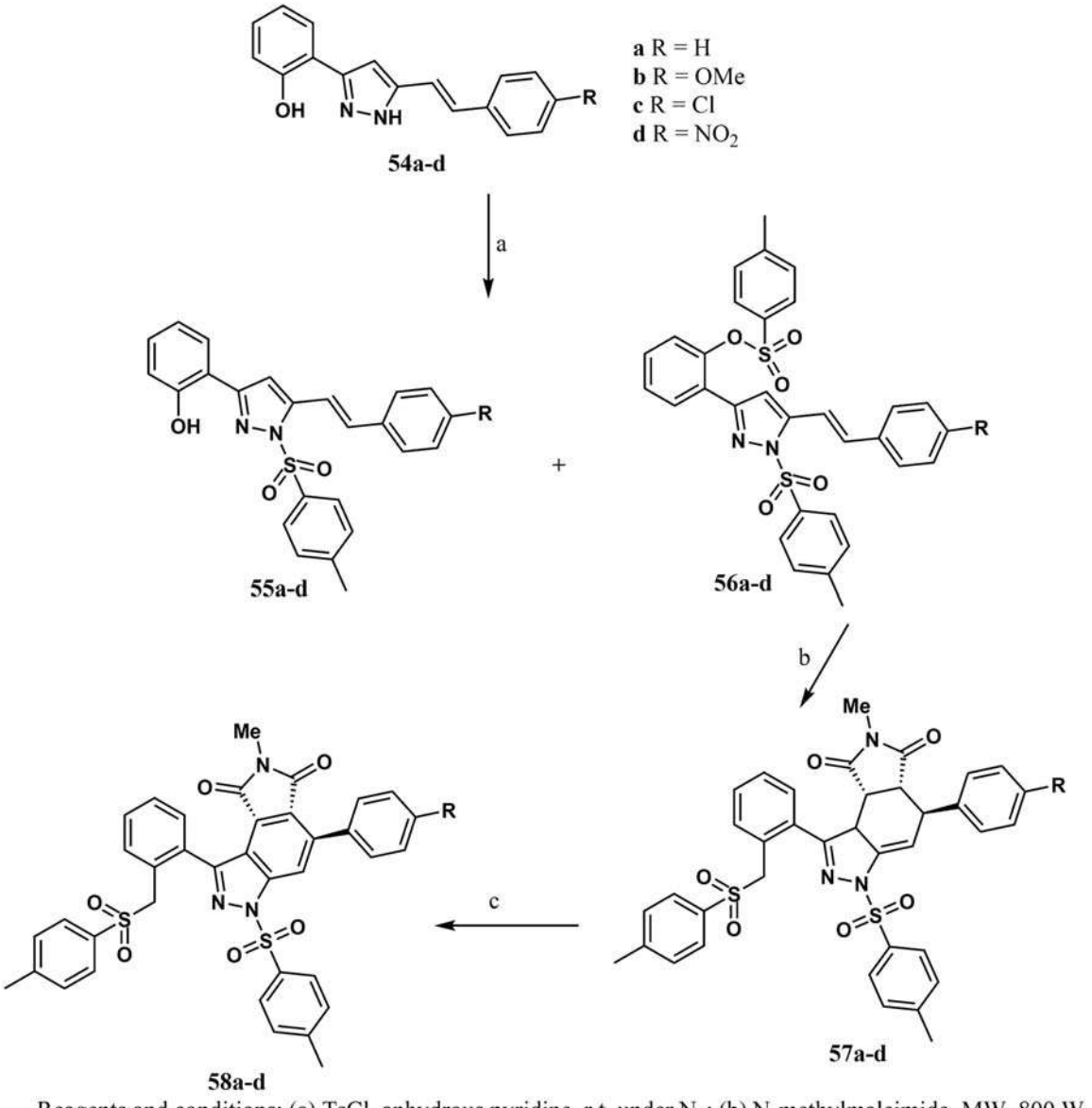
SCHEME 11.11 Synthesis of *N*-tosyl-5-fluoro-3-cycloalkyliminoindazole **50**.



SCHEME 11.12 Synthesis of indazole derivative **51**.



SCHEME 11.13 Synthesis of indazole derivatives in different methods.



Reagents and conditions: (a) TsCl, anhydrous pyridine, r.t. under N_2; (b) N-methylmaleimide, MW, 800 W, 1,2,4-TCB (cat.); (c) DDQ, 1,2,4-TCB, 170 °C, under N_2.

SCHEME 11.14 Synthesis of **55a–d** and **56a–d** by tosylation of (*E*)-3(5)-(2-Hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles **54a–d**.

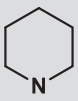
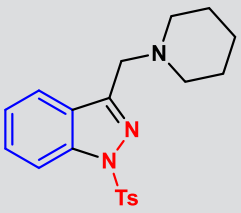
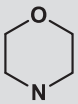
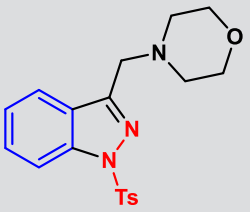
further 40 min. After this treatment and purification of the reaction mixture, the cycloadduct was isolated at 40% yield and 58% of the starting material was recovered (Table 11.5). Since the increase in reaction time and amount of *N*-methylmaleimide did not contribute to the complete consumption of the starting material, we performed the cycloaddition reaction of (*E*)-5-styryl-1-tosyl-3-(2-tosyloxyphenyl)-1*H*-pyrazoles **56b–d** with *N*-methylmaleimide under similar conditions. The expected cycloadducts **57b** and **57c** were obtained at low isolated yields, thus confirming the poor reactivity of these pyrazoles. In the case of pyrazole **56d**, no cycloadduct was formed, with only extensive degradation of the starting material being observed (Table 11.4). To improve the yields of the Diels–Alder reaction, we performed the reaction under pressure using sealed vials and different solvents (DMF and NMP) but the desired cycloadducts were not obtained (Table 11.5) [76].

Practical and environmentally friendly synthesis of 3-aminomethyl-*N*-tosyl-indazoles is developed. The in situ formed vinyl azines are reacted with amines to furnish amino functionalized antihydrazones in excellent yields. Subsequent copper-catalyzed cyclization at ambient temperature is effective and desired compounds are obtained in short reaction times. Based on the reported work on copper-catalyzed cyclizations [77], it was decided to utilize *N*,*N*′-dimethylethylenediamine (DMEDA), as a ligand and CuI as a copper source. The reactions were carried out at room temperature in air, and in all entries, full conversion was achieved in less than

TABLE 11.5 Reaction conditions and yields of 55a–d and 56a–d by tosylation of (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles 54a-d.

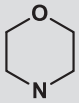
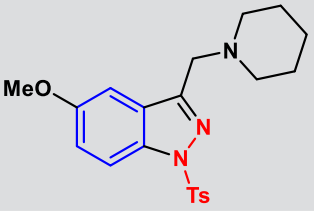
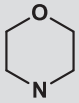
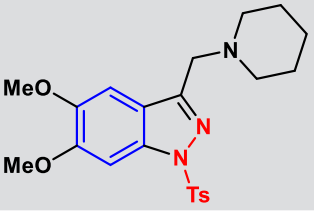
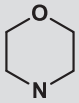
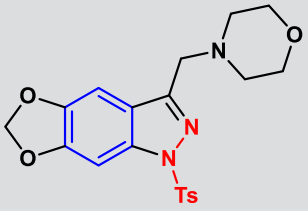
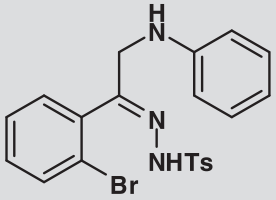
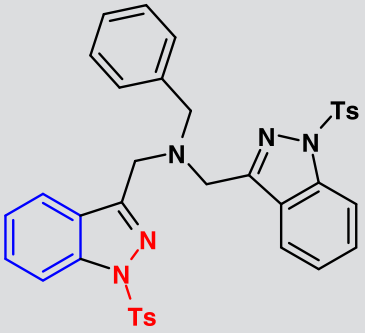
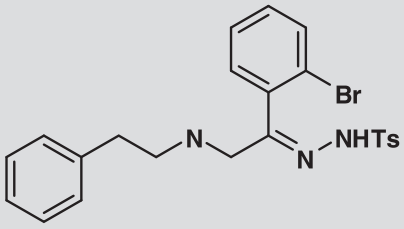
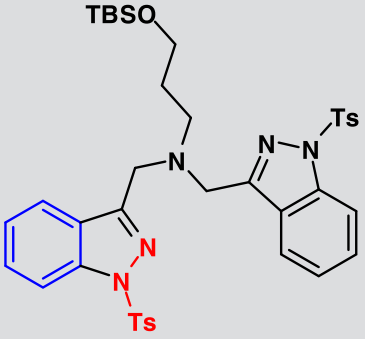
R	54 (mmol)	TsCl (equiv)	Time (h)	Yield 55 (%)	Yield 56 (%)	Recovered 54 (%)
54a, H	2.7	2.2	72	38	41	-
54a, H	1.6	3.0	48	20	42	-
54a, H	3.1	4.0	72	Trace	42	-
54b, OMe	2.6	3.0 + 1.5	72 + 48	5	52	17
54b, OMe	4.4	4.0	72	3	39	42
54c, Cl	1.0	3.0	96	32	18	-
54c, Cl	3.4	4.0	72	20	80	-
54c, Cl	1.5	4.0	72	9	48	-
54d, NO_2	1.6	4.0	28	2	16	-
54d, NO_2	1.6	4.0	48	6	11	-
54d, NO_2	1.6	2.2 + 2.0	24 + 48	11	-	33

TABLE 11.6 Synthesis of different *N*-tosyl indazoles 60a–i.

Entry	R	R´	Product (60a–i)	Yield[a] (%)
1		H		92
2		H		100

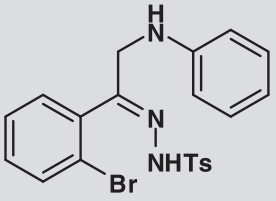
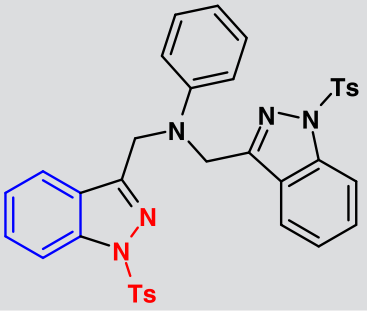
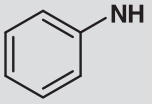
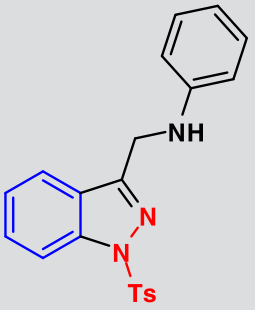
(*Continued*)

TABLE 11.6 (Continued)

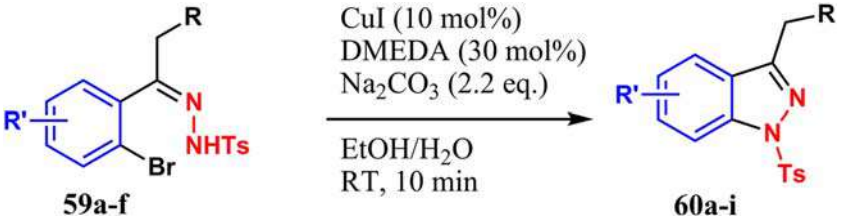
Entry	R	R´	Product (60a–i)	Yield[a] (%)
3		OMe		99
4		di-OMe		92
5		–OCH_2O–		95
6		H		98
7		H		95

(*Continued*)

TABLE 11.6 (Continued)

Entry	R	R´	Product (60a–i)	Yield[a] (%)
8		H		54
9		H		100

[a]*Isolated yield.*



SCHEME 11.15 Formation of *N*-tosyl indazoles **60a–i**.

10 min with the results summarized in Scheme 11.4. The starting materials **59a–f** (Table 11.6) were simply slurried in EtOH/H_2O (1:1 for entries 1–5 and 2:1 for entries 6–9) (Table 11.5), treated with Na_2CO_3, and stirred for 2 min. DMEDA (0.7 M solution in EtOH) and CuI were added and the reactions were monitored by TLC (hexane/EtOAc 1:1 or 2:1). After aqueous workup, products **60a–i** were obtained in excellent yield with no need for chromatographic purification [78] (Scheme 11.4; Scheme 11.15).

11.3.2 Biological activities of *N*-sulfonyl benzimidzole

11.3.2.1 5-HT$_6$ antagonists

Indazoles are excellent replacements for indoles as potent and selective 5-HT_6 antagonist cores. Cole [79] and Zhou [80] reported 1-sulfonylindazoles with a basic amine such as piperazine (**61**) or an aminoalkoxy side chain **62** (Fig. 11.14) at the 4-position as potent 5-HT_6 antagonists. It should be noted that this particular sulfonyl group is one of the optimal sulfonyl groups for several classes of 5-HT_6 ligands. The amino side chain can be replaced by other amino groups (e.g., **63**) and the 6-position was found to be the optimal position for some of the chemical series as demonstrated by Liu and Robichaud [81]. Liu, Robichaud, and Bernotas further demonstrated that the sulfonyl group can be migrated from the 1-position to the 3-position of the indazole core to provide compounds with great potency and improved physical properties (i.e., water solubility) [82–84].

1-Sulfonylindazole derivatives **64–66** (Fig. 11.15) were evaluated for their binding affinity to the human 5-HT6 receptor in a standard competition binding assay [85] and the results are summarized in Table 11.6. A range of

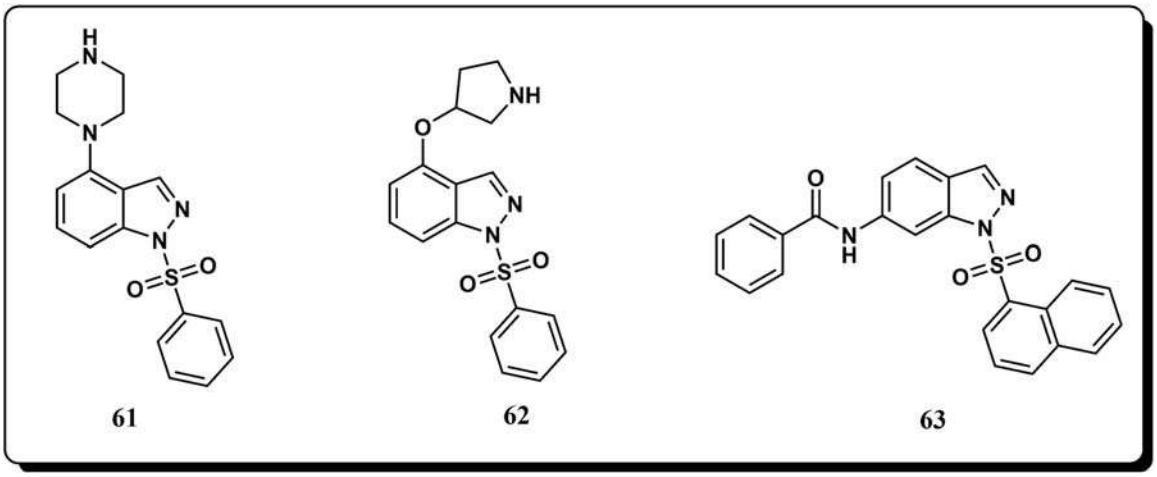


FIGURE 11.14 Structure of 5-HT6 antagonists 1-sulfonylindazole **61-63**.

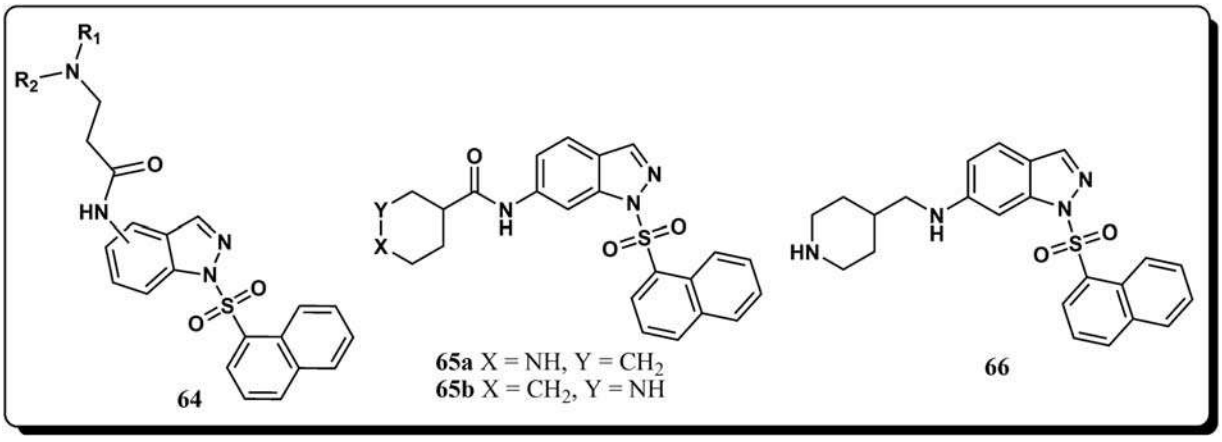


FIGURE 11.15 Structure of *N*-sulfonylindazole **64-66**.

arylsulfonyl groups was explored and, in particular, the 1-naphthalenesulfonyl group was identified to be one of the optimal sulfonyl groups. Compounds **64a–c** were then synthesized with an acyclic amino alkyl group at the 4–6 positions of the indazole to identify the optimal amine regiochemistry for this core.

Clearly, the data shows that substitution of the 6-position is preferred, as exemplified by compound **6c** with a potency of 0.5 nM at the 5-HT_6 receptor. Further substitution on the basic nitrogen appendage of **64c** was then explored for **64d–g** (Table 11.7) to further elucidate the SAR of the amine moiety. Although the small alkyl substitution **64d–f** affords minimal loss of potency (by 2–fourfold), larger alkyl groups (e.g., **64g**) reduce affinity significantly (by >30-fold). In addition, compounds with a cyclic amino moiety were prepared in which both the 3- and 4-piperidinyl derivatives **65a** and **65b** displayed excellent affinity (*Ki* = 2.3 and 1.3 nM, respectively).

The reduced analog **66a** (Table 11.8) was prepared and exhibited a >eightfold loss in potency compared to amide 7a. This would suggest that the hydrogen bonding properties of the amide are making a key interaction in the receptor site, contributing to increased 5-HT_6 affinity. Alternatively, the amide bond of **65a** and **65b** may have provided a favorable conformational change for 5-HT_6 affinity. Selected compounds were further evaluated for their functional activity in a 5-HT_6 receptor cyclase assay [85]. All of the indazole derivatives evaluated showed full antagonism as determined by blockage of 5-HT induced cyclic AMP (cAMP) formation. The data is summarized in Table 11.8.

Compounds **64c, 65a**, and 65b, which displayed excellent potency in both binding and cyclase functional assays, were further profiled by their selectivity against a panel of receptors including several other 5-HT receptor subtypes, adrenergic a2A, and dopamine D2 receptors. In general, all three compounds showed >500-fold selectivity over all the receptors except for 5-HT2B. Since 5-HT2B agonism activity has been associated with adverse cardiovascular effects,15 of the compounds were then screened for their potential agonist activity in a FLIPR

TABLE 11.7 5-HT_6 binding affinity of 1-sulfonylindazoles[a].

Compound	position	R_1	R_2	*Ki* (nM)
64a	4	H	H	7.9
64b	5	H	H	50
64c	6	H	H	0.5
64d	6	CH_3	H	1.2
64e	6	CH_3	CH_3	1.8
64f	6	CH_3CH_2	CH_3CH_2	2.1
64g	6	$–CH_2\ CH_2\ CH_2\ CH_2\ CH_2–$	–	15
65a	6	–	–	2.3
65b	6	–	–	1.3
66	6	–	–	18

[a]*Displacement of [3H]-LSD binding to cloned human 5-HT6 receptors stably expressed in HeLa cells. Ki values were determined in triplicate.*

TABLE 11.8 Cyclase functional activity of selected 1-sulfonylindazoles[a].

Compound	IC_{50} (nM)	*I*max (%)
64c	11	100
64d	26	100
64e	53	100
64f	260	100
64g	170	100
65a	8	100
65b	10	100

[a]*Antagonism of 5-HT stimulated cAMP formation in HeLa cells stably transfected with human 5-HT_6 receptors.14 IC50 and Imax values were determined in triplicate.*

assay [86]. To our satisfaction, no activity was observed for all three compounds at concentrations of 0.1 nM-10 lM in this functional assay.

The solubility, cytochrome P450 inhibition, and in vitro PK properties of **64c**, **65a**, and **65b** of the three compounds have excellent water solubility (> 100 lg/mL @ pH 7.4), good human and modest rat microsomal stability, and good brain penetration. In addition, no major P450 inhibition was observed for these compounds [81].

11.3.2.2 Antiepilepsy

Using this template, several alternate basic side chains were examined in place of ethylamine or piperazine. This approach is exemplified by 3-aminopropionamide (67), which shows an impressive affinity for the 5-HT_6 receptor for a nonpiperazine, with a *Ki* of 0.5 nM, and proved to be a functional antagonist [87]. If the distance between the basic group and the heterocycle is increased further, there is a precipitous loss in affinity. However, the basic side chain could be substituted at the 4thposition of the indazole while retaining excellent affinity. For example, either compound **67** or **68** (Fig. 11.16) has a 5-HT_6 *K*i of 1 nM [87]. Chemically closer to the piperazine moiety is the aminoazetidine group that can be introduced with retention of activity. It is worth noting that in this case, the indazole geometry is inverted and the point of attachment of the sulfonyl group is in the 3-position, leaving a relatively acidic indazole NH. The principal therapeutic targets of the Wyeth team are similar to Roche and GSK: enhancement of cognition and memory in human diseases, such as AD, and treatment for epilepsy [87].

11.3.2.3 HDAC inhibitor activity

HDAC inhibitors are grouped chemically into four classes: hydroxamic acids, benzamides, short-chain fatty acids, and cyclic tetrapeptides. To date, many studies on HDAC inhibitor development have focused on hydroxamic acids. The hydroxamic acid moiety has been identified as a crucial motif interacting with HDAC by chelation of a zinc ion at the catalytic site in the case of trichostatin A and suberoylanilide hydroxamic acid (1, *N*-hydroxy-*N*´-phenyloctanediamide or SAHA) [88] and has attracted numerous investigations into the development of hydroxamic acid derivatives. The development of selective isotype HDAC inhibitors that can avoid the side effects of HDAC treatment is a significant task and an increasing number of investigations are focusing on the development of selective isotype HDAC inhibitors.

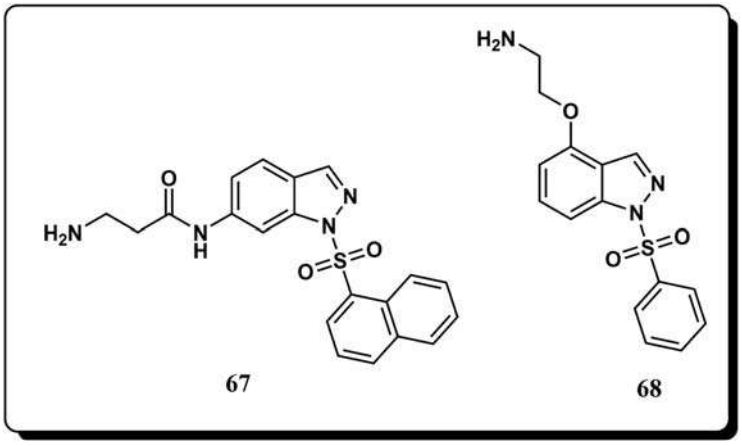


FIGURE 11.16 Structure of anti-epilipsy compounds **67** and **68**.

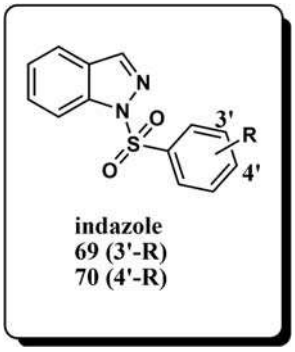


FIGURE 11.17 Structure of HDAC inhibitors **69** and **70**.

The synthetic compounds comprise the following three structural features of HDAC inhibitors: a Zn^{2+}-binding group, a hydrophobic linker, and a surface recognition cap group. Literature surveys indicated that indole as well as indazole serves as a cap recognition moiety in many HDAC inhibitors [89]. In an attempt to produce HDAC inhibitors with indole as a cap group, it was planned to interchange the cap and linker parts, and the effect of various azaindoles on the antiproliferative activity of HDAC inhibitors was considered. As a result, a series of indolyl/ azaindolylsulfonylcinnamic hydroxamates **69** and **70** (Fig. 11.17) were investigated for their HDAC biological assays [90].

11.4 *N*-Sulfonyl triazoles

11.4.1 Chemistry of *N*-sulfonyl triazoles

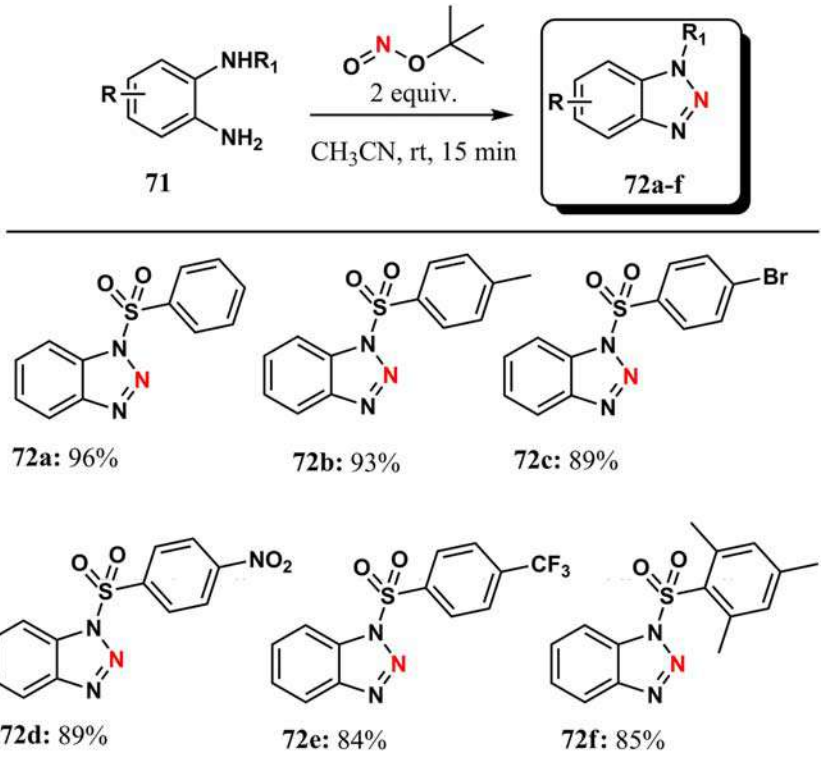
It studied the chemistry of *N*-nitrosamines [91,92] the recently demonstrated applications of *tert*-butyl nitrite in *N*-nitrosation of secondary amines [93] and oxidative dimerization of thioamides to 1,2,4-thiadiazoles under mild conditions [94]. In continuation, it was reported *tert*-butyl nitrite mediated the conversion of *o*-phenylenediamines into benzotriazoles at room temperature (Scheme 11.16).

With optimized conditions in hand, the transformation of various substituted *o*-phenylenediamines into corresponding benzotriazoles was investigated (Scheme 11.16). 1,2-Phenylenediamines bearing electron-donating groups (e.g., methyl and *tert*-butyl) and withdrawing groups (e.g., halogens, nitro group, trifluoromethane, etc.) underwent diazotization smoothly. These reactions provided the corresponding benzotriazoles in quantitative yields within 15 min at room temperature (Scheme 11.16, **72a–f**). It is noteworthy that the substituents present on the aryl ring (i.e. EDG or EWG) did not influence the reaction yield and time. Further investigation of the conversion of various mono-*N*-sulfonyl and *N*-acyl 1,2-phenylenediamines into corresponding benzotriazoles using *tert*-butyl nitrite under optimized conditions. All these substrates underwent triazolation smoothly and gave the corresponding *N*-sulfonyl and *N*-acyl benzotriazoles at 84%–96% yields within 15 min at room temperature (**72a–f**) [95].

Despite various advantages, an alternative method that is convenient, catalyst-free, and handled easily to enable *N*-sulfonylation of imidazoles is desirable. An alternative method for the *N*-sulfonylation of imidazoles without any catalyst is using NFSI as the sulfonyl source [33,96–98] and $NaHCO_3$ as a base under air conditions (Scheme 11.17).

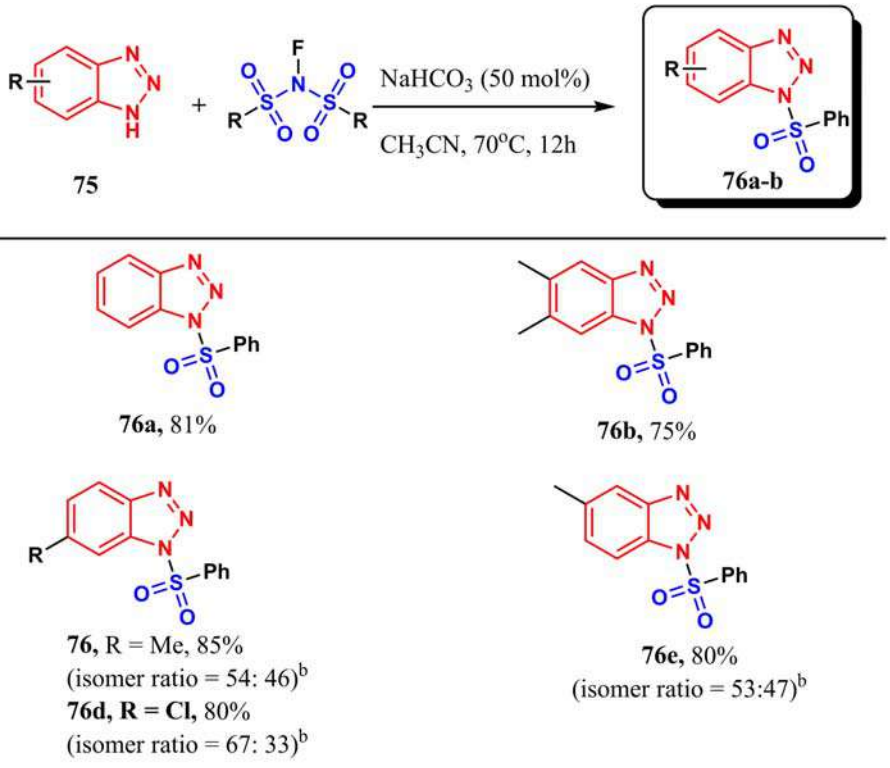
With the optimal conditions, the generality of this method was explored, and the results are summarized in Scheme 11.17.

Furthermore, this method could realize the *N*-sulfonylation of benzotriazole. The benzotriazole gave the corresponding product at an 81% yield (**76a**). 5,6-Dimethyl benzotriazole delivered the desired product at a 75% yield (**76b**). 5-Methylbenzotriazole led to the products at 85% yields with an isomeric ratio of 54:46 (**76c**). Meanwhile, 5-cholobenzotriazole afforded a **76d** in 80% yield with an isomeric ratio of 67:33. Methyl-benzotriazole gave the desired products **76e** at an 80% yield (53:47) [35].



[a] Reaction conditions: Substrate (1 mmol), TBN (2 equiv.) in acetonitrile (5 mL) at room temperature.
[b] Isolated yields.
[c] Reaction was performed using $NaNO_2$/AcOH .

SCHEME 11.16 Synthesis of benzotriazoles using *tert*-butyl nitrite in acetonitrile[a,b].



Reaction conditions: **75** (0.3 mmol), NFSI (0.45 mmol), $NaHCO_3$ (50 mol %), and CH_3CN (2 mL) at 70°C under air for 12 h.
Yields refer to the isolated yields. A mixture of N_1- and N_3-sulfonylated products.

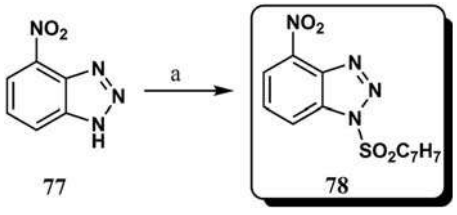
SCHEME 11.17 The sulfonylation of benzotriazole.

Katritzky et al. well explored the chemistry of benzotriazole moiety for many decades [99–101], although 4-nitro benzotriazoles is relatively less explored [102,103].

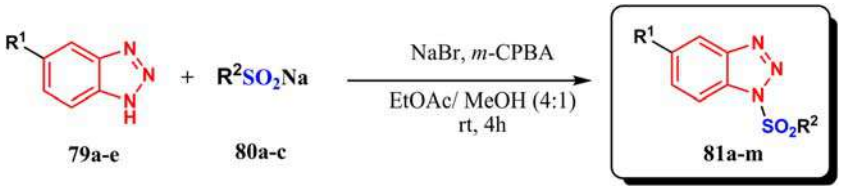
The reaction of 4-nitrobenzotriazole with sodium hydroxide and DMF-without the addition of alkyl halides was carried out at room temperature but did not result in yellow compound formation. Further, on heating, this solution above 45°C resulted in degradation of 4-nitrobenzotriazole, and the same yellow compound was isolated. Thus, the reaction of alkyl halides with 4-nitrobenzotriazole in sodium hydroxide and DMF was tried under cold conditions, but yellow impurity was still found, besides the isomer products. Upon NMR analysis, the impurity was found to be 3-nitrobenzene-1,2-diamine. Consequently, alkylation was carried out under milder conditions using potassium carbonate and dry DMF for 30 min, stirring at room temperature. Here, the alkyl product tosyl derivative **78** was prepared and isolated as described in Scheme 11.18 [104].

A convenient procedure is developed for the preparation of *N*-sulfonylbenzotriazoles from sodium sulfinates, benzotriazoles, and sodium bromide in the presence of *m*-chloroperbenzoic acid as oxidant. This radical sulfonylation proceeds efficiently at room temperature under neutral conditions, affording the corresponding *N*-sulfonylbenzotriazoles with moderate to good yields in a short time. Based on the extensive screening process, we arrived at the optimal reaction conditions (Scheme 11.19). Next, the one-pot sulfonylation of 1.0 equiv of benzotriazoles **79a–e** with 1.8 equiv of sodium sulfinates [15] (**80a–c**), 1.2 equiv of NaBr, and 1.3 equiv of *m*-CPBA in EtOAc/ MeOH (4:1) at room temperature for 4 h was investigated. As a consequence, a series of corresponding *N*-sulfonylbenzotriazoles (**81a–m**) were obtained. The results are summarized in Table 11.9, whereas the sulfonylation was compatible with the studied benzotriazoles **79a–e**, affording the corresponding sulfonylbenzotriazoles **81a–m** in moderate to good yields (Table 11.9, entries 1–12). It was obvious that sodium benzenesulfinate **80a** had the best effect in the reaction compared with the other two sodium sulfinates, and sodium methylsulfinate **80c** usually resulted in moderate yields. When 5-methylbenzotriazole **79b** and 5-chlorobenzotriazole **79c** were used in the reaction, these monosubstituted benzotriazoles typically gave 5-substituted and 6-substituted mixture products. Because the mixtures were difficult to isolate, the ratios of 5-substituted products to 6-substituted products were finally determined to be nearly 1:1 by ^{1}H NMR analysis (entries 4–9). Under the same reaction conditions, 1,2,4-triazole **79e** was also treated with **80a**, but the product **81m** was obtained with a somewhat lower yield, 38% (entry 13). To explore the efficiency and generally of this methodology, indole was treated under the same reaction conditions. However, the reaction resulted in a 2-sulfonylated product *via* a radical addition and then an elimination process [105]. 5-Nitroindazole and tetrazole, which have two or four nitrogen atom heterocycles, respectively, were also checked, but the desired *N*-sulfonylated products were not obtained. Therefore, the new and convenient *N*-sulfonylation was suitable for triazoles [19].

A convenient procedure was developed for the preparation of *N*-sulfonylbenzotriazoles from sodium sulfinates and benzotriazoles using molecular iodine [106] as a catalyst *via* the S–N bond formation reaction [107–110]. This catalytic radical sulfonylation proceeds efficiently in the air at room temperature under neutral conditions, and in a short reaction time, to afford the corresponding *N*-sulfonylbenzotriazoles in good yields, thus extending the catalytic application of molecular iodine in organic synthesis [111]. Based on the extensive screening process, it arrived at the optimal reaction conditions in which the catalytic reaction of 1.0 equiv. of benzotriazoles (**82a–e**) with 3.0 equiv. of sodium sulfinates (**83a–c**) and 0.2 equiv. of I_2 in EtOAc-H_2O (10:1) at room temperature for 3 h was investigated. As a consequence of that, a series of corresponding *N*-sulfonylbenzotriazoles **84a–e** were obtained. The results are summarized in Table 11.10, in which the I_2-catalyzed reaction was compatible with the studied benzotriazoles **82**, affording the corresponding sulfonylbenzotriazoles **84a–m** in moderate to excellent yields (Table 11.10, entries 1–12). It was obvious that sodium benzenesulfinate **83a** had the best effect in the reaction compared with the other two sodium sulfinates, and sodium methylsulfinate **83c** usually

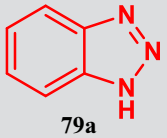
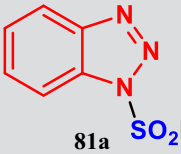
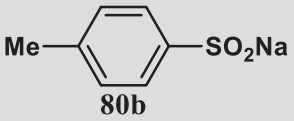
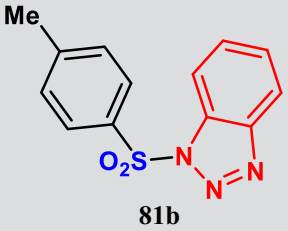
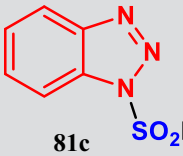
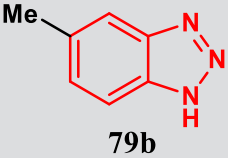
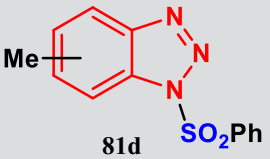
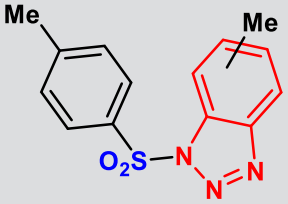
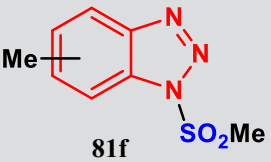
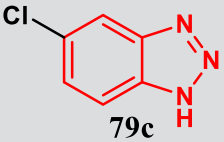
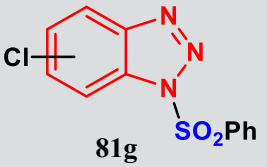
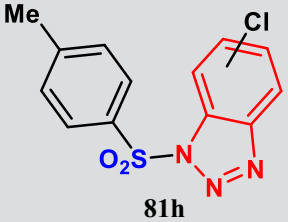


SCHEME 11.18 Alkylation under mild basic conditions. Reagents and Conditions: pyridine, reflux, 30 min., $C_7H_7SO_2Cl$.



SCHEME 11.19 Sulfonylation of benzotriazoles **81a–m**.

TABLE 11.9 Preparation of *N*-sulfonylbenzotriazoles 81a–m.

Entry	Benzotriazole 79	Sodiumsulfinate 80	Product 81	Yield (%)
1	 **79a**	$PhSO_2Na$ **80a**	 **81a**	90
2	**79a**	 **80b**	 **81b**	70
3	**79a**	$MeSO_2Na$ **80c**	 **81c**	50
4	 **79b**	**80a**	 **81d**	70
5	**79b**	**80b**	 **81e**	62
6	**79b**	**80c**	 **81f**	40
7	 **79c**	**80a**	 **81g**	78
8	**79c**	**80b**	 **81h**	72

(*Continued*)

TABLE 11.9 (Continued)

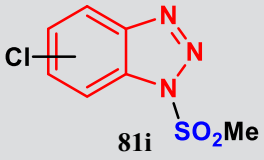
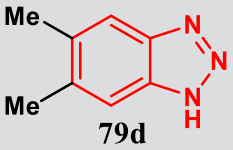
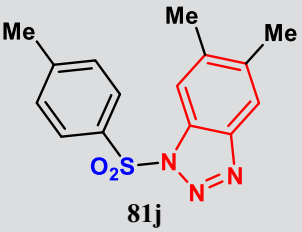
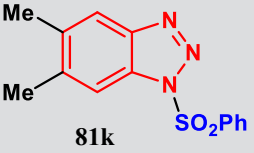
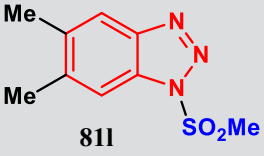
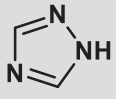
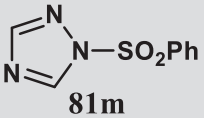
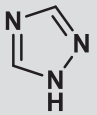
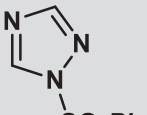
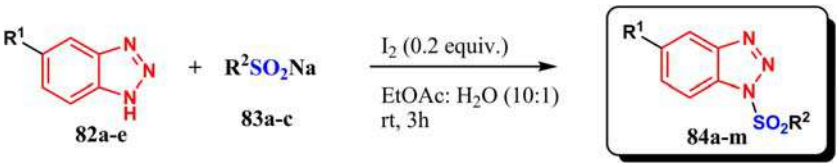
Entry	Benzotriazole 79	Sodiumsulfinate 80	Product 81	Yield (%)
9	**79c**	**80c**	 **81i**	48
10	 **79d**	**80a**	 **81j**	82
11	**79d**	**80b**	 **81k**	68
12	**79d**	**80c**	 **81l**	45
13	 **79e**	**80a**	 **81m**	38

TABLE 11.10 Preparation of *N*-sulfonylbenzotriazoles 84a-m.

Entry	82a–e (R^1)	83a–c (R^2)	Product 84a–m	Yield(%)[a]
1	H	Ph	77a	97
2	H	4′-MeC_6H_4	77b	78
3	H	Me	77c	61
4	Me	Ph	77d	99
5	Me	4′-MeC_6H_4	77e	86
6	Me	Me	77f	68
7	Cl	Ph	77g	82
8	Cl	4′-MeC_6H_4	77h	70
9	Cl	Me	77i	58
10	4, 5-diCH_3	Ph	77j	87
11	4, 5-diCH_3	4′-MeC_6H_4	77k	72
12	4, 5-diCH_3	Me	77l	60
13	 **82e**	Ph	 **84m**	48

[a]*Isolated yields.*

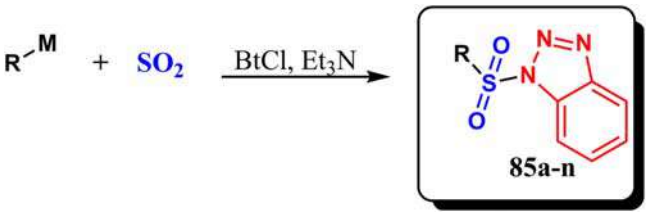


SCHEME 11.20 *N*-sulfonylation of benzotriazoles using I_2 as a catalyst.

resulted in moderate yields. When 5-methylbenzotriazole **82b** and 5-chlorobenzotriazole **82c** were used in the reaction, these monosubstituted benzotriazoles typically gave 5-substituted and 6-substituted mixture products which were difficult to be isolated, and by ^{1}H NMR analysis, the ratios of 5-substituted products to 6-substituted products are ranging from 1:1 to 2:3 (entries 4–9). Under the same reaction conditions, 1,2,4-triazole **82e** was also treated with **83a**, but the product **84m** was obtained with a somewhat low yield of 48% (entry 13).

To explore the efficiency and generally of our methodology, as the representative of one nitrogen atom heterocycles, indole resulted in the 2-sulfonylated product, not the desired *N*-sulfonylated product [105]. Under the same reaction conditions, heterocycles with two nitrogen atoms and four nitrogen atoms were also checked; however, the desired *N*-sulfonylated products were not obtained [111] (Scheme 11.20).

1-(Alkylsulfonyl)- and 1-(arylsulfonyl)benzotriazoles react with sodium azide in acetonitrile to give the corresponding alkanesulfonyl and arenesulfonyl azides [112]. It was developed a general and facile method for the preparation of 1-sulfonylbenzotriazoles **85** as a practical alternative to the frequently labile and often difficult to access sulfonyl halides [113]. 1-Sulfonylbenzotriazoles **85** provide efficient *N*-sulfonylation of amines and C-sulfonylation of nitriles, heteroaromatics, sulfones, and esters to produce -cyanoalkyl sulfones, sulfonylheteroaromatics, -sulfonylalkyl sulfones and esters of -sulfonyl acids, respectively (Scheme 11.21) [18]. They are also useful in the synthesis of *N*-acylbenzotriazole from the corresponding carboxylic acid [114–116]. Herein we report the application of 1-sulfonylbenzotriazoles to the preparation of sulfonyl azides.1-Sulfonylbenzotriazoles **85a–n** are accessible from aryl- and alkyllithium or Grignard reagents



SCHEME 11.21 Preparation of *N*-sulfonyl benzotriazole **85a–n**.

TABLE 11.11 Preparation of 1-(alkylsulfonyl)- and 1-(arylsulfonyl)benzotriazoles 85a–n.

85	R	M	Yield[a] (%)	mp (°C)	Lit. mp (°C)
a	*N*-butyl	Li	68	oil	oil
b	Cyclohexyl	MgCl	74	118–119	117–119
c	4-tolyl	MgBr	90	131–132	133–134
d	2-thienyl	Li	80	142–144	143–144
e	1-methyl-1*H*-indol-2-yl	Li	22	131–133	131–132
f	2-furyl	Li	85	108–109	107–109
g	2-pyridyl	Li	73	130–132	132–135
h	1-methyl-1*H*-indol-2yl	Li	82	146–149	147–150
i	2-benzofuryl	Li	75	147–148	147–148
j	3-pyridyl	Li	50	128–130	128–129
k	5-ethyl-2-furyl	Li	60	96–97	147–148
l	2-thiazolyl	Li	11	114–116	–[b]
m	5-methyl-2-thienyl	Li	45	104–106	–[b]
n	5-methyl-2-furyl	Li	35	114–116	–[b]

[a] *Isolated yields.*
[b] *Novel compound.*

by reaction with sulfur dioxide and 1-chlorobenzotriazole (Table 11.11) [113].

The 1,2,3-Triazole scaffold was synthesized using the reaction of the corresponding alkynes with tosyl azide using click chemistry (CuAAC) (Scheme 11.22) [117] at room temperature using literature procedure [118].

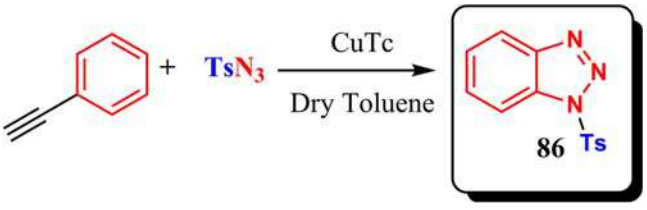
NBS or NIS mediated direct S-N bond formation between azoles and sodium sulfinates **88** is described (Scheme 11.23). The reaction shows good substrate scope and tolerates a wide range of functionalities in both azoles and sodium sulfinate substrates. Under the optimized reaction conditions, the scope of azole **87** and sodium sulfinates was examined. Additionally, triazole **87** was tolerated in this reaction, leading to product **89** with moderate to good yields [119].

On this basis, through the fragment-based drug design strategy, Becerra's group designed and prepared a library of *N1*-benzenesulfonyl derivatives of BT [20]. Following the procedure reported by Katrinsky [17], all compounds were prepared by sulfonylation. The group determined the biological in vitro activity of *NN*-benzenesulfonylbenzotriazole (compound **90**) on the protozoan parasite *TrypaNosoma cruzi* [120]. Different concentrations of *N*-benzenesulfonylbenzotriazole were tested on *epimastigote* and *trypomastigote* forms, demonstrating that the derivative had an in vitro growth inhibitory dose-dependent activity against epimastigotes. Particularly, after incubation for 72 h, the parasite number in epimastigotes form decreases by about 50% at 25 mg/mL and by 64% at 50 mg/mL. In the same conditions, BT, used as a reference compound, did not show any antitrypanosomal activity. Compound (**90**) appeared to be even more effective on trypomastigotes, the infective form of the parasite. Indeed, in earlier time points, a concentration of 50 mg/mL of this compound induced trypomastigotes dead 95% higher than in epimastigote forms. On the contrary, BT was less effective, causing only 21% of dead parasites at the same concentration [121] (Fig. 11.18).

11.4.2 Biological activities of *N*-sulfonyl benzotriazoles

11.4.2.1 Sodium hydrogen exchanger inhibitory activity

The widely used benzotriazole is in aircraft deicing and antiicing fluids (ADAF) as an anticorrosive agent during the winter. In the United States, more than 80 million liters of sewage water that is contaminated with ADAFs are released into the environment every year [122]. Most of the ADAFs are ethylene glycol-based mixtures that contain benzotriazole. Previous studies have shown that benzotriazoles exhibit potential impacts on the environment. It is reported that the life span of freshwater species is reduced by the presence of benzotriazole in water. This may be due to their inability to adapt to environmental pH and temperature changes [123].



SCHEME 11.22 Synthesis *N*-tosyl benzotriazole **86**.

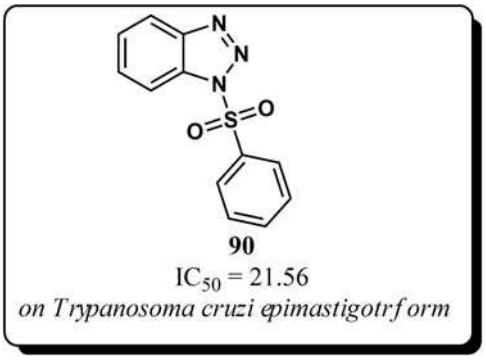
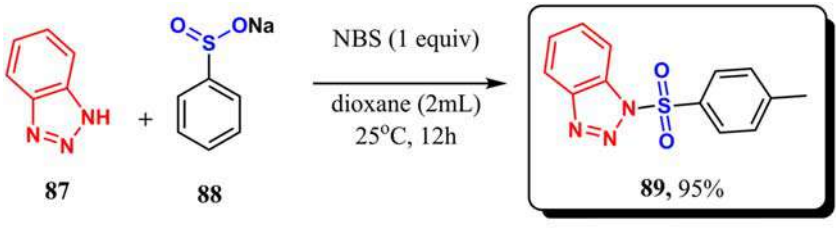


FIGURE 11.18 Structure of the effective *N*-benzenesulfonylbenzotriazole **90** on the protozoan parasite *Trypanosoma cruzi*.



[a] Reaction conditions:**87** 0.5 mmol, **88** 1.0 mmol, oxidant 0.5 mmol, 1,4-dioxane 2 mL, 12 h, under air

SCHEME 11.23 Reactions of azole **87** with sodium sulfinates **89**.

The intracellular acid-base imbalance may be caused by metabolic, respiratory, and environmental factors [124]. This homeostasis is maintained mainly by monovalent cation/proton exchangers that catalyze active efflux of Na + and/or K + in exchange for H + from outside the cell, i.e. Na + (K +)/H + exchangers. Benzotriazole derivatives **91a,b** (Fig. 11.19) were synthesized and evaluated for their Sodium hydrogen exchanger-1 inhibitory potential. All compounds inhibit Sodium hydrogen exchanger-1 in the in vitro platelet swelling assay. This is perhaps the first report of NHE-1 inhibitory activity of benzotriazole. The 1-alkyl benzotriazole derivatives were found to be more active than the 2-alkyl isomers. The activity increases with an increase in chain length of alkyl moiety. Potency increased from that of benzotriazole (IC_{50} = 192.68 M) to heptyl derivative (IC_{50} = 59.23 M). The introduction of an electronegative oxygen atom further increased potency as shown by the benzoyl (compound **91a**, IC_{50} = 51.57 M) and sulfonyl groups (compound **91b**, IC_{50} = 50.89 M) [125].

FIGURE 11.19 Structure of sodium hydrogen exchanger Inhibitors **91a,b**.

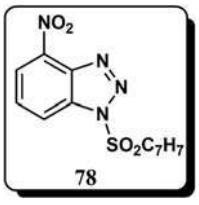


FIGURE 11.20 Structure of Platelet aggregation inhibition **78**.

11.4.2.2 Platelet aggregation inhibition activity

The facile alkylation of 4-nitrobenzotriazole under basic conditions and the synthesized derivatives were tested for their potential ADP induced platelet aggregation inhibition activity in comparison with standard drug ticagrelor (selective P2Y12 inhibitor).

The nitro group at the 4-position is highly activating toward alkylation reactions (under strongly basic conditions) and results in the formation of degradation products like 3-nitrobenzene-1,2-diamine, which makes isolation of alkyl products very difficult.

The reaction under mild basic conditions (potassium carbonate and DMF) was optimized so that is devoid of any degradation product. This is perhaps the first report of 4-nitrobenzotriazole derivatives possessing platelet aggregation inhibitory activity. Generally, activity increases with an increase in length of the alkyl chain, and 1-alkyl positional isomers were found to be more potent than 2-alkyl isomers. The benzoyl derivative **78** (Fig. 11.20) was found to be the most potent 2-Benzyl-4-nitro-2*H*-benzotriazole; IC_{50} = 0.82±0.19 mM] and sulfonyl derivative. Furthermore, compound **78** possessed P2Y12 binding affinity as confirmed by VASP/P2Y12 phosphorylation assay [104].

11.4.2.3 Antibacterial activity

A series of benzenesulfonyl compounds containing a BZT moiety was investigated for their antifungal and antibacterial activities. Compounds (**92** and **93**) showed the highest activity against *E. coli* ATCC 25922; in addition, **92** (Fig. 11.21) presented bactericidal activity against *E. coli* and *Staphylococcus aureus* at 8.6 mM. The ability of **92** to generate superoxide anion ($O^{\bullet -2}$) was measured and it showed more stimuli in *S. aureus* compared to sulfathiazole, indicating that **92** can be involved in the oxidative stress of bacteria. None of the compounds inhibited the growth of the dermatophytes strains at the tested concentration (250 g/mL) [20].

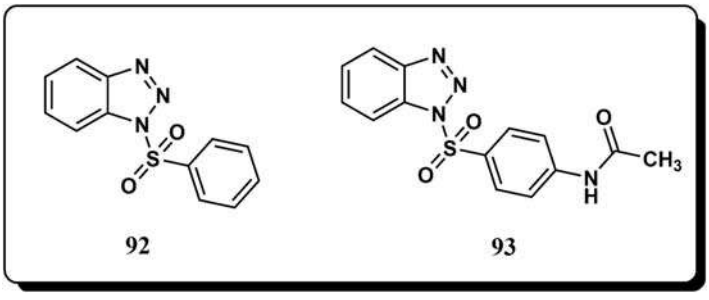


FIGURE 11.21 Structures of the antibacterial N-sulfonated benzotriazoles **92** and **93**.

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Chapter 12

N-Sulfonated *N*-benzoazines: Synthesis and medicinal chemistry

12.1 Introduction

It is evident that nitrogen-containing heterocyclic systems hold special importance in the field of organic chemistry and medicinal chemistry where an electron-rich *N*-heterocycle can donate or accept protons in addition to the ability to form a network of weak interactions [1]. Moreover, various *N*-heterocycles act as an integral part of our DNA and RNA in the form of purines and pyrimidine bases [1]. The list of FDA-approved drugs has at least 59% (2014) of small molecule drugs that bear at least one *N*-heterocycle [2]. This can be attributed to the wide range of pharmacological activity exerted by such drugs including anticancer [3], anti-bacterial, anti-viral [4], anti-malarial [5], anti-mycobacterial [6], anti-microbial [7] and anti-diabetic action [8].

On the other hand, sulfonyl group presented as sulfones or sulfonamides takes part in the structure of various pharmacologically active small molecules. This functional group has the advantage of the ability to be easily incorporated into the core ring structure or constrain a side chain in a small molecule along with its ability to form hydrogen bond interaction which enhances the drug-target interaction [9].

In this chapter, a brief overview of *N*-sulfonyl-six membered heterocycles is offered from the organic synthetic aspect and medicinal chemistry aspects.

12.2 *N*-Sulfonyl-cinnolines

12.2.1 Medicinal chemistry aspects

Cinnoline is a 1,2-benzodiazine that is considered an interesting moiety in the medicinal field. For example, cinoxacin (Fig. 12.1) is an anti-bacterial agent that is used for the treatment of urinary tract infections. However, it possesses high phototoxicity. As a result, Vargas et al. synthesized the corresponding cinoxacin naphthyl ester (Fig. 12.1) which had an acceptable photostability and exhibited anti-bacterial action against *Escherichia coli* [10].

Human neutrophil elastase enzyme (HNE) has been identified as a therapeutic target for the treatment of different lung injuries. The enzyme is implicated in the killing of pathogens, regulation of inflammation and tissue homeostasis, and chemotaxis [12,13]. An increase in the HNE enzyme has been associated with acute respiratory distress [14], chronic obstructive pulmonary disease [15], cystic fibrosis [16], and rheumatoid arthritis [17]. Sivelastat (Elaspol, Fig. 12.1) is an approved inhibitor for HNE with a 4-sulfamoyl-phenyl-pivalate fragment which is necessary for its action [18,19]. Researchers had been working to develop new inhibitors for HNE. A series of different scaffolds such as indazoles, 7-azaindazoles, cinnolinnone, and isoxazolones had activity against the target enzyme in the nanomolar range and all bearing an N-CO group instead of 4-sulfamoyl-phenyl-pivalate substitution present originally in Sivelastat. Crocetti et al. combined the previously mentioned scaffolds and replaced the N-CO group with 4-sulfamoyl-phenyl-pivalate substitution to generate different series of HNE inhibitors [11]. The cinnoline derivatives **1a** and **1b** (Fig. 12.1) showed promising activity towards HNE. Compound **1a** showed the most potent activity among all the designed compounds showing that the N-CO group can be replaced with 4-sulfamoyl-phenyl-pivalate however such replacement was not advantageous for potency [11].

12.2.2 Synthetic aspects

The Synthesis *N*-arylsulfonyl-cinnolines reported by Crocetti et al. in one step by reaction of the appropriate substrate **2a, b** with 4-(chlorosulfonyl)phenyl pivalate **3** (Scheme 12.1).

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00012-4

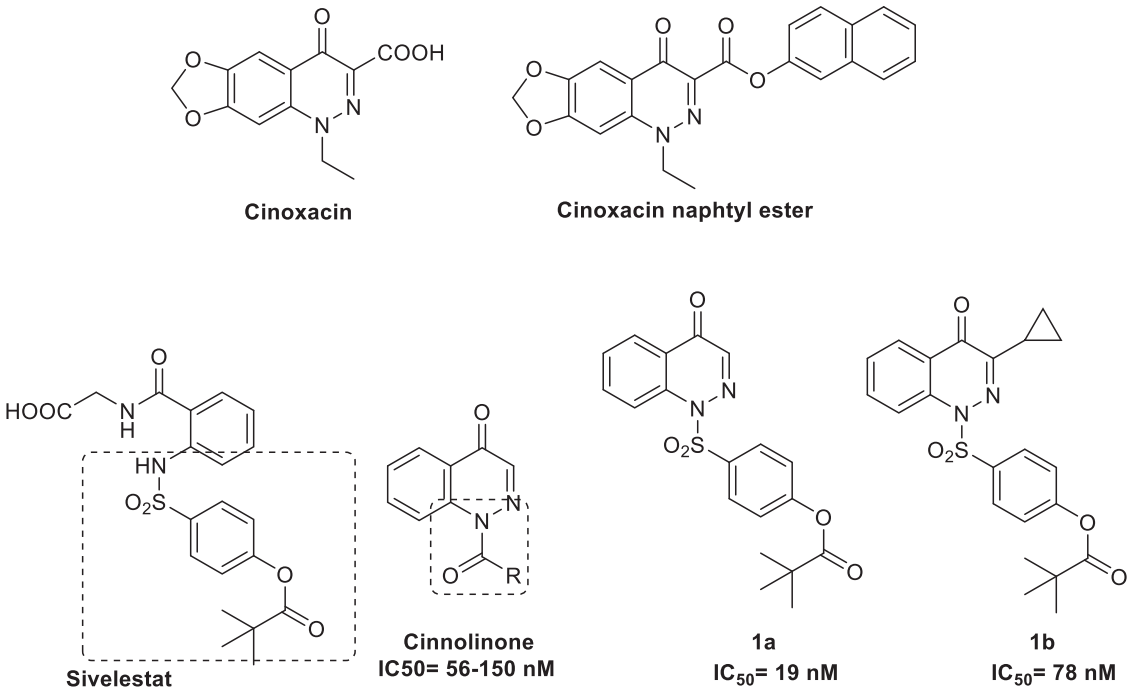
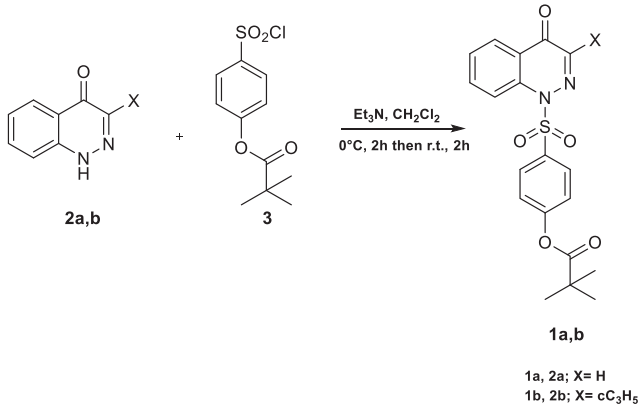


FIGURE 12.1 Some HNE inhibitors [11].



SCHEME 12.1 Synthesis of *N*-arylsulfonyl-cinnolines [11].

12.3 *N*-Sulfonyl-phthalazine

12.3.1 Medicinal chemistry aspects

Phthalizine is the 2,3-diaza analog of cinnoline, quinoline, and quinoxaline. Phthalazine scaffold has been of great importance in agricultural and medicinal fields. Various FDA-approved and investigational drugs possess phthalazine scaffolds such as MY5445 [20], Vatalanib [21], IM-023911 [22], Taladegib [23], Carbazerine, and Budralazine [24] (Fig. 12.2).

Despite the wide variety of phthalazine-based small molecules either FDA approved for human use or in development phases; there are scarce reports concerning *N*-sulfonated phthalazine. The sole report in this regard was by Takeuchi et al. reporting a weak skeletal muscle relaxant effect of compound **4a** (Scheme 12.2) [25].

12.3.2 Synthetic aspects

12.3.2.1 Synthesis of N*-methyl/phenylsulfonyl phthalazine*

The synthesis of *N*-methyl/phenylsulfonyl phthalazine was reported by Takeuchi et al. utilizing a reissert-type reaction of phthalazine with methanesulfonyl or benzenesulfonyl chloride and trimethyl phosphite in acetonitrile has emerged as straightforward access to monophosphonate derivatives (**4a** or **4b**) bearing a sulfonyl group Scheme 12.2 [25].

12.3.2.2 Synthesis of 3,4-dihydrobenzo[f] phthalazines

The synthesis of dihydrobenzo*[f]*phthalazines was achieved starting with the appropriate yneallenones **5** and sulfonyl hydrazides **6**. The reaction proceeded to form dihydrobenzo*[f]*phthalazines (**8a-d**) through the formation of naphthalen-1-ol intermediate **7**. For the reaction to proceed to its completion Fu and his co-workers utilized iodine and tert-butyl hydroperoxide as catalysts. The cyclization of **7** to yield the final product (**8a-d**) required the use of triethylamine (Scheme 12.3) [26].

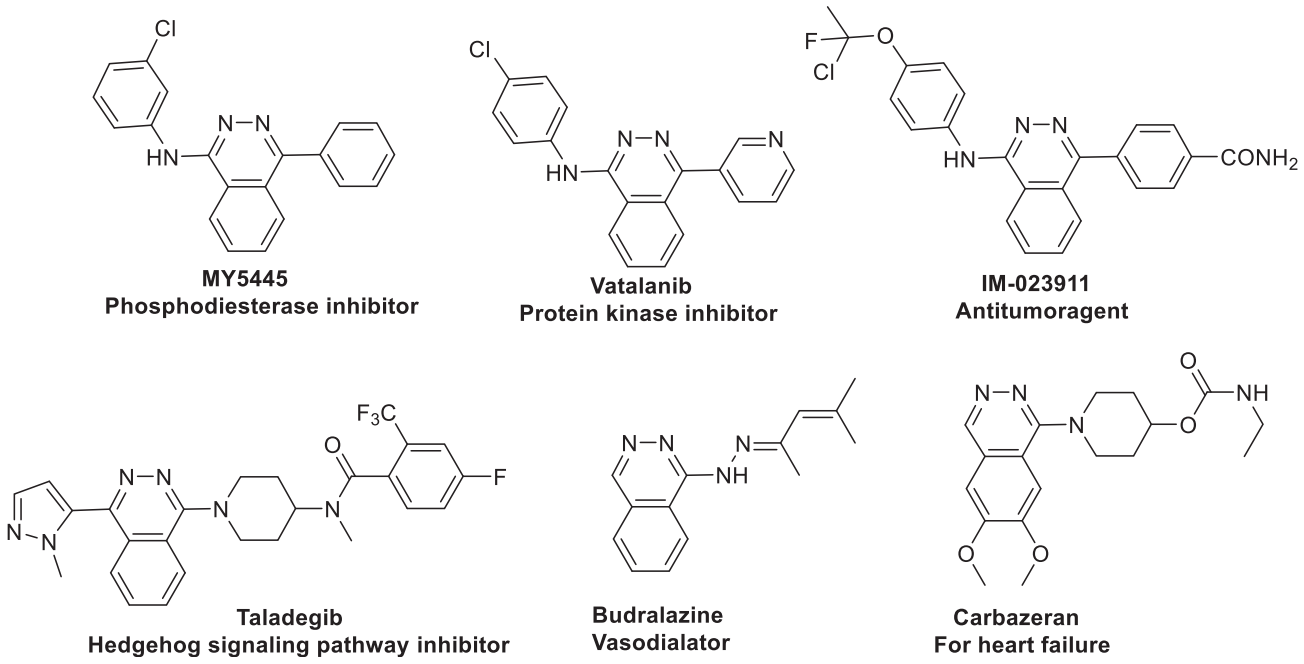
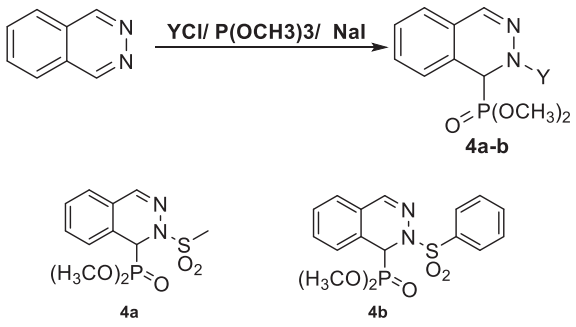


FIGURE 12.2 Phthalazine-based small molecules of pharmacological significance [24].



SCHEME 12.2 Synthesis of *N*-methyl/phenylsulfonyl phthalazine.

12.4 *N*-Sulfonyl-quinazolines

12.4.1 Medicinal chemistry aspects

Quinazolines are considered one of the most attractive bicyclic heteroaromatic scaffolds due to their wide range of biological activities including anti-viral and anti-cancer activities [27].

Erlotinib and Prazosin (Fig. 12.3) are examples of quinazoline based drugs that are used as an anti-cancer agent and as a treatment for high blood pressure, respectively [28]. Several quinazoline based drugs have been reported as pan tyrosine-protein kinase (KIT) mutant kinase inhibitors, trans-membrane voltage-gated sodium channel inhibitors, and phosphoinositide-3-kinase (PI3K) inhibitors (Fig. 12.3) [27].

Unfortunately, despite the great importance of quinazoline ring in the pharmaceutical field, reports of *N*-sulfonated quinazoline for medical applications have not been found.

12.4.2 Synthetic aspects

12.4.2.1 The preparation of dihydroquinazolines via metal-free [4 + 2] cycloaddition of ynamides with nitriles

A TfOH mediated [4 + 2] cycloaddition of ynamides with various nitriles was utilized by Wu et al., to obtain various *N*-sulfonyl-dihydroquinazolines **9** with excellent yields in a stereoselective manner (Scheme 12.4) [27]. The plausible reaction mechanism is reported in Fig. 12.4 [27].

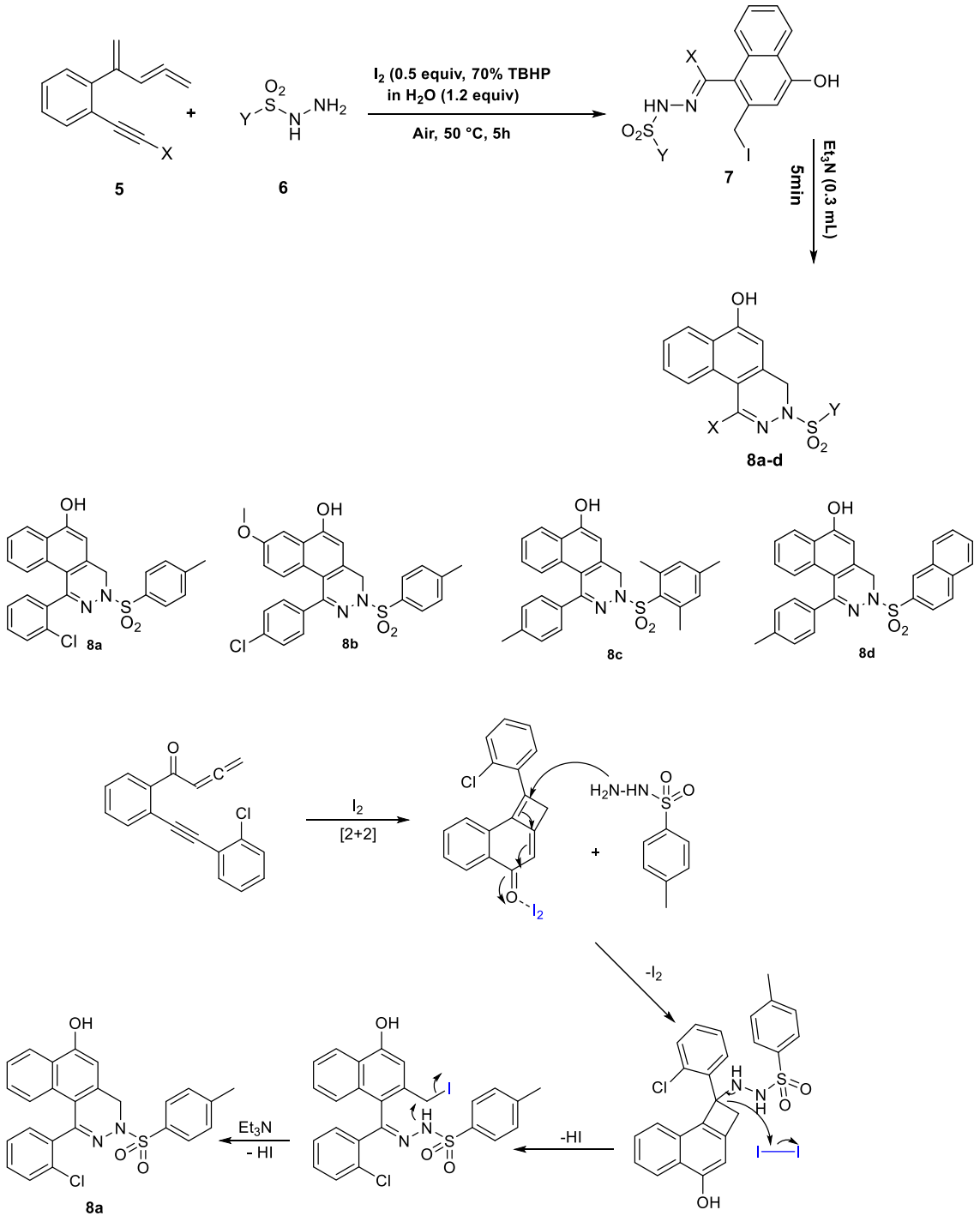
12.4.2.2 Synthesis of imidazo- and pyrimido [1,2-b]-1,2-benzothiazine-6,6-dioxides

Reacting thiazine derivative **10** with different aldehydes in the presence of pyridine gives fused pyrimidine (**11a-d, 13, and 15**) as investigated by Rajagpoal et al. (Scheme 12.5) [29].

12.5 *N*-Sulfonyl-quinolines, – isoquinolines and their derivatives

12.5.1 Medicinal chemistry aspects

Both quinoline, isoquinolines, and their reduced forms (dihydro-, tetrahydroisoquinoline and quinoline) are regarded as advantageous scaffolds in the field of medicinal chemistry which participated in building various pharmacologically active small molecules. Whether obtained from natural sources or synthetic origins the compounds based on isoquinolines and quinolines have a



SCHEME 12.3 Synthesis of 3,4-dihydrobenzo*[f]*phthalazines and proposed mechanism for forming compound **8a** [26].

wide range of activities such as, anti-bacterial, anti-diabetic, anti-viral, anti-malarial, anti-mycobacterial, and anti-cancer (Fig. 12.5) [30–32].

In the literature, various reports were found concerning the development of *N*-sulfonated quinolines and *N*-sulfonated–isoquinolines with possible medical significance.

A series of *N*-sulfonyl-quinolines and -isoquinolines bearing an acetamido moiety (**16a-i**) were designed and synthesized by Eles et al. They showed excellent activity as bradykinin B1 receptor antagonists (Fig. 12.6). All the compounds showed K_i on the nano-molar scale. Compound **16a** bearing a 1,2,3,4-tetrahydroquinolin-2-ylacetamide, showed good antagonistic activity but poor

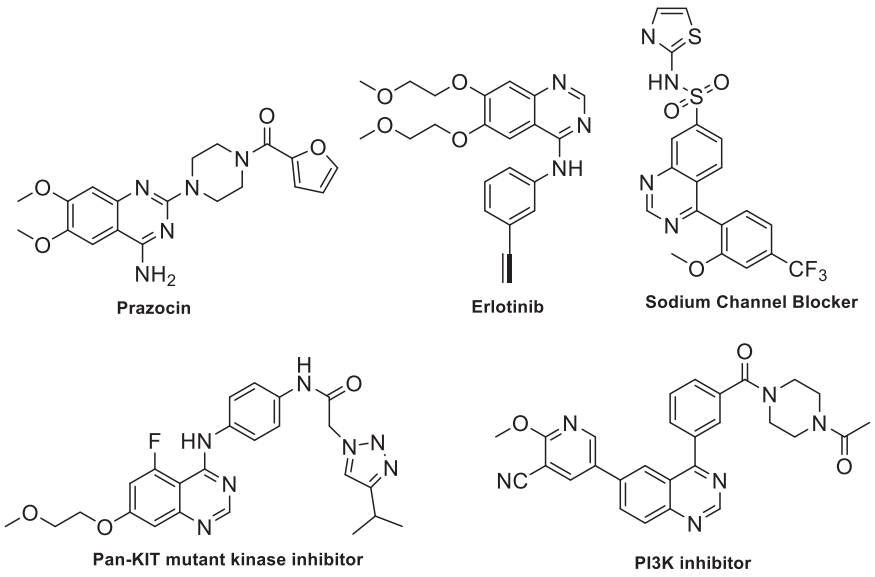
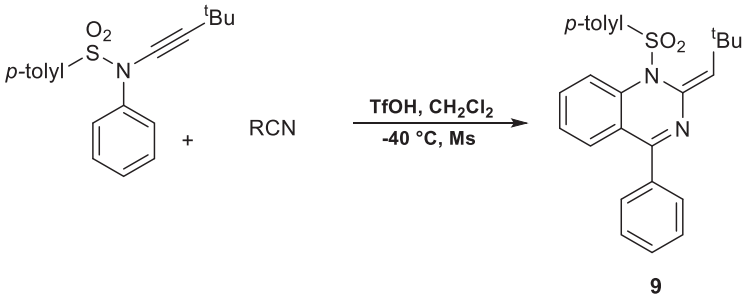


FIGURE 12.3 Chemical structures of some quinazoline derivatives of pharmacological significance.



SCHEME 12.4 The preparation of dihydroquinazolines *via* metal-free [4 + 2] cycloaddition of ynamides with nitriles [27].

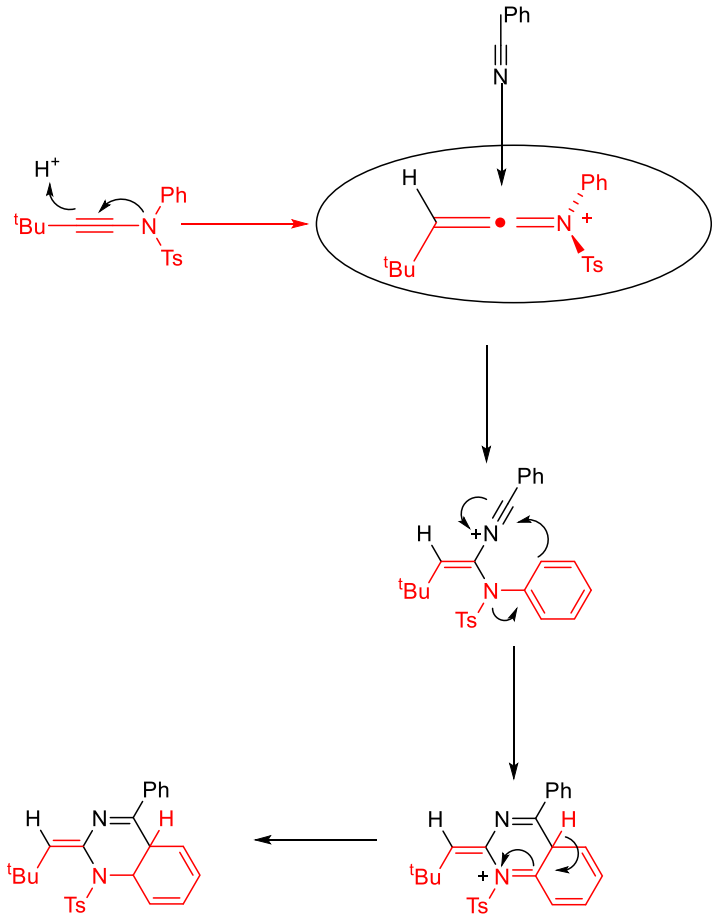
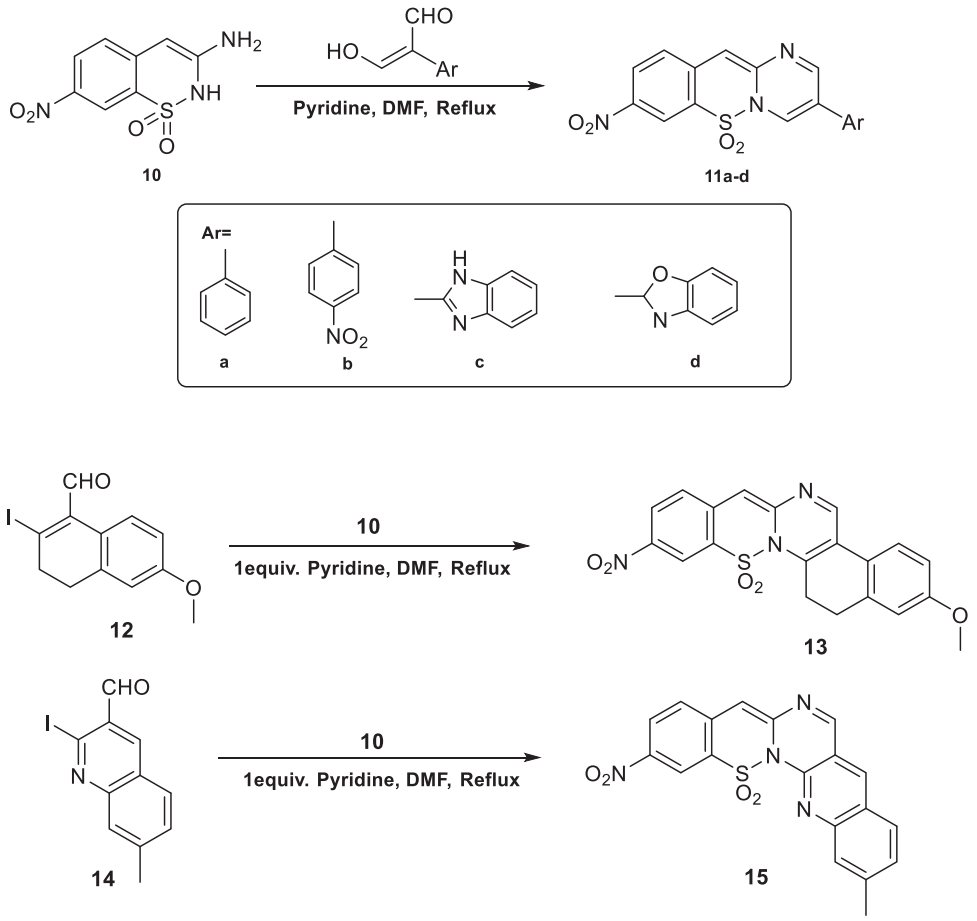


FIGURE 12.4 Proposed mechanism of action for the synthesis of dihydroquinazolines *via* metal-free [4 + 2] cycloaddition of ynamides with nitriles.



SCHEME 12.5 Synthesis of imidazo- and pyrimido [1,2-b]-1,2-benzothiazine-6,6-dioxides [29].

stability when incubated with liver microsomal enzymes. So, Eles et al. continued their investigation by studying the effect of the central phenyl on the receptor affinity and metabolic stability. Utilizing 1,2,3,4-tetrahydroisoquinolin-3-ylacetamide core (compounds **16b** and **16c**). Compound **16b** showed poor activity however **16c** showed promising antagonistic activity, but poor metabolic stability. The alteration of the side chain yielded compounds (**16d-f**) with compound **16f** showing the highest affinity with improved metabolic stability [34].

It was concluded that the incorporation of a less flexible side chain caused a dramatic decrease in receptor affinity as observed in compounds **16d** and **16g**. Also, the 1,2,3,4-tetrahydroisoquinoline derivative **16i** showed the highest antagonistic activity and the best metabolic stability [34].

In earlier efforts, Font et al. had synthesized a series of substituted quinolines (**17a- h**, Fig. 12.7) and tested their activity against human immuno deficiency virus (HIV) reverse transcriptase enzyme among other quinoline-carboxylate derivatives. Unfortunately, the presented compounds showed weak activity against the target enzyme [35].

In the work done by Sidorenko and co-workers for obtaining the sulfonyl derivatives of both quinoline (**18a-d**) and isoquinolines (**19a-k**) as anti-microbial agents (Fig. 12.8). The anti-microbial activity of both series was tested and the results showed that the anti-bacterial activity of the indolyl-dihydroisoquinoline derivatives increased by increasing the electronegativity of the arenesulfonamide component. The replacement of the arenesulfonamide with alkyl sulfonamide had little impact on the activity.

The quinoline series of these compounds showed slightly higher activity when compared to the first series [36].

The efforts of Probst et al. discovered two compounds **20** and **21** (Fig. 12.9) bearing a phenylsulfonyl-4,5-dihydro-*1H*-pyrazolo[4,3-c]quinoline moiety. Both compounds exhibited γ-secretase inhibitory activity along with good metabolic stability and entered human clinical trials for the treatment of Alzheimer's disease [37].

12.5.2 Synthetic aspects

Font et al. utilized the Reissert method to obtain different *N*-sulfonyl quinoline derivatives by treating the

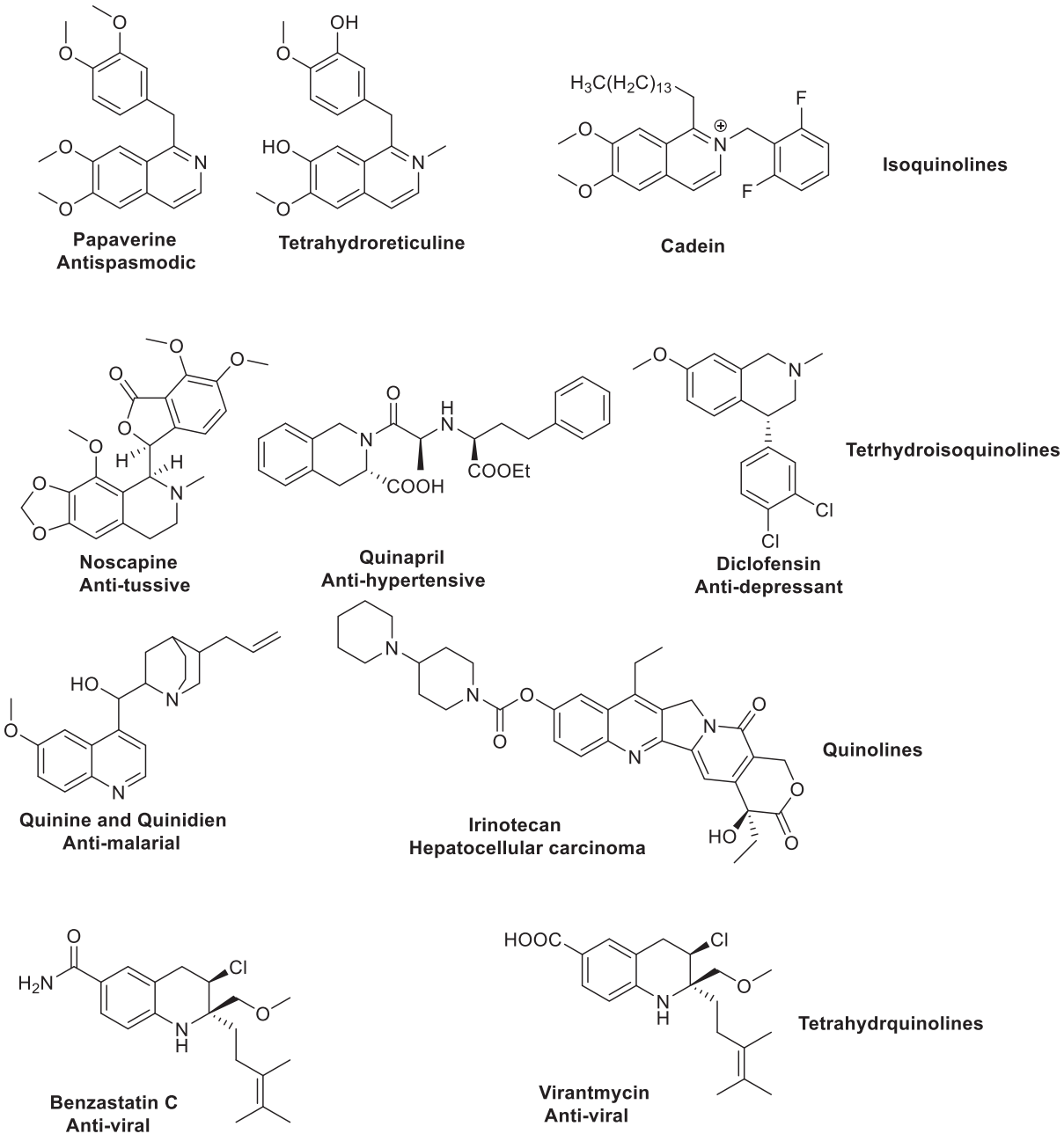


FIGURE 12.5 Some pharmacologically active isoquinolines, tetrahydroquinolines, quinolines and tetrahydroquinolines [30,33].

substituted quinoline with the appropriate sulphonyl chlorides instead of the standard acyl halides used in the reported method in presence of trimethylsilyl cyanide (TMSCN), CH_2C1_2, and $A1C1_3$ (Scheme 12.6) [35]. The plausible reaction mechanism is shown in Fig. 12.10.

A similar method was adopted to synthesize a series of the *N*-sulfonyl derivatives of dihydroisoquinolines was reported by Sidorenko and co-workers (Scheme 12.7) [36].

For the synthesis of compounds, **20a** (Figs. 12.9) and **21** Probst et al. utilized the synthetic strategy illustrated in Scheme 12.8. They reported that the synthetic strategy deployed in Scheme 12.9 was inefficient due to problems of sulfonylation in case of large substituents. In addition, the cyclization step was limited for electron-deficient aryl rings such as pyridine. So, Scheme 12.8 was better adapted for the synthesis of the target compounds [37].

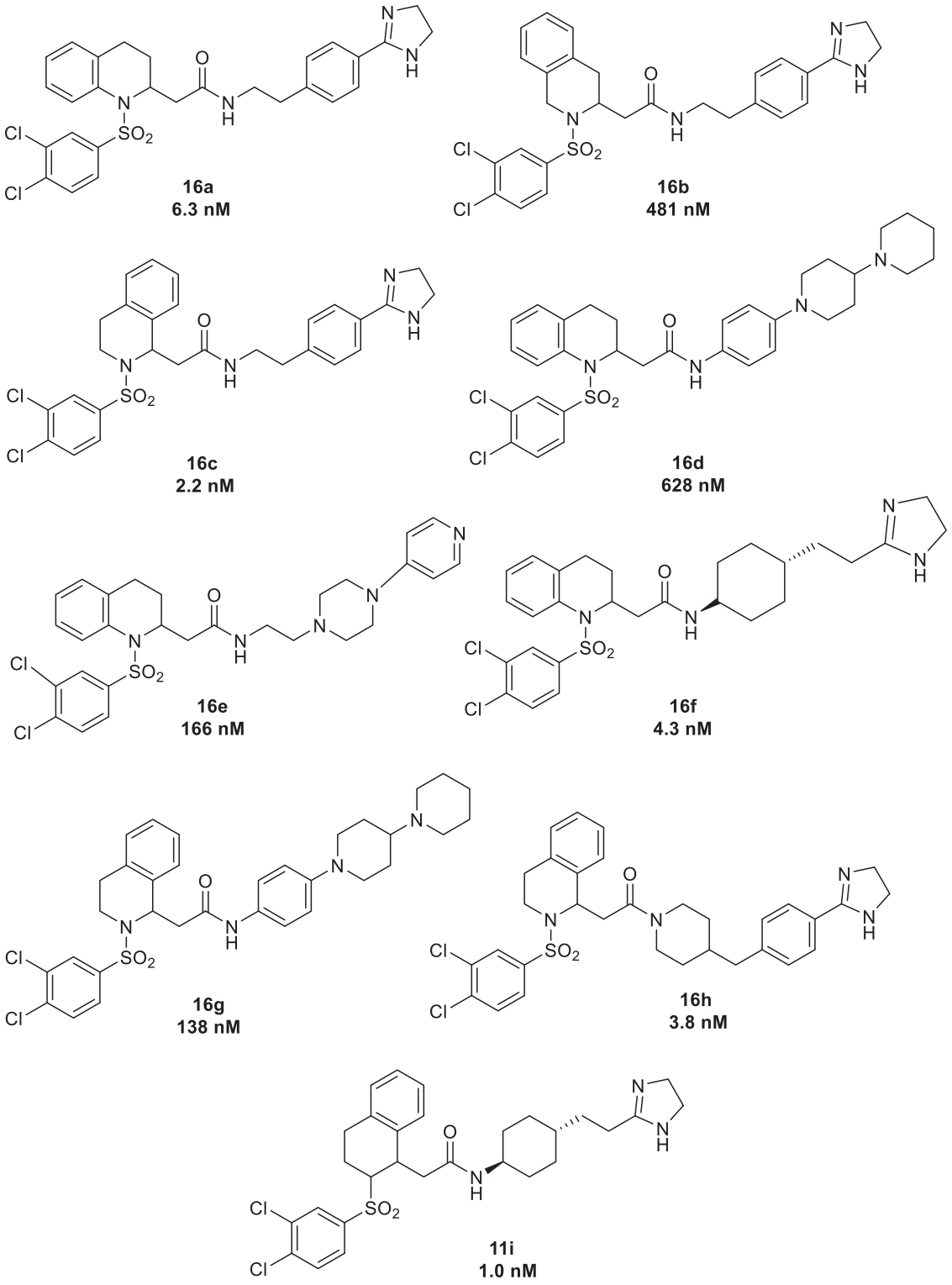


FIGURE 12.6 *N*-sulfonyl-1,2,3,4-tetrahydroquinoline and *N*-sulfonyl-1,2,3,4-tetrahydroisoquinoline derivatives acting as bradykinin receptor antagonists [34].

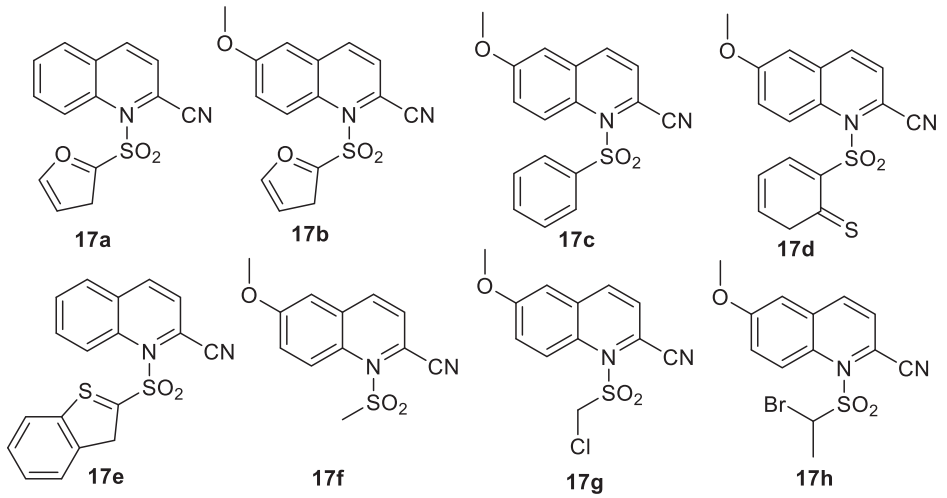


FIGURE 12.7 *N*-sulfonyl quinoline derivatives studied for HIV reverse transcriptase inhibitors [35].

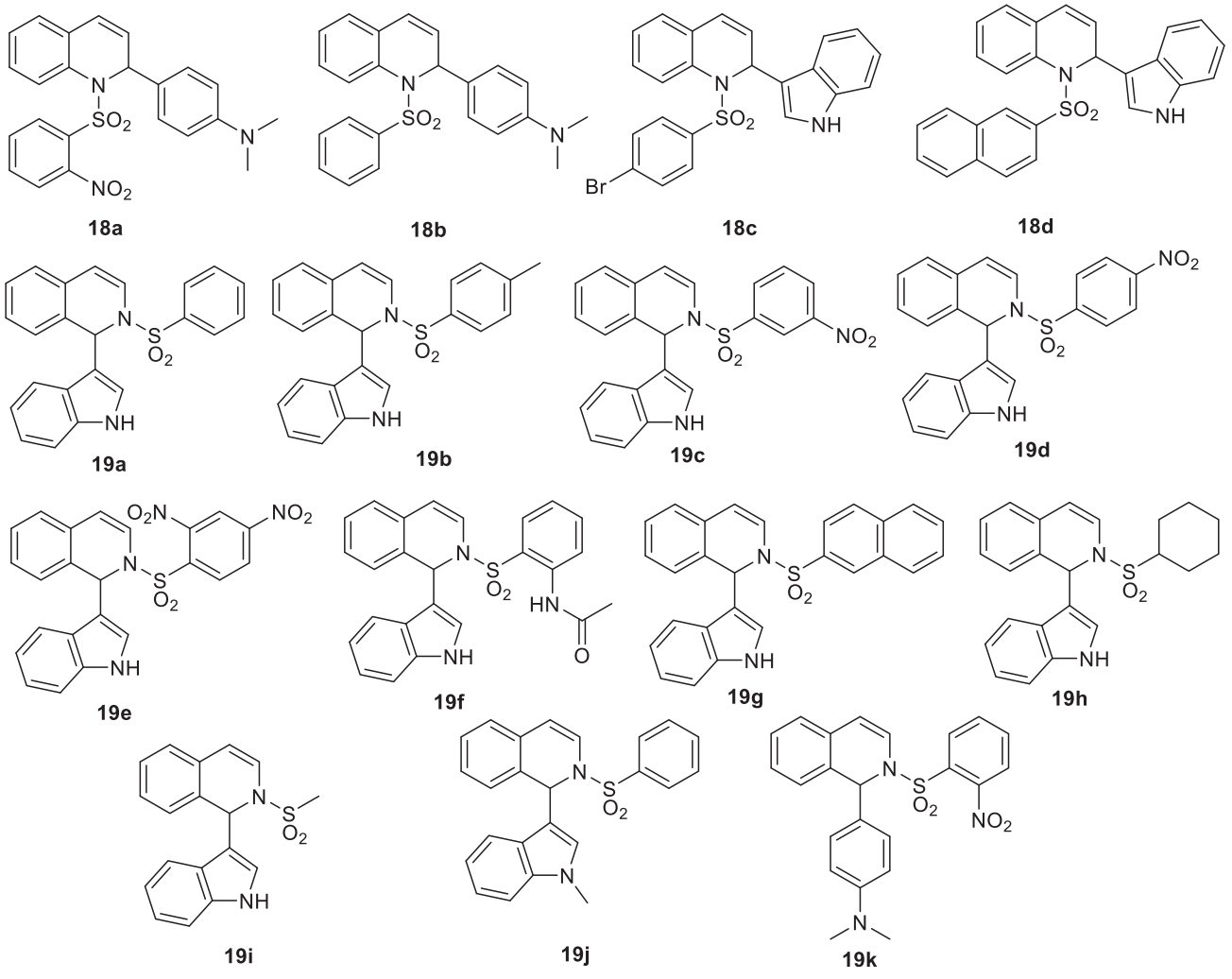


FIGURE 12.8 *N*-sulfonyl derivatives of both quinolines (18a-d) and isoquinolines (19a-k) as anti-microbial agents [36].

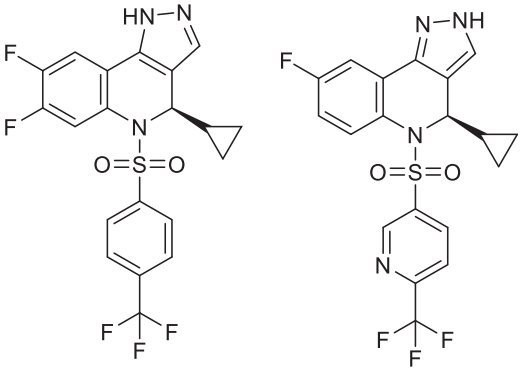
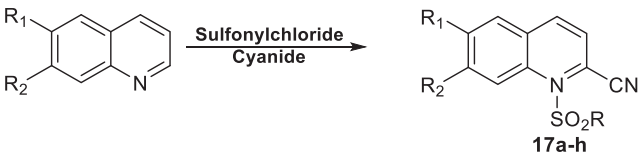


FIGURE 12.9 Chemical structures of γ-secretase inhibitors bearing a phenylsulfonyl-4,5-dihydro-*1H*-pyrazolo[4,3-c]quinoline moiety [37].



SCHEME 12.6 Synthesis of *N*-sulfonyl quinoline derivatives *via* Reissert method [35].

12.6 *N*-Sulfonyl-quinolinones

12.6.1 Medicinal chemistry aspects

Quinolinones (quinolones) belong to the quinolone family and they are classified as oxoquinolines as they bear an extra carbonyl moiety at any position of the quinoline core. The importance of quinolones arose with the synthesis of the naphthiridine derivative, nalidixic acid [38] (Fig. 12.11), which was found to have an anti-bacterial effect but its use was limited due to poor clinical response [39]. The flexibility of synthesizing different quinolone derivatives allowed the development of the fluoroquinolones which had a broad spectrum anti-bacterial activity [39]. Norfloxacin (Fig. 12.11) was the first fluoro-quinolone synthesized with a fluorine atom at position 6 of the quinolone ring. Unfortunately, norfloxacin showed poor pharmacokinetics which limited its applications to urinary tract infections. Optimization of fluoroquinolone's substitutions led to the development of other anti-bacterial derivatives with better pharmacokinetic and pharmacodynamics profiles such as ciprofloxacin (Fig. 12.11) which had an excellent oral bioavailability and is considered one of the most prescribed antibiotics at present [39,40].

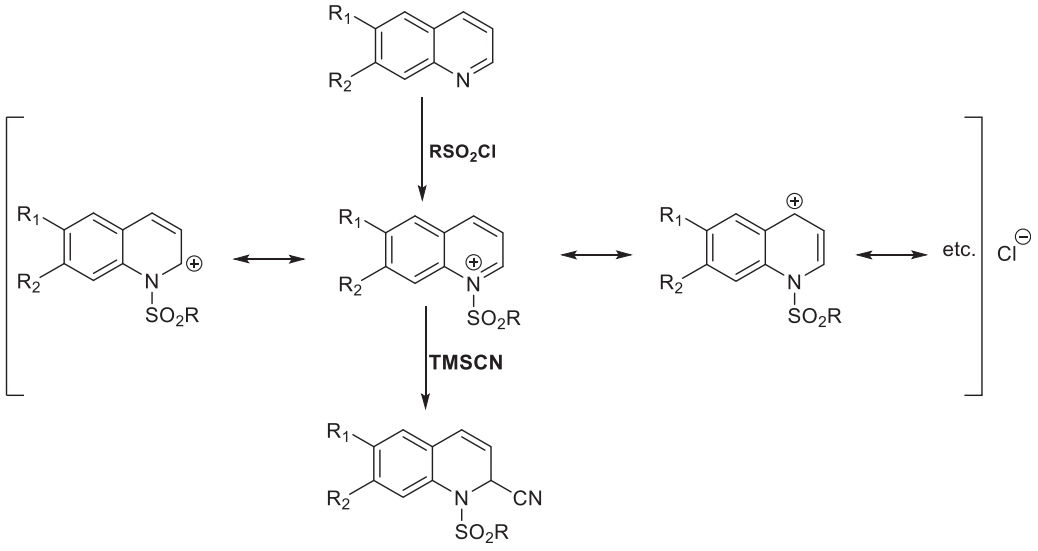
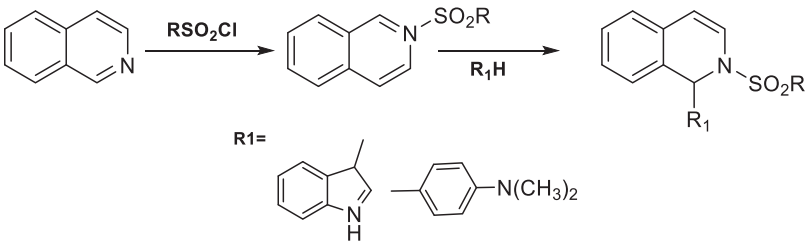
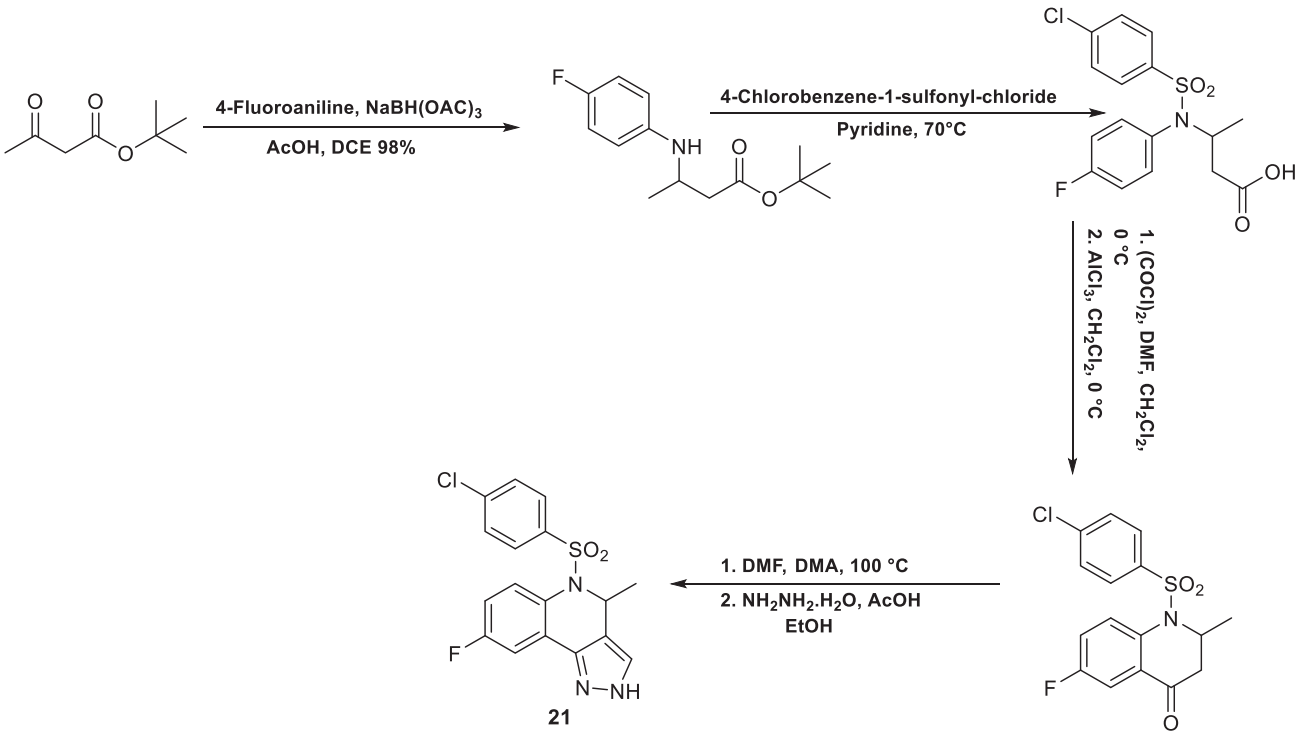


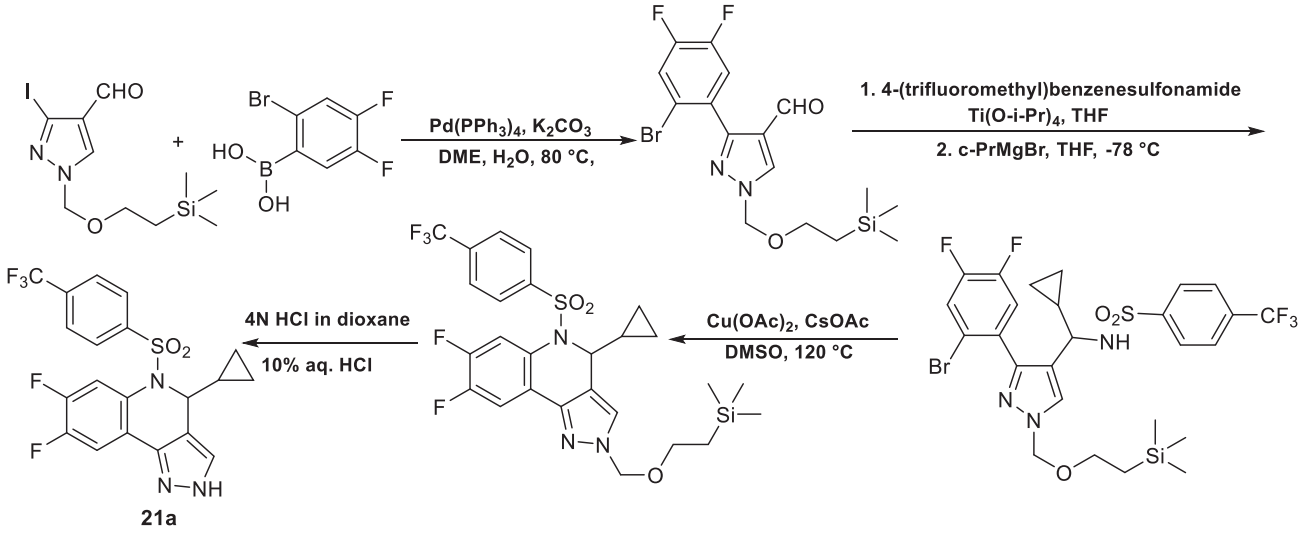
FIGURE 12.10 Mechanism of reaction plotted in Scheme 12.6.



SCHEME 12.7 Synthesis of sulfonyl derivatives of dihydroisoquinoline [36].



SCHEME 12.8 Efficient synthetic route for phenylsulfonyl-4,5-dihydro-*1H*-pyrazolo[4,3-c]quinoline derivatives as reported by Probst et al. [37].



SCHEME 12.9 First synthetic route for phenylsulfonyl-4,5-dihydro-*1H*-pyrazolo[4,3-c]quinoline derivatives as reported by Probst et al. [37].

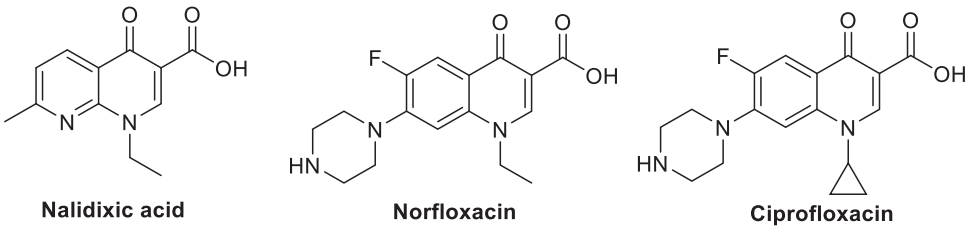


FIGURE 12.11 Chemical structures of nalidixic acid and some milestone quinolone-based antibiotics.

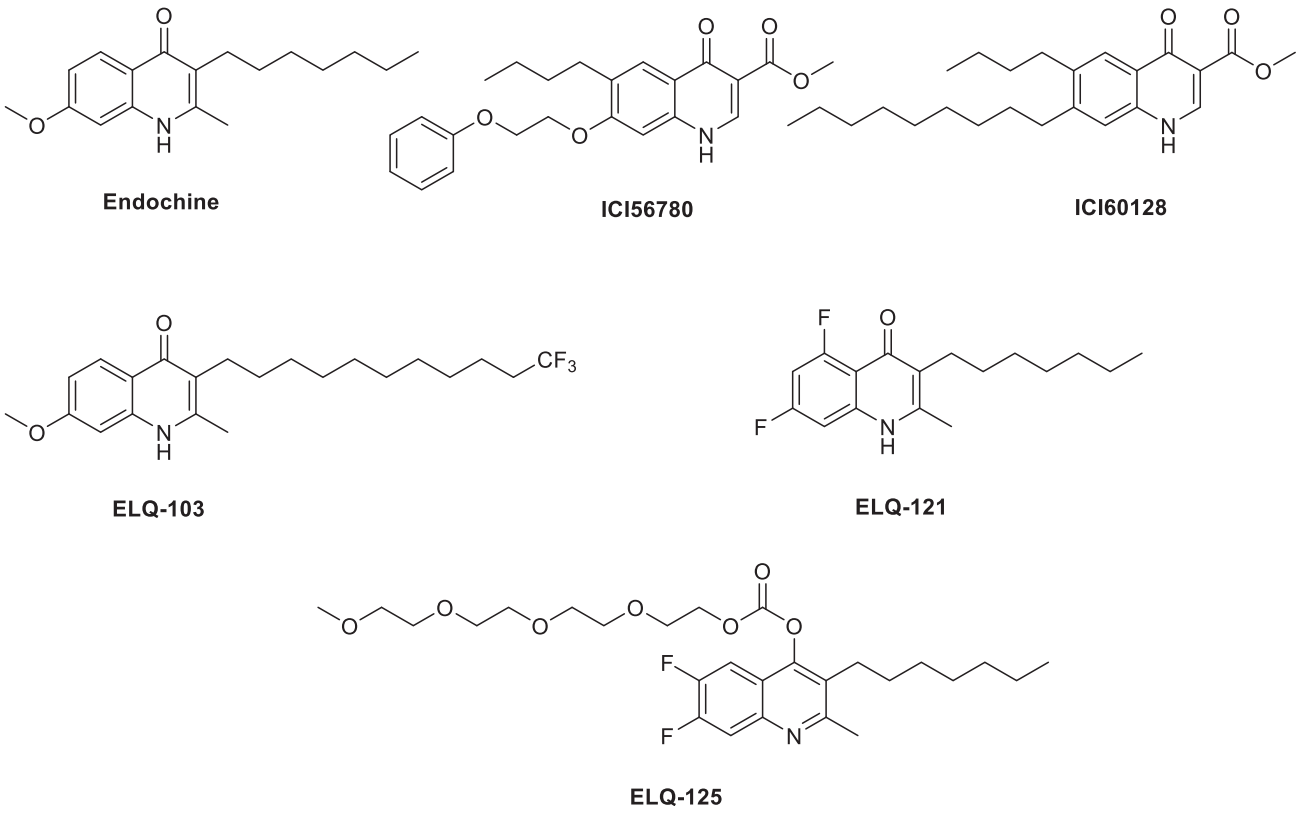


FIGURE 12.12 Chemical structures of some quinolone based anti-malarial agents.

On the other hand, the need to develop new anti-malarial drugs had urged the researchers to develop new drugs due to the continuous resistance of Plasmodium species. So, endochine was developed earlier in 1948 by Bayer but showed rapid metabolism in rodent models. In the 1970s a series of 4-oxo-quinoline 3-esters based its structure (Fig. 12.12) known as endochine-like quinolones (ELQ) [41–45]. ELQs such as ICI 56780 and ICI 60128 showed excellent activity against malaria in monkeys and rodent models in the treatment and prophylaxis of malaria at all of its stages and including chloroquine-resistant strains [46]. Despite the effectiveness of both agents, rapid resistance was developed in rodent models. The barriers to developing new quinolone-based anti-malarial agents continued to rise especially with the presence of barriers such as poor solubility and chemical instability and tautomerism and possible cardiotoxicity [47]. Later on, ELQ-103 (Fig. 12.12) was developed by extension of 3-heptyl chain of endochin with an 11-carbon chain (undecyl chain) terminated by a trifluoromethyl group by Riscoe and Winter. ELQ-103 showed double the activity of chloroquine with decreased cross-resistance with atovaquone when tested in vitro [43]. But due to poor solubility, the in vivo efficacy of ELQ-103 was limited due to its poor solubility [5]. The solution to this problem was attempted by changing the substitution pattern on the quinolone core which finally resulted in the emergence of ELQ-121 (Fig. 12.12) as a new lead with potency up to 10 folds higher than ELQ-103 and better metabolic stability. However, ELQ-121 shared higher cross-resistance with atovaquone and poor solubility. The solubility problem of ELQ-121 was resolved by linking a polyethylene group to the quinolon's oxygen (ELQ-125, Fig. 12.12) [48].

In addition to their anti-bacterial and anti-malarial effect, several quinolone-based derivatives showed promising anti-cancer activity. The proposed mechanism of action was the inhibition of topoisomerase II through the formation of a cleavable complex that can be identified as small breaks in the double strands of DNA and the formation of small toxic fragments of DNA, in addition to the possible intercalation of the DNA [39,49,50]. Utilizing the characteristics of the pre-existing fluoroquinolones, Foroumadi et al. studied the effect of introducing *N*-substituted piperazinyl at C_7 of either ciprofloxacin or norfloxacin. This single modification had changed the biological activity from anti-bacterial to cytotoxic effect. The *O*-methyl-oxime derivative **22a** (Fig. 12.13) had been found to be 95 times more cytotoxic than norfloxacin [51].

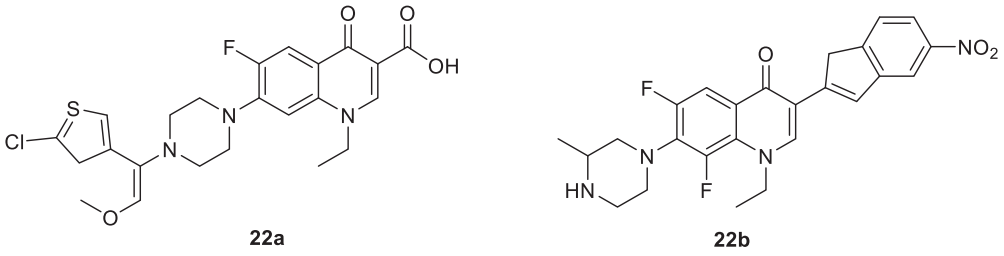


FIGURE 12.13 Some quinolone-based anti-cancer derivatives.

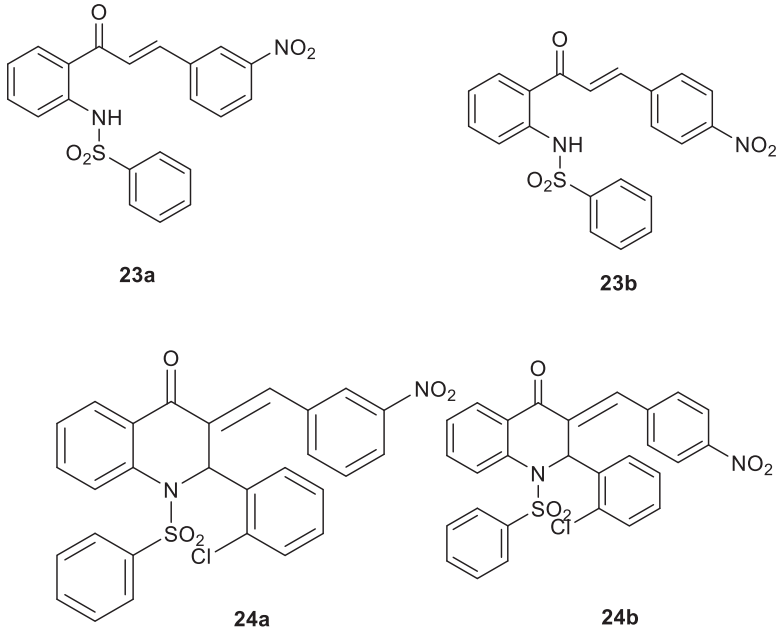


FIGURE 12.14 Some sulfonated-chalcone derivatives with their respective quinolone derivatives have significant cytotoxic effects [60].

Also, the introduction of a benzoxazole at C_3 in addition to a 3-metyl-piperazin-1-yl substitution at C_7 and a C_6 fluorine substitution (**22b**, Fig. 12.13) had a potent cytotoxic effect against oral epidermal, ovarian and hepatocellular carcinomas [52].

The biological activities of quinolone-based derivatives are not exclusive to the aforementioned activities. It also extends to have anti-viral activity, anti-fungal, and some showed anxiolytic, anti-Alzheimer's, and anti-inflammatory action [53–59].

d'Oliveira and co-workers had investigated how the conversion of 2′-sulfonamide chalcones to the respective quinolone derivatives affected the cytotoxicity and the glutathione reactivity. Compounds **23a** and **23b** (Fig. 12.14) had been synthesized along with their respective cyclic-quinolone analogs **24a** and **24b** (Fig. 12.14) and their in vitro cytotoxicity were tested on prostate cancer (PC-3), colon cancer (HCT-116) and glioblastoma (SF-295) cell lines. The results revealed that; compounds **23a, 23b**, and **24b** showed promising cytotoxic activity with more than 75% of inhibition of cell proliferation. However, a clear relationship between ring substitution and the cytotoxic effect could not be established. Also, it was clear that the cytotoxic activity of the four compounds was not related to their glutathione reactivity [60].

In their quest to develop new pesticides, Vaz et al. developed a machine learning model utilizing a training set of molecules with known biological activity [61]. The proposal was that potential candidates should bear α, β-unsaturated systems, sulfonamide, and a nitro group as they are frequently found in many commercially available pesticides. All the previous characteristics can be combined in a quinolone core (4-oxo-1,4-dihydroquinoline) especially since it was reported that various efficient pesticides had a quinolone skeleton in their structure (Fig. 12.15) [62–65]. Based on the generated model, three dihydroquinolone (**25a-d**) were synthesized (Fig. 12.16).

The designed molecules had a range of predictable biological activities against *Tobaco mosaic* virus, anti-fungal activity against *Fusarium oxysporum* which is evident in the predicted pesticide activity [61].

The same group continued their work by synthesizing compound **25b** and its *p*-nitro analog (**25d**, Fig. 12.16).

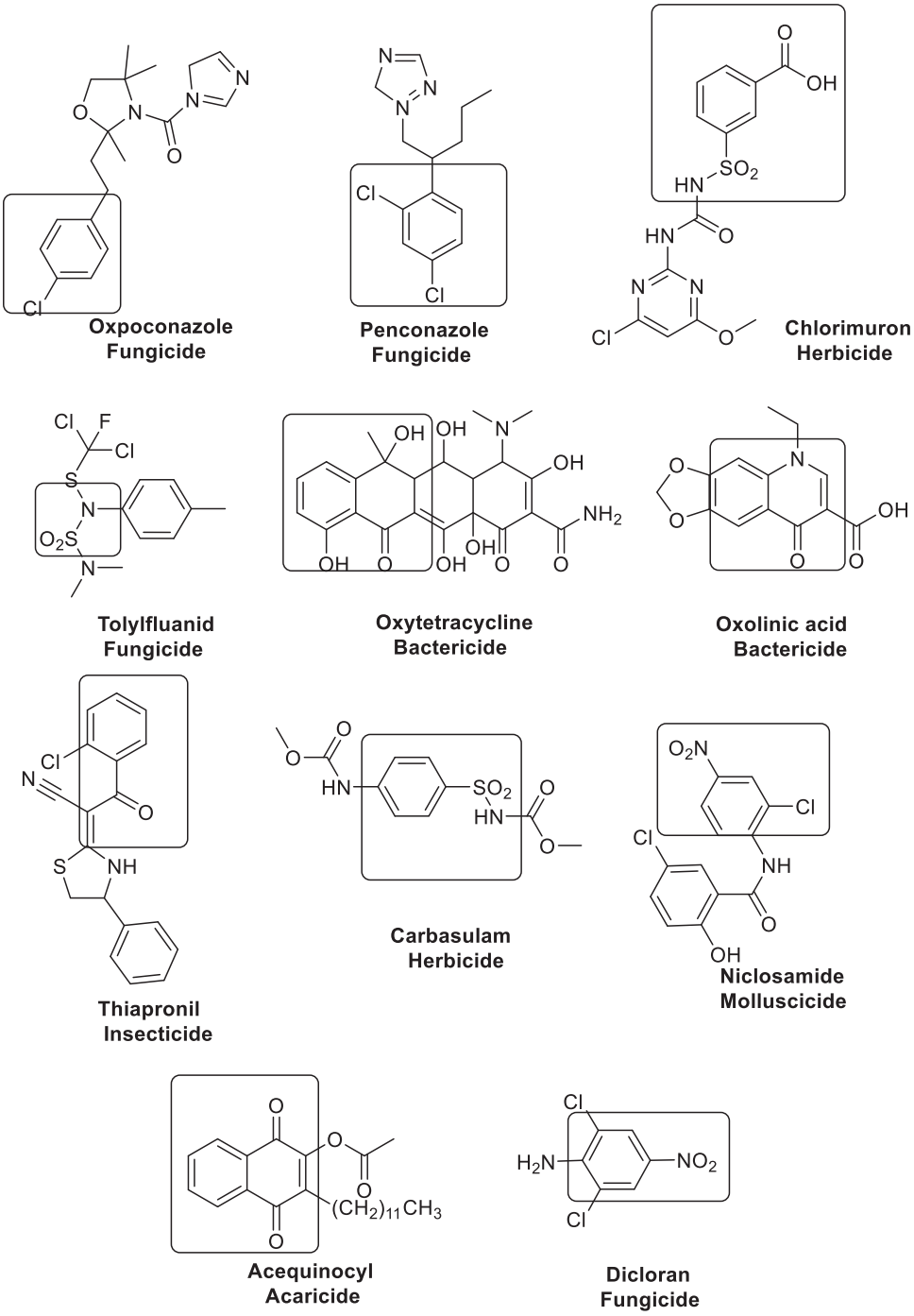


FIGURE 12.15 Some biologically active molecules are used for building a machine learning model for the design of a new pesticide (privileged scaffolds are highlighted) [61].

The anti-fungal activity of both compounds against *Aspergillus niger* fungus takes thiophanate-methyl and fluconazole as reference compounds. The anti-fungal activity expressed as minimum inhibitory concentration (MIC) is shown in Table 12.1. As can be seen, both compounds presented promising anti-fungal activity against *A. niger*. Furthermore, the authors utilized their previously generated machine learning model to predict a map showing the atomic and fragment contributions of both compounds for the anti-fungal activity aided by quantitative structure activity relationship (QSAR) models (Fig. 12.17). For *A. niger* the generated map showed that all atoms except for the nitro group had a positive contribution to the experimentally proved anti-fungal activity [66].

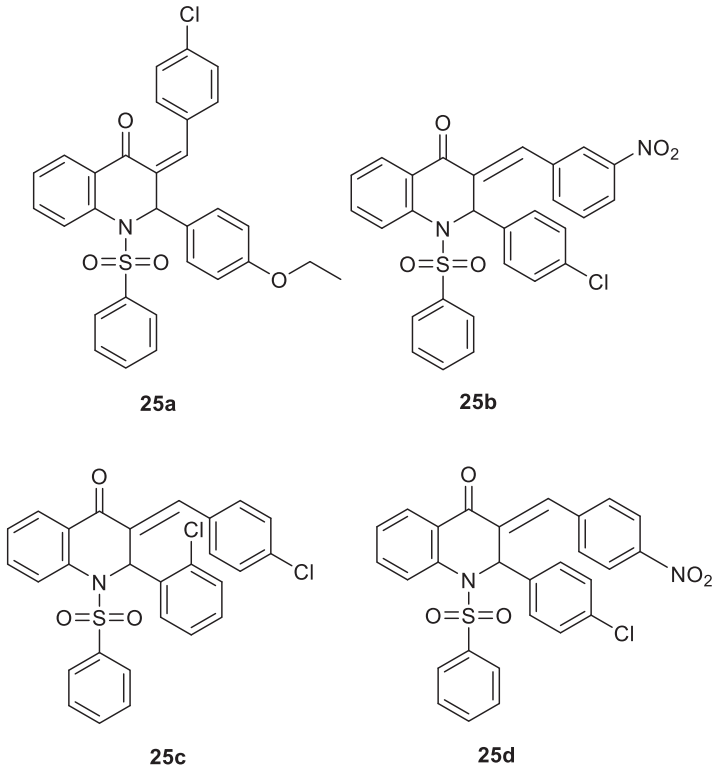


FIGURE 12.16 Dihydroquinolone derivatives designed for expected pesticide activity by machine learning model [61].

TABLE 12.1 In vitro anti-fungal activity of compounds 25b and 25d against *Aspergillus niger*.

Compound	MIC (mg/L)
25b	12
25d	25
Thiophanate-methyl	50
Fluconazole	12

In the efforts to develop new phosphodiesterase-4 (PDE4) inhibitors for the treatment of asthma, Montana et al. had developed a series of different compounds bearing an aryl sulfonamide moiety or endocyclic sulfonamide nitrogen presented in *N*-sulfonated−isoquinolone (**26a and b**) and *N*-sulfonated−quinolone (**27**, Fig. 12.18). The synthesized compounds possessed excellent PDE4 inhibitory activity in the micromolar range [67].

On the other hand, Faidallah and his co-authors had developed a series of various new 2-oxo-1,4-disubstituted-1,2,5,6-tetrahydrobenzo*[h]*quinoline-3-carbonitriles derivatives among which compounds **28a-r** (Fig. 12.19) had *N*-sulfonated moiety. The authors had tested the anti-cancer and anti-viral activity of the synthesized compounds and found that compound **28h** presented good anti-cancer activity against human colon carcinoma (HCT29) and human hepatocellular carcinoma (HePG2) cell lines [68].

Finally, Kim et al. described the synthesis of two compounds with chalcone−quinolone hybrid nucleus (**29a** and **29b**) and tested them for the inhibition of the trans-sialidase from *Trypanosoma cruzi* (Fig. 12.20) [69].

12.6.2 Synthetic aspects

12.6.2.1 Sulfonyl chalcones and their quinolinone derivatives

Chalcones have numerous applications in organic synthesis [70]. One important synthetic application of chalcones was their use in a single-step synthesis of chalcone−quinolone hybrid compounds which are useful in therapeutics [60,69,71]. Some studies reported the biological activities of such compounds with the nucleus shown in Fig. 12.21.

For example, Kim et al. described the synthesis of compounds **29a** and **29b** (Fig. 12.20) with this nucleus *via* acid catalysis in methanol [69]. The plausible reaction mechanism of cyclization for quinolone derivatives is shown in Fig. 12.22.

On the other hand, d'Oliveira et al. [60] described the synthetic route for chalcone-quinolone derivatives **24a** and **24b** (Fig. 12.14) *via* basic catalysis in an ethanolic medium as shown in Scheme 12.10 [71].

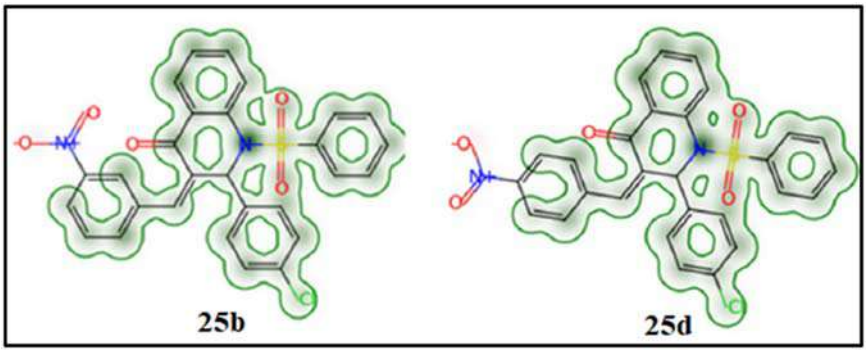


FIGURE 12.17 Predicted contribution map for the anti-fungal activity of compounds **25b** and **25d**. Green clouds indicate the active/non-toxic contribution of an atom or fragment [66].

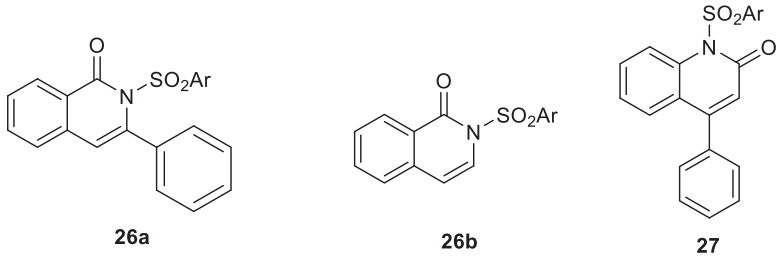


FIGURE 12.18 *N*-sulfonated−isoquinolone and *N*-sulfonated−quinolone developed as PDE4 inhibitors [67].

12.6.2.2 One-pot synthesis of aryl-sulfonyl quinolone derivatives

Wang group [72] disclosed easy access to structurally 3,4-diaryl substituted quinolones using one-pot method through alkylation/acylation of ortho-tosylaminophenyl substituted para-quinone methides followed by an intramolecular 1,6-conjugate addition and oxidation sequence Scheme 12.11. Confirmation of this novel method was done by treating compound **32a** with excess $AlCl_3$. The expected de-*tert*-butylation product **33** was produced in good yield Scheme 12.12. The plausible reaction mechanism is depicted in Fig. 12.23 [72]

12.6.2.3 Synthesis of N-sulfonyl γ and δ-lactams via transition metal-free oxidative catalysis

Bo-Han Zhu and co-workers developed an efficient, facile, and transition metal-free oxidative catalysis approach for the synthesis of *N*-sulfonyl γ and δ-lactams. $NaBAr^F{}_4$-Catalyzed Oxidative cyclization of 1,5-and 1,6-diynes allowed the divergent and practical synthesis of valuable heterocycles. With the transition metal-free conditions, the reaction scope was studied as shown in Scheme 12.13, 1,6-diynes **34**, afforded the desired 2-quinolinones **35** under the optimized reaction conditions [73]. $NaBAr^F{}_4$-catalyzed oxidative diyne cyclization is illustrated in Fig. 12.24. Also, a representative example of the plausible reaction mechanism is depicted in Fig. 12.25.

12.6.2.4 Synthesis of N-sulfonyl-oxoquinoline heterocycles

Chi and co-workers had gained great contribution to the construction of oxoquinoline scaffolds through single-step, efficient chemo- and stereoselective domino methods using simple starting materials and catalysts [74]. Oxoquinoline-type cores are found as bioactive molecules naturally such as meloscine, epimeloscine, and scandine, and in synthetic molecules such as compounds exhibiting anti-mycobacterial [75] and anti-schizophrenia activities [76]. Density function theory was used to study the possible mechanisms and origin of selectivity in *N*-heterocyclic carbene (NHC)-catalyzed reactions of saturated aliphatic esters with amino enones [77]. Scheme 12.14 illustrates the NHC-catalyzed transformation reactions of saturated esters while Scheme 12.15 illustrates the activation and transformation routes of a saturated ester under NHC organocatalysis [77].

12.7 *N*-Sulfonyl quinoxaline

12.7.1 Medicinal chemistry aspect

Quinazolines are the bioisosteres of quinolones and naphthalene *N*-heterocycles. Like the quinolone family, a quinaxoline-containing compound present in a wide range of biological activities with medicinal importance [78,79]. In addition to the synthetic quinoxaline derivatives, it presents a common substructure for various naturally

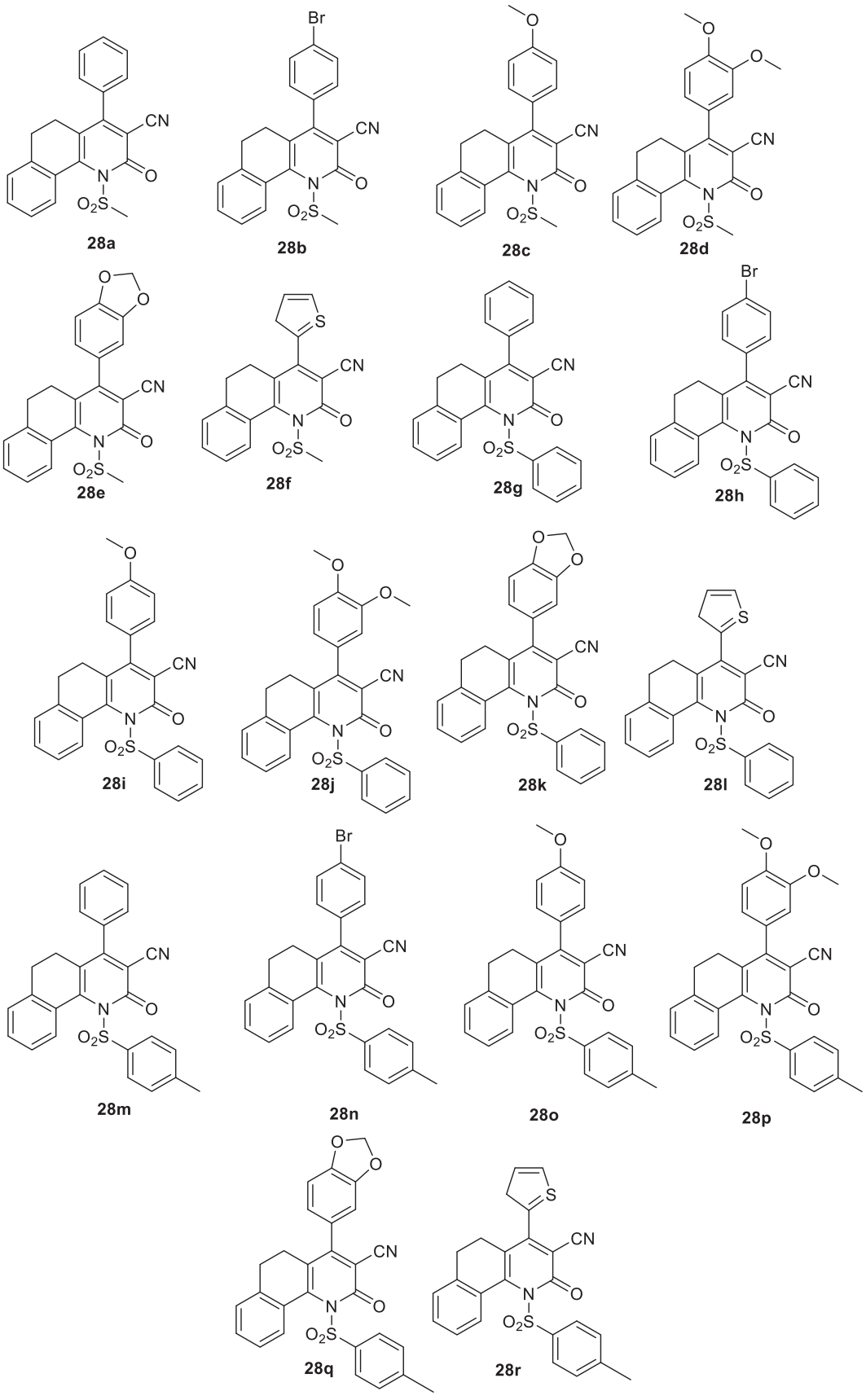
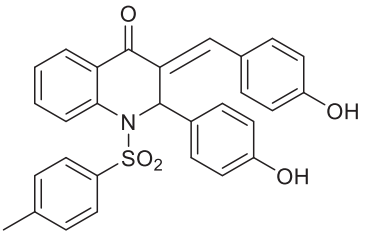
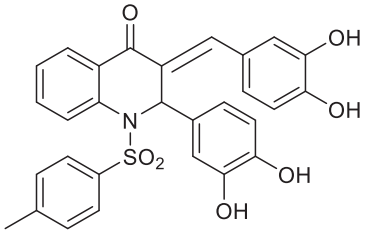


FIGURE 12.19 A series of 2-oxo-1,4-disubstituted-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitriles synthesized as possible anti-cancer and anti-viral activity [68].



29a
IC50= 30 mM



29b
IC50= 0.6 mM

FIGURE 12.20 Chalcone−quinolinone derivatives as inhibitors for trans-sialidase from *Trypanosoma cruzi* [69].

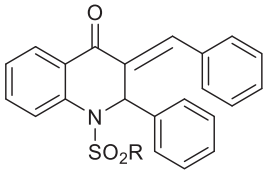


FIGURE 12.21 Chalcone−quinolone hybrid nucleus with reported medicinal importance.

occurring compounds. Echinomycin (Fig. 12.26) is a natural depsipeptide with potential anti-bacterial, anti-viral and anti-cancer activity [79]. Echinomycin belongs to a family of non-ribosomal quinomycins that include also; triostin A, and SW-163s which are important secondary metabolites acting as bisintercalators [80]. In addition, different quinoxaline derivatives such as CNQX, YM90K, YM872, LU112313, and NBQX had been reported to have potential neuropharmacological activity *via* the antagonism of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) [81].

Grazoprevir (Fig. 12.26) is known as a novel quinoxaline-based anti-viral agent approved for the treatment of different resistant genotypes of hepatitis-C virus (HCV) [82,83]. Voxilaprevir is another anti-viral agent that bears a quinoxaline moiety [84]. Other quinoxaline derivatives served as anti-viral agents such as GW420867x, S-2720, and HBY097 (Fig. 12.26) which are non-nucleoside reverse transcriptase inhibitors (NNRT) that showed great potential in the treatment of HIV [85,86].

In addition, brimonidine (Fig. 12.26) is a selective α_2-adrenoceptor agonist which reduces intraocular pressure and is approved for the treatment of glaucoma and reducing ocular hypertension [87].

Several researchers had reported the importance of *N*-sulfonated- quinoxalines. In 2009 Xu et al. reported the efficacy of compounds **36a-j** (Fig. 12.27) as NNRT. The in-house screening was performed leading to the identification of compound **36a** as a lead compound that shared the quinoxaline moiety with GW420867x and HBY097 (Fig. 12.26). However, instead of the iso-propyloxy carbonyl group in N_4 position; compound **31a** had a heteroarylsulfonyl moiety [88].

Two series of compounds were developed one with 6-fluoro-N^4-(quinoline-8-sulfonyl)-3,4-dihydroquinoxalin-2(*1H*)-one and the other with 6-fluoro-3-methyl-4-(2-methyoxycarbonylthiophene-3-sulfonyl)-3,4-dihydroquinoxa-lin-2(*1H*) −one derivative [88]. All the compounds showed inhibition of HIV-1 replication in the micromolar range. Compound **36d** showed the most potent activity and it appeared that the size C_3-substitution affected the potency of the designed compounds drastically. For example, replacing the methyl group at C_3 with an ethyl group caused a 25-fold drop in activity. Exploring the effect of replacing the 6-fluoro with a 6-chloro atom was also studied which was advantageous in some cases but definitely not detrimental for activity.

Furthermore, the binding mode of compound **36d** was studied computationally using the FlexX algorithm in SYBYL 6.9 software. The docked compound showed a similar binding mode to Efavirenz. The quinoxaline scaffold participated in hydrophobic interaction with Leu100, Val106, Leu234, Pro236, and Tyr318. In addtition, 2-methoxylcarbonyl-3-sulfonylthiophene fragment lay in the hydrophobic pocket formed by Pro95, Tyr181, Tyr188, and Trp229. Hydrogen bonding interaction formed between Lys101 and the amino (NH) of quinoxaline. This binding mode may explain the effect of increasing the bulk of C_3 substitution as it sterically interferes with Val106, Val179, and Gly190 (Fig. 12.28).

In the quest for developing new non-peptide Bradykinin B1 Receptor Antagonists (**37a-g**), Xu et al. initiated a high throughput screening of the Merk sample collection. The screening resulted in compound **37a** (Fig. 12.29) as a lead compound which had a K_i value of 1.4 μM binding to BK-B_1 receptor in its racemic form while its binding to BK-B_2 receptor it had a K_i value higher than 10 μM.

Optimization of the lead compound **37a** was performed by studying the structure-activity relationship which was aided by docking of **37a** into the homology

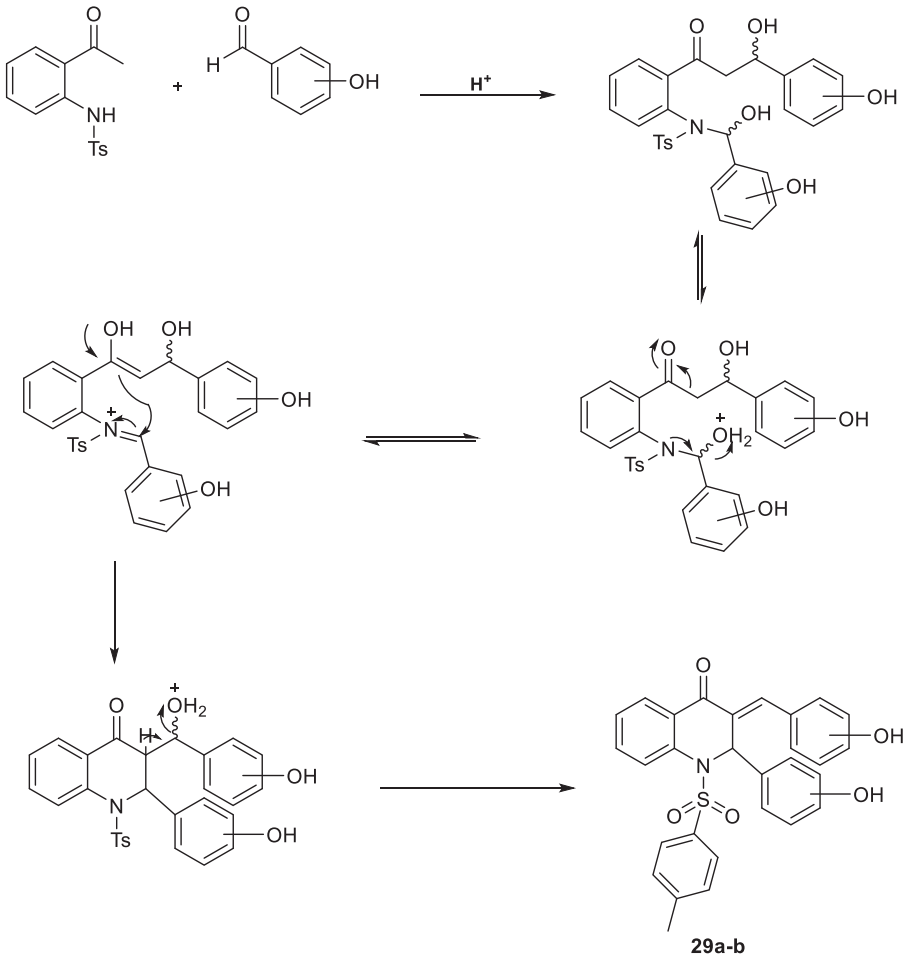
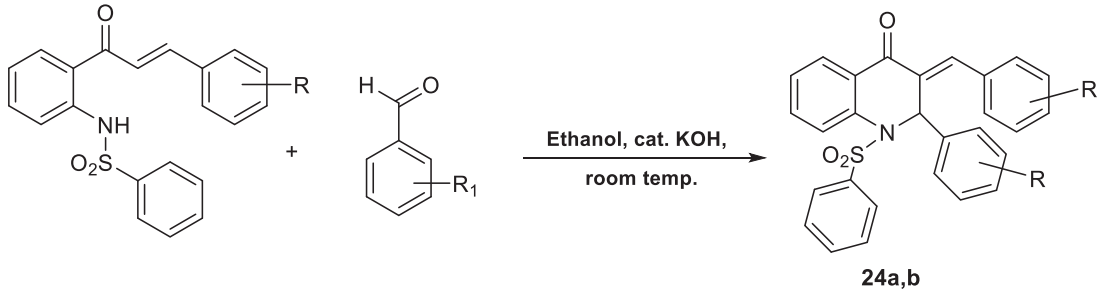
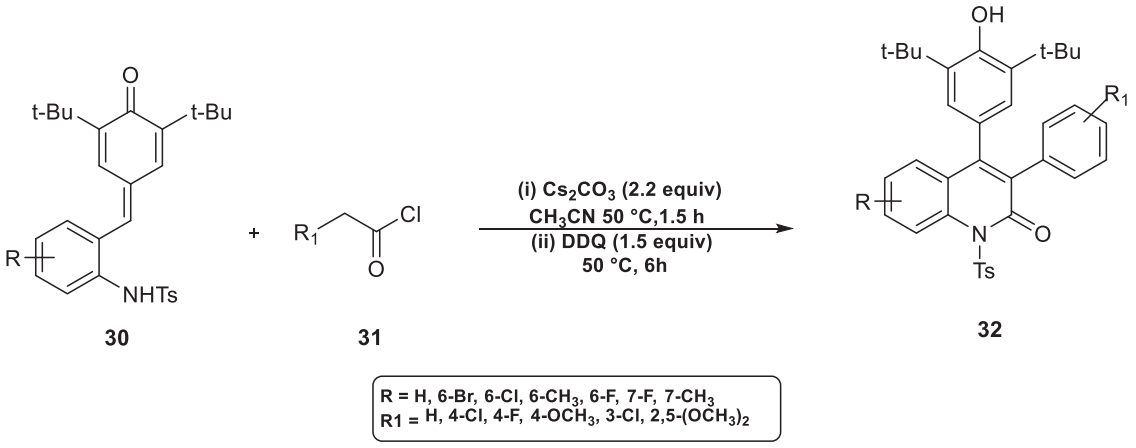


FIGURE 12.22 Reaction mechanism of cyclization for quinolone derivatives.

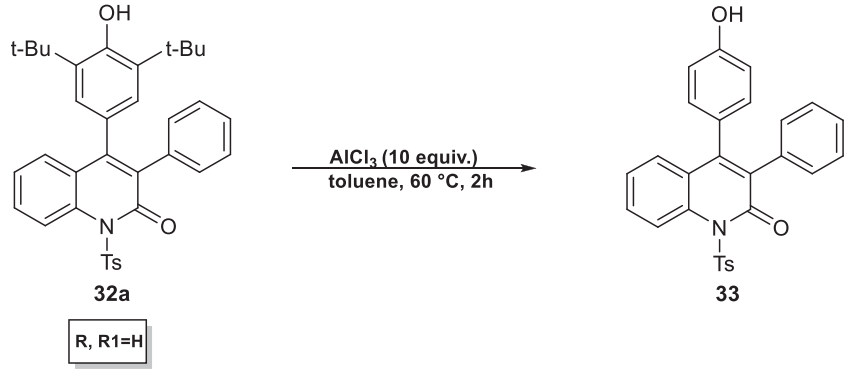


SCHEME 12.10 Synthetic route for chalcone-quinolone derivatives *via* basic catalysis in the ethanolic medium [60]. The same technique was utilized to synthesize **25a-d** by Vaz et al. [61,66].

model of the BK-B1 receptor (Fig. 12.30). The docking study revealed that **37a** had interacted with the transmembrane domain-3 (TM-3) and TM-7. The aromatic ring and the dihydroxyquinoxaline scaffold rested in the hydrophobic pocket formed by residues Ile97, Trp98, Trp103, Ile113, and Phe302. The sulfonamide group formed a hydrogen bond interaction with Gln295. So, based on the docking study, it was clear that; the phenylsulfonamide group played a crucial role in the receptor binding. Compound **37b** was more potent than the lead compound in its racemic form with K_i of 335 nM. Its *R*-isomer showed better activity with K_i of 302 nM.



SCHEME 12.11 Synthetic route for 3,4-diaryl substituted quinolones using one-pot method [72].



SCHEME 12.12 Confirmatory route to prove the reaction plotted in Scheme 12.11.

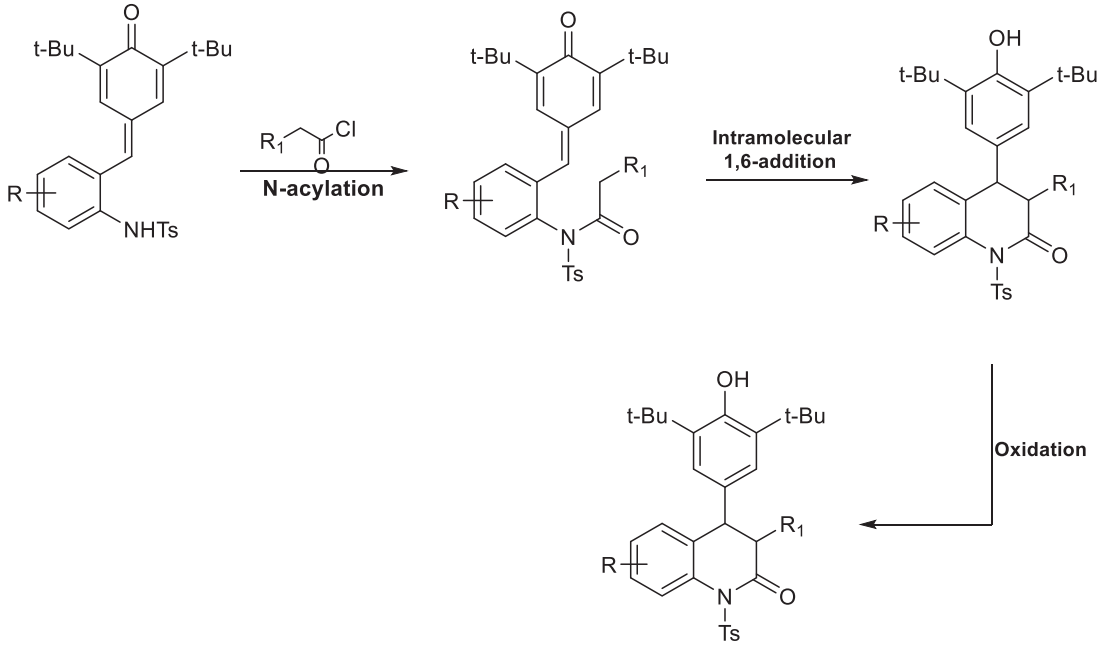
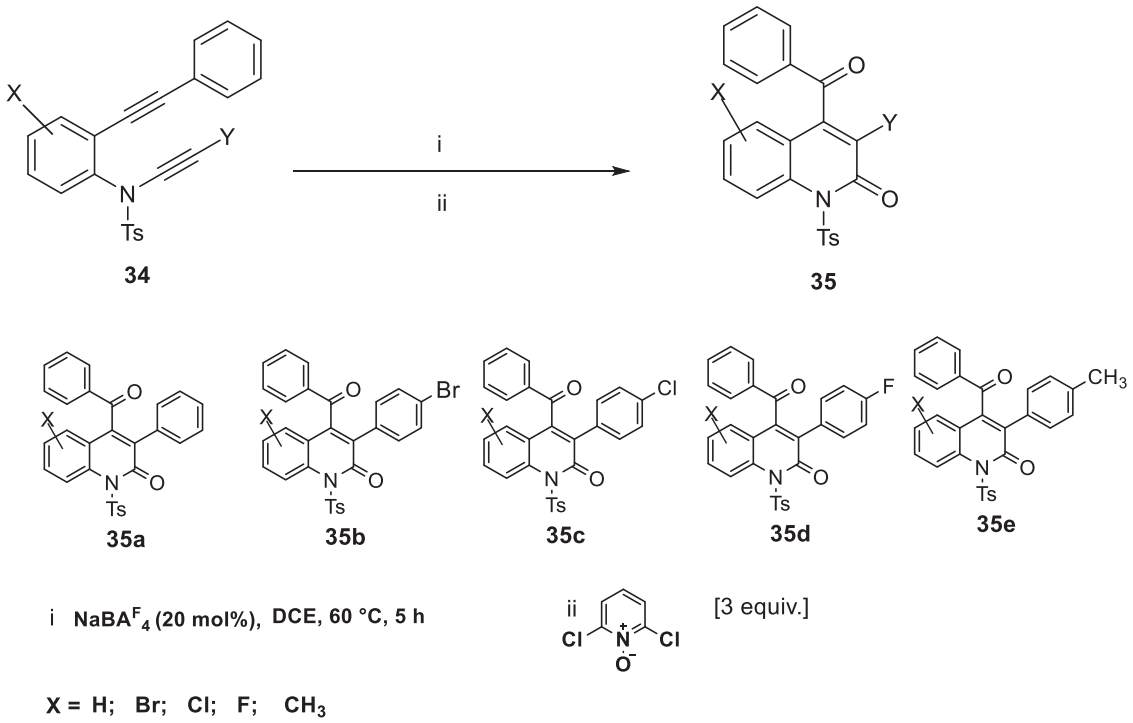


FIGURE 12.23 Proposed mechanism for the reaction plotted in Schemes 12.11 and 12.12.



SCHEME 12.13 Synthesis of *N*-sulfonyl γ and δ-lactams *via* transition metal-free oxidative catalysis [73].

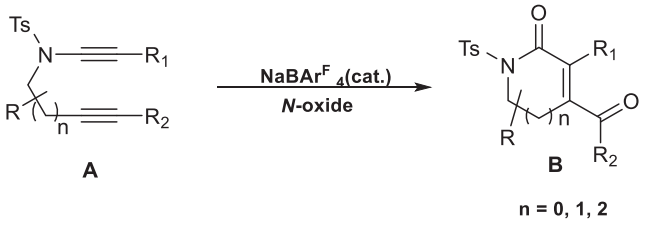


FIGURE 12.24 An illustration for NaBAr$^F_4$-catalyzed oxidative diyne cyclization.

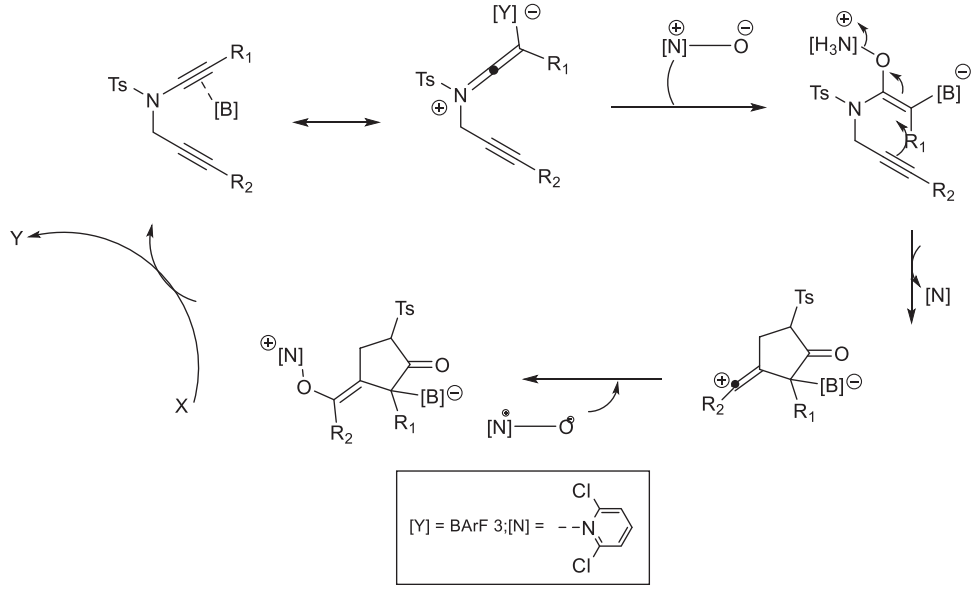
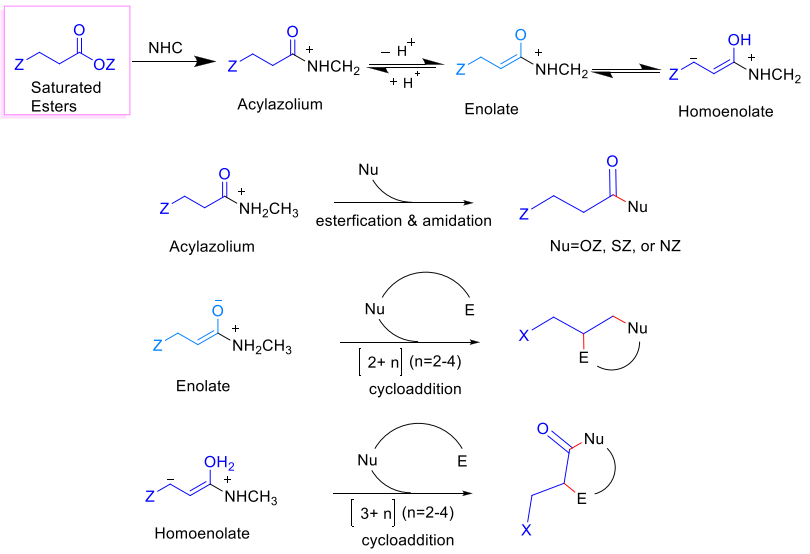
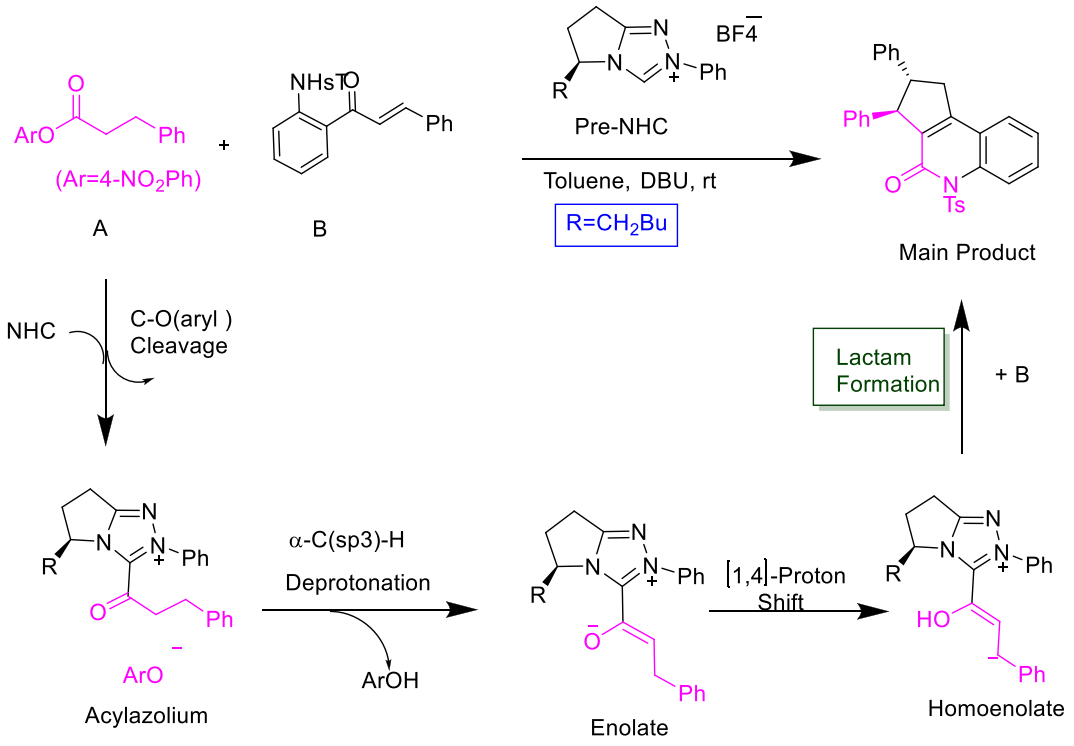


FIGURE 12.25 A representative example of the plausible reaction mechanism (Scheme 12.13) [73].



SCHEME 12.14 NHC- Organocatalysis [77].



SCHEME 12.15 Possible Activation and Transformation Routes of a Saturated Ester under NHC-catalyzed transformation reactions [77].

Replacing the trimethyl-phenyl in compounds **37a** and b with 3,4-dichloro phenyl yielded compound **37c** which had a comparable activity. Variation of the phenyl amide substituent caused a drastic change in potency. Finally, compounds **37f** and **37e** were the most potent antagonists among the designed series [89]. Also, the stereoisomers of each compound appeared to play an important role in the receptor binding [89].

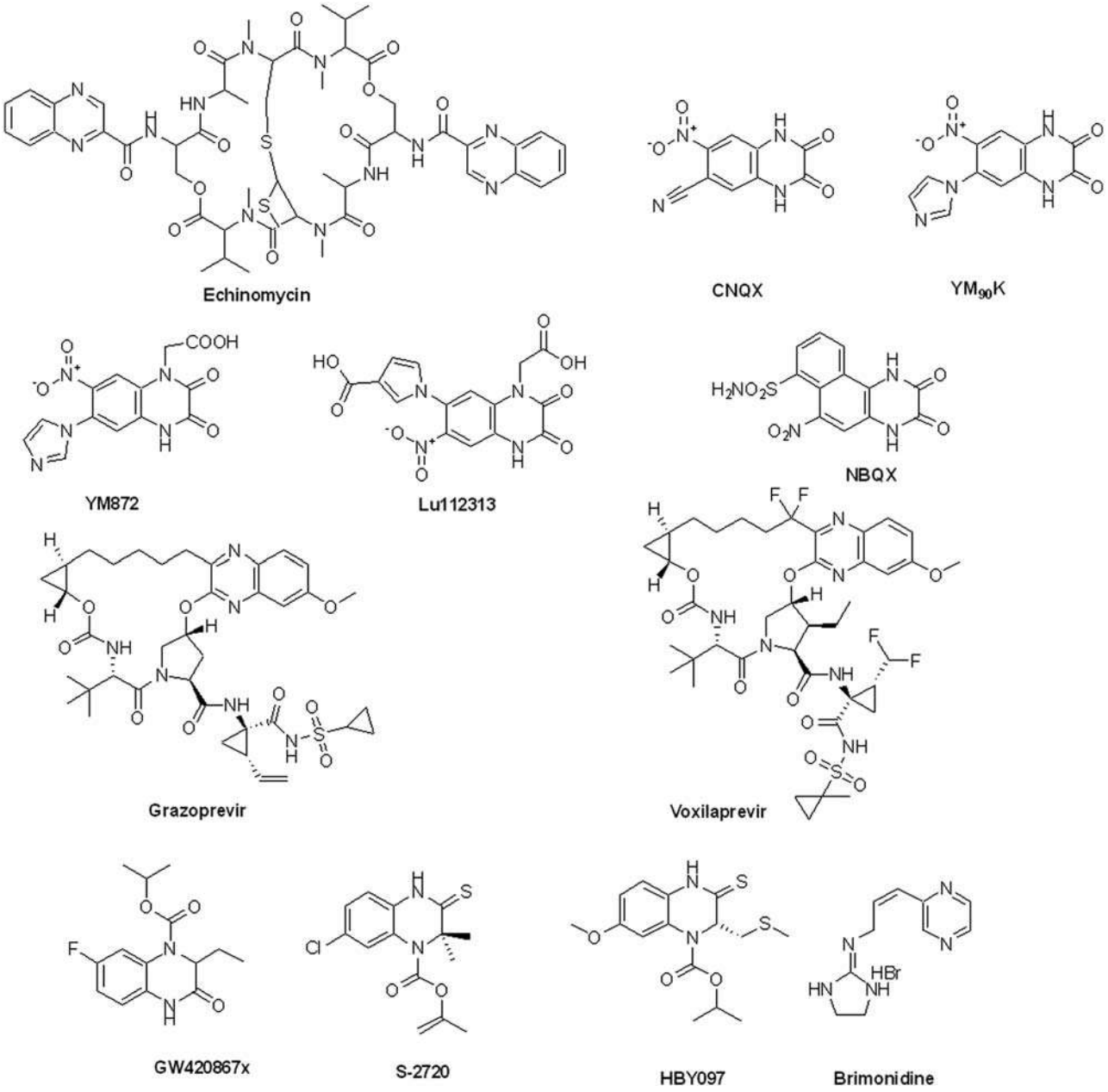


FIGURE 12.26 Some quinoxaline based small molecules of clinical significance.

12.7.2 Synthetic aspects

12.7.2.1 Synthesis N-*arylsulfonylquinoxaline*

In 2009, XU group disclosed the new chemical entities of 6-fluoro-N^4-(quinoline-8-sulfonyl)-3,4-dihydroquinoxalin-2-(*1H*)-one (**38**) and its analog 6-fluoro-3-methyl-4-(2-methyoxycarbonylthiophene-3-sulfonyl)-3,4-dihydroquinoxa-lin-2(1H)-one (**39**), Fig. 12.31. The quinoxalinone series **41** were prepared by the reductive cyclization of **40** in situ in moderate to high yield which upon sulfonylation in the presence of pyridine afforded the desired quinoxalinone derivatives (**36a-j**, Scheme 12.16) [88].

12.7.2.2 Synthesis of N^1*-arylsulfonyl-2-quinoxalinones*

Scheme 12.17 shows two different pathways for the synthesis of the target compounds **44**. The first was by the electrophilic substitution of arene-sulfonyl chloride to the compounds **42** and the other by the nucleophilic substitution of sodium arenesulfinates to compounds **43** [90].

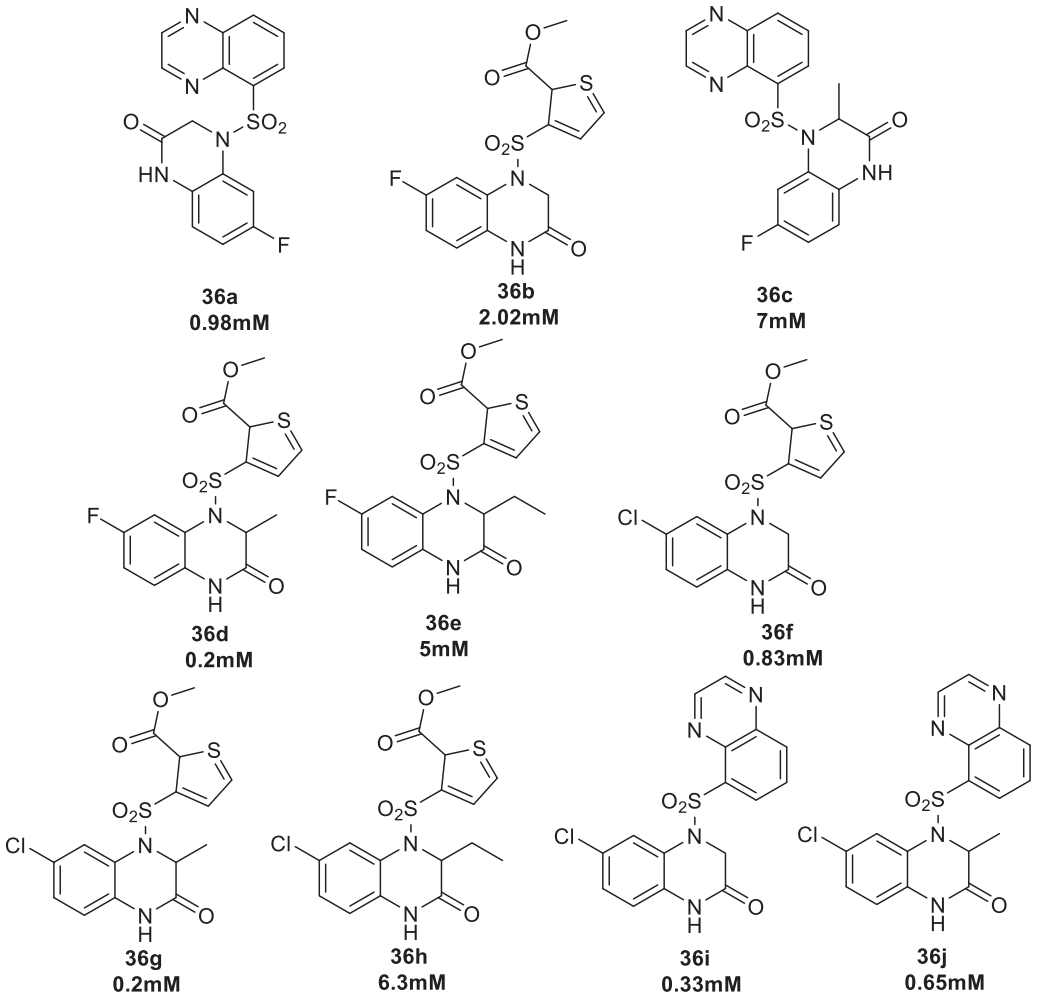


FIGURE 12.27 6-Fluoro-N^4-(quinoline-8-sulfonyl)-3,4-dihydroquinoxalin-2(*1H*)-one and its analog 6-fluoro-3-methyl-4-(2-methyoxycarbonylthiophene-3-sulfonyl)-3,4-dihydroquinoxa-lin-2(1H)-one dreivatives as NNRT inhibitors.

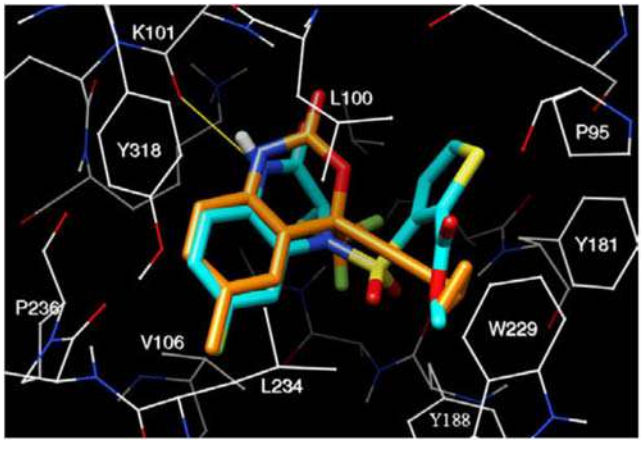


FIGURE 12.28 Docked pose of compound **36d** into the active site of HIV-1 reverse transcriptase [88].

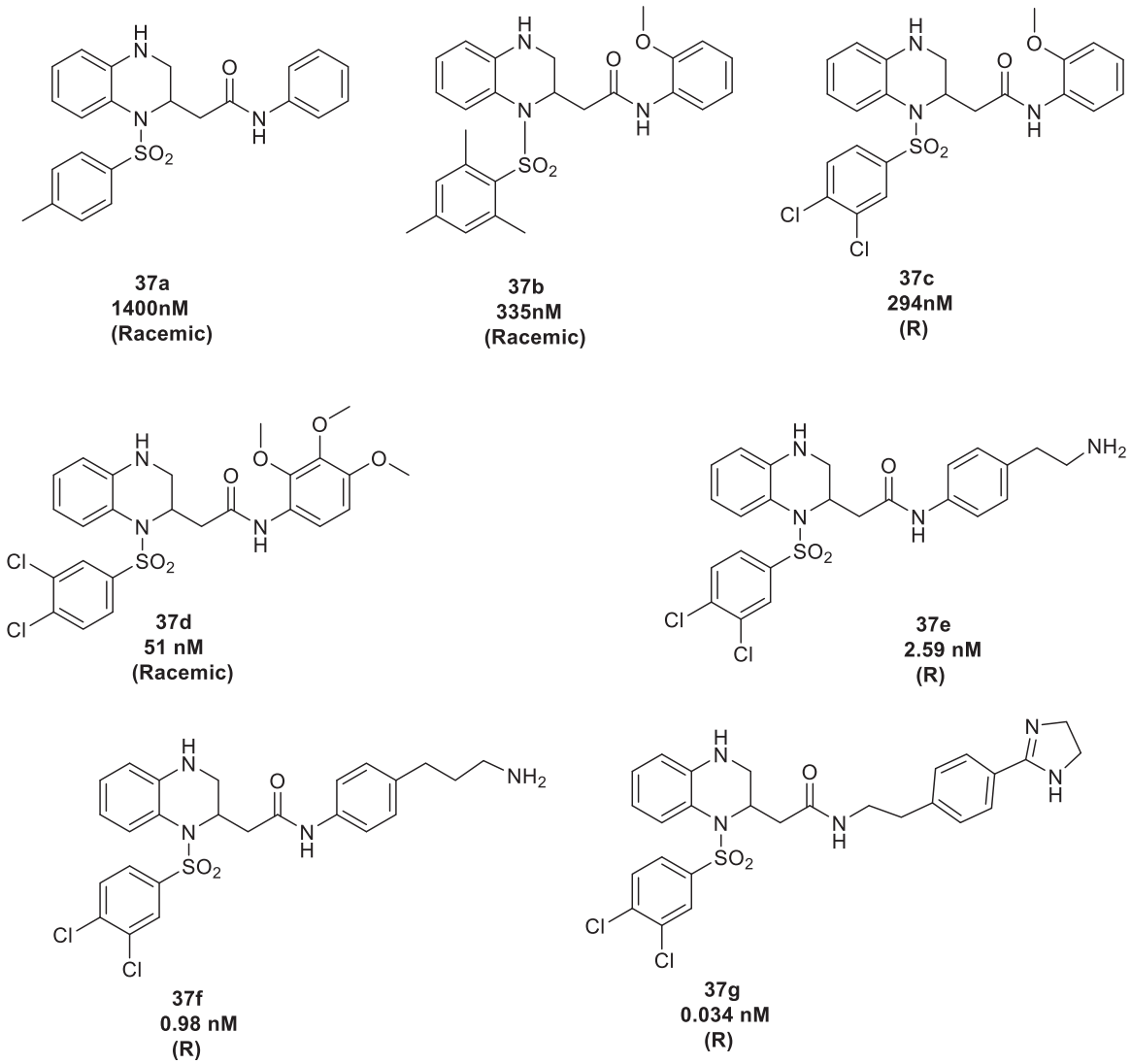


FIGURE 12.29 Quinoxaline-based Non-peptide Bradykinin B1 Receptor Antagonist [89].

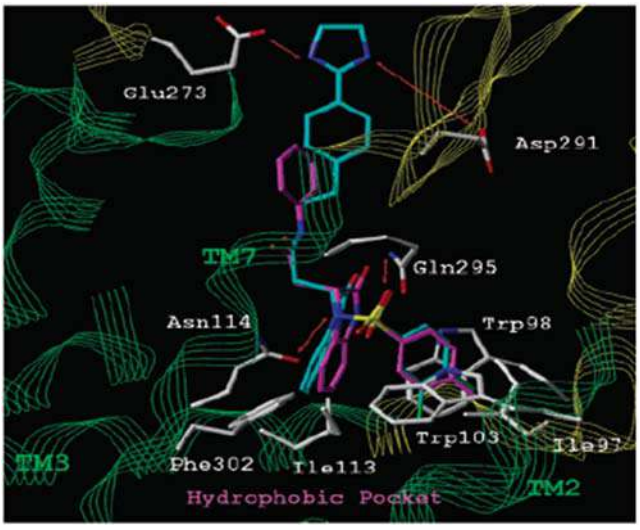
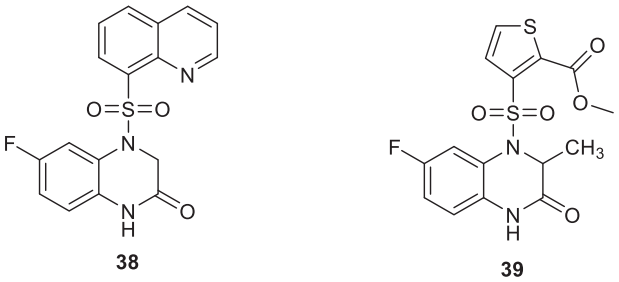


FIGURE 12.30 Compound **37a** docked into the constructed homology model of BK-B1 [89].

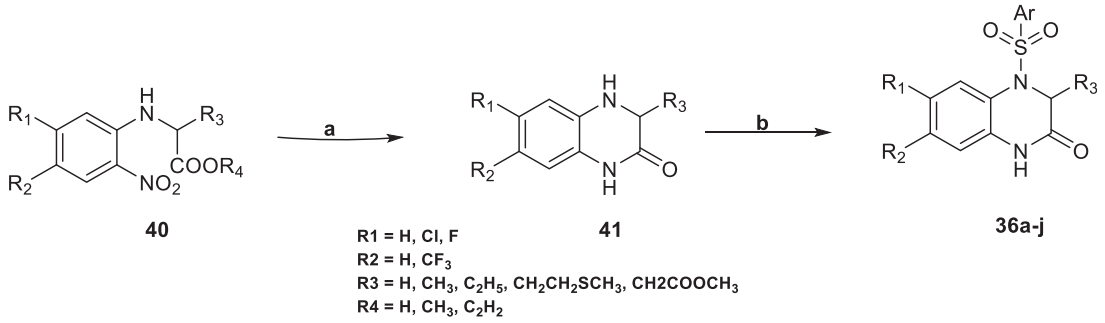


38 39

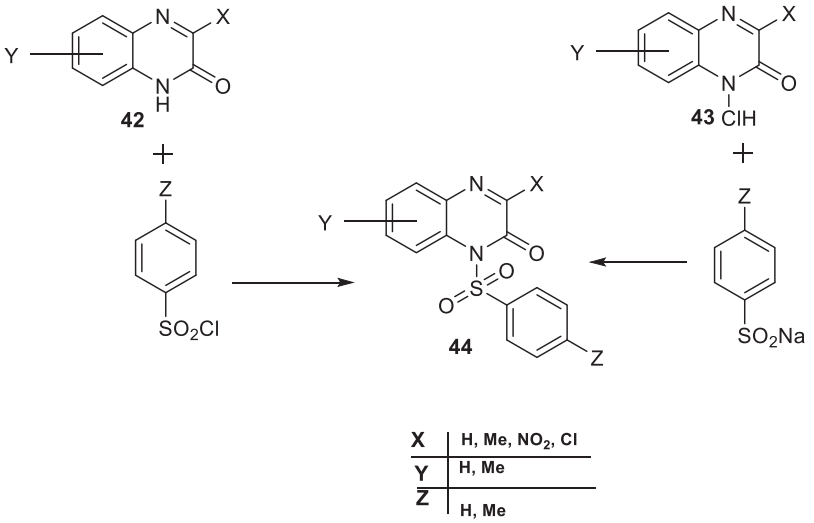
FIGURE 12.31 New *N*-arylsulfonylquinoxaline proposed by Xu et al.

12.7.2.3 Synthesis of multisubstituted dihydroquinoxalin-2-one

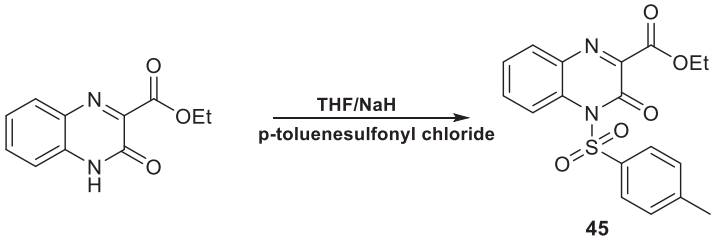
Miyamaru and co-workers reported a modified umpolung reaction of α-imino esters using organometallic reagents under argon which gave *N*-alkylated product of dihydroquinoxaline **45** in good yield (Scheme 12.18) [91].



SCHEME 12.16 Synthesis of compounds **36a-j**.



SCHEME 12.17 Synthesis of N^1-arylsulfonyl-2-quinoxalinones [90].



SCHEME 12.18 Synthesis of multisubstituted dihydroquinoxalin-2-one.

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Chapter 13

Patents and applications of *N*-sulfonated *N*-heterocycles

13.1 Introduction

N-Sulfonyl heterocycles have been explored for various bioactivities and several compounds containing this moiety have already been developed as commercial products. Thus, it is only natural to find different marketed drugs bearing *N*-sulfonyl heterocycles. Some marketed Phosphodiesesterase 5 inhibitors such as Sildenafil and Vardenafil are currently marketed for the treatment of erectile dysfunction (ED) and pulmonary hypertension [1−3]. In the field of antibiotics, Aztreonam bears *N*-sulfonyl heterocycle. Aztreonam is a beta-lactam antibiotic (monobactam) and is the first discovered monobactam with broad-spectrum antibacterial activity [4,5]. Mezlocillin is another semisynthetic ampicillin that has a *N*-sulfonyl heterocycle and possesses good antibacterial activity for the treatment of different skin, genito-urinary tract, hepatobiliary and CNS infections [6]. Some nonsteroidal anti-inflammatory drugs also have *N*-sulfonyl heterocycle scaffolds, such as Piroxicam and Meloxicam. Both are used for the treatment of osteoarthritis and rheumatoid arthritis [7,8]. Brinzolamide is a carbonic anhydrase inhibitor that bears *N*-sulfonated *N*-heterocycle that is used for reducing intraocular pressure and thus for the treatment of ocular hypertension or open-angle glaucoma [9,10]. Also, Sulthiame is another carbonic anhydrase inhibitor that offers a therapeutic efficacy for treating childhood focal epilepsy and can be used as an adjunct therapy in other refractory epilepsies [11]. Almotriptan is used for the treatment of migraine through its agonistic effect on serotonin receptors (5-HT) [12,13]. A thiazide diuretic (Polythiazide) has been approved for the treatment of hypertension and edema [14]. The Janus kinase (JAK) inhibitor, Baricitinib, can inhibit both JAK1 and JAK2 and is used for the treatment of moderate to severe rheumatoid arthritis that showed poor response to at least one tumor necrosis factor (TNF) antagonist [15]. Fig. 13.1 shows the collective chemical structures of the aforementioned *N*-sulfonyl heterocycles.

On the other hand, as research continues, new investigational drugs bearing the scaffold of interest emerged. New agents for the treatment of ED are now under investigation, such as Mirodenafil. Mirodenafil is also proposed for the treatment of urologic diseases and renal insufficiency [15]. Also, Gisadenafil is currently undergoing investigation for the treatment for prostatic hyperplasia [16]. Fasudil is a Rho kinase inhibitor that is being investigated for the treatment of carotid stenosis [17,18]. The atypical tricyclic antidepressant Tianeptine has shown a useful effect in the treatment of depression through the inhibition of 5-HT reuptake [19]. Pictilisib has shown pan class I phosphatidylinositol kinase inhibitory activity, which made it a proposed candidate for the treatment of cancer [20]. The metalloproteinase inhibitor, Prinomstat, showed efficacy as an antineoplastic agent in small cell lung carcinoma [21]. Relacatib is a cathepsin K inhibitor that was found to be of use for the treatment of osteoporosis and metastatic bone cancer [22,23]. Cerdulatinib is a SYC/JAK inhibitor that can be used for patients with relapsed/refractory peripheral T-cell lymphoma [24]. The bradykinin- B2 receptor antagonist Anatibant was found to be efficient in the treatment of traumatic brain injury [25]. For the treatment of calcified aortic valve stenosis, Ataciguat is currently being investigated [25]. Elubrixin was in phase II clinical trial but the trials were ceased due to lack of efficacy [26]. The orally administered Verubecestat has been investigated for the treatment of Alzheimer's disease [27]. In the quest for developing dual TNFα-converting enzyme and matrix metalloprotease-13 inhibitors, Aprastat was studied for its efficacy in the treatment of active rheumatoid arthritis [28]. Fig. 13.2. Contains the chemical structures of the previously given investigational drugs.

In this chapter, a brief description of some applications of *N*-sulfonyl heterocycles is overviewed briefly.

13.2 Three membered *N*-sulfonyl heterocycles

13.2.1 *N*-Sulfonyl aziridine

Aziridine is a heterocyclic cyclopropane ring containing one nitrogen atom. The aziridine ring is a privileged scaffold especially in organic synthesis due to its unique

N-Sulfonated-*N*-Heterocycles. DOI: https://doi.org/10.1016/B978-0-12-822179-2.00004-5

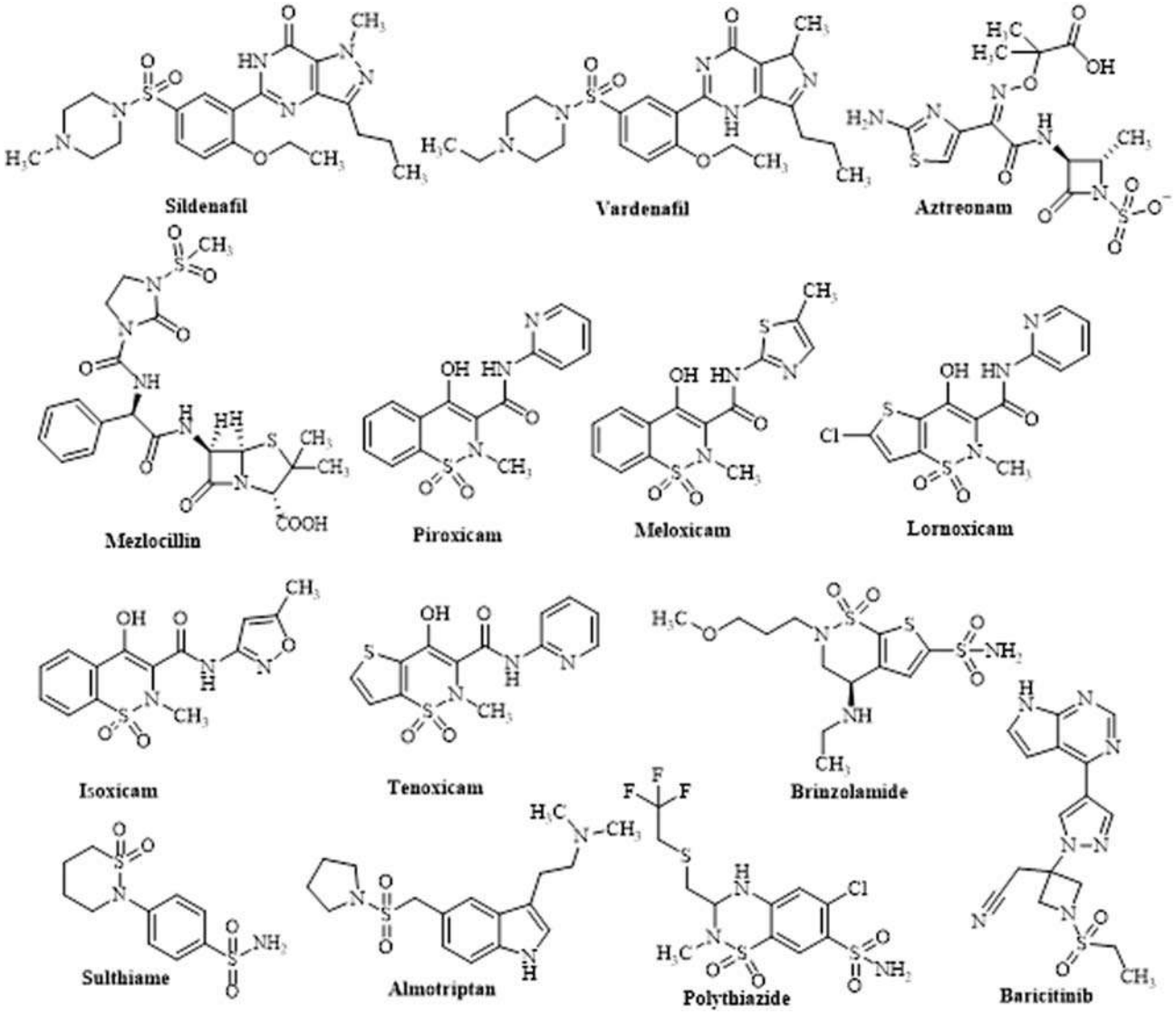


FIGURE 13.1 Clinically approved *N*-sulfonyl heterocycles.

chemistry. Many alkaloids containing at least one aziridine ring are therapeutic agents for the treatment of cancer and bacterial infections (Fig. 13.3). Various research articles and patents have described the utility of the aziridine ring in organic synthesis [29,30].

Few patents have reported therapeutically or industrially useful *N*-sulfonyl aziridine compounds. However, *N*-sulfonyl aziridine derivatives have been found useful in the synthesis of useful compounds. For example; the *N*-sulfonyl aziridine derivative with the general formula **1** (Fig. 13.4) was used in the preparation of compounds with the general formula **2**. The prepared compounds were claimed to be effective in the treatment of fungal infections [31].

13.3 Four-membered *N*-sulfonyl heterocycles

13.3.1 *N*-Sulfonyl-azetidine and azetidine derivatives

13.3.1.1 Medical applications of azetidine derivatives

Azetidine is a four-membered polar ring containing one basic nitrogen atom. This ring is characterized by being rigid, polar, and has a high Fsp^3 character. However, the ring displays great challenges in its synthesis. So, only a few drugs are approved containing azetidine rings [32]. Most prominently, the azetidine ring is found in approved

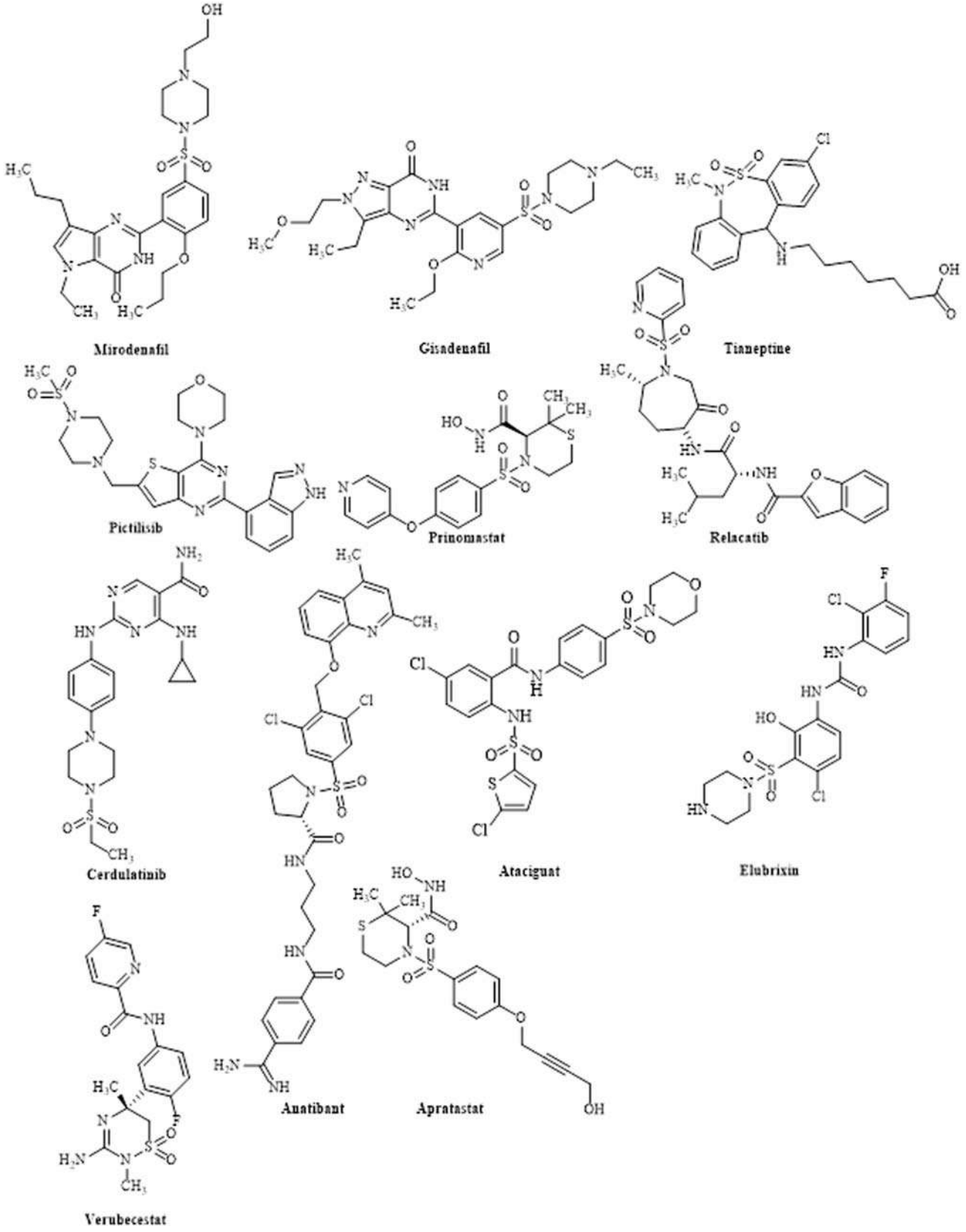


FIGURE 13.2 Clinically investigated *N*-sulfonyl heterocycles.

β-lactam antibiotics such as Clavulanic acid, Tazobactam, Benzyl penicillin, and Ceftriaxone (Fig. 13.5) [33,34]. Also, Siponimod (Fig. 13.5) is a regulator of sphingosine receptors and is currently approved for the treatment of multiple sclerosis (MS) [35]. Finally, Cobimetinib (Fig. 13.5) is an approved drug for the treatment of various cancers including breast cancer and melanoma bears, an azetidine ring [36]. Various factors affect the growing interest in incorporating the azetidine ring into developing therapeutics. First, the synthetic strategies to incorporate

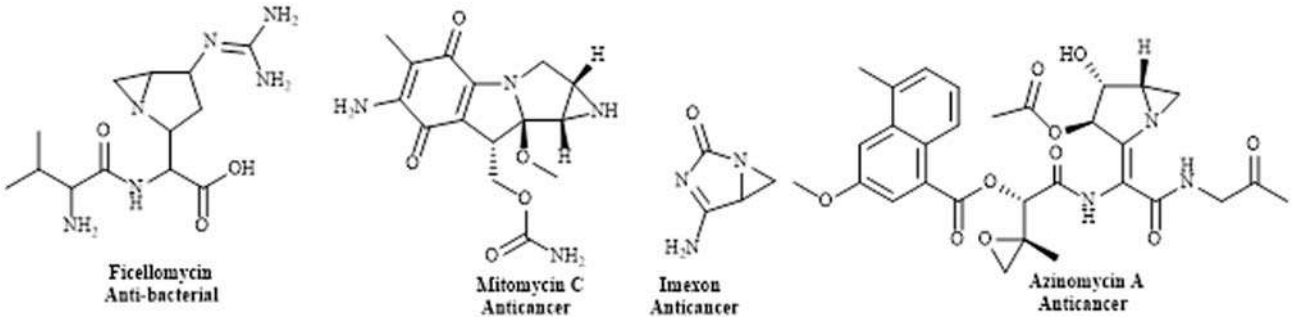


FIGURE 13.3 Some aziridine-based compounds with therapeutic activity.

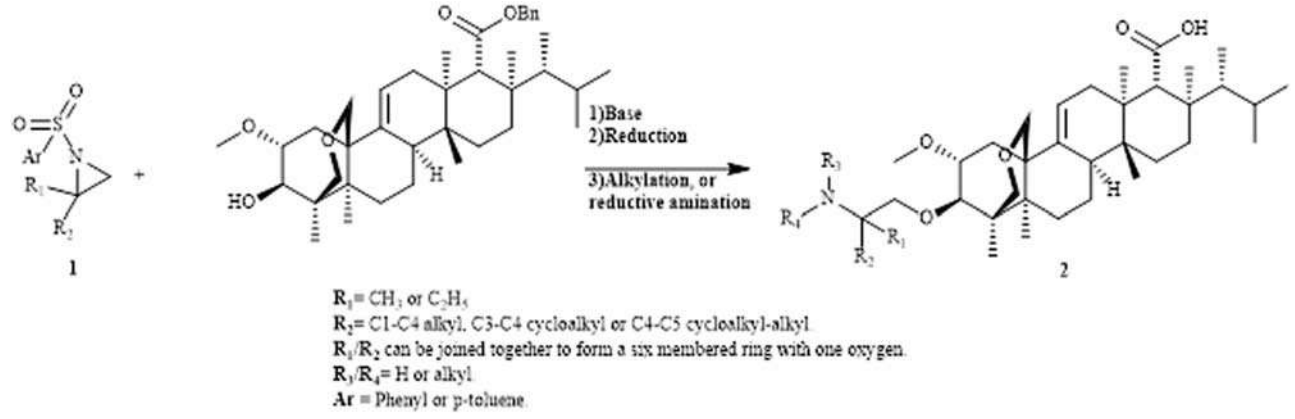


FIGURE 13.4 The utility of *N*-sulfonated aziridine in the synthesis of antifungal agents.

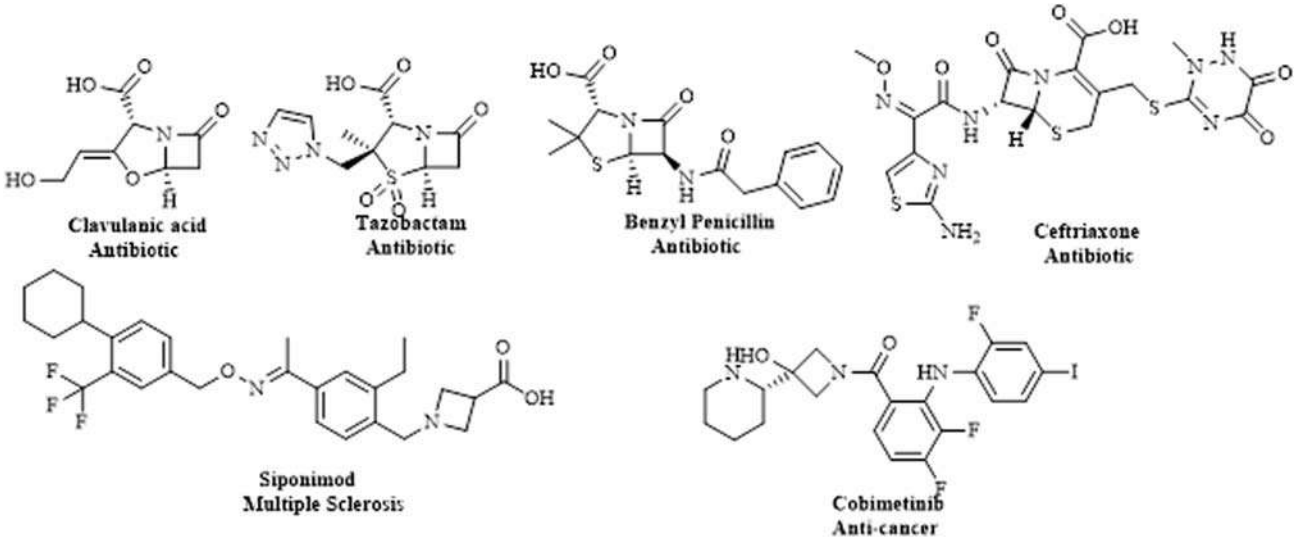


FIGURE 13.5 Clinically approved azetidine derivatives.

the ring into a molecule are currently growing [32]. Second, the incorporation of an azetidine ring enhances the solubility of the molecule by replacing an unsaturated ring [37]. Third, the azetidine ring can help in shifting the metabolism or reducing the metabolism of the drug molecule [32]. Nevertheless, the presence of an azetidine ring in a molecule certainly makes it liable to ring-opening reactions at acidic and neutral pH in some cases, reducing lipophilicity and glutathione reactivity [38–40].

13.3.1.2 N-Sulfonyl azetidine derivatives for the treatment of hyperlipidemia

ATP citrate lyase (ACLY) is an enzyme that catalyzes the reaction of citrate and CoA to form both acetyl-CoA and oxaloacetate. Acetyl-CoA is a one-carbon source that is utilized in different biological processes including lipogenesis and chloesterogenesis as well as acetylation reactions of histones and proteins [41].

ACLY inhibitors are promising therapeutics for the treatment of atherosclerosis, diabetes, obesity, and cancer [42]. Leit de Moradei and associated researchers reported the investigation of various *N*-heterocycles as inhibitors of ACLY. Some of those compounds (**3a–d**) are presented in Fig. 13.6 bearing *N*-sulfonyl azetidine moiety [43].

INDY is the acronym for I'm Not Dead Yet which is used to express the nonelectrogenic dicarboxylate and citrate transporter. The role of INDY was initially observed in D. melanogaster with a significant role in the life span and regulation of metabolism. In D. melanogaster, INDY encodes an electroneutral tricarboxylate carrier which is expressed in organs involved in energy homeostasis. Long-lived flies with low levels of expressed INDY showed low expression of insulin-like proteins and an overall reduction in body fat. Cytosolic citrate is the primary carbon source for the biosynthesis of fatty acids, cholesterol, and lipoproteins. Also, citrate affects glycolysis and β-oxidation. The plasma membrane carrier mINDY is responsible for transporting citrate across the cell membrane. mINDY is mainly expressed in the liver and other metabolically active organs, allowing it to play a vital role in different metabolic processes. Thus, the regulation of INDY can be beneficial in the treatment of metabolic diseases such as diabetes and obesity [44].

In 2018, Zahn, Grit, *et al.* reported an efficient method for a multi-step synthesis of (*E*)-*N*-(2-fluorobenzyl)-1-(styrylsulfonyl)azetidine-3-carboxamide. Starting from (*E*)-2-phenylethene-1-sulfonyl chloride and Me azetidine-3-carboxylate hydrochloride and other related compounds. The selected compounds (**4a–e**, Fig. 13.7) were evaluated

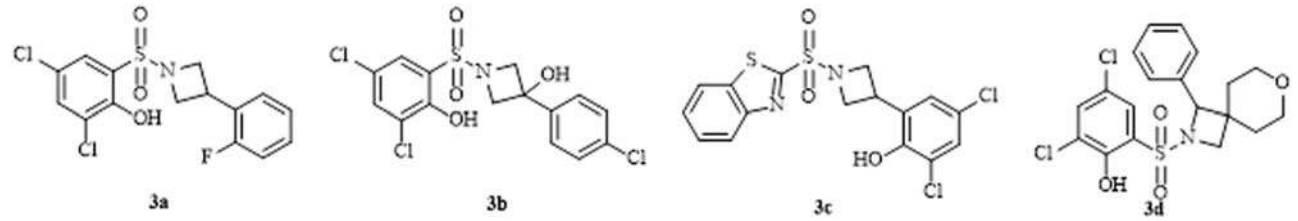


FIGURE 13.6 *N*-Sulfonyl azetidine derivatives as ATP citrate lyase inhibitors.

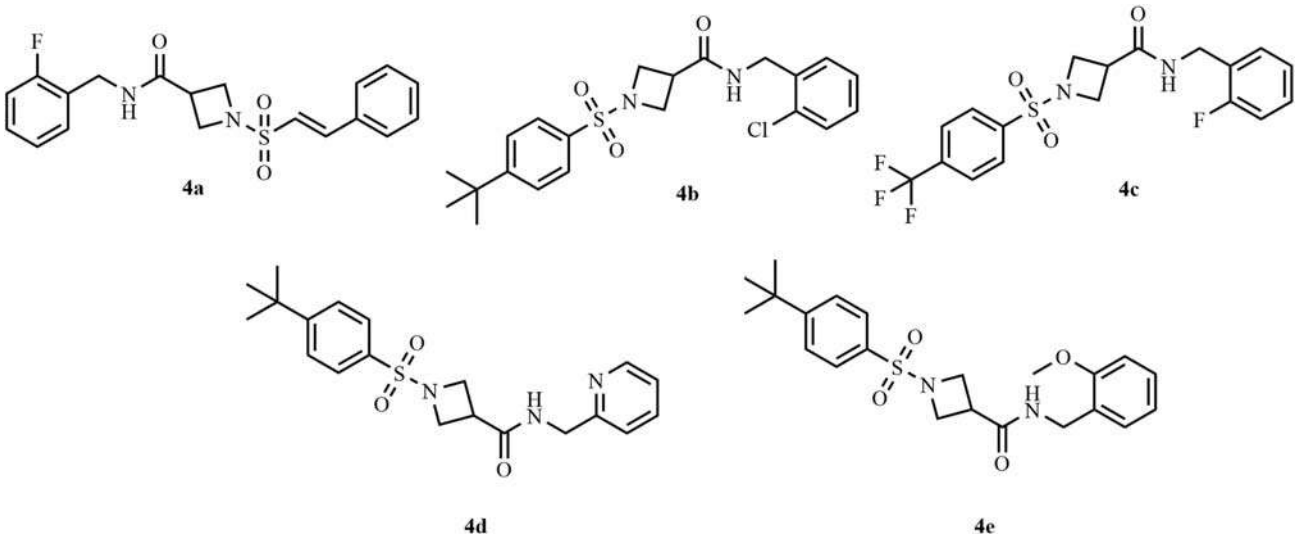


FIGURE 13.7 *N*-Sulfonyl azetidine derivatives as citrate transporter inhibitors.

as inhibitors of citrate transporter activity. These compounds are used for the treatment of obesity and diabetes, in particular type 2 diabetes and other metabolic diseases, as well as for the treatment of age-related diseases [45].

13.3.1.3 N-Sulfonyl azetidine derivatives for the treatment of muscular degradation disorders

Baricitinib (Fig. 13.8) is a ccJAK3 inhibitor used for treating muscular degradation, such as atrophy, dystrophic disorders, and cachectic states [46].

13.3.1.4 N-Sulfonyl azetidine derivatives for the treatment of cardiac diseases

Cardiac diseases are often characterized by altered contractions (active forces) or myocardium passive tension (passive forces). The main source for both forces is the cardiomyocytes, which are specialized striated muscles containing sarcomeres. Sarcomeres are a set of highly ordered protein complexes aligned longitudinally giving the heart muscle its striated appearance. The active forces of the heart are generated by the action of actins and myosins, while the passive forces are generated by the action of titins. Troponin (Tn) is a protein complex that acts as the anchoring complex of actin filaments. Troponin consists of three subunits: troponin C (TnC), troponin I (TnI), and troponin T (TnT). TnI has an inhibitory region that inhibits the movement of tropomyosin from the myosin-binding site on the actin filaments. TnC is the calcium-binding subunit that binds calcium, allowing TnC to bind to TnI in the switch peptide region. That binding eventually leads to the occurrence of contractions. Various cardiac diseases have been linked to troponins [47,48]. To increase the activity of cardiac sarcomere, Ashcraft and the associated team synthesized and evaluated a novel series of bis-amide-*N*-sulfonated azetidine derivatives (**5a–g**, Fig. 13.9) as cardiac sarcomere modulators. These compounds may bind to the TnC/TnI interface to increase the activity of the cardiac sarcomere [49].

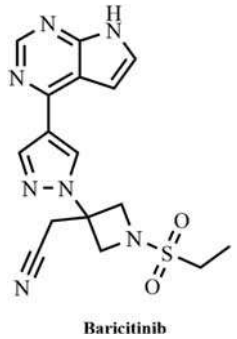


FIGURE 13.8 The *N*-sulfonyl azetidine derivative "Baricitinib" for the treatment of muscular degenerative disorders.

13.3.1.5 N-Sulfonyl azetidine derivatives for the treatment of cancer

Compounds **6a–l** (Fig. 13.10) have been described in injectable compositions for their effect on killing liver and lung cancer cells [50].

A series of heteroaryl compounds was presented by Kim *et al.* to explore the possible inhibitory effect of the claimed compounds on the Mer enzyme in a trial to find a new therapy for cancer [51]. Among the presented compounds, compound **7** (Fig. 13.11) was claimed to be useful as a Mer inhibitor [51]. Mer is a tyrosine kinase belonging to the TAM receptors family. TAM receptors (Tyro3, Axl, and Mer) are expressed in tissue macrophages and dendritic cells. Recently, Mer and its ligand (protein S) were found to be expressed on T-cell receptor-activated human CD8 + cells. TAM receptors are also expressed in endothelial cells, neurons, and male primordial cells [52].

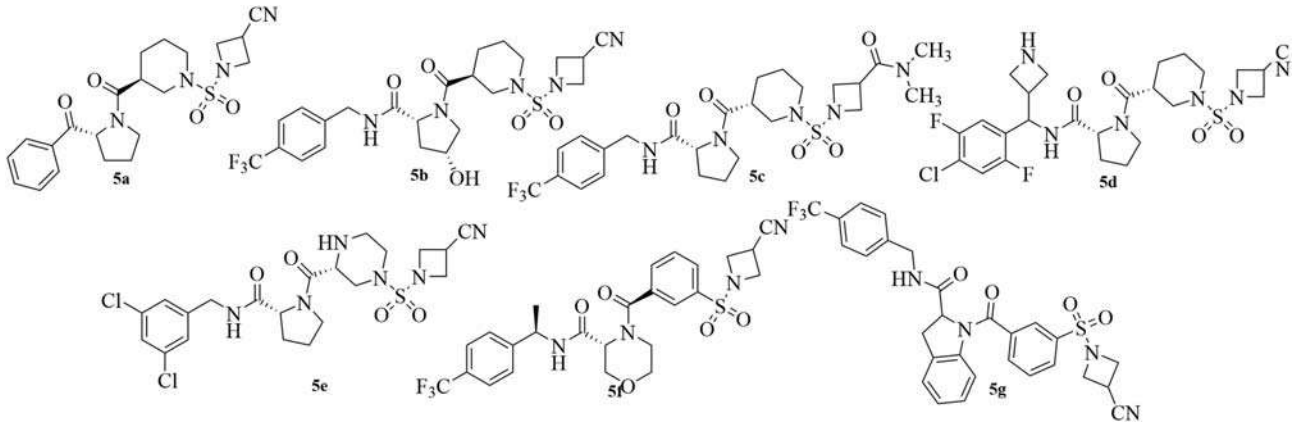


FIGURE 13.9 *N*-Sulfonyl azetidine derivative as modulators of cardiac sarcomeres.

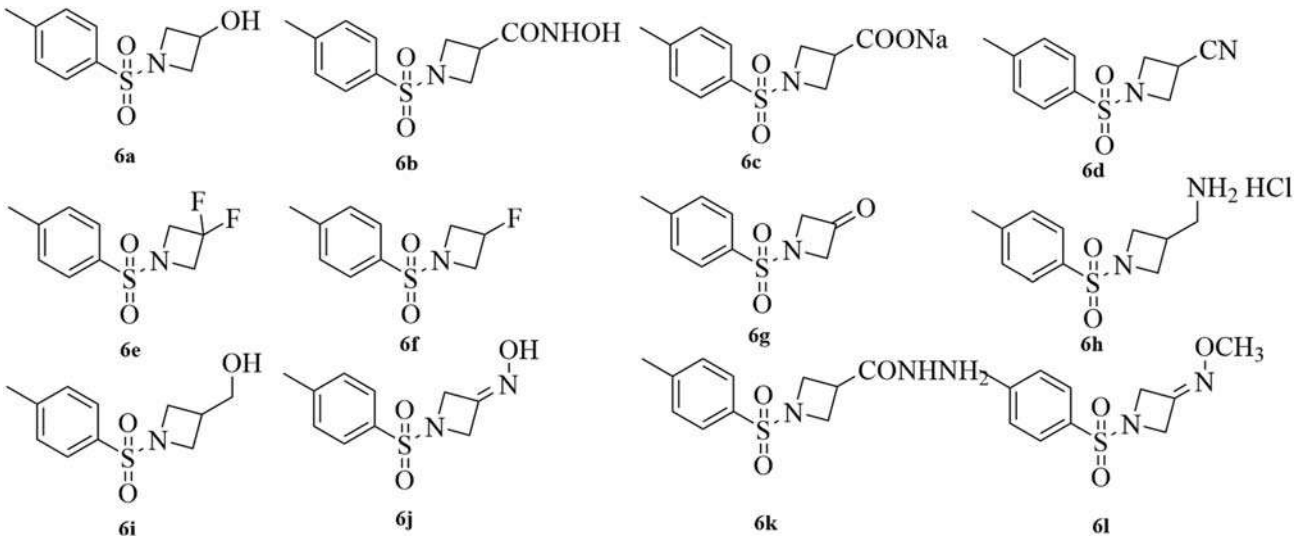


FIGURE 13.10 *N*-Sulfonyl azetidine derivative as anticancer agents.

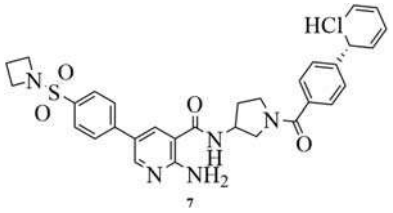


FIGURE 13.11 *N*-Sulfonyl azetidine derivative as Mer inhibitor.

13.3.1.6 N-Sulfonyl azetidine derivatives for the treatment of inflammation and related disorders

The styrylsulfonyl-azetidine **8a** and **8b** (Fig. 13.12) derivatives were tested as inhibitors for interleukin-1 activity [53].

13.4 Five membered *N*-sulfonyl heterocycles

13.4.1 *N*-Sulfonyl imidazole and imidazoline derivatives

13.4.1.1 Medical applications of imidazole and imidazoline derivatives

The imidazole ring is a five-membered aromatic *N*-heterocycle that is widely presented in many endogenous molecules such as histidine amino acid, biotin, and histamine (Fig. 13.13) [54]. Imidazole is an electron-rich ring that makes the ring easy to form a variety of interactions with any biological target. Many marketed drugs contain at least one imidazole scaffold and are used in the treatment of hypertension, fungal infections, bacterial infections, cancer, and peptic ulcer and some are used as immunosuppressants [54,55].

On the other hand, the imidazoline ring, specifically 2-imidazoline derivatives, is best known for its activity on α-adrenergic receptors and imidazoline (I) receptors. Imidazoline is the reduced form of the imidazole ring and has wide applications in organic synthesis. Various drugs bearing substituted imidazoline moiety have been approved as α-adrenergic receptor modulators, antihistamines, muscle relaxants, antihypertensives, and anticancer [56,57]. Fig. 13.14 presents some representative examples of clinically approved imidazoline containing drugs. In the following, some anticancer agents bearing both imidazoline and imidazolone derivatives are abstracted from their respective patents.

13.4.1.2 N-Sulfonyl imidazole and imidazoline derivatives for the treatment of cancer

Yoon and co-workers introduced a series of arylsulfonylimidazolone derivatives and tested their activity as anticancer agents. Fig. 13.15 shows representative examples (**9a**–**h**) which have been tested against A549, KB, colo205, and SK-OV-3 cancer cell lines [58].

In other efforts, Li *et al.* published a series of *N*-heterocyclic compounds with expected tubulin inhibitory activity. Some of the developed compounds had *N*-sulfonated imidazole core as shown in compounds bearing the general formula **10**. Fig. 13.16 shows some examples of the prepared compounds (**10a**–**c**, Fig. 13.16). The inventors also discussed the general structure activity relationship of the introduced compounds. In brief, it was concluded that *N*-sulfonated imidazole derivatives with

formula **10** showed moderate activity with IC_{50} in the μM range. The presence of 3,4,5-trimethoxy substitution on the phenyl ring (I) was optimal for the activity where the removal of one methoxy group led to a loss of cytotoxic activity. Also, 4-fluoro analogs showed good cytotoxic activity, which meant that the methoxy substitutions could be replaced by a fluoride substitution. In addition, the fluoro substitution provided better metabolic stability. On the other hand, shifting the fluoro to position 3 abolished the activity. Finally, the relative position of the two phenyl rings to each other is important for activity. For example, shifting ring III to position 1 instead of 4 on the imidazole ring (ring II) caused a drastic decrease in cytotoxic activity [59].

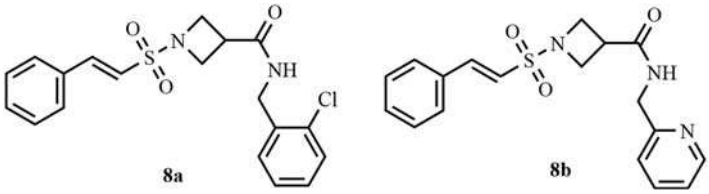


FIGURE 13.12 *N*-Sulfonyl azetidine derivative as inhibitors of interleukin-1 activity.

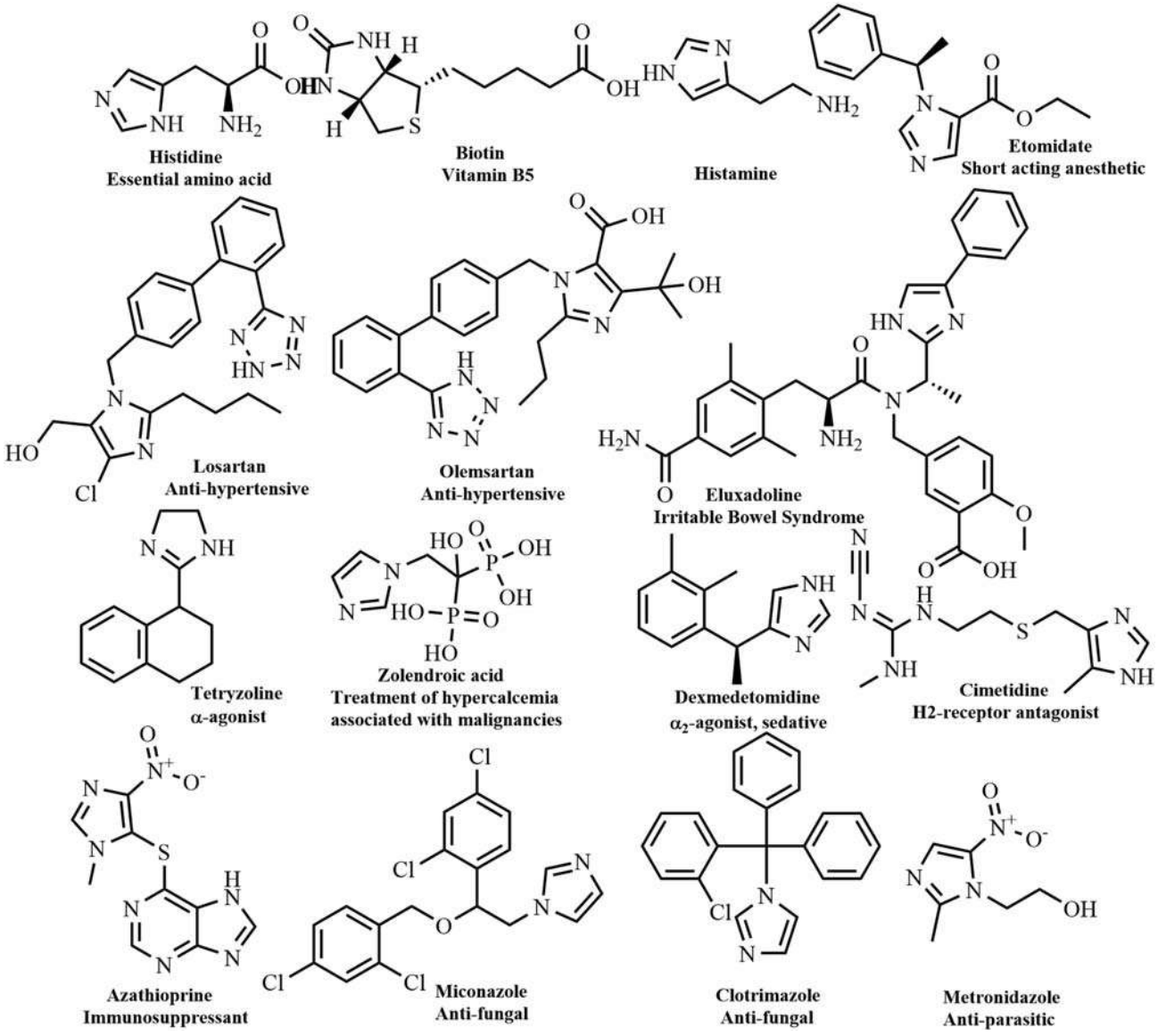


FIGURE 13.13 Clinically approved drugs containing imidazole scaffold.

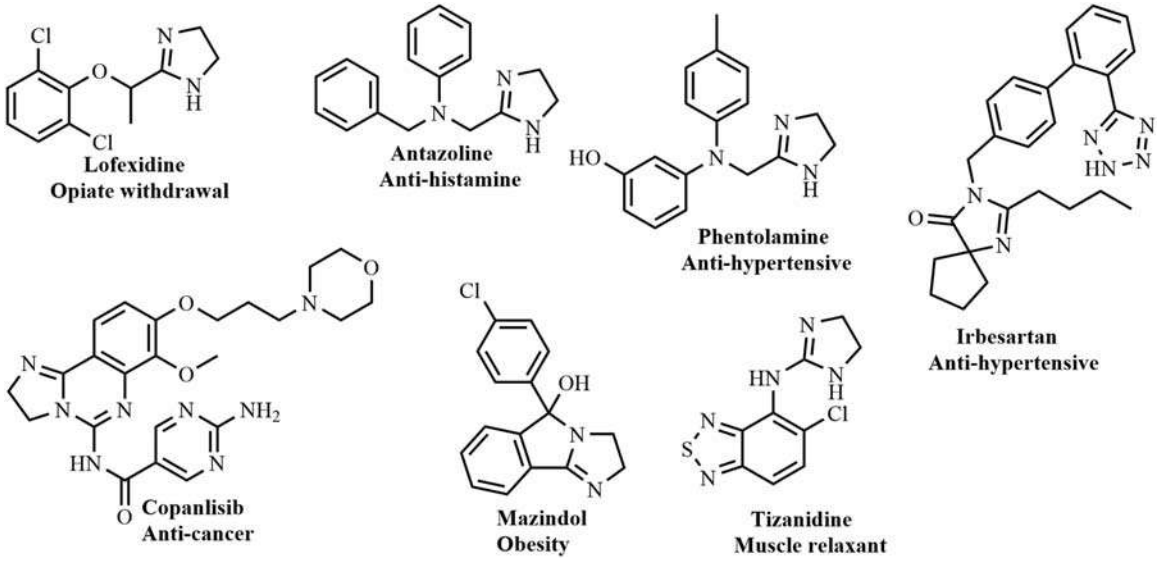


FIGURE 13.14 Clinically approved drugs containing imidazoline scaffold.

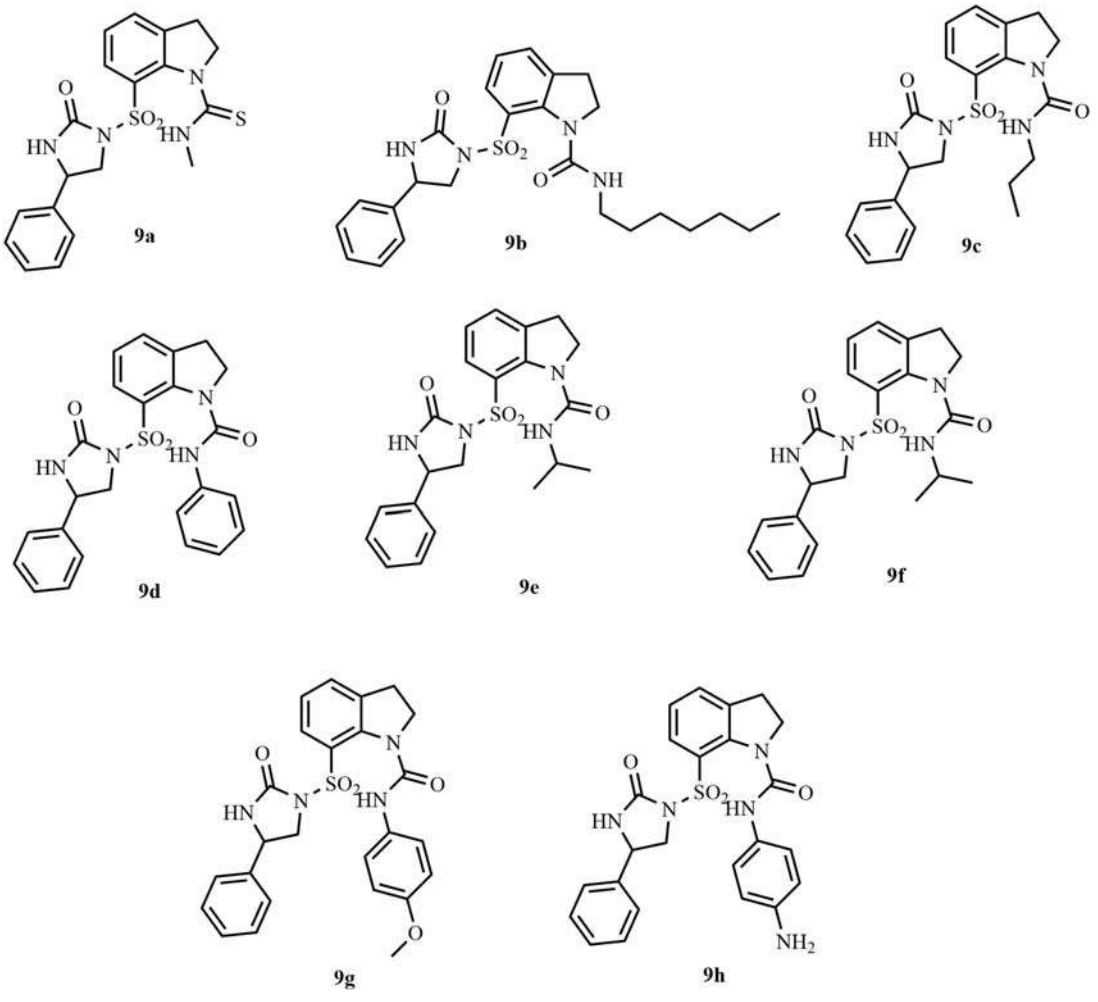


FIGURE 13.15 Arylsulfonylimidazolone as anticancer agents.

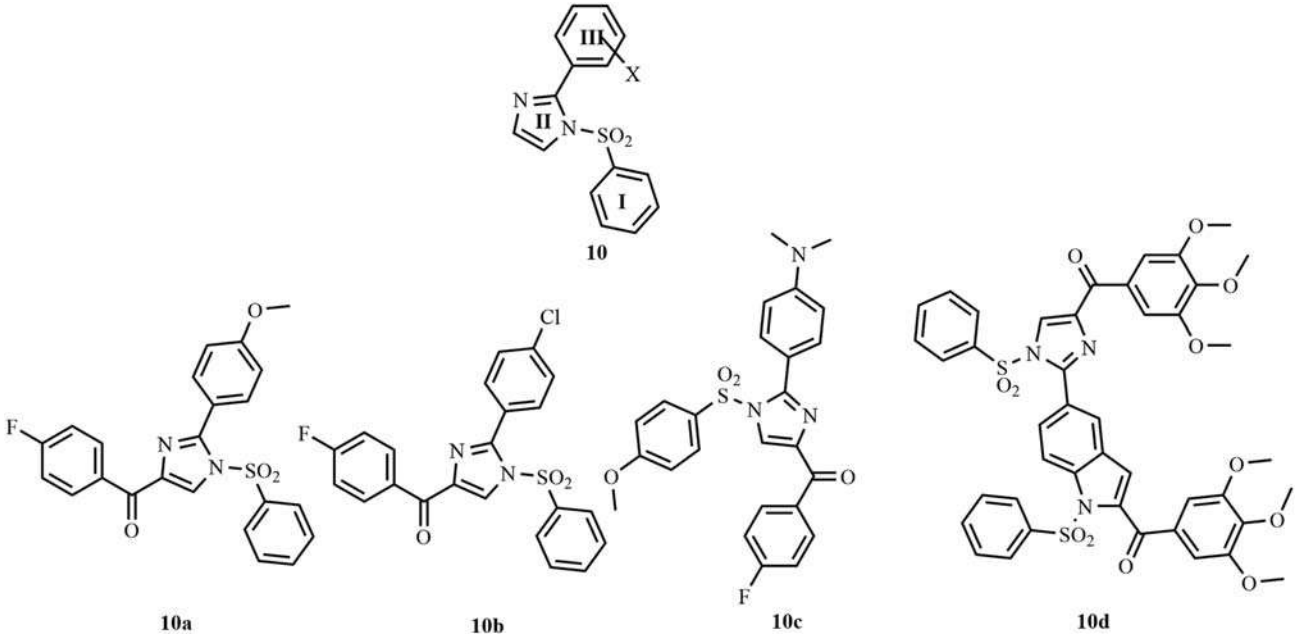


FIGURE 13.16 *N*-Sulfonyl imidazole derivatives as expected tubulin inhibitors.

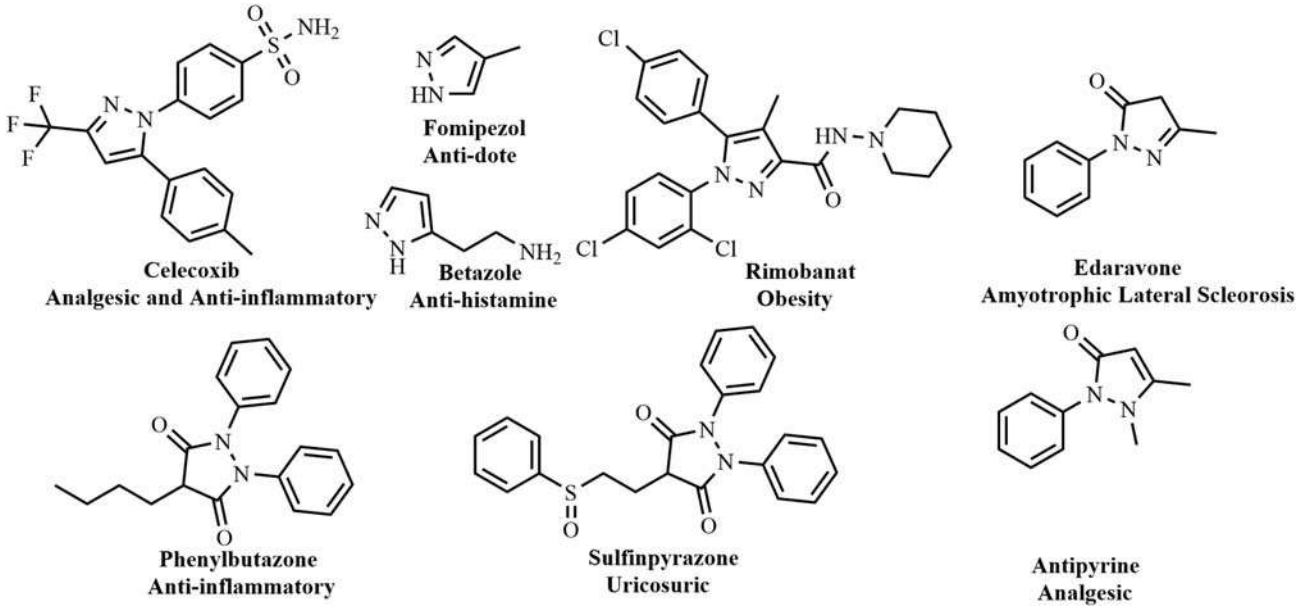


FIGURE 13.17 Clinically approved drugs containing pyrazole scaffold.

13.4.2 *N*-Sulfonyl pyrazole derivatives

13.4.2.1 Medical applications of pyrazole derivatives

Pyrazole is another example of five-membered *N*-heterocycles which have been found to be useful in the medical field. Various natural products such as Pyrazofurin contain the privileged pyrazole ring. Other synthetic derivatives of pyrazole are currently used as drugs for the treatment of various diseases. Examples of drugs with pyrazole scaffold are demonstrated in Fig. 13.17 [60].

Few patents reported clinical or other applications for *N*-sulfonyl pyrazole derivatives. For example, Arasappan and co-workers reported the synthesis of various 2-amino-*N*-heteroaryl nicotinamide derivatives, some of which had *N*-sulfonated pyrazole scaffold (compounds **11a–e**, Fig. 13.18). The compounds were suggested to block sodium channels ($Na_{v1.8}$) and thus were proposed for the

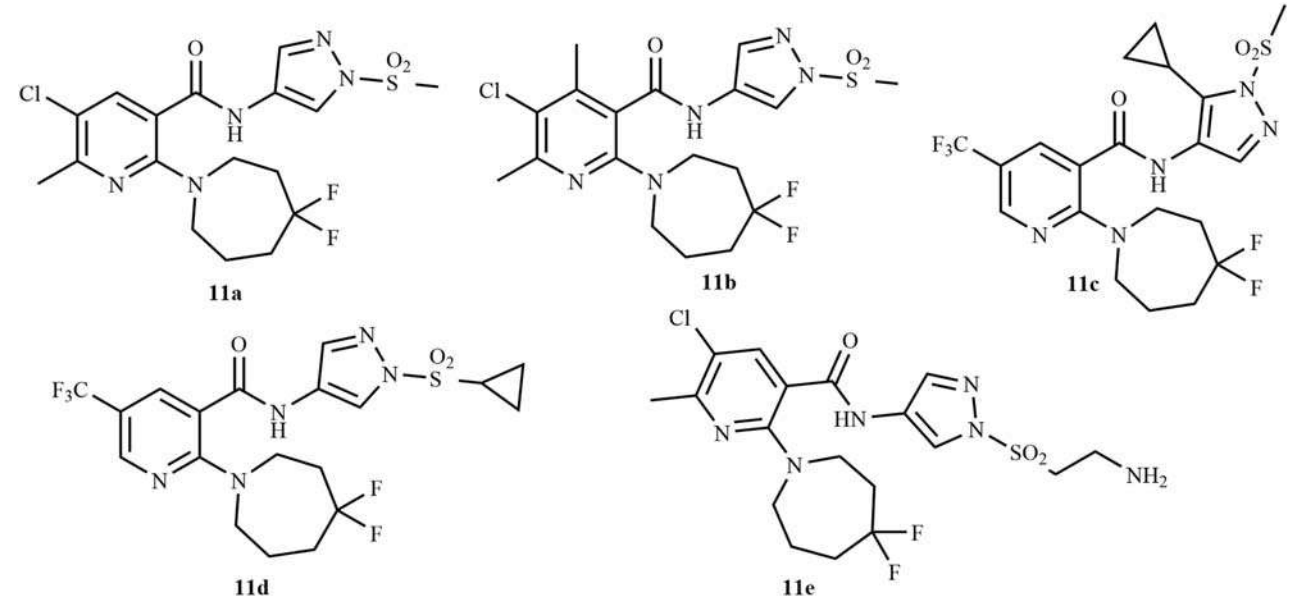


FIGURE 13.18 *N*-Sulfonyl pyrrole derivatives as $Na_v1.8$ antagonists.

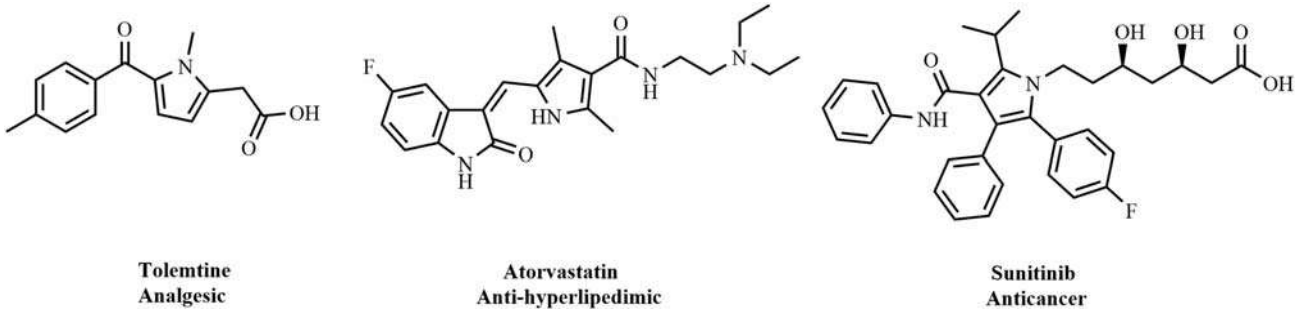


FIGURE 13.19 Clinically approved drugs containing pyrrole scaffold.

treatment, prevention, and amelioration of pain disorders, cough disorders, acute itch disorders, and chronic itch disorders [61]. $Na_v1.8$ receptors are voltage-gated sodium channels that are implicated in chronic pain conditions such as neuropathic pain and inflammatory pain [62].

13.4.3 *N*-sulfonated pyrrole and pyrrolidine

13.4.3.1 Medical applications of pyrrole and pyrrolidine derivatives

Pyrrole scaffold has been incorporated into many active drugs acting as anticancer, antihyperlipidemic, antiinflammatory, and antifungal agents. The pyrrole ring is also a reactive scaffold for polymerization, inhibiting corrosion, solvent for resins, and intermediate in organic synthetic reactions [63]. Fig. 13.19 demonstrates a few examples of approved drugs with a pyrrole core.

Similarly, many drugs currently in use contain the saturated pyrrole ring (pyrrolidine). The incorporation of the pyrrolidine ring into the molecule significantly affects its stereochemistry and geometry due to the noncoplanarity of the ring [64]. Fig. 13.20 offers examples of some approved drugs having a pyrrolidine nucleus.

13.4.3.2 N-Sulfonyl pyrrole for pain management

Arasappan and co-workers had reported the synthesis of various 2-amino-*N*-heteroaryl nicotinamide derivatives, some of which had *N*-sulfonyl pyrrole scaffold. The compound **12** (Fig. 13.21) was proposed as an inhibitor for $Na_v1.8$ type sodium channel. Thus, it has been proposed for the treatment, prevention, and amelioration of pain disorders, cough disorders, acute itch disorders, and chronic itch disorders [61].

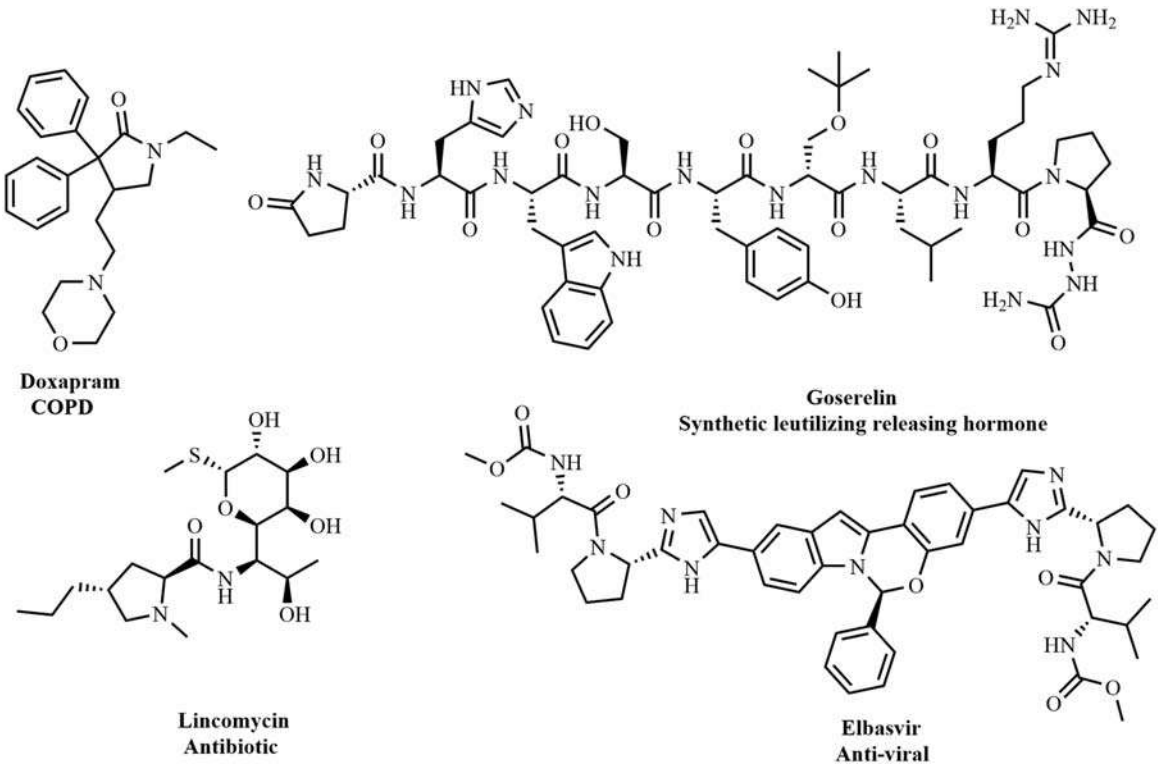


FIGURE 13.20 Clinically approved drugs containing pyrrole scaffold.

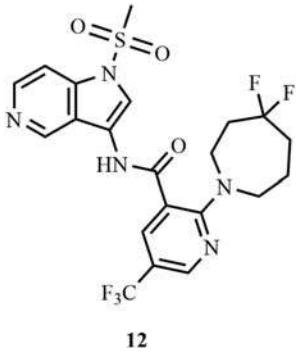


FIGURE 13.21 *N*-Sulfonyl pyrrole derivative as $Na_v1.8$ inhibitor.

13.4.3.3 N-Sulfonyl dihydro pyrrole and pyrrolidine for cancer treatment

Ubiquitin-specific peptidase 9X (USP9X) is a member of the USP family of deubiquitinases (DUBs) and is a key regulator of protein homeostasis for protein substrates, including several that are known to be important in cancer. In 2020, a patent was revealed discussing several compounds bearing fused pyrrole ring, compounds **12a**−**d**, as shown in Fig. 13.22. The compounds were reported to have USP9X inhibitors [65].

In similar efforts, Lynes *et al*. reported similar compounds as USP9X inhibitors claiming their efficacy as a treatment for cancer. Example compounds (**13a**−**m**) are presented in Fig. 13.23 [66]. In the patent cited before by Kim *et al*., some of the compounds developed had a core of *N*-sulfonyl pyrrolidine and *N*-sulfonyl pyrrole (**14a**−**g**, Fig. 13.24) which were found to be useful as Mer inhibitors for cancer treatment [51].

13.5 Six membered *N*-sulfonyl heterocycles

13.5.1 *N*-Sulfonyl piperazine derivatives

13.5.1.1 Medical applications of piperazine derivatives

The piperazine ring is a saturated ring with two nitrogen atoms that exert a special effect on the pharmacokinetics of the molecule once incorporated into it. The presence of the piperazine ring alters the pKa of a molecule significantly as it increases its water solubility, which makes it an appropriate scaffold for obtaining the desired pharmacokinetic profile. The piperazine ring can be found in many centrally acting drugs exerting their action on histamine receptors, serotonin receptors, dopaminergic receptors, and adrenergic receptors [67,68]. Fig. 13.25 demonstrates some examples of marketed drugs with piperazine moiety incorporated within.

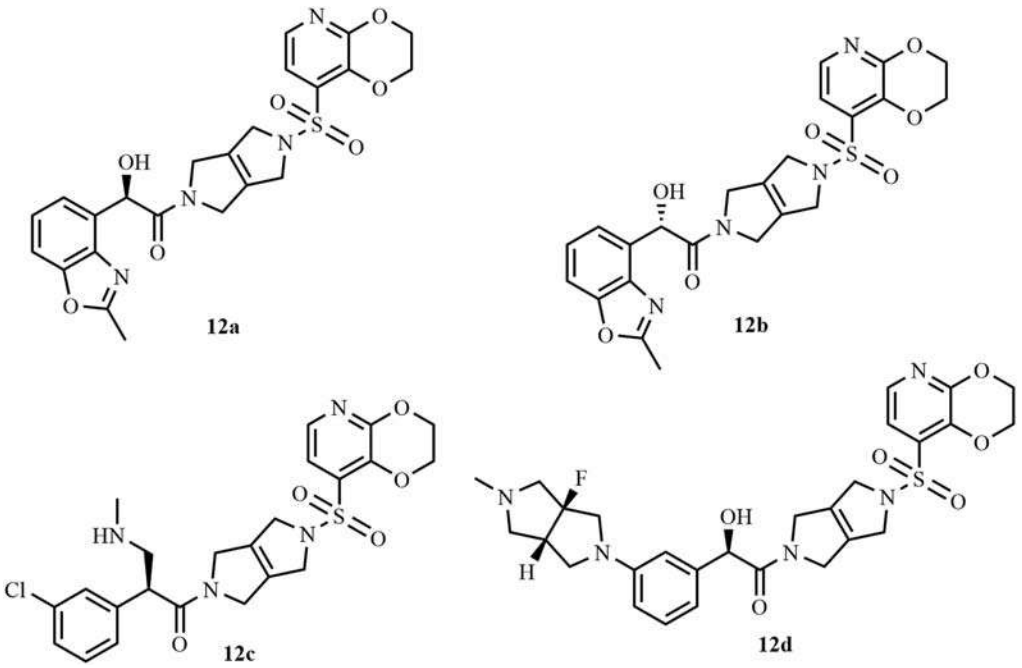


FIGURE 13.22 *N*-Sulfonyl pyrrole derivative as USP9X inhibitors.

13.5.1.2 N-Sulfonyl piperazine for pain management

Heer *et al*. reported the development of a series of *N*-sulfonyl piperazine derivatives as $Ca_{2.2}$ and $Ca_{3.2}$ channel blockers for the treatment of pain. For example, compounds (**15a**−**m**, Fig. 13.26) were claimed to be specifically useful for this purpose [69].

13.5.1.3 N-Sulfonyl piperazine for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is known to be a neurodegenerative disorder and is the most common cause of dementia. Many theories are laid down to hypothesize the root cause of the disease; the first is the formation of small protein plaques known as β-amyloid, amyloid-β (Aβ), and the formation of neurofibrillary tangles (NFT) which are composed of hyperphosphorylated tau protein. The accumulation of Aβ is proposed to be the main cause of AD initiating the formation of NFTs followed by neuroinflammation and consequently neurodegeneration. The formation of Aβ starts with the cleavage of Aβ precursor protein (APP) by β- and γ-secretases. Although the current therapeutics for AD only enhance the quality of life and slow down the disease progression, inhibitors for β- and γ-secretases are considered a promising strategy for finding an ultimate solution for AD [70]. Konradi and co-workers reported the synthesis of bridged *N*-bicyclic sulfonamido inhibitors for γ-secretase among which *N*-sulfonated-piperazine bicycles were reported (**16a**−**f**, Fig. 13.27) and the compounds were proposed as possible treatments for AD [71].

13.5.1.4 Treatment of diseases correlated to the production of reactive oxygen species

The role of reactive oxygen species (ROS) has been clarified in the pathogenesis of many diseases. The NADPH oxidase/dual oxidases (NOX/DUOX) are the major producers of ROS in these diseases. Blocking the production of ROS *via* NOX/DUOX inhibition can provide a new therapeutic strategy for preventing or treating diseases such as cancer, diabetes, hypertension, atherosclerosis, Parkinson's disease, Alzheimer's disease, schizophrenia, and a vast majority of other diseases [72−76]. In the quest to provide novel piperazine-based inhibitors for the NOX enzyme, Ganesh *et al*. discussed the synthesis of various piperazine derivatives, some bearing *N*-sulfonyl piperazine core with the general formula **17** (Fig. 13.28) [77].

13.5.2 *N*-Sulfonyl piperidine derivatives

13.5.2.1 Medical applications of piperazine derivatives

The piperidine ring is known to have great use as a building block in organic synthesis. Also, piperidine derivatives have a wide variety of clinical applications, either as centrally

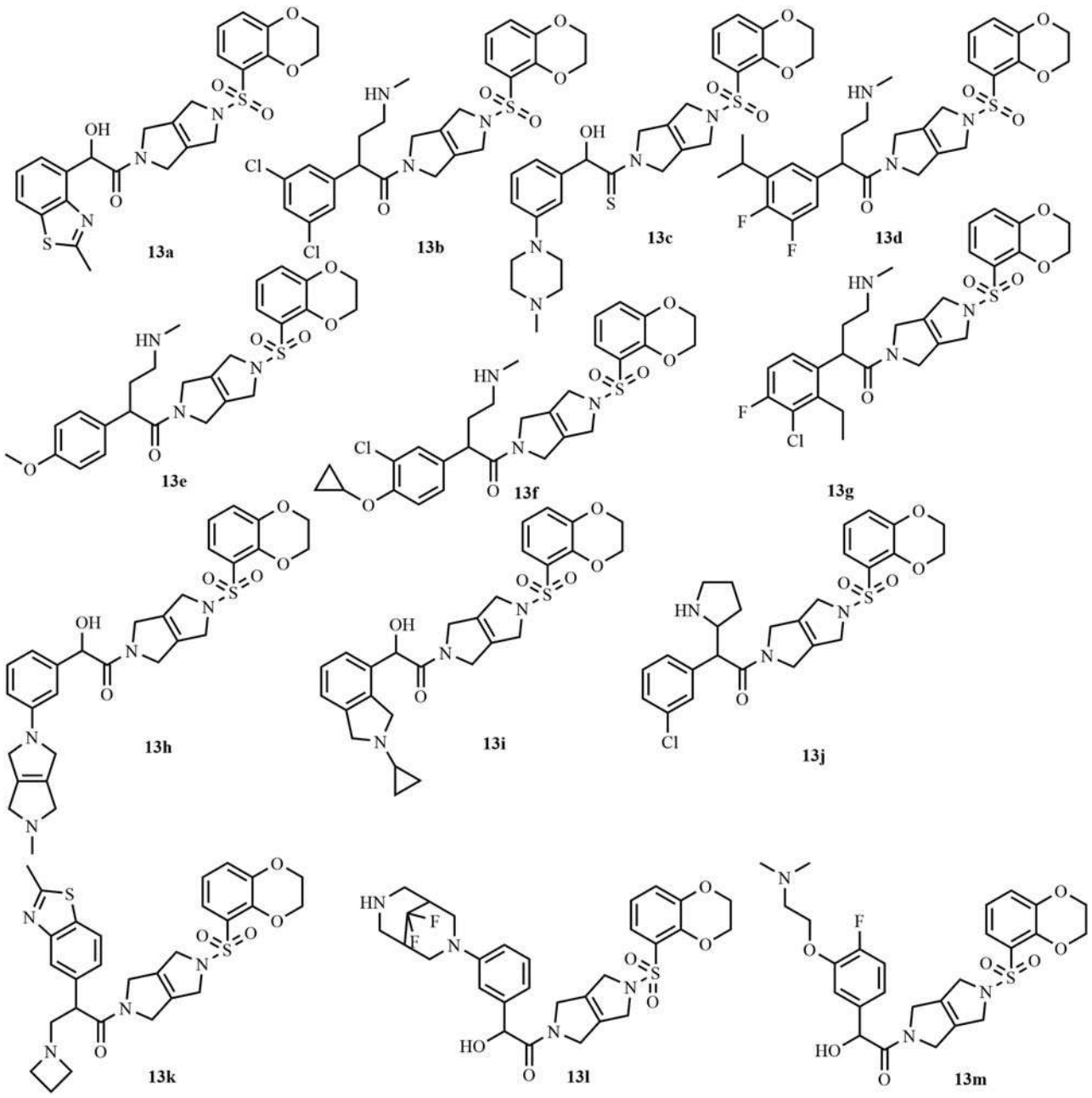


FIGURE 13.23 Examples of some *N*-sulfonyl pyrrole derivatives such as USP9X inhibitors.

acting drugs, analgesics, anticancer or antibacterial drugs. Fig. 13.29 displays some representative examples of some FDA-approved piperidine-containing drugs [78].

13.5.2.2 N-Sulfonyl piperidine for the treatment of Alzheimer's disease

In the patent mentioned earlier by Konardi *et al.*, some of the claimed compounds are presented as bridged *N*-bicyclic piperazine sulfonamido inhibitors for γ-secretase (**18a**−**g**, Fig. 13.30) and the compounds were proposed as possible treatments for AD [71].

13.5.2.3 N-Sulfonyl piperidine as ATP citrate lyase inhibitors

Leit de Moradei *et al*. presented a series of ACLY inhibitors among which some *N*-sulfonyl piperazine derivatives were reported (**compounds 19a** and **19b**, Fig. 13.31) [43].

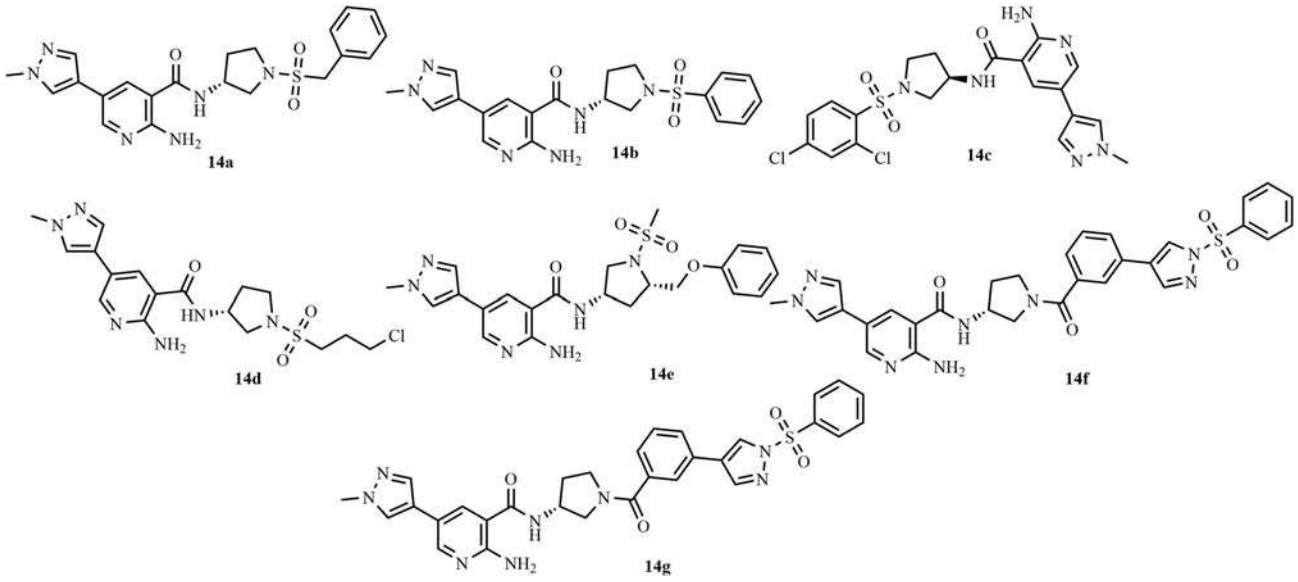


FIGURE 13.24 *N*-Sulfonyl pyrrolidine and *N*-sulfonyl pyrrole as Mer inhibitors.

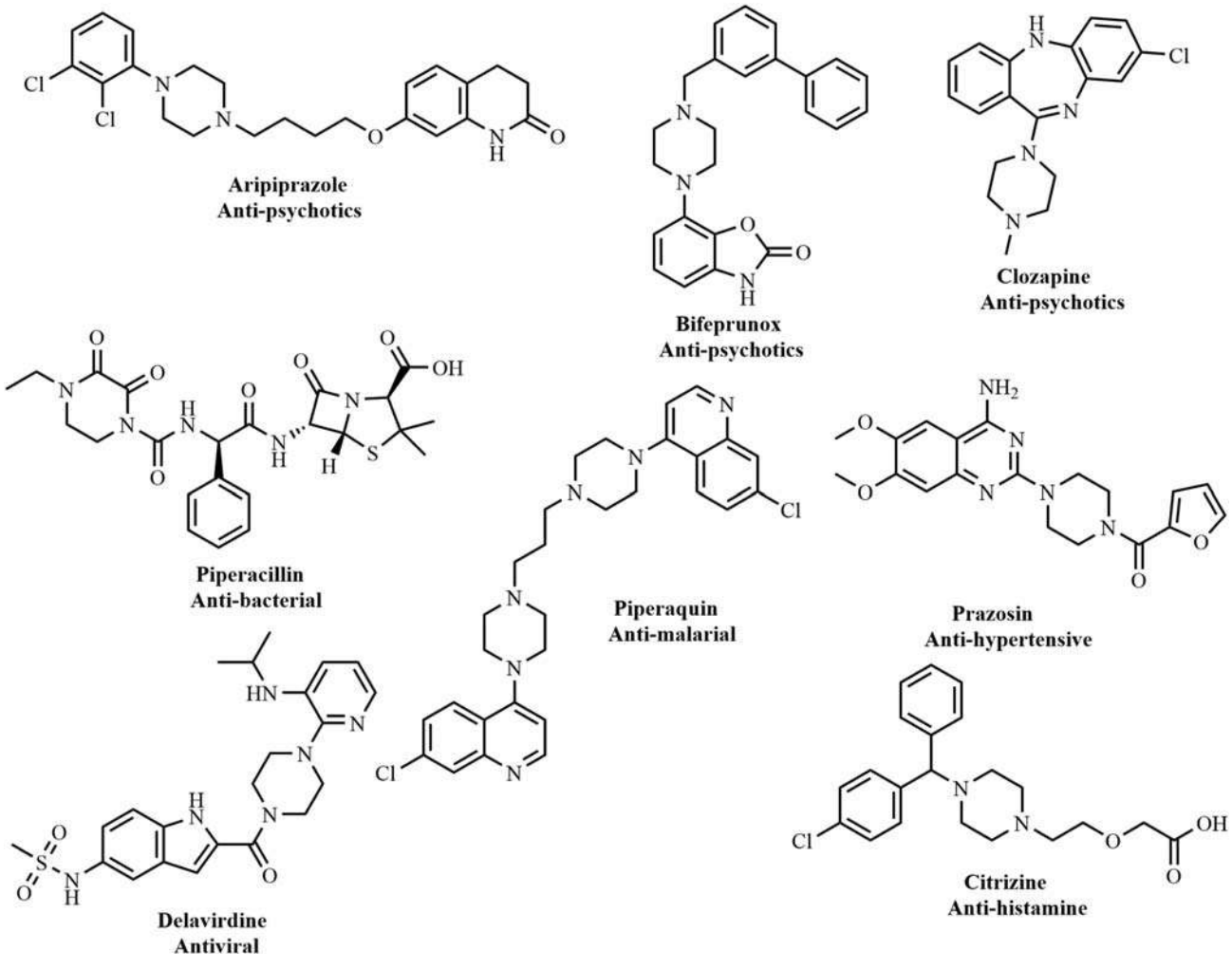


FIGURE 13.25 Clinically approved drugs containing a piperazine scaffold.

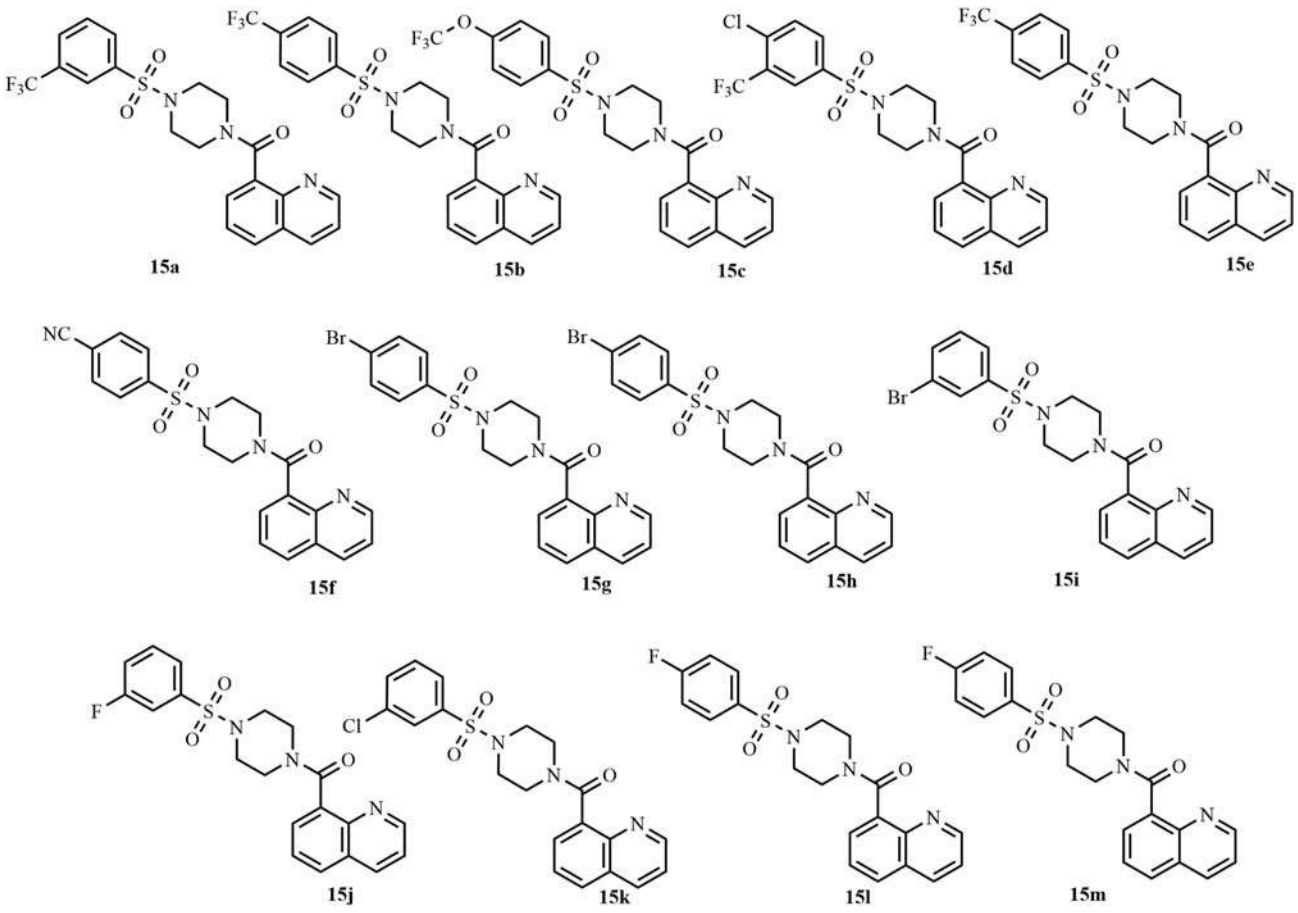


FIGURE 13.26 *N*-Sulfonyl piperazine for pain management.

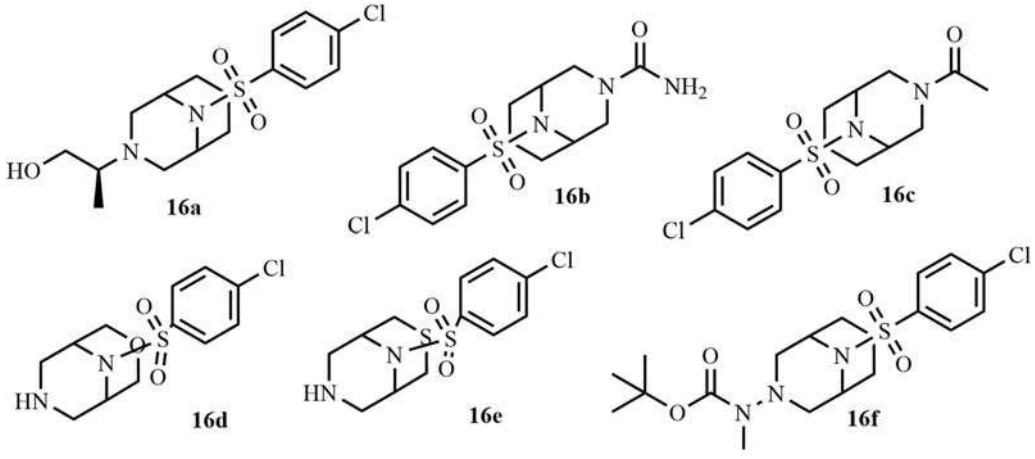
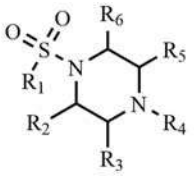


FIGURE 13.27 Bridged bicyclic *N*-sulfonyl piperazine for the treatment of Alzheimer's disease.

13.5.3 *N*-Sulfonyl pyrazine derivatives

13.5.3.1 Medical applications of pyrazine derivatives

Pyrazine derivatives are present in many natural products and comprise an important scaffold in medicinal chemistry. The noncondensed pyrazine ring is currently found in about 12 FDA-approved drugs. However, the ratio of pyrazine core in new lead compounds is significantly less than other 6 membered heterocycles such as pyridine. The presence of a pyrazine ring in a compound increases the interactions between the compound with the



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R_1/R_4= Alkyl, carbocyclyl, aryl, or heterocyclyl both can be substituted with Ra either the same or different
$R_2/R_3/R_5/R_6$= Can be the same or different of the following;
H, alkyl, halogen, NO_2, CN, OH, NH_2, SH, CHO, COOH, CON, alkoxy, alkylthio, alkylamino, alkylamino, alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.
Each one of $R_2/R_3/R_5/R_6$ can be substituted with the same group or different groups selected form R_a.
R_a= Alkyl, halogen, NO_2, CN, OH, NH_2, SH, CHO, COOH, CON, alkoxy, alkylthio, alkylamino, alkylamino, alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.

FIGURE 13.28 *N*-Sulfonyl piperazine as NOX inhibitors.

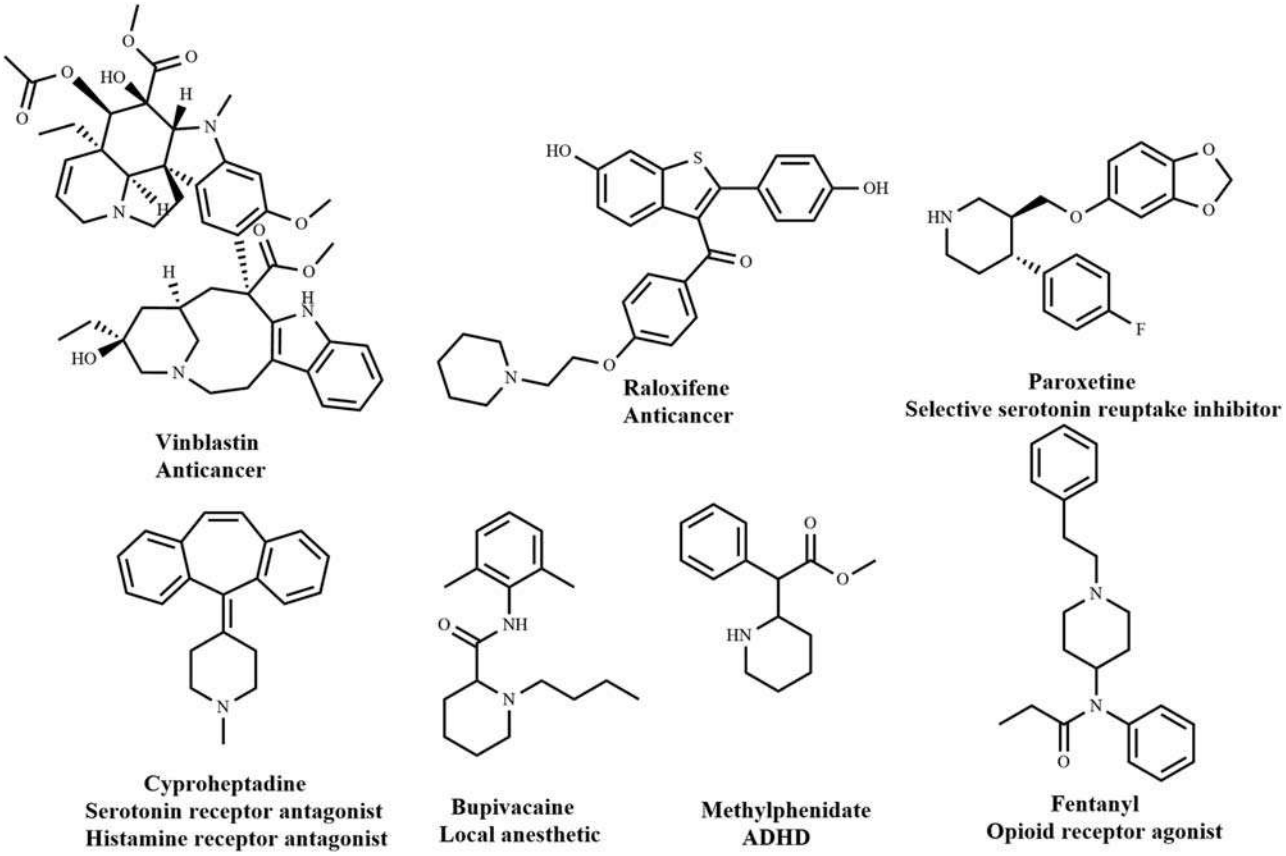


FIGURE 13.29 Clinically approved drugs containing a piperidine scaffold.

target protein. For example, the nitrogen atom can interact by hydrogen bonding, the ring offers various π-interactions and the nitrogen can form a metal bond with co-factors in the protein [79]. Fig. 13.32 displays some pyridazine-based approved drugs along with their clinical significance.

13.5.3.2 N-Sulfonyl pyrazine derivatives for pain management

Tissue trauma, inflammation anoxia, and low pH activate the *de Novo* synthesis of bradykinin (BK) and kallidin (Lys-BK) from kininogen precursors. The newly synthesized BK causes a wide range of effects starting with

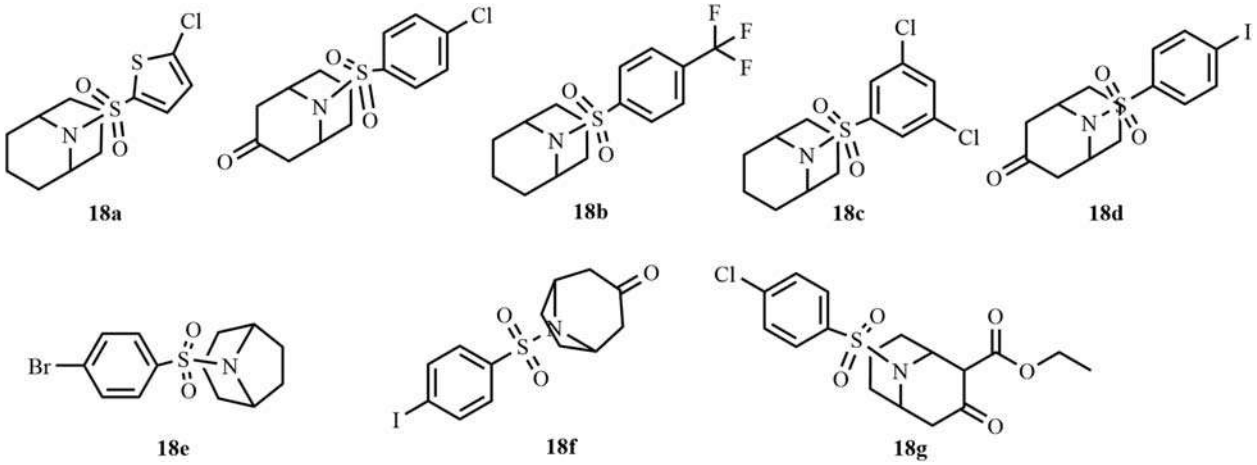


FIGURE 13.30 Bridged bicyclic *N*-sulfonyl piperidine for the treatment of AD.

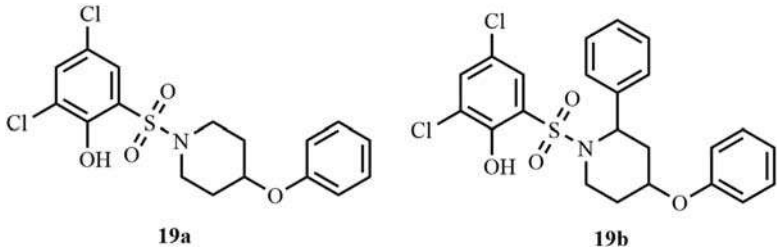


FIGURE 13.31 *N*-Sulfonyl piperidine derivatives as ATP citrate lyase inhibitors.

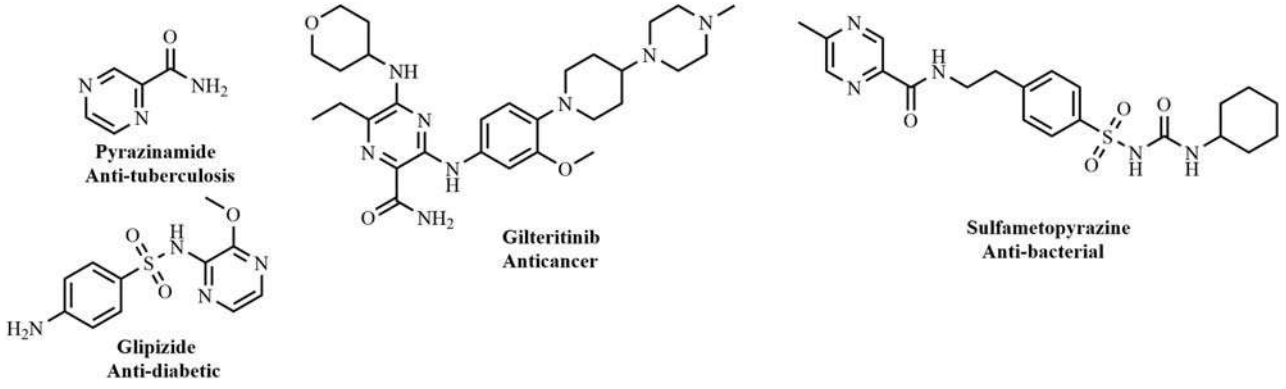


FIGURE 13.32 Clinically approved drugs bearing a pyridazine scaffold.

muscle contraction to activation of sympathetic neurons. The effects exerted by BK and Lys-BK are implicated in pain conditions including cardiac pain, inflammation, pain, and arthritis. Both BK and Lys-BK are rapidly degraded by the action of tissue-specific peptidases into the active peptide (des-Arg) BK and (des-Arg) kallidin, which has been reported to be the major metabolites in humans and the major proinflammatory peptide which can induce vasodilation, increased vascular permeability and bronchoconstriction. The action of BK and kallidin act on two types of bradykinin receptors designated B1 and B2. B1 is not normally expressed in most tissues and its expression is induced upon injury or tissue damage, which makes it an important target for the development of antiinflammatory and analgesic agents [80,81]. In 2007, Chen *et al.* published a patent revealing a series of *N*-arylsulfonyl-tetrahydro-pyridazines as B1 receptor antagonists. Examples of the novel compounds can be

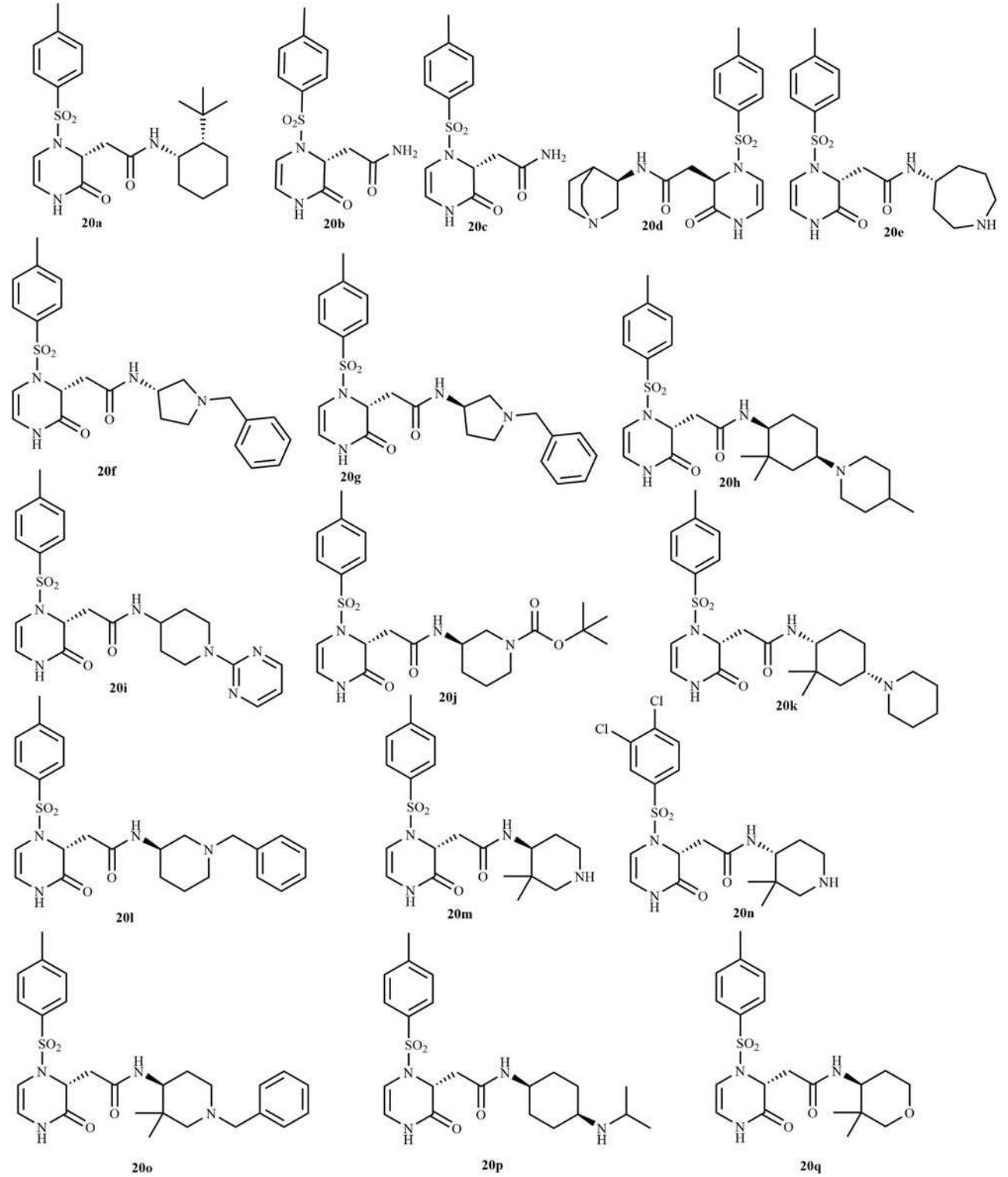
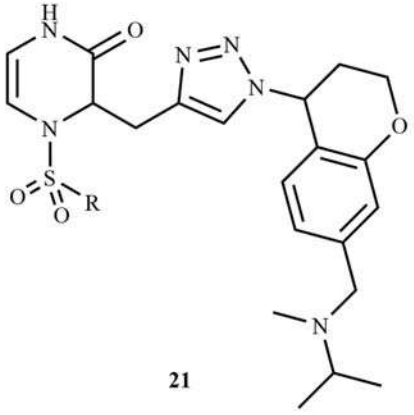


FIGURE 13.33 *N*-Sulfonyl pyrazine as B1 antagonists.

viewed in Fig. 13.33 (**20a**−**q**). The authors claimed that the compounds are antagonists for B1 receptors and hence can be used for the treatment of inflammation-related conditions and management of pain [80].

In similar efforts, Aya *et al.* reported a series of triazole derivatives of the general formula **21** (Fig. 13.34) bearing *N*-sulfonyl pyrazine scaffold as a treatment for painful and inflammatory conditions *via* antagonism of B1 receptors [82].



21

R is one selected from the following groups

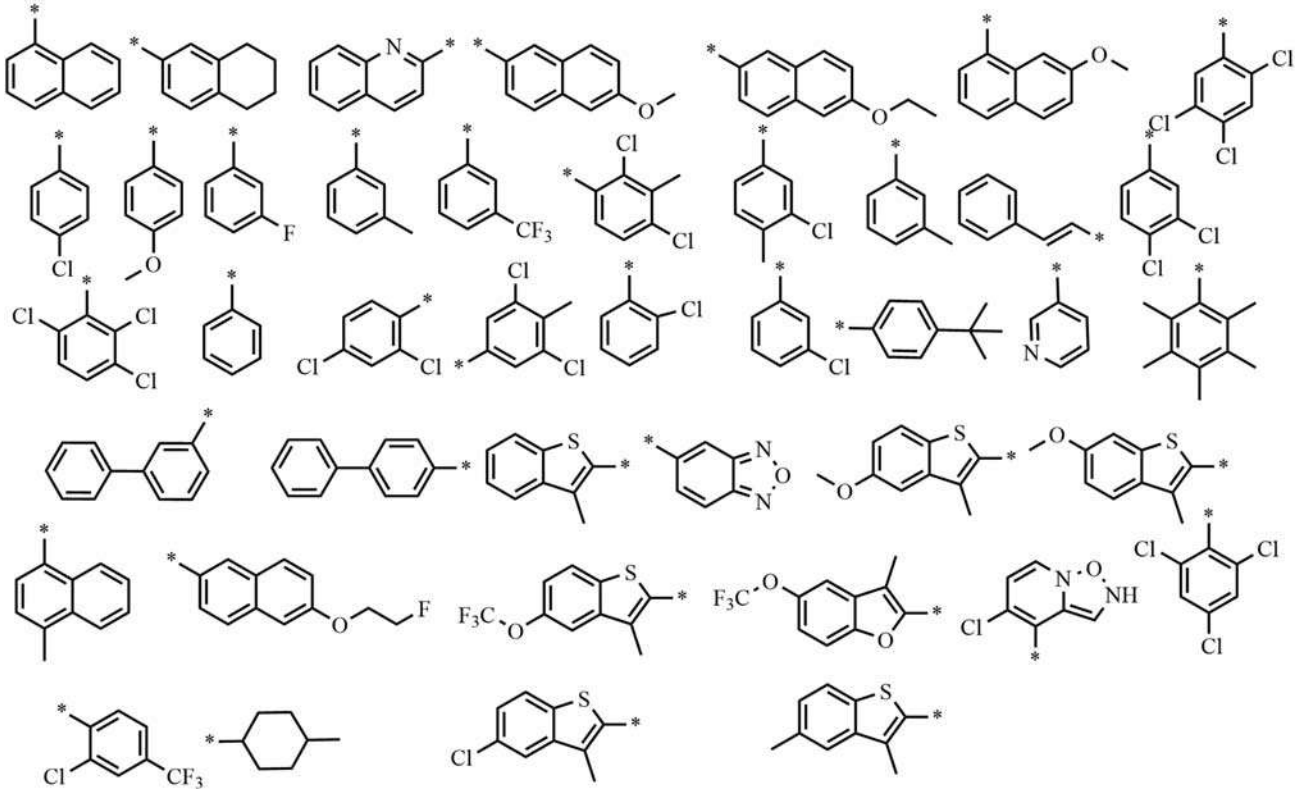


FIGURE 13.34 The general formula for triazole derivatives bearing *N*-sulfonated pyridazines as B1 receptor antagonists.

13.6 Fused *N*-sulfonyl heterocycles

13.6.1 *N*-Sulfonyl azaindoles

13.6.1.1 Medical applications of azaindole derivatives

Azaindole consists of a pyrrole ring fused with a pyridine ring and can serve as a bioisosteric replacement for the indole ring [83]. The ring has been recognized as a reactive and potent scaffold in modulating various biological processes. Azaindole is prominently found in many tyrosine kinase inhibitors and therapeutic agents acting as nicotinic agonists, CCR2 antagonists, and melanin agonists [84,85]. Fig. 13.35 shows some representative examples of azaindole-based drugs acting as anticancer agents.

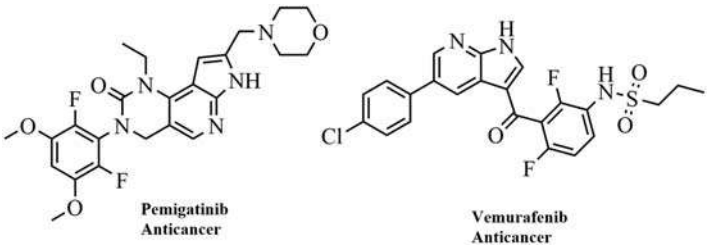
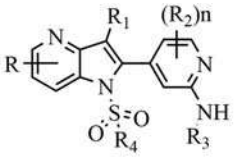


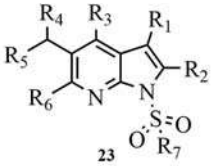
FIGURE 13.35 Azaindole drugs with anticancer activity.



22

R= One or more of the following;
CH_3, OCH_3, halogen, -CN, (C1-C6)alkyl, (C2-C6)alkenyl, (C1-C6)alkoxy, (C3-C8) cycloalkyl, hydroxy(C1-C3)alkyl, (C1-C6)alkylamino-, (C1-C6)alkylamino, (C1-C6)alkyl, 5-6 membered heteroaryl, heterocyclic, O-heterocyclic, $-NR_aR_b$, $-CONR_5R_6$, -COORc, $-COR_c$,$-SO_2$ R_c,$-CHCF_2COOCH_2OH$ or $CHCF_2CONH_2$.
R_1= Heterocyclic or heterobicyclic group unsubstituted or substituted with one or more of the following;
H, $-CH_3$, OCH_3, halogen, $-CF_3$, $-CHF_3$, - CN, (C1-C6)alkyl, (C1-C6)alkoxy or $-SO_2$ (C1-C6) alkyl.
R_2= One or more of the following; H, halogen, halo (C1-C6) alkyl or -CN.
R_3= H, (C1-C6) alkyl, (C3 -C8)cycloalkyl, $-CONHR_d$, $-COOR_4$, $-COR_4$ or - SO_2R_4.
R_4= H, (C1-C6)alkyl, (C3-C8)cycloalkyl, heterocyclylalkyl-, heterocyclyl(C1-C3)alkylamino(C1-C3)alkyl- or (C1-C3)alkylamino(C1-C3)alkyl.
R_a/ R_b= H, alkyl or Ra and Rb can be taken together with the nitrogen atom to which they are attached to form a 5-7 membered heterocyclic ring.
R_c= H or (C1-C6)alkyl

FIGURE 13.36 *N*-Sulfonyl azaindole as transforming growth factor-beta antagonists.



23

R_1/ R_2/ R_7= Independently can be; -H, (C1-C6)alkyl, (C1-C6)alkoxy, halogen, CN, (C3 -C7)cycloalkyl.
R_3= (C5 -C14)aryl, (C3 -C7)cycloalkyl, (C2 - C9)heterocycle, and (C2 -C9)heteroaryl.
The heteroatom chosen for the heterocycle or heteroaromatic ring can be S, N Or O.
Each heterocyclic ring or heteroaromatic ring can be substituted by;
(C1 -C6)alkyl, (-C6)alkoxy, butoxycarbonyl and oxo.
R_4/ R_5/ R_6= -H, (C1- C6)alkyl, (C1-C6)alkoxy, halogen, CN or (C3 -C7)cycloalkyl.
R_5 and **R_6** can be linked together with a carbon to form a cycloalkyl or a heterocycle.

FIGURE 13.37 *N*-Sulfonyl azaindole for the treatment of HIV.

13.6.1.2 N-Sulfonyl azaindole derivatives for treatment of inflammation

The transforming growth factor-beta (TGFβ) is a multifunctional cytokine that is responsible for the control of different crucial cellular processes such as; proliferation, migration, adhesion, angiogenesis, and tumor suppression. Alteration of TGFβ has been reported in several diseases such as; cancers, inflammatory, cardiovascular, and muscular disorders. Hence, various patents have reported efforts to find TGFβ antagonists. Bristol Mayers Squibb has reported the synthesis of a series of compounds with general formula **22** (Fig. 13.36) to treat autoimmune diseases, inflammatory tissue disorders, and cancers [86].

13.6.1.3 N-Sulfonyl azaindoles for treatment of HIV

De La Rosa *et al.* reported the synthesis of a series of comopounds with the general formula **23** (Fig. 13.37) for the treatment of HIV [87].

13.6.1.4 N-sulfonyl azaindole for pain management

Arasappan and co-workers had reported the synthesis of various 2-amino-*N*-heteroaryl nicotinamide derivatives, some of which had *N*-sulfonated azaindoles scaffold (**24**, Fig. 13.38). The compounds were suggested to block sodium channels (Nav1.8) and thus were proposed for the treatment, prevention, and amelioration of pain disorders, cough disorders, acute itch disorders, and chronic itch disorders [61].

13.6.2 *N*-Sulfonyl benzimidazole

13.6.2.1 Medical applications of benzimidazole derivatives

Benzimidazole and its analogs have been an understudy for the past hundred years. Benzimidazole can be utilized as an intermediate or a scaffold for the development of various small molecules of medical significance. Various benzimidazole derivatives have been proven to be effective anthelmentics, such as Flubendazole, Cambendazole, and Thiabendazole [88,89]. Some benzimidazole-based derivatives were found to be useful antibacterial agents, such as compound I, which showed antibacterial action when tested against *Pseudomonas aeruginosa, Streptococcus pyogenes, Staphylococcus aureus, Bacillus subtilis,* and *Staphylococcus epidermidis* [90]. Other benzimidazole derivatives have been approved for their anticancer action, such as; Carbedazim (microtubule inhibitor) and Veliparib (PARP inhibitor) [91–93]. Various proton pump inhibitors (PPIs) are currently approved for the treatment of peptic and duodenal ulcers such as Omeprazole and Pantoprazole [94,95]. Some reported antipsychotics also bear a benzimidazole core. For example, Dorperidol and Benperidol [95]. Fig. 13.39 shows the chemical structures of the aforementioned compounds.

The applications of *N*-sulfonated-benzimidazoles have been reported in many patents over the years.

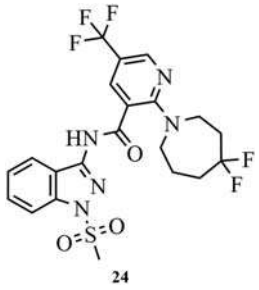


FIGURE 13.38 *N*-Sulfonyl azaindole for pain management.

13.6.2.2 N-Sulfonyl benzimidazole derivatives for the treatment of obesity

Sirtuin-6 (SIRT6) is a member of the sirtuin family that is responsible for the regulation of various physiological processes like intermediary metabolism, genomic stability, aging, and tumorigenesis. Considering glucose metabolism, SIRT6 is considered an appealing target for the treatment of type 2 diabetes mellitus (T2DM) due to evidence of its involvement in glucose transport, uptake, and glycolytic enzymes [96]. Compound **25** (Fig. 13.40) was found to be an active modulator for SIRT6 and has been proposed for the treatment of obesity, obesity-related diseases, and T2DM [97].

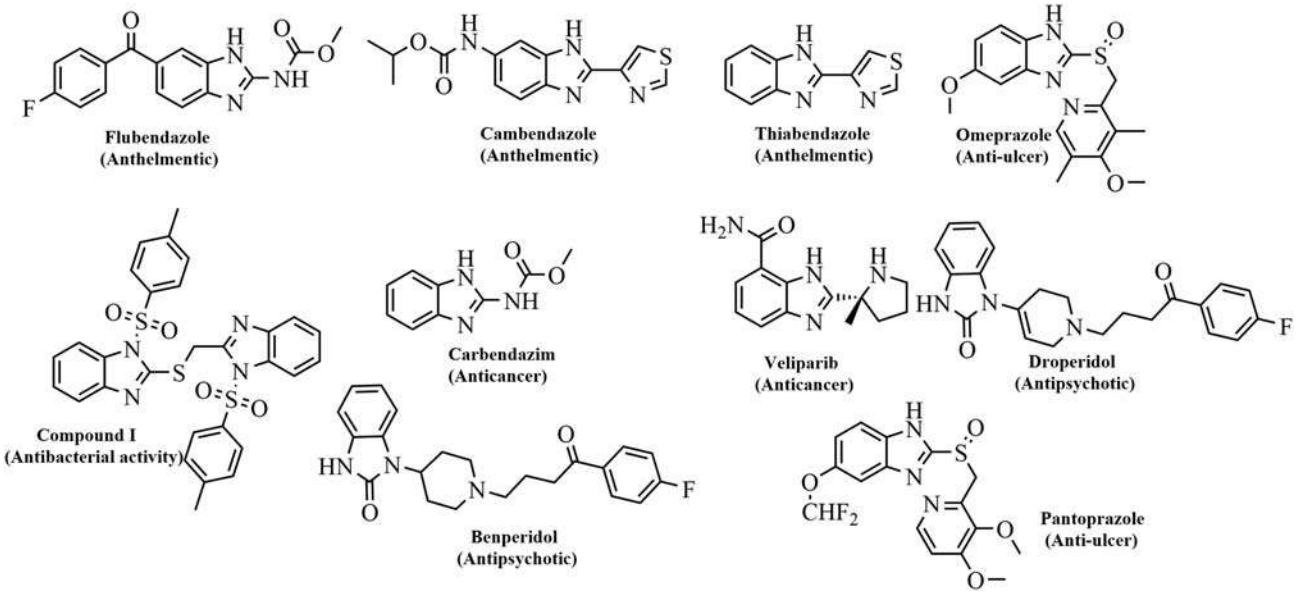
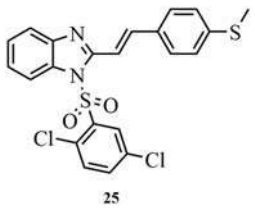


FIGURE 13.39 Examples of different medically significant benzimidazole derivatives.

In other work, compounds with the general formula **26a–b** (Fig. 13.41) were found to have a modulating activity on peroxisome proliferator-activated receptors. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and have been proven to be key regulators of lipid homeostasis. There are three subtypes: PPARs α, β, and γ. The γ-subtype is known as PPARG, which is modulated by the action of antidiabetic agents such as Pioglitazone and Rosiglitazone [98].

13.6.2.3 N-Sulfonyl benzimidazole derivatives as anticancer agents

The normal cellular metabolism produces noncanonical nucleotides. The incorporation of such nucleotides into the DNA results in multiple issues including, mispairing, and mutations and can lead to cellular death. Nucleotide pyrophosphatases are considered the house cleaning enzymes that break down those nucleotides into their mono/di-phosphate form. Those enzymes were found to be over-expressed in multiple forms of cancers. One of those enzymes is all-α nucleoside triphosphate (NTP) pyrophosphatase-1, also known as DCTPP1. DCTPP1 is responsible for the regulation of the dNTP nucleoside pool in the cell as it has noncanonical nucleosides similar to 5-methyl-dCTP, 5-formyl-dCTP and 5-iodo-dCTP. The modulation of DCTPP1 function can regulate the nucleoside homeostasis in the cell which is helping in the treatment of various diseases such as inflammation and cancers [99]. Fig. 13.42 shows *N*-sulfonated benzimidazole derivatives **27** studied for their anticancer effect *via* modulation of DCTPP1 function [100].



25

FIGURE 13.40 Chemical structure of benzimidazole derivative for the treatment of obesity.

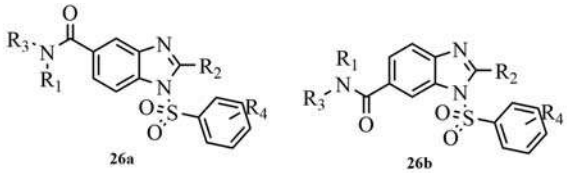
Microtubules have an important role in controlling different processes in the cell, specifically the formation of the mitotic spindle during mitosis. Microtubules are composed of a heterodimeric protein (α and β tubulin protein) that bind in head and tail fashion to form polymeric tubes of thirteen profillamnets. Targeting tubulin seems like an attractive strategy for the treatment of cancer [101]. Over the years, various tubulin inhibitors have been reported with Vinca alkaloid being one of the most famous tubulin inhibitor agents [101,102].

Compounds of general formula **28a** and **28b** (Fig. 13.43) were reported to be useful tubulin inhibitors. The therapeutic effect of these compounds extended to the treatment, reducing the severity, reducing the risk, or inhibition of cancer, metastatic cancer, drug-resistant tumors, drug-resistant cancer, and various forms of cancer. Specifically, the presented compounds showed special effectiveness in cancers such as; prostate, breast, ovarian, skin cancer, melanoma, bladder cancer, lung cancer, colon cancer, leukemia, lymphoma, head and neck, pancreatic, esophageal, renal, glioma, and glioblastoma [103].

Many cancers develop resistance to chemotherapeutic agents *via* various mechanisms. One of these mechanisms is the overexpression of aldehyde dehydrogenase (ALDH) enzymes. Aldehyde dehydrogenases are responsible for the metabolism of toxic aldehydes, preventing their accumulation in the body [104]. Many ALDH isoforms have been linked to cancer progression including; ALDH1A [105], ALDH3A1 [106], and ALDH18A1 [107]. Reducing the activity of ALDHs can contribute to the therapeutic effect of chemotherapeutic agents by limiting their metabolism in cancer cells. Compounds with general formula **29** (Fig. 13.44) were proposed to inhibit the activity of ALDH3A1 and were found to increase the efficacy of cancer treatment [108].

13.6.2.4 N-Sulfonyl benzimidazole derivatives as antibacterial agents

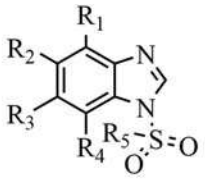
Compound **30** (Fig. 13.45) has been described for the treatment of *Helicobacter pylori* infections when



26a 26b

R_1= H, mono- or multi-substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocycle, cycloalkylalkyl, or heterocyclylalkyl.
If R_1 is substituted the substitution can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, halogen, NO2, C=O, COR', methylenedioxy, OR, N(R'), alkyl- S(O)SO.NR, and alkoxyl.
R_2= H or alkyl.
R_3= Alkyl, mono- or multi-substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, or heterocyclylalkyl.
If substituents are to be present, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, halo, NO2, CN, COR1, methylenedioxyl.
R_4= Pyridine, pyridine fused with phenyl or a substituted phenyl, halo, NO2, COR, CN, OR, NR, tetrazolyl, alkyl, alkylsulfoxide, aryl, heteroaryl, substituted heteroaryl.

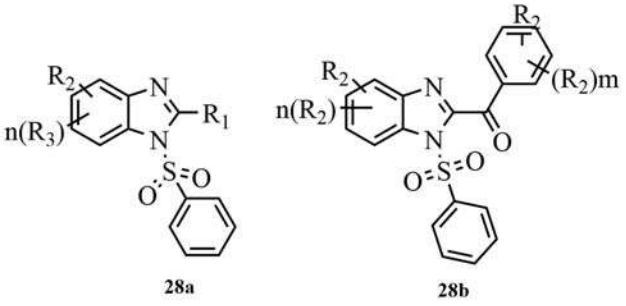
FIGURE 13.41 The general formula of benzimidazole derivatives for the treatment of obesity.



27

R_1= H, halogen, CN, $CH(CF_3)OH$, $C(CF_3)_2OH$, $C(OH)_2CF_3$, $-N_3$, $-NO_2$, N-alkyl substituted with one or more halogens.
R_2= H, halogen, CN, C1-C6 alkyl optionally substituted by one or more halogen(s), $-N_3$, $-NO_2$.
R_3= H, halogen, CN, C1-6 alkyl optionally substituted by one or more halogen(s), $-N_3$, $-NO_2$, H, halogen.
R_4= H or NO2
R_5= H, halogen, -CN, R, $-CH(CF_3)OH$, $-C(CF_3)_2OH$, $-C(OH)_2CF_3$, $-N_3$, $-NO_2$, -N-alkyl substituted with one or more halogens.
*R_1/R_2, R_2/R_3 and/or R_4/R_5 can be linked together through carbon atoms they are attached to forming a fused 5- or 6-membered ring.
The formed ring can contain 1-3 heteroatoms along with 1-2 double bonds.
The fused ring(s) can be substituted by one or more substituents (halogen, C1-C3 alkyl which can be substituted with one or more halogen).

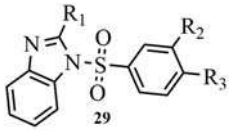
FIGURE 13.42 The general formula of benzimidazole derivatives of DCTPP1 modulation.



28a 28b

R_1= H, halogen, phenyl substituted at C3 or C5 with R_a, R_b or R_c.
R_2= H, halogen, CF_3, NO, OH, OCH or CN, CH_3, alkyl, alkenyl, O-alkyl or O-aryl.
R_3= H, halogen, CF_3, NO, OH, OCH or CN, CH_3, alkyl, alkenyl, cycloalkyl, aryl, O-alkyl, O-aryl, or phenyl substituted at C3 or C5 with R_1.
n= Positive integer (0-3).
m= Positive integer (0-4).
R_a= C1-C3 alkylene substituted with OH, NO_2, NH_2, alkylamine, alkyl, N_3 and CN.
R_b= 2-, 3- or 6-indolyl. The indolyl moiety can be substituted at C1 with CH_3, alkyl, benzyl, or $-SO_2Ph$.
R_c= Naphthyl substituted at C5, C6, or C7 with R_b.

FIGURE 13.43 The general formula of *N*-sulfonated-benzimidazole derivatives as tubulin inhibitors.



29

R_1= CH_3 and NH_2.
R_2= H, CH_3 and OCH_3.
R_3= F, Cl, CH_3 and OCH_3

FIGURE 13.44 The general formula of *N*-sulfonated-benzimidazole derivatives as ALDH3A1 inhibitors.

administered in suitable pharmaceutical form with a β-lactam antibiotic such as but not limited to amoxicillin [109].

13.6.2.5 N-Sulfonyl benzimidazole derivatives as antiviral agents

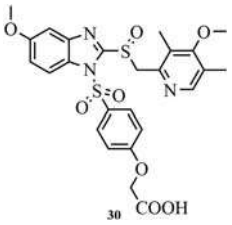
Compounds of general formula **31** (Fig. 13.46) have been tested for their antiviral activity against Myxoviruses and paramyxoviruses [110].

13.6.2.6 N-Sulfonyl benzimidazole derivative as immuno-modulators

Innate immunity plays an important role in forming the body's reaction against external pathogens. The immunity proceeds its role through pattern recognition receptors like toll-like receptors and nucleotide-binding oligomerization domain (NOD) like receptors (NLRs) which

recognize the microbial components and trigger the innate immunity in response. NOD1 and NOD2 were the first identified NLRs [111]. NOD1 recognizes the peptidoglycan of Gram-negative bacteria and some Gram-positive bacteria. On the other hand, NOD2 recognizes muramyl dipeptide produced in all bacteria. Once activated, both NOD1 and NOD2 trigger several pro-inflammatory pathways such as nuclear factor κB (NF-κB), and mitogen-activated protein kinases [112]. Developing small molecules that can modulate NOD1/NOD2 signaling can find useful applications for treating several diseases like arthritis, leprosy, and other inflammatory diseases [113]. Compounds with the general formula **32** and **33** (Fig. 13.47) have been reported to modulate NOD1 and NOD2 signaling. In this invention, Roth and co-workers claimed that the use of such compounds can help in preventing inflammatory response in diseases like Crohn's disease, ulcerative colitis, pancreatitis, arthritis, asthma, psoriasis, Alzheimer's disease, cardiovascular disease (arteritis), diabetes and sepsis [114].

N-Sulfonated benzimidazole of general formulas **34a–b** (Fig. 13.48) were found to act as ligands for aryl hydrocarbon receptors (AhR), thus useful in the treatment of ailments of autoimmune origin such as; diabetes mellitus, celiac disease, hepatitis and psoriasis [115]. AhR is a ligand-activated receptor belonging to the Per-Arnt-Sim receptor family. AhR mediates the cellular response to toxins and is believed to be crucial for regulating the immune response in animals and humans. Regulation of such receptors can contribute to the treatment of different autoimmune diseases [116].



30

FIGURE 13.45 The chemical structure of compound **30** as an antibacterial agent.

13.6.3 *N*-Sulfonyl benzotriazole derivatives

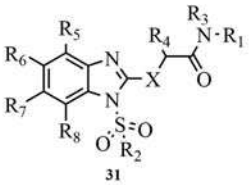
13.6.3.1 Medical applications of benzotriazole derivatives

Benzotriazole derivatives (Fig. 13.49) are an important class of heterocyclic compounds discovered in the late 1960s and possessing a wide variety of biological activities, such as antimicrobial [117,118], antitumor [119], antiparasitic [120], antiviral [121], and plant growth regulator [122]. Other pharmacological activities such as potassium channel activator [123] and choleretic [124] have also been reported [125].

The following is a brief literature review on the different patent applications of *N*-sulfonyl benzotriazole derivatives;

13.6.3.2 N-Sulfonyl benzotriazole derivatives as anticancer agents

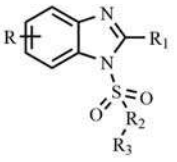
Heat shock protein 70 (HSP70) protein expression is often constitutively increased under stressful conditions in tumor samples and after chemotherapy [126]. This overexpression is necessary for the survival of the cancer cell and resistance to chemotherapy or radiation therapy [127–129]. An invention providing a method for the synthesis of compounds of formula **35** (Fig. 13.50) targeting



31

X= S, SO, or SO_2.
R_1= Carbocyclyl, aryl, or heterocyclyl which can be substituted with;
alkyl, halogen, CN, OH, NH, SH, CHO, CO, $CONH_2$, alkoxy, alkylthio, alkylamino, aminoalkyl, (alkyl) amino, alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.
R_2= Alkyl or aryl which can be substituted with;
alkyl, halogen, CN, OH, NH, SH, CHO, CO, $CONH_2$, alkoxy, alkylthio, alkylamino, aminoalkyl, (alkyl) amino, alkylsulfmyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl.
R_3= H or Alkyl
R_4= H or alkyl which can be substituted with one of the following groups; halogen, NO_2, CN, OH, OCF_3, CF_3, NH_2, CHO, CO, $CONH_2$, NH, C_2H_5, CH_3, OCH_3, OC_2H_5, $COCH_3$, $NHCH_3$, NHC_2H_5, $NH(CH_3)_2$, $NH(C_2H_5)_2$, $N(CH_3)(C_2H_5)$, CONH, $CONHCH_3$, $CONHC_2H_5$, , $CON(CH_3)_2$, $CON(C_2H_5)_2$, $CON(CH_3)(C_2H_5)$, $SHCH_3$, SHC_2H_5, SCH_3, SC_2H_5, SO_2NCH_3, $COOC_2H_5$, carbocyclyl, aryl, or heterocyclyl.
R_5, R_6, R_7= H, halogen, CN, OH, OCF3, CF3, NH, formyl, COO, SO_2NH, CH_3, C_2H_5, OCH_3, OC_2H_5, $COCH_3$, CH_3COO, $COOC_2H_5$, $NHCH_3$, NHC_2H_5, $NH(CH_3)_2$, CONH C_2H_5, $CON(CH_3)2$, $CON(C_2H_5)2$, $CON(CH_3)(C_2H_5)$, SCH_3, SC_2H_5, SO2NCH3, SOC_2H_5, SO_2, $SO_2C_2H_5$, carbocylyl or heterocyclyl.
R_8= H, halogen, CN, OH, OCF_3, CF_3, NH, formyl, COO, SO_2NH, CH_3, C_2H_5, OCH_3, OC_2H_5, $COCH_3$, CH_3COO, $COOC_2H_5$, $NHCH_3$, NHC_2H_5, $NH(CH_3)_2$, $CONHC_2H_5$, $CON(CH_3)_2$, $CON(C_2H_5)_3$, $CON(CH_3)(C_2H_5)$, SCH_3, SC_2H_5, SO_2NCH_3, SOC_2H_5, SO_2, $SO_2C_2H_5$, carbocylyl or heterocyclyl.

FIGURE 13.46 The general formula of *N*-sulfonated-benzimidazole derivatives as antiviral agents.

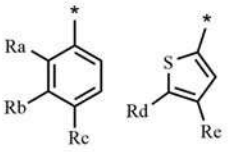


32

R= H, C1-C3 alkyl, C1-C3 alkenyl, C1-C3 alkoxy, C1-C3 haloalkyl, C1-C3 alkylamino, NH_2, $COCH_2NH$, NO_2, CN, halogen, $COOR_a$, or -C(O)N(R_b)(R_c) , $NH(CH_2)_3OH$, or $-CH_2NHCHO$
R_1= H, NH_2, SH, C1-C3, alkylthio, C1-C3 alkoxy, OH, -N(R_b)(R_a), C1-C3 alkylamino, C1-C3 alkylaminoacetyl.
R_2= Can be present or absent, if present -(CH_2)n
R_3= Aryl, heteroaryl, cycloalkyl or heterocyclyl
R_a, R_b, R_c =H or C1-C3 alkyl.

33

R_1= NH_2, H, $NH(CH_2)_3OH$, CH_3, or -CH2NHCHO
R_2=



R_3=H, C1-C6 alkyl, C3 -C6 cycloalkyl, or NH_2.
R_4= H, C1-C6 alkyl, C1-C6 fluoroalkyl, C3-C6 cycloalkyl, C3-C6 cycloalkyl substituted with F, C1-C6 alkoxy, C3 -C6 cycloalkoxy, or F.
R_5= H, C1-C6 alkyl, C1-C6 alkyl substituted with F, C3-C6 cycloalkyl, C3-C6 cycloalkyl substituted with F, halogen, COOH, or a carboxyl ester
Ra/ Rd/ Re= H or halogen
R_b= H, C1-C6 alkyl, C1-C 6 alkyl substituted with one or more of the following;
F, C3-C6 cycloalkyl, C3 -C6 cycloalkyl substituted with one or two F, C1-C6 alkoxy, C3-C6 cycloalkoxy, or halogen.
R_c= H, NO_2, C1-C6 alkyl, C1-C6 alkyl substituted with one or more of the following;
F, C3 -C6 cycloalkyl, C3-C6 cycloalkyl substituted with F, C1-C6 alkoxy, C1-C6 alkoxy substituted with F, C3-C6 cycloalkoxy, C3-C6 cycloalkoxy substituted with F, halogen.
***Rd and Re can be attached through one or two carbons to form a 5- 6 membered ring.**

FIGURE 13.47 The general formula of *N*-sulfonated-benzimidazole derivatives as modulation of NOD1/NOD2 signaling.

specifically HSP70 was reported. These compounds may represent a new type of immunotherapeutic molecules against cancer.

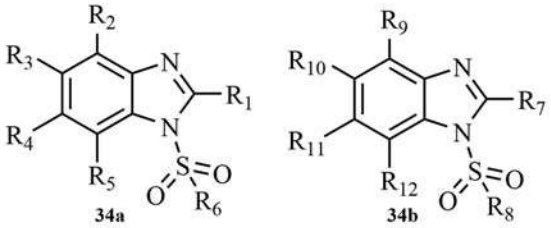
All of the above-mentioned compounds showed inhibitiory activity against HSP70 protein in the micromolar range. Compounds **35a** and **35b** showed the most potent activity (Table 13.1) [130].

13.6.3.3 N-Sulfonyl benzotriazole derivatives for treatment of HIV

1-((2-(4-Nitrophenoxy)phenyl)sulfonyl)-1*H*-benzo[*d*][1,2,3]triazole **36** (Fig. 13.51) was reported by Tariq *et al.* as a structural analog of the viral-encoded gene virion infectivity factor (Vif) inhibitor [131]. This invention relates to different compounds that inhibit human immunodeficiency virus (HIV) replication where HIV-I infectivity is highly dependent on (Vif) [132].

13.6.3.4 N-Sulfonyl benzotriazole derivatives as phosphate transport inhibitors

Hyperphosphatemia or elevated serum phosphate levels can result from decreased phosphate excretion, increased phosphate intake, or a disorder that shifts intracellular phosphate to extracellular space (e.g., hyperparathyroidism or impaired renal function, *etc*.. . .). Long-time hyperphosphatemia often leads to disturbance in calcium and phosphorus metabolism. This invention involves different compounds that inhibit phosphate transport in rabbit



34a **34b**

$\mathbf{R_1}$= Substituted or unsubstituted C6-C14 aryl; substituted or unsubstituted C5-C14 heteroaryl; substituted or unsubstituted C5-C10 heterocyclyl; substituted or unsubstituted C1-C10 alkyl, or substituted or unsubstituted C3-C10 cycloalkyl.
$\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_5}$= H, halogen, CN, OCF_3, substituted or unsubstituted C1-C10 alkyl, substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted C3-C8 heterocycloalkyl, substituted or unsubstituted C1-C6 alkoxy, $SO_2\mathbf{R_a}$, $CO_2\mathbf{R_a}$ or $CON\mathbf{R_aR_b}$.
*$\mathbf{R_1/R_2}$, $\mathbf{R_2/R_3}$, and $\mathbf{R_3/R_4}$ pairs, together with the carbon atoms to which they are attached, forms an optionally substituted 5 or 6 membered cycloalkenyl, heterocyclenyl, aryl or heteroaryl.
$\mathbf{R_6}$= Substituted or unsubstituted C6-C14 aryl; substituted or unsubstituted C5-C14 heteroaryl; substituted or unsubstituted C5-C14 heterocyclyl; substituted or unsubstituted C1-C10 alkyl, or substituted or unsubstituted C3-C10 cycloalkyl; substituted or unsubstituted C2-C10 alkenyl, or substituted or unsubstituted C2-C10 alkynyl.
$\mathbf{R_7}$= Substituted or unsubstituted C6-C14 aryl; Substituted or unsubstituted C5-C10 heteroaryl; Substituted or unsubstituted C5-C10 heterocyclyl; Substituted or unsubstituted C1-C10 alkyl, or Substituted or unsubstituted C3-C10 cycloalkyl.
$\mathbf{R_8}$= Substituted or unsubstituted C6-C10 aryl; substituted or unsubstituted C5-C10 heteroaryl; substituted or unsubstituted C5-C10 heterocyclyl; Substituted or unsubstituted C1-C10 alkyl, or Substituted or unsubstituted C3-C10 cycloalkyl.
$\mathbf{R_9}$, $\mathbf{R_{10}}$, $\mathbf{R_{11}}$ and $\mathbf{R_{12}}$= H, halogen, CN, Substituted or unsubstituted C1-C10 alkyl, Substituted or unsubstituted C3-C10 cycloalkyl, Substituted or unsubstituted C1-C6 alkoxy, $SO_2\mathbf{R_c}$, $COO\mathbf{R_c}$, or $CON\mathbf{R_cR_d}$.
$\mathbf{R_a}$, $\mathbf{R_b}$, $\mathbf{R_c}$ and $\mathbf{R_d}$= Independently can be H, substituted or unsubstituted C1-C10 alkyl, substituted or unsubstituted C3-C10 cycloalkyl.

FIGURE 13.48 The general formula of *N*-sulfonated-benzimidazole derivatives as ligands for AhR receptor.

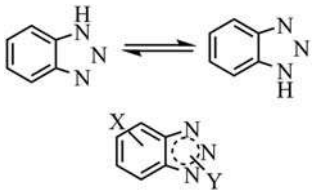
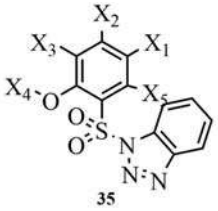


FIGURE 13.49 1*H*-Benzo[*d*][1,2,3]triazole derivatives.



35

$\mathbf{X_1}$= H, a halogen atom, a C1-C8 alkyl group, preferably a C1-C3 alkyl group.
$\mathbf{X_2}$= H, a halogen atom, a C1-C8 alkyl group, preferably a C1-C3 alkyl group.
$\mathbf{X_3}$= H, a halogen atom, a C1-C8 alkyl group, preferably a C1-C3 alkyl group.
$\mathbf{X_4}$= C1-C8 alkyl group, preferably a C1-C3 alkyl group.
$\mathbf{X_5}$= H, a halogen atom, a C1-C8 alkyl group, preferably a C1-C3 alkyl group.

FIGURE 13.50 *N*-Sulfonyl-benzotriazole derivatives as anti-HSP70.

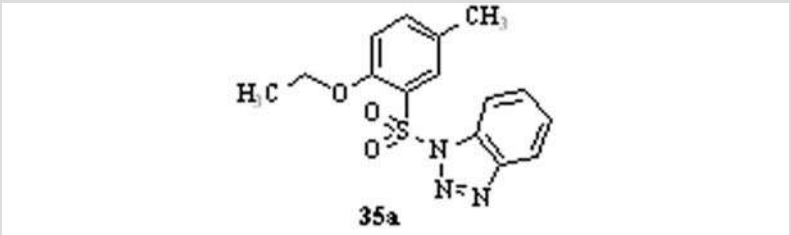
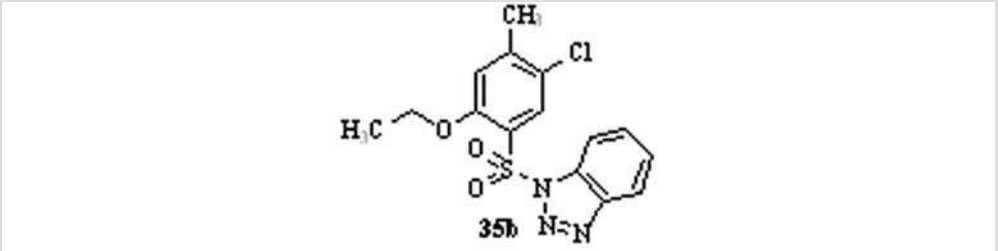
intestinal brush border membrane vesicles. One of these compounds is 1-(phenylsulfonyl)-1*H*-benzo*[d]* [1,2,3]triazole (**37**, Fig. 13.52). Therapy for inhibition of intestinal phosphate transport will decrease serum phosphate levels [133].

13.6.3.5 N-Sulfonyl benzotriazole derivatives as human melanin-concentrating hormone receptor antagonists

Melanin-concentrating hormone (MCH) is a cyclic hypothalamo- pituitary peptide hormone originally identified in the pituitary of Salmonid (teleost fish) [134]. Mammalian MCH has been reported to regulate food intake and energy homeostasis [134,135]. A variety of processes are included in this invention; one of these processes is identifying a chemical compound (new, known, or unknown) that specifically binds to a mammalian MCH1 receptor under suitable conditions and detecting the specific binding of these chemical compounds to the mammalian MCH1 receptor [136]. MCH1 receptors involve one of the following;

1. Contacting cells containing DNA encoding and expressing on their cell surface a mammalian MCH1 receptor.
2. Contacting a membrane preparation from cells transfected with DNA encoding and expressing on their cell surface the mammalian MCH1receptor.

TABLE 13.1 Activity profile of compounds 35a and 35b.

Structure and name	IC_{50} (μM)
 35a 1-((2-ethoxy-5-methylphenyl)sulfonyl)-1*H*-benzo[*d*][1,2,3]triazole	19.6
 35b 1-((5-chloro-2-ethoxy-4-methylphenyl)sulfonyl) -1*H* -benzo[*d*][1,2,3]triazole	0.2

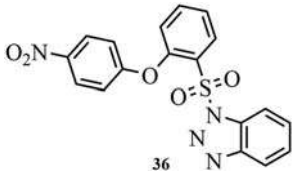

36

FIGURE 13.51 Chemical structure of compound **36** as an antiviral inhibitor.

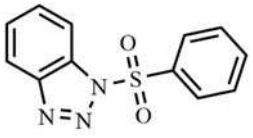

37

FIGURE 13.52 Chemical structure of compound **37** as phosphate transport inhibitor.

3. Separately, contacting cells express on their cell surface the mammalian MCH1 receptor.
4. Separately contacting a membrane fraction from a cell extract of cells expressing on their cell surface the mammalian MCH1 receptor. One of the tested compounds is 1-((2-nitrophenyl)sulfonyl)-*1H*-benzo*[d]* [1,2,3]triazole (**38**, Fig. 13.53) [136].


38

FIGURE 13.53 Chemical structure of compound **38** as MCH1 receptor antagonist.

This invention relates to different compounds that are effective in decreasing body mass and treating depression and/or anxiety [136].

Also, Bharat's group and Marzabadi's group reported the same idea using compound **38** and different scaffolds. They modified a method of feeding behavior that involves administering to the subject an amount of a compound effective to decrease the consumption of food [136–138].

13.6.3.6 N-Sulfonyl benzotriazole derivatives in the industry

13.6.3.6.1 Manufacturing a photo thermographic film

This application relates to a process of photothermographic materials having high sensitivity and excellent preservation stability and excellent lightfastness of images are obtained Fig. 13.54 [139]. It is a continuation in part of the Japanese Patent Application in reference [118] and is also, treated with different compounds (**39a–h**) in other applications [140,141].

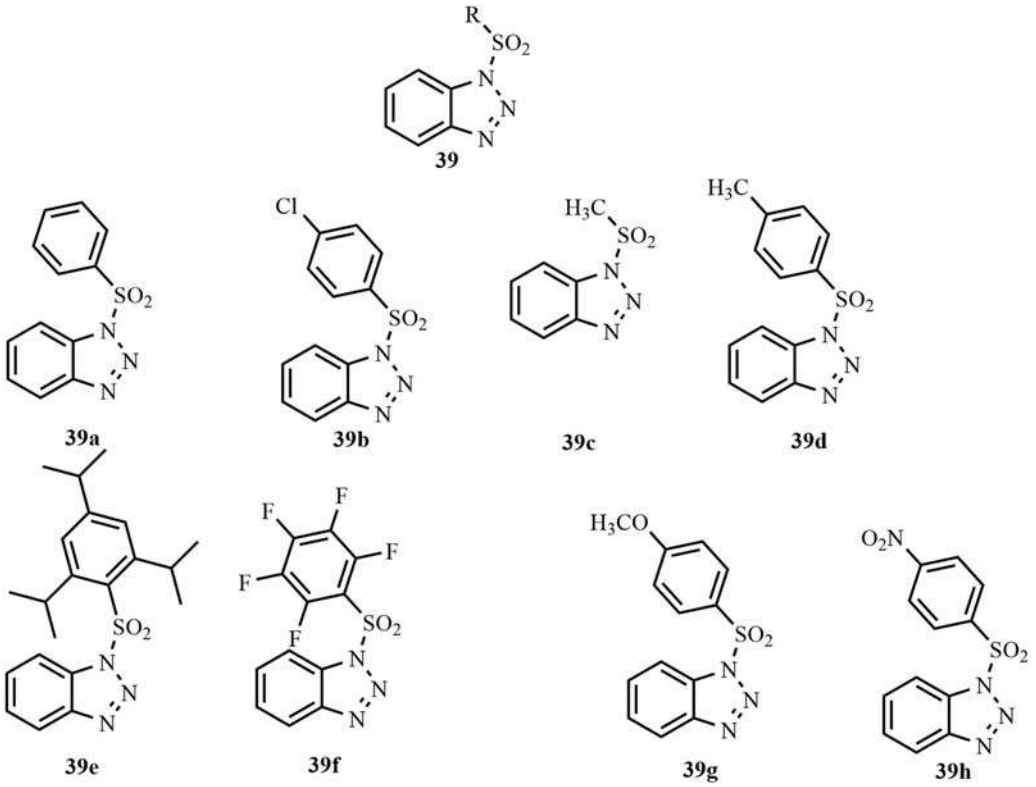


FIGURE 13.54 The general formula of benzotriazole derivative as a useful application in the manufacturing of photo thermographic film.

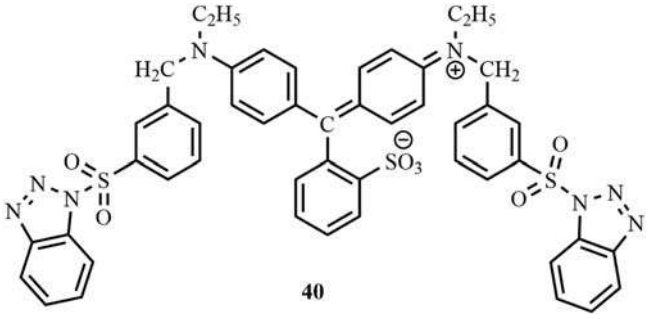


FIGURE 13.55 *N*-Sulfonyl benzotriazole derivative **40**, for manufacturing novel colored compounds.

13.6.3.6.2 Process for manufacturing novel colorant compound

Color filters are important parts and indispensable for displaying color images on liquid crystal displays. The invention reported a method for the synthesis of a triphenylmethane colorant (**40**, Fig. 13.55) that can be applied for use as coloring agents and in electronic materials such as optical recording colorants. Also, it relates to a blue resist composition for use in a color filter comprising at least one of the colorant compounds [142].

13.6.4 *N*-Sulfonyl indole derivatives

13.6.4.1 Medical applications of indole derivatives

Indole is one of the versatile scaffolds in medicinal chemistry. It has a weak basic character due to the involvement of the lone pair of the incorporated nitrogen in the resonance of the aromatic bicyclic structure. The indole ring can participate in a wide range of chemical reactions, particularly in C3 for example, electrophilic substitution, carbon lithiation, oxidation, and cycloaddition. In addition, indoles can be involved in a variety of biochemical reactions such as spore formation, plasmid stability, biofilm formation, and virulence in bacteria [143].

Indole-based compounds, either naturally occurring or synthetic, have their usefulness as therapeutic agents in the treatment of cancer, bacterial and viral infections, emesis, migraine, and hypertension. Examples of some natural and synthesized indole derivatives can be seen in Fig. 13.56 [143,144].

13.6.4.2 N-Sulfonyl indole for inflammation-related disorders

The role of eosinophiles is prominent in the case of the proinflammatory stage in allergic disorders, parasitic infections, and some malignancies. Eosinophiles are

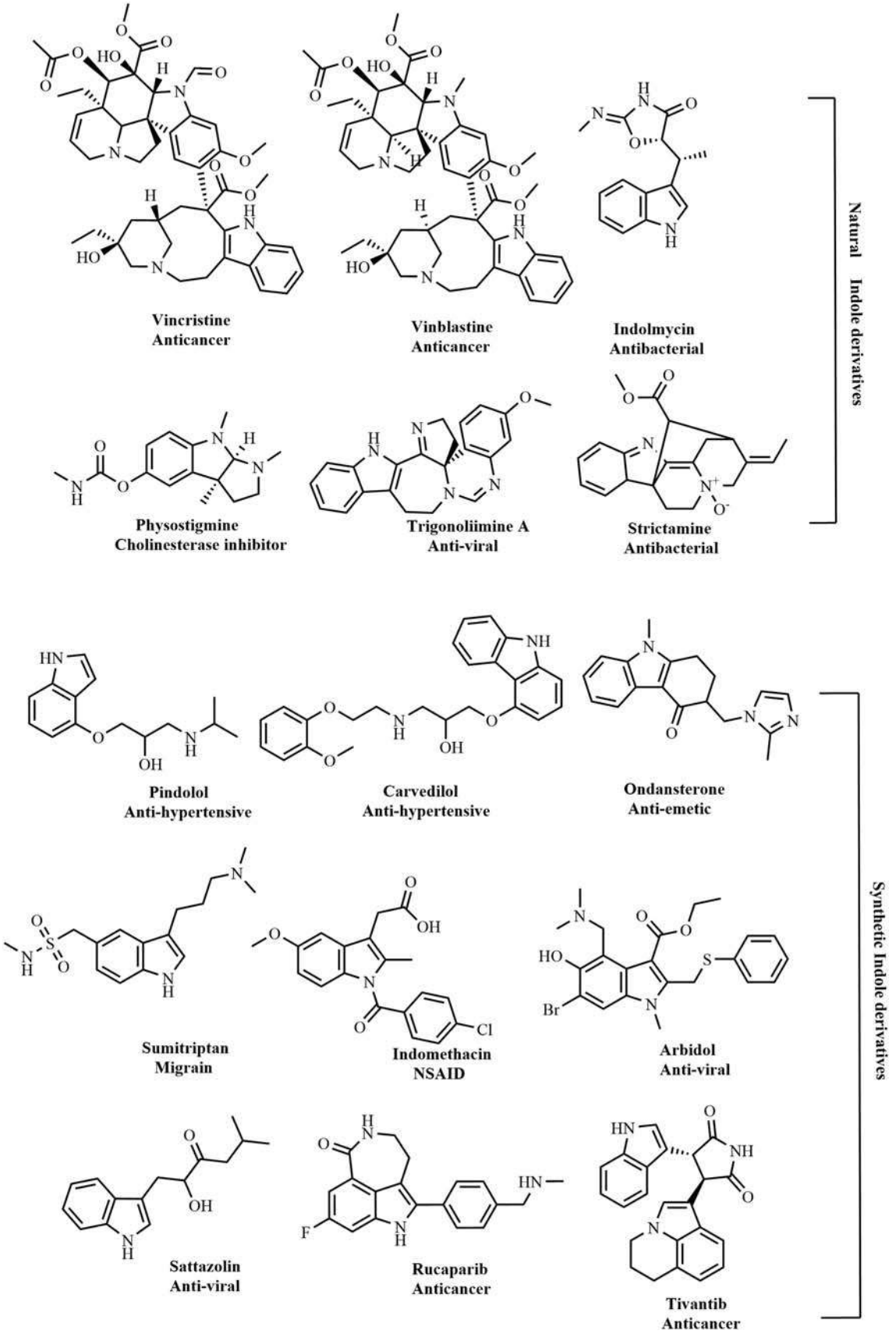
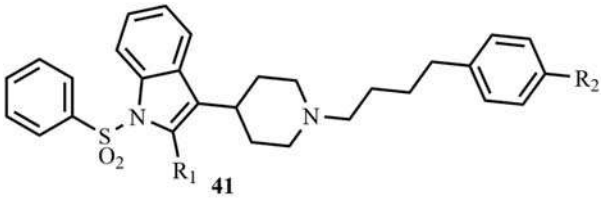


FIGURE 13.56 Examples of some natural and synthetic indole-based drugs.

regulated by the action of chemokines, specifically eotaxin, which has been identified as the most selective chemoattractant. Chemokines are a superfamily of cytokines that participate in leukocyte migration and accumulation of inflammatory cells at the inflammation site. On the other hand, chemokine receptors are G-protein coupled receptors and the major chemokine receptor operational in eosinophiles is the chemokine receptor CCR-3, which is expressed by eosinophiles, basophiles, and some Th2 lymphocytes. So, CCR-3 plays a distinct role in allergic response and its major ligand is eotaxin, which, upon binding to the receptor, triggers a series of events including the activation of mitogen-activated kinase, polymerization of actin, and granule release. Also, the activation of CCR-3 receptors leads to a respiratory burst which can be inhibited by different therapeutic agents such as staurosporin, genistein, and wortmannin. The action of these therapeutic agents strongly suggests the involvement of several kinases, including the protein kinase -C and phosphatidylinositol 3-kinase (PI3K) [145]. Due to the major role played by CCR-3 receptors in asthma, the CCR-3 receptor antagonist offers a plausible solution for treating the disease [146].



R1= C_2H_5 or CH_2OCH_3
R2= H or F

FIGURE 13.57 The general formula of *N*-sulfonyl indole as CCR-3 modulators.

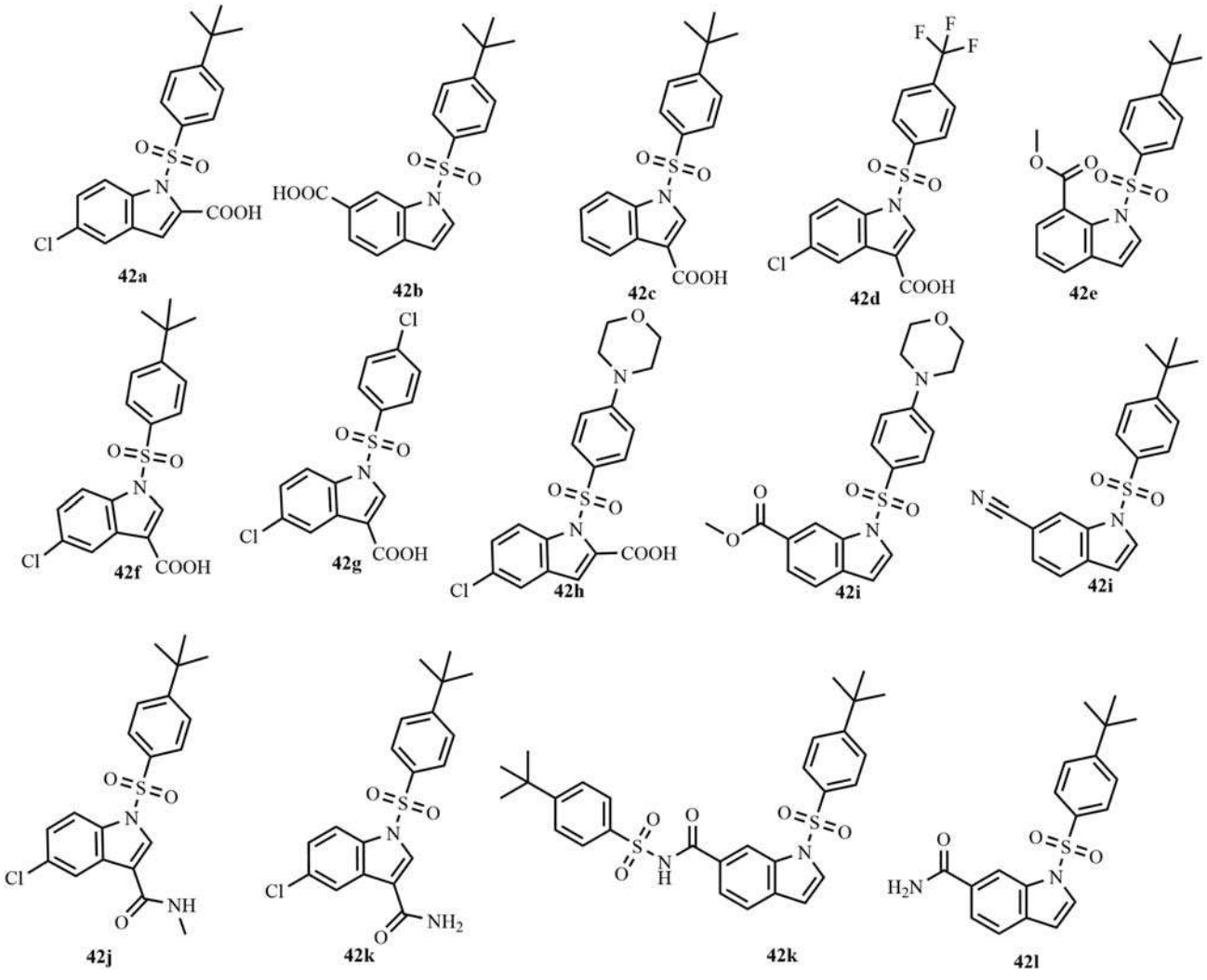


FIGURE 13.58 1-Benzenesulfonyl-1 *H*-indole derivatives as CCR9 inhibitors.

In 2012, Martyres and co-workers reported a patent explaining the development of different piperidyl-propane-thiole derivatives, among which *N*-sulfonated indole derivatives of the general formula **41** (Fig. 13.57) were reported. The authors explained the utility of the developed small molecules as CCR-3 modulators [147].

Chemokine ligand 25 (CCL25) is a chemokine that is expressed by the thymus gland and acts as a ligand for the chemokine receptor-9 (CCR-9). CCL25 plays a major role in homing the T-lymphocytes to the gut mucosa, specifically the epithelial cells. CCL25 has been identified to be implicated in inflammatory bowel diseases such as Crohn's disease, in addition to some inflammation-related disorders such as psoriasis, dermatitis, and asthma [148].

Several 1-benzenesulfonyl-1*H*-indole derivatives were reported for expected CCR9 inhibitory activity. Examples of the reported compounds (**42a-l**) are demonstrated in Fig. 13.58 [149].

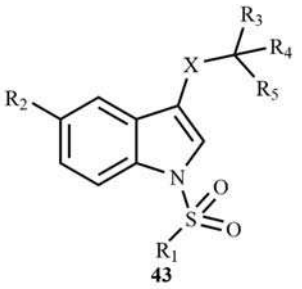
The PPAR family includes PPARα, PPARβ/δ, and PPARγ, which are a group of nuclear receptors activated by oxidized and nitrated fatty acids along with prostaglandins (PGA2 and 15d-PGJ2) in the inflammatory process. The activation of PPAR results in the control of the pro-inflammatory response. Nonsteroidal antiinflammatory drugs ($NSAID_S$) activate PPAR in addition to arachidonic acid. PPARα is expressed mainly in the liver and less commonly in the heart, kidney, skeletal muscles, and intestine, where it plays an important role in fatty acid oxidation, lipid metabolism, and inflammation. On the other hand, PPARβ/δ is expressed in hepatocytes, macrophages, and adipocytes where it controls lipid metabolism, glucose homeostasis, and inflammation [150–152]. PPAR receptor modulators are reported to be beneficial in the treatment of atherosclerosis [153] and chronic inflammatory diseases such as arthritis and inflammatory bowel syndrome and neurodegenerative diseases such as Alzheimer's disease [154].

Lin *et al.* reported various PPAR modulators among which various *N*-sulfonyl indole derivatives were presented bearing a core with general formula **43**, Fig. 13.59 [154].

In similar efforts, Dean *et al*. claimed the efficacy of the example compounds **44a–m** (Fig. 13.60) as PPAR modulators [155].

13.6.4.3 N-Sulfonyl indole derivatives for the treatment of peptic ulcer

The term peptic ulcer is used to define the gastric injury caused by acid secretion disrupting the gastric mucosa. Peptic ulcers can occur in the stomach, duodenum, esophagus, or Meckel's diverticulum. The occurrence of peptic ulcers is related to the hypersecretion of gastric acid which accompanies many factors such as stress, the use of NSAIDs, or infection by *H. pylori* [156]. The treatment of peptic ulcers usually includes therapeutic agents that can reduce acid secretion such as antacids ($Al(OH)_3$ and $Mg(OH)_2$), histamine receptor-2 (H_2) antagonists (Famotidine and Nizatidine), proton pump inhibitors (PPIs, Omeprazole, Pantoprazole, and Lansoprazole). Also, the use of cytoprotective agents such as misoprostol and sucralfate increases the production of protective mucosa [157]. PPIs are selective irreversible inhibitors of the H^+/K^+ ATPase pump available as prodrugs that require an acidic medium for activation [158–160]. However, due to their long-term inhibition of the H^+/K^+



43

X= -S-, -O- or -N optionally substituted with $\mathbf{R_2}$.
$\mathbf{R_1}$= un substituted or substituted group selected from the following; (C1- C6) alkyl, (C2-C6) alkenyl, (C2- C6) alkynyl, cycloalkyl, heterocycloalkyl, aryl, hetroaryl, aralakyl, heteroaralky.
If $\mathbf{R_1}$ is designated as substituted alkeyl or alkynyl the substitutions must not contain S, SO or SO_2.
$\mathbf{R_2}$= H, halogen, or unsubstituted or substituted one following groups; (C1-C6) alkyl, allyl,(C1-C6) cycloalkyl, heterocycloalkyl, aryl, aralyl, heteroaryl, alkoxy, amine, amide or sulfonamide.
$\mathbf{R_3}$= COOH or isosteres of COOH
$\mathbf{R_4}$ and $\mathbf{R_5}$= unsubstituted or substituted group selected form the following; H, (C1- C6) alkyl, (C1-C6) cycloalkyl, heterocycloalkyl, unsubstituted or substituted aryl or aralyl or a heteroaryl.

FIGURE 13.59 *N*-Sulfonyl indoles as peroxisome proliferator-activated receptor modulators.

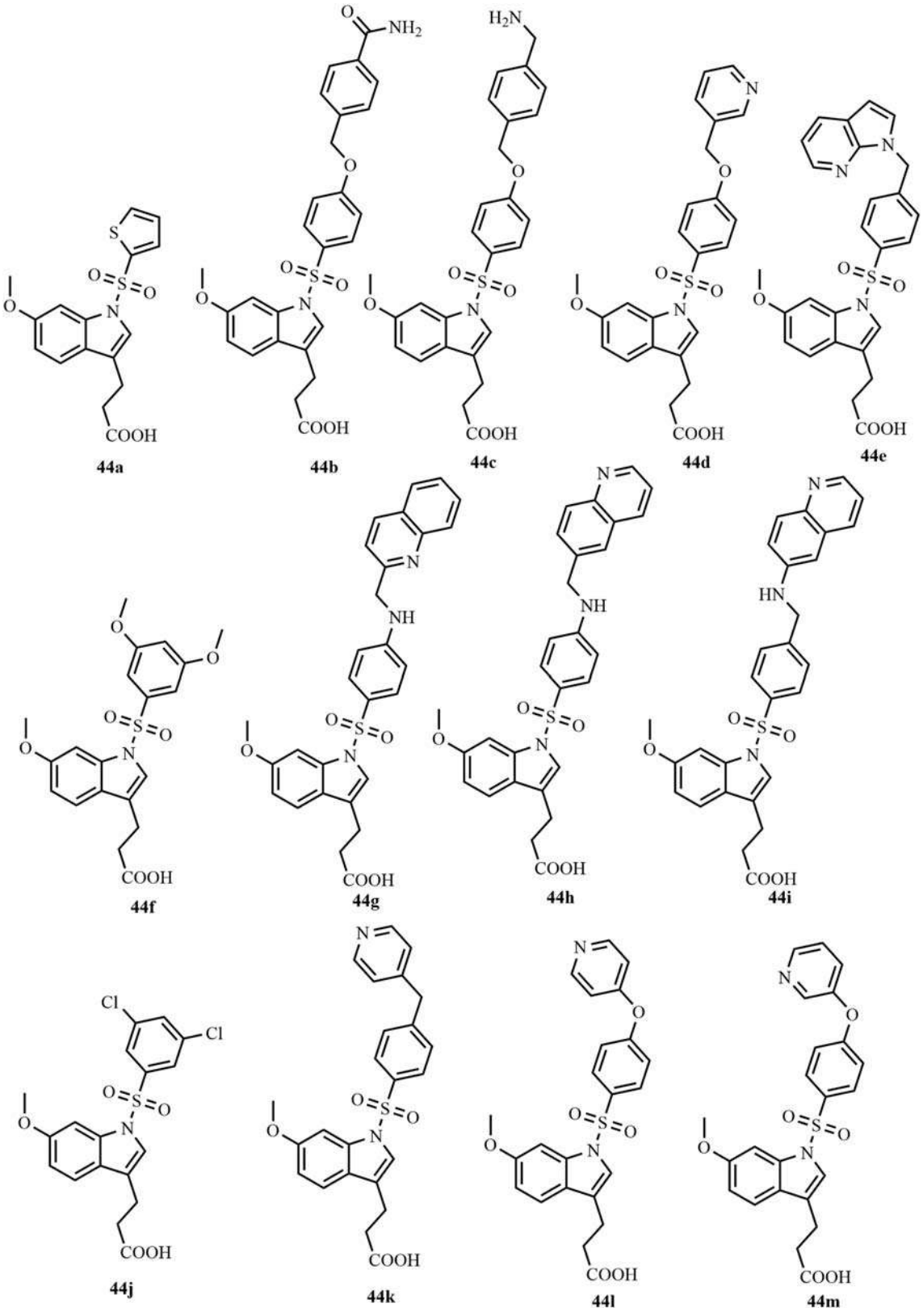


FIGURE 13.60 *N*-Sulfonyl indoles as peroxisome proliferator-activated receptor modulators.

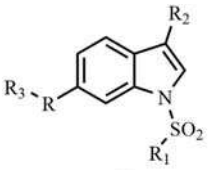
ATPase pump, it is accompanied by problematic side effects such as the promotion of bacterial growth, increased expression of the proton pump, and finally the increase of tumorigenesis due to increased gastrin secretion [160]. In the search for new PPIs with reversible inhibitory action, Kyung *et al.*, reported a series of sulfonyl indoles with the general structure **45**, (Fig. 13.61). The claimed compounds showed efficacy as reversible PPIs and offered the possible use of the developed compounds in the treatment of peptic ulcers and other hyperacidity-related conditions such as gastritis or reflux esophagitis [160].

13.6.4.4 N-Sulfonyl indole derivatives for the treatment of Hepatitis B

Hepatitis B virus is a noncytohepatic DNA virus of the family *Hepadnaviridae*. It causes problematic chronic hepatitis B (CHB) which affects nearly 260 million patients annually and can develop more serious hepatic conditions such as hepatocellular carcinoma, liver failure, and cirrhosis in about one-third of the infected patients [161–163]. The available therapeutic agents for CHB such as interferon-α, and nucleoside/nucleotide analogs cannot offer a radical treatment for the disease due to their inability to eradicate the covalently closed circular DNA (cccDNA) from the infected hepatocytes. So, most of the research for finding new cures for CHB is directed to the inhibitors of cccDNA [161]. Indeed, Cuconati and co-workers had reported different series of compounds all bearing a sulfamoyl group, among which compounds of the general formula **46** (Fig. 13.62) were discovered using high throughput screening on HepDE19 cells [163].

13.6.4.5 N-Sulfonyl indole derivatives as anticancer agents

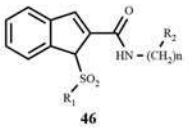
Dalton *et al.* reported the synthesis and biological activity of different indole derivatives among which various *N*-sulfonated indoles (**47a–l**, Fig. 13.63) have been found to have cytotoxic activity against prostate cancer cell lines



45

R_1= Phenyl unsubstituted or substituted with 1-3 substituent selected from **R_{1a}**, pyridinyl which can be unsubstituted or substituted with **R_{1b}**.
R_2= $-CH_2NHCH_3$, $-CH_2$, $NHCH_2$, CH_3, $-CH_2N(CH_3)_2$, $-CH_2$(pyrrolidin-l-yl), $-CONHCH_2$, $-CON(CH_3)_2$, -COOCH or $-NHCH_3$.
R_3= Pyrimidinyl optionally substituted with C1-C4 alkoxy or a halogen, Pyridine unsubstituted or substituted with 1-2 substituents of **R_{3a}**, phenyl unsubstituted with 1-3 substituents of **R_{3a}**.
R_{1a}= C1-C6 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, halogen, phenyl or CN.
R_{1b}= C1-C4 alkoxy or haolgen.
R_{3a} = C1-C6 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, or a halogen.

FIGURE 13.61 *N*-Sulfonyl indoles as proton pump inhibitors.



46

R_1= Optionally substituted phenyl, unsubstituted of substituted C1-C6 alkyl which can be linear or branched, unsubstituted or substituted C3-C7 cycloalkyl, or unsubstituted or substituted heteroaryl.
Any substituent can be chosen form R_2.
X= $(CH(CH_2)m)n$
n= 0-1
m= 1-2.
R_2= OH, OCH_3, OC_2H_5, OC_3H_7, $COCH_3$, OC_2H_5, OC_3H_7, $COOCH_3$, $COOC_2H_5$ $COOC_3H_7$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, NH_2, $NHCH_3$, $N(CH)_3$, NHC_2H_5, CH_2F, CHF_2, CF_3, CCl_3, CBr_3, SO_2H, SO_2CH_3, CO_2Ph, CN, NO_2, oxo or a heterocycle.
The heterocycles can be chosen from the group below;

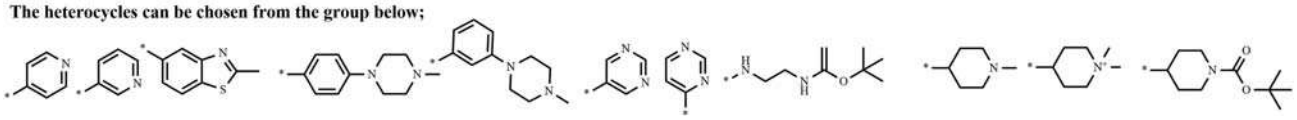
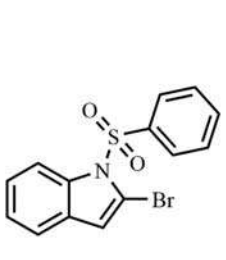
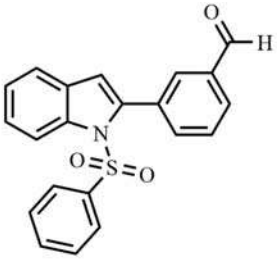


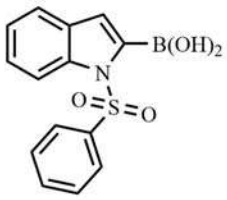
FIGURE 13.62 *N*-Sulfonyl indoles for the treatment of Hepatitis B.



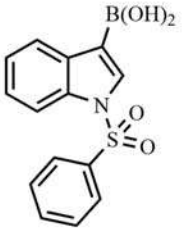
47a
IC_{50}= 29.6- 69.3



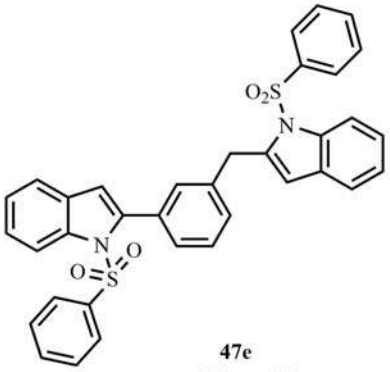
47b
IC_{50}= 11.5- 23.2



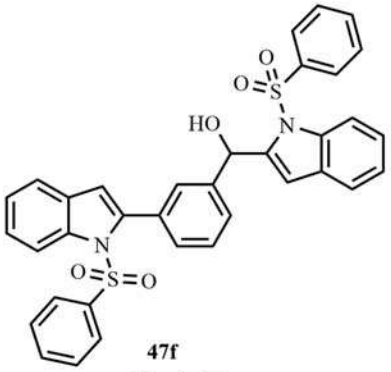
47c
IC_{50}= 23.1- 80.8



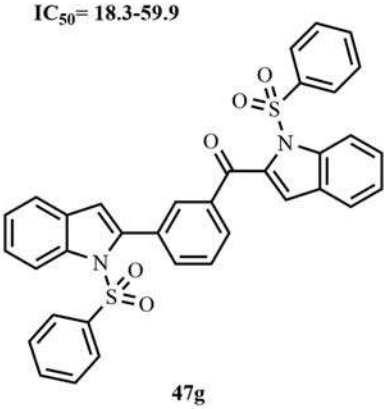
47d
IC_{50}= 18.3-59.9



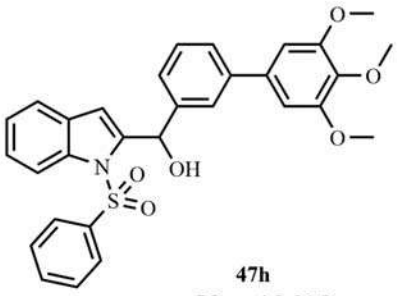
47e
IC_{50} > 100



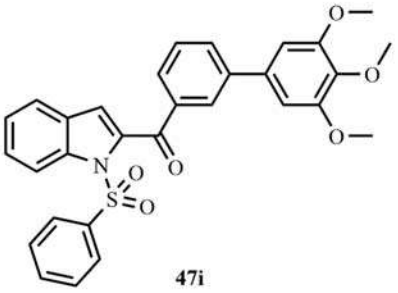
47f
IC_{50} > 100



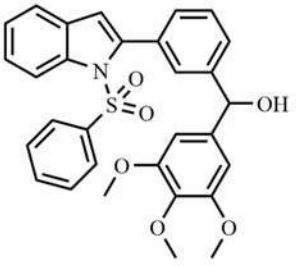
47g
IC_{50} > 100



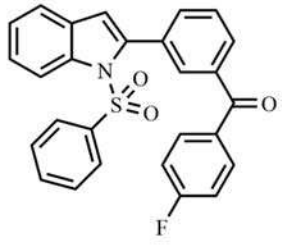
47h
IC_{50}= 4.2-21.8



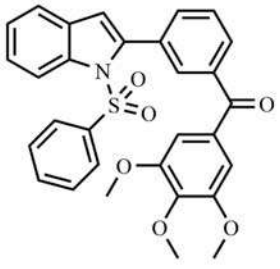
47i
IC_{50}= 4.2-58.9



47j
IC_{50}= 10.1-61.5



47k
IC_{50}= 0.55-4.01



47l
IC_{50}= 7.8-68.5

FIGURE 13.63 *N*-Sulfonyl indole derivatives as anticancer agents.

(LNCaP, PC-3, DU-145, and PPC-1), bladder cancer cell lines (TSU-Pr1), and one fibroblast cell line (CV-1). All the example compounds were found to have low cytotoxicity against the fibroblast cell line (IC_{50} >100 μM). The di-indole derivatives showed no cytotoxic activity on all the tested cell lines. The authors claimed the activity of the series was attributed to tubulin inhibition and hence were suggested for treatment or prevention of various forms of cancer, particularly prostate, breast, ovarian, skin (e.g., melanoma), bladder, lung, colon, leukemia, renal, and CNS cancers (e.g., glioma, glioblastoma) [103].

Other efforts have been published in 2011 by Chen and co-workers reporting a series of indolyl and indolyl-hydroxamate as histone deacetylase inhibitors [164]. The research group reported the growth inhibitory concentration of some of the presented examples (**48a–t**, Fig. 13.64) against 4 cell lines; lung carcinoma (A549), breast cancer (MDA-MB-231), liver cancer (Hep-3B and HA22T) and compared the activity with a standard histone deacetylase inhibitor, Vorinostat (SAHA) [165]. The reported results are presented in Table 13.2 [164].

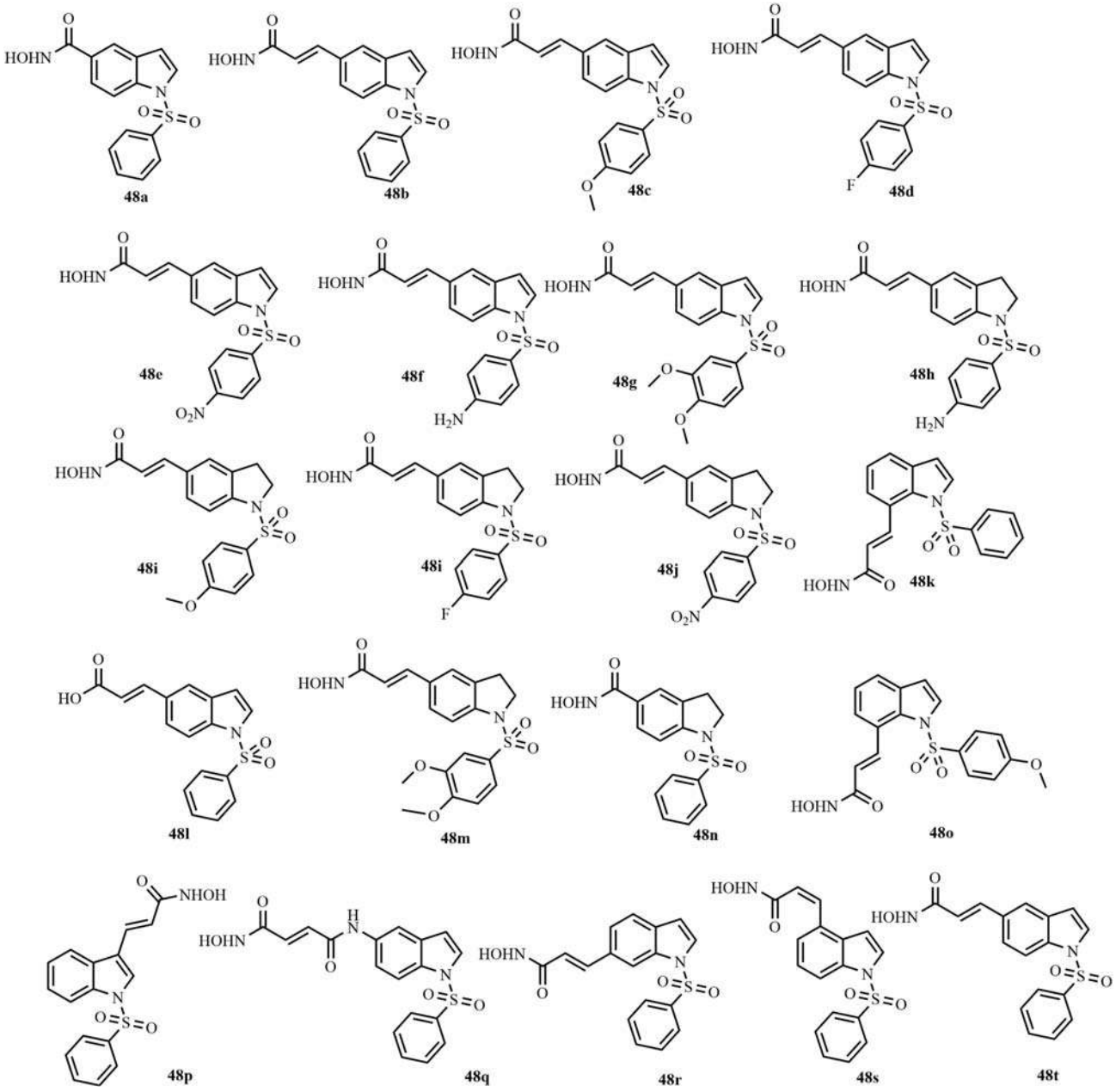


FIGURE 13.64 *N*-Sulfonyl indole derivatives as anticancer agents.

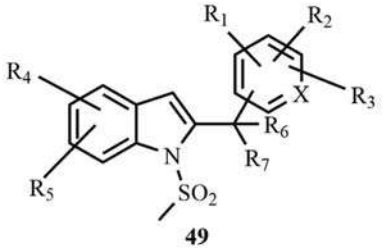
TABLE 13.2 Inhibitory growth concentration 50% of *N*-sulfonated indole derivatives.

Cell line / Compound	A549	MDA-MB-231	Hep-3B	HA22T
48c	1.31	0.75	0.55	1.56
48d	1.59	0.66	0.64	2.3
48e	2.12	0.75	0.56	1.98
48 f	>10	>10	>10	>10
48i	0.32	0.16	0.14	0.54
48j	0.60	0.37	0.25	1.2
48k	0.80	0.45	0.28	0.74
48l	>10	>10	>10	>10
SAHA	2.37	0.97	0.69	2.24

Data reported as IG_{50}, μM.

13.6.4.6 N-Sulfonyl indole derivatives for the treatment of Parkinson's disease

For the treatment of neurodegenerative diseases, especially Parkinson's disease, a patent was published in 2011 reporting a series of *N*-sulfonated indole derivatives bearing the core structure **49** (Fig. 13.65) as selective agonists of NURR-1/RXRα and NURR-1/RXRγ heterodimers [166].



49

R_1= H, 2-F or 2-OCH_3
R_2= H or 2-OH
R_3= *p*-$COOCH_3$, *p*-COOH, *m*-$COOCH_3$ or *m*-COOH
R_4= H, 5-Cl, 5-CF_3 or 4-CF_3
R_5= H or 6-CF_3.
R_6= H or OH.
R_7= H or CH_3
X= CH or 3-N

FIGURE 13.65 *N*-Sulfonated indole core structure as selective agonistic of NURR-1/RXR α and NURR-1/RXR γ heterodimers.

13.6.4.7 N-Sulfonyl indole derivatives for the treatment of obesity

Angbrant *et al.* reported the activity of several *N*-sulfonated indoles fused with an azepine ring creating a tricyclic core as presented in the example compounds (**50a**–**50w**, Fig. 13.66) as 5-HT6 receptors modulators. Hence, the authors proposed their use for the treatment of obesity as well as in the treatment or prophylaxis of other central nervous system-related disorders such as anxiety, depression, panic attacks, memory disorders, and cognitive disorders [167].

Also, another patent reported several *N*-sulfonated indole derivatives with general formula **51** (Fig. 13.67) active against 5-HT6 receptors and proposed their usefulness in the treatment of obesity [168].

Another series of *N*-sulfonated indole was reported for their affinity for 5-HT6 receptors among various *N*-sulfonated heterocycles such as azaindole and pyridine. The compounds were presented as selective modulators of 5-HT6 receptor activity for the treatment of central nervous system-related disorders, whether motor, mood, behavioral, psychiatric disorders, Parkinson's disease, depression, bipolar depression, epilepsy, or Alzheimer's disease. The authors also claimed the usefulness of the presented compounds for the treatment of feeding disorders such as bulimia, and anorexia. Representative examples (**52a**–**52o**) are shown in Fig. 13.68 [169].

13.6.4.8 Other medical uses of N-sulfonyl indole

Sesha *et al.* reported the use of various benzofuran- carboxamide derivatives as prodrugs for the antidepressant agent Vilazodone in an attempt to decrease its gastrointestinal side effects and improve its pharmacokinetic properties. In this patent, the authors reported two series of benzofuran-2-

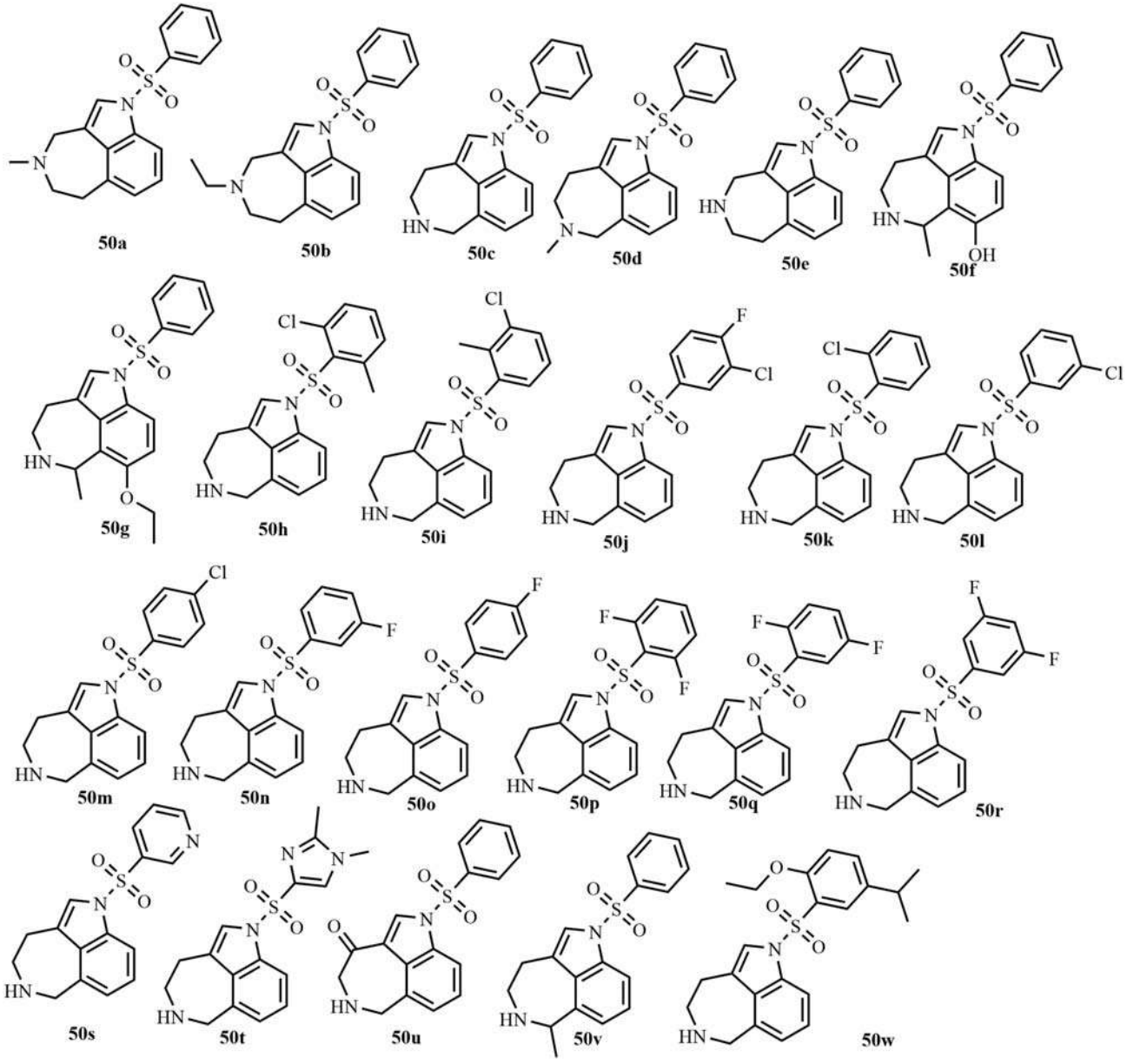


FIGURE 13.66 Tricyclic compounds bearing *N*-sulfonyl indole as 5-HT6 receptors.

carboxamide bearing *N*-sulfonated indole scaffold presented in general formula **53a** and **53b** (Fig. 13.69) [170].

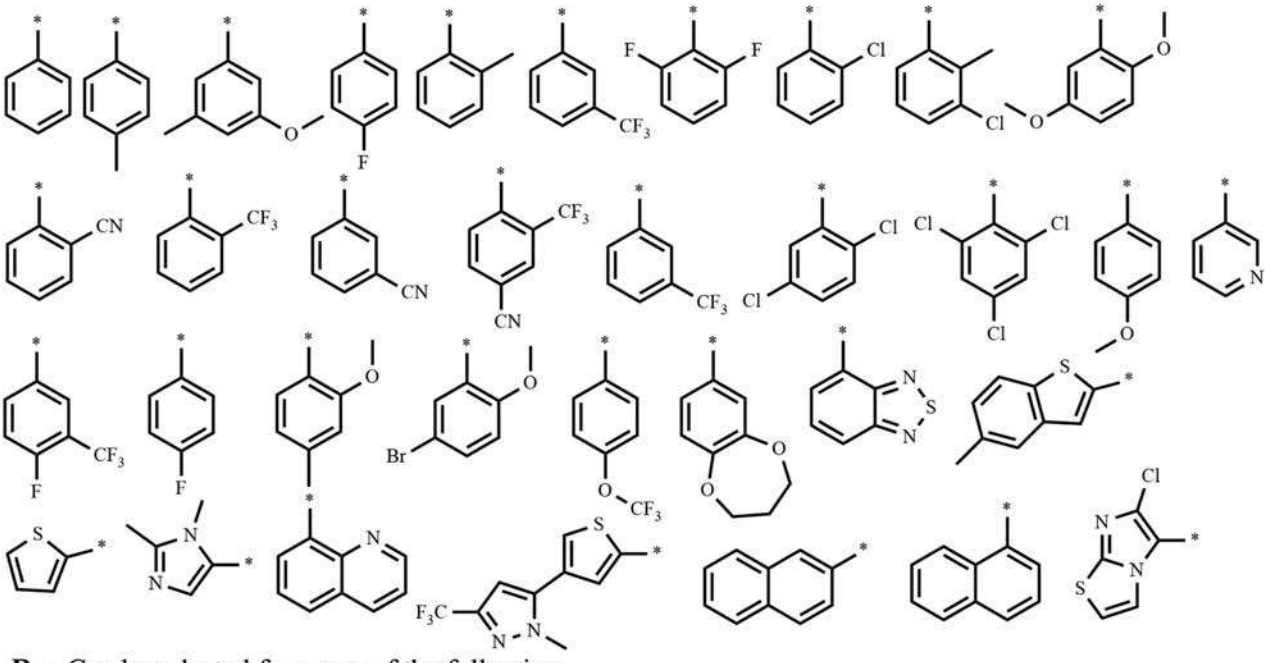
13.6.5 *N*-Sulfonyl quinoline and *N*-sulfonyl isoquinoline derivatives

13.6.5.1 Medical applications of quinoline and isoquinoline derivatives

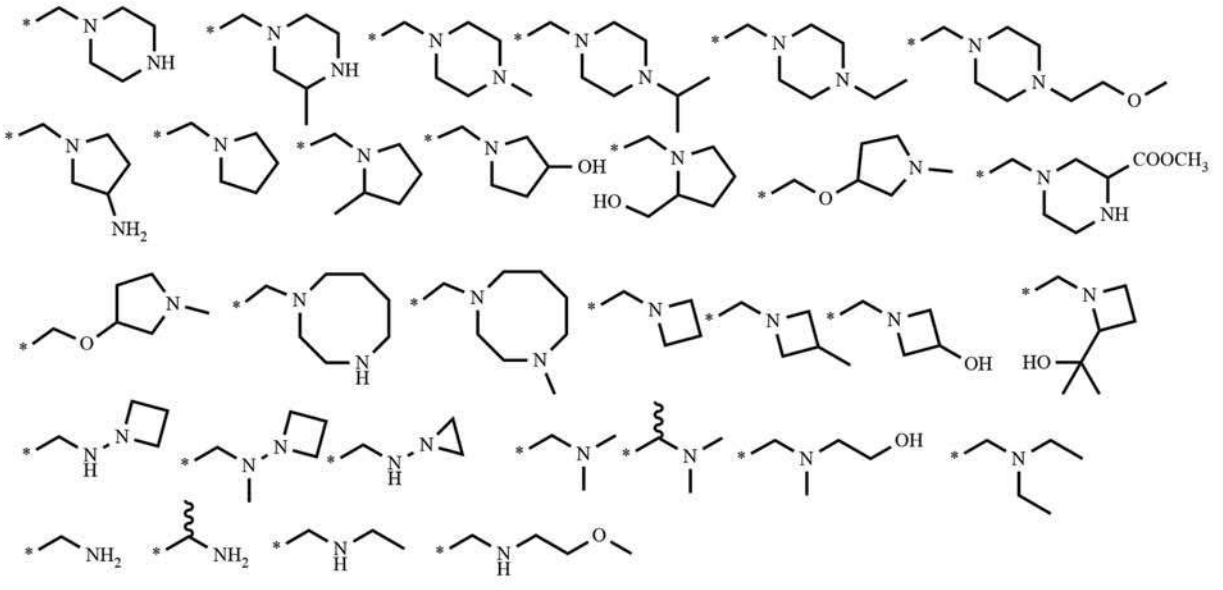
The quinoline scaffold is beyond any doubt one of the most prominent scaffolds utilized in the field of medicine. Specifically, quinoline derivatives found a special rank in the development of new drugs, especially anticancer agents [171]. The quinoline ring offers an easily accessible and good scaffold for optimization through various synthetic approaches [171]. In addition, isoquinoline is an interesting scaffold that has been of great utility in the development of new pharmaceuticals either approved or under clinical development for treating respiratory diseases, cancer, infectious diseases, or diseases related to the central nervous system [172]. In addition to the importance of quinoline and isoquinoline-based synthetic derivatives, various natural alkaloids have been retrieved from natural sources and used for their therapeutic properties [173]. Fig. 13.70 illustrates some examples of quinoline and isoquinoline derivatives approved for therapeutic use.

51

R_1= Can be selected from one of the following;



R_2= Can be selected from one of the following;



R_3= H, OCH_3, $-OC_2H_5$, $-OC_2H_4Ph$, $-OCH(CH_3)_3$ or OH.

R_4= H, $-OCH_3$, $-OC_2H_5$, F, $-OCON(CH_3)_2$, OH or CF_3.

R_5= H or OCH3.

FIGURE 13.67 *N*-Sulfonyl indole derivatives as 5-HT6 receptors.

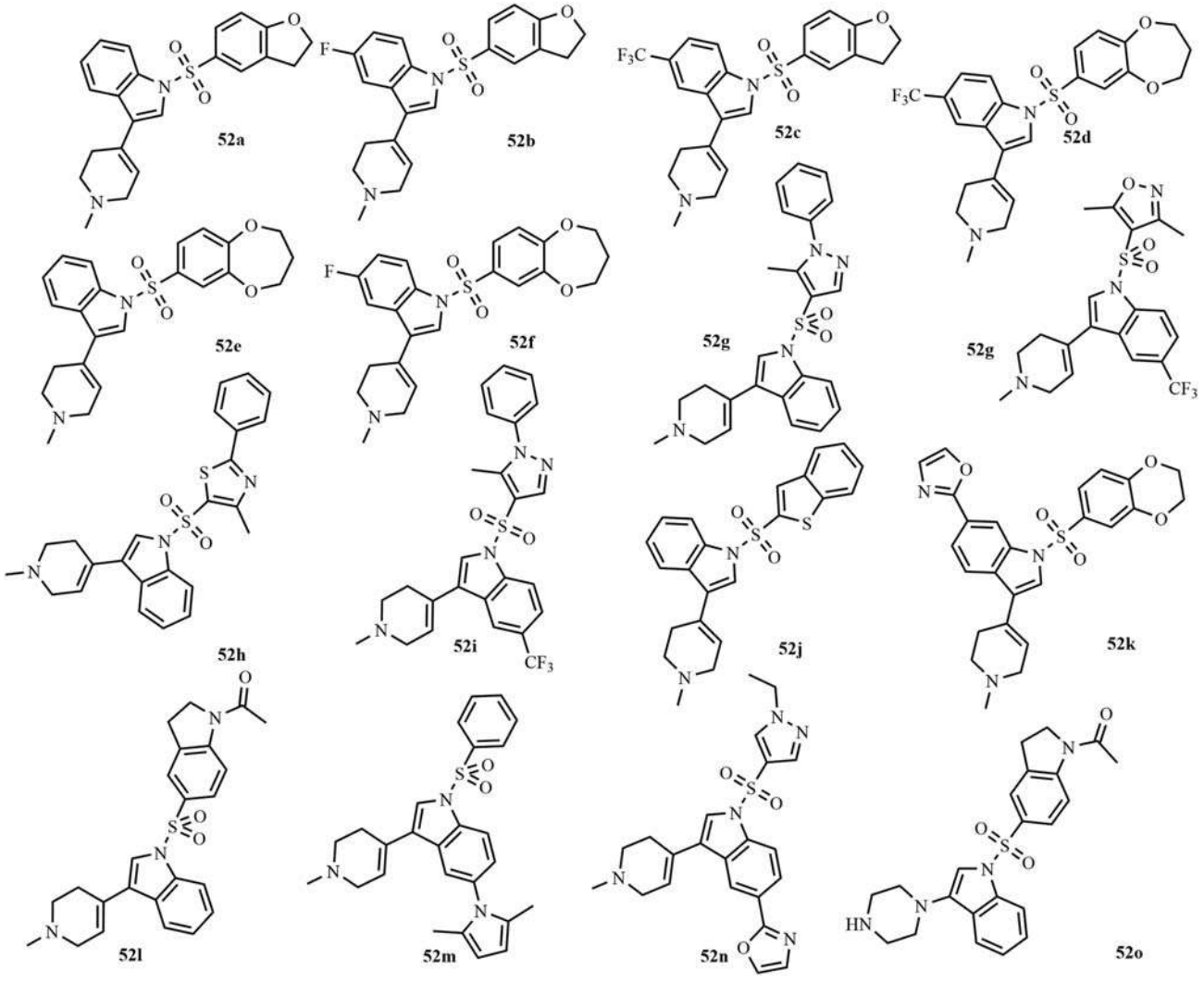
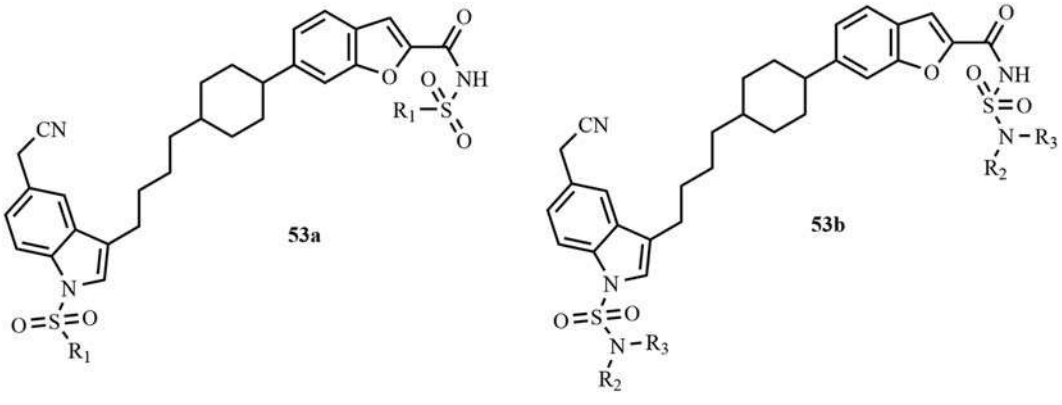


FIGURE 13.68 *N*- Sulfonyl indole for the treatment of central nervous system disorders.



R_1= (C1-C4) alkyl unsubstituted or substituted with a halogen methyl is preferred, benzyl or other arylalkyls, phenyl unsubstituted or substituted with one or more halogen(s), OCH_3, NH_2 or NO_2.
R_2 and R_3= Can be independantly chosen from; H, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl.

FIGURE 13.69 *N*-Sulfonyl benzofuran-2-carboxamide derivatives as prodrugs for vilazodone.

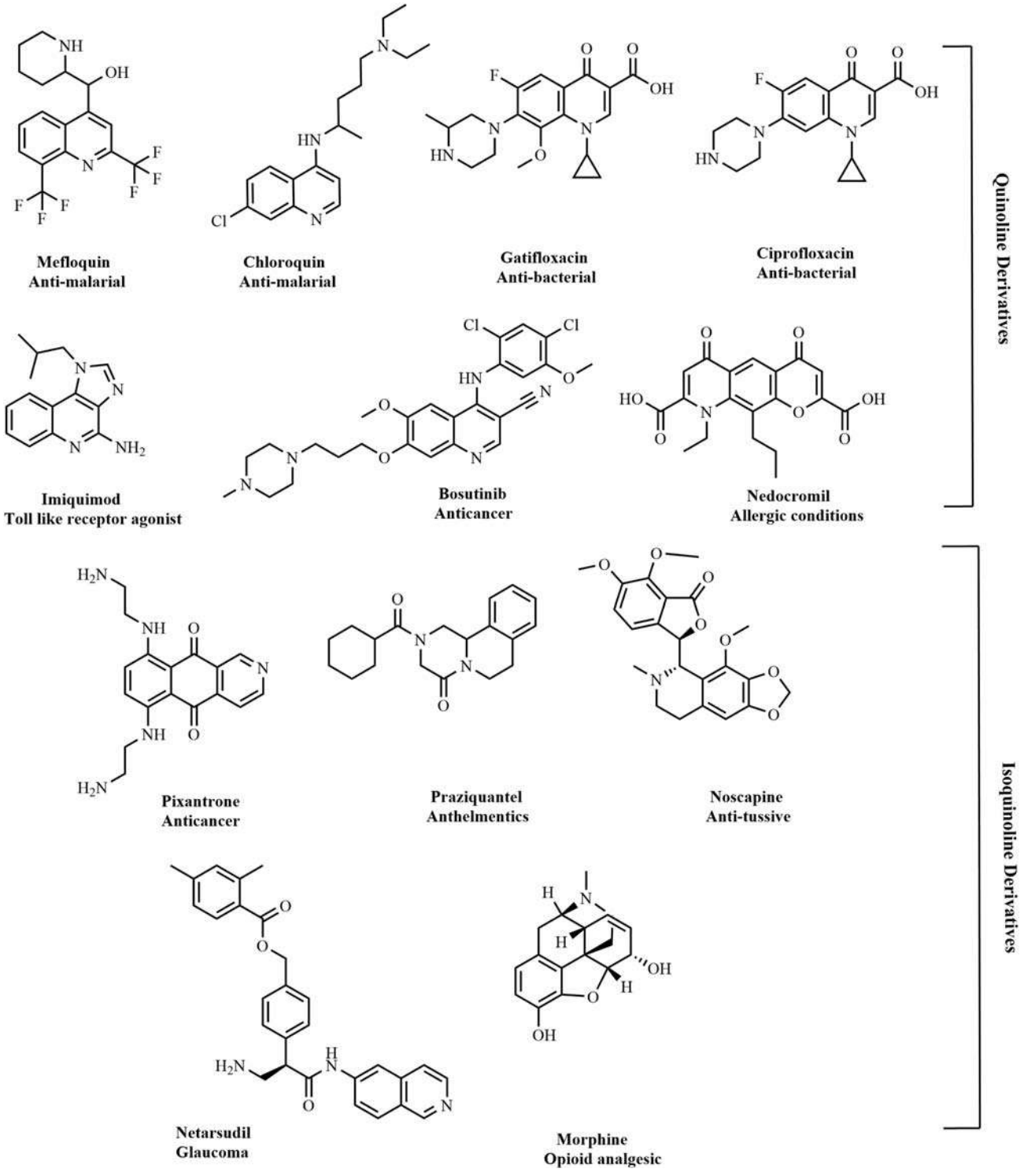


FIGURE 13.70 Quinoline and isoquinoline-based drugs.

13.6.5.2 N-Sulfonyl quinoline and N-sulfonyl isoquinoline derivatives for the treatment of cancer

DNA is constantly damaged by different endogenous or exogenous agents resulting in double or single-strand breaks. In a normal cell, the damaged DNA can be repaired over time by DNA repair machinery. However, in a malignant cell, the rate of double-strand breaks is higher, which gives a rise in gene nutrition and instability, resulting in tumor progression. The liver X receptors (LXRα/NR1H3, LXRβ/NR1H2) are a group of nuclear

receptors mastering the transcription factors controlling the transcription of lipogenic and tumorigenic genes which are responsible for lipid metabolism and tumorigenesis. The expression of LXR is associated with dyslipidemia, obesity, cardiovascular diseases, and, as reported recently, cancers [174]. In the efforts for modulating LXR receptors for cancer treatment, a series of *N*-sulfonyl tetrahydroisoquinoline-based compounds were synthesized and their activity against LXR was investigated. Compounds **54a–c** (Fig. 13.71) were reported as an inverse agonists to the claimed receptor. LXR inverse agonists can be helpful in the treatment of being used to treat cancer or other hyperproliferative diseases, as well as atherosclerosis and coronary artery disease [175].

Retinoic acid-related orphan receptor-γ (RORγ) is the orphan, an orphan nuclear receptor that regulates the maturation of Th17 cells and the expression of IL-17. Retinoids are the ligand for this type of receptor where β-carotenes and vitamin A are converted into their active form in the liver. Cell membrane RORs are involved in the activation of certain protein kinases and hence have been studied extensively in cancer. Also, ROR receptor activity has been linked to atherosclerosis, autoimmune diseases, allergies, and liver dysfunction [176,177].

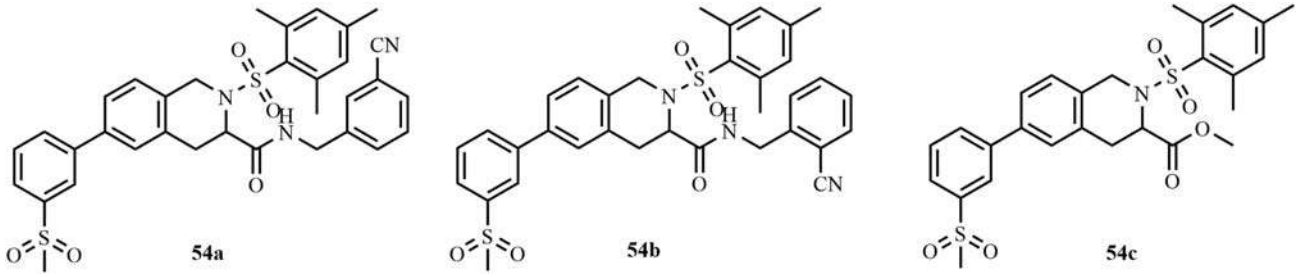
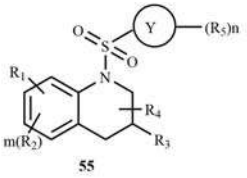


FIGURE 13.71 *N*-Sulfonyl tetrahydroisoquinoline as liver X receptor inverse agonists.



R_1= Is chosen from one of the following; (C4-C7) cycloalkenyl, (C3-C7) cycloalkyl, or an 8-10 membered, bicyclic partially saturated carbocyclyl.
Each R_1 group can be optionally substituted with 1- 3 of R_a.
R_2= Can be selected from one of the following; halogen, (C1-C6) alkyl, (C1-C6) haloalkyl, or (C3-C6) cycloalkyl.
R_3= H, (C1-C6) alkyl, (C1-C3) haloalkyl, (C3-C6) cycloalkyl, -(C1-C6) alkylene, (C3-C6) cycloalkyl, -O-(C1-C6-alkylene)-CO-(C1-C6 alkyl), -N(R_b)-(C1-C6-alkylene)-COO-R_b or -N(R_b)-(C1-C6-alkylene)-C(O)-(C1-C6-alkyl).
Each alkyl, cycloalkyl or alkylene group of R3 can be substituted with one or two substituents chosen from R_c.
R_4= (C1-C6) alkyl, (C1-C3) haloalkyl, or F.
Y= Phenylene, 5-6 membered heteroarylene, or (C3-C6)-heterocycloalkylene.
R_a= halogen, (C1-C6) haloalkyl, (C1-C6) alkyl, (C3-C6) cycloalkyl,(C1-C6) alkoxy, (C1-C6) haloalkoxy, -S-(C1-C6-alkyl), OH, CN, and -(SO_4)m
R_b=(C1-C6) alkyl or (C3-C6) cycloalkyl.
R_c= -CO2Rb, -C(O)N(Rb)(Rb), -C(O)-N(Rb)-(C1-C4) alkylene), -CN, halogen, OH, (C1-C6) alkoxy, (C1-C6) haloalkoxy, (C1-C6) haloalkyl, or -N(R_b)(R_b), -N(R_b)-C(O)-N-(R_b)(R_b).
m= 0-3.
n= 1-3.

FIGURE 13.72 Tetrahydroquinoline sulfonamides as related orphan receptor-γ modulators.

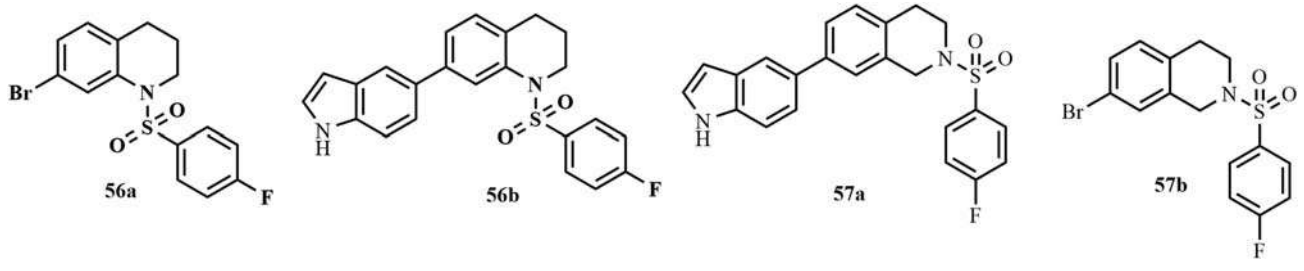


FIGURE 13.73 *N*-Sulfonyl quinoline and *N*-sulfonyl isoquinoline for the treatment of multidrug-resistant cancers.

Tetrahydroquionoline sulfonamide compounds with the general formula **55** (Fig. 13.72) were claimed to modulate the activity of the RORγ. Thus, it can be effective in the treatment of cancer [178].

In another patent cited earlier by Li *et al.* *N*-sulfonyl quinoline (**56a–b**, Fig. 13.73) and *N*-sulfonyl tetrahydroisoquinoline compounds (**57a–57b**, Fig. 13.73) were claimed to be effective in the treatment of multidrug-resistant (MDR) cancers [59].

13.6.6 Other *N*-Sulfonyl heterocycles

De Francesco and co-workers introduced a patent that displayed a series of *N*-sulfonated heterocycles for treatment, decreasing the viral load of HBV. Compounds **58a–o** (Fig. 13.74) had the sulfonyl group in a thiadiazine-1,1-dioxide heterocycle. While compounds **59a–c** (Fig. 13.75) had the sulfonyl moiety incorporated in a thiadiazepine-1,1-dioxide scaffold [179,180].

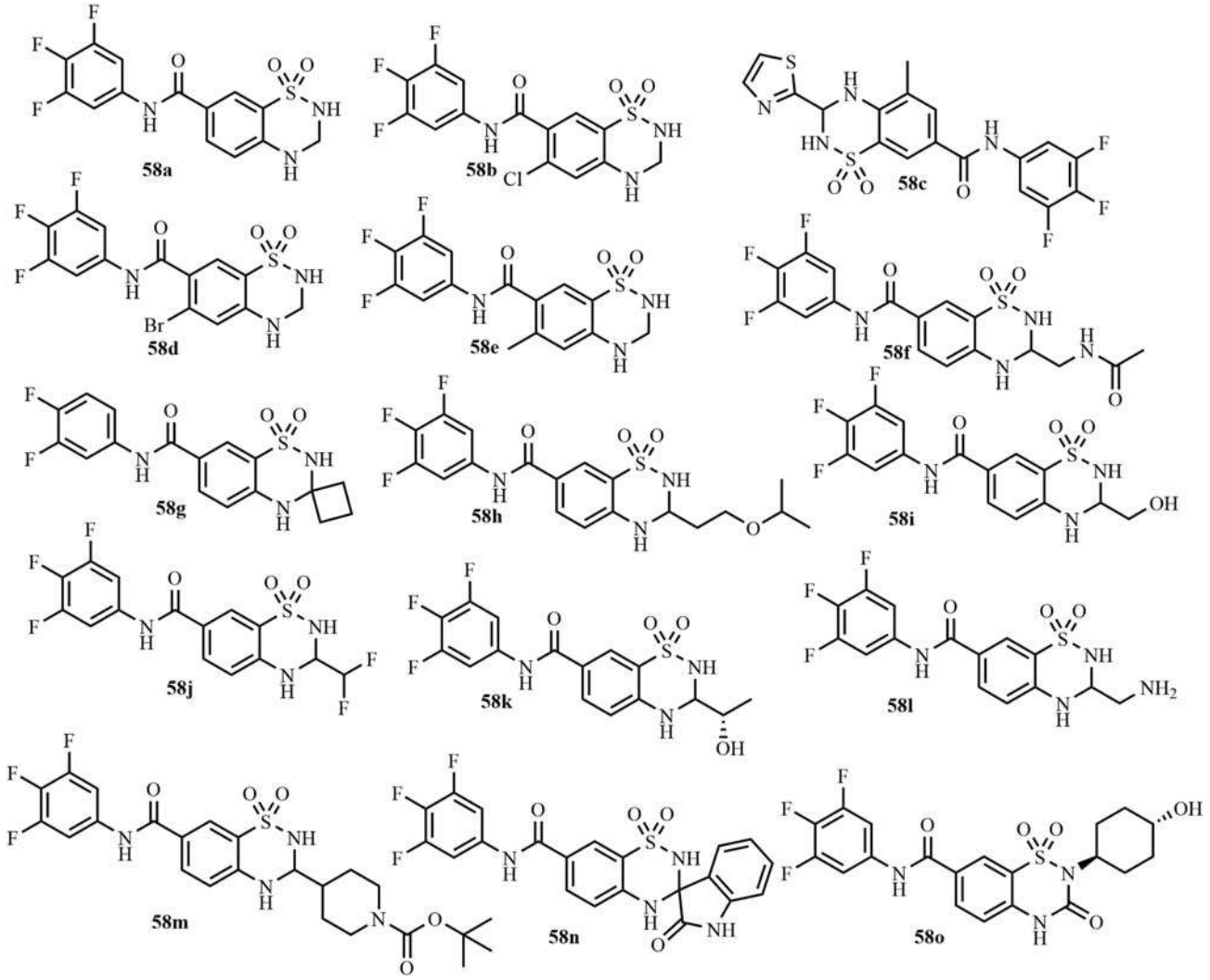


FIGURE 13.74 *N*-Sulfonyl thiadiazine-1,1-dioxide for the treatment of HBV.

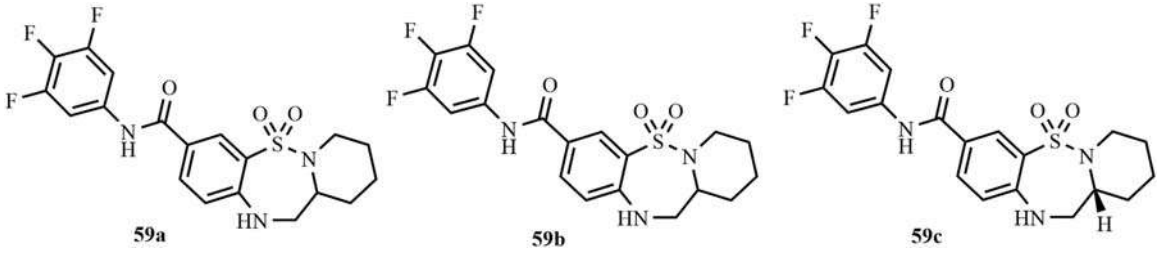


FIGURE 13.75 *N*-Sulfonyl thiadiazepine for the treatment of HBV.

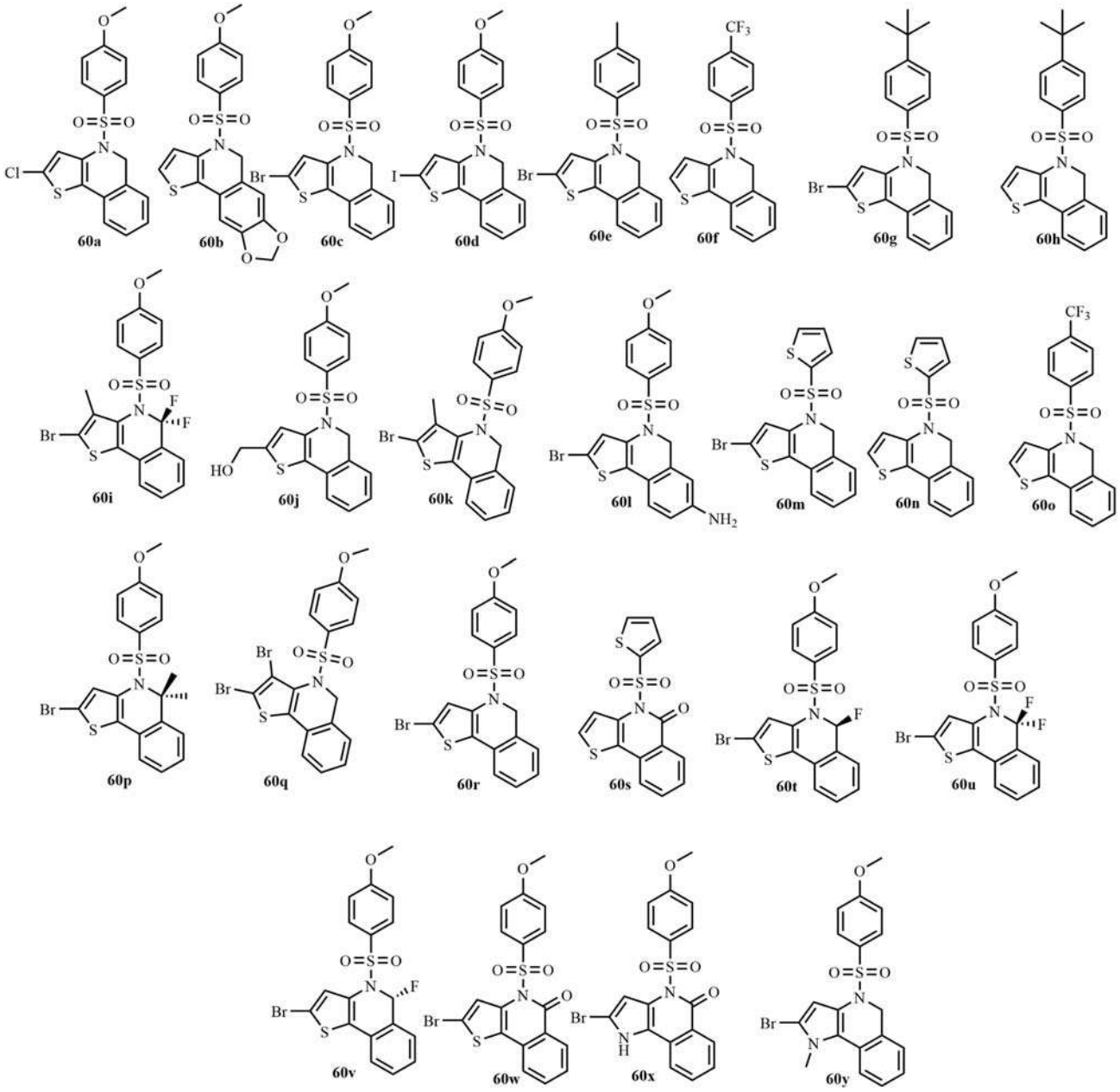


FIGURE 13.76 *N*-Sulfonyl thienoisoquinoline derivatives for the treatment of cancer.

Forgione and a co-worker developed thienoisoquinoline derivatives (**60a**−**y**, Fig. 13.76) and claimed their usefulness for the treatment of cancer if used with other anticancer or antimitotic agents to be administered either concomitantly or sequentially [181].

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Index

Note: Page numbers followed "*f*" and "*t*" refer to figures and tables, respectively.

B

C

D

E

F

G

H

I

O

P

Q

R

S

T

U

V

Y

Z

N-Sulfonated-*N*-Heterocycles

Synthesis, Chemistry, and Biological Applications

Galal H. Elgemeie, Rasha A. Azzam, Wafaa A. Zaghary, Ashraf A. Aly, Nadia H. Metwally, Mona O. Sarhan, Elshimaa M. Abdelhafez, and Rasha E. Elsayed

N-Sulfonated-N-Heterocycles covers the synthesis, chemistry, and biological applications of these compounds, focusing on pioneering synthetic approaches, mechanistic insights, and their limitations, as well as recent advances in this field. The synthesis of some of *N*-sulfonated-*N*-heterocycles and their transformation to other useful cyclic and acyclic compounds are discussed, as well as their uses as useful intermediates in the preparation of polymeric and medicinal materials. This book includes detailed methods and protocols, and the focus on applications makes this resource an essential guide for all researchers in the area of organic, medicinal, and polymeric synthetic study.

Key Features

- Reviews the use of *N*-sulfonated-*N*-heterocycles as important precursors for synthesis of biologically active compounds including information on synthetically useful transformations of *N*-sulfonated-*N*-heterocycles
- Covers this previously unreviewed branch of heterocycles and their biological evaluation in detail
- Features over 500 schemes to illustrate different synthetic pathways used for the synthesis of *N*-sulfonated-*N*-heterocycles

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