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A Review on Recent Approaches to the Asymmetric Synthesis of Aziridines Derivatives

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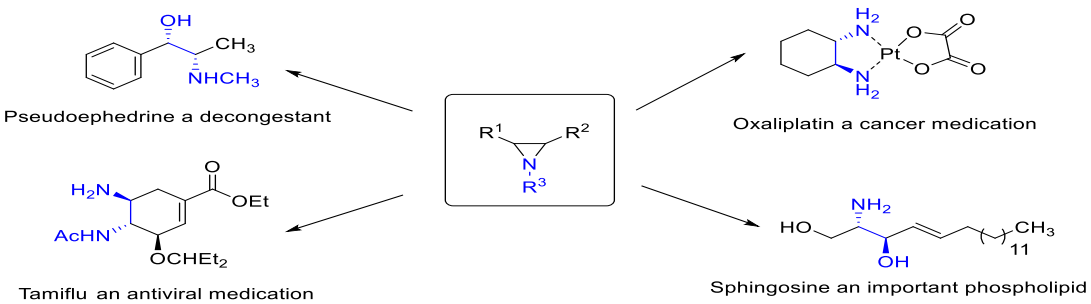
ABSTRACT

The aziridines are an important class of heterocyclic compounds that are used for the synthesis of high valuable compounds containing biological and natural products. This review summarizes the recent advances in asymmetric synthesis of aziridines derivatives employing different strategies under different conditions.

1. Introduction

Aziridines are saturated three-membered ring compounds containing a nitrogen and two carbon atoms.[1] The first report on the synthesis of aziridines derivatives from 2-bromoethylamine hydrobromide in the presence of catalytic amounts of silver oxide as a catalyst was given by Gabriel in 1888.[2,3] The interior angles of aziridines are 60° which are considerably less than preferential tetrahedral angle (109.5°). The non-ideal bond angles result angle strain and additional instability in these heterocyclic organic compound. Forasmuch as nucleophilic attack on the aziridine derivatives allow ideal bond angles in tetrahedral carbon to be restored, the aziridine derivatives show high electrophilic reactivity.[4]

The aziridine derivatives are valuable intermediates in organic synthetic transformations as a wide variety of important compounds, such as natural products exhibiting diverse biological activities and medical compounds, could be synthesized by opening their three-membered ring. The preparation of Pseudoephedrine, Sphingosine, Tamiflu and Oxaliplatin are many interesting examples in the pharmaceutical industry that utilizes an aziridine ring moiety as the key synthetic intermediate (Scheme 1).[5]



Scheme 1. The some important medical compounds can be prepared by aziridine derivatives ring opening

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In addition, the aziridine derivatives can be found within many natural products and synthetic compounds, which they exhibit a wide range of biological activities. This can be illustrated with the Food and Drug Administration (FDA) approved drugs Mitomycin C, Azicemicin A, Miraziridine A, Madurastatin A1, Ficellomycin, and Azinomycin A,B, which contain aziridine ring (Figure 1).[6]

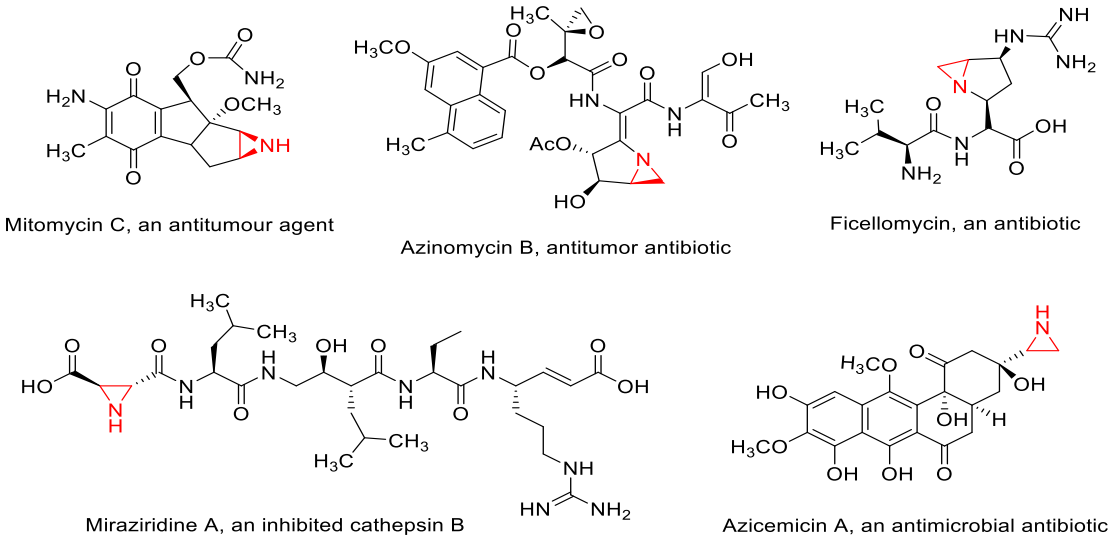
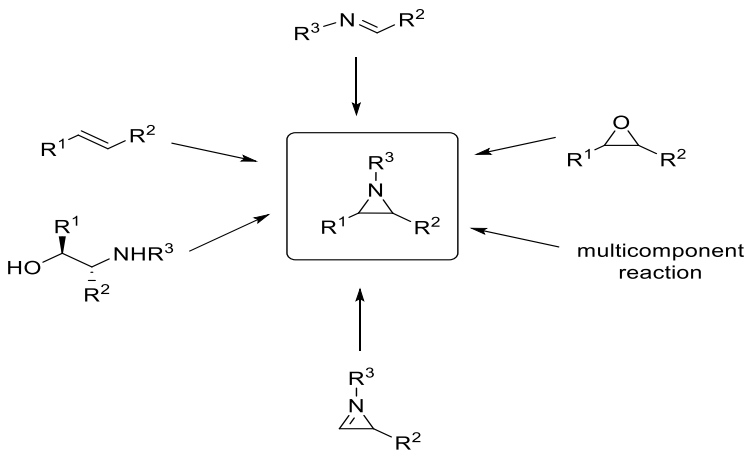


Figure 1. Some FDA-approved drugs containing aziridine rings

Therefore, the development of methods for producing of aziridine rings, especially chiral aziridines, always gets prior importance from both academic and industrial points of view. During the last decade, various approaches have been provided for producing of aziridine rings. In the present review, we have described the important and new achievements in the preparation of chiral aziridine rings. This review covers the literature which have almost all been reported during the past 5 years.

Aziridination represents a very important transformation in the field of synthetic chemistry and has been widely used to produce aziridines in both an academic and industrial scale/setting. A variety of methods have been developed to prepare aziridines derivatives, such as direct aziridination of alkenes, closure of amino alcohols, direct conversion of epoxides into to aziridines, multicomponent reaction, aziridination of imines and nucleophilic addition to 2*H*-azirines (Scheme 2).[7]

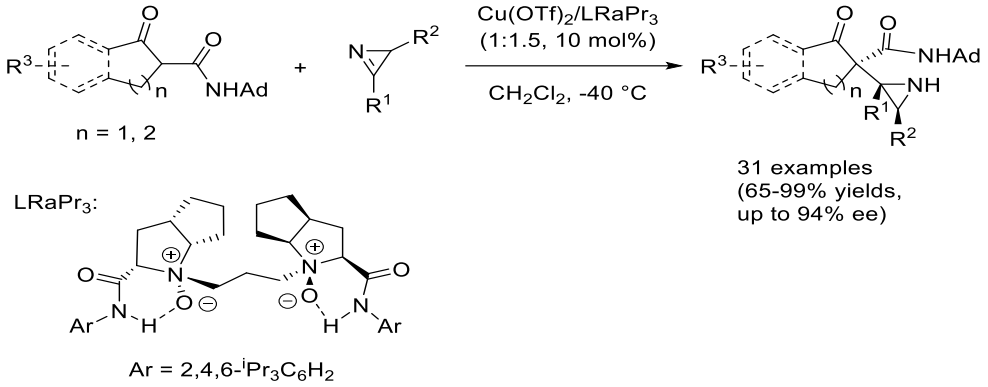
2. Synthesis of Aziridines Derivatives



Scheme 2. Various approaches for synthesis of aziridine rings

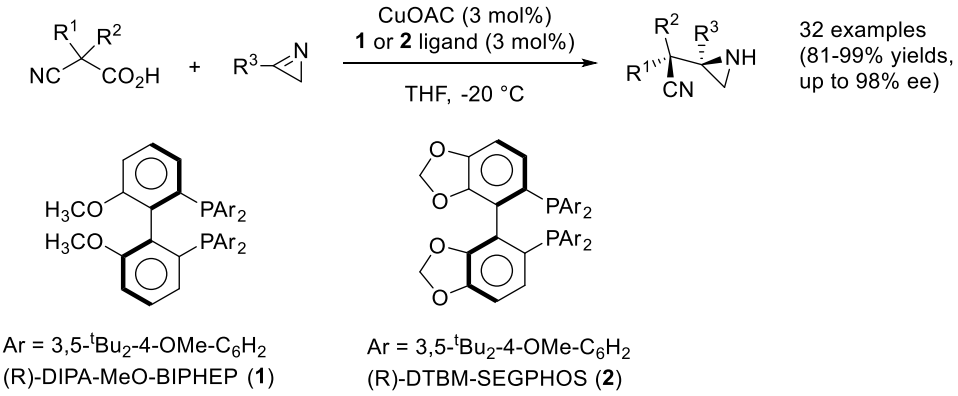
2.1. *Nucleophilic Addition to 2H-azirines*

An asymmetric nucleophilic addition of tertiary carbon nucleophiles to 2*H*-azirines using chiral *N,N'*-dioxide/Cu^{II} complex as a catalyst has been presented by Lin et al. The method afforded the corresponding chiral aziridines in mostly high yields and excellent enantiomeric purity under mild conditions (Scheme 3).



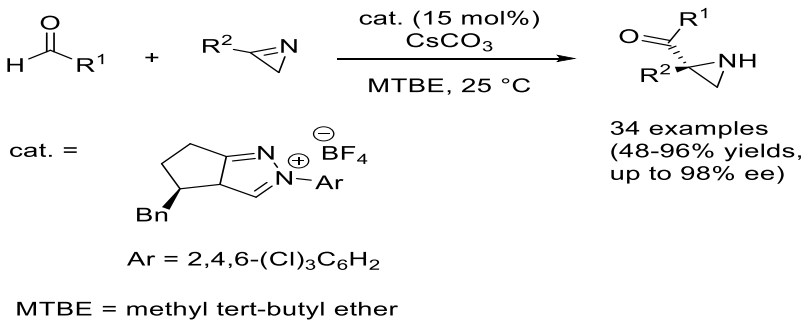
Scheme 3. The Cu^{II} complex-catalyzed asymmetric addition of tertiary carbon nucleophiles to 2*H*-azirines

In 2019, the research group Yin presented a copper(I)-catalyzed decarboxylative Mannich reaction between α,α-disubstituted cyanoacetic acids and various 2*H*-azirines. They applied 3 mol% of (R)-DIPA-MeO-BIPHEP (**1**) or (R)-DTBM-SEGPHOS (**2**) as ligand and 3 mol% of CuOAc at -20 °C and a series of chiral aziridines were obtained in good to high yields, diastereoselectivity, and enantioselectivity (Scheme 4). It is interesting to note that the method generates adjacent chiral tetrasubstituted and acyclic quaternary stereocenters.[9]



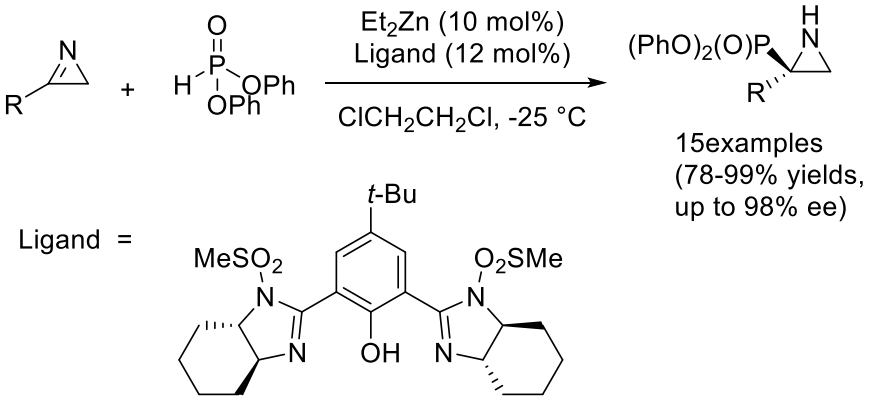
Scheme 4. The reaction between α,α-disubstituted cyanoacetic acids and 2*H*-azirines in the presence of copper(I) catalyst

Wang and co-workers established a method for the preparation of chiral aziridines *via* enantioselective aza-benzoin reaction of aldehydes with 2*H*-azirines (Scheme 5). The reaction was carried out in methyl tert-butyl ether (MTBE) at room temperature with the use of chiral Nheterocyclic carbene as catalyst. Various aromatic and heteroaromatic aldehydes reacted with 2*H*-azirines derivatives, this led to the production of optically active aziridines in good to excellent yields with excellent enantioselectivities.[10]



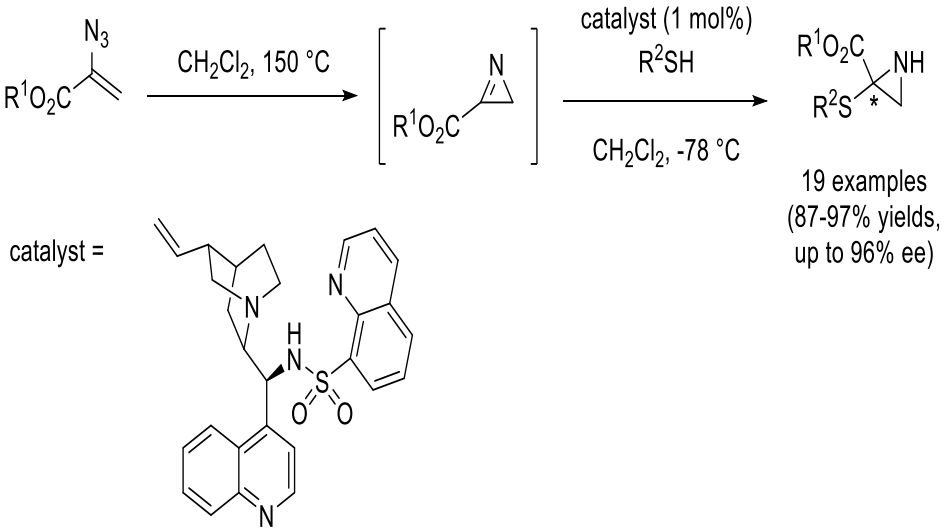
Scheme 5. Synthesis of aziridines via enantioselective reaction of aldehydes with 2H-azirines

An asymmetric nucleophilic addition of phosphites to 2*H*-azirines in the presence of novel chiral bis(imidazoline)/Zn^{II} catalysts, has been reported by Nakamura and Hayama (Scheme 6). The reaction was conducted at -25 °C, and for a number of examples the corresponding aziridines were obtained in good yield with high enantioselectivity.[11]



Scheme 6. Enantioselective reaction of phosphites with 2*H*-azirines

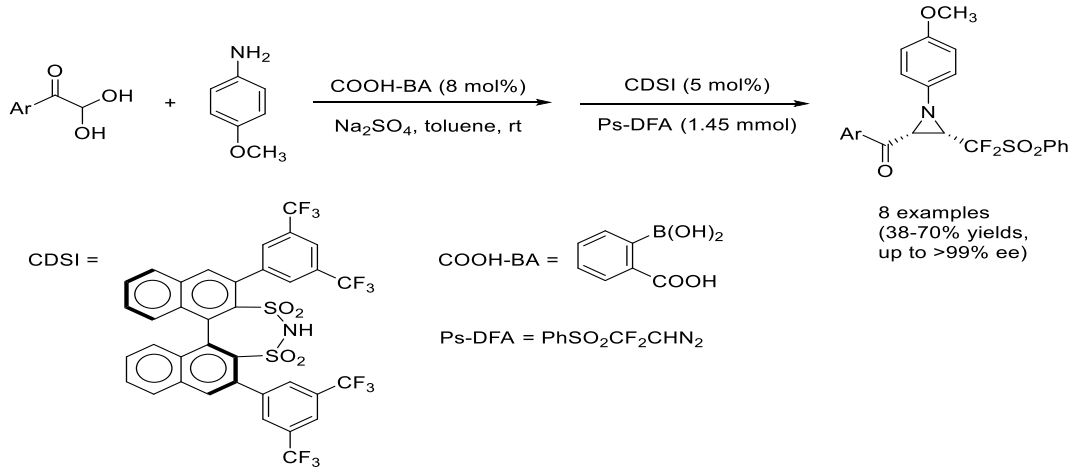
Nakamura and co-workers described first catalytic enantioselective reaction of 2*H*-azirines with thiols (Scheme 7)**.** A large number of 2*H*-azirines, which were generated in situ by heating α-azidoacrylates, were treated with thiols in the presence of cinchona alkaloid sulfonamide catalysts in CH_2Cl_2 at -78 °C to afford the aziridines derivatives in high to excellent yields and with high enantioselectivities. The authors also showed that the synthesized aziridines can be converted into various chiral compounds such as oxazolines, aziridylamides and α-sulfonyl esters.[12]



Scheme 7. The catalytic enantioselective reaction of *in situ* generated 2*H*-azirines with thiols to afford aziridines derivatives

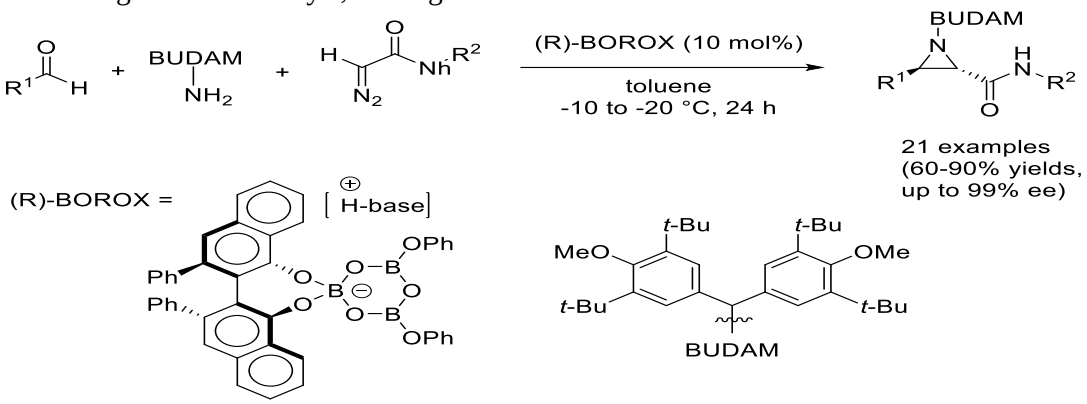
2.2. *Multicomponent Reaction for Synthesis of Aziridines*

More recently in 2020, a diastereo- and enantioselective reaction to achieve CF_2-functionalized aziridines has been rdeveloped (Scheme 8). The authors showed that *in situ*-generated aldimines from reaction of phenylglyoxal monohydrate and 4-methoxyaniline in the presence Brønsted acid, were treated with difluorodiazoethyl phenyl sulfone ($PhSO_2CF_2CHN_2$). This multicomponent reaction afforded the corresponding CF_2-functionalized aziridines mostly in good yields and with excellent stereoselectivities, under mild conditions.[13]



Scheme 8. Preparation of chiral CF_2-substituted aziridines

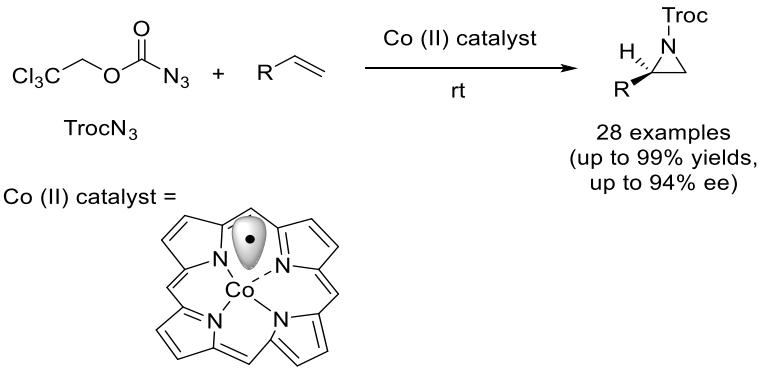
The research group of Wulff reported a one-pot multicomponent reaction of amines, aldehydes, and diazo compounds using BOROX catalyst, leading to a novel asymmetric synthesis of trans-aziridines derivatives (Scheme 9).[14]



Scheme 9. Multicomponent asymmetric synthesis of trans-aziridines

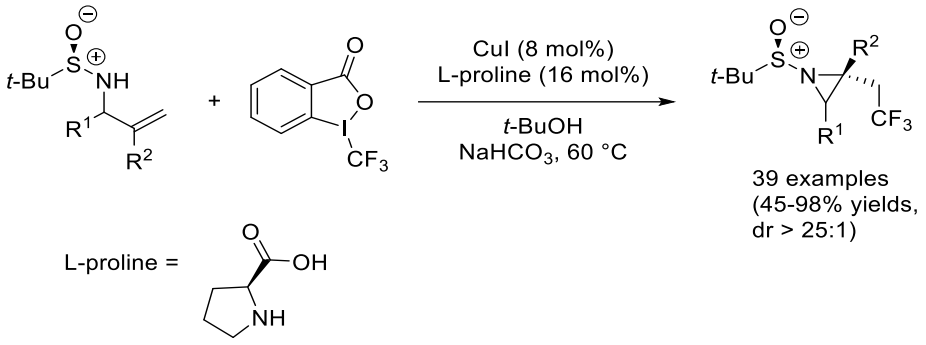
2.3. Aziridination of Alkenes

A new report on the enantioselective aziridination of olefins catalyzed by a Co(II)-based metalloradical system was published by Zhang *et al.* in 2021. In this transformation carbonyl azides was used as an effective nitrogen sources for asymmetric aziridination of carbon-carbon double bonds. The reaction was carried out at room temperature and led to the chiral aziridine products in good to excellent yields and high enantioselectivities (Scheme 10).[15]



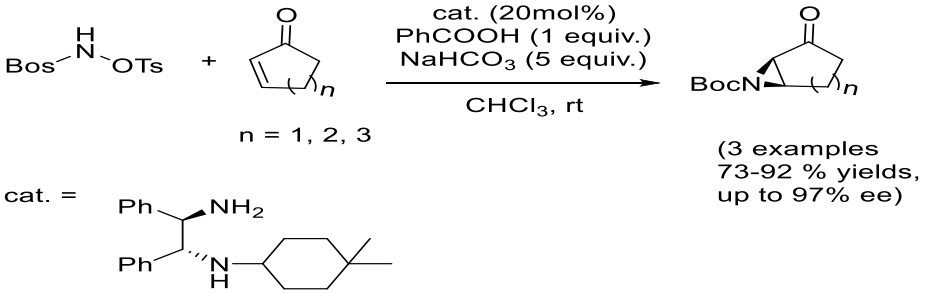
Scheme 10. Enantioselective aziridination of olefins using Co(II)-based metalloradical system

A copper(I)-catalyzed process for synthesis of aziridines possessing multiple chiral substitutions was reported by Qin and co-workers in 2020. This system introduced a Cu(I)/L-proline complex as an effective catalysts. The reaction was performed in the presence of in sodium bicarbonate in *t*-BuOH at 60 °C and offers a straightforward access to CF_3-containing aziridines bearing either an α-tertiary or a α-quarternary stereocenter in good yield and with high diastereoselectivity (Scheme 11).[16]



Scheme 11. Synthesis of aziridines with multiple chiral substitutions

A highly effective organocatalytic system for asymmetric aziridination of cyclic enones has been reported. The catalytic asymmetric aziridination proceeded using (1R,2R)-1,2-diphenylethylenediamine derivative producing chiral aziridine ketones in high yields with up to 99% ee (Scheme 12).[18]

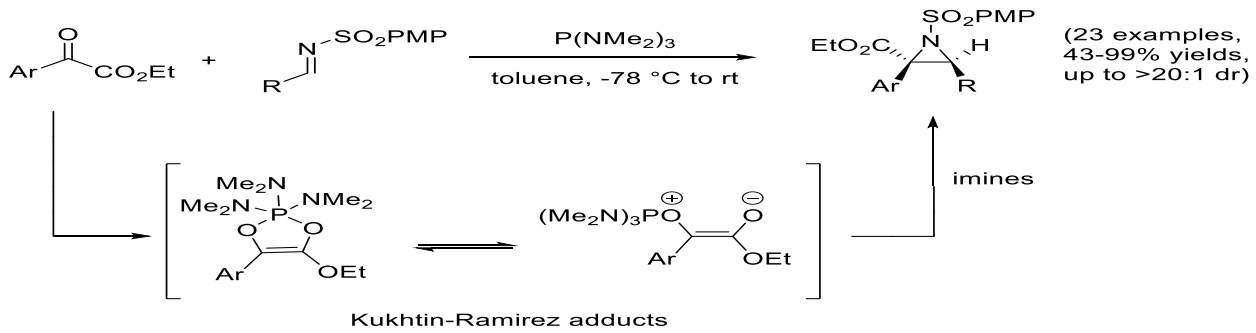


Scheme 12. Asymmetric aziridination of cyclic enones

2.4. Aziridination of Imines

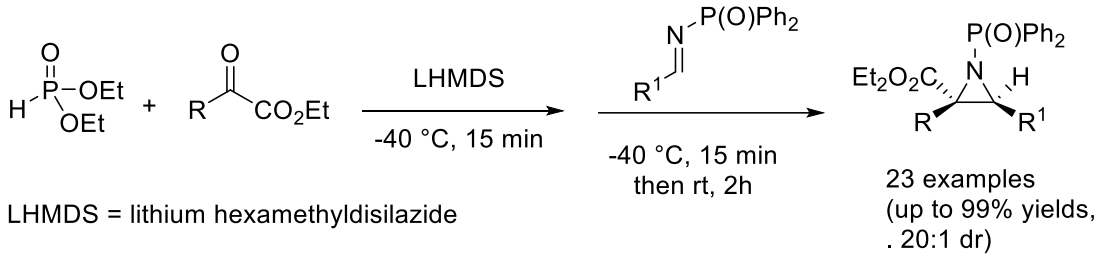
$P(NMe_2)_3$-mediated diastereoselective aziridination of imines with α-ketoesters has been elaborated by Jiang and co-workers. In the presence of $P(NMe_2)_3$ the aziridination reaction could be conducted in toluene, at or below room temperature, to afford a range of aziridine-2-carboxylates in good to excellent yields and high diastereoselectivities (up to 99:1 dr). The diastereoselectivity obtained was found to be dependent on steric hindrance from substituents on the substrates (Scheme 13).

The authors proposed a mechanism that involves Kukhtin-Ramirez adducts possess in the initial step, followed by reaction of the Kukhtin-Ramirez adducts with *N*-sulfonyl imines compounds to form the aziridine-2-carboxylates products.[18]



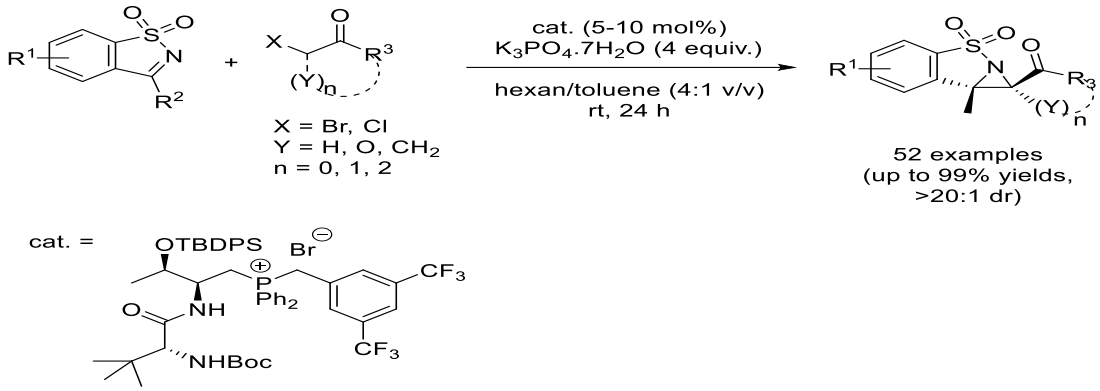
Scheme 13. The preparation of aziridine-2-carboxylates

Lu et al. have reported an efficient method based on phosphate diester initiated coupling of α-ketoesters with *N*-diphenylphosphinyl imines in the presence of lithium hexamethyldisilazide (LHMDS) for preparation of trans-aziridine-2-carboxylates (Scheme 14). In this approach, the trans-aziridine-2-carboxylates were achieved in high yields with excellent diastereoselectivities.[19]



Scheme 14. Diethyl phosphite-initiated coupling of α-ketoesters and iminesa

Wang et al. described an efficient procedure for the enantioselective aziridination of imines. A large number of cyclic imines were treated with α-halogenated ketones in the presence of amino acid-derived bifunctional phosphonium salts as phase-transfer promoters under mild reaction conditions (Scheme 15). A wide variety of highly functionalized aziridines were prepared in high yields with excellent diastereoand enantioselectivities (up to >20:1 dr and >99.9% ee).[20]



Scheme 15. Enantioselective synthesis of aziridines

3.Conclusions

In summary, various protocols have been provided for producing of aziridine rings. In the present review, we have described the important and new achievements in the preparation of chiral aziridine rings. We believe, this review will be helpful for organic chemists and even biochemists and pharmacologists.

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