

Stereoselective reactions with imines*

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Abstract: By the activation of general imines or using activated imines (*N*-tosylimines or *N*-diphenyl-phosphinoylimines), we developed three types of stereoselective reactions with imines: aldol reaction, allylation, and aziridiation, and optically active 2-imidazolines and aziridines were obtained. According to experimental evidences, Sakurai-Hosomi reactions in the presence of catalytic amount of TBAF was demonstrated to be a fluoride-triggered autocatalytic mechanism. In addition, optically active 2,3-diamino acids were also synthesised conveniently by chemical transformations of 2-imidazolines.

INTRODUCTION

Nitrogen containing compounds are very widely distributed in nature and are essential to life, they play a vital role in the metabolism of all living cells. At present, greater than 75% drugs and drug candidates incorporate amine functionality [1]. The synthesis of these nitrogen-containing compounds by the easily available imine is one of the most important and convenient routes. However, as compared with the counterpart, C=O double bond, C=N double bond is a less explored area. C=N double bond and C=O double bond are seemingly very similar, but some differences do exist between them (a) imines are not always easily prepared, especially for the ketimine; (b) for the aliphatic imines, if there is an α -hydrogen, the imines can be isomerized to enamines [2]; (c) aldehydes or ketones have no geometric isomer, but two geometric isomers are possible in imines, in general, the *trans*-isomer is usually preferred by stereochemical consideration; (d) by the difference in electronegativity [2], their reactivity toward nucleophilic addition are quite different, it is well recognised that aldehyde is more reactive than imines toward nucleophilic reagent. Recently, several examples have shown that the relative reactivity of aldehydes and aldimines could be reversed by using some kinds of metal complexes or Lewis acids. Many synthetic methods by imines have been developed [3]. In this account, our research work on stereoselective reactions with imines (Scheme 1), especially aldol reaction, allylation, aziridination of imines and their applications in organic synthesis are reviewed.

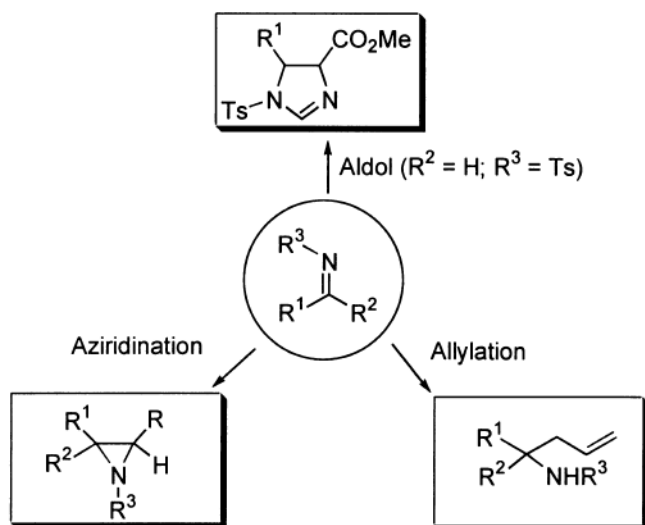
ALDOL REACTIONS WITH IMINES

The construction of five-membered nitrogen-containing heterocycles, such as oxazoline and imidazoline, has received considerable attention because of the wide application of these compounds to the synthesis of biologically active compounds [4]. Gold complex-catalysed aldol reactions of isocyanoacetate and aldehydes have been reported to give 4,5-disubstituted-2-oxazolines efficiently [5a,5b]. One of us found that the above reaction could also be catalysed by using a dihydride ruthenium complex successfully [5c]. We further turned our attention to the similar aza-aldol reaction.

When *N*-alkyl or *N*-aryl-substituted imines were used instead of aldehydes in these reactions, no products were isolated. Given the low reactivity of imines in nucleophilic addition, a strong electron-withdrawing group, i.e. sulfonyl, was introduced on the nitrogen atom of imines in order to activate the

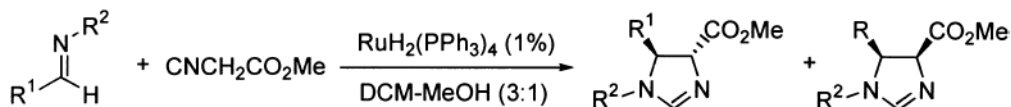
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Scheme 1

C=N double bond. Fortunately, we found that transition metal complexes catalysed the reaction smoothly. The optimum condition is as follows: $\text{RuH}_2(\text{PPh}_3)_4$ /25 °C/MeOH:DCM (3:1) (Scheme 2).



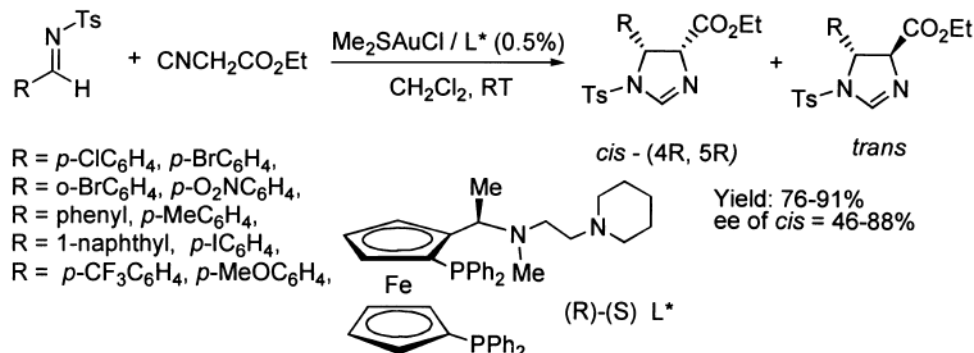
R^1 = Aryl or *t*-Bu
 R^2 = Ts or PhSO_2

Yield: 75-90%
 $\text{trans} : \text{cis} = 84:16\text{-}95:5$

Scheme 2

The reaction occurs with *N*-sulfonylimines prepared from aromatic, heterocycle, α,β -unsaturated, and *t*-Bu-aldehydes. In all cases, the *trans*-2-imidazolines were obtained with high selectivity and yield [6]. The results indicate that Ru(II)-complex-catalysed aldol reactions of *N*-sulfonylimines are highly efficient in yield and stereoselectivity under neutral condition.

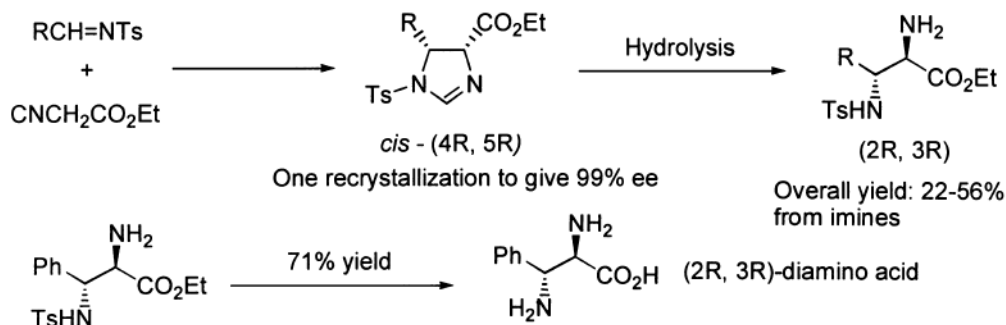
In 1986, Hayashi and Ito *et al.* reported an elegant asymmetric synthesis using cationic bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate catalysed aldol reaction in the presence of chiral ferrocenylphosphine ligands. The reaction of methyl isocyanacetate with aldehydes catalyzed by cationic chiral gold complexes showed high enantioselectivity with enantiomeric excess as high as 97–99%. To probe the ability of the above catalyst with chiral ferrocenylphosphine ligand to induce the enantioselectivity in the similar aldol reaction with imines, we examined the reaction under identical conditions. On treatment of methyl isocyanacetate with *N*-tosyl-*p*-chlorobenzaldimine in the presence of cationic chiral gold(I) complex, the ee values of *cis* and *trans*-2-imidazolines obtained is low (14%). Interestingly, when the neutral gold(I) complex Me_2SAuCl with chiral ferrocenylphosphine was used as catalyst, the asymmetric induction of this reaction could be brought to good levels (Scheme 3).



Scheme 3

By screening some ferrocenylphosphines ligands and Au(I) species, the optimum reaction condition is as follows: $\text{Me}_2\text{SAuCl/L}^*/\text{DCM}/25^\circ\text{C}$, and moderate to good ee values were obtained [7]. The best result (88% ee) was obtained in the use of *N*-tosyl-*p*-iodobenzaldimines and ethyl isocyanoacetate in the present condition. Though the ee is not very high, it can be efficiently upgraded by a single recrystallization from THF/hexane to obtain optically pure 2-imidazolines.

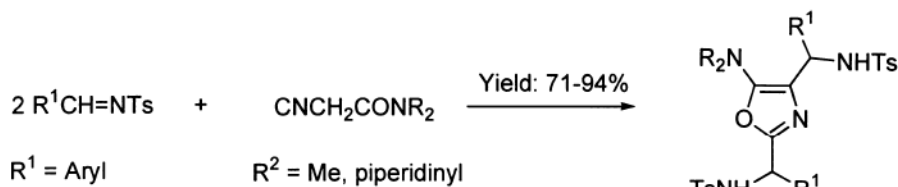
The imidazolines obtained by this reaction can be used in the the synthesis of various substituted 2,3-diamino acids or diamino alcohols (6), which are constituents of some peptidic antibiotics as well as other biologically active molecules. Optically pure 2,3-diamino acids can also be obtained by the simple hydrolysis and deprotection of these chiral 2-imidazolines that were upgraded by crystallisation (Scheme 4).



Scheme 4

Since five-membered heterocycles containing nitrogen atoms have extensive applications in the synthesis of biologically active compounds, our continuing interest in catalytic aldol reaction has led us to extend the catalytic reaction of isocyanoacetate to isocyanoacetamide. However, no desirable 2-imidazoles were obtained, unexpected heterocyclic compound oxazoles were gained (Scheme 5). Control experiment was carried out in DCM at room temperature between isocyanoacetamide and *N*-tosylimines with no transition metal catalyst. Surprisingly, the same yellow solid was isolated in high yield. By the analysis of ^1H NMR, elemental analysis and FAB-MS data, we found that this was an addition product of one equivalent isocyanoacetamide with two equivalent *N*-sulfonylimines [8].

The results of ^1H NMR/ D_2O exchange and IR indicated two active hydrogens in the addition products which was assigned as NH group, IR showed no sign of the presence of isocyano and amide carbonyl functionalities, indicating the ring closure of amide carbonyl on the isocyanide carbon. Thus the structure of addition product was identified as 2,4-disubstituted-5-amino-1,3-oxazole as shown in Scheme 5 and confirmed by X-ray crystallographic analysis.



Scheme 5

Oxazoles have attracted considerable interest as starting materials and important building block for the synthesis of more complex molecules and macrocyclic antibiotics. The reaction of *N*-sulfonylimines with isocyanoacetamide reported herein provides a facial and efficient method for the construction of trisubstituted oxazoles with same or different 2,4-disubstituted groups. Moreover, the trisubstituted oxazoles can be easily converted into the corresponding polyamines, dipeptides and useful building blocks for the synthesis of the biologically active compounds.

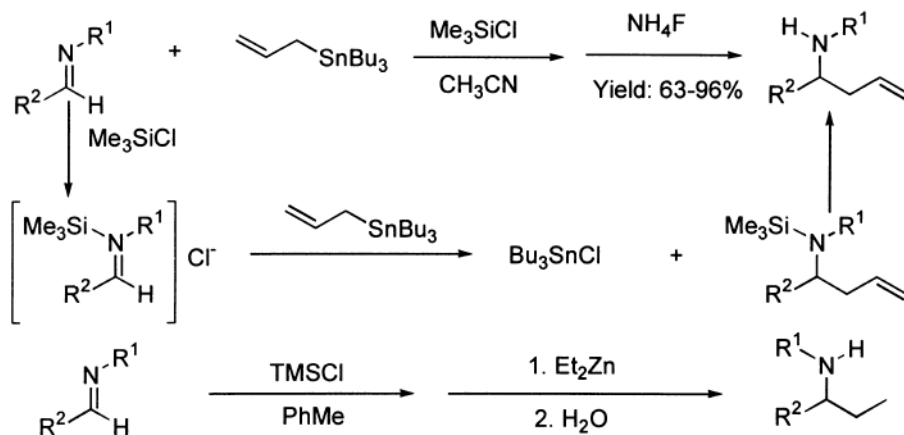
ALLYLATION WITH IMINES

Homoallylamines are important building blocks. Addition of allylic organometallic species to imines and its derivatives constitutes a potentially valuable method for the preparation of homoallylamines [1]. In the

continuing interest in nitrogen-containing polyfunctionalized compounds [9], we studied three types of allylations with general imines.

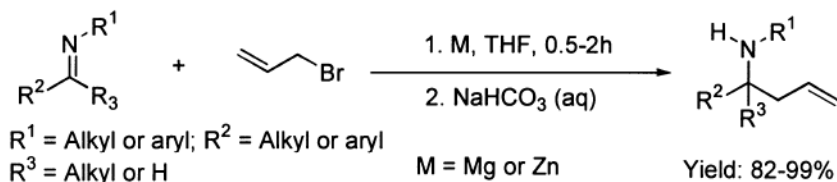
III-1. Allylstannane allylation of aldimines activated by trimethylchlorosilane: The selectivity and functional group compatibility of the allylation by allylstannane make this reaction complementary to other organometallic reactions in constructing carbon-carbon bonds. Today the Lewis acid-promoted addition of allylstannane to aldehydes is well established as a powerful synthetic method. On the contrary, only a handful of papers on the allylation reaction of imines by allylstannane were reported. In general, the difficulty of the nucleophilic addition to aldimines lies in the low reactivity of imines towards nucleophilic addition of allylstannane. Similar to addition of aldehydes, Lewis acid activation of aldimines with $\text{BF}_3 \cdot \text{OEt}_2$ or TiCl_4 has also been employed in the allylation of aldimines by allylstannane. The yields were only fair to good even under careful manipulation. Therefore, the new activation method is still an important target. Recently, TMSCl was used to promote the allylation of the $\text{C}=\text{O}$ bond by allylstannane. Based on this strategy, we developed a practical method for allylation of aldimines using the silicon based reagents for activation of imines with the advantage of the easily removable silicon group [10]. The best condition (Scheme 6) is as follows: $\text{Me}_3\text{SiCl}/\text{MeCN}/\text{RT}$.

The activation of imines through the formation of iminium salt with TMSCl renders the allylation by allylstannane to be an easy, efficient and high yield reaction. This reaction provides an easy access of transforming aldimines to homoallylamines. In addition, by the activation of TMSCl , we also realized the addition of diethyl zinc to general imines [11] (Scheme 6).



Scheme 6

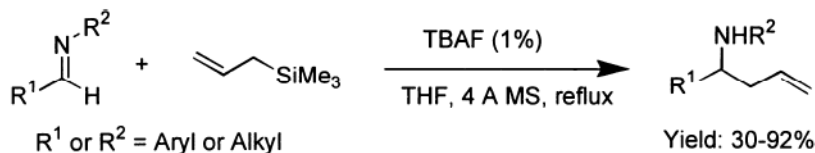
III-2. Mg and Zn mediated allylation of imines with allyl bromide: Barbier-type imines allylation is an alternative route to homoallylamines [12], the mild reaction condition, function group compatibility, high yield could be their merits. However, practical methods for the synthesis of homoallylamines *via* Barbier-type reaction with easily available metal remains undeveloped. We report herein that aldimines and ketimines are efficiently allylated by magnesium foil or commercial zinc powder without any activator under simple Barbier-type conditions [13] (Scheme 7).



Scheme 7

Imines derived either from aromatic, aliphatic, heteroaryl, and α,β -unsaturated aldehydes or from aromatic and aliphatic ketones, all reacted with the *in situ* generated allylic metallic species in the usual way to produce the corresponding homoallylamine in excellent yields. These results contrast with that of the reported Barbier-type allylation system and the readily made allylic organometallic reagents in term of high efficiency and less limitation for the substrates.

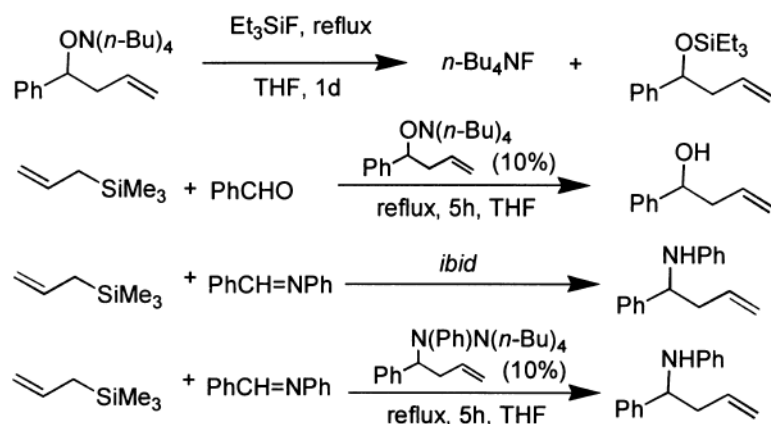
III-3. Fluoride-triggered allylation of imines with trimethylallylsilane and experimental evidences: Sakurai and Hosomi *et al.* described the allylation of carbonyl compounds with allyltrimethylsilane under Lewis acid condition or in the presence of catalytic quantities of fluoride ions [14]. In contrast to the reaction with C=O bond, little is known about its aza-analogue, that is the reaction between allylsilane and aldimine to give homoallylamine. Recently, only the allylation of aldimines with excess amount of fluoride were reported [15]. To the best of our knowledge, the reaction of allylsilane with imines in the presence of catalytic amount of fluoride anion has never been reported. By optimising the reaction conditions, Sakurai-Hosomi reactions with imines in the presence of catalytic amount of fluoride anion came true. The condition is as follows: *n*-Bu₄NF (1%)/THF/4Å MS/reflux (Scheme 8). The yields are good.



Scheme 8

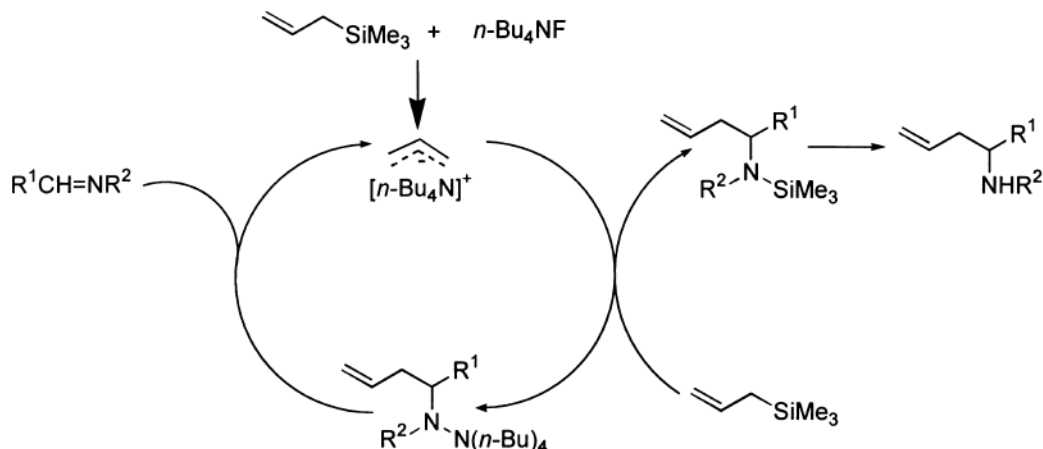
The reaction of allylsilane with an imine bears close analogy to the reaction with a carbonyl compounds. For the latter reaction, the so-called Sakurai-Hosomi reaction, two possible mechanisms have been proposed. The first mechanism they proposed is a fluoride ion catalysed reaction [14]. The key point is that the released TMSF reacts again with alcoholate salt to regenerate the fluoride ion. However, the same author worried about the low boiling point of Me₃SiF (16.4 °C) which might not exist in the reaction system. Anyhow, this mechanism is still mentioned even in a recent monograph of review book [16]. The second is an autocatalytic mechanism, the fluoride ion just served as an initiator of reaction and no more involved in the catalytic cycle, the strong basic alcoholate salt reacts with allylsilane and then regenerate the active species and complete the catalytic cycle. The authors, however, did not preclude the possibility of participation of a hypervalent silicon intermediate [CH₂=CHCH₂SiFMe₃]⁻. These two mechanisms appear in the author review article as two possible alternatives without affirmative conclusion.

We deem that the first fluoride catalyzed reaction is probably not operate, not only because the low boiling point of Me₃SiF, but also due to the bond energy of Si-F (561 kJ/mol) is much higher than that of Si-O (442 kJ/mol) and Si-N bond (316 kJ/mol). So the metathesis between Me₃SiF and alkoxy anion is not favourable thermodynamically. In order to clarify this point, we synthesized the Et₃SiF, and key intermediate alkoxy anion which was included both in fluoride catalyzed mechanism and autocatalytic mechanism. First, when Et₃SiF and tetrabutylammonium alkoxy anion salt were refluxed together in THF, no triethylsilyl alkyl ether formed even for a prolonged time. This indicated that Me₃SiF could not act as a catalytic species to regenerate the fluoride ion. Furthermore, when catalytic amount of alkoxy anion was used in place of fluoride for the Sakurai-Hosomi reaction of allylsilane with aldehyde or imine, both homoallyl alcohol and homoallylamine were obtained in good yields (Scheme 9). The last reaction of Scheme 9 confirmed directly that the tetra-*n*-butylammonium salt of the amide could catalyse the reaction with imines.



Scheme 9

The experimental evidences showed that the fluoride ion only served as a trigger in this reaction, could not act as a catalytic species to regenerate $n\text{-Bu}_4\text{NF}$. It also showed that the autocatalytic cycle formed by the alkoxide ion is most probable and the fluoride catalysed mechanism should be rejected. Based on this argument, a possible mechanism of allylation of imines with allyltrimethylsilane is proposed (Scheme 10).

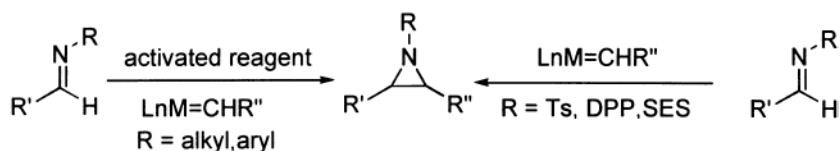


Scheme 10

Allylation of aldimines with allyltrimethylsilane triggered by catalytic amount of TBAF under mild condition and easy workup is realised. The method represents the first example of catalytic allylation of imines by allylsilane.

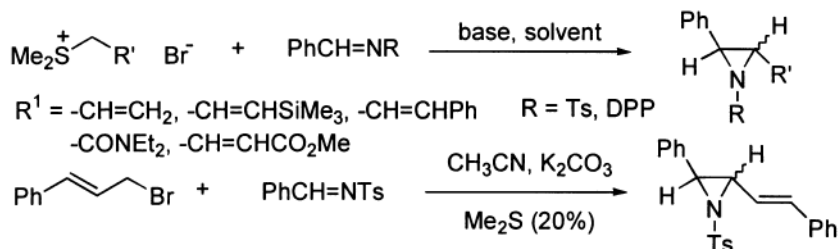
AZIRIDINATION WITH IMINES

The fact that aziridination *via* an ylide route has not been extensively explored may be rationalized by the relatively low reactivity of common N -alkyl and N -arylimines toward nucleophilic attack as compared to that of carbonyl compounds and α,β -unsaturated compounds (cyclopropanation). The low reactivity of an ordinary imine can be enhanced by either introducing an electron-withdrawing group on the N -atom or by using a Lewis acid to activate the $\text{C}=\text{N}$ bond (Scheme 11).

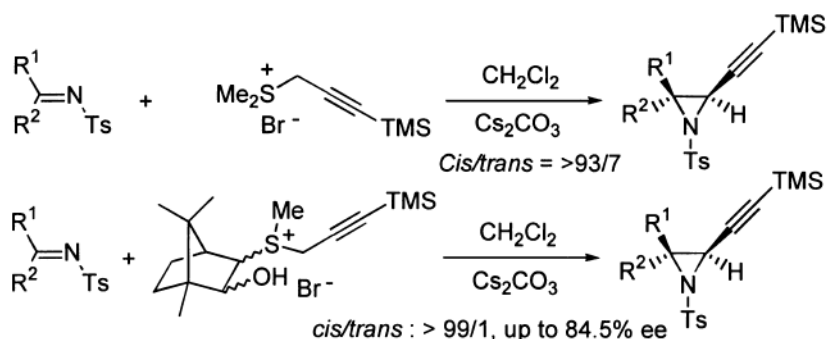


Scheme 11

Semiempirical AM1 calculations indicated that the qualitative order of electrophilicity is $\text{PhCH}=\text{NTs} > \text{PhCH}=\text{NDPP} > \text{PhCHO} \gg \text{PhCH}=\text{NPh}$. Fortunately, activated N -tosylimines or N -diphenylphosphinoylimines can smoothly react with all kinds of semistabilized sulfonium ylides to give aziridines [17]. A catalytic aziridination is also realised by employing a catalytic amount of Me_2S under solid-liquid phase transfer conditions [18] (Scheme 12).



Scheme 12



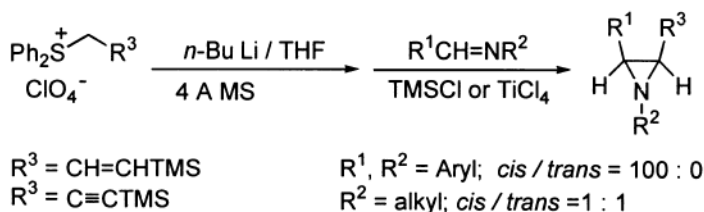
Scheme 13

In all of the above reactions, a mixture of *trans/cis* isomers was obtained. After numerous investigations, exclusive *cis* selectivity was achieved by the reaction of *N*-sulfonylimines with propargylic ylides under phase-transfer conditions [19] (Scheme 13).

The high stereoselectivity enabled us to realize a reagent-controlled asymmetric aziridination by an ylide route. Chiral sulfonium salts were synthesized by the reaction of camphor-derived chiral sulfides with 3-bromo-1-trimethylsilylpropyne. Under solid-liquid phase transfer conditions, optically active acetylenylaziridines [19] were obtained in high yields and moderate to good ee values. Opposite asymmetric induction was achieved with sulfonium salts containing *exo* and *endo*-sulfido groups.

The addition of carbenoids or ylides to a C=N double bond has been demonstrated as a synthetic strategy for aziridination in recent years. However, the ylide and carbenoids methodologies can only be applied to an activated imine, that is C=N double bonds with an *N*-electron-withdrawing group, such as Ts, DPP or SES [17–19]. No report appeared for the reaction of a nonactivated imine with a semistabilized or stabilized ylide. Considering the vigorous conditions required for the deprotection and the difficulties in the preparation of activated imines from certain carbonyl compounds, developing a general and facile method for the aziridination of common *N*-alkyl and *N*-aryl imines is a challenge.

Encouraged by the successful activation of imines by Lewis acids in allylation reactions [10] and aziridination of $\text{BF}_3 \cdot \text{OEt}_2$ activated imines with ethyl diazoacetate [20], we examined the $\text{BF}_3 \cdot \text{OEt}_2$ and TMSCl activation of imines in the ylide reaction for the preparation of vinyl- and ethynyl-aziridines [21] (Scheme 14). A variety of aromatic aldimines, either *N*-aryl or *N*-alkyl, could be aziridinated with good to excellent yields, but aziridination failed when aliphatic aldimines were used as substrates. The stereoselectivity of the aziridination is strongly dependent on the nature of the group on the nitrogen atom of the imines: *N*-aryl aromatic aldimines gave purely the *cis*-aziridine, while *N*-alkyl aromatic aldimines gave a mixture of *cis* and *trans* aziridines.



Scheme 14

CONCLUSION

Stereoselective reactions with imines are important approach to obtain nitrogen-containing compounds. By the activation of general imines or using activated imines (*N*-tosylimines or *N*-diphenylphosphonylimines), we developed three types of reactions with imines, aldol reaction, allylation, and aziridiantion, optically active 2-imidazolines and aziridines were also obtained. In addition, the mechanism of Sakurai–Hosomi reaction in the presence of catalytic amount of TBAF have been discussed, the fluoride ion catalysed mechanism is precluded according to experimental evidences, the

fluoride-triggered autocatalytic mechanism is a most probable one. By the chemical transformations of reaction products of imines, we synthesized optically active 2,3-diamino acids and some chiral building blocks. These features, together with the generality of these methods and easy available imines, make these reactions valuable tools for organic synthesis.

ACKNOWLEDGEMENTS

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