# Lewis acid promoted aziridination of imines with semistabilized sulfonium ylides: highly stereoselective synthesis of vinyl- and ethynyl-aziridines

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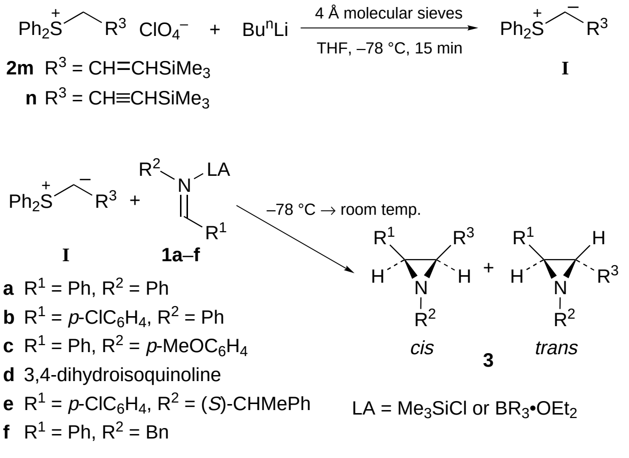
***cis*-Vinyl- and *cis*-ethynyl-aziridines are furnished in high yields and high stereoselectivity by aziridination of unactivated *N*-aryl or *N*-alkyl imines with S-ylides in the presence of Lewis acids.**

The addition of carbenoids[1] or ylides[2] to a C=N double bond has been demonstrated as a synthetic strategy for asymmetric aziridination in recent years, and is regarded as an alternative methodology to the reaction between nitrenoids and a C=C double bond.[3] However, the ylide and carbenoid methodologies can only be applied to an activated imine, that is to C=N double bonds with an *N*-electron withdrawing group (*N*-EWG), such as *p*-tolylsulfonyl (tosyl),[1a,2] diphenylphosphinyl (DPP)[2a,4] or 2-(trimethylsilyl) ethylsulfonyl (SES).[2a] Although the preparation of aziridines from an unactivated imine with an ylide has been documented, the ylide used is restricted to active ylides such as dimethylsulfonium methide or dimethylsulfoxonium methide, *i.e.* methylene transfer to C=N bond. No report has appeared of the reaction of an unactivated imine with a semistabilized or stabilized ylide. Considering the vigorous conditions required for the deprotection of the tosyl group from the *N*-atom[5] and the difficulties in the preparation of *N*-tosyl,[6a,b] *N*-DPP[6c] and *N*-SES[6d] imines from certain carbonyl compounds, developing a general and facile method for the aziridination of common *N*-alkyl and *N*-aryl imines with stabilized or semistabilized ylides is still a challenge. Encouraged by the successful activation of imines by Lewis acids in the allylation reaction,[7] we examined $BF_3{\bullet}OEt_2$ and $Me_3SiCl$ activation of imines in the ylide reaction for the preparation of vinyl- and ethynyl-aziridines. In a recent paper,[8] ethyl diazoacetate was used to react with a $BF_3{\bullet}OEt_2$ activated imine in the preparation of aziridines, which promoted us to report our own results. Thus, a new and general ylide aziridination of common *N*-alkyl and *N*-aryl imines with semistabilized allylic or prop-2-ynylic sulfonium ylides in the presence of $BF_3{\bullet}OEt_2$ or $Me_3SiCl$ has been successfully realized not only with high yields but also with high stereoselectivity, and disclosed these results herein (Scheme 1).



**Scheme 1**

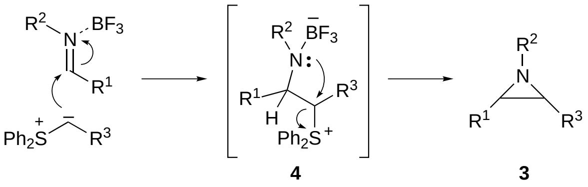
Treatment of a THF solution of sulfonium salts **2** with 1 equiv. of *n*-butyllithium at −78 °C for 15 min gave a deep-red solution of sulfonium ylide.[9] This was added to an equimolar THF solution of imine **1** and $Me_3SiCl$ (method A) or $BF_3{\bullet}OEt_2$ (method B) at the same temperature with stirring. The temperature of the mixture was allowed to rise to room temperature, and aziridine **3** was formed as the only product. In the absence of $Me_3SiCl$ or $BF_3{\bullet}OEt_2$, no aziridine **3** was formed even on extended stirring under the same conditions. In terms of the yield of aziridine, the reaction proceeded more efficiently using $BF_3{\bullet}OEt_2$ as Lewis acid (method B) than $Me_3SiCl$. The ratio of the *cis*- and *trans*-products was determined by $^1H$ NMR analysis. Our best results were obtained in THF in the presence of 4 Å molecular sieves and are summarized in Table 1.†

As shown, a variety of aromatic aldimines, either *N*-aryl or *N*-alkyl, could be aziridinated with good to excellent yield, 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 imine: *N*-aryl aromatic aldimines gave purely the *cis*-aziridine (entries 1–12), while *N*-alkyl aromatic aldimines gave a mixture of *cis* and *trans* aziridines (entries 17–22). By not using an

**Table 1** Preparation of 2-vinylaziridines **3m** and 2-ethynylaziridines **3n** by the reaction of γ-trimethylsilyl-allyl and -prop-2-ynyl sulfonium ylides and aldimines mediated by Lewis acids[a]

| | **1** | | | | | |
|---|---|---|---|---|---|---|
| Entry | $R^1$ | $R^2$ | **2** | Method[b] | % Yield (**3**)[c] | *cis* : *trans*[d] |
| 1 | Ph | Ph | **2m** | A | 89 (**3ma**) | 100 : 0 |
| 2 | Ph | Ph | **2m** | B | 92 (**3ma**) | 100 : 0 |
| 3 | Ph | Ph | **2n** | A | 83 (**3na**) | 100 : 0 |
| 4 | Ph | Ph | **2n** | B | 89 (**3na**) | 100 : 0 |
| 5 | *p*-$ClC_6H_4$ | Ph | **2m** | A | 75 (**3mb**) | 100 : 0 |
| 6 | *p*-$ClC_6H_4$ | Ph | **2m** | B | 91 (**3mb**) | 100 : 0 |
| 7 | *p*-$ClC_6H_4$ | Ph | **2n** | A | 85 (**3nb**) | 100 : 0 |
| 8 | *p*-$ClC_6H_4$ | Ph | **2n** | B | 84 (**3nb**) | 100 : 0 |
| 9 | *p*-$MeOC_6H_4$ | Ph | **2m** | A | 68 (**3mc**) | 100 : 0 |
| 10 | *p*-$MeOC_6H_4$ | Ph | **2m** | B | 83 (**3mc**) | 100 : 0 |
| 11 | *p*-$MeOC_6H_4$ | Ph | **2n** | A | 69 (**3nc**) | 100 : 0 |
| 12 | *p*-$MeOC_6H_4$ | Ph | **2n** | B | 74 (**3nc**) | 100 : 0 |
| 13 | 3,4-Dihydroisoquinoline | | **2m** | A | 80 (**3md**) | 50 : 50 |
| 14 | 3,4-Dihydroisoquinoline | | **2m** | B | 82 (**3md**) | 50 : 50 |
| 15 | 3,4-Dihydroisoquinoline | | **2n** | A | 67 (**3nd**) | 60 : 40 |
| 16 | 3,4-Dihydroisoquinoline | | **2n** | B | 92 (**3nd**) | 50 : 50 |
| 17 | *p*-$ClC_6H_4$ | (*S*)-CHMePh | **2m** | B | 87 (**3me**) | 54 : 46 |
| 18 | *p*-$ClC_6H_4$ | (*S*)-CHMePh | **2n** | B | 65 (**3ne**) | 50 : 50 |
| 19 | Ph | Bn | **2m** | A | 76 (**3mf**) | 50 : 50 |
| 20 | Ph | Bn | **2m** | B | 93 (**3mf**) | 50 : 50 |
| 21 | Ph | Bn | **2n** | B | 65 (**3nf**) | 52 : 48 |
| 22 | Ph | Bn | **2n** | B | 76 (**3nf**) | 53 : 47 |

[a] All reactions were carried out at −78 °C with a ratio of imine **1**: sulfonium salt **2**: $Bu^nLi$ = 1 : 1.1 : 1.1 on a 0.5 mmol scale in THF with 4 Å molecular sieves. [b] Method A: $Me_3SiCl$ used as activator; Method B: $BF_3{\bullet}OEt_2$ used as activator. [c] Isolated yields based on imine. [d] Determined by 300 MHz $^1H$ NMR analysis.



Scheme 2

*N*-tosyl imine, this reaction can be extended to include cyclic imines, such as dihydroisoquinoline (entries 13–16).

Activation of the imine by complexion with the Lewis acids, followed by nucleophilic addition of the ylide, results in the formation of intermediate **4** (Scheme 2). Subsequent ring closure and loss of diphenyl sulfide gave aziridines **3**. Aggarwal[2a] and Yamamoto[10] recently rationalized the fact that the *cis*-aziridine isomer is the thermodynamic product. In our procedure, the *cis* stereoselectivity of the reaction might come from the 1,2-steric interaction in the three-membered ring between the aryl group (this is the largest group) and either of the substitutes. The mixture of *cis* and *trans* *N*-alkylaziridines may result from weak steric interaction among the substituents on the three-membered ring, thus giving almost no selectivity.

In summary, we have demonstrated an efficient method for the preparation of various $\alpha$-unsaturated substituted aziridines from aryl imines and semistabilized prop-2-ynylic and allylic sulfonium ylides in the presence of $BF_3{\cdot}OEt_2$ with high *cis*-selectivity. It extends the scope of the ylide route to aziridination, without the need to prepare an *N*-EWG imine, and may also be applied to cyclic imines. In comparison to the recent work of diazoacetate with imines,[8] the present method gives higher yields with high *cis*-stereoselectivity and no sign of the formation of significant amounts of by-product. It represents an improvement over our previous routes[2b,c] and may be applied to the preparation of functionalized aziridines. The introduction of chirality into this reaction is being investigated.

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## Footnotes

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† *Typical experimental procedure*: A 25 ml flask containing a magnetic stirrer bar was charged with sulfonium salt **2m** (240 mg, 0.6 mmol), 4 Å molecular sieves (1 g) and anhydrous THF (4 ml), the mixture was cooled to −78 °C under $N_2$, and treated with $Bu^nLi$ (0.4 ml; 1.6 M in hexanes) (Aldrich) with stirring. After 15 min, a mixture of imine **1a** (91 mg, 0.5 mmol) and $BF_3{\cdot}OEt_2$ (1.0 equiv.) was added at the same temperature and stirring was continued until the temperature rose to room temperature. The reaction mixture was filtered on a short column of neutral $Al_2O_3$ to remove inorganic salts. The filtrate was concentrated and chromatographed on a column of neutral $Al_2O_3$ with light petroleum (bp 60–90 °C)–EtOAc–$NEt_3$ (10 : 1 : 0.5) as eluent to give pure *cis*-**3ma** (135 mg, 92%).

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