

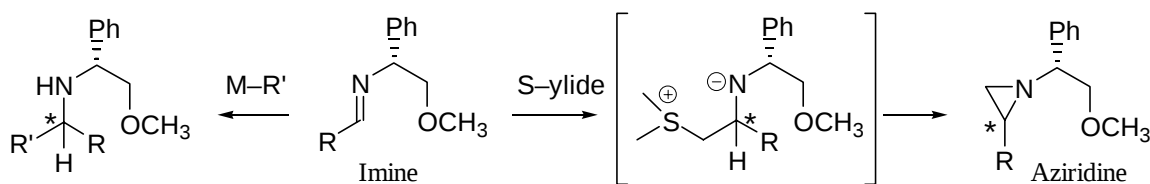
**FACILE ASYMMETRIC SYNTHESIS OF AZIRIDINE DERIVATIVES
VIA THE DIASTEREOSELECTIVE REACTION OF CHIRAL IMINES
WITH DIMETHYLSULFONIUM METHYLIDE****

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Abstract- A simple method for the synthesis of chiral 2-substituted aziridine derivatives is described. The reaction pathway consists of the diastereoselective addition of dimethylsulfonium methylide to chiral imines derived from (*R*)-phenylglycinol and various aldehydes.

Chiral aziridine derivatives are of interest not only for theoretical reasons but also because of their high reactivity arising from the release of strain energy inherent in a small ring. Use of reactive aziridine derivatives as intermediates in the asymmetric synthesis of several classes of compounds has been widely explored,¹ and many preparative methods have been developed for their synthesis.² Among various synthetic methods for chiral aziridine derivatives, one of most promising is aziridination through the reaction of a chiral imine with a sulfur ylide³ which involves stereocontrolled nucleophilic addition as the first step, followed by intramolecular nucleophilic substitution. However, the ylide methodologies can be applied only to an activated imine, that is, to the C=N double bonds with an *N*-electron withdrawing group such as *p*-tolylsulfonyl.⁴ This is a severe limitation of this methodology, especially because harsh conditions are generally required to cleave the strong sulfonamide bond. Despite recent advances, the tosyl group remains difficult to be removed from a sensitive substrate.



Scheme 1

We recently showed that chiral imines prepared from (*R*)-*O*-methylphenylglycinol (**1**)⁵ and aldehydes react

** This paper is dedicated to the celebration of the 70th birthday of Professor A. I. Meyers.

with organometallic reagents in a stereoselective manner.⁶ These findings provided the possibility for a reaction of chiral imines (non-activated imines) with dimethylsulfonium methylide in place of organometallic reagents to produce chiral aziridine derivatives. Herein, we report a simple method for the synthesis of chiral 2-substituted aziridine derivatives from various chiral imines and dimethylsulfonium methylide.

First, the starting chiral imines (**2a-n**) were prepared as follows. Condensation of several aliphatic aldehydes (ethanal, propanal, butanal, 2-methylpropanal, 2,2-dimethylpropanal, and 3-methyl-2-butanal) with **1** in CH₂Cl₂ in the presence of anhydrous MgSO₄ gave sensitive chiral imines (**2a-f**). Fluoral and aromatic aldehydes (4-trifluoromethylbenzaldehyde, 4-chlorobenzaldehyde, benzaldehyde, 4-tolualdehyde, 3-anisaldehyde, 4-anisaldehyde, and veratraldehyde) gave chiral imines (**2g-n**) in quantitative yields when heated in toluene with azeotropic removal of water. Reaction of chiral imines (**2a-n**) with an excess amount of dimethylsulfonium methylide prepared from trimethylsulfonium iodide in THF with 1 equiv. of *n*-butyllithium at 0°C,⁷ gave the desired aziridine derivatives (**3a-n**) in moderate to good yields with high diastereomeric excesses. The experimental results are presented in Table 1.

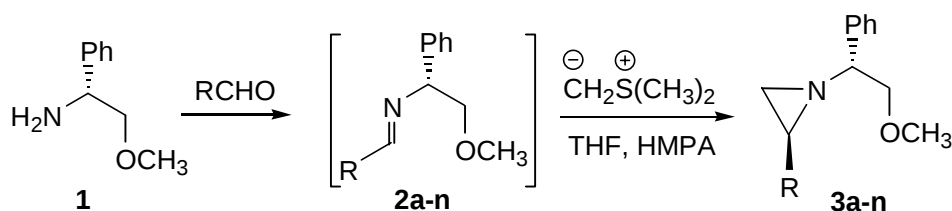


Table 1. Synthesis of chiral aziridines (**3a-n**)⁸

product	R	ratio of S-3 : R-3 ^{a)}	yield of 3 (%)	[α] _D of S-3 ^{b)}
a	CH ₃	> 99 : < 1	79.1	-63.1° (1.00)
b	CH ₂ CH ₃	> 99 : < 1	81.0	-72.6° (1.17)
c	CH ₂ CH ₂ CH ₃	> 99 : < 1	91.7	-50.3° (1.02)
d	CH(CH ₃) ₂	> 99 : < 1	81.4	-81.3° (1.00)
e	C(CH ₃) ₃	> 99 : < 1	90.1	-54.4° (1.00)
f	CH=C(CH ₃) ₂	91.3 : 8.7	78.4	-64.4° (1.11)
g	CF ₃	91.6 : 8.4	71.1	-70.1° (1.00)
h	<i>p</i> -C ₆ H ₄ CF ₃	95.6 : 4.4	84.0	+128.4° (1.05)
i	<i>p</i> -C ₆ H ₄ Cl	93.3 : 6.7	64.0	+164.8° (1.06)
j	C ₆ H ₅	95.4 : 4.6	89.0	+127.6° (1.15)
k	<i>p</i> -C ₆ H ₄ CH ₃	91.9 : 8.1	67.0	+143.7° (1.04)
l	<i>m</i> -C ₆ H ₄ OCH ₃	91.9 : 8.1	69.0	+125.1° (1.09)
m	<i>p</i> -C ₆ H ₄ OCH ₃	94.1 : 5.9	67.0	+138.5° (1.00)
n	<i>m,p</i> -C ₆ H ₃ (OCH ₃) ₂	90.4 : 9.6	61.0	+119.0° (1.02)

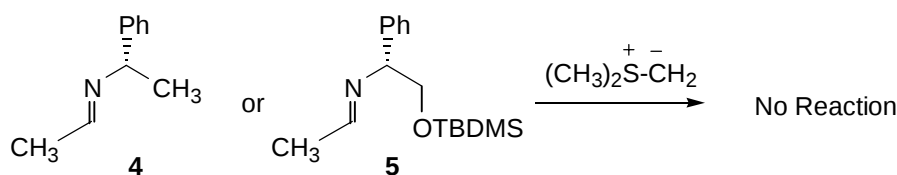
a) Estimated by the ¹H-NMR (270 MHz) spectral analysis.

b) Specific rotations (c 1.0-1.2, CHCl₃).

It was found that with either reaction substrate, the reaction proceeded with a good yield. Generally, in the

reaction of sulfur ylide with imine, yield is high for activated imine, but is low for non-activated imine. In our case, the reaction proceeded in a good yield even if a non-activated imine was used.

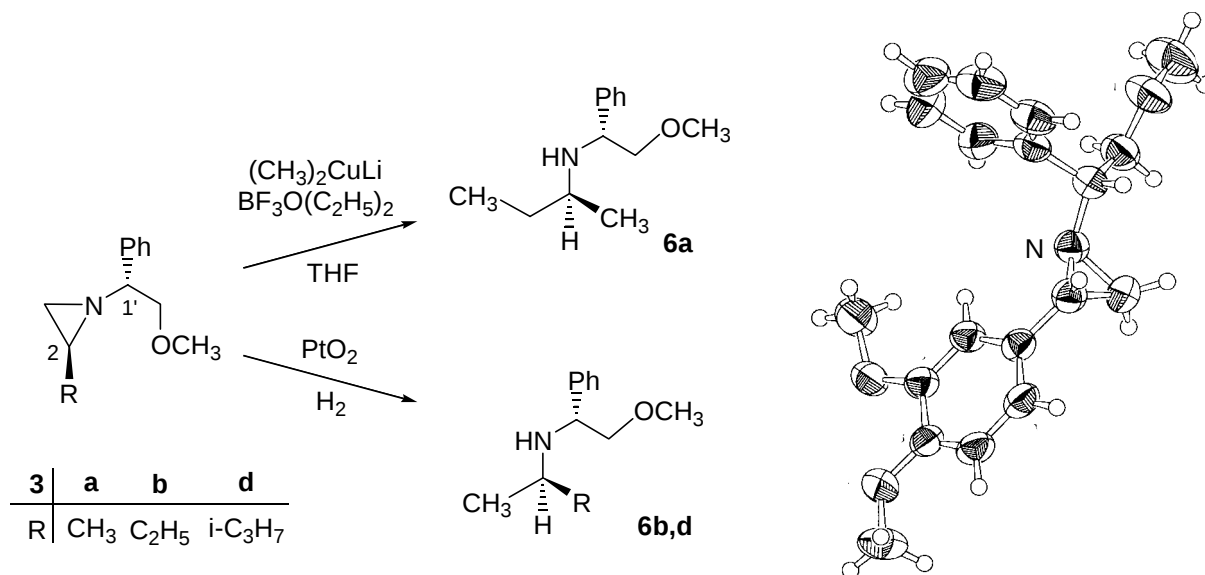
Following experiments were done to examine differences in this reactivity. When the imine (**4**) having no oxygen functional group is used for the substrate, the reaction does not occur at all. Furthermore, raw materials were collected by the reaction in which the imine (**5**) bearing a sterically bulky oxygen function was employed as the substrate. These results indicate that an oxygen atom is obviously involved in this reaction.



Scheme 2

Moreover, since this reaction does not occur at all when the ylide is produced using NaH or sodium bistrimethylsilylamide instead of *n*-butyllithium, the lithium ion appears to play an important role in the reaction.

Stereoselectivity of these reactions is comparatively excellent. In particular, only one diastereomer was produced when aliphatic aldehyde was used. We deduced the stereochemistries of newly formed asymmetric carbons as follows. Reaction of **3a** having a aliphatic substituent in the 2 position of aziridine ring with dimethylcopperlithium in the presence of $\text{BF}_3\text{-O}(\text{C}_2\text{H}_5)_2$ gave known optically active **6a** as a single product. Also, reductive ring cleavage of **3b,d** resulted in the high yields of known compounds (**6b,d**). Thus, on the basis of the known signs of optical rotations and the absolute configurations of **6a,b,d**,⁹ the configurations of **3a,b,d** are unambiguously assigned as 2*S*,1'*S*. In the case of **3n** which had a aromatic substituent, the structure was verified by X-Ray crystal analysis.



Scheme 3

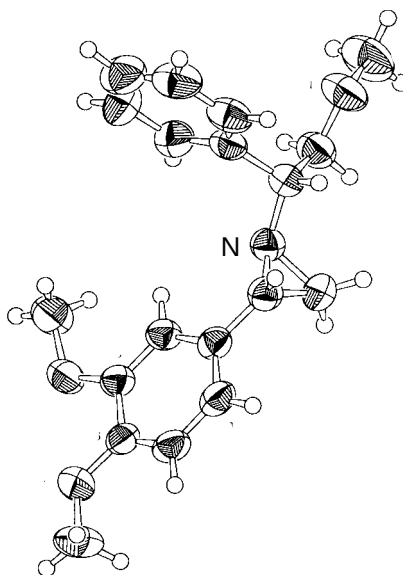


Figure. ORTEP drawing of **3n**

Taking into account of structural similarity the configurations of the other aziridines are deduced based on the signs of optical rotations.

An oxygen function of imine and lithium ion seems necessary to explain the mechanism of this reaction. Thus, the high degree of stereocontrol in this reaction may be attributed to a highly ordered transitional state resulting from significant chelation of the oxygen atom and imino nitrogen to the lithium atom and subsequent delivery of the sulfur ylide from the least hindered face of carbon-nitrogen double bond.

Thus, the proposed method appears to be useful for the synthesis of chiral aziridines because, compared with the results of similar reactions reported in the literatures,¹⁰ the chemical and stereoselective outcomes of the reaction described here were superior. Further studies by our research team on the synthetic aspects of this reaction are in progress.

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8. Typical procedure (**3c**): A solution of *n*-butyllithium (10.5 mL, 1.6M in hexane, 16.8 mmol) was added dropwise over several minutes to a stirred solution of powdered trimethylsulfonium iodide (3.41 g, 16.7 mmol) and HMPA (3.0 g, 16.7 mmol) in 30 mL of dry THF under nitrogen at 0°. After stirring for 20 min, a solution of chiral imine (**2c**) in 5 mL of dry THF, which was prepared from **1** (1.0 g, 6.7 mmol) and butanal (0.48 g, 6.7 mmol), was added. After stirring for 30 min at 0°, the resulting mixture was diluted with 30 mL of water and extracted with ether (2 x 30 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na₂SO₄, and evaporated to give the residue, which was subjected to column chromatography on silica gel. Elution with 30% AcOEt in hexane afforded chiral aziridine (**3c**) (1.34 g, 91.7%) as a colorless oil.
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