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Stereoselective synthesis of CF_3-substituted aziridines by Lewis acid-mediated aziridination of aldimines with diazoacetates

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Abstract—Treatment of trifluoroacetaldehyde *N*,*O*-acetal with diazoacetate in the presence of a Lewis acid furnished CF_3-substituted aziridinecarboxylates in good yields. Both *cis* and *trans* isomers were obtained stereoselectively by the proper choice of the ester substituents. Use of a chiral diazoacetate derived from (*R*)-pantolactone led to highly diastereoselective aziridination (94% de). © 2003 Elsevier Science Ltd. All rights reserved.

Organofluorine compounds have attracted the attention of synthetic organic chemists due to their potential activity both in the fields of material sciences and biological sciences.[1] We reported that an *N*,*O*-hemiacetal **1a**, derived from trifluoroacetaldehyde ethyl hemiacetal,[2] is a stable and useful synthetic equivalent of a trifluoromethylated aldimine. Thus, on treatment of **1a** with silyl enolates in the presence of $GaCl_3$, Mannich-type reaction took place smoothly to furnish β-trifluoromethyl-β-amino carbonyl compounds in high yields.[3]

Aziridines are important synthetic intermediates for the synthesis of nitrogen–containing compounds, and numerous kinds of synthetic reactions for aziridines have been reported.[4,5] Lewis acid–catalyzed aziridination of aldimine with diazoacetate have been reported for the preparation of aziridines. Although a number of catalysts such as $BF_3{\cdot}OEt_2$,[6] $InCl_3$,[7] $Sc(OTf)_3$,[8] Ir catalyst,[9] CH_3ReO_3,[10] and others[11] have been developed, yields are not always high due to the formation of the by-products. Lewis acid-catalyzed aziridination of a chiral diazoacetate and an imine equivalent proceeded with low diastereoselectivity.[12] Enantioselective aziridination has been reported lately.[13] As part of our research projects directed towards the development of CF_3-containing compounds, we studied Lewis acid–catalyzed aziridination reaction of **1a** with diazoacetates. We wish to report herein that, on treatment of diazoacetates with **1a** in the presence of a Lewis acid, CF_3-substituted aziridines were obtained in high yields.[14,15] Both *cis* and *trans* isomers were obtained highly stereoselectively by the proper choice of the ester substituents. Furthermore, chiral synthesis of the CF_3-substituted aziridine was achieved highly diastereoselectively by use of (*R*)-pantolactone as a chiral auxiliary.

At the outset, Lewis acid-mediated aziridination of an isopropyl diazoacetate with **1a** was studied, and the results are shown in Table 1. $BF_3{\cdot}OEt_2$ was found to be effective for the aziridination. An aziridinecarboxylate **2** was thus obtained in a moderate yield with high *cis* selectivity (entry 1). Addition of MS 3A improved the chemical yield significantly (entry 2). It was found that the stereochemistry of the products depended on the ester substituents. The *cis* isomer was generally obtained preferentially as expected. The isopropyl ester exhibited the highest *cis* selectivity. It is noted that use of a 2,6-di-*t*-butyl-4-methylphenyl diazoacetate (BDA)[16] in the co-existence of $SnCl_4$ resulted in the reversal of stereoselectivity, and a *trans* isomer **3** was obtained preferentially (entry 7). Although BDA was demonstrated to be a reagent of choice for the *trans* selective Rh-catalyzed cyclopropanation, use in the aziridination had not been reported. Furthermore, *trans* selective aziridination had not been reported in the Lewis acid-mediated aziridination with imine and diazoacetate except one case.[10]

Aziridination with α-diazo ketones also proceeded smoothly and the corresponding aziridines were obtained in favor of the *cis* isomer (entries 7, 8). Although Lewis acid-catalyzed aziridination of imine with diazoacetate generally gave enamines as side products, the *N*,*O*-acetal **1a** did not generate corresponding products and furnished aziridine in high yields. It is

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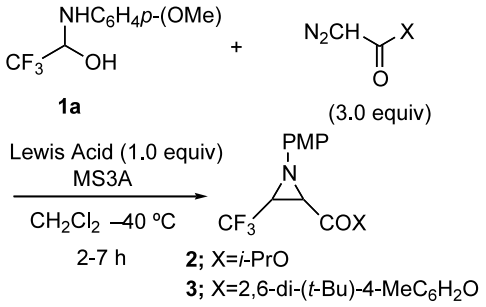
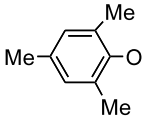
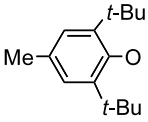
Table 1. Effect of ester substituent



Entry	X	Lewis Acid	Yield/%	*cis* :*trans*
1[a]	*i*-PrO	BF_3•OEt_2	56	93:7
2	*i*-PrO	BF_3•OEt_2	96	92:8
3	*c*-HexO	BF_3•OEt_2	89	85:15
4	*t*-BuO	BF_3•OEt_2	72	88:12
5		$SnCl_4$	78	77:23
6		$SnCl_4$	86	10:90
7	Ph	BF_3•OEt_2	88	79:21
8	2-Furyl	BF_3•OEt_2	73	84:16

[a] In the absence of MS 3A.

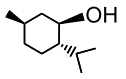
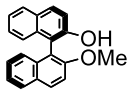
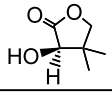
supposed that the strong electro-withdrawing CF_3 group suppressed the side process.

Diastereoselective aziridination was next studied. Although Jørgensen already reported $Cu(OTf)_2$-catalyzed diastereoselective aziridination of *N*-methylidene aniline trimer with (–)-menthyl diazoacetate, the diastereoselectivity was as low as 25%.[12] The results of the BF_3·OEt_2-mediated aziridination of the *N*,*O*-acetal **1a** and chiral diazoacetate derived from optically active alcohol in CH_2Cl_2 are shown in Table 2.

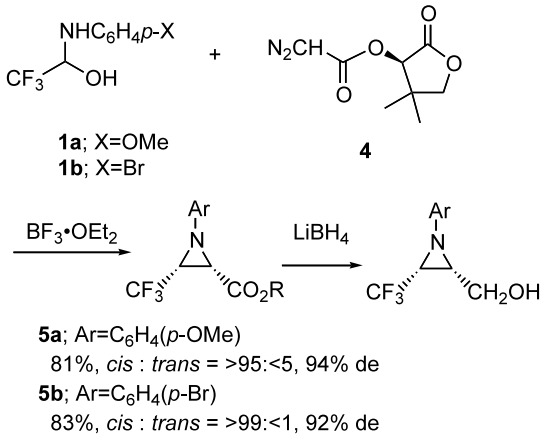
Although menthol and binaphthol monomethyl ether were not effective (entries 1, 2), (*R*)-pantolactone turned out to be highly effective as a chiral auxiliary group. BF_3·OEt_2-catalyzed aziridination of **1a** with a chiral diazo ester derived from (*R*)-pantolactone **4**[18,19] exhibited both high *cis* selectivity (>95:<5) and excellent diastereoselectivity (94% de).

The absolute stereochemistry of the major diastereomer of the aziridine **5a** was determined to be (2*S*,3*R*) by X-ray crystallographic analysis of the corresponding *N*-*p*-BrC_6H_4 substituted aziridine **5b**, which was readily prepared from **1b** and **4** under the identical reaction conditions (Scheme 1).

Table 2. Diastereoselective aziridination

Entry	ROH	Yield/ %	*cis*:*trans*
1[a]		51	73 (53:47):27 (54:46)
2[b]		trace	*trans* only (6:4~7:3)
3[c]		81	>95:<5 (94% de)[d]

[a] BF_3·OEt_2 was employed at rt in CH_3CH_2CN
[b] $SnCl_4$ was used at rt.
[c] BF_3·OEt_2 was used at –40°C.
[d] Diastereomeric excess of the *cis* isomer.



Scheme 1.

Present protocol provides the highest diastereoselectivity in the Lewis acid-mediated aziridination with aldimine and diazoacetate. Reductive removal of the chiral auxiliary[17] furnished a chiral aziridine in a good yield.[20]

In summary, we have reported stereoselective synthesis of CF_3-substituted aziridine carboxylates. Both *cis* and *trans* isomers were obtained highly stereoselectively by the proper choice of the ester substituents of diazoacetate. Chiral synthesis of CF_3-substituted aziridinecarboxylate was achieved with excellent diastereoselectivity by use of (*R*)-pantolactone as a chiral auxiliary.

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