Facile Synthesis of Aziridines from Imines and Diazoesters or Aldehydes, Amines, and Diazoesters Using a Catalytic Amount of Lanthanide Triflate

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In the presence of a catalytic amount of lanthanide triflate ($Ln(OTf)_3$), imines reacted with ethyl diazoester in hexane at room temperature to afford the corresponding aziridines in high yields with high diastereoselectivities. Based on these reactions, three-component reactions of various types of aldehydes, an amine, and ethyl diazoester have been developed to provide a general efficient route to aziridine derivatives.

Aziridines are useful intermediates for the synthesis of amino acids and other nitrogen-containing compounds such as amino alcohols, amino thiols, etc.[1] For the preparation of aziridines, several useful methods have been developed; for example, ring closure of amino alcohols,[2] ring opening of epoxides using metal azides,[3] addition of α-haloester enolates to imines,[4] transition metal-catalyzed nitrene transfer,[5] carbene transfer,[6] etc. Among these, the carbene transfer reactions of imines with a carbene species are one of the most efficient methods for the preparation of aziridines. Actually, some useful methods using the carbene transfer reactions have been reported, however, substrate limitation, particularly low yields in reactions using imines derived from aliphatic aldehydes, still remains as a severe problem.

Recently, we have found that lanthanide triflates ($Ln(OTf)_3$) are efficient Lewis acid catalysts for the activation of nitrogen-containing compounds such as imines[7] and hydrazones.[8] While stoichiometric amounts are required for the activation of imines using typical Lewis acids, a catalytic amount of $Ln(OTf)_3$ is enough to complete various fundamental reactions of imines. Moreover, the triflates are quantitatively recovered after the reactions are completed and can be reused. In the course of our investigations to develop useful synthetic reactions using $Ln(OTf)_3$ as catalysts, reactions of imines with carbene species were investigated.

First, *N*-benzylidene aniline was treated with ethyl diazoester in the presence of 10 mol% of $Sc(OTf)_3$ in acetonitrile at 0 °C. While the desired aziridine was obtained in a 34% yield, side reaction products, α-substituted enamino ester **1** and α-unsubstituted enamino ester **2**, were produced in a total yield of 59%. To improve the yield of the desired aziridine, several reaction conditions were examined (Table 1). While lower yields were observed using $Sc(OTf)_3$ in several solvents, the yield was improved to 77% when $Yb(OTf)_3$ was used as a catalyst in hexane, albeit a 20% yield of side reaction products was obtained. From a mechanistic consideration, the formation of side reaction products (**1** and **2**) was expected to decrease by the increasing electron density of the nitrogen atoms of imines, and the use of *N*-benzyl-type imines instead of *N*-aromatic imines was examined. When the reaction of *N*-diphenylmethylimine **3** with ethyl diazoester was carried out in the presence of 10 mol% of $Yb(OTf)_3$ in hexane at room temperature (rt), the desired aziridine was obtained in an 83% yield with high diastereoselectivity (*cis/trans* = 95/5). It is noted that no formation of **1** and **2** was observed and that hexane was the best solvent while the catalyst ($Yb(OTf)_3$) was slightly dissolved in this solvent.

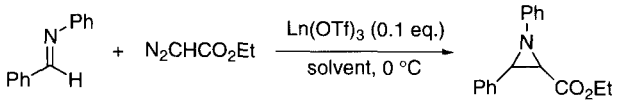
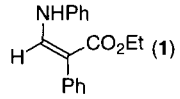
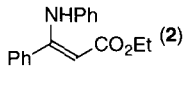


Table 1. Effect of $Ln(OTf)_3$ and solvents

Ln	Solvent	Yield /%[a]
Sc	CH_3CN	34 (59)
Sc	CH_2Cl_2	37 (55)
Sc	toluene	27 (57)
Sc	THF	35 (52)
Sc	hexane	53 (37)
Sc	Et_2O	53 (32)
Yb	hexane	77 (20)
Yb	Et_2O	65 (18)

[a]Numbers in parentheses are total yields of **1** and **2**.





Other imines were examined and the results are summarized in Table 2. Several imines derived from aromatic aldehydes reacted with ethyl diazoester smoothly to afford the corresponding aziridines in high yields with excellent diastereoselectivities. On the other hand, imines derived from aliphatic aldehydes, particularly imines having α-hydrogen atoms, are known to be unstable. Actually, only one example of an imine derived from an aliphatic aldehyde was reported in aziridine formation in the literature,[6e,f,k] and the example was the pivalaldehyde-derived imine, which has no α-hydrogen atom. To solve the above aliphatic imine problem in the aziridine synthesis, three-component coupling reactions of aldehydes, amines, and ethyl diazoester were examined. We have already developed $Ln(OTf)_3$-catalyzed three-component reactions of aldehydes, amines, and silyl nucleophiles[9] or dienes or dienophiles[10] for the synthesis of β-amino esters, ketones, tetrahydroquinolines, dihydropyridines, etc. In these reactions, while $Ln(OTf)_3$ gave the desired three-component coupling adducts in high yields, no adduct or only low yields of the adducts were obtained by using other typical Lewis acids such as

$TiCl_4$, $AlCl_3$, $SnCl_4$, or BF_3•OEt_2. In the presence of a catalytic amount of $Yb(OTf)_3$, several aldehydes, amines, and ethyl diazoester were combined in hexane at rt, and the results are summarized in Table 3.[11] Not only aromatic aldehydes, but also several aliphatic aldehydes reacted smoothly under these conditions to afford the corresponding aziridines in high yields with good to high diastereoselectivities. Phenylglyoxal also worked well. It is noteworthy that aziridine formation from aliphatic imines having α-protons have been achieved for the first time according to these reactions.

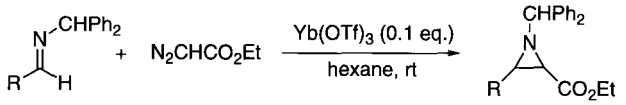


Table 2. Reactions of imines

R	Yield /%	*cis*/*trans*
Ph	89	93/7
p-MePh	75	95/5
p-MeOPh	90	94/6
p-ClPh	81	94/6
p-NO_2Ph	83	93/7
1-naphthyl	82	94/6

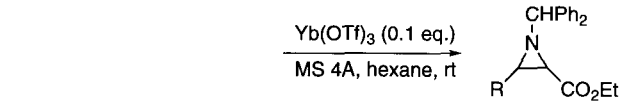


Table 3. Three-component reactions

R	Yield /%	*cis*/*trans*
Ph	83	95/5
PhCO	85	94/6
c-C_6H_{11}	82	93/7
i-C_3H_7	82	91/9
i-C_4H_9	86	70/30
n-C_4H_9	60	85/15

In summary, a new method for the preparation of aziridines has been developed. The method is based on $Ln(OTf)_3$-catalyzed reactions of imines with ethyl diazoester, and three-component coupling reactions of aldehydes (including aliphatic aldehydes having α-protons), an amine, and ethyl diazoester have been successfully carried out to afford the corresponding aziridines in high yields with high diastereoselectivities.

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11 A typical experimental procedure for the synthesis of aziridines using the three-component coupling reactions is as follows. An aldehyde (0.4 mmol), diphenylmethylamine (0.4 mmol), $Yb(OTf)_3$ (0.04 mmol), and MS 4A (125 mg) were combined in hexane (3 ml) at 0 °C. After the mixture was stirred for 1 h at the same temperature, ethyl diazoester (0.8 mmol) was added. The mixture was stirred at rt for 12 h and saturated $NaHCO_3$ aq. was then added to quench the reaction. After a usual work up, the crude product was chromatographed on silica gel to afford the corresponding aziridine.