Pergamon

Tetrahedron Letters 42 (2001) 9089–9092

TETRAHEDRON LETTERS

# Scandium triflate-catalyzed 1,3-dipolar cycloaddition of aziridines with alkenes†

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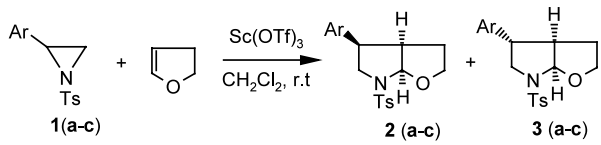
Received 20 August 2001; revised 9 October 2001; accepted 19 October 2001

**Abstract**—Phenyl aziridines undergo 1,3-dipolar cycloaddition efficiently with olefins such as cyclic enol ethers and allyltrimethylsilane in the presence of a catalytic amount of $Sc(OTf)_3$ at ambient temperature to afford the corresponding pyrrolidine derivatives in high yields with high regioselectivity. 

Aziridines are versatile building blocks for the synthesis of many nitrogen containing bioactive molecules.[1] They are known to react with various nucleophiles and their ability to undergo regioselective ring-opening reactions contributes largely to their synthetic value. As a result, several procedures have been developed for the ring opening of aziridines with various nucleophiles such as organometallic reagents,[2] silyl nucleophiles,[3] Wittig reagents,[4] amines[5] and hydroxyl compounds,[6] but the procedures for their opening with alkenes are scarce.[7] Moreover, these methods require stoichiometric amounts of Lewis acids, very low temperatures and anhydrous reaction conditions to obtain the desired products. Therefore, there is merit in developing a truly catalytic process for the synthesis of substituted pyrrolidines from phenyl aziridines and alkenes. Lanthanide triflates are unique Lewis acids that are currently of great research interest. They are quite stable to water and reusable, as well as highly effective for the activation of nitrogen containing compounds. Therefore, lanthanide triflates are unique catalysts compared to conventional Lewis acids in several carbon–carbon bond forming reactions and have found a wide application in organic synthesis.[8] In addition, these metal triflates can be used either in aqueous or in non-aqueous media and the reactions can be conveniently carried out under mild conditions and do not require anhydrous conditions or an inert atmosphere. However, there is no report on the use of lanthanide triflates for the ring opening of aziridines with alkenes.

In continuation of our interest on the use of $Sc(OTf)_3$ for various transformations,[9] we herein report a novel and efficient protocol for the cyclocondensation of aryl aziridines with cyclic enol ethers using a catalytic amount of scandium triflate. The starting *N*-tosyl aryl aziridines were easily prepared from styrenes and chloramine-T using catalytic amounts of elemental iodine.[10] The treatment[11] of aryl aziridines with 2,3-dihydrofuran in the presence of 3 mol% $Sc(OTf)_3$ in dichloromethane at 0°C resulted in the formation of azaoxa cycloadducts as a mixture of **2** and **3** in good yields (Scheme 1).

In all the reactions, the product was obtained as a mixture of **2a** and **3a** in a ratio of 1:1, which were separated by column chromatography. The stereochemistry of the product **2a** was assigned on the basis of coupling constants and NOE studies. The coupling constant $J_{a-b}=5.8$ Hz between Ha ($\delta$ 5.97)-Hb ($\delta$ 3.25) and the presence of NOE cross peaks between Ha–Hb, Hb–Hc and Ha–Hc indicate a structure with *cis*-fusion with the phenyl ring is an *exo* configuration (Fig. 1). In the product **3a**, similar to product **2a**, the two five-membered rings are *cis*-fused. The coupling constant $J_{a-b}=6.0$ Hz between Ha ($\delta$ 5.72)-Hb ($\delta$ 2.83) and the presence of an NOE cross peak between Ha and Hb




**Scheme 1.**

*Keywords*: aziridines; scandium triflate; cycloaddition; pyrrolidines.

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† IICT Communication No. 4859.

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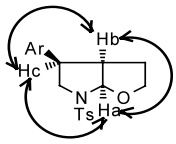
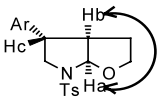
PII: S0040-4039(01)02008-1



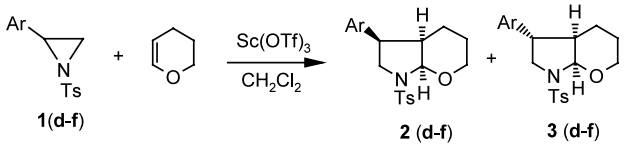

**2a** *exo*

**Figure 1.**



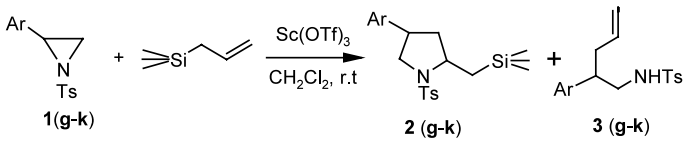

**3a** *endo*

**Figure 2.**




Ar: **d** = Ph: **e** = 4-$CH_3$-$C_6H_4$; **f** = 4-Cl-$C_6H_4$

**Scheme 3.**




Ar: **g** = $C_6H_5$; **h** = 3-Cl-$C_6H_4$; **i** = 4-Cl-$C_6H_4$; **j** = 4-Br-$C_6H_4$; **k** = 4-$CH_3$-$C_6H_4$

**Scheme 4.**

again shows that Ha is *cis* to Hb and that the phenyl ring is in an *endo* configuration (Fig. 2).

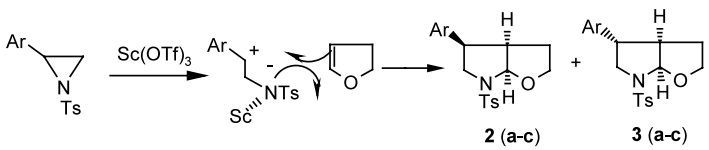
The formation of the products may be explained by the (3+2) cycloaddition between the aziridine and the cyclic enol ether. Scandium triflate activates the *N*-tosyl group in the aziridine to cleave the benzylic C–N bond resulting in the formation of a 1,3-dipole which is trapped by the nucleophilic olefin to afford the desired pyrrolidine (Scheme 2).

In a similar fashion, aryl aziridines reacted smoothly with 3,4-dihydro-2*H*-pyran in the presence of 3 mol% $Sc(OTf)_3$ in dichloromethane at 0°C to give the respective azaoxa [3.2.0] cycloadducts as a mixture of **2** and **3** in good yields (Scheme 3).

In these reactions, the products were also obtained as a mixture of **2** and **3** in a ratio of 1:1, which were separated by column chromatography. The structure of the products were assigned on the basis of coupling constants and NOE cross peaks. The coupling constant $J_{a-b}=5.0$ Hz, for **2**, indicates a structure with *cis*-fusion and an *exo* phenyl ring, which is further supported by the presence of NOE cross peaks between Ha–Hb, Hb–Hc and Ha–Hc. In product **3**, $J_{a-b}=3.8$ Hz and the presence of an NOE between Ha and Hb shows a structure with *cis* fusion and an *endo* phenyl ring. Furthermore, the assigned structures of **2** and **3** are in agreement with the literature.[7b] In all these cases, the reactions proceeded efficiently at 0°C, under mild reaction conditions and in good yields. Further, the treatment of aryl aziridines with allyltrimethylsilane in the presence of 5 mol% scandium triflate at ambient temperature resulted in the formation of a mixture of the highly substituted pyrrolidine **2** with a small amount of the γ-amino olefinic adduct **3** (Scheme 4).

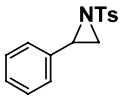
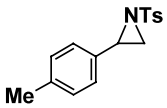
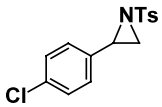
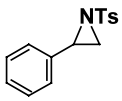
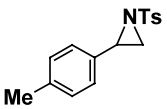
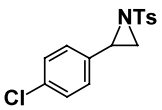
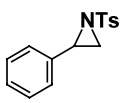
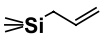
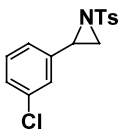
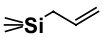
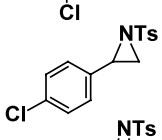
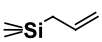
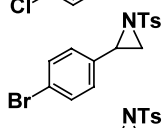
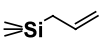
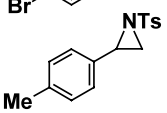
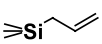
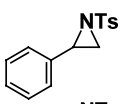
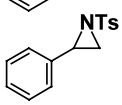
The five-membered pyrrolidines were obtained as a mixture of *cis* and *trans* isomers in a ratio of 1:1, which were inseparable on TLC. Similarly, various substituted aryl aziridines reacted well with allyltrimethylsilane to afford the corresponding pyrrolidines. In all these cases, the reactions proceeded smoothly at ambient temperature and the products were obtained in high yields within 1.5–3 h. Among various metal triflates like $In(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$ and LiOTf, scandium triflate was found to be the more efficient in terms of yields and reaction time. The catalyst, $Sc(OTf)_3$ was recovered from the aqueous layer during work-up and reused in subsequent reactions without any decrease in activity. Several examples illustrating this novel and general method for the synthesis of pyrrolidines are listed in Table 1.

In summary, we have demonstrated $Sc(OTf)_3$ as a novel and highly efficient Lewis acid for the synthesis of substituted pyrrolidines from aryl aziridines and olefins. The method offers several advantages over conventional methods, which include mild reaction conditions, high yields of products, operational simplicity, catalytic amounts of $Sc(OTf)_3$, reusability of the catalyst and simple experimental/work-up procedures. These advantages make it a useful and attractive process for the synthesis of highly substituted pyrrolidines.




**Scheme 2.**

**Table 1.** $Sc(Otf)_3$-catalyzed synthesis of pyrrolidine derivatives[a]

| Entry | Aziridine | Olefin | Reaction time (h) | Yield[b] (%) |
|---|---|---|---|---|
| a |  |  | 1.5 | 72[c] |
| b |  |  | 2.5 | 70[c] |
| c |  |  | 2.5 | 65[c] |
| d |  |  | 1.0 | 78[c] |
| e |  |  | 2.0 | 70[c] |
| f |  |  | 2.0 | 68[c] |
| g |  |  | 2.0 | 90[d] |
| h |  |  | 3.5 | 83[d] |
| i |  |  | 4.0 | 80[d] |
| j |  |  | 3.5 | 81[d] |
| k |  |  | 1.5 | 85[d] |
| l |  |  | 2.5 | 70 |
| m |  |  | 3.5 | 75 |

a All products were characterized by $^1H$ NMR, IR and mass spectra

b Isolated and unoptimized yields

c Two diastereomers were obtained in a ratio of 1:1 and also isolated by column chromatography

d Ratio of 2:3 was determined by $^1H$ NMR spectra of the products after isolation of pure products

## Acknowledgements

B.V.S., P.S.H. and I.P. thank CSIR, New Delhi for the award of fellowships.

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11. Experimental procedure: A mixture of aryl aziridine (2 mmol), enol ether (3 mmol) and scandium triflate (3 mol%) in dichloromethane (10 mL) was stirred at 0°C for the specified time required to complete the reaction. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×15 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure *exo* and *endo* isomers. Spectral data for product **2a**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.45 (m, 1H), 1.68 (m, 1H), 2.43 (s, 3H), 3.25 (m, 1H), 3.35 (m, 2H), 3.55–3.62 (m, 1H), 3.68 (dq, 1H, 3.8, 8.7 Hz), 3.90 (dd, 1H, $J=6.8$, 9.5 Hz), 5.97 (d, 1H, $J=5.8$ Hz), 7.08 (d, 2H, $J=8.0$ Hz), 7.25–7.30 (m, 5H), 7.85 (d, 2H, $J=8.0$ Hz). $^{13}$C NMR ($CDCl_3$, proton decoupled): $\delta$ 21.53, 26.67, 29.71, 45.40, 47.83, 49.30, 68.16, 94.56, 96.17, 126.94, 127.09, 127.50, 127.60, 127.82, 128.61, 128.89, 129.40, 137.96, 143.02. **3a**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.78–1.82 (m, 1H), 2.02–2.08 (m, 1H), 2.45 (s, 3H), 2.83 (ddd, 1H, $J=1.6$, 8.0, 13.8 Hz), 3.18 (dd, 1H, $J=7.4$, 15.0 Hz), 3.30 (dd, 1H, $J=8.0$, 9.5 Hz), 3.75 (dd, 1H, $J=7.4$, 9.5 Hz), 3.84 (ddd, 1H, $J=5.8$, 9.5, 10.2 Hz), 3.97 (ddd, 1H, $J=2.3$, 8.0, 8.7 Hz), 5.72 (d, 1H, $J=6.0$ Hz), 7.10 (d, 2H, $J=8.0$ Hz), 7.25–7.37 (m, 5H), 7.83 (d, 2H, $J=8.0$ Hz). $^{13}$C NMR ($CDCl_3$, proton decoupled): $\delta$ 21.52, 29.65, 31.28, 47.70, 50.94, 54.56, 66.98, 93.92, 127.11, 127.22, 127.72, 128.61, 128.84, 129.52, 140.46, 143.49. **2d**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.13–1.48 (m, 4H), 2.30–2.42 (m, 1H), 2.47 (s, 3H), 3.19 (dd, 1H, $J=8.3$, 14.9 Hz), 3.45–3.62 (m, 2H), 3.87 (d, 2H, $J=8.3$ Hz), 5.31 (d, 1H, $J=4.9$ Hz), 7.10 (d, 2H, $J=8.0$ Hz), 7.23–7.38 (m, 5H), 7.85 (d, 2H, $J=8.0$ Hz). $^{13}$C NMR ($CDCl_3$, proton decoupled): $\delta$ 20.25, 21.72, 43.85, 45.09, 53.56, 65.80, 127.48, 127.89, 128.86, 129.57, 130.05, 136.85, 139.37, 143.49. **3d**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.30–1.82 (m, 4H), 2.13–2.17 (m, 1H), 2.45 (s, 3H), 3.43–3.70 (m, 4H), 3.90–3.95 (m, 1H), 5.32 (d, 1H, $J=3.8$ Hz), 7.18 (d, 2H, $J=8.0$ Hz), 7.22–7.35 (m, 5H), 7.83 (d, 2H, $J=8.0$ Hz). $^{13}$C NMR ($CDCl_3$, proton decoupled): $\delta$ 20.25, 21.72, 43.71, 45.10, 53.45, 65.80, 87.89, 127.48, 127.89, 128.86, 129.57, 130.05, 136.85, 139.37, 143.49.