# Zinc Triflate as Lewis Acid in Nucleophilic Addition to Cyclic *N*-Acyliminium Ions

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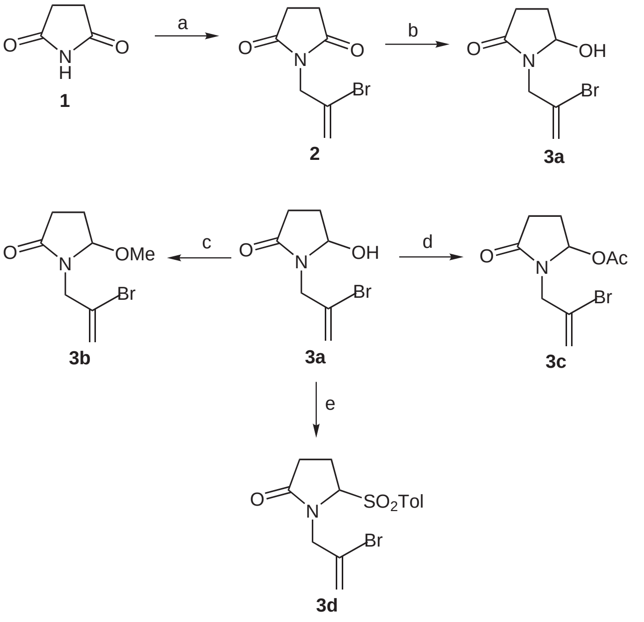
**Abstract:** Zinc triflate-mediated nucleophilic addition of allyltrimethylsilane, silyl enol ethers and terminal acetylenes to cyclic *N*-acyliminium ions at room temperature in $CH_2Cl_2$ is described. The corresponding α-substituted heterocycles were obtained in moderate to good yields. The versatility of this reagent was demonstrated in the one-pot generation of the *N*-acyliminium ion and the zinc alkynylide species, followed by their coupling reaction to afford propargylic adducts in moderate yields.

**Key words:** zinc triflate, nucleophilic addition, *N*-acyliminium ions

*N*-Acyliminium ions are versatile electrophilic species with many applications in the synthesis of nitrogen-containing compounds, particularly those involving the addition of carbon nucleophiles to its electrophilic center.[1] *N*-Acyliminium ions are more electrophilic than the corresponding iminium species due to the presence of the electron-withdrawing acyl group at the nitrogen atom and for most synthetic applications they are generated in situ from α-haloalkyl, α-hydroxyalkyl, α-alkoxyalkyl, α-acyloxyalkyl, or α-sulfonyl amides, lactams, or carbamates in view of their limited stabily and high reactivity. Lewis acids ($BF_3·OEt_2$, $TiCl_4$, $SnCl_4$, $InCl_3$, $NbCl_5$) and silylating agents (TMSOTf) are used to assist the formation of the electrophilic intermediate, followed by the addition of carbon nucleophiles to form the C–C bond.[1–3] However, the search for additional protocols to perform Lewis acid mediated nucleophilic additions to iminium and *N*-acyliminium ions aiming high yield and tolerance of functional groups is actively pursued in organic synthesis, particularly those which provide concomitant formation of both the nucleophilic and electrophilic species in the same pot.

In this context, metal triflates are an interesting alternative because numerous examples in the literature have demonstrated the ability of metal triflates to promote C–C bond formation under mild conditions.[4] Particularly, zinc triflate is an effective catalyst for aldol reactions of silyl enol ethers with aldehydes,[5] ring-opening of chiral aziridines,[6] preparation of N(1)- and N(2)-alkylated tetrazoles via displacement of alcohols,[7] regioselective synthesis of 3-alkylindoles,[8] enantioselective reduction of α-alkoxy ketones[9] and enantioselective radical conjugate additions.[10] Recently, Ishimaru reported the combination of zinc triflate and water in the stereoselective Mannich-type reaction of chiral aldimines with 2-silyloxybutadienes.[11] Furthermore, the work by Carreira and co-workers has shown that zinc alkynylides can be generated by the reaction of alkynes with zinc triflate and a tertiary amine.[12] However, to the best of our knowledge there has been no report describing the ability of zinc triflate to promote the formation of *N*-acyliminium ions and their in situ trapping by nucleophiles.[1] In this work, we report our results on the zinc triflate-mediated nucleophilic additions of allyltrimethylsilane, silyl enol ethers and terminal acetylenes to cyclic *N*-acyliminium ions.



**Scheme 1** *Reagents and conditions*: (a) NaH (60% in mineral oil), DMF, 0 °C, 15 min; then, 2,3-dibromopropene, 0 °C to r.t., 3 h, 65%; (b) i. $Et_3BHLi$, THF, –78 °C, 2 h, 85%; (c) HCl–MeOH 2 mol $L^{-1}$, 0 °C to r.t., 18 h, 98%; (d) $Ac_2O$, $Et_3N$, DMAP, 0 °C to r.t., 18 h, 72%; (e) $CHCl_3$, $p$-$CH_3C_6H_4SO_2Na·xH_2O$, $HCO_2H$ (aq), r.t., 48 h, 78%.

The competence of zinc triflate to promote the generation of cyclic *N*-acyliminium ions, followed by the addition of allyltrimethylsilane (**4**) to provide the corresponding α-substituted heterocycle was initially evaluated with lactam **3b**, prepared from imide **2** as described in Scheme 1. We initially screened the effect of the solvent and found out $CH_2Cl_2$ to be the best choice. The use of 20 mol%

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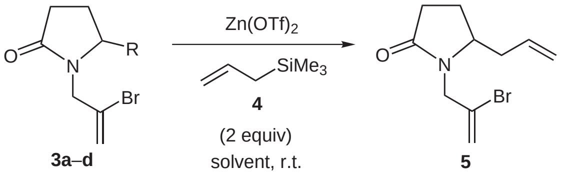
excess of zinc triflate provided the best yield of pyrrolidine **5** (78% yield, Table 1, entry 3) with lower yields being observed when sub-stoichiometric amounts were employed (Table 1, entries 4 and 5). Surprisingly, the yields of allyl pyrrolidine **5** prepared from *N*-acyliminium ion precursors **3c** and **3d** (Table 1, entries 7 and 8) which display better leaving groups at C-α were lower than those obtained from **3a** (Table 1, entry 6) and **3b** (Table 1, entry 3).

**Table 1** Zn(OTf)$_2$-Mediated Addition of Allyltrimethylsilane (**4**) to *N*-Acyliminium Ions Derived from **3a**–**d**



| Entry | Substrate (*R*) | Solvent | Zn(OTf)$_2$ (equiv) | Yield of **5** (%)[a,17] |
|---|---|---|---|---|
| 1 | **3b** (R = OMe) | Toluene | 1.2 | 52 |
| 2 | **3b** (R = OMe) | MeCN | 1.2 | 60 |
| 3 | **3b** (R = OMe) | $CH_2Cl_2$ | 1.2 | 78 |
| 4 | **3b** (R = OMe) | $CH_2Cl_2$ | 0.5 | 26 |
| 5 | **3b** (R = OMe) | $CH_2Cl_2$ | 0.25 | 15 |
| 6 | **3a** (R = OH) | $CH_2Cl_2$ | 1.2 | 65 |
| 7 | **3c** (R = OAc) | $CH_2Cl_2$ | 1.2 | 38 |
| 8 | **3d** (R = $SO_2$Tol) | $CH_2Cl_2$ | 1.2 | 61 |

[a] Chemical yields after column chromatography.

The scope of this transformation was evaluated next employing α-methoxy pyrrolidines and piperidines **6**–**9** under the reaction conditions employed in entry 3, Table 1. The corresponding α-allyl substituted products **10**–**13** (Figure 1) were isolated in moderate to good yields[3] with better results being observed with five-membered precursors **3b** and **7** when compared to the corresponding six-membered analogues **6** and **8** (Table 2). The resonance stabilized *N*-acyliminium ion derived from α-methoxy tetrahydroisoquinoline **9** also provided the corresponding allyl derivative in good yield (entry 5, Table 2).

Silyl enol ethers **14** and **15** also proved to be competent nucleophiles when reacted with *N*-acyliminium ions precursors **3b** and **6**–**9** affording **16**–**22** in moderate to good yields (Figure 2, Table 3).[13]

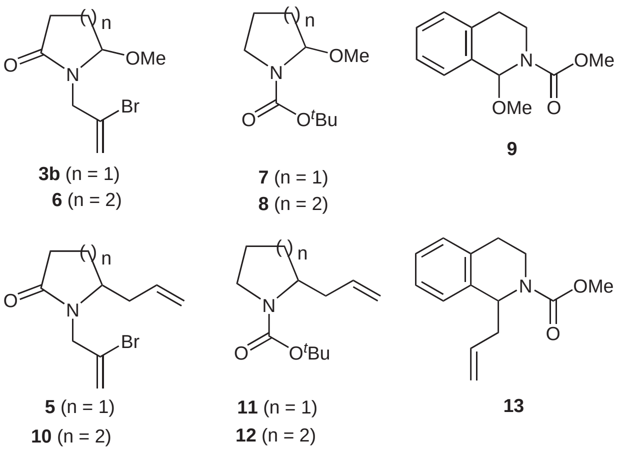


**Figure 1**

**Table 2** Zn(OTf)$_2$-Mediated Allylation Reaction of Cyclic *N*-Acyliminium Ions Derived from **3b** and **6**–**9**

| Entry[a] | Substrate | Product (%)[b] |
|---|---|---|
| 1 | **3b** | **5** (78) |
| 2 | **6** | **10** (52) |
| 3 | **7** | **11** (68) |
| 4 | **8** | **12** (52) |
| 5 | **9** | **13** (72) |

[a] Reactions were carried out employing 1.2 equiv of Zn(OTf)$_2$, 2.0 equiv of allyltrimethylsilane (**4**) in $CH_2Cl_2$ at r.t.
[b] Chemical yields after column chromatography.

As before, better yields of the corresponding coupling products were observed when six-membered *N*-acyliminium ions were involved (Table 3, entries 1, 3 and 5). These results may be due to a difference in the intrinsic electrophilic character of the five- and six-membered *N*-acyliminium ions[14] and/or in their relative rates of formation. In fact, the reaction of silyl enol ether **14** and α-methoxy lactam **6** (Table 3, entry 2) provided significant amounts (ca. 30% yield) of the corresponding unsaturated lactam suggesting the lower reactivity of the corresponding six-membered *N*-acyliminium ion. In the reactions of prochiral silyl enol ether **15** with α-methoxy carbamates **7** and **8**, the preferential formation of *erythro*-**20** and *erythro*-**21** (Table 3, entries 5 and 6, respectively) was observed with higher diastereoisomeric ratio being achieved in the reaction of six-membered α-methoxy carbamate **8** (Table 3, entry 6).[2b,15] Such behavior has been observed before in our studies involving the addition of titanium(IV) enolates of *N*-acyl-2-oxazolidinones to exocyclic five- and six-membered *N*-acyliminium ions precursors and might be related to the lower reactivity of six-membered vs. five-membered exocyclic *N*-acyliminium ions toward nucleophiles.

Finally, based on the results recently reported by Carreira and co-workers on the addition of in situ generated zinc alkynylide to *N*-acyliminium prepared from aldimines and acid halides,[16] we explored the ability of zinc triflate to promote a related sequence of events starting from substrates **3b** and **6**–**9**. In fact, treatment of a mixture of *N*-acyliminium ion precursors, acetylene and Zn(OTf)$_2$ in toluene–$CH_2Cl_2$ at room temperature with $Et_3N$ and TMEDA provided the corresponding propargylic adducts

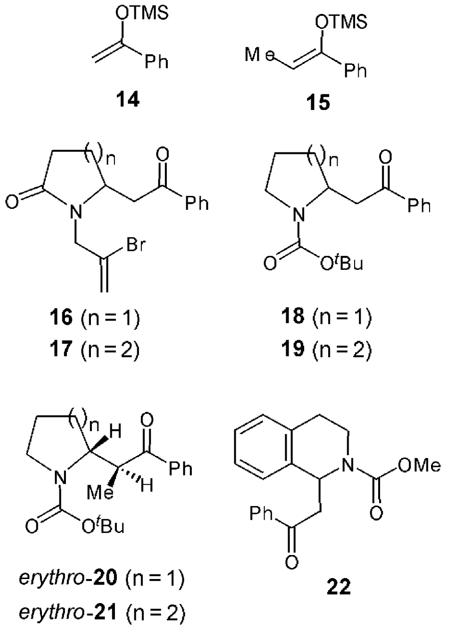


**Figure 2**

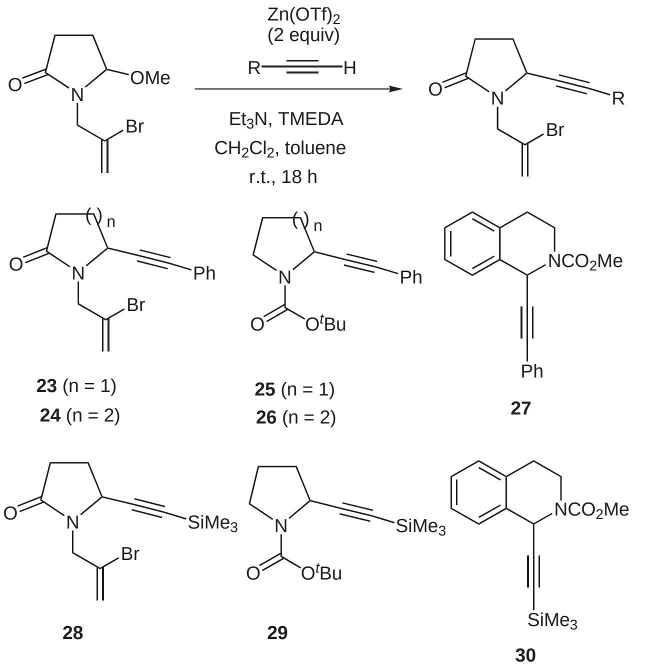
**Table 3** Zinc Triflate-Mediated Addition Reaction of Silyl Enol Ethers **14** and **15** to Cyclic *N*-Acyliminium Ions Derived from **3b**, **6**–**9**

| Entry[a] | Substrate | Sylil enol ether | Product (%)[b] |
|---|---|---|---|
| 1 | **3b** | **14** | **16** (69) |
| 2 | **6** | **14** | **17** (50) |
| 3 | **7** | **14** | **18** (71) |
| 4 | **8** | **14** | **19** (68) |
| 5 | **7** | **15** | *Erythro*-**20** (80, dr = 4:1)[c] |
| 6 | **8** | **15** | *Erythro*-**21** (63, dr = 10:1)[c] |
| 7 | **9** | **14** | **22** (80) |

[a] Reactions were carried out employing 1.2 equiv of Zn(OTf)$_2$, 1.2 equiv of silyl enol ether in $CH_2Cl_2$ at r.t.
[b] Chemical yields after column chromatography.
[c] The dr was determined by GC analysis.

**23**–**30** in moderate yields (Scheme 2, Table 4). Studies are now underway in order to extend the scope of this protocol to other *N*-acyliminium ions and acetylenes.

In summary, the use of zinc triflate as a Lewis acid in nucleophilic additions to a series of cyclic *N*-acyliminium ions afforded the corresponding products in moderate to good yields. The versatility of this reagent was demonstrated in the in situ generation of the *N*-acyliminium ion and zinc alkynylide, followed by their reaction to afford propargylic adducts in moderate yields.



**Scheme 2**

**Table 4** Zinc Triflate-Mediated Addition Reaction of Acetylenes to Cyclic *N*-Acyliminium Ions Derived from **3b**, **6**–**9**

| Entry[a] | Substrate | Acetylene | Product (%)[b] |
|---|---|---|---|
| 1 | **3b** | H–C≡C–Ph | **23** (58) |
| 2 | **6** | H–C≡C–Ph | **24** (42) |
| 3 | **7** | H–C≡C–Ph | **25** (59) |
| 4 | **8** | H–C≡C–Ph | **26** (40) |
| 5 | **9** | H–C≡C–Ph | **27** (69) |
| 6 | **3b** | H–C≡C–SiMe$_3$ | **28** (58) |
| 7 | **7** | H–C≡C–SiMe$_3$ | **29** (48) |
| 8 | **9** | H–C≡C–SiMe$_3$ | **30** (60) |

[a] Reactions were carried out employing 2.0 equiv of Zn(OTf)$_2$, 1.2 equiv of acetylene, 1.0 equiv of $Et_3N$ and 1.0 equiv of TMEDA in $CH_2Cl_2$–toluene at r.t.
[b] Chemical yields after column chromatography.

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(15) For clarity, only the structures of the major diastereoisomers *erythro*-**20** and *erythro*-**21** are depicted in Table 3. Data for *erythro*-**20**, see ref. 2b.
Data for *erythro*-**21**: $^1$H NMR ($CDCl_3$, 298 K): δ = 1.13 (d, *J* = 6.95 Hz, 3 H), 1.30–1.70 (s, 6 H); 1.50 (s, 9 H), 2.65–2.79 (s, 1 H), 4.02–4.23 (m, 2 H), 4.69–4.82 (s, 1 H), 7.50–7.60 (m, 3 H), 7.99 (d, *J* = 6.95 Hz, 2 H). $^{13}$C NMR ($CDCl_3$, 298 K): δ = 15.4, 19.6, 25.4, 27.6, 28.5, 38.8, 39.3, 53.0, 79.8, 128.4, 129.0, 133.5, 137.1, 155.6, 203.5. IR (KBr, film): 2974, 2933, 1685, 1415, 1365, 1170, 1147, 968 $cm^{-1}$. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.92; H, 8.51; N, 4.41. Found: C, 71.59; H, 8.24; N, 4.37.

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(17) **Representative Procedure.**
To a suspension of $Zn(OTf)_2$ (0.24 mmol) in dry $CH_2Cl_2$ (1 mL) at r.t. was added a substrate **3b** (0.20 mmol), diluted in dry $CH_2Cl_2$ (1 mL). After 10 min, allyltrimetylsilane (**4**, 0.40 mmol) was added. The mixture was stirred 3 h at r.t. and quenched with sat. $NaHCO_3$ (2 mL), extracted with $CH_2Cl_2$ (2 × 5 mL), dried with anhyd $Na_2SO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (5% MeOH in $CHCl_3$) to afford **5** in 78% yield.
Data for compound **5**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.74 (m, 1 H), 2.14 (m, 2 H), 2.34 (m, 3 H), 3.68 (m, 2 H), 4.60 (d, *J* = 15.8 Hz, 1 H), 5.10 (s, 1 H), 5.12 (d, *J* = 15.8 Hz, 1 H), 5.58 (s, 1 H), 5.65 (m, 1 H), 5.75 (s, 1 H). $^{13}$C NMR (300 MHz, $CDCl_3$): δ = 23.4, 29.8, 37.2, 48.2, 56.2, 118.9, 119.1, 128.2, 132.5, 175.2. IR (KBr, film): 3076, 2976, 2920, 1695, 1639, 1426, 1254, 1113, 915 $cm^{-1}$. HMRS (EI): *m/z* calcd for $C_{10}H_{14}NOBr$: 245.0239; found: 245.0242.