An Efficient Ring-Opening Reaction of Aziridines with Alkynes Catalyzed by CuOTf

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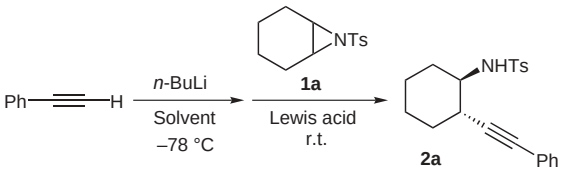
Abstract: The alkynylation of activated aziridines in the presence of a catalytic amount of CuOTf provided the corresponding ring-opened products in high yields.

Key words: aziridines, alkynylation, Lewis acids, copper(I) triflate, ring-opening reaction

Aziridines are widely used as intermediates in organic synthesis.[1] Their synthetic utilities are mainly owing to their ability to undergo regioselective ring-opening reactions with various nucleophiles. However, the most often used reagents are those O-,[2] S-[3] and N-[4] nucleophiles and a few examples were reported using carbon nucleophiles, such as Grignard reagents, organolithiums, Wittig reagents, cuprates and malonates, in the ring-opening reaction of aziridines.[5] In addition, there was structural limitation when alkynyllithiums were the reagents, only aziridines derived from acyclic alkenes gave good results.[6] As a program aimed at the applications of aziridines in organic synthesis,[7] we explored the use of alkynes as nucleophile in the ring-opening reaction of aziridines and found that CuOTf is an effective catalyst in the alkynylation of aziridines. Herein, we would like to report our preliminary results of Cu-catalyzed alkynylation of aziridines.

Initially, phenylacetylene was added to a solution of *n*-BuLi in *n*-hexane at –78 °C and the mixture was stirred for 30 minutes at the same temperature. Then aziridine **1a**, 10 mol% of Lewis acid in solvent were added (Equation 1). As shown in Table 1, Et_2O was a better solvent than THF (entries 1 and 2). CuOTf was the best catalyst among the tested Lewis acids such as $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, $In(OTf)_3$, $Cu(OTf)_2$, AgOAc or $CuClO_4$ (entry 2–8) and corresponding homopropargyl amine was obtained in 96% yield (entry 2). Control experiment showed that the yield of the product decreased to 20% in the absence of Lewis acid (entry 10). The amount of *n*-BuLi was important for the reaction and two equivalents of BuLi were necessary. When the amount of *n*-BuLi was reduced to 1.0 equivalent, the yield dropped sharply (entry 7 vs. 9). If more than two equivalents of BuLi was used, the result was same as that using two equivalents of BuLi. However, the reason is unknown at the moment.



Equation 1

Table 1 Ring-Opening Reaction of Aziridine **1a** with Phenylacetylene under Various Reaction Conditions[a]

Entry	Solvent	Lewis acid	Time (h)	Yield (%)[b]
1	THF	CuOTf [c]	46	26
2	Et_2O	CuOTf	45	96
3[d]	Et_2O	$BF_3{\cdot}OEt_2$	72	20
4	Et_2O	$In(OTf)_3$	72	25
5	Et_2O	$Cu(OTf)_2$	46	58
6	Et_2O	AgOAc	46	64
7	Et_2O	$CuClO_4$	45	64
8	Et_2O	$Sc(OTf)_3$	24	18
9[e]	Et_2O	$CuClO_4$	43	25
10	Et_2O	–	45	20

[a] Phenylacetylene:*n*-BuLi:aziridine:Lewis acid = 2:2:1:0.1.
[b] Isolated yield based on aziridine.
[c] CuOTf was used as $(CuOTf)_2{\cdot}C_6H_6$, as purchased.
[d] 1.0 Equivalent of $BF_3{\cdot}OEt_2$ was used.
[e] Phenylacetylene:*n*-BuLi:aziridine:Lewis acid = 1.1:1.1:1:0.1.

To show the usefulness of this CuOTf-catalyzed ring-opening reaction of aziridines, a variety of alkynes and various aziridines were tested (Equation 2) and the results are shown in Table 2.[8]

It can be seen from Table 2 that various aziridines with an electro-withdrawing group at nitrogen atom and several alkynes are suitable for this CuOTf-catalyzed reaction to afford the corresponding ring-opening products in good to excellent yields. The reactivity of aziridines derived from

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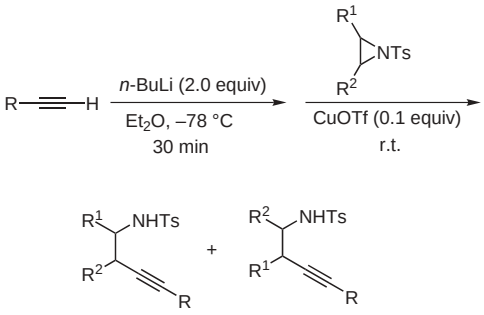


Equation 2

cycloalkenes was lower than that from acyclic alkenes but good to excellent yields could be obtained with longer reaction time (entry 1 vs. 5). Aromatic alkyne had higher reactivity than aliphatic alkyne (entry 8 vs. 10). All of the reactions with bicyclic aziridines gave products with *anti*-stereochemistry, which were confirmed by the coupling constant of **2a** (J = 9.9 Hz for two cyclic methine hydrogens at the trans-positions, entries 1–4). For aziridines derived from terminal alkenes only terminal-attacked products were obtained because of steric hindrance of the alkyl substituent (entries 5–10) and for phenyl substituted aziridine **1h**, the reaction gave two products resulting from internal as well as terminal attack of the nucleophile (entry 11).

In conclusion, a simple and convenient procedure using a variety of alkynes as nucleophile in the ring-opening reaction of aziridines was developed. Homopropargyl amines were provided in high yields. The investigations on the extension of the reaction to other substrates and on the asymmetric version of the reaction are under progress in our laboratory.

Table 2 Ring-Opening Reaction of Aziridines **1** with Alkynes Catalyzed by CuOTf[a]

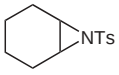
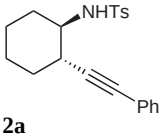
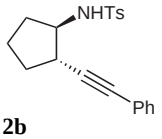
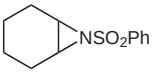
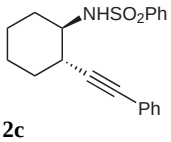
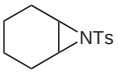
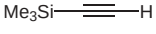
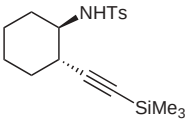
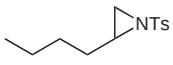
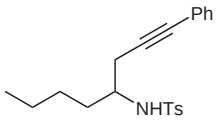
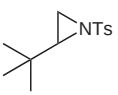
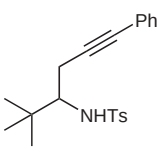
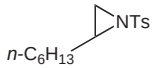
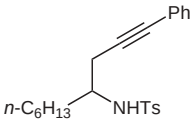
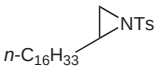
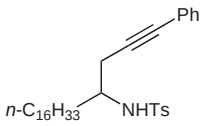
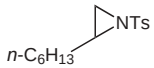
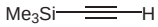
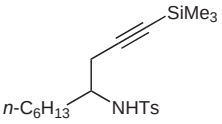
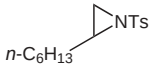
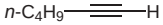
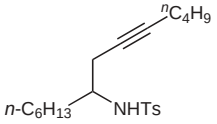
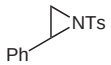
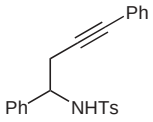
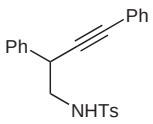
Entry	Substrate	Alkyne	Product	Time (h)	Yield (%)[b]
1	 **1a**		 **2a**	45	96
2	 **1b**		 **2b**	72	71
3	 **1c**		 **2c**	30	88
4	 **1a**		 **2aa**	72	72
5	 **1d**		 **2d**	26	95
6	 **1e**		 **2e**	48	42

Table 2 Ring-Opening Reaction of Aziridines **1** with Alkynes Catalyzed by CuOTf[a] (continued)

Entry	Substrate	Alkyne	Product	Time (h)	Yield (%)[b]
7	 **1f**		 **2f**	20	93
8	 **1g**		 **2g**	20	91
9	 **1f**		 **2fa**	45	80
10	 **1f**		 **2fb**	80	81
11[c]	 **1h**		 **2h**  **3h** **2h**/**3h** = 3/1	36	69

[a] Alkyne:*n*-BuLi:aziridine:CuOTf = 2:2:1:0.1.
[b] Isolated yield based on aziridine.
[c] The ratio of **2h**/**3h** was determined by ^{1}H NMR.

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(8) **General Experimental Procedure:** Alkyne (0.5 mmol) was added to a mixture of *n*-BuLi in *n*-hexane (0.5 mmol) and Et_2O (4.0 mL), which was precooled to –78 °C and the mixture was stirred for 30 min at the same temperature. Then CuOTf (10 mol%) and aziridine (0.25 mmol) were added. The resulting mixture was stirred at r.t. until complete consumption of substrate (monitored by TLC). The reaction mixture was quenched with 5 mL of sat. NH_4Cl aq solution. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4. The solvent was removed in vacuum and the crude product was purified by flash column chromatography on silica gel to provide corresponding homopropargyl amine. All products were fully characterized by ^{1}H NMR, mass spectrometry, infrared spectrometry and elemental analysis. The ^{1}H NMR spectra of the products are as follows (300 MHz, $CDCl_3$, 25 °C, TMS):

***N*-(2-Phenyl-1-ynyl-cyclohexyl)-4-methyl-benzenesulfonamide (2a):** ^{1}H NMR: δ = 1.24–1.27 (m, 4 H), 1.46–1.69 (m, 2 H), 1.99–2.05 (m, 1 H), 2.24–2.28 (m, 1 H), 2.31 (s, 3 H), 2.41–2.49 (m, 1 H), 3.02–3.12 (m, 1 H), 4.81 (d, *J* = 5.4 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 7.12–7.29 (m, 5 H), 7.75 (d, *J* = 8.4 Hz, 2 H).

***N*-(2-phenyl-1-ynyl-cyclopentyl)-4-methyl-benzenesulfonamide (2b):** ^{1}H NMR: δ = 1.45–1.53 (m, 1 H), 1.68–1.75 (m, 3 H), 2.04–2.15 (m, 2 H), 2.32 (s, 3 H), 2.69–2.74 (m, 1 H), 3.52–3.56 (m, 1 H), 4.80 (d, *J* = 6.0 Hz, 1 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.23–7.29 (m, 5 H), 7.78–7.82 (m, 2 H).

***N*-(2-phenyl-1-ynyl-cyclohexyl)-benzenesulfonamide (2c):** ^{1}H NMR: δ = 1.21–1.69 (m, 6 H), 1.99–2.05 (m, 1 H), 2.23–2.27 (m, 1 H), 2.42–2.50 (m, 1 H), 3.07–3.13 (m, 1 H), 4.88 (d, *J* = 5.4 Hz, 1 H), 7.24–7.47 (m, 8 H), 7.87–7.89 (m, 2 H).

***N*-(2-trimethylsilanyl-1-ynyl-cyclohexyl)-4-methyl-benzenesulfonamide (2aa):** ^{1}H NMR: δ = 0.13 (s, 9 H), 1.48–1.64 (m, 6 H), 1.89–1.94 (m, 1 H), 2.21–2.33 (m, 2 H), 2.43 (s, 3 H), 2.89–2.94 (m, 1 H), 4.80 (d, *J* = 3.6 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H).

1-Phenyl-4-*N*-(*p*-toluenesulfonyl)aminooctyne-1 (2d): ^{1}H NMR: δ = 0.82 (t, *J* = 6.6 Hz, 3 H), 1.19–1.25 (m, 4 H), 1.56–1.62 (m, 2 H), 2.41 (s, 3 H), 2.48 (d, *J* = 5.1 Hz, 2 H), 3.36–3.46 (m, 1 H), 4.71 (d, *J* = 9.3 Hz, 1 H), 7.26–7.37 (m, 7 H), 7.78 (d, *J* = 8.1 Hz, 2 H).

1-Phenyl-5,5-dimethyl-4-*N*-(*p*-toluenesulfonyl)aminohexyne-1 (2e): ^{1}H NMR: δ = 0.98 (s, 9H), 2.28–2.36 (m, 1H), 2.39 (s, 3H), 2.49-2.56 (m, 1H), 3.16-3.23 (m, 1H), 4.89 (d, *J* = 10.5 Hz, 1H), 7.24-7.35 (m, 7H), 7.79 (d, *J* = 8.1 Hz, 2H).

1-Phenyl-4-*N*-(*p*-toluenesulfonyl)aminodecyne-1 (2f): ^{1}H NMR: δ = 0.85 (t, *J* = 6.9 Hz, 3 H), 1.17–1.29 (m, 8 H), 1.52–1.62 (m, 2 H), 2.41 (s, 3 H), 2.50 (d, *J* = 4.8 Hz, 2 H), 3.37–3.45 (m, 1 H), 4.67 (d, *J* = 9.0 Hz, 1 H), 7.26–7.38 (m, 7 H), 7.78 (d, *J* = 8.1 Hz, 2 H).

1-Phenyl-4-*N*-(*p*-toluenesulfonyl)aminoicosyne-1 (2g): ^{1}H NMR: δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.17–1.30 (m, 28 H), 1.57–1.64 (m, 2 H), 2.41 (s, 3 H), 2.49 (d, *J* = 4.8 Hz, 2 H), 3.36–3.44 (m, 1 H), 4.65 (d, *J* = 9.3 Hz, 1 H), 7.26–7.38 (m, 7 H), 7.77–7.79 (m, 2 H).

1-Trimethylsilanyl-4-*N*-(*p*-toluenesulfonyl)aminodecyne-1 (2fa): ^{1}H NMR: δ = 0.15 (s, 9 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 1.15–1.26 (m, 8 H), 1.88–2.04 (m, 2 H), 2.27–2.31 (m, 2 H), 2.43 (s, 3 H), 3.28–3.33 (m, 1 H), 4.61 (d, *J* = 9.0 Hz, 1 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H).

8-*N*-(*p*-toluenesulfonyl)aminotetradecyne-5 (2fb): ^{1}H NMR: δ = 0.85 (t, *J* = 6.6 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 1.16–1.25 (m, 8 H), 1.38–1.47 (m, 6 H), 2.12–2.16 (m, 2 H), 2.17–2.21 (m, 2 H), 2.43 (s, 3 H), 3.24–3.31 (m, 1 H), 4.63 (d, *J* = 9.6 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 7.75–7.78 (m, 2 H).

1,4-Diphenyl-4-*N*-(*p*-toluenesulfonyl)aminobutyne-1 (2h) and 1,3-Diphenyl-4-*N*-(*p*-toluenesulfonyl)aminobutyne-1 (3h): (2h/3h = 3:1) ^{1}H NMR: **2h**: δ = 2.35 (s, 3 H), 2.85 (m, 2 H), 4.56 (*dd*, *J* = 6.3, 12.8 Hz, 1 H), 5.20 (d, *J* = 6.6 Hz, 1 H), 7.12–7.41 (m, 12 H), 7.63 (d, *J* = 8.4 Hz, 2 H); **3h:** δ = 2.41 (s, 3 H), 3.21–3.41 (m, 2 H), 3.99 (dd, *J* = 6.3, 8.1 Hz, 1 H), 4.72–4.76 (m, 1 H), 7.12–7.41 (m, 12 H), 7.73 (d, *J* = 8.4 Hz, 2 H).