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## Lewis Acid-catalyzed [3 + 2]Cycloaddition of Alkynes with *N*-Tosylaziridines via Carbon—Carbon Bond Cleavage: Synthesis of Highly Substituted 3-Pyrrolines

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A novel, efficient, and highly regioselective Lewis acid-catalyzed [3 + 2] cycloaddition of alkynes with azomethine ylides, which are easily obtained from *N*-tosylaziridines via C–C bond heterolysis at room temperature was developed. Moderate enantioselectivity (70% ee) can be achieved by the application of the commercially available chiral Pybox 7 as the ligand.

3-Pyrroline and pyrrolidine derivatives are common structural scaffolds in natural products and bioactive molecules. Interest in their chemistry continues unabated due to their wide usefulness as biologically active agents and as key intermediates in the organic synthesis.<sup>1</sup> Examples include the clinical candidate GSK625433,<sup>2a</sup> the chemotherapeutic natural product erysovine,<sup>2b</sup> and kinesin spindle protein inhibitor<sup>2c</sup> (Figure 1). Consequently, the efficient construction of these molecules has received significant attention. Among strategies available, the 1, 3-dipolar cycloaddition of azomethine ylides with alkynes is considered as the most straightforward convergent one.<sup>3</sup>

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<sup>(4)</sup> For the [3 + 2] Cycloaddition of azomethine ylides with electrondeficient alkynes, see: (a) Huisgen, R. Angew. Chem. Chem., Int. Ed. Engl. 1963, 2, 633. (b) Huisgen, R. Angew. Chem. Chem., Int. Ed. Engl. 1968, 7, 321. (c) Woodward, R. B.; Hoffmann, R. Angew. Chem., Int. Ed. Engl. 1969, 8, 781. (d) Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. J. Org. Chem. 1999, 64, 346. (e) Ishii, K.; Kido, M.; Noji, M.; Sugiyama, S. Org. Biomol. Chem. 2008, 6, 3186. (f) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. Org. Lett. 2003, 19, 3487. (g) Burrell, A. J. M.; Coldham, I.; Waston, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. J. Org. Chem. 2009, 74, 2290. (h) Bobeck, D. R.; Warner, D. L.; Vedejs, E. J. Org. Chem. 2007, 72, 8506.



**Figure 1.** Natural product and bioactive compounds containing 3-pyrroline scaffold.

Electron-deficient alkynes are widely used for these transformations,<sup>4</sup> in contrast, only a few examples of using electron-rich alkynes as the dipolarophile have been explored.<sup>5</sup> Herein, we wish to report a novel  $Sc(OTf)_3$ -catalyzed highly regioselective formal [3 + 2] cycloaddition of alkynes with azomethine ylides, which are obtained from the selective C–C bond cleavage of *N*-tosylaziridines under mild conditions, providing a facile, efficient route to highly substituted 3-pyrroline.

Aziridines, highly ring strained but readily accessible three membered cyclic amines, have been extensively studied in past years.<sup>6</sup> The chemistry of aziridines is contributed largely by the reactivity of C–N bonds. For example, the C–N bond cleavage of *N*-tosylaziridines under the catalysis of Lewis acid would produce a masked 1,3-dipole, which readily reacts with versatile dipolarophiles such as alkynes,<sup>7</sup>

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aldehydes/ketones<sup>8,9</sup> and nucleophiles.<sup>10</sup> However, the generation of azomethine ylides via C–C heterolysis of aziridines has been rarely explored in previous literatures due to the relatively high barrier (ca. 29 kcal mol<sup>-1</sup>).<sup>11</sup> Very recently, our group has successfully realized the C–C bond cleavage<sup>12</sup> of *N*-tosylarylaziridinyl dicarboxylate<sup>13</sup> under the catalysis of Lewis acid, leading to reactive *N*-tosylazomethine ylide, which can undergo 1,3-dipolar cycloaddition with aldehydes and electron-rich alkenes. During this study, we envisaged that electron-rich alkynes may be applied as dipolarophiles to undergo 1,3-dipolar cycloaddition to afford the corresponding highly substituted 3-pyrrolines.





entry	catalyst	solvent	time (h)	$\mathrm{yield}^{b}\left(\%\right)$	<b>3a:4a</b> <sup>c</sup>
1	$AgSbF_6$	DCM	24	9	
2	Y(OTf) <sub>3</sub>	DCM	8	42	7.7:1
3	In(OTf) <sub>3</sub>	DCM	3	71	
4	Yb(OTf) <sub>3</sub>	DCM	7	53	20:1
5	Cu(OTf)3	DCM	8	41	>20:1
6	Fe(OTf) <sub>3</sub>	DCM	10	54	>20:1
7	Sc(OTf) <sub>3</sub>	DCM	3	84	
8	Mg(OTf) <sub>2</sub>	DCM	10	24	2.2:1
9	$MgI_2$	DCM	8	10	1.6:1
10	Bi(OTf) <sub>3</sub>	DCM	8	22	5:1
11	$Sn(OTf)_2$	DCM	3	83	
12	$Ni(ClO_4)_2 \cdot 6H_2O$	DCM	9	43	>20:1
13	Sc(OTf) <sub>3</sub>	DCE	7	70	
14	Sc(OTf) <sub>3</sub>	toluene	10	61	

<sup>*a*</sup> Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), 5 mol % catalyst, and 200 mg of activated 4 Å MS in 4 mL of solvent at room temperature. <sup>*b*</sup> Isolated yield . <sup>*c*  $^{1}$ H NMR ratio. PMP = 4-methoxyphenyl.</sup>

We started to test our hypothesis by using *N*-tosylaziridine **1a**<sup>14</sup> and alkyne **2a** as model substrates. Initially, **1a** and **2a** were subjected to the solution of 5 mol % of AgSbF<sub>6</sub> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, the reaction yielded **3a** as a single regioisomer in only 9% isolated yield (Table 1, entry 1). Other commercially available and common used Lewis acids such as Y(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub>, Bi(OTf)<sub>3</sub>, Fe(OTf)<sub>3</sub>, Mg(OTf)<sub>2</sub>, MgI<sub>2</sub> and Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O were next investigated. The regiomer **4a** was formed in some cases. Finally, the best result is obtained by using 5 mol % of Sc(OTf)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>, affording **3a** in 84% isolated yield as a single regiomer (Table 1, entry 7). Other tested solvents such as 1, 2-dichloroethane, toluene cannot give better result. The structure of **3a** was confirmed by X-ray crystallography analysis.<sup>15</sup>

With the optimal reaction conditions in hand, the scope of this Lewis-acid catalyzed 1, 3-dipolar cycloaddition

<sup>(5)</sup> For the [3 + 2] cycloaddition of azomethine ylides with electronrich alkynes, see: (a) Butler, R. N.; Coyne, A. G.; Macardle, P.; Cunningham, D.; Burke, L. A. J. Chem. Soc., Perkin, Trans. 1 2001, 1391. (b) Friebolin, W.; Eberbach, W. Helv. Chim. Acta 2001, 84, 3822. An alternative method for synthesis of 3-pyrrolines via cycloaddition of azomethine ylides with nitroalkenes and subsequent elimination, see: (c) Carrie, R. Bull. Soc. Chim. Fr. 1987, 325.

**Table 2.** Study of the Reaction Scope by Variation of the Aziridine Component<sup>a</sup>



	aziridine <b>1</b>				
entry	$\operatorname{Ar}^1$	R	time (h)	isolated yield (%)	
1	Ph	Et ( <b>1a</b> )	3	<b>3a</b> (84)	
2	$4\text{-FC}_6\text{H}_4$	Et (1b)	3	<b>3b</b> (83)	
3	$4\text{-}\mathrm{Cl}\mathrm{C}_6\mathrm{H}_4$	Et (1c)	2	<b>3c</b> (84)	
4	$4\text{-BrC}_6\text{H}_4$	Et (1d)	2	<b>3d</b> (87)	
5	$4-NCC_6H_4$	$\operatorname{Et}\left(\mathbf{1e}\right)$	2	<b>3e</b> (87)	
6	$4-NO_2C_6H_4$	$Et(\mathbf{1f})$	1.5	<b>3f</b> (91)	
7	$4 - MeC_6H_4$	$\operatorname{Et}\left(\mathbf{1g}\right)$	4	3g(71)	
8	$4 - i - \Pr C_6 H_4$	Et (1h)	6	<b>3h</b> (65)	
9	$3-MeC_6H_4$	Et (1i)	4	<b>3i</b> (76)	
10	$2\text{-BrC}_6\text{H}_4$	Et (1j)	2	<b>3j</b> (85)	
11	Ph	Me (1k)	2	<b>3k</b> (83)	
12	Ph	<i>i</i> -Pr ( <b>11</b> )	3	<b>31</b> (80)	

<sup>*a*</sup> Reaction conditions: **1b** (0.4 mmol), **2a** (0.8 mmol), 5 mol % of catalyst, and 200 mg of activated 4 Å MS in 4 mL of solvent at room temperature.

reaction was explored with a variety of aziridines 1, and the results are summarized in Table 2. In general, various electron-donating and electron-withdrawing groups on the aryl moiety of 1 are compatible, affording the desired 3-pyrrolines in good yields with excellent regioselectivity. For example, the reactions of 4-halophenyl aziridines 1b, 1c, 1d and 2-bromophenyl aziridine 1j afford good yields of the corresponding products 3b, 3c, 3d and 3j as a single regiomer, respectively (Table 2, entries 2–4, 10). Aziridines with a strong electron-withdrawing -CN (1e) or  $-NO_2$  (1f) can also offer the desired cycloadducts 3e and 3f in excellent yields under standard conditions (Table 2, entries 5–6). The corresponding methyl (1k) or isopropyl dicarboxylates (1l) are also compatible, indicating that the ester does not affect the reaction (Table 2, entries 11–12).

We next turned to study the scope of this transformation with a series of internal alkynes (Scheme 1). In general, the reactions of various internal alkynes 2 with different electron-nature proceed smoothly to furnish the desired cycloadduts 3m-3u in 62-82% yields with excellent Scheme 1. Reaction of 1 with Various Alkynes<sup>a</sup>



 $^a$  Reaction conditions: aziridines (0.4 mmol), alkynes (0.8 mmol), 5 mol % of catalyst, and 200 mg of activated 4 Å MS in 4 mL of solvent at room temperature.

regioselectivity. It is noteworthy that the alkynyl bromide and TMS-protected alkyne are tolerant under the reaction conditions, producing cycloadducts 3q and 3s, which may easily undergo further functional group transformation via transition metal-catalyzed cross-coupling reaction. Furthermore, electron-deficient propiolates are also compatible for this 1,3-dipolar cycloaddition reaction. For example, 3-pyrrolines 3r and 3u could be produced in moderated yields from the corresponding 3-(4-methoxyphenyl)propiolate and 3-p-tolylpropiolate. However, the reactions with other tested terminal alkynes such as 1-ethynyl-4-methylbenzene, ethynyl benzene and methyl 4-ethynylbenzoate cannot occur, indicating that the electron-rich alkyne and electron-deficient alkynes may proceed different reaction pathway, that is, the electron-rich alkynes favor the interaction of the HOMO of the dipolarophile with the LUMO of the dipole that leads to the formation of the new bonds, whereas electron-deficient ones favor the inverse of this interaction.<sup>16</sup>

To compare the reactivity of internal alkyne with the terminal one or the aldehyde, conjugated 1,3-diyne 2k and 3-(4-methoxyphenyl)propiolaldehyde 2l were prepared and subjected to the reaction conditions (eqs 1–2). To

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our surprise, the [3 + 2] cycloaddition reactions take place highly chemoselectively at the position of the terminal alkyne and the aldehyde, affording the corresponding cycloadducts **3v** and **6** in good yields, respectively.



Our preliminary results showed that the combination of scandium triflate with the commercially available Pybox  $7^{17}$  can catalyze the [3 + 2] cycloaddition reaction, affording the desired cycloadduct **3p** in 70% ee (eq 3). The control experiment by variation of the ratio of the aziridine **1a** and **2e** showed that the present transformation does not exhibit kinetic resolution in the presence of chiral catalyst.



Synthetic applications of 3-pyrroline **3** have been showcased by the selective transformations of the representative compound **3k** (Scheme 2). 2,3,5-Trisubstituted pyrrole **8** could be obtained by decarboxylation/elimination in 65% yield by the treatment of **3k** with NaCl in DMSO at 160 °C for 3 h under N<sub>2</sub>.<sup>18</sup> Reductive hydrogenation of **3k** by Pd/C in THF would afford the highly substituted pyrrolidine **9** in Scheme 2. Synthetic Applications



85% yield with a good diasteroselectivity, which could undergo further decarboxylation/elimination to give trisubstituted 3,4-dihydro-2H-pyrrole **10** under the same conditions as above.

In summary, we have demonstrated an efficient, highly regioselective 1,3-dipolar cycloaddition reaction of alkynes and reactive *N*-tosylazomethine ylides, obtained from Lewis acid catalyzed C-C bond cleavage of *N*-tosyl aziridines under mild conditions, providing highly substituted 3-pyrrolines in good yields as a single regioisomer. Moderate enantioselectivity can be achieved by the application of Pybox 7 as a chiral ligand. Synthetic applications were also studied by the reductive hydrogenation and decarboxylation/elimination reactions. After further ligand modification and screening, we believe that better enantioselectivity can be realized. Further studies including asymmetric catalysis and expansion of the scope of dipolarophiles are ongoing in this laboratory and will be reported in due course.

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**Supporting Information Available.** Experimental details, characterization data for new compounds. This material is available free of charge via the Internet at http://pubs. acs.org.

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<sup>(15)</sup> CCDC 834825 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge form The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data\_request/cif.

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