

## Lewis Acid-Promoted Carbon–Carbon Bond Cleavage of Aziridines: Divergent Cycloaddition Pathways of the Derived Ylides

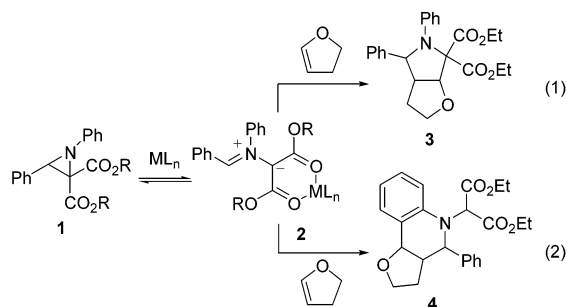
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Received November 25, 2003; E-mail: jsj@unc.edu

The chemistry of aziridines is dominated by the reactivity of the carbon–nitrogen bonds.<sup>1,2</sup> The most notable exception to this reactivity pattern is the thermal or photochemical electrocyclic ring opening of aziridines to give azomethine ylides as transient intermediates resulting from carbon–carbon bond cleavage.<sup>3–7</sup> This reaction manifold enjoys a prominent role in pyrrolidine synthesis due to the facility with which the derived 1,3-dipoles may be trapped in [3+2] cycloaddition reactions;<sup>8–10</sup> however, the development of mild variants of this C–C bond heterolysis is largely unexplored.<sup>11</sup> Herein, we document reaction conditions that, to the best of our knowledge, achieve the first productive cycloadditions of azomethine ylides obtained from Lewis acid-promoted carbon–carbon bond cleavage of aziridines. The constitution of the cycloadduct obtained is further shown to be strongly dependent on the identity of the alkene trap employed.

The activation barrier for electrocyclic carbon–carbon bond cleavage in a prototypical *N*-aryl-2,3-diester aziridine was measured by Huisgen to be ca. 29 kcal/mol, which translates to rather forcing conditions in thermal dipolar cycloadditions.<sup>12</sup> Our interest in developing mild, selective [3+2] cycloadditions of aziridines led us to the report of Carrie that described LiClO<sub>4</sub> as a Lewis acid capable of achieving carbon–carbon bond cleavage in aziridine **1**.<sup>13,14</sup> <sup>1</sup>H NMR spectroscopy indicated quantitative conversion of that aziridine to its derived lithium coordinated azomethine ylide **2**.<sup>13,14</sup> Despite the large effective concentration of the ylide in that system, no rate acceleration was observed in cycloadditions with an electron-poor dipolarophile (dimethyl fumarate, 85 °C). We hypothesized a metal-coordinated ylide such as **2** would be extremely electron-poor, thus belonging to type III in the Sustmann classification system of 1,3-dipolar cycloadditions: HOMO/LUMO matching suggests that rate acceleration should be observed with electron-rich dipolarophiles.<sup>15</sup> This reactivity pattern has been experimentally confirmed and is disclosed in this Communication.




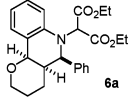

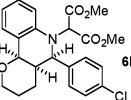

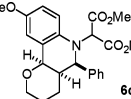

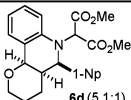

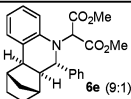

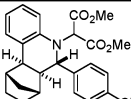

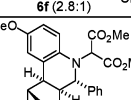

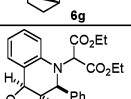
To evaluate the possibility of effecting metal-promoted cycloadditions involving **1**, a representative selection of Lewis acids including Mg(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub>, Cu(OTf)<sub>2</sub>, Sc(OTf)<sub>3</sub>, and SnCl<sub>2</sub> were tested in their ability to form adduct **3** in the presence of dihydrofuran. In addition to the anticipated [3+2] cycloadduct **3** (eq 1), a [4+2] cycloadduct (**4**) was concurrently formed (eq 2).

This adduct is most likely derived from a Mannich-type addition to the ylide, followed by intramolecular Friedel–Crafts alkylation.

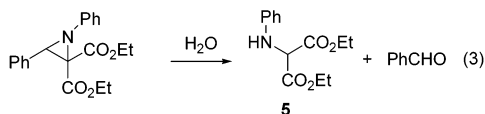
The primary focus of the initial screen was to optimize the ratio (**3** + **4**):**5**. This ratio was taken as a measure of reaction efficiency, because any unreacted aziridine is immediately hydrolyzed upon workup, yielding the substituted aniline **5** (eq 3).<sup>16</sup> Zn(II) salts, in particular ZnCl<sub>2</sub>, were most suitable in this respect and were selected for further examination.

Under optimal conditions, cycloadditions were performed using a variety of aziridines and electron-rich alkenes (eq 4). Cyclic dipolarophiles were observed to proceed primarily or exclusively through the [4+2] pathway, yielding highly substituted tetra-

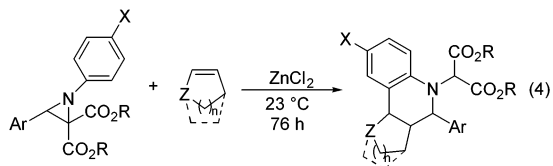
**Table 1.** Zn(II)-Promoted [4+2] Cycloadditions of Aziridines and Electron-Rich Alkenes (Eq 4)<sup>a</sup>

entry	olefin (equiv)	X, Ar	product (d.r.)	yield <sup>b</sup> ([4+2]/[3+2])
1 <sup>e</sup>	 (15.1)	H, Ph	 <b>6a</b>	79% (15:1)
2	 (15.1)	H, 4-ClPh	 <b>6b</b>	72% (7.8:1)
3	 (15.1)	MeO, Ph	 <b>6c</b>	65% (26:1)
4	 (15.1)	H, 1-Np	 <b>6d</b> (5.1:1)	49% <sup>c</sup>
5 <sup>f</sup>	 (3.0)	H, Ph	 <b>6e</b> (9:1)	82%
6	 (3.0)	H, 4-ClPh	 <b>6f</b> (2.8:1)	71%
7	 (3.0)	MeO, Ph	 <b>6g</b>	80%
8 <sup>g</sup>	 (21.7)	H, Ph	 <b>4</b> (10:1)	55% <sup>d</sup> (3.5:1)

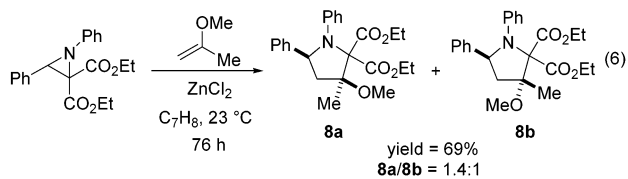
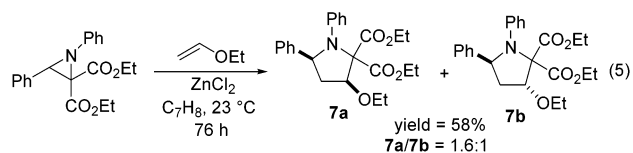
<sup>a</sup> Aziridine (1.0 equiv), ZnCl<sub>2</sub> (1.2 equiv). <sup>b</sup> Isolated yield of analytically pure [4+2] adducts only, except where noted. <sup>c</sup> Diastereomers inseparable. <sup>d</sup> Yield is combined for both [4+2] and [3+2] products. <sup>e</sup> Solvent for entries 1–4 is THF. <sup>f</sup> Solvent for entries 5–7 is CH<sub>2</sub>Cl<sub>2</sub>. <sup>g</sup> Solvent for entry 8 is toluene.



hydroquinolines with excellent diastereoselectivity (Table 1).<sup>17</sup> Only in the case of 2,3-dihydrofuran (entry 8) does the [3+2] pathway become substantial.

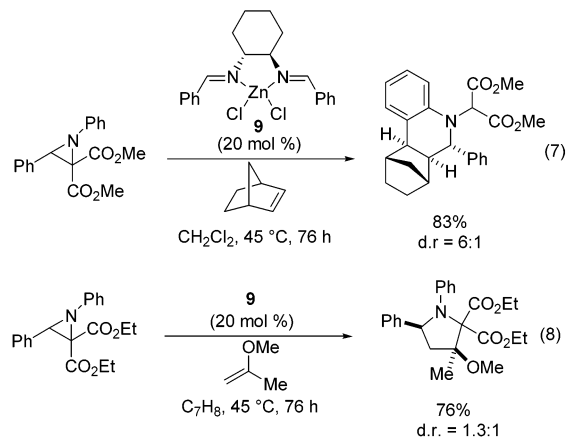


Acyclic enol ethers intercept the metal-coordinated ylide via a different mechanistic pathway: in the cases of ethyl vinyl ether (eq 5) and 2-methoxypropene (eq 6), only the [3+2] pathway is observed. The derived pyrrolidines are produced in 58% and 69% yield, respectively, with modest diastereocontrol. It is important to note that we have been unable to effectively perform these cycloadditions in the absence of Lewis acid. Dihydrofuran yields none of the [4+2] or [3+2] adduct under thermal conditions (toluene, sealed tube, 160 °C, 2 d) in the presence of **1**, while [3+2] adduct **8** is obtained in only 16% yield under the same conditions using 2-methoxypropene. These experiments indicate that Lewis acid promotion is essential and provide additional support for the type III classification of this family of cycloadditions. It is not clear from the available data whether **7** and **8** are formed by concerted or stepwise mechanisms. The cause for bifurcation in mechanism from [4+2] to [3+2] is also not known, but may be steric in nature.



Efforts to render the reaction catalytic in Lewis acid have been successful. ZnCl<sub>2</sub> alone provides only modest yields, but the derived bis(imine) complex (*N,N'*-dibenzylidencyclohexane-1,2-diamine)-ZnCl<sub>2</sub> provided good yields in both the [4+2] and the [3+2] cycloadditions at 20 mol % catalyst loading (eqs 7,8). The ZnCl<sub>2</sub> complex was more effective than the analogous Zn(OTf)<sub>2</sub> complex. While the products exhibited <5% enantiomeric enrichment, the results demonstrate that these mild cycloadditions may be conducted under catalytic conditions.

This study has documented productive metal-promoted and metal-catalyzed aziridine carbon–carbon bond cleavage reactions. The divergent [4+2] and [3+2] cycloadditions that result indicate that these processes may be useful for synthesis of a range of structurally dissimilar nitrogen-containing heterocycles. Development of enantioselective variants and an examination of the broader scope of these reactions are topics of current investigation.



**Acknowledgment.** This work was supported by an NSF CAREER grant (CHE-0239363). J.S.J. acknowledges a Nontenured Faculty Award from 3M. The authors thank Dr. P. S. White for X-ray crystallography.

**Supporting Information Available:** Experimental procedures and analytical data for all new compounds; structural and stereochemical proofs for all new compounds (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.
- (2) Dahanukar, V. H.; Zavialov, L. A. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918–927.
- (3) (a) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, 3123–3126. (b) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, 4363–4367. (c) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, 397–404.
- (4) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753–1755.
- (5) Deshong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309–2315.
- (6) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056–7066.
- (7) Garner, P.; Dogan, O.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71–85.
- (8) Harwood, L. M.; Vickers, R. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Ed.; Pearson, W. H., Eds.; Wiley and Sons: New York, 2002; Vol. 59, pp 169–252.
- (9) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 653–732.
- (10) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1–177.
- (11) Other important methods of azomethine ylide synthesis include, but are not limited to, nucleophilic attack of imines on carbenes: (a) Padwa, A.; Dean, D. C.; Osterhout, M. H.; Precedo, L.; Semones, M. A. *J. Org. Chem.* **1994**, *59*, 5347–5357. (b) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487–3490. Condensation of  $\alpha$ -amino esters with aldehydes: (c) Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Williams, C. E. *Synlett* **1993**, 777–780. (d) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089–6098. (e) Blazey, C. M.; Heathcock, C. H. *J. Org. Chem.* **2002**, *67*, 298–300. Desilylation of  $\alpha$ -silyliminium salts: (f) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441–5444.
- (12) Huisgen, R.; Scheer, W.; Mäder, H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 602–604.
- (13) Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1978**, 1195–1198.
- (14) Complex **2** is neutral; for examples of enolates derived from imines of  $\alpha$ -amino esters (2-aza-allyl anions), see: Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817–5820.
- (15) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569–593.
- (16) Texier, F.; Carrie, R. *Bull. Soc. Chim. Fr.* **1971**, 4119–4128.
- (17) Analogous products have been obtained from Lewis acid-promoted cycloaddition of *N*-aryl imines with electron-rich alkenes. See, for example: (a) Gilchrist, T. L.; Stannard, A.-M. *Tetrahedron Lett.* **1988**, *29*, 3585–3586 and references therein. (b) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357–7360.

JA0397963