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Construction of Three Contiguous Tertiary Stereocenters from Aziridines in One Step

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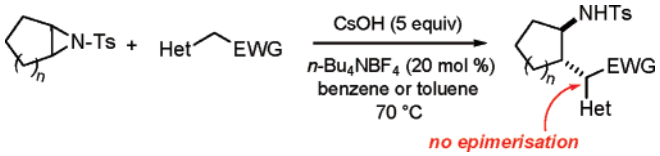
ABSTRACT



A range of active methylene nucleophiles were found to participate in ring-opening of tosylated aziridines under mild phase-transfer catalyzed conditions. High isolated yields coupled with a 1:1 reaction stoichiometry and high levels of relative stereocontrol are distinguishing features of this method. The products are obtained without epimerization, underscoring the optimal conditions afforded by the phase-transfer catalysis for connecting active methylene nucleophiles and weakly electrophilic N-tosylated aziridines.

A formidable feature of many complex molecules is the presence of a C−C−C−N structural unit that incorporates contiguous quaternary or tertiary stereocenters. Catalytic asymmetric reactions have extended the availability of highly functionalized products with contiguous stereocenters from simple starting materials.[1] Although high levels of enantioselectivity have been attained in the addition of carbon nucleophiles to imines, relative stereochemistry continues to be a significant challenge.[2] Products resulting from the asymmetric Michael addition of active methylene compounds to carbon electrophiles can theoretically give up to three chiral centers.[3] Despite the tremendous amount of work in this field[4] such reactions to date are underdeveloped.[5]

As part of a program in diastereoselective carbon−carbon bond formation, we considered ring-opening of disubstituted aziridines with prochiral carbon nucleophiles as a possible one-step access to highly substituted motifs from simple precursors (Scheme 1). If a stereochemically controlled ring opening of an aziridine with a prochiral carbon nucleophile can be realized, convergence of syntheses that rely on linchpin operations will be possible.[6] To date, there have been no examples of useful ring openings of aziridines with prochiral carbon nucleophiles.[7] Aziridines are weak electro-

(1) For recent reviews of Mannich reactions see: (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (b) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999. (e) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (f) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(2) For recent examples see: (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Cordova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383. (c) Ibrahem, I.; Cordova, A. *Chem. Commun.* **2006**, *16*, 1760. (d) Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3146. (e) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, *11*, 1191. (f) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (g) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (h) Terada, M.; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, 133. (i) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077. (j) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (k) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 2896. (l) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem Soc.* **2005**, *127*, 16408. (m) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079. (n) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476 and references therein.

(3) For recent reviews on conjugate addition to nitroalkenes, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov D. A. In *Nitroalkenes, Conjugated Nitro Compounds*; Wiley: New York, 1994. For a general review on enantioselective conjugate addition, see: (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

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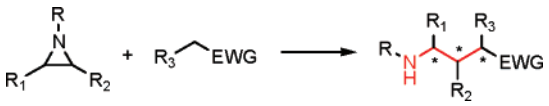
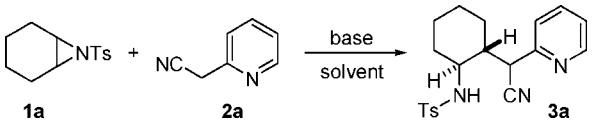
Scheme 1. Ring-Opening of Aziridines with Prochiral Nucleophiles



Scheme 2. Optimization of Reaction Conditions



philes and require nucleophilic reagents that are normally generated under strongly basic conditions. The need to use a strong base (e.g., NaH, LiTMP) limits the reagent and substrate scope and affects stereochemical outcome.[8] A noteworthy exception is efficient and mild dessymetrization of meso-aziridines with cyanide, which recently emerged from the Shibasaki group.[9]

Herein, we describe a highly diastereoselective ring-opening of meso-aziridines with a wide range of active methylene nucleophiles. This method allows to easily obtain up to three contiguous stereocenters (Scheme 2).

From a long list of prochiral carbon nucleophiles we focused on heterocyclic derivatives because of the widespread occurrence of heterocyclic fragments within natural products and pharmaceuticals.[10] Commercially available pyridin-2-yl acetonitrile **2a** served as a model.[11] A room-temperature reaction between aziridine **1a** and nitrile **2a** with NaH was ineffective (Table 1, entry 1). Elevating the temperature gave a complex reaction mixture, and the product of ring-opening was obtained in a disappointing 17% yield as a mixture of diastereomers (entry 2). Weaker bases (Et_3N, K_2CO_3, Cs_2CO_3, CsOH) proved less efficient and did not promote any reaction even at elevated temperatures, even though **2a** is known to readily undergo irreversible electrophilic attack on acid chlorides, activated halo(het)arenes, alkyl halides, and esters under these conditions.[12] On the other hand, application of strong bases or elevating the reaction temperature has led to several unidentified byproducts. The intermolecular base-promoted dimerization of nitrile **2a** is among the factors that contribute to low chemoselectivity.[13] Despite the disappointing selectivity and low yield, isolation of **3a** was significant in showing that 2-azahetarylacetonitriles, progenitors of tertiary nitrile-substituted stereocenters, participate in the aziridine ring-opening. In an attempt to generate the nucleophilic species without using a strong base, we evaluated phase-transfer

Table 1. Optimization of Reaction Conditions

entry	solvent/temp/time	base	**3a** (%)[a]
1	DMF/0 °C/5 h	NaH	n.r.
2	THF−DMSO/0 °C → 45 °C/12 h	NaH	17
3	different solvents 80 °C/5 h	Et_3N or K_2CO_3 or Cs_2CO_3 or $CsOH·H_2O$	n.r.
4	benzene/70 °C/2 h	$CsOH·H_2O$; PTC [b]	86[c]
5	benzene/70 °C/2 h	CsOH (50 w/w aq) or $CsOH·H_2O$; PTC (20%)[b]	94[c]

[a] n.r. = no reaction. [b] *n*-Bu_4NBF_4 was used as the phase transfer catalyst. [c] Yield of isolated **3a** after chromatography from reaction carried out on 0.5 mmol scale.

(4) For recent examples of asymmetric catalytic conjugate addition to nitroalkenes see: (a) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984. (b) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321. (c) Lu, S.; Du, D.; Xu, J.; Zhang, S. *J. Am. Chem. Soc.* **2006**, *128*, 7418. (d) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (e) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (f) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (g) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (h) Poulsen, T. B.; Bell, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2006**, *4*, 63. (i) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1254. (j) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (k) Xu, Y.; Zou, W.; Sunden, H.; Ibrahem, I.; Cordova, A. *Adv. Chem. Catal.* **2006**, *348*, 418. (l) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (m) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (n) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995. (o) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611 and references therein.

(5) For examples of the construction of three contiguous stereocenters adjacent to nitrogen atom in one step see: (a) Gui-Ling, Z.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 7417. (b) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312. (c) Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. *Org. Lett.* **2005**, *7*, 4539. (d) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 349. (e) Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913−916.

(6) For our recent inroads in developing linchpin-based strategies, see: Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772.

(7) For recent reviews see: (a) Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (d) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (e) McCoull, W.; Davis, F. A. *Synthesis*, **2000**, *10*, 1347. (f) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599.

(8) For examples of aziridine-ring-opening with C-nucleophiles see: (a) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *Org. Lett.* **2005**, *7*, 3295. (b) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509. (c) Mueller, P.; Riegert, D.; Bernardinelli, G. *Helv. Chim. Acta* **2004**, *87*, 227. (d) Stamm, H. *J. Prakt. Chem.* **1999**, *341*, 319. (e) Pen-Yuan, L.; Gunter, B.; Stamm, H. *J. Prakt. Chem.* **1993**, *335*, 23 and references therein.

(9) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.

(10) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, England, 2002.

(11) For synthesis of starting materials **1a** and **1b** see: (a) Ando, T.; Kano, D.; Minakata, S.; Rya, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485−13494. For **1c**: (b) Warnhoff, H.; Thiemig, H. A. *Chem. Ber.* **1985**, *118*, 4473−4485. For **1d**: (c) Mordini, A.; Russo, F.; Valachi, M.; Zani, L.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron*, **2002**, *58*, 7153−7164. For **2b**: (d) Das, J.; Laxman Rao, C. V.; Sastry, T. V. R. S.; Roshaiah, M.; Sankar, P. G.; Khadeer, A.; Kumar, M. S.; Mallik, A.; Selvakumar, N.; Iqbal, J.; Trehan, S. *Bioorg. Med. Chem. Lett.* **2005**, *12*, 337−343. For **2c**: (e) Moon, M. P.; Komin, A. P.; Wolfe, J. F.; Morris, G. F. *J. Org. Chem.* **1983**, *48*, 2392−9. For **2d**: (f) Zohdi, A. O.; Hussein, F.; Mohamed, G. S. *Heteroat. Chem.* **1999**, *10*, 508−516. For **2f**: (g) Fischer, F. *Can. J. Chem.* **1978**, *56*, 3072, 3076. For **2g**: Volovenko, Y. M.; Kupchevskaya, I. I.; Litvenko, S. V.; Babichev, F. S. *Ukr. Khim. Zhurn.* **1991**, *54*, 419−23. For **2h**: Danner, P.; Bauer, M.; Phukan, P.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, *2*, 317−325.

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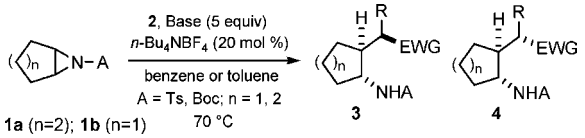
(13) Gutsche, C. D.; Voges, H. W. *J. Org. Chem.* **1967**, *32*, 2685.

catalysis.[14] To our delight, quaternary ammonium salts were found to catalyze smooth ring-opening. The best results were achieved with CsOH and *n*-Bu_4NBF_4 (Scheme 3).[15] We were

Scheme 3. Construction of Contiguous Stereocenters from Aziridines and Active Methylene Nucleophiles.



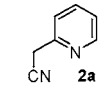
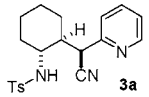
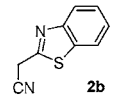
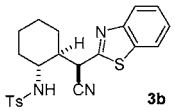
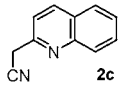
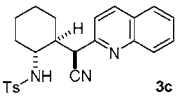
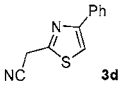
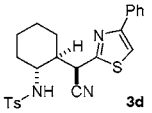
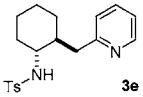
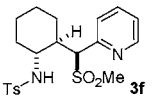
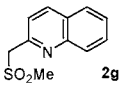
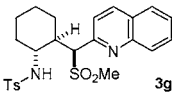
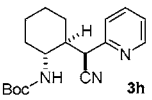
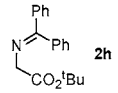
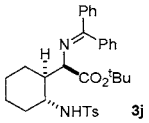
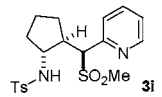
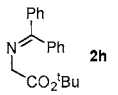
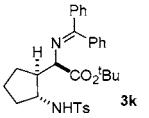
gratified to observe a clean conversion of aziridine **1a** into the ring-opened product **3a** within 2 h in 94% isolated yield (Table 1, entry 5). A wide range of carbon nucleophiles participated in ring-opening of aziridines with high diastereoselectivities (Table 2).

The most interesting feature of this reaction are kinetic control of product formation and lack of epimerization. The *S,S,R* stereochemistry of the major diastereomer was assigned on the basis of 2D NMR and X-ray crystallographic analysis. Interestingly, the AM1 calculations suggest that the minor product, the *R,S,R* diastereomer, is more stable by only 0.33 kcal/mol. These facts suggest that the stereoselectivity is not thermodynamic in origin but is kinetically controlled and that epimerization does not operate under the reaction conditions.

To verify this hypothesis, the pyridine derivative **3a** was subjected to the reaction in the presence of D_2O (CsOH−D_2O-benzene, 80 °C, 3 h). While the NH proton underwent exchange, no deuterium incorporation into the methyne functionality was detected, confirming the kinetic selectivity (Figure 1).[16] The epimerization via intramolecular proton transfer to amide anion can account for poor diastereoselectivity with the nitrile-stabilized carbanions.[17] The intramolecular epimerization does not operate here, because alkylation of an active methylene derivative gives rise to a methine product with lower CH-acidity, which does not epimerize under phase transfer conditions.[18]

In contrast to our observations with aziridines, ring opening of epoxides with phenylacetonitrile under similar PTC-conditions delivers no diastereoselectivity.[19] The C−C bond-formation in our reaction likely occurs with the appropriate

Table 2. Construction of Contiguous Stereocenters from Aziridines and Active Methylene Nucleophiles

entry	nuclephile	product	yield[a]	dr3/4[b]
1	 2a	 3a	94%[e]	96:4 > 99:1[c]
2	 2b	 3b	92%[d]	86:14
3	 2c	 3c	71%[e]	93:7
4	 3d	 3d	60%[e]	> 99:1[c]
5	 2e	 3e	64%[d]	—
6	 2f	 3f	95%[e]	95:5 > 99:1[c]
7	 2g	 3g	92%[e]	> 95:5
8	 2a	 3h	30%[e]	95:5 > 99:1[c]
9	 2h	 3j	52%[d]	80:20 > 99:1[c]
10	 2f	 3i	96%[e]	> 99:1
11	 2h	 3k	52%[d]	83:17

[a] Isolated yields for reactions carried out on 1 mmol scale. [b] Determined by ^{1}H NMR or/and chiral HPLC. [c] dr after recrystallization. [d] CsOH monohydrate was used as a base. [e] CsOH 50% w/w aq solution was used.

geometry as described in Figure 2 so as to minimize steric interactions.

The 1:1 stoichiometry of the reaction is notable for an alkylation process, especially with competing background reactions. The reaction mixture initially acquires a deep color characteristic of the anion being generated, which subsequently disappears to give almost colorless solution. Commercially available nitriles **2b**−**d**, glycine derivative **2h**, and readily accessible methylsulfonate derivatives **2f** and **2g** were

(14) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994.

(15) Several tetrabutylammonium salts (Bu_4NX, X = Cl, Br, and I) were reported to be effective in aziridine ring-opening. The X-opened products were obtained. For instance, see: Fan, R. H.; Zhou, Y. G.; Zhang, W. X.; Hou, X. L.; Dai, L. X. *J. Org. Chem.* **2004**, *69*, 335. This fact suggests that selection of the optimal quaternary ammonium salt counterion is important to avoid undesired products.

(16) Subjecting diastereomerically pure **3a** to NaH/THF at 50 °C for 30 min resulted in a 3:2 mixture of diastereomers.

(17) Viteva, L.; Gospodova, T.; Stefanofsky, Y.; Simova, S. *Tetrahedron* **2005**, *61*, 5855.

(18) For recent reviews on asymmetric phase-transfer catalysis, see: (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000, p 123.

(19) Marković, R.; Dimitrijević, G.; Aleksić, V. *J. Chem. Research (S)* **1997**, 66.

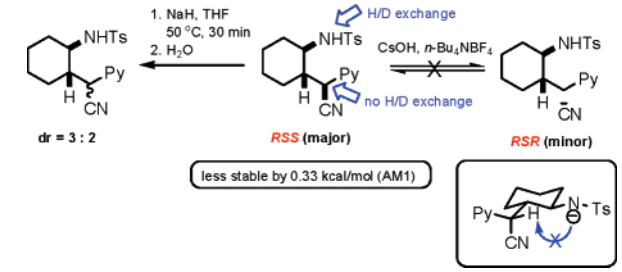


Figure 1. Epimerization and deuterium exchange of **3a**.

successfully used as nucleophiles (Table 2). The reaction can be performed on a multigram scale, and we anticipate no issues with further scale-up. Furthermore, simple recrystallization upgrades the diastereomeric purity of each product to >99%.

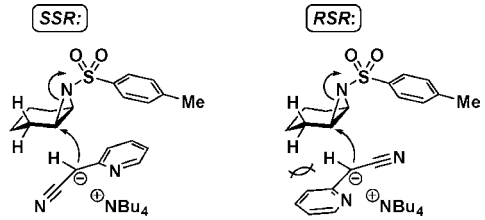
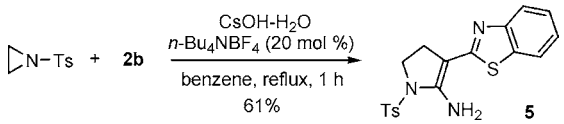


Figure 2. Mechanistic rationale for observed diastereoselectivity of **3a**.

The ester **2e** proved to be an interesting substrate (entry 5) furnishing the pyridine derivate **3d** as the only product, through hydrolysis and decarboxylation of the initially generated adduct. Consequently, **2e** represents an α-picoline-anion equivalent. *N*-Tosyl cyclopentenimine **1b** underwent efficient ring-opening with methylsulfonyl derivative **2f** and ester **2h** (entries 10 and 11). Although we have focused on fused meso-aziridines, nonfused systems also proved to be highly reactive. Thus new method provides access to 3,4-dihydro-2-aminopyrrole system through the ring-opening followed by intermolecular Thorpe cyclization (Scheme 4).

Scheme 4. Ring-Opening of Nonfused Aziridines



In closing, in our search for the construction of contiguous stereocenters next to nitrogen, we have discovered that diverse carbon nucleophiles can be used in aziridine ring-openings under mild conditions with high levels of relative stereocontrol and without concomitant epimerization. The phase-transfer catalysis affords optimal reactivity between active methylene nucleophiles and weakly electrophilic aziridines. The reaction can be performed in a 1:1 stoichiometry. Since many active methylene anion precursors and aziridines can be easily prepared or purchased, this finding should significantly expand availability of aziridine-based C−C disconnections in synthesis.

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Supporting Information Available: Experimental procedures, characterization data for all unknown compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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