ORGANIC LETTERS

2009
Vol. 11, No. 24
5698−5701

Unexpected Multiple Electrophilic Addition Reaction of (*Z*)-Alk-2-en-4-ynoates with *N*,*N*-Dibromo-*p*-toluenesulfonamide ($TsNBr_2$): A Highly Diastereoselective Synthesis of Densely Functionalized Aziridines

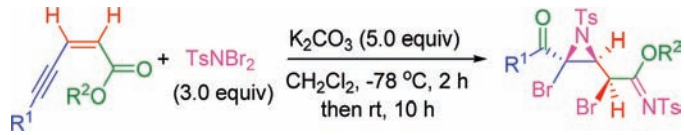
Ruwei Shen[†] and Xian Huang*[,†,‡]

Department of Chemistry, Zhejiang University, Hangzhou 310028, P. R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China

huangx@mail.hz.zj.cn

Received October 24, 2009

ABSTRACT



A novel electrophilic addition reaction of (*Z*)-alk-2-en-4-ynoates and $TsNBr_2$ is reported, providing a facile and highly stereoselective synthesis of densely functionalized aziridine derivatives.

Aziridines, the smallest saturated azaheterocycles, are structurally unique and possess many interesting chemical properties.[1,2] They have been widely employed as valuable intermediates for the synthesis of a variety of heterocycles including α-lactams, tetrahydropyridines, indolizidine, and alkaloids.[3] Moreover, the aziridine skeleton also shows up in naturally occurring compounds with interesting bioactivity[4] and has been frequently found as a key structural unit in synthetic pharmaceuticals for antibacterial, antileukemic, antibiotic, and anticancer treatment.[5] Thus, developing efficient approaches to aziridine derivatives, particularly with high stereoselectivity, is of considerable importance, and much effort has been devoted to this area.[6,7] We reported herein a facile synthesis of a novel class of densely functionalized

[†] Zhejiang University.
[‡] Chinese Academy of Sciences.

(1) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (b) Padwa, A. *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 1, pp 1−104.

(2) (a) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93–124. (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (c) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (d) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (e) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(3) (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (b) Kumar, K. S. A.; Chaudhari, V. D.; Puranik, V. G.; Dhavale, D. D. *Eur. J. Org. Chem.* **2007**, 4895. (c) Kumar, K. S. A.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol. Chem.* **2008**, *6*, 703. (d) Smith, A. B., III; Kim, D. *Org. Lett.* **2004**, *6*, 1493. (e) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995. (f) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357. (g) Caldwell, J. J.; Craig, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2631. (h) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem.* **2005**, *3*, 213.

(4) (a) Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305. (b) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049. (c) Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohnos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184. (d) Gerhart, F.; Higgins, W.; Tardif, C.; Ducep, J. *J. Med. Chem.* **1990**, *33*, 2157.

(5) (a) Han, I.; Kohn, H. *J. Org. Chem.* **1991**, *56*, 4648. (b) Skibo, E. B.; Islam, I.; Heileman, M. J.; Schultz, W. G. *J. Med. Chem.* **1994**, *37*, 78. (c) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177. (d) Dahanukar, V. H.; Zavialov, I. A. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918.

10.1021/ol902446h
Published on Web 11/18/2009

C-bromine-substituted aziridines[8] from an unprecedented highly regio- and stereoselective electrophilic addition reaction of (*Z*)-alk-2-en-4-ynoates with *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$).

Electrophilic addition of unsaturated C−C bonds with various electrophiles is one of the most important transformations, which has been continuously explored in the search for highly selective reactions.[9] Recently, the utility of $TsNBr_2$ as an electrophilic reagent has attracted our attention because of its simplicity, efficiency, and unique chemical behavior.[10] In addition to acting as a typical source of a bromonium ion, this reagent also could provide sulfonamide as the nucleophilic counterpart to construct C−N bonds, serving as a good aminobromination reagent.[11] Previously we found that the electrophilic addition of 2,3-allenoates with $TsNBr_2$ could proceed with high regio- and stereoselectivity, affording a variety of 3-bromo-4-oxo-*N*′-tosyl-2-alkenoxylimidic acid derivatives.[12] The unique reactivity demonstrated in this reaction prompts us to further study its interaction with other unsaturated substrates. When the reaction of (*Z*)-ethyl 5-phenylpent-2-en-4-ynoate **1a** (0.35 mmol) and $TsNBr_2$ (0.35 mmol) was performed in CH_2Cl_2 with K_2CO_3 (2.0 equiv) at −65 °C to room temperature, we obtained a white solid **2a** (83 mg) together with 52% of **1a** recovered (eq 1). The reaction showed good selectivity as the diastereomeric ratio indicated from the ^1H NMR spectra was up to 9:1. From spectroscopic and X-ray diffraction analysis, we finally identified that **2a** contained a C-bromine-substituted aziridine unit together with three stereogenic centers. Structure of the dominating isomer of **2a** was shown in Figure 1.[13]

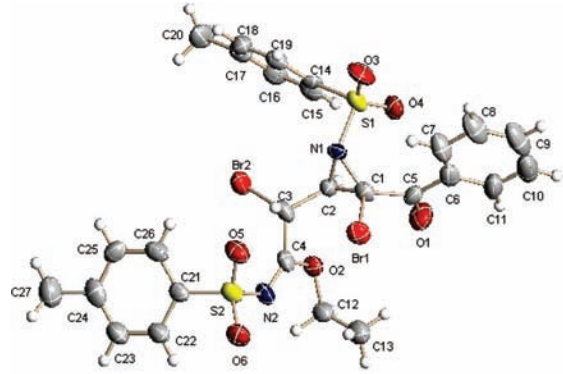
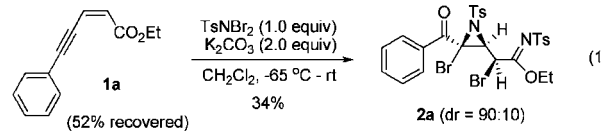


Figure 1. ORTEP representation of the major isomer of **2a**.



With these promising results, we next focused our efforts on optimization of this reaction. The yield of **2a** significantly increased as more equivalents of $TsNBr_2$ were used (Table 1, entries 1−6). When **1a** (0.35 mmol) was treated with $TsNBr_2$ (3.0 equiv) in the presence of K_2CO_3 (5.0 equiv) at −78 °C for 2 h followed by slowly warming to room temperature and stirring for another 10 h, the reaction furnished **2a** in 71% yield with a 91:9 diastereomeric ratio, which was established as the standard conditions for subsequent studies (entry 6). In addition to the formation of **2a** in the reaction, we also detected a trace amount of byproduct **3a** after careful examination of the crude products. Although the obtained amount of **3a** was not enough for a full characterization to confirm the precise structure, we supposed based on the ^1H NMR spectrum and ESIMS analysis that **3a** might be the ester derivative of **2a**, which prompted us to speculate that the formation of **3a** may result from the presence of a small amount of H_2O in the reaction system.[14] Therefore, the reaction of **1a** and $TsNBr_2$ in the presence of H_2O (10 equiv) at −78 °C was immediately conducted following a similar procedure. It was found that under these conditions the reaction proceeded as well to give 58% yield of **2a**, while a considerable amount of **3a** (7%) was also formed. The structure of **3a** was finally established based on X-ray crystallography.[15] Furthermore, it was also

(6) (a) Schaumann, E.; Kirschning, A. *Synlett* **2007**, 177. (b) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (c) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (d) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145.

(7) For recent examples for the synthesis of aziridines, see: (a) Concellon, J. M.; Rodriguez-Solla, H.; Bernad, P. L.; Simal, C. *J. Org. Chem.* **2009**, *74*, 2452. (b) Musio, B.; Clarkson, G. J.; Shipman, M.; Florio, S.; Luisi, R. *Org. Lett.* **2009**, *11*, 325. (c) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351. (d) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 58760. (e) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354. (f) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 68445. (g) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453. (h) Concellón, J. M.; Álvarez, J. R.; Garcı´a-Granda, S.; Dı´az, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4333. (i) Zheng, J.-C.; Liao, W.-W.; Sun, X.-X.; Sun, X.-L.; Tang, Y.; Dai, L.-X.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5789. (j) Roth, P.; Somfai, P.; Andersson, P. G. *Chem. Commun.* **2002**, 1752.

(8) For review on C-heteroatom-substituted azirdines, see: Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.

(9) (a) Armstrong, A.; Convine, N. J. One or More CC Bonds Formed by Addition: Addition of Carbon Electrophiles and Nucleophiles to CC Multiple Bonds. *Compr. Org. Funct. Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier, 2004; pp 287−311. (b) Larock, R. C. Synthesis of Heterocycles and Carbocycles by Electrophilic Cyclization of Alkynes. *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 2, pp 51−99. (c) Smit, W. A.; Caple, R. I.; Smoliakova, P. *Chem. Rev.* **1994**, *94*, 2359. (d) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354. (e) Ma, S. *Pure Appl. Chem.* **2007**, *79*, 261.

(10) For preparation of $TsNBr_2$, see: Saburo, A.; Kenzo, O. *J. Am. Chem. Soc.* **1954**, *76*, 693.

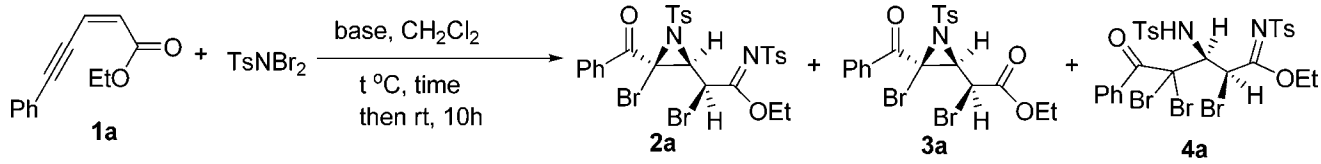
(11) (a) Kharasch, M. S.; Priestley, H. N. *J. Am. Chem. Soc.* **1939**, *61*, 3425. (b) Terauchi, H.; Kowata, K.; Minematsu, T.; Takemura, S. *Chem. Pharm. Bull.* **1977**, *25*, 556. (c) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. (d) Revesz, L.; Blum, E.; Wicki, R. *Tetrahedron Lett.* **2005**, *46*, 5577. (e) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526. (f) Phukan, P.; Chakraborty, P.; Kataki, D. *J. Org. Chem.* **2006**, *71*, 7533.

(12) Shen, R.; Huang, X. *J. Org. Chem.* **2007**, *72*, 3961.

(13) X-ray crystal data for **2a**: $C_{27}H_{26}Br_2N_2O_6S_2$; MW = 698.44; Triclinic, space group *P*-1; a = 11.298(2), b = 11.271(2), c = 12.235(2) Å; α = 74.563(3), β = 72.728(3), γ = 72.866(3), V = 1394.2(4) Å^3, T = 293 (2) K, Z = 2, ρ_{calcd} = 1.664 Mg/m^3, μ = 3.102 mm^{-1}, λ = 0.71073 Å; F(000) 704, independent reflections (R_{int} = 0.0450), 7423 reflections collected; refinement method, full-matrix least-squares refinement on F_2; goodness-of-fit on F_2 = 1.096; final R indices [$I > 2\sigma(I)$] R_1 = 0.0657, wR_2 = 0.2017.

(14) The trace amount of H_2O may be from the reagents used.

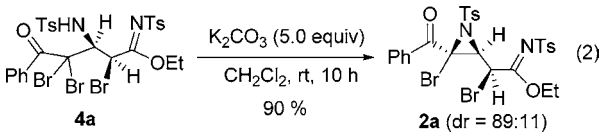
Table 1. Optimization of the Reaction Conditions of (*Z*)-Ethyl 5-Phenylpent-2-en-4-ynoate **1a** with $TsNBr_2$ to Yield Aziridine **2a**[a]



entry	$TsNBr_2$ (equiv)	t (°C)	time (h)	base[c]	yield (%)[d] 2a	3a	4a	dr (**2a**)[e]
1	2	−65	-	K_2CO_3	51[f]	trace	-	90:10
2	2	−78	-	K_2CO_3	55[f]	trace	-	90:10
3	2.5	−78	-	K_2CO_3	60[f]	trace	-	90:10
4	3	−78	-	K_2CO_3	63	trace	-	90:10
5	3	−78	1	K_2CO_3	67	trace	-	91:9
6	3	−78	2	K_2CO_3	71	trace	-	91:9
7	3	−78	2	-	-	-	68	
8	3	−78	2	Na_2CO_3	-	-	63	
9	3	−78	2	Li_2CO_3	-	-	44	
10	3	−78	2	K_2CO_3+ H_2O (10 equiv)	58	7[g]	-	91:9

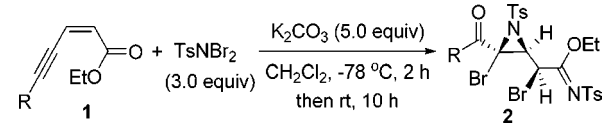
[a] The reactions were carried out on a scale of 0.35 mmol of **1a** in 3 mL of CH_2Cl_2 and quenched with saturated Na_2SO_3 after completion. CH_2Cl_2 was distilled once from CaH_2. [b] Reaction time at the specified temperature before the reaction mixture was slowly warmed to room tempterature. [c] 5.0 equiv was used. [d] Isolated yields. [e] Deduced by H NMR. [f] Small amount of **1a** was observed by TLC after completion. [g] dr = 92:8 (deduced by ^1H NMR).

found that the presence of K_2CO_3 is crucial. When the reaction was conducted in the absence of K_2CO_3, **4a**[16] was isolated as the main product (entry 7). Further experiments demonstrate that treatment of **4a** with K_2CO_3 in CH_2Cl_2 led to the formation of **2a** in 90% yield, indicating that **4a** might be the possible intermediate in the reaction (eq 2). Notably, Li_2CO_3 and Na_2CO_3 were both ineffective to furnish azirdine **2a** (entries 8 and 9).



The scope of the reaction was investigated under the established conditions. As indicated in Table 2, a variety of (*Z*)-alk-2-en-4-ynoates **1** that bear aromatic groups including *p*-Me, *p*-MeO, *m*-Me, *p*-Cl, and *p*-Et substituted phenyl groups were applicable, affording the corresponding aziridines **2** in good yields with high stereoselectivity (entries 1−6). Notably, the cyclohexenyl and cyclopropyl groups, i.e., **1g** and **1h**, were also tolerated in the reaction, affording the corresponding products **2g** and **2h** in 65% and 68% yields, with the dr value of 89:11 and 87:13, respectively. However, when (*Z*)-ethyl non-2-en-4-ynoate **1i** was employed, the reaction gave the product **2i** in 42% yield, together with the monoaddition product **2i′** in 21% yield (entry 9), which indicates that the substituent at the terminus of the alkyne may have a significant effect on the outcome of the reaction.

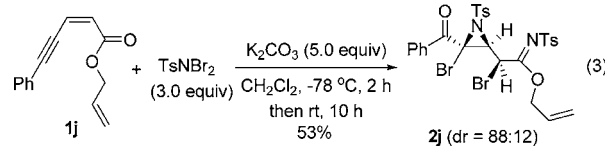
Table 2. Reaction of (*Z*)-Alk-2-en-4-ynoates **1** with $TsNBr_2$ to Yield Polyfunctional Aziridine Derivatives **2**[a]



entry	R	**2**	yield (%)[b]	dr[c]
1	Ph	**2a**	71	91:9
2	*p*-MeC_6H_4	**2b**	70	91:9
3	*p*-MeO C_6H_4	**2c**	68	92:8
4	*m*-Me C_6H_4	**2d**	66	93:7
5	*p*-Et C_6H_4	**2e**	69	93:7
6	*p*-Cl C_6H_4	**2f**	70	90:10
7	1-cyclohexenyl	**2g**	65	89:11
8	cyclopropyl	**2h**	68	87:13
9	*n*-Bu	**2i** (**2i′**)[d]	42 (21)	85:15

[a] **1** (0.35 mmol), $TsNBr_2$ (1.05 mmol), K_2CO_3 (1.75 mmol), CH_2Cl_2 (3 mL). [b] Isolated yields. [c] Deduced by ^1H NMR. [d] The exact structure was not determined (for spectral data, see Supporting Information).

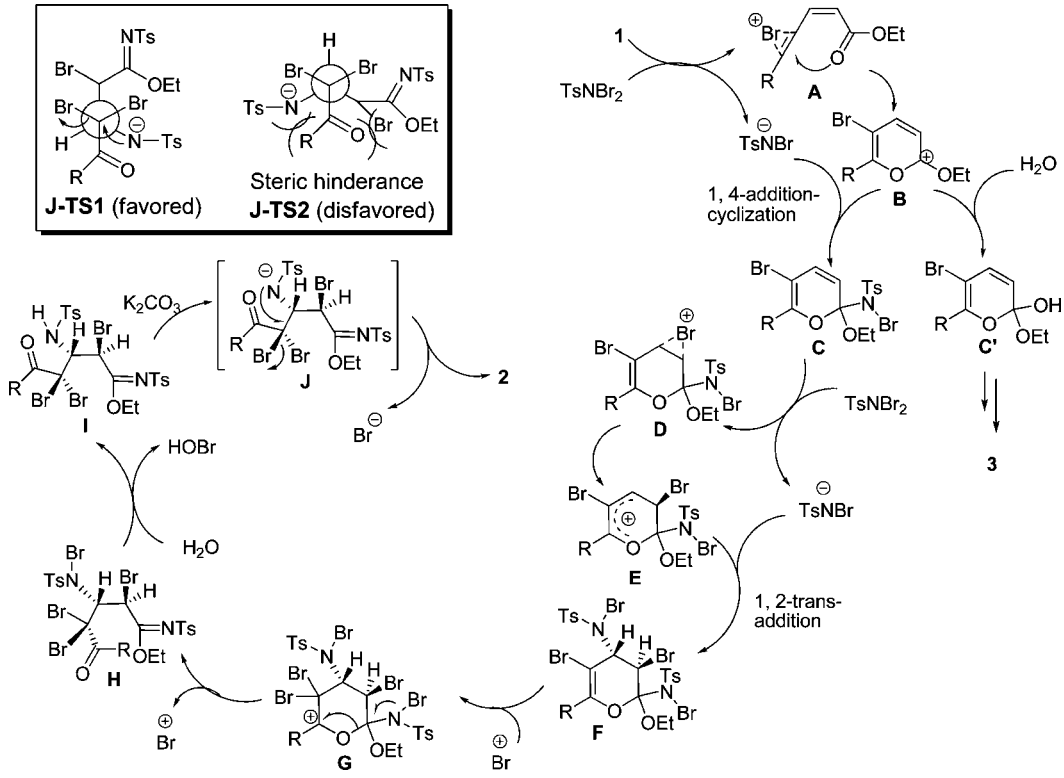
Furthermore, we also examined the reaction of $TsNBr_2$ and (*Z*)-allyl 5-phenylpent-2-en-4-ynoate **1j**. The attached allyl group was also tolerated, affording the corresponding aziridine **2j** in 53% yield (eq 3).



On the basis of the obtained results, we proposed a plausible mechanism as depicted in Scheme 1. First, the

(15) X-ray crystal data for **3a**, see Supporting Information.
(16) X-ray crystal data for **4a**, see Supporting Information.

Scheme 1. Proposed Mechanism for the Formation of Aziridines



bromonium ion generated from $TsNBr_2$ reacts with the relatively electron-rich triple bonds of **1** to produce bromiranium ion **A**. The participation of the ester carbonyl group may facilitate the formation of a cyclic cation **B** via a regioselective 6-endo attack, which then is subjected to the nucleophilic attack of $[TsNBr]^-$ to produce cyclic intermediate **C**. The second step of electrophilic addition may occur to give a relatively stable cyclic cation **E** via bromiranium ion **D**, which is followed by a highly stereoselective nucleophilic attack, furnishing the polyfuctionilized dihydropyran **F**, wherein the installed bromonium atom and [TsNBr] group are in trans position. Then, the double bonds of **F** may be subjected to the electrophilic addition of another bromonium ion to produce an oxygen-stabilized carboncation **G**, which further evolves into the possible intermediate **H** with loss of a bromonium ion. **H** may be quite unstable and easily react with H_2O to form the sulfonamide **I**, which then lose a proton in the presence of K_2CO_3 and undergo a highly stereoselectively intramolecular SN2 reaction to yield the final product **2**. The high stereoselectivity of this step can be explained by the fact that the intramolecular SN2 reaction of intermediate **J** proceeds with a remarkable preference via a less steric hindrance transition state **J-TS1**, forming the aziridine unit wherein the bromonium atom is in trans position to the hydrogen atom. The formation of byproduct **3** may originate from a similar process of the possible intermediate **C′**.

In conclusion, we have observed a highly regio- and stereoselective electrophilic addition reaction of (*Z*)-alk-2-en-4-ynoates and $TsNBr_2$, resulting in a novel class of C-bromine-substituted aziridine derivatives containing three stereogenic centers. The reaction involves a consecutive process of multibonds formation including C−N, C−O, and C−Br bonds with high regio- and stereoselectivity. Studies into the scope and limitation of the reaction as well as the detailed mechanism and synthetic application of the afforded densely functionalized aziridines are being pursued in our laboratory.

Acknowledgment. Financial support from the National Natural Science Foundation of China (Project NO. 20732005 & 20872127) and National Basic Research Program of China (973 Program, 2009CB825300) is gratefully acknowledged.

Supporting Information Available: Spectroscopic data for **2a**−**j**, **2i′**, **3a**, and **4a**. X-ray crystal data for **2a**, **3a**, and **4a**. Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902446H