ORGANIC LETTERS

2009
Vol. 11, No. 5
1119−1122

Tandem Ring-Opening/Closing Reactions of *N*-Ts Aziridines and Aryl Propargyl Alcohols Promoted by *t*-BuOK

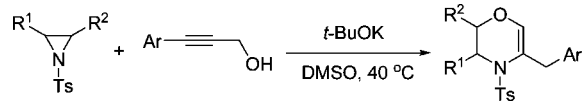
Liang Wang,[†,‡] Qi-Bin Liu,[†] Duo-Sheng Wang,[†] Xin Li,[†] Xiu-Wen Han,[†] Wen-Jing Xiao,[*,‡] and Yong-Gui Zhou[*,†]

State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China, and Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

ygzhou@dicp.ac.cn; wxiao@mail.ccnu.edu.cn

Received December 11, 2008

ABSTRACT



***t*-BuOK was found to be an effective promoting reagent for tandem ring-opening/closing reactions of various *N*-Ts aziridines and aryl propargyl alcohols to afford dihydroxazine derivatives in moderate to good yields. A plausible reaction mechanism has been proposed.**

Aziridines were recognized as versatile building blocks and widely applied in the synthesis of natural products and medicinal reagents.[1] Hitherto many excellent examples about using aziridines for the construction of functionalized acyclic molecules by ring-opening reactions have been reported.[2] Due to ring constrain aziridines readily undergo ring-opening reactions with nucleophiles to form amines.[3] In the past decades, tandem reactions of designed precursors brought great attention to the construction of complicated compounds.[4] Owing to the advantages of greatly enhancing synthetic efficiency, forming two or more bonds in one pot, and avoiding the purification procedures of intermediates, the tandem reaction played a very important role in modern organic synthetic chemistry.[5] Thus, the exploration of tandem reactions of easily available aziridines was highly desirable.

[†] Dalian Institute of Chemical Physics.
[‡] Central China Normal University.

(1) For the recent reviews, see: (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. Aziridines and Azirines: Monocyclic. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 1A, p 1. (b) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (c) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (e) Rayner, C. M. *Synlett* **1997**, 11. (f) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (g) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (h) Kasai, M.; Kono, M. *Synlett* **1992**, 778. (i) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (j) Hou, X. L.; Wu, J.; Fan, R. H.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181.

(2) For selected recent examples, see:(a) Sun, X.; Ye, S. Q.; Wu, J. *Eur. J. Org. Chem.* **2006**, 4787. (b) Savoia, D.; Alvaro, G.; Fabio, R. D.; Gualandi, A. *J. Org. Chem.* **2007**, *72*, 3859. (c) Li, P.; Forbeck, E. M.; Evans, C. D.; Joullié, M. M. *Org. Lett.* **2006**, *8*, 5105. (d) Diao, T.; Sun, X.; Fan, R.; Wu, J. *Chem. Lett.* **2007**, *36*, 604. (e) Siebert, M. R.; Yudin, A. K.; Tantillo, D. J. *Org. Lett.* **2008**, *10*, 57. (f) Wu, J.; Sun, X.; Sun, W. *Org. Biomol. Chem.* **2006**, *4*, 4231. (g) Liu, H.; Pattabiraman, V. R.; Vederas, J. C. *Org. Lett.* **2007**, *9*, 4211.

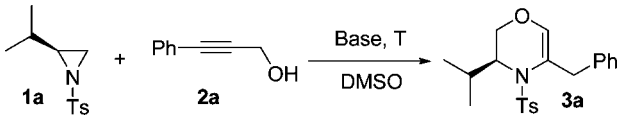
(3) For selected examples, see: (a) Heinrich, M. R.; Martin, I. P.; Zard, S. Z. *Chem. Commun.* **2005**, 5928. (b) Sureshkumar, D.; Gunasundari, T.; Saravanan, V.; Chandrasekaran, S. *Tetrahedron Lett.* **2007**, *48*, 623. (c) Kim, Y.; Ha, H.-J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, J. H.; Min, S. K.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407. (d) Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 5295. (e) Sureshkumar, D.; Koutha, S. M.; Chandrasekaran, S. *J. Am. Chem. Soc.* **2005**, *127*, 12760. (f) Han, H.; Base, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109. (g) Wu, J.; Sun, X.; Xia, H.-G. *Eur. J. Org. Chem.* **2005**, 4769. (h) Wu, J.; Sun, X.; Li, Y. *Eur. J. Org. Chem.* **2005**, 4271.

(4) For reviews, see:(a) Meijere, A. D.; Zezschwitz, P. V.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Hussain, M. M.; Walsh, P. J. *Acc. Chem. Res.* **2008**, *41*, 883. (c) Sun, X. L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (d) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (e) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (g) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (h) Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (i) Bur, S. K.; Padwa, A. *Tetrahedron* **2007**, *63*, 5341.

10.1021/ol802862p CCC: $40.75
Published on Web 02/03/2009

In this letter, a novel tandem ring-opening/closing reaction of azridines and arylpropargyl alcohols promoted by *t*-BuOK is reported.

Table 1. Optimization of Reaction Conditions[a]



entry	base	temp (°C)	yield (%)[b]
1	*t*-BuOK	20	29
2	*t*-BuOK	40	69
3	*t*-BuOK	60	62
4	*t*-BuOK	80	30
5	*t*-BuONa	40	61
6	MeONa	40	43
7	DABCO	40	0

[a] Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), base (1.5 equiv). [b] Isolated yield based on **2a**.

Recently, in the course of our research on the synthesis of new functionalized olefins and asymmetric hydrogenations, we needed the ring-opening product of *N*-Ts aziridine **1a** with phenyl propargyl alcohol **2a**.[6] The studies commenced with the ring-opening reaction of *N*-Ts aziridine **1a** with phenyl propargyl alcohol **2a** mediated by *t*-BuOK in DMSO at 60 °C. Surprisingly, a new cyclic dihydroxazine **3a** was obtained, instead of the expected simple ring-opening product, via a tandem ring-opening/closing sequence. The structure of compound **3a** was assigned by ^{1}H and ^{13}C NMR, DEPT, COSY, HMBC, and mass spectrocopy analysis (see the Supporting Information), and further unambiguously verified by X-ray diffraction of its analogue **3i** (Figure 1). This discovery represents a new method for the construction of six-membered dihydroxazine derivatives.

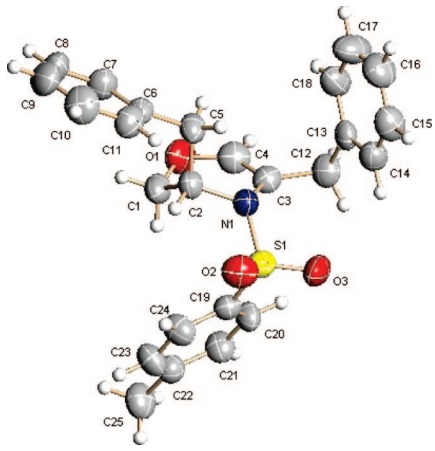
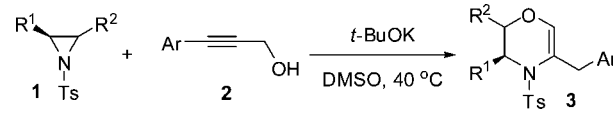


Figure 1. X-ray structure of compound **3i**.

With this unexpected result in hand, optimization of the reaction conditions was carried out. To evaluate the effect of temperature and bases on the reactivity and yield, chiral aziridine **1a** and phenyl propargyl alcohol **2a** were chosen as model substrates. The reaction could proceed smoothly to afford **3a** with 62% yield in the presence of 150 mol % of *t*-BuOK in DMSO at 60 °C (Table 1, entry 3). However, by increasing the reaction temperature to 80 °C, the yield decreased from 62% to 30% (Table 1, entry 4). By decreasing the reaction temperature from 60 to 40 °C, the yield was slightly improved from 62% to 69% (Table 1, entry 2), while low yield was obtained when the reaction was performed at 20 °C. Accordingly, 40 °C was selected as the optimal reaction temperature for further examinations. Subsequently, we examined the effect of various bases (Table 1, entries 2 and 5−7) in DMSO at 40 °C and found that the base had significant influence on the reaction. The application of *t*-BuONa to the reaction afforded **3a** with slightly lower yield (Table 1, entry 5 vs 2). Compared with *t*-BuOK, MeONa afforded the product with only 43% yield. With the utilization of organic base DABCO, no expected product was detected (Table 1, entry 7). The reaction medium was also investigated, and it was found that only DMSO gave good results.

With the optimal reaction conditions established, the scope of these tandem ring-opening/closing reactions was then studied. As revealed in Table 2, a wide range of aryl propargyl alcohols were suitable for this transformation in moderate to good yields regardless of electronic and steric effects (Table 2, entries 1−6, 10, and 11). Propargyl alcohols containing an electron-donating group on the benzene ring (e.g., methyl at the meta position) gave 64% yield (Table 2, entry 4). Replacement of the methyl group by the strong electron-withdrawing trifluoromethyl at the meta position of phenyl also afforded the corresponding product in 78% yield (Table 2, entry 2). Other fused and heteroaromatic systems, such as naphthyl and thiophen-2-yl-substituted propargylic

Table 2. Reaction of *N*-Ts Aziridines **1** and Aryl Propargyl Alcohols **2** Promoted by *t*-BuOK at 40 °C[a]



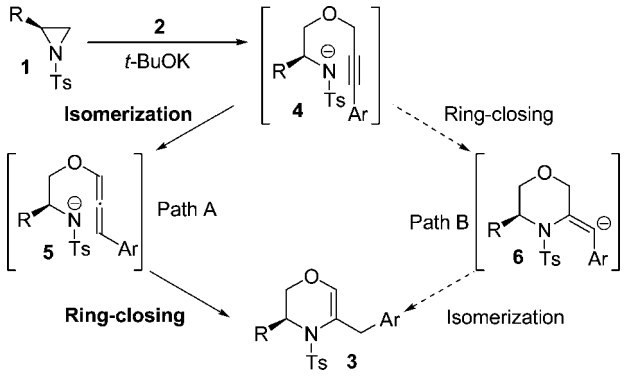
entry	R^1	R^2	Ar	product	yield[b]
1	*i*-Pr	H	Ph	**3a**	69
2	*i*-Pr	H	3-$CF_3C_6H_4$	**3b**	78
3	*i*-Pr	H	1-naphthyl	**3c**	66
4	*i*-Pr	H	3-$CH_3C_6H_4$	**3d**	64
5	*i*-Pr	H	4-BrC_6H_4	**3e**	74
6	*i*-Pr	H	thiophen-2-yl	**3f**	70
7	Me	H	Ph	**3g**	65
8	*i*-Bu	H	Ph	**3h**	73
9	Bn	H	Ph	**3i**	22
10	Me	H	3-$CF_3C_6H_4$	**3j**	70
11	*i*-Bu	H	3-$CF_3C_6H_4$	**3k**	64
12	$-(CH_2)_4-$		Ph	**3*l***	54
13	H	H	1-naphthyl	**3m**	49

[a] Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), *t*-BuOK (1.5 equiv). [b] Isolated yield based on **2**.

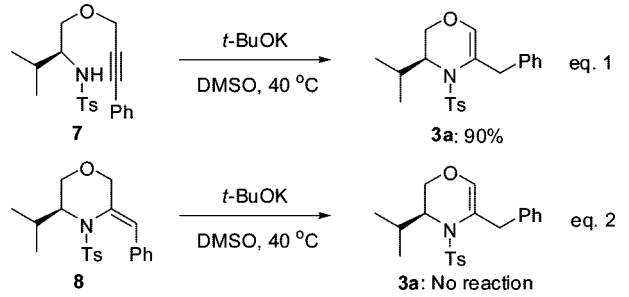
alcohols (Table 2, entries 3 and 6), could be employed in this reaction, and the corresponding products **3c** and **3f** were obtained in 66% and 70% yields, respectively.

A broad range of chiral monosubstituted aziridines including methyl, isopropyl, isobutyl, and benzyl (Table 2, entries 1 and 7−9) were investigated. Both methyl and isobutyl aziridines worked well in the tandem process, gaving 65% and 73% yield, respectively (Table 2, entries 7 and 8). However, the reaction of benzyl-substituted aziridine gave a lower yield probably because of its steric hindrance (Table 2, entry 9). Note that both the disubstituted and unsubstituted aziridines were well tolerated (Table 2, entries 12 and 13).

Scheme 1. Proposed Mechanism



On the basis of the above results, a possible mechanism was proposed (Scheme 1). The aryl propargyl alcohol was deprotonated by *t*-BuOK first to form the oxygen nucleophile, which then attacked the *N*-Ts aziridine to generate a new nucleophilic intermediate **4**. To demonstrate this process, compound **7**, a neutral form of intermediate **4**, was prepared by a two-step procedure. [7] The reaction of **7** in the presence of *t*-BuOK in DMSO at 40 °C did give the expected product **3a** in 90% isolated yield (eq 1).



Afterward, there could be two pathways to form the target molecule. Through path A, the intermediate **4** underwent the isomerization of the triple bond to form the allene species **5**. The intramolecular nucleophilic attack therefore forms the product **3**. Alternatively, path B involves the intermediate **6**, which could be obtained via 6-*exo*-cyclization of **4**. Subsequent double bond isomerization results in the formation of product **3**. To differentiate the two pathways, compound **8**, as a precursor for the formation of intermediate **6** under the reaction condition, was synthesized by Cu-catalyzed cyclization of compound **7**, [8] and then subjected to reaction under the same condition. However, no isomerization occurs even with extended reaction time with **8** being recovered quantitatively (eq 2). Therefore, path B could be ruled out as a possible route.

To confirm the existence of intermediate **5**, compound **7** and 150 mol % of *t*-BuOK were mixed in DMSO at 25 °C. During the course of the reaction, the allene intermediate **5a** could be detected by TLC. However, the isolation of unstable **5a** in its pure form was unsucessful. Alternatively, we carried out the reaction (shown in eq 1) in d_6-DMSO, and the reaction was monitored by ^{1}H NMR. As shown in Figure 2, the changes in the ^{1}H NMR spectra of intermediate **7** could be observed during the reaction process. The H^a and H^b signals of **7** gradually weakened and completely disappeared after 90 min at 25 °C. Two new signals[9] (δ 6.95 and 7.03), which were assigned as the character signals of allene, were obsevered clearly. So, according to the above experiments, path A should be the possible reaction route.

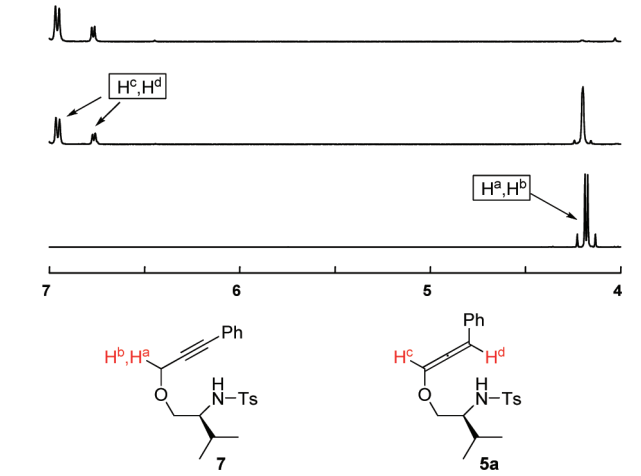
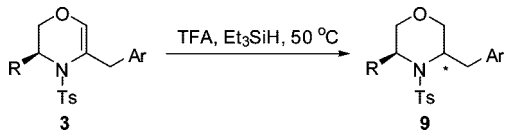


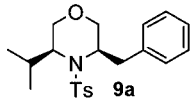
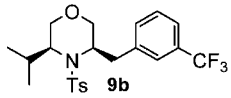
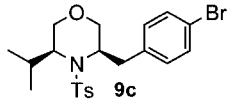
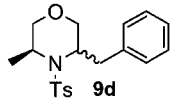
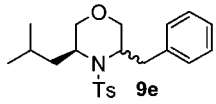
Figure 2. Changes in ^{1}H NMR spectra of compound **7** in d_6-DMSO, detection of allene intermediate.

The synthetic utility of this methodology was demonstrated in a highly efficient route to morpholine derivatives by an ionic hydrogenation, which was the important structural motif of diverse pharmacologically active compounds (Table 3, entries 1−5).[10] To our surprise, for isopropyl-substituted

(5) For selected recent examples, see: (a) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (b) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (c) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (d) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (e) Shi, F.-Q.; Li, Xin.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503. (f) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (g) Fan, R.; Wang, W.; Pu, D.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5905. (h) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Rabbe, G. *Nature* **2006**, *441*, 861. (i) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *Org. Lett.* **2006**, *8*, 3853. (j) Gao, K.; Wu, J. *Org. Lett.* **2008**, *10*, 2251.

Table 3. Synthesis of 3,5-Disubstituted Morpholine Derivatives by Ionic Hydrogenation of **3**[a]

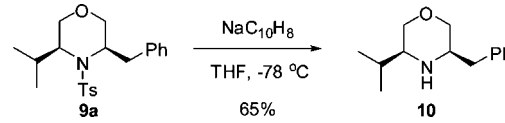


entry	product **9**	dr[b]	yield (%)[c]
1	 **9a**	>95:5	73
2	 **9b**	>95:5	64
3	 **9c**	>95:5	67
4	 **9d**	54:46	91
5	 **9e**	50:50	92

[a] Reaction conditions: **3** (0.25 mmol), TFA (trifluoroacetic acid 1 mL), Et_3SiH (3.0 equiv), 50 °C. [b] Determined by ^1H NMR. [c] Isolated yield based on the **3**.

dihydroxazines, only cis morpholine derivatives were observed in the hydrogenation by TFA/Et_3SiH at 50 °C (Table 3 entries 1−3). However, for the methyl- and isobutyl-substituted dihydroxazines, a diastereomeric mixture of the desired morpholine derivatives was obtained (Table 3 entries 4 and 5). The absolute configuration of product **9a** was confirmed by COSY, HMBC, and NOSY analysis (see the Supporting Information). Noteworthy, the tosyl group of morpholine derivatives **9a** could be readily removed and converted to chiral 3,5-disubstituted morpholine **10** in 65% yield (Scheme 2).

Scheme 2. Deprotection of the Tosyl Group in **9a**



In conclusion, an efficient and unprecedented route to dihydroxazine derivatives via tandem ring-opening/closing reactions of *N*-Ts aziridines with aryl proparglic alcohols has been developed. This strategy offers a concise platform for the construction of six-membered ring systems under mild conditions with high atom economy. A plausible reaction mechanism has been proposed to elucidate this novel tandem process. Further investigation on the range of the current reaction is in progress.

Acknowledgment. Financial support from National Natural Science Foundation of China (20621063 and 20672112) and Dalian Institute of Chemical Physics (K2007F1), Chinese Academy of Sciences.

Supporting Information Available: Experimental procedures and characterization data including X-ray diffraction analysis data of compound **3i** and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802862P

(6) (a) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (d) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260.

(7) See the Supporting Information.

(8) Kundu, N. G.; Chaudhuri, G.; Upadhyay, A. *J. Org. Chem.* **2001**, *66*, 20. See the Supporting Information.

(9) (a) Tius, M. A.; Hu, H.; Kawakami, J. K.; Petersen, J. B. *J. Org. Chem.* **1998**, *63*, 5971. (b) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895.

(10) For a review see: (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L. V.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641. For recent examples, see: (b) Yar, M; Mcgarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784. (c) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100. (d) Dhooghe, M.; Vanlangendonck, T.; Tömroos, K. W.; Kimpe, N. D. *J. Org. Chem.* **2006**, *71*, 4678. (e) Pedrosa, R.; Andrés, C.; Mendiguchía, P.; Niero, J. *J. Org. Chem.* **2006**, *71*, 8854. (f) Henegar, K. E. *J. Org. Chem.* **2008**, *73*, 3662. (g) Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1054. (h) Leijondahl, K.; Borén, L.; Braun, R.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 2027. (i) Sladojevich, F.; Trabocchi, A.; Guarna, A. *Org. Biomol. Chem.* **2008**, *6*, 3328. (j) Zhang, P.; Cedilote, M.; Cleary, T. P.; Pierce, M. E. *Tetrahedron Lett.* **2007**, *48*, 8659.