JOC*Note*

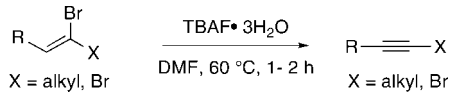
Conversion of Bromoalkenes into Alkynes by Wet Tetra-*n*-butylammonium Fluoride

Masaru Okutani and Yuji Mori*

Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan

mori@ccmfs.meijo-u.ac.jp

Received September 23, 2008

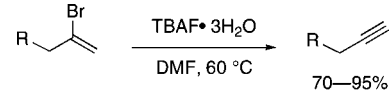


Tetra-*n*-butylammonium fluoride was found to be a mild and efficient base for the elimination reaction of bromoalkenes. Treatment of 1,1-dibromoalkenes, (*Z*)-1-bromoalkenes, and internal bromoalkenes with 5 equiv of TBAF•$3H_2O$ in DMF yielded terminal and internal alkynes in high yields without undue regard to the presence of water.

Terminal alkynes are important functional groups, acting as versatile building blocks and synthetic intermediates in organic synthesis. Recent progress with transition metal-catalyzed carbon−carbon coupling reactions such as Sonogashira coupling reactions, Pauson−Khand reactions, and metatheses has also proven the importance of terminal acetylenes.[1] One of the methods for the preparation of terminal alkynes is dehydrohalogenation of haloalkenes with bases such as alkoxides, alkali hydrides, and alkali metal amides. The disadvantage of these methods is the need for a very strong base as well as strictly anhydrous reaction conditions. It is therefore important to develop a new method that can tolerate moisture or water. In this context, we have recently reported that tetra-*n*-butylammonium fluoride trihydrate (TBAF•$3H_2O$) induces dehydrobromination of 2-bromoalkenes to give the corresponding terminal acetylenes in high yields (Scheme 1).[2]

This acetylene formation is interesting in that TBAF is a weak base and that TBAF contains water. The potential ability of a fluoride anion to act as a base might be predicted by formation of a strong H−F bond (569 kJ mol^{-1}).[3] Since the function of a fluoride anion depends upon the initial formation of a hydrogen bond to a reactant molecule, any water present in the reaction mixture is considered to reduce its effectiveness.[4] Therefore, the elimination reaction by TBAF without undue regard to the presence of water provides a useful method, because the commercially available solid TBAF contains 3 mol of water and a THF solution of TBAF also contains approximately 5% water. In this paper, we wish to extend the scope of the TBAF-induced elimination reaction to 1,1-dibromoalkenes, (*Z*)-1-bromoalkenes, and internal bromoalkenes as substrates.

SCHEME 1



1-Bromoalkynes are key building blocks for the synthesis of di- and polyynes[5] and *N*-alkynyl compounds[6] by metal-catalyzed coupling reactions. They are commonly obtained by bromination of terminal alkynes with NBS/$AgNO_3$[7] or PPh_3/CBr_4.[8] Dehydrobromination of 1,1-dibromoalkenes, which can be obtained by the Ramirez and Corey−Fuchs procedures,[9] also provides a useful method for preparing 1-bromoalkynes. The common bases employed for dehydrobromination are strong bases such as DBU,[10] *t*-BuOK,[11] LiHMDS,[12] and NaHMDS.[13] TBAF is

* Corresponding author. Phone: +81-52-839-2658. Fax: +81-52-834-8090.

(1) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Tsuji, J., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2000.

(2) Okutani, M.; Mori, Y. *Tetrahedron Lett.* **2007**, *48*, 6856–6859.

(3) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.

(4) For anhydrous TBAF, see: (a) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112–2114. (b) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216–3219. (c) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.

(5) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 551−561. (b) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647. (c) Kim, S.; Lee, Y. M.; Kang, H. R.; Cho, J.; Lee, T.; Kim, D. *Org. Lett.* **2007**, *9*, 2127–2130. (d) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601–3604. (e) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2004**, *69*, 3488–3492. (f) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844. (g) Abele, E.; Rubina, K.; Fleisher, M.; Popelis, J.; Arsenyan, P.; Lukevics, E. *Appl. Organomet. Chem.* **2002**, *16*, 141–147.

(6) (a) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925–928. (b) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821. (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170–4177. (d) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154. (e) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369. (f) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014. (g) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.

(7) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727–729.

(8) Wagner, A.; Heitz, M. P.; Mioskowski, C. *Tetrahedron Lett.* **1990**, *31*, 3141–3144.

(9) (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

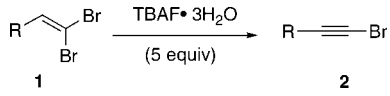
(10) (a) Ratovelomanana, V.; Rollin, Y.; Gébéhenne, C.; Gosmini, C.; Périchon, J. *Tetrahedron Lett.* **1994**, *35*, 4777–4780. (b) Quesada, E.; Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Tetrahedron* **2006**, *62*, 6673–6680. (c) Hashimoto, M.; Komano, T.; Nabeta, K.; Hatanaka, Y. *Chem. Pharm. Bull.* **2005**, *53*, 140–142. (d) Morita, N.; Moriyama, S.; Shoji, T.; Nakashima, M.; Watanabe, M.; Kikuchi, S.; Ito, S.; Fujimori, K. *Heterocycles* **2004**, *64*, 305–316. (e) Mamane, V.; Hannen, P.; Fuerstner, A. *Chem. Eur. J.* **2004**, *10*, 4556–4575. (f) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932.

(11) (a) Okamura, W. H.; Zhu, G.-D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W.; Mueller, L. J. *J. Org. Chem.* **2002**, *67*, 1637–1650. (b) Scott, L. T.; Cooney, M. J.; Otte, C.; Puls, C.; Haumann, T.; Boese, R.; Smith, A. B., III.; Carroll, P. J.; de Meijere, A. *J. Am. Chem. Soc.* **1994**, *116*, 10275–10283. (c) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359–1362.

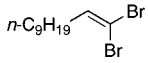
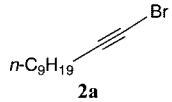
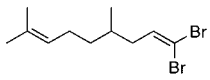
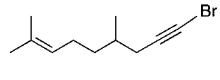
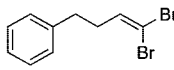
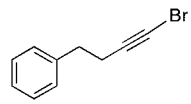
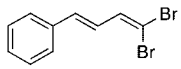
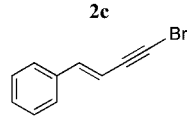
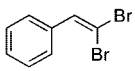
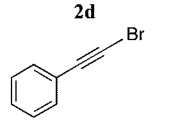
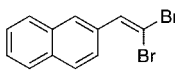
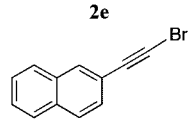
(12) (a) Bach, P.; Nilsson, K.; Svensson, T.; Bauer, U.; Hammerland, L. G.; Peterson, A.; Wallberg, A.; Oesterlund, K.; Karis, D.; Boije, M.; Wensbo, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4788–4791. (b) Wong, L. S.-M.; Sharp, L. A.; Xavier, N. M. C.; Turner, P.; Sherburn, M. S. *Org. Lett.* **2002**, *4*, 1955–1957. (c) Giacobbe, S. A.; Di Fabio, R.; Baraldi, D.; Cugola, A.; Donati, D. *Synth. Commun.* **1999**, *29*, 3125–3135.

10.1021/jo802101a CCC: $40.75
Published on Web 11/13/2008

TABLE 1. Dehydrobromination of 1,1-Dibromoalkenes



1 **2**

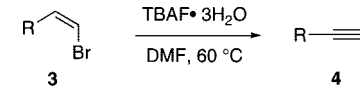
Entry	1	Reaction conditions	2	(%)
1	 **1a**	THF rt, 40 h 60°C, 3 h DMF rt, 22 h 60°C, 0.5 h	 **2a**	82 86 83 87
2	 **1b**	DMF 60°C, 1 h	 **2b**	88
3	 **1c**	DMF 60°C, 1 h	 **2c**	80
4	 **1d**	DMF 60°C, 0.5 h	 **2d**	92
5	 **1e**	DMF 60°C, 0.5 h	 **2e**	80
6	 **1f**	DMF 60°C, 1.0 h	 **2f**	90

also effective for this purpose, although there have been only a few examples of its use reported in the literature.[14] The reported elimination reactions utilizing TBAF were all carried out in THF and required prolonged reaction times, usually 4−48 h, to go to completion. We therefore examined the TBAF-induced dehydrobromination in DMF, which would be expected to accelerate dehydrobromination since the basic properties of the fluoride ion would increase in polar aprotic solvents.[3]

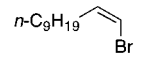
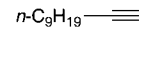
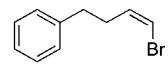
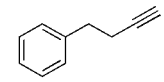
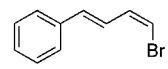
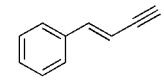
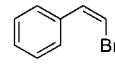
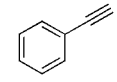
Several 1,1-dibromoalkenes were subjected to dehydrobromination by TBAF. When a solution of dibromoalkene **1** and TBAF·$3H_2O$ (5 equiv) in DMF was heated at 60 °C, dehydrobromination was completed within 1 h to give bromoacetylenes **2** in high yield (Table 1).[15] Comparable experiments of **1a** with 5 equiv of commercially available TBAF in THF (1 M solution) required a more prolonged reaction time (entry 1). Clearly, DMF is a better solvent in facilitating the dehydrobromination.

To investigate the mechanism of this reaction, we examined the reactivity of (*Z*)- and (*E*)-1-bromoalkenes **3** and **5** toward

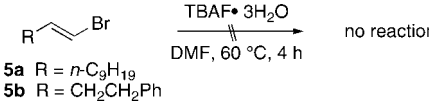
TABLE 2. Dehydrobromination of (*Z*)-1-Bromoalkenes.



3 **4**

Entry	3	Time (h)	4	(%)
1	 **3a**	2	 **4a**	89
2	 **3b**	2	 **4b**	80
3	 **3c**	2	 **4c**	92
4	 **3d**	1	 **4d**	98

SCHEME 2



TBAF in DMF. (*Z*)-1-Bromoalkenes **3** were prepared by the Pd-catalyzed stereoselective hydrogenolysis of 1,1-dibromoalkenes with Bu_3SnH,[16] and (*E*)-1-bromoalkenes **5** were synthesized by the reaction of alkynes with DIBALH followed by bromine.[17] Treatment of (Z)-1-bromoalkenes with TBAF under the standard reaction conditions yielded the expected products in high yield after 2 h (Table 2).[18] However, (*E*)-isomers **5** proved difficult to dehydrobrominate and starting materials were recovered with more than 90% yield after 4 h (Scheme 2). This result is in sharp contrast to the reaction with strong bases such as *n*-BuLi and *t*-BuOK in which both (*E*)- and (*Z*)-1-bromoalkenes can be dehydrohalogenated.[19] These results suggest that dehydrobromination of 1,1-dibromoalkenes by TBAF proceeds via an *anti*-elimination transition state (Figure 1).

We next extended the dehydrobromination by TBAF to internal bromoalkenes. Although strong bases have conventionally been used to eliminate HBr from internal bomoalkenes,[20] fluoride-induced dehydobromination would be expected to serve as a mild procedure in this case. (*Z*)-Trisubstituted alkenes **6**

(13) (a) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026–3038. (b) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956–5960. (c) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419. (d) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529–3530.

(14) (a) Souli, C.; Avlonitis, N.; Calogeropoulou, T.; Tsotinis, A.; Maksay, G.; Biro, T.; Politi, A.; Mavromoustakos, T.; Makriyannis, A.; Reis, H.; Papadopoulos, M. *J. Med. Chem.* **2005**, *48*, 5203–5214. (b) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2265–2267. (c) Diaz, D.; Martin, T.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 7231–7233. (d) Gonzalez, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108. (e) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

(15) Dehydrobromination of **1a** with 3 equiv of TBAF·$3H_2O$ in DMF was not complete after 3 h at 60°C. The use of more than 4 equiv of TBAF·$3H_2O$ is necessary to achieve a complete conversion of **1** to **2**.

(16) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965–8975.

(17) Posner, G. H.; Tang, P.-W. *J. Org. Chem.* **1978**, *43*, 4131–4136.

(18) For related reports on the elimination of (*Z*)-1-chloro- and iodoalkenes by TBAF, see:(a) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655–2657. (b) Uwai, K.; Oshima, Y.; Sugihara, T.; Ohta, T. *Tetrahedron* **1999**, *55*, 9469–9480. (c) Lee, L. H.; Lynch, V.; Lagow, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2805–2809. (d) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576–9577.

(19) (a) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039–6042. (b) Rodriguez, J. G.; Martin-Villamil, R.; Lafuente, A. *Tetrahedron* **2003**, *59*, 1021–1032. (c) Ottow, E.; Rohde, R.; Schwede, W.; Wiechert, R. *Tetrahedron Lett.* **1993**, *34*, 5253–5256. (d) Sarandeses, L. A.; Mascarenas, J. L.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, *33*, 5445–5448. (e) Avignon-Tropis, M.; Berjeaud, J. M.; Pougny, J. R.; Frechard-Ortuno, I.; Guillerm, D.; Linstrumelle, G. *J. Org. Chem.* **1992**, *57*, 651–654. (f) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917–4920. (g) Pianetti, P.; Rollin, P.; Pougny, J. R. *Tetrahedron Lett.* **1986**, *27*, 5853–5856. (h) Ondruschka, B.; Remmler, M.; Zimmermann, G.; Krueger, C. *J. Prakt. Chem. (Leipzig)* **1987**, *329*, 49–54. (i) Schuda, P. F.; Heimann, M. R. *J. Org. Chem.* **1982**, *47*, 2484–2487.

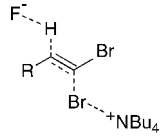
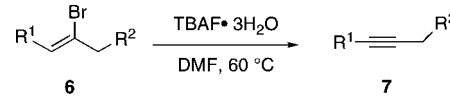


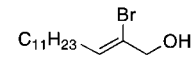
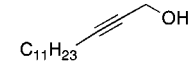
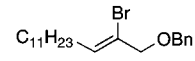
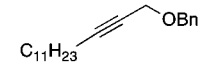
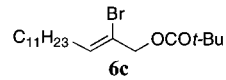
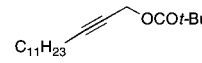
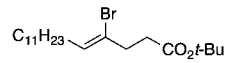
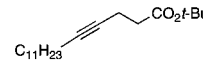
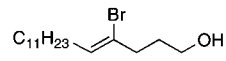
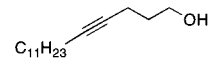
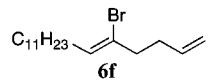
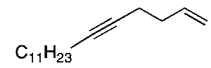
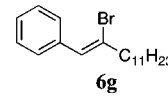
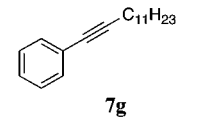
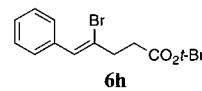
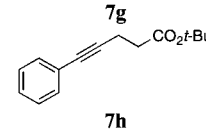
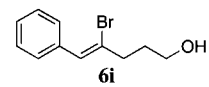
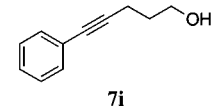
FIGURE 1. *Anti*-elimination of 1,1-dibromoalkenes.

were synthesized from (*Z*)-α-bromo-α,*β*-unsaturated aldehydes,[20d,21] involving transformation into the corresponding α-bromoallyl bromides followed by alkylation with *tert*-butyl lithioacetate.[22] When bromoalkenes **6** were heated at 60 °C in DMF in the presence of 5 equiv of TBAF, dehydrobromination proceeded smoothly to give the corresponding internal alkynes in high yield (Table 3). We were initially concerned about concomitant allene formation,[20c] but an allene was not detected in any case. The allylic alcohol **6a** listed in entry 1 was a special case that required a much longer reaction time (22 h), while elimination of HBr in other cases was completed after 2 h. The low reactivity of **6a** could be explained by participation of the allylic hydroxy group proximate to the olefinic hydrogen to be abstracted, which could trap the fluoride anion by forming a hydrogen bond.[23] Such a proximate effect of the hydroxy group was not observed when the hydroxy group was protected with benzyl and pivaloyl groups (entries 2 and 3). Bis(homoallylic) alcohols **6e** and **6i** also dehydrobrominated without trouble since the hydroxyl group is too remote to trap the fluoride ion entering the reaction center. The marked difference in reactivity between **6a** and other bromoalkenes (**6b**−**i**) is a characteristic feature of fluoride-induced dehydrobromination. The decreased yield of **7c** (entry 3) was attributable to partial hydrolysis of the pivaloyl group of the starting material and the product by hydroxide ion, which can be present in wet TBAF. The corresponding bromoallylic alcohol and acetylenic alcohol were isolated in 16% and 5% yields, respectively.

In conclusion, TBAF was found to be an efficient and mild base in the dehydrobromination of terminal and internal bromoalkenes to the corresponding alkynes. The elimination reaction can be carried out with commercially available TBAF·$3H_2O$ in DMF, and the water tolerance and the absence of metal salts make this method attractive. This procedure provides a reasonable alternative to other methods that require strong bases and anhydrous conditions.

TABLE 3. Dehydrobromination of Trisubstituted Bromoalkenes



Entry	6	Time (h)	7	(%)
1	 **6a**	22	 **7a**	83
2	 **6b**	1.5	 **7b**	98
3	 **6c**	1.5	 **7c**	73
4	 **6d**	1.5	 **7d**	98
5	 **6e**	2	 **7e**	96
6	 **6f**	2	 **7f**	90
7	 **6g**	2	 **7g**	99
8	 **6h**	2	 **7h**	98
9	 **6i**	2	 **7i**	97

Experimental Section

Representative Procedure for Dehydrobromination of Bromoalkenes. Bromoalkene (**6b**, 190 mg, 0.5 mmol) was dissolved in 2.5 mL of DMF. TBAF·$3H_2O$ (0.78 g, 2.5 mmol) was added to the solution and the reaction mixture was heated at 60 °C for 2 h (TLC). The reaction mixture was cooled to room temperature and diluted with diethyl ether (50 mL). The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to give **7b** (144 mg, 96%) as a colorless oil: IR ($CHCl_3$), 2223, 1496, 1455, 1354, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 1.26−1.41 (16H, m), 1.53 (2H. quint, J = 7.3 Hz), 2.24 (2H, tt, J = 7.3, 2.4 Hz), 4.16 (2H, t, J = 2.4 Hz), 4.58 (2H, s), 7.28−7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 28.6, 28.9, 29.1, 29.3, 29.5, 29.6 (2 × C), 31.9, 57.7, 71.3, 75.8, 87.4, 127.7, 128.1 (2 × C), 128.4 (2 × C), 137.7; HREIMS *m/z* calcd for $C_{21}H_{32}O$ 300.2453, found 300.2464.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 18590020) from the Japan Society for the Promotion of Science.

Supporting Information Available: Characterization data for compounds **2a**−**f** and experimental procedures, characterization data, and ^1H NMR spectra for compounds **6a**−**i** and **7a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802101A

(20) Dehydrobromination of internal bromoalkenes: (a) Ma, Y.; Ramirez, A.; Singh, K. J.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 15399–15404. (b) Myers, A. G.; Sogi, M.; Lewis, M. A.; Arvedson, S. P. *J. Org. Chem.* **2004**, *69*, 2516–2525. (c) Guzmán-Durán, A.; Guzmán, E.; Pannell, K. H.; Lloyd, W. D. *Synth. Commun.* **2003**, *33*, 3271–3283. (d) Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675–2678. (e) Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227–1231. (f) Nakamura, T.; Namiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635–2645. (g) Schuda, P. F.; Heimann, M. R. *J. Org. Chem.* **1982**, *47*, 2484–2487.

(21) Allen, C. F.; Edens, C. O. In *Organic Synthesis*; Wiley: New York, 1955; Collect. Vol. III, pp 731−733.

(22) For the preparation of **6a**−**i**, see the Supporting Information.

(23) (a) Clark, J. H.; Miller, J. M. *J. Chem. Soc., Perkin 1* **1977**, 1743–1745. (b) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768–2780.