ORGANIC LETTERS

2009
Vol. 11, No. 1
165−168

Homologation of Boronic Esters with Lithiated Epoxides for the Stereocontrolled Synthesis of 1,2- and 1,3-Diols and 1,2,4-Triols

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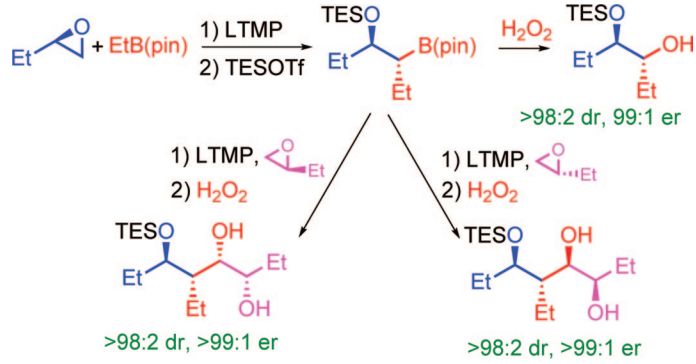
Received November 17, 2008

ABSTRACT



Lithiated epoxides react stereospecifically with boronic esters to give *syn*-1,2-diols, a process that can be used iteratively to create triols containing four stereogenic centers.

Although the chemistry of lithiated epoxides has a long history,[1] it is only in recent years, particularly through asymmetric lithiation, that their potential in synthesis has been realized.[2] A range of reactions have been reported reflecting both the carbanionic and carbenic reactivity of these intermediates. On the basis of our interests in the reactions of sulfur ylides[3] and Hoppe's and Beak's lithiated carbamates (*O*- and *N*-linked) with boranes/borate esters,[4] the corresponding reactions of lithiated epoxides with the same electrophiles seemed to hold significant promise for synthesis.[5] Thus, we hoped that following ate complex formation (**1**) and 1,2-metalate rearrangement, a β-alkoxy boronic ester **2** would be formed (with control over stereochemistry), which could be oxidized to the corresponding diol **3** or elaborated further (Scheme 1).

(1) (a) Cope, A. C.; Tiffany, B. D. *J. Am. Chem. Soc.* **1951**, *73*, 4158–4161. (b) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428–2433.

(2) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3326. (b) Doris, E.; Dechoux, L.; Miokowski, C. *Synlett* **1998**, 337–343. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642. (d) Hodgson, D. M.; Tomooka, K.; Gras, E. *Top. Organomet. Chem.* **2003**, *5*, 217–250. (e) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1–22. (f) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942.

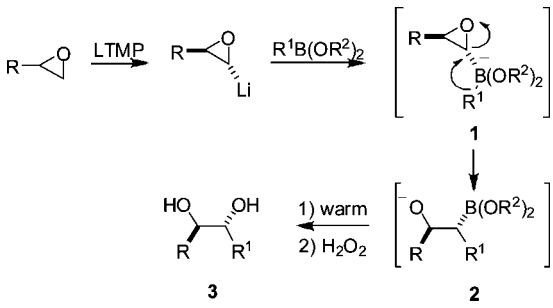
(3) (a) Aggarwal, V. K.; Fang, G.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642–1643. (b) Fang, G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 359–362. (c) Fang, G.; Wallner, O. A.; di Blasio, N.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.

(4) (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491–7494. (b) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E.; Adams, H.; Fang, G.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 141–143. For a short review, see: O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734–2736. See also: Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069. Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773–776.

(5) For related reactions of lithiated aziridines with boronic esters, see: Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, in press.

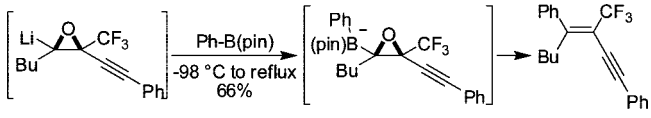
10.1021/ol802651b CCC: $40.75
Published on Web 12/09/2008

Scheme 1. Proposed Reaction of Lithiated Epoxides with Boronic Esters



However, Shimizu had previously reported that reactions of β-CF_3-substituted lithiated epoxides with boranes and boronic esters gave the corresponding alkenes instead (Scheme 2).[6] Evidently, the intermediate β-alkoxyboronic

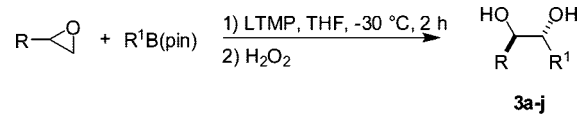
Scheme 2. Shimizu's Reactions of Lithiated Epoxides with Boronic Esters



ester (related to **2**) is unstable and undergoes a rapid boron-Wittig-type elimination.[7] Related intermediates involving boranes had previously been generated by reaction of dimesitylboronmethyl lithium with aldehydes and ketones, which led to alkenes, alcohols, or diols depending on the reaction conditions and nature of the subsituents.[8] This ominous literature precedent made us embark on our own studies with a degree of trepidation.

We began our studies using the simple Hodgson protocol[9] for the generation of lithiated epoxides using LTMP and a terminal epoxide with in situ trapping of ethyl boronic acid pinacol ester, an electrophile that we expected to be compatible with LTMP.[10] This protocol has been limited to the trapping of lithiated epoxides with TMSCl, an electrophile that is also compatible with LTMP.[8] Brief optimization of the stoichiometry of base and boronic ester, temperature, and time provided a set of conditions under which a *syn* diol was formed with complete diastereoselectivity and in good yield (Table 1, entry 1).[11] These conditions were applied to a range of alkyl boronic esters and were found to be general (Table 1, entries 1−5). Phenyl boronic acid pinacol ester was also tested, but competing elimination was now observed with this substrate, indicating that the β-alkoxyboronic ester bearing an adjacent phenyl group is prone to elimination (Table 1, entry 5).

Table 1. Homologation of Boronic Esters Using Lithiated Terminal Epoxides



entry	R	R^1	yields [%] (product)
1	*n*-Bu	Et	76 (**3a**)
2	*n*-Bu	$PhCH_2CH_2$	73 (**3b**)
3	*n*-Bu	c-Hex	83 (**3c**)
4	*n*-Bu	c-Pr	86 (**3d**)
5	*n*-Bu	Ph	57 (**3e**)[a]
6	$CH_2CH_2CHCH_2$	Et	47 (**3f**)[b]
7	*i*-Pr	Et	65 (**3g**)
8	*t*-Bu	Et	38 (**3h**)
9	CH_2OTBS	Et	54 (**3i**)
10	Et (*R*)	$PhCH_2CH_2$	70 (**3j**) (er 99:1)[c]

[a] 25% of 1-phenyl-1-hexene was also isolated. [b] The reaction was run at 4 °C. [c] The enantiomeric ratio (er) was determined by chiral HPLC (Chiralcel AD column).

A variety of aliphatic epoxides were also tested, including the epoxide derived from glycidol (Table 1, entry 9), and again single diastereomers were formed in all cases in moderate to good yields (Table 1, entries 6−10). The use of enantiopure l-butenoxide, easily accessible by Jacobsen HKR[12] and now commercially available, was also tested, and as expected, the diol **3j** was formed with complete retention of enantiopurity (Table 1, entry 10).

The perfect diasterocontrol observed is in keeping with the mechanism shown in Scheme 1 in which the initial lithiation occurs *trans* to the epoxide substituent.[9,13] Trapping

(6) (a) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 6947–6948. (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Minezaki, H.; Hata, T.; Hiyama, T. *Tetrahedron* **2003**, *59*, 9811–9823.

(7) Related reactions with R_3Al or R_2Zn also furnish alkenes. See: (a) Ukaji, Y.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 5165–5168. (b) Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 2783–2786. (c) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275–5280. (d) Tanigushi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **2000**, *41*, 6201–6205.

(8) (a) Pelter, A.; Singaram, B.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 635–636. (b) Pelter, A.; Buss, D.; Pitchford, A. *Tetrahedron Lett.* **1985**, *41*, 5093–5096. (c) Kawashima, T.; Yamashita, N.; Okazaki, R. *J. Am. Chem. Soc.* **1995**, *117*, 6142–6143. (d) Pelter, A.; Peverall, S.; Pitchford, A. *Tetrahedron* **1996**, *52*, 1085–1094.

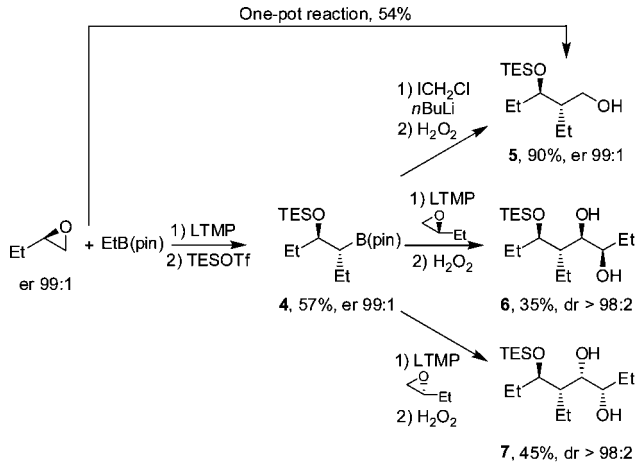
(9) Hodgson, D. M.; Reynold, N. J.; Coote, S. J. *Tetrahedron Lett.* **2002**, *43*, 7895–7897.

(10) In situ trapping is necessary since the lithiated epoxide is thermally unstable. See ref 8.

(11) **General Procedure for the Homologation of Boronate with Epoxides Leading to Diols 3.** A 10-mL Schlenk tube was charged with the corresponding epoxide (0.50 mmol) and boronate (1.00 mmol, 1.00 M in THF). The resulting solution was thereafter cooled to −30 °C followed by dropwise addition of freshly prepared lithium 2,2,6,6-tetramethylpiperidide (1.00 mmol). The reaction mixture was then stirred for 2 h at −30 °C at which time the reaction flask was transferred to an ice bath and NaOH (1.0 mL, 2.0 M) and H_2O_2 (0.50 mL, >30% w/v) were added. The reaction mixture was stirred an additional 2 h at 4 °C and was then diluted with H_2O (5 mL) and extracted with DCM (4 × 7 mL). The combined organic layer was dried over magnesium sulphate. The organic solvents were then removed, and the crude product was subjected to silica gel flash chromatography.

(12) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.

Scheme 3. Iterative Homologation of Borate Esters



of the lithiated epoxide with the boronic ester occurs with retention of stereochemistry and following 1,2-migration and oxidation finally furnishes the *syn* diol. Although elimination of the β-alkoxy boronate has been reported to be rapid, it is evidently very sensitive to the nature of substituent. Strong electron-withdrawing groups (e.g., CF_3) promote elimination, whereas donating groups (this work) inhibit this pathway. Aryl groups are in between, and so competing elimination is observed.

The power of the methodology lies in the potential to further elaborate the boronic ester intermediate. Thus, treatment of (*R*)-butenoxide, as before, with LTMP in the presence of ethyl boronic acid pinacol ester followed directly by addition of TESOTf gave the β-silyloxy-boronic ester **4** in good yield. One-carbon homologation with chloromethyl lithium followed by oxidation gave the 1,3-diol **5** in high yield and with the same er as the starting epoxide (Scheme 3).[14] Furthermore, the two homologation processes could be effectively concertinaed into a one-pot process with equal efficiency and selectivity! Lithiated (*R*)-butenoxide and (*S*)-butenoxide could also be employed to effect the second homologation leading to the substituted *syn* or *anti* 1,3-diols (**6** and **7**, respectively) with complete control over stereochemistry; no other stereoisomers could be detected. These motifs are commonly found in natural products.

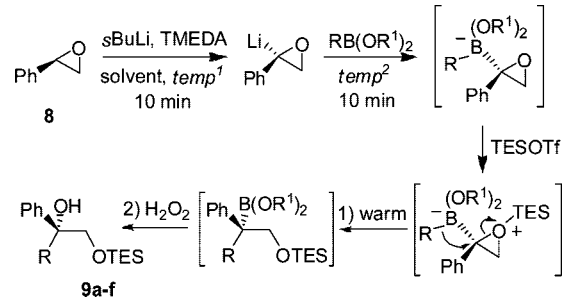
Finally, we have explored the use of styrene oxide **8** in this chemistry. In this case it was known that deprotonation occurs adjacent to the phenyl group, and Florio had shown that lithiation and trapping with electrophiles at −98 °C occurred with complete retention of stereochemistry.[15]

(13) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103–2104.

(14) (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687–1689. (b) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150–3155.

(15) (a) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448. (b) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330–3335. (c) Florio, S.; Aggarwal, V. K.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191–4194. (d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A.; Cuocci, C. *Org. Lett.* **2006**, *8*, 3923–3926. (e) For a review, see: Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, 1359–1369.

Table 2. Homologation of Boronic Esters Using Lithiated Styrene Oxide



entry	borate esters	condition[a]	yield [%]	er[b]
1	EtB(pin)	A	69 (**9a**)	50:50
2	EtB(pin)	B	87 (**9a**)	70:30
3	EtB(neop)[c]	B	66 (**9a**)	86:14
4	EtB(neop)	C	87 (**9a**)	95:5[d]
5	$PhCH_2CH_2B$(neop)	C	78 (**9b**)	95:5
6	c-HexB(neop)	C	69 (**9c**)	99:1
7	allylB(neop)	C	86 (**9d**)	96:4
8	*p*-MeO-PhB(neop)	C	80 (**9e**)	94:6
9	*p*-F-PhB$(OR^1)_2$[e]	C	63 (**9f**)	99:1
10	PhB(pin)	A	69 (**9g**)	

[a] Condition A: THF, $temp^1 = -98$ °C, $temp^2 = -98$ to −78 °C. Condition B: THF, $temp^1 = -98$ °C, $temp^2 = -98$ °C. Condition C: Et_2O, $temp^1 = -115$ °C, $temp^2 = -110$ °C. Temperatures were measured with an internal thermometer. [b] The er were calculated using chiral HPLC (Chiracel AD or OD-H columns). [c] neop = neopentyl. [d] An er of 97:3 was obtained using *tert*-butyl methyl ether as solvent. [e] The neopentyl boronic ester was insoluble in ether at −110 °C and so 2,2-diethyl-1,3-propanediol boronic ester was employed instead.

However, aware that the intermediate β-alkoxy boronate was prone to elimination, we decided to trap the alkoxide with TESOTf as it was being generated.[16] TESOTf could also activate the epoxide toward ring opening and thus promote the 1,2-metalate rearrangement. Thus, treatment of styrene oxide with *s*-BuLi-TMEDA at −98 °C, followed by addition of EtB(pin) and 10 min later TESOTf, and then warming and subsequent oxidation resulted in formation of alcohol **9a** in 69% yield. Clearly, through in situ trapping of the alkoxide with TESOTf we were able to completely suppress the boron-Wittig elimination process with substrates that were especially prone to elimination.[17] However, we were shocked to find that the product was completely racemic (Table 2, entry 1, condition A)! This was despite following Florio's conditions (generation and trapping of the lithiated epoxides at −98 °C) with which they had achieved 98:2 er selectivity with a range of electrophiles.[15a] Maintaining low temperature after the addition of the boronic ester led to an improved er (entry 2) and further improvements were achieved by (i) using the less hindered and so more reactive

(16) These conditions could not be applied to entry 5, Table 1 in order to limit the extent of elimination since the procedure involves deprotonation of the epoxide in the presence of the boronic ester. If TESOTf was also present, it would simply trap the lithiated epoxide as it was being generated.

(17) In the absence of TESOTf, elimination dominated even at low temperature.

neopentyl boronic ester (entry 3) and (ii) changing the solvent from THF to ether, which also allowed us to reduce the temperature further (entry 4, conditions C).[18] These conditions gave 95−97:5−3 er. A small variation was observed with different runs probably reflecting a degree of variability in temperature control. These conditions were applied to a range of boronic esters and were found to be general (entries 6−10).

The diols obtained represent an extremely important class of bioactive compounds and yet are very difficult to prepare in high er by asymmetric dihydroxylation of 1,1-disubstituted olefins (the poorest class of substrates for this otherwise powerful reaction).[19]

In conclusion, we have shown that terminal epoxides can be lithiated and trapped with boronic esters to give *syn*-1,2-diols with complete diastereoselectivity. The process is easily rendered asymmetric and can be used to create triols containing four stereogenic centers through a second homologation with control over relative and absolute stereochemistry. The process can be further extended to the generation of 1,2-diols bearing quaternary stereogenic centers, thus providing a useful route to these especially challenging motifs.

Acknowledgment. F.S. thanks the Deutscher Akademischer Austausch Dienst (DAAD) for a postdoctoral fellowship. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award and EPSRC for a Senior Research Fellowship. We thank Frontier Scientific for generous donation of boronic acids and boronic esters. We thank EPSRC for support of this work and Merck for unrestricted research support.

Supporting Information Available: Full experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **3a**−**j**, **4**−**7**, and **9a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **General Procedure for the Homologation of Boronates with Styrene Oxide Leading to Compounds 9.** A 10-mL Schlenk tube was charged with (*R*)-styrene oxide (46 μL, 0.40 mmol) and TMEDA (180 μL, 1.20 mmol) in 2.75 mL of ether. The resulting solution was thereafter cooled to −115 °C followed by dropwise addition of *s*-BuLi (1.3 M in hexanes, 370 μL, 0.48 mmol). The resulting mixture was stirred at −115 °C for 10 min. A solution of the corresponding boronic ester (0.50 mmol) in ether (1.25 mL) was then slowly added, and the mixture was then stirred at −110 °C for 10 min. TES-OTf (113 μL, 0.50 mmol) was added, and the resulting mixture was allowed to warm to room temperature. The reaction flask was transferred to an ice bath, and 3 mg of 2,6-di-*tert*-butyl-4-methylphenol was added, followed by a mixture of NaOH (1.0 mL, 2.0 M) and H_2O_2 (0.50 mL, >30% w/v), previously degassed under vacuum. The reaction mixture was stirred an additional 10 min at room temperature and was then diluted with H_2O (5 mL) and extracted with ether (4 × 7 mL). The organic solvents were then removed, and the crude product was subjected to silica gel flash chromatography.

(19) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Wang, X.; Zak, M.; Maddess, M.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4865–4869.