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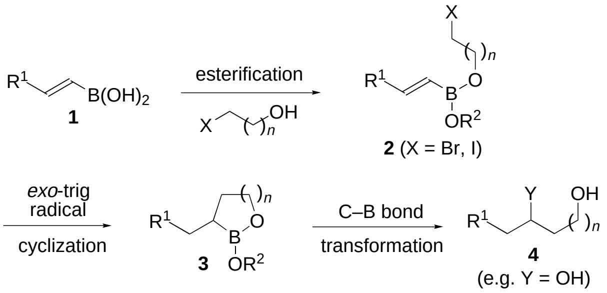
The First Boron-Tethered Radical Cyclizations and Intramolecular Homolytic Substitutions at Boron[**]

Robert A. Batey[*] and David V. Smil

Silicon-tethered radical cyclizations, first reported by Nishiyama et al.[1] and Stork et al.,[2] are a useful strategy for the construction of C–C bonds. Numerous syntheses have incorporated these processes, usually for hydroxymethylations of allylic alcohols,[1–3] and these reactions account for approximately half of the publications in the field of silicon-tethered chemistry. The success of temporary silicon connections in radical chemistry, together with our ongoing interest in developing new reactions of organoboron compounds,[4] led us to consider employing boron in an analogous tethering role. Narasaka et al. used phenylboronic acid to tether dienes and dienophiles together through O-B-O linkages in Diels–Alder reactions,[5] but there are no examples of this strategy in free-radical chemistry. Carboni et al. demonstrated both intermolecular free-radical additions to alkenylboranes and radical cyclizations with alkenylboranes.[6] We now report the first boron-tethered radical cyclizations for the synthesis of 1,3-, 1,4-, and 1,5-diols. The general strategy employs the covalent C-B-O linkage of boronic esters as a tether (Scheme 1).[7] We envisaged that the ease of synthesis of the precursor boronic acids **1** and esters **2** and the synthetic versatility of the C–B bond[8] in the cyclic products **3** would significantly expand the scope of tethered-radical processes.



Scheme 1. General strategy for boron-tethered radical cyclizations of alkenylboronic esters **2**.

The requisite (*E*)-alkenylboronic acids **1** were obtained in good yields by hydroboration of the corresponding alkynes with the dimethyl sulfide complex of dibromoborane[9] (R^1 = alkyl) or catecholborane[10] (R^1 = aryl). Treatment of **1** with 2-bromoethanol, 2-iodoethanol, or 3-bromopropanol in THF in the presence of 4 Å molecular sieves at room temperature over 24 h readily afforded the (*E*)-alkenylboronic esters **2**. The precursors **2** were then subjected to free-radical conditions by using Corey's catalytic tributylstannane method.[11] Heating **2a–f** (substrates with *n*-alkyl or aryl substituents at the β-alkenyl position) to 55 °C in THF for 48 h, in the presence of the radical initiator dimethyl-2,2′-azobisisobutyrate (DAB),[12] gave the boracycles **3**, which were not isolated, but immediately oxidized with trimethylamine *N*-oxide (TMANO)[13] to the 1,3- or 1,4-diols **4a–f** (Table 1), that is, the products of 5- or 6-*exo*-trig radical cyclization, respectively. No products resulting from 6-*endo*-trig or 7-*endo*-trig cyclization were isolated or observed in the crude reaction mixture, and this indicates an *exo*:*endo* selectivity of greater than 95:5.[14] Initial attempts to perform these cyclizations in refluxing THF gave lower yields (10–40% below those with optimized conditions) due to competing direct reduction of the C–Br bond of **2**. Ionic reduction of **2** by the sodium cyanoborohydride co-reductant in the absence of radical initiator was demonstrated to be increasingly competitive

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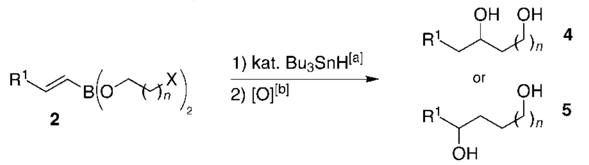
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

Table 1. Intramolecular cyclization of boronic esters **2** to diols **4** or **5**.

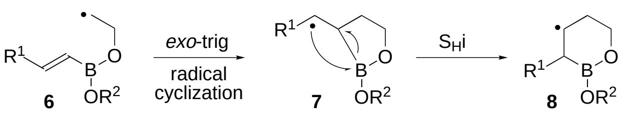


Substrate	R^1	X	*n*	Product	Yield [%][c]
2a	Pr	Br	1	**4a**	81
2b	Bu	Br	1	**4b**	77
2c	Ph	Br	1	**4c**	63
2d	*p*-tolyl	Br	1	**4d**	65
2e	Pr	Br	2	**4e**	85
2f	Ph	Br	2	**4f**	75
2g	Pr	I	1	**4a**	73
2h	Ph	I	1	**4c**	68
2i	*i*Pr	Br	1	**5a**	83
2j	*t*Bu	Br	1	**5b**	67
2k	Chx	Br	1	**5c**	77

[a] Substrate **2** in THF (0.1 M), Bu$_3$SnH (0.01 equiv), NaBH$_3$CN (2.5 equiv), DAB (0.4 equiv), 55 °C, 48 h. [b] Cyclization product in benzene (0.05 M), TMANO (5.0 equiv), 80 °C, 24 h; H$_2$O, 80 °C, 24 h. [c] Yields of isolated products after column chromatography.

with increasing temperature. An optimal reaction temperature of 55 °C, the operational threshold of the radical initiator, effectively decreases the formation of direct reduction products. Cyclizations can also be conducted with stoichiometric amounts of tributylstannane at high dilution to minimize direct reduction, but the catalytic tributylstannane method, aside from providing higher yields, is more convenient due to the greater ease of product purification. The *Z* analogue of **2b**[15] also cyclized readily and gave diol **4b** in 72 % yield. Comparable results were obtained with the iodides **2g** and **2h** as the radical precursors. A preliminary attempt to use less than two equivalents of bromoethanol per boronic acid was also made. However, treatment of the diisopropyl esters[16] of alkenylboronic acids with one equivalent of bromoethanol followed by free-radical cyclization and oxidation resulted in 20–40 % lower yields of the 1,3-diols. The tethered nature of the radical process was unambiguously established by attempting to cyclize 2-hex-1-enyl-[1,3,2]dioxaborolane in the presence of 2-bromoethanol (1:20 and 10:1 ratio) and (*E*)-hexenylboronic acid in the presence of 1-bromo-2-(*tert*-butyldimethylsiloxy)ethane. In both cases, tethering of the reactive species as boronate esters is precluded, and cyclization products were not observed.

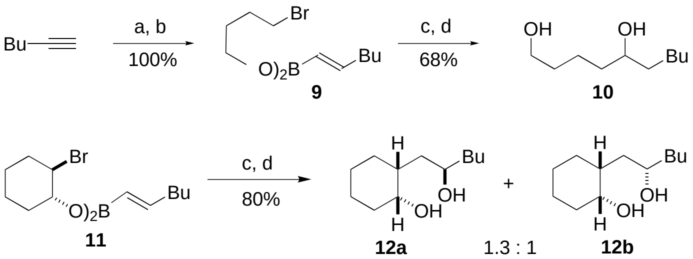
Surprisingly, for the substrates **2i**–**k** with *sec*- or *tert*-alkyl substituents at the *β*-alkenyl position, 1,4-diols **5** rather than the expected 1,3-diols **4** were isolated (Table 1)![17] These results suggest that following 5-*exo*-trig cyclization of **6**, the boracyclic radical intermediate **7** rearranges to radical **8** before trapping an H atom from tributylstannane (Scheme 2). The high selectivity for formation of **4** or **5**, depending upon the substituents, is particularly noteworthy. Although the origin of this effect is not clear, presumably for **2i**–**k**, the extra steric bulk of R^1 lowers the rate of H atom trapping by the corresponding radicals **7** and facilitates an intramolecular homolytic substitution (S$_{\mathrm{H}}$i)[18, 19] at boron.[20, 21] Treatment of **2k** using the standard stoichiometric tributylstannane method (benzene, 55 °C) at higher stannane concentrations gave mixtures of the 1,4-diol **5c** and cyclohexyl-1,3-butanediol (**4g**). The product ratio **5c**:**4g** decreased steadily with increasing concentration of stannane: 7.9:1 (0.1 M), 4.8:1 (0.25 M), 3.3:1 (0.5 M) to 2.6:1 (0.75 M), as the efficiency of H atom trapping by the stannane relative to S$_{\mathrm{H}}$i rearrangement increases. Reaction of **2j** in the presence of a stoichiometric amount of tributyltin deuteride (0.1 M) gave the 1,4-diol **5b** with a D atom in the 3-position; this confirms that the rearrangement is a radical reaction.



Scheme 2. Tandem radical cyclization and S$_{\mathrm{H}}$i mechanism leading to 1,4-diols **5** for R^1 = *i*Pr, *t*Bu, and Chx (cyclohexyl).

Intermolecular S$_{\mathrm{H}}$i reactions of carbon-centered radicals at boron centers have been observed in the gas phase,[22] but to our knowledge this is the first intramolecular S$_{\mathrm{H}}$i reaction at boron and the first to involve a boronic ester. An alternative mechanism for this transformation involves *β* scission to give an (RO)$_2$B$^\bullet$ radical. We consider that such an unprecedented *β* scission is unlikely, because the (RO)$_2$B$^\bullet$ radical formally has five electrons in the valence shell of boron. Indeed, the energy barriers for the degenerate S$_{\mathrm{H}}$i rearrangement and the *β* scission reaction of the (HO)$_2$BCH$_2$CH$_2$$^\bullet$ radical were calculated as 11.7 and 47.6 kcal mol^{-1}, respectively (MP2/6-31G*//UHF/6-31G*).[23]

Ring opening of THF with an alkenyldibromoborane provides ready access to the 4-bromobutylboronates **9** without the need for boronic acid intermediates (Scheme 3).[24] Treatment of **9** under the standard conditions efficiently gave the 1,5-diol **10**, which is formed by a rare example of a 7-*exo*-trig radical cyclization.[25] A preliminary attempt to elucidate the diastereoselectivity of a boron-tethered cyclization was conducted with the boronate **11**, prepared in an analogous manner to **9** by ring opening of cyclohexene oxide (2 equiv) at 0 °C with (*E*)-hexenyldibromoborane. However, treatment of **11** according to the standard protocol led to an inseparable 1.3:1 mixture of the diastereomeric 1,4-diols **12**,[26] which result from a tandem cyclization and S$_{\mathrm{H}}$i rearrangement mechanism (Scheme 3).[27]



Scheme 3. Syntheses of **10** and **12**. a) HBBr$_2$·SMe$_2$, CH$_2$Cl$_2$, room temperature; b) THF, room temperature; c) Bu$_3$SnH (cat.), NaCNBH$_3$, DAB (cat.), THF, 55 °C; d) TMANO, 80 °C; H$_2$O, 80 °C.

We have demonstrated the first boron-tethered free-radical reactions and shown that they are a useful alternative to the widely used silicon-tethered radical processes. In some cases rearranged products are observed that result from a subsequent intramolecular S_Hi reaction at boron. Further studies and applications of both boron-tethered free-radical cyclizations and S_Hi reactions at boron are in progress.

Experimental Section

Radical cyclization of **2a**: To a 0.1M solution of **2a** (1.96 g, 6.00 mmol) in THF was added $NaBH_3CN$ (942 mg, 15.0 mmol), DAB (552 mg, 2.40 mmol), and Bu_3SnH (16 µL, 0.06 mmol) at room temperature under nitrogen. The reaction mixture was stirred vigorously and heated to 55 °C for 48 h, during which a fine precipitate formed. After cooling the mixture to room temperature, the solvent was removed in vacuo. The residue was then taken up in dichloromethane (20 mL), filtered, and the solvent removed in vacuo. The residual oil was then dissolved in benzene (120 mL), and TMANO (3.33 g, 30.0 mmol) was added. The light yellow solution was stirred vigorously and heated at reflux for 24 h. Water (20 mL) was then added, and the resulting two-phase system stirred for an additional 24 h at 85 °C. After cooling the mixture to room temperature, the layers were separated, and the aqueous layer extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residual oil by column chromatography on silica gel (20% ethyl acetate/hexanes as eluent) afforded **4a**[28] (642 mg, 4.86 mmol) as a clear, colorless oil (81% yield): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.70-3.56$ (m, 3H), 3.06 (brs, 2H), 1.72–1.57 (m, 3H), 1.50–1.28 (m, 5H), 0.90 (t, $J = 7.1$ Hz, 3H,).

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[27] The structural assignment for both diastereomers of **12** was confirmed by X-ray crystal structure determinations of the corresponding bis-*p*-nitrobenzoate esters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-102654 and CCDC-102655. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223–336–033; e-mail: deposit@ccdc.cam.ac.uk).

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