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Tethered α-boryl radical cyclizations of haloalkyl boronates

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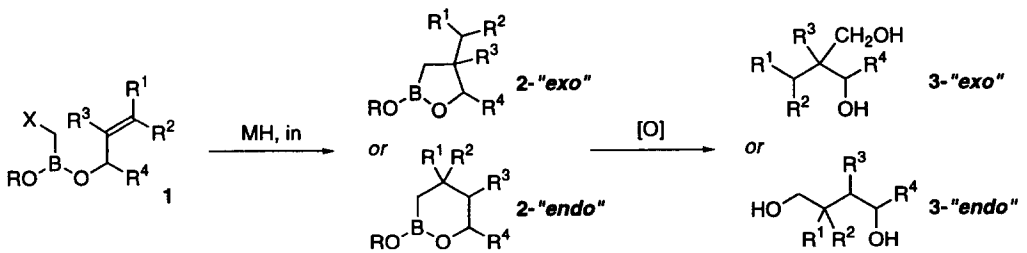
Abstract

Boroalkyl radicals readily cyclize onto alkenyl and alkynyl traps tethered via a C–B–O linkage. Oxidative cleavage of the C–B bond of the temporary connection following cyclization affords 1,3-diols in good yields.

Keywords: boronates; radical reactions; cyclization; diols.

The intramolecular cyclizations of silylmethyl or α-silyl radicals described by Nishiyama[1] and Stork[2] over a decade ago were the first reported examples of silicon-tethered processes, and have since found wide application,[3] principally for the stereoselective synthesis of 1,3-diols. In contrast to α-silyl radical reactions, the reactions of α-boryl radicals have only recently received attention from synthetic chemists. Carboni and co-workers were the first to describe a cyclization of an α-boryl radical,[4] and our group described the first intermolecular additions to electron-deficient and electron-rich radical alkenes, as well as their addition to allyl stannanes.[5] However, our attempts to add α-boryl radicals intermolecularly to more sterically demanding alkene traps (i.e. *cis*- or *trans*-disubstituted and trisubstituted alkenes) have resulted in unsatisfactory yields of adducts. We now report our preliminary results on the use of a boron-tethered approach, that overcome the problems observed in the intermolecular additions of α-boryl radicals, and the application to the synthesis of simple 1,3-diols (Scheme 1).



Scheme 1.

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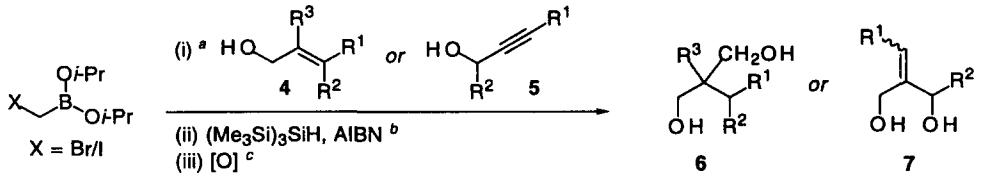
Having recently demonstrated the viability of alkenyl boronates in boron-tethered intramolecular radical cyclizations,[6] we envisaged that boromethyl and boroalkyl radicals could be similarly tethered to suitable radical traps, via a C–B–O temporary connection, and would hence undergo addition more efficiently than their intermolecular counterparts. In addition, the tether would be expected to act as a stereochemical controlling element in the cyclization. The general strategy employed involves radical cyclization of **1** (formed by transesterification of diisopropyl (halomethyl)boronates with an allylic alcohol) to the intermediate boracycles **2**-'*exo*' or **2**-'*endo*' depending on the mode of cyclization (Scheme 1). Oxidation then leads to the formation of the 1,3-diol **3**-'*exo*' or 1,4-diols **3**-'*endo*'. We were particularly interested in comparing the boron-tethered results to those obtained with the silicon-tethered approach, since both the shorter C–B versus C–Si bond lengths, and the tricoordinate boron versus tetracoordinate silicon geometry, would be expected to affect the 5-*exo*-trig and 6-*endo*-trig transition states for cyclization.

Diisopropyl (bromomethyl)boronate was prepared following the protocol of Matteson and Michnick,[8] and diisopropyl (iodomethyl)boronate was accessible via the modified procedure of Wallace and Zong.[9] Ditransesterification was then achieved via treatment with 2 equivalents of an allyl or propargyl alcohol **4** or **5**, at room temperature in dry hexanes (Table 1). Cyclization under radical conditions was first explored using the substrate derived from **4d** and the catalytic tributylstannane method.[10] Unfortunately, using these conditions in THF (0.10 M), direct reduction of the halide precursor predominated, and only a trace amount of the 5-*exo*-cyclization product **6d** was isolated following oxidation with basic hydrogen peroxide.[11] Based on previous work with these conditions, we suspect that direct ionic reduction by the co-reductant, sodium cyanoborohydride occurred.[5a] Consequently, the use of stoichiometric tributyltin hydride in benzene was examined, but although the yield of isolated product increased to about 31%, direct reduction by a radical pathway was significant. Tris(trimethylsilyl)silane (TTMSS),[12] a reagent known to trap radicals with lower efficiency than tributyltin hydride, was used in benzene (0.10 M) to curb the degree of direct reduction,[13] resulting in an increase in the yield of **6d** to 82% (Table 1, Entry 5).

A number of allyl and propargyl alcohols were also tested as radical traps in order to gauge the scope of the reaction and to establish the favored mode of cyclization (Table 1). Cyclization onto alkenes and alkynes unsubstituted at the terminal position showed exclusive 5-*exo*-trig cyclization giving rise to 1,3-diols (Table 1, Entries 1, 8, 9, 12 and 15), and both NMR and GC analysis of crude reaction mixtures following oxidation failed to detect the presence of any 6-*endo*-trig cyclization products.[14] Mono- and di-*n*-alkyl substitution at the terminus of the alkene or alkyne (Table 1, Entries 2–4, 7, 13 and 14) produced similar results, as did terminal aryl substitution (Table 1, Entries 5, 6, 10 and 11). A substantial erosion in yield was observed in the cyclization of alkenes bearing a proximal methyl group because of the greater steric hindrance of the tertiary olefinic carbon (Table 1, Entries 8–11). In these cases 5-*exo*-trig cyclization is presumably slower and more dilute reaction conditions were required to minimize increasingly competitive direct reduction of the α-boryl radical. Only with a TTMSS concentration of 0.01 M do the product yields become synthetically useful. Interestingly, no 6-*endo*-trig cyclization was evident despite the more favorable steric aspects of the alkene terminus. This result is sharply in contrast with observations for the analogous substrate employing a silicon tether where 6-*endo*-trig cyclization was found to predominate.[1] The use of iodide precursors (Table 1, Entries 4, 6, 9, 11 and 14) did not appreciably affect yields, whereas use of mixed isopropyl allyl boronates (i.e. where only 1 equivalent of the alcohol precursor was used) resulted in a decrease in yield (e.g. 62% for the case of **6d** obtained from the bromide). Oxidation of the C–B bond in the boracycles **2** can also be achieved using trimethylamine-*N*-oxide[7] which should allow extension of this methodology to substrates containing C–Si or O–Si functionality. Preliminary investigations into the stereoselectivity of these boron-tethered radical cyclizations were demonstrated using the racemic

Table 1



Entry	Substrate	R^1	R^2	R^3	X	Product	Yield (%)[e]
1	**4a**	H	H	H	Br	**6a**	68
2	**4b**	Et	H	H	Br	**6b**	70
3	**4c**	Pr	H	H	Br	**6c**	75
4	**4c**	Pr	H	H	I	**6c**	72
5	**4d**	Ph	H	H	Br	**6d**	82
6	**4d**	Ph	H	H	I	**6d**	77
7	**4e**	Me	Me	H	Br	**6e**	71
8	**4f**[d]	H	H	Me	Br	**6f**	43
9	**4f**[d]	H	H	Me	I	**6f**	40
10	**4g**[d]	Ph	H	Me	Br	**6g**	46
11	**4g**[d]	Ph	H	Me	I	**6g**	42
12	**5a**	H	H	-	Br	**7a**	62
13	**5b**	Me	H	-	Br	**7b**	65
14	**5b**	Me	H	-	I	**7b**	61
15	**5c**	H	Me	-	Br	**7c**	62

[a] Alcohol **4** or **5** (2 equiv.), hexanes, r.t.

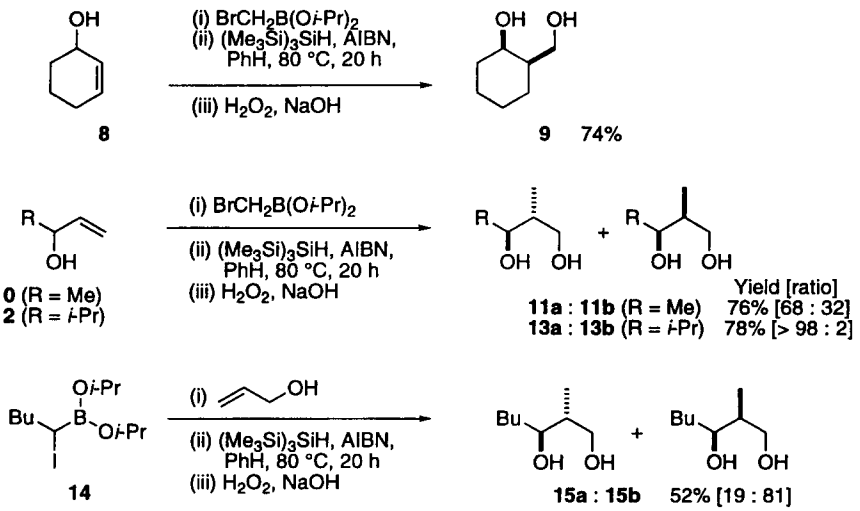
[b] $(Me_3Si)_3SiH$ (1.2 equiv.), AIBN (0.4 equiv.), PhH, $[(Me_3Si)_3SiH] = 0.10$ M, 80 °C, 20 h.

[c] NaOH (5 equiv.), H_2O_2 (5 equiv.), H_2O, r.t., 2 h.

[d] $[(Me_3Si)_3SiH] = 0.01$ M.

[e] Yields are for chromatographically purified material and are calculated from the diisopropyl (halomethyl)boronate.

substrates **8**, **10** and **12** (Scheme 2). Esterification of the bromomethyl boronate was achieved using 2 equivalents of the alcohols, and without isolation of the intermediate boronates **1**. Cyclization using **8** produced the anticipated *cis* 1,3-diol **9** as the sole product via an intermediate *cis* fused oxaborolane. Cyclization of **10**, a 4-substituted hexenyl radical, gave a 68:32 mixture of 1,3-diols **11a** and **11b**, with the major *anti* diastereomer originating through the pseudoequatorial disposition of both methyl substituents in the Beckwith–Houk transition state.[15] However, selectivity for the *anti* diastereomer of **13** was greater than 98:2 for the cyclization of **12**. These latter results are comparable to those observed for analogous substrates employing a silicon tether, with the exception that no products originating from 6-*endo*-trig cyclization were isolated.[1] An initial attempt at the cyclization of a 1-substituted hexenyl radical, a transformation very rarely accomplished by means of a silicon tether,[16] was conducted using α-haloalkyl boronate **14**[17] (Scheme 2). As expected with a Beckwith–Houk transition state, the *syn* diastereomer of the product 1,3-diol **15** now predominates.[15] However, the cyclization of **14** is more difficult, presumably for steric reasons, and shows a lower yield attainable only via slow addition of the TTMSS.



Scheme 2.

In summary, we have demonstrated the viability of intramolecular α-boryl radical cyclizations, processes that represent an important extension of boron-tethered radical cyclizations. A formal 'hydro-hydroxymethylation' of an allylic or propargylic alcohol can be achieved, without the formation of undesirable side-products resulting from 6-*endo*-trig cyclization, which sometimes occurs in silicon-tethered reactions. The lack of such products in the boron-tethered approach presumably reflects the shorter C–B bond length and the tricoordinate geometry of the boronate. The extension of this approach to other substrates is the subject of ongoing studies in our laboratory.

Acknowledgements

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13. General experimental procedure: To a solution of diisopropyl (bromomethyl)boronate (1.00 g, 4.48 mmol) in dry hexanes (45 mL) was added the allyl or propargyl alcohol (8.96 mmol), and the reaction mixture stirred at rt for 16 h. The solvent and isopropanol were then removed in vacuo to afford a colorless oil, to which was immediately added benzene (53.8 mL), TTMSS (1.66 mL, 5.38 mmol), and AIBN (295 mg, 1.79 mmol). The resulting solution was heated to reflux for 20 h, cooled to rt, and the solvent was removed in vacuo. After dissolving the residue in water (20 mL), NaOH (894 mg, 22.4 mmol) was added, followed by the dropwise addition of hydrogen peroxide (50% w/w in water, 1.52 mL, 22.4 mmol). The reaction mixture was stirred for 2 h at rt and acidified to ca. pH 7 with 5N HCl and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to a yellow oil. Purification by column chromatography (silica gel, ethyl acetate/hexanes eluent) afforded the desired 1,3-diol.
14. In each case, following removal of silane and allyl/propargyl alcohol residues, ^{13}C NMR showed only one -CH_2OH signal, and only one peak was observed by GC analysis. For both methods of analysis, authentic samples of **6a** and **7a** were also run for comparison.
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17. Diisopropyl (α-iodopentyl)boronate **14** was prepared via chloromethyllithium based one carbon homologation of diisopropyl butylboronate, followed by halogen exchange to the iodide (see: Matteson, D. S.; Majimdar, D. *Organometallics* **1983**, *11*, 1529–1535).