Bromo-Boronolactonization of Olefins[1]

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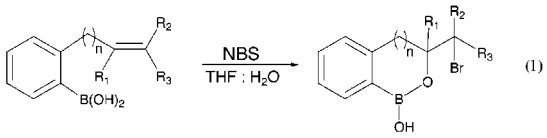
Exposure of a variety of mono- and disubstituted *ortho*-alkenylarylboronic acids to NBS in THF/H_2O under neutral conditions affords bromo-boronolactones, in some instances, with exceptional regiocontrol. The adducts, analogous to those formed by carboxylic acids, are shown to be useful synthetic intermediates.

Introduction

Boronic acids are widely known for their facile transesterification, even with comparatively hindered alcohols.[2] In particular, their proclivity for binding and discrimination among polyols has found numerous applications in carbohydrate and analytical chemistry.[3] They have also emerged as versatile intermediates for a variety of cross-couplings[4] with organic electrophiles largely as a consequence of their low toxicity, ease of preparation, and stability. More recently, considerable attention has been focused on alternative modes of reactivity for boronic acids and on extending their synthetic utility.[5] Herein, we report the facile formation of bromo-boronolactones via exposure of *ortho*-alkenylarylboronic acids to *N*-bromosuccinimide (NBS) in THF/H_2O (eq 1). The overall process provides opportunities



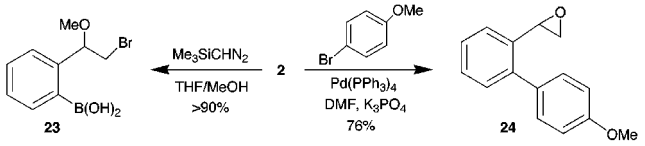
(1)

for regio- and stereochemical control at centers distal to the boronic acid and introduces a template from which new synthetic initiatives can be launched. Even though the first arylboronolactone was prepared in 1957 by Torssell,[6] its structure has only recently been confirmed spectroscopically,[7] and relatively little is known about the reactivity of this intriguing class of heterocycles.[8]

Results and Discussion

Results from the cyclization of some representative *ortho*-alkenylarylboronic acids are summarized in Table 1. In contrast to the halolactonization[9] of their cognates, i.e., carboxylic acids, boronic acids undergo preferential boron−bromine exchange at basic pHs. Under neutral conditions at 0 °C, however, bromo-boronolactonization predominates. The best yields are obtained in THF/H_2O rather than in THF or MeOH alone; NBS is preferable to Br_2. As anticipated for a styrenyl olefin,[9] annulation of boronic acid **1** proceeds in a Markovnikov sense to give lactone **2** (entry 1) as the exclusive isomer in good yield. This structure assignment was confirmed by transesterification of **2** with pinanediol and acetylation to give **20**, whose ^1H NMR revealed a one proton doublet of doublets at 6.67 ppm, consistent with a benzylic acetate. Likewise, the 1,2- and 1,1-disubstituted styrenes **3** and **5** gave rise to γ-lactones **4** (entry 2) and **6** (entry 3), respectively. The presence of an electron-donating group on the aryl ring improves the closure to lactone, as in the transformation of **7** to **8** (entry 4), compared with unactivated examples (cf. **1**). Markovnikov addition again predominates for the terminal olefin **9**, which affords bromo-boronolactone **10** (entry 5) as the sole product. Adducts **12** and **14**, obtained from boronic acids **11**[10] (entry 6) and **13** (entry 7),

Scheme 1



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(1) Presented in part at the 219th American Chemical Society National Meeting, San Francisco, CA, March 26−30, 2000; ORGN abstract 577.

(2) Boronic acid review: Torssell, K. In *Progress in Boron Chemistry*; Steinberg, H., McCloskey, A. L., Eds.: MacMillan Co.: New York, 1964; Vol. 1, Chapter 9.

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(10) Bromohydrin formation using the pinanediol ester of **11** favors the opposite regioisomer by a 5:1 ratio, presumably as a consequence of the steric influence of the bulky bicyclic ester.

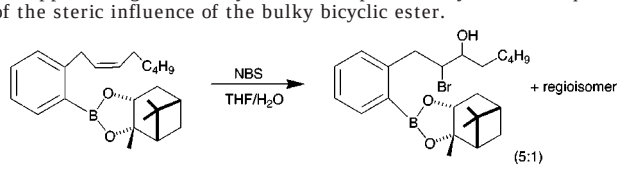

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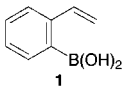
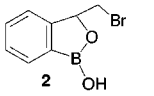
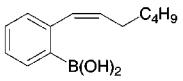
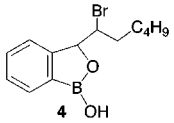
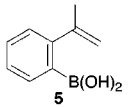
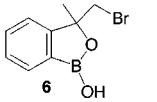
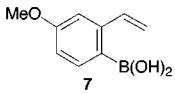
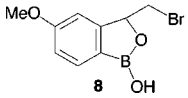
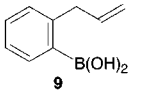
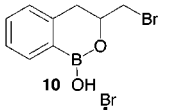
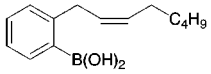
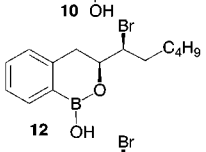
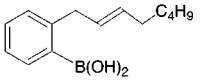
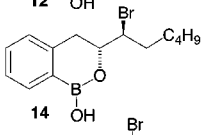
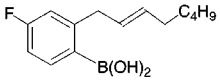
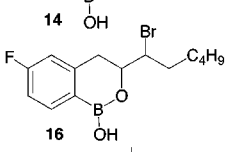
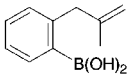
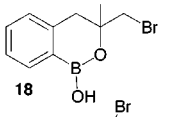
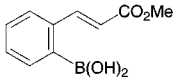
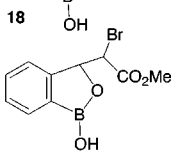
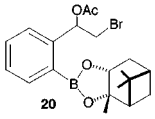
Table 1. Bromo-Boronolactonizations

Entry	Boronic acid	Bromo-boronolactone	Yield (%)
1	 **1**	 **2**	85
2	 **3**	 **4**	85
3	 **5**	 **6**	92
4	 **7**	 **8**	92
5	 **9**	 **10**	80
6	 **11**	 **12**	83
7	 **13**	 **14**	81
8	 **15**	 **16**	76
9	 **17**	 **18**	91
10	 **19**		0

respectively, are more revealing. Their respective *threo* and *erythro* stereochemistries are consistent with the well established[9] halonium ion mechanism of carboxylate halolactonizations. More significantly, the regiochemical outcomes are most consistent with the direct interception of the bromonium intermediate by a nucleophilic boronic acid. The alternative mechanism of prior bromohydrin formation followed by lactonization seems highly unlikely, as evident from the treatment of **21** with NBS under the same reaction conditions. The latter reaction is nonselective and yields an almost equal mixture of bromohydrin regioisomers **22a** and **b**. A somewhat diminished but still useful yield of δ-lactone **16** is obtained from **15**, despite the deactivating effect of a *para*-fluoro group (entry 8). Even in the case of **17**, creation of a tertiary lactone proceeds smoothly, furnishing an excellent yield of **18** (entry 9). On the other hand, *trans*-cinnamate **19** (entry 10) is recovered unchanged even after extended exposure to NBS. This is in agreement with the generally sluggish participation of electron-poor olefins in halolactonizations under similar conditions.[11]

The synthetic potential of the boronolactones was briefly auditioned using oxaborol **2** (Scheme 1). Exposure to excess Me_3SiCHN_2, followed by removal of all volatiles transformed **2** into methyl ether **23** in excellent yield. Under typical Suzuki conditions, **2** underwent facile cross-coupling and concomitant ring closure to give epoxybiphenyl **24**. On the basis of these initial results, we anticipate halo-boronolactones and related intermediates will find wide utility in synthesis.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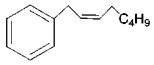
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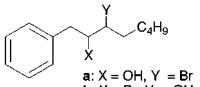
22
a: X = OH, Y = Br
b: X = Br, Y = OH

Experimental Section

General. All experiments were conducted under an argon atmosphere. Chromatography and routine laboratory procedures were as reported unless otherwise stated.[12] NBS was freshly recrystallized from water. As a consequence of spontaneous aggregation and/or anhydride formation by boronic acids, and to a lesser extent by boronolactones, melting points and elemental analyses are difficult to reproduce.[13] For the same reason, it was generally necessary to record NMR spectra in D_2O-saturated $CDCl_3$ at concentrations <2 mg/0.6 mL to obtain first-order spectra. Further structural confirmation was achieved by (1) conversion of the boronic acids/boronolactones to the corresponding cyclic esters with pinacol or pinanediol and/or (2) oxidation to the corresponding phenol with peracid and peracetylation (vide infra). Pinacolboronate esters were prepared from arylbromides[14] or aryltriflates[15] as described.

Preparation of Boronic Acids from Pinacolboronate Esters. Sodium periodate (1.8 mmol) was added to a room-temperature solution of pinacolboronate ester (0.6 mmol) in THF/H_2O (4:1, 5 mL). The mixture was stirred until homogeneous, and then 2 N HCl (0.2 mL) was added. After 12 h, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Further purification was achieved as noted below for the individual boronic acids.

General Procedure for Bromo-Boronolactonization. *N*-Bromosuccinimide (0.6 mmol) was added portionwise to a stirring, 0 °C solution of boronic acid (0.5 mmol) in THF/H_2O (4:1, 5 mL). After 6 h, the reaction was diluted with ethyl acetate (10 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was suspended in ether (5 mL), filtered, and concentrated in vacuo. Chromatographic purification of the residue [SiO_2 PTLC, EtOAc/hexane (1:3)] afforded the corresponding bromo-boronolactone (see Table 1).

Chemical Characterization of Bromo-Boronolactones. To further confirm their structures, the bromo-boronolactones in Table 1 were subjected to peracid oxidation and peracetylation as follows: *m*-CPBA (0.24 mmol) was added portionwise to a 0 °C solution of bromo-boronolactone (0.2 mmol) in anhydrous CH_2Cl_2 (5 mL). After 1.5 h, the mixture was diluted with an equal volume of water, washed with 10% aqueous sodium bicarbonate solution and brine, dried, and concentrated in vacuo. Chromatographic purification of the residue [SiO_2, EtOAc/hexane (1:3)] afforded the corresponding phenol (70−80%).

Excess acetic anhydride (0.1 mmol) was added dropwise to a 0 °C solution of the above phenol (0.05 mmol) and anhydrous

(11) For example see, Dalton, D. R.; Dutta, V. P. *J. Chem. Soc. B* **1971**, 85−89. Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 193−195. However, bromohydrin formation with α,β-unsaturated carbonyls is highly dependent upon the reaction parameters and reagents: Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* **1955**, *77*, 2549.

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(15) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450.

pyridine (0.2 mmol) in dry CH_2Cl_2 (2 mL). After 3 h, the mixture was diluted with CH_2Cl_2 (5 mL), washed with water and brine, dried, and concentrated in vacuo. Chromatographic purification of the residue [SiO_2, EtOAc/hexane (1:4)] led to the corresponding peracetylated phenol (80−85%).

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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