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Cyclic Alkenyl Boronic Half Acid Synthesis and Applications

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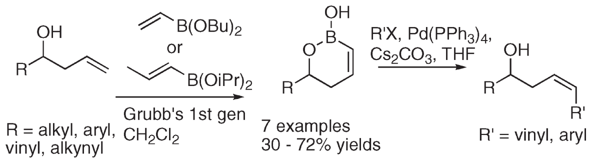


The synthesis of cyclic alkenyl boronic half acids from vinyl and propenyl boronic esters and homoallylic alcohols by ring-closing metathesis is reported. The method is compatible with both conventional and microwave heating and comparable yields are obtained under both conditions. The cyclic alkenyl boronic acids participate in Suzuki−Miyaura coupling reactions in good yields.

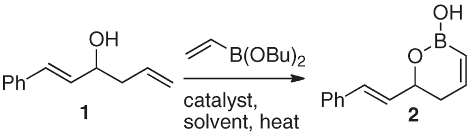
The utility of alkenyl boronic acids and esters in organic synthesis is well established. Alkenyl boronates are versatile substrates, which are converted to aldehydes,[1] ketones,[1] amines,[1] halides,[2] and the corresponding alkenes.[3] The stereospecific Suzuki−Miyaura cross-coupling reaction of the boronic acid or ester with aryl, vinyl, or alkyl halides results in the conversion of the boronate to aryl, vinyl, or alkyl groups.

A variety of well-established methods exist for the formation of alkenyl boronic acids and esters.[5−7] Recently, cross-metathesis of alkenes has emerged as a new method of accessing disubstituted and trisubstituted alkenylboronates from simple monosubstituted and disubstituted alkenyl boronates.[8] Marciniec and co-workers reported a complementary process for the preparation of di- and trisubstituted alkenyl boronates by the transfer of a boryl group [B(OR)$_2$] from one alkene to another (*trans*-borylation) using a ruthenium hydride catalyst.[9]

Limited reports of di- and trisubstituted cyclic boronic half acids exist.[10] In previously reported cross-couplings of this type of cyclic boronic ester, reactions occur at the carbon−boron bond, which results in the liberation of a tethered alcohol that could be used for further transformations.[11] Due to the stereospecificity of the Suzuki−Miyaura reaction, the double bond geometry is retained, which in the case of simple cyclic alkenyl boronic acids leads to *cis*-olefins, which are challenging to make by other methods.[7] Thus far, the Suzuki−Miyaura reaction of cyclic alkenyl boronic half acids has been limited to the preparation of α,β-unsaturated carbonyl compounds.[10d]

In this communication, we report the synthesis of monosubstituted cyclic alkenyl boronic half acids, or oxaborinenes, through ring-closing metathesis of acyclic alkenyl boronic esters with homoallylic alcohols. In addition, we expand the utility of the cyclic alkenyl boronic half acids in Suzuki cross-coupling reactions. This work represents a new way to access disubstituted *cis*-alkenes through cross-metathesis, which is known to provide predominately *trans*- or *E*-alkenes.[12]

An initial study was undertaken to establish the optimal conditions for the transesterification of vinyl boronic acid dibutyl ester with homoallylic alcohols followed by ring-closing metathesis to yield cyclic alkenyl boronic half acids. On the basis of previous work, an acyclic alkynyl boronic ester or an acyclic allyl boronic ester was needed.[10a,b] Thus, 1-phenyl-1,5-hexadien-3-ol **1** and vinyl boronic acid dibutyl ester were allowed to react with varied catalyst, solvent, and heating methods (eq 1). The two commercially available Grubbs catalysts were tested in dichloromethane (DCM) and toluene under both conventional heating and microwave heating conditions.



(eq. 1)

The results shown in Table 1 indicate that the optimal conditions involve ring closing under conventional heating

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(11) (a) Oh-e., T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2207. (b) Falck, J. R.; Bondlela, M.; Venkataraman, S. K.; Srivnivas, D. *J. Org. Chem.* **2001**, *66*, 7148–7150.

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TABLE 1. Optimization of Conditions for Cyclic Alkenyl Boronic Acids

entry	catalyst	heat	solvent	yield, %
1	**3**	reflux	toluene	33
2	**3**	reflux	CH_2Cl_2	62
3	**3**	mw	toluene[a]	58
4	**3**	mw	CH_2Cl_2[b]	58
5	**4**	reflux	toluene	25
6	**4**	reflux	CH_2Cl_2	21
7	**4**	mw	toluene	37
8	**4**	mw	CH_2Cl_2	44

[a]Microwave conditions for reactions run in toluene: 150 W, 100 °C, 200 psi, 4 h. [b]Microwave conditions for reactions run in methylene chloride: 150 W, 90 °C, 200 psi, 4 h.

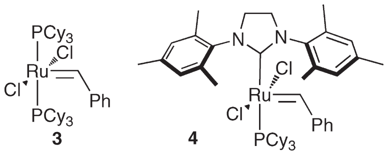
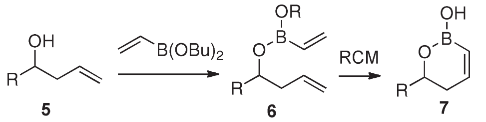
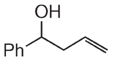
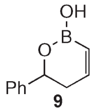
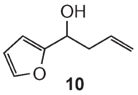
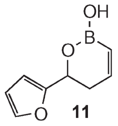
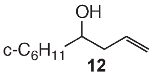
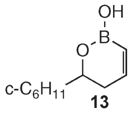
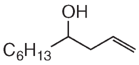
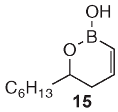
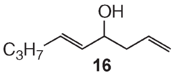
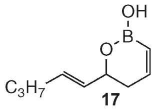
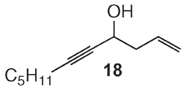
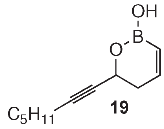

3 **4**

FIGURE 1. Metathesis catalysts.

TABLE 2. Scope of the Alkenyl Boronic Half Acids



Entry	Starting alcohol	Product	Yield[a]	Yield[b]
1	**1**	**2**	70%	72%
2	 **8**	 **9**	70%	66%
3	 **10**	 **11**	60%	50%
4	 **12**	 **13**	53%	63%[c]
5	 **14**	 **15**	53%	57%[c]
6	 **16**	 **17**	55%	57%[c]
7	 **18**	 **19**	33%	33%

[a]Conditions: alcohol (1 equiv), vinyl boronic acid dibutyl ester (2 equiv), catalyst **3** (10 mol %), CH_2Cl_2 (0.1 M). [b]Conditions: alcohol (1 equiv), propenyl boronic acid diisopropyl ester (3 equiv), catalyst **3** (10 mol %), CH_2Cl_2 (1 M). [c]Propenyl boronic acid isolated prior to esterification.

in DCM with bis(tricyclohexylphosphine)benzylideneruthenium(IV) chloride (Grubbs first generation catalyst) **3** (Figure 1). In most cases, toluene is not as effective as DCM as a solvent. Microwave conditions yield comparable results in DCM with catalyst **3**. Previous work reported by Schreiber and Micalizio indicates that 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidynylidene)(dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium **4** (Grubbs second generation catalyst) was optimal for the ring-closing metathesis of both allyl boronic esters and alkynyl boronic esters with unsaturated alcohols.[10a,b] The reaction time for conventional heating is 24 h versus 4 h under the microwave conditions.

The proposed reaction sequence for the formation of the cyclic half acids involves the transesterification of the boronic acid dibutyl ester, followed by ring-closing metathesis.[10a,b] Although cross metathesis of alkenes generally provides the *trans*-alkene, in this reaction, the cyclic boronic half acid **7** with the *cis*-alkene is formed exclusively under the reaction conditions. It is likely that transesterification of the alcohol with the vinyl boronic acid to form mixed boronic ester **6** occurs prior to ring-closing metathesis, which delivers the observed selectivity for the *cis*-alkene. Proton NMR analysis of the product supports the structure of the boronic half acid product **7**. Coupling constants of the vinyl protons in *trans*-alkenyl boronic esters are around 18 Hz, while the coupling constants of the alkenyl protons in the half boronic acids are close to 12 Hz.

The scope of the method is demonstrated with a variety of alkyl, aryl, and alkenyl homoallylic alcohols. As shown in Table 2, the yields of the aryl-substituted alcohols are slightly higher than those of the alkyl-substituted alcohols. The use of propargylic homoallylic alcohol **18**, entry 7, led to a separable 1:1 mixture of two products, which accounts for the low isolated yield of the desired boronic acid.

Due to the expense of vinyl boronic acid dibutyl ester (> \$100 per 5 g) and the challenge of preparing vinyl boronic acid due to its ready polymerization, we explored the possibility of using a propenyl boronic acid ester as a more cost-effective alternative in the formation of the cyclic alkenyl boronic half acids. The previously reported use of propenyl boronates used the propenyl boronic acid pinacol ester, which will not undergo transesterification. Thus, we prepared 1-propene-1-boronic acid by a modified procedure, and then esterified the acid with isopropyl alcohol in hexanes. The modified procedure eliminated the need for cryogenics, prevented the use of the carcinogenic benzene since hexanes and water form an azeotrope with similar qualities to benzene and water,[13] and allowed the easy removal of hexanes. The propenyl boronic acid diisopropyl ester was generated and used without purification.

The use of the propenyl boronic acid diisopropyl ester in place of vinyl boronic acid dibutyl ester resulted in the formation of the desired cyclic alkenyl boronic half acids with yields of the desired acids comparable to those of previous work. On the basis of the comparability of the conventional heating and microwave heating in the initial study, the application of the propenyl boronate was tested in a microwave to determine the feasibility of using the microwave for

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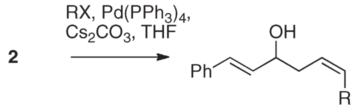
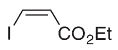
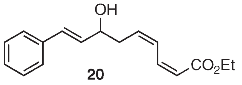
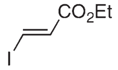
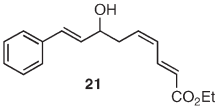
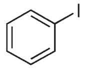
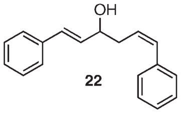
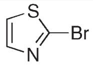
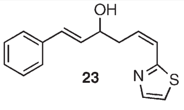
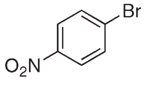
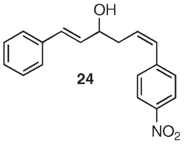
(13) At 62 °C, 94% hexane, 6% water and at 69 °C 91% benzene, 9% water, respectively. Gordon, A. J.; Ford, R. A. *The Chemist's Companion*. A Handbook of Practical Data, Techniques, and References; Wiley-Interscience: New York, 1972; pp 25–29.

TABLE 3. Suzuki Coupling of Cinnamyl Oxaborinene or 6-(2-Phenylethenyl)-2-hydroxy-1,2-oxaborin-3-ene[a]



Substrate	Product	Yield
	 20	70%
	20	70%[b]
	 21	35 %
	 22	75%
	 23	51%
	 24	70%

[a] Conditions: 6-cinnamyloxaborole (1 equiv), halide (1 equiv), $Pd(PPh_3)_4$ (1 equiv), Cs_2CO_3 (1 equiv), THF, 90 °C, 30 min, 100 W. [b] Conditions: 6-cinnamyloxaborole, halide, $Pd(OAc)_2$, BINAP, aqueous NaOH, THF.

the cyclic boronic acid synthesis. The microwave also was used for the convenience of the shorter reactions.

In certain cases, a small amount of an inseparable byproduct was formed, which required the isolation of propenyl boronic acid prior to formation of the isopropyl boronic ester. The slightly lower yields relative to the studies with the commercially available vinyl boronic acid dibutyl ester can be attributed to impure propenyl boronic acid. The use of the propenyl boronate ester starting material allowed the formation of a single cyclic boronic acid from the propargyl-substituted starting material **18**.

The cyclic boronic half acids are good substrates for Suzuki coupling reactions. These boronic half acids offer advantages in the Suzuki reaction allowing for the formation of a new carbon–carbon bond, liberating a masked alcohol functional group and maintaining the *cis*-double bond geometry.

The Suzuki–Miyaura reactions were conducted in the microwave for 30 min at 90 °C and 100 W with $Pd(PPh_3)_4$ as the catalyst and cesium carbonate as the base. Both alkenyl and aryl halides were suitable electrophiles for the cross-coupling reactions. The use of ethyl *cis*-3-iodoacrylate[10d] and ethyl *trans*-3-iodoacrylate as electrophiles allowed the generation of conjugated *Z*,*Z*- and *Z*,*E*-dienoates. Conjugated trienoate **20** undergoes isomerization after extended periods of time. The phenyl- and nitrophenyl-substituted *Z*-alkenes **22** and **24**, respectively, are stable indefinitely (Table 3). However, thiazole product **23** decomposes in air. The reactions of the liberated alcohol are being explored currently.

In conclusion, the synthesis of cyclic alkenyl boronic half acids has been reported. Conventional and microwave heating are effective for the formation of these boronic acids from homoallylic alcohols and alkenyl or propenyl boronic esters with Grubb's first generation catalyst. These substrates undergo Suzuki coupling reactions to create new carbon–carbon bonds and release an alcohol functional group that can be further functionalized. Additional results in terms of the Suzuki coupling reactions are forthcoming.

Experimental Section

General Procedure for Cyclic Vinyl Boronic Half Acid Synthesis. To a round-bottomed flask charged with dry dichloromethane was added Grubbs catalyst **3** (10 mol %). The stirred solution was degassed with N_2 for 3 min, then the alcohol (1.0 equiv) and vinyl boronic acid dibutyl ester (2.0–3.0 equiv) were added. The solution was degassed for another 3 min, then the stirred solution was heated to reflux for 24 h. After 24 h, the solution was allowed to cool to room temperature and then concentrated by rotary evaporation. The dark oil was purified by flash column chromatography beginning with 10% ethyl acetate–90% hexanes and ending with 20% ethyl acetate–80% hexanes.

6-(2-Phenylethenyl)-2-hydroxy-1,2-oxaborin-3-ene (2): IR (ν, cm^{-1}) 3406, 3025, 2926, 1604, 1494, 1408; ^1H NMR ($CDCl_3$, ppm) δ 7.39–7.19 (m, 5H), 6.9 (br d, J = 12.75 Hz, 1H), 6.6 (d, J = 16 Hz, 1H), 6.3 (dd, J = 16 Hz, 6 Hz, 1H), 5.7 (d, J = 12 Hz, 1H), 4.8–4.71 (m, 1H), 4.14 (br s, 1H), 2.49–2.27 (m, 2H); ^{13}C NMR δ (ppm) 151, 133, 132, 128, 127, 125, 74, 35; HRMS (EI) $[M]^+$ calcd for $C_{12}H_{13}BO_2$ 200.1003, found 200.1010.

6-Phenyl-2-hydroxy-1,2-oxaborin-3-ene (9): IR (ν, cm^{-1}) 3215 (m), 3064, 3027, 2958, 2927, 2871, 1603, 1417, 1350, 1322; ^1H NMR ($CDCl_3$, ppm) δ 7.32–7.19 (m, 5H), 6.94–6.89 (m, 1H), 5.8 (d, J = 11.25 Hz, 1H), 5.11–5.04 (m, 1H), 4.06 (s, 1H), 2.48–2.37 (m, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 151, 128, 127, 125, 76, 38; HRMS (EI) $[M]^+$ calcd for $C_{10}H_{11}BO_2$ 174.0847, found 174.0852.

6-Furyl-2-hydroxy-1,2-oxaborin-3-ene (11): IR (ν, cm^{-1}) 3218, 2957, 2925, 2855, 1732, 1606, 1463, 1416, 1378, 1317; ^1H NMR ($CDCl_3$, ppm) δ 7.37 (d, 1H, J = 4.75 Hz), 6.93 (br d, 1H, J = 12.25), 6.33 (d, 1H, J = 1.75 Hz), 6.28 (d, 1H, J = 3 Hz), 5.76 (dd, 1H, J = 2 Hz, 12.25 Hz), 5.14 (dd, 1H, J = 4.5 Hz, 11 Hz), 4.39 (s, 1H), 2.8–2.45 (m, 2H); ^{13}C NMR ($CDCl_3$, ppm) δ 151, 142, 110, 107, 68, 33; HRMS (EI) $[M]^+$ calcd for $C_8H_9BO_3$ 164.0639, found 164.0636.

6-Cyclohexyl-2-hydroxy-1,2-oxaborin-3-ene (13): IR (ν, cm^{-1}) 3396, 3210, 3019, 2925, 2852, 1605, 1506, 1448, 1412, 1320; ^1H NMR ($CDCl_3$, ppm) δ 6.9 (br d, 1H, J = 11.8 Hz), 5.66 (d, 1H, J = 12 Hz), 3.89 (s, 1H), 3.79 (q, 1H, J = 7.3 Hz), 2.2–2.15 (m, 2H), 1.9–0.9 (m, 11H); ^{13}C NMR ($CDCl_3$, ppm) δ 152, 149, 78, 43, 32, 29, 26, 25; HRMS (EI) $[M]^+$ calcd for $C_{10}H_{17}BO_2$ 180.1316, found 180.1321.

6-Hexyl-2-hydroxy-1,2-oxaborin-3-ene (15): IR (ν, cm^{-1}) 3211, 3020, 2956, 2857, 1605, 1410, 1320; ^1H NMR ($CDCl_3$, ppm) δ 6.8 (d, 1H), 5.62 (d, 1H, J = 10 Hz), 3.98 (s, 1H), 2.18–2.06 (m, 2H), 1.6–1.3 (m, 10H), 0.83–0.79 (m, 3H); ^{13}C NMR ($CDCl_3$, ppm) δ 151, 74, 38, 36, 33, 30, 29, 26, 23, 14; HRMS (EI) $[M]^+$ calcd for $C_{10}H_{19}BO_2$ 182.1473, found 182.1470.

6-(1-Pentenyl)-2-hydroxy-1,2-oxaborin-3-ene (17): IR (ν, cm^{-1}) 3211, 2960, 2926, 1605, 1410, 1318, 1260; ^1H NMR ($CDCl_3$, ppm) δ 6.84 (d, 1H, J = 12 Hz), 5.7–5.5 (m, 3H), 4.6–4.45 (m, 1H), 3.98 (s, 1H), 2.28–2.22 (m, 2H), 2.05–1.96 (m, 2H), 1.46–1.32

(m, 2H), 0.9 (t, 3H, J = 7.25 Hz); ^{13}C NMR (CDCl$_3$, ppm) δ 151, 134, 132, 75, 36, 35, 30, 23, 15; HRMS (EI) [M]$^+$ calcd for $C_9H_{15}BO_2$ 166.1160, found 166.1167.

6-(1-Heptynyl)-2-hydroxy-1,2-oxaborin-3-ene (19): IR (ν, cm^{-1}) 3426, 3023, 2930, 2859, 2239, 1607, 1414, 1352, 1317; ^{1}H NMR (CDCl$_3$, ppm) δ 6.85 (br d, 1H, J = 12 Hz), 5.73 (d, 1H, J = 12.25 Hz), 4.84−4.78 (m, 1H), 4.30 (s, 1H), 2.51−2.42 (m, 2H), 2.22−2.16 (m, 2H), 1.52−1.44 (m, 2H), 1.31−1.24 (m, 4H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR (CDCl$_3$, ppm) δ 150, 86, 65, 35, 32, 28, 23, 18, 14; HRMS (FAB) [M + H]$^+$ calcd for $C_{11}H_{18}BO_2$ 193.1390, found 193.1394 .

Modified Procedure for Propenyl Boronic Acid Diisopropyl Ester. Trimethyl borate (40 mmol) was added to 50 mL of anhydrous diethyl ether in a 500 mL round-bottomed flask equipped with an addition funnel and submerged in an ice/acetone bath. A 0.5 M solution of propenyl magnesium bromide in THF (50 mmol) was added to the addition funnel, then added dropwise to the trimethyl borate solution over 30 min. The solution was allowed to stir for an hour, then 70 mL of 30% aqueous HCl was added. The aqueous layer was extracted four times with diethyl ether, then the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated until a solid began to form. Isopropanol (80 mmol) was added along with 100 mL of hexanes. The round-bottomed flask was equipped with a Dean−Stark trap, then the solution was heated to reflux. When no additional water was generated, the solution was concentrated under reduced pressure to provide impure propenyl boronic acid diisopropyl ester, which was used for cyclic alkenyl boronic half acid preparation.

Modified Procedure for Propenyl Boronic Acid Diisopropyl Ester with Isolation of Solid Propenyl Boronic Acid. Trimethyl borate (40 mmol) was added to 50 mL of anhydrous diethyl ether in a 500 mL round-bottomed flask equipped with an addition funnel and submerged in an ice/acetone bath. A 0.5 M solution of propenyl magnesium bromide in THF (50 mmol) was added to the addition funnel, then added dropwise to the trimethyl borate solution over 30 min. The solution was allowed to stir for an hour, then 70 mL of 30% aqueous HCl was added. The aqueous layer was extracted four times with diethyl ether, then the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated until a solid began to form. Hexanes (50 mL) was added to the round-bottomed flask, then the solid precipitate was collected by vacuum filtration. The filtrate was concentrated under vacuum without heat, to provide additional solid product, which was collected by vacuum filtration. The solid was rinsed with hexanes. This process was repeated for a total of five times to provide 2−4 g of propenyl boronic acid as a mixture of *cis*- and *trans*-isomers. The propenyl boronic acid was esterified with isopropyl alcohol as described previously.

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Supporting Information Available: General methods, general procedure for Suzuki couplings, spectroscopic data for **20**−**24**, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.