JOC Notes

Synthesis of Functionalized Vinyl Boronates via Ruthenium-Catalyzed Olefin Cross-Metathesis and Subsequent Conversion to Vinyl Halides

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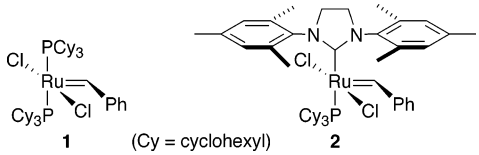
Abstract: Functionalized vinyl pinacol boronates suitable for Suzuki cross-coupling reactions are synthesized using ruthenium-catalyzed olefin cross-metathesis of 1-propenyl pinacol boronate and various alkenes, including functionalized and 1,1-disubstituted alkenes. The resultant boronate cross products are stereoselectively transformed into predominantly *Z*-vinyl bromides and *E*-vinyl iodides. The vinyl bromides may be synthesized in a two-step, one-pot synthesis from a variety of olefins, resulting in a *Z*-selective formal vinyl bromide cross-metathesis reaction.

Vinyl boronic acids and esters are versatile intermediates in organic synthesis.[1] The boronate moiety can be converted into hydrogen,[1c] an aldehyde or ketone,[1c,2] a halide,[3] an amine,[2] or an alkyl group.[4] Most notably, 1-alkenylboron compounds are excellent components in Suzuki cross-coupling reactions.[5] Alkyne hydroboration is usually employed to prepare vinyl boron reagents.[1c,6] This protocol can deliver high yields of products under mild conditions. However, terminal alkynes often require several steps to prepare, and their inherent reactivity can be problematic.[7] In addition, β,β-disubstituted vinyl boronates cannot be synthesized by alkyne hydroboration.[8]

Olefin cross-metathesis has become a viable synthetic strategy for the generation of highly functionalized alkenes,[9,10] due to the development of ruthenium catalysts such as **1**[11] and **2**.[12] Cross-metathesis offers an



attractive alternative to alkyne hydroboration for vinyl boronate synthesis. Alkenes are more easily prepared and have low reactivity as compared to alkynes, and the number of commercially available alkenes far exceeds that of terminal alkynes. We have previously reported the first cross-metathesis of pinacol vinyl boronate **5** and an aliphatic terminal olefin,[13] and Danishefsky has successfully applied this methodology to the synthesis of Suzuki macrocyclization precursors.[14] In this paper, we report the development of a new, synthetically more accessible boronate cross partner and the extension of vinyl boronate cross-metathesis to functionalized and 1,1-disubstituted olefins. The boronate cross products can be converted stereoselectively into either *E*- or *Z*-vinyl halides.

Scheme 1 illustrates our synthesis of the boronate cross partners.[15] We could not isolate boronic acid **3** due to its rapid polymerization upon concentration,[16] but **3** could be directly converted into **5**. Boronic acid **4** is also prone to polymerization, but it is more stable than **3**.[17] In our synthesis of **4**, we were able to isolate a white, air-stable solid in 10−20% yield by recrystallization from benzene. This product appeared by NMR to be **4**.[18] Compound **4** could also be esterified in situ to form **6**. Both **4** and **6** were variable mixtures of *E*- and *Z*-isomers. Compounds **5** and **6** were purified using silica gel chromatography,

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(3) (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786−5788. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456−6457.

(4) (a) Brown, H. C.; Bhat, N. G. *J. Org. Chem.* **1988**, *53*, 6009−6013. (b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Vara Prasad, J. N. V. *J. Org. Chem.* **1988**, *53*, 239−246.

(5) (a) Miyaura, N. Organoboron Compounds. *Top. Cur. Chem.* **2002**, *219*, 11−59. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(6) Beletskaya. I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957−5026.

(7) Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, *2*, 185−213.

(8) β,β-Disubstituted vinyl boronates can be synthesized using haloboration. For examples, see: (a) Suzuki, A. *Pure Appl. Chem.* **1986**, *58*, 629−638. (b) Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 1811−1814.

(9) For recent reviews of olefin metathesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Kotha, S.; Sreenivasachary, N. *Indian J. Chem., Sect. B* **2001**, *40*, 763−780.

(10) For a review of cross-metathesis, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, in press.

(11) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(13) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58−71.

(14) Njardarson, J. T.; Biswas, K.; Danishefsky, S. J. *J. Chem. Soc., Chem. Commun.* **2002**, *23*, 2759−2761.

(15) Matteson, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 4228−4233.

(16) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968−4971.

(17) Braun, J.; Normant, H. *Bull. Soc. Chim. Fr.* **1966**, *8*, 2557−2564.

(18) The material that we isolated is a mixture of **4**, its corresponding cyclic trimer, and probably small amounts of higher oligomers. The predominant species as detected by GC/MS is the cyclic trimer. In addition, the boronic acids in this mixture may be partially hydrated. Attempts to remove any excess water (using vacuum) from **4** after recrystallization resulted only in decomposition. However, the solid obtained after recrystallization was already of adequate purity to participate in cross-metathesis reactions, which work for both the monomeric and the trimeric versions of **4**.

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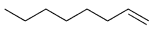
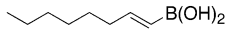
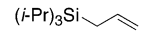
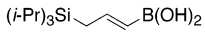
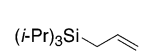
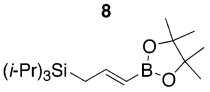
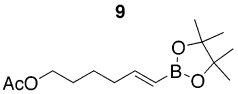
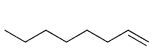
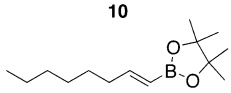
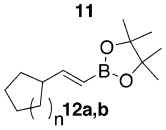
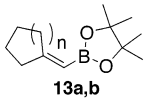
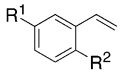
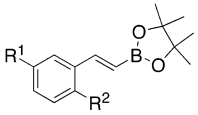
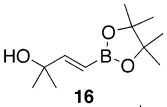
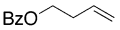
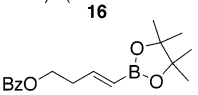
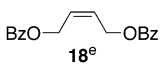
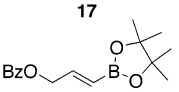
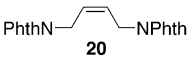
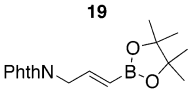
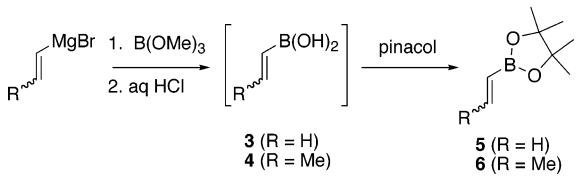
TABLE 1. Vinyl Boronate Cross-Metathesis[a]

entry	cross partner	vinyl boronate[b]	cross product	isolated yield (%)	$E:Z$[c]
1		**4**	 **7**	31	> 20 : 1
2		**4**	 **8**	55	> 20 : 1
3a 3b		**5** **6**	 **9**	86 99	7 : 1 10 : 1
4a 4b		**5** **6**	 **10**	60 65 (61)	10 : 1 13 : 1 (> 20 : 1)
5		**6**[d]	 **11**	83	9 : 1
6a (n = 1) 6b (n = 2)		**6** **6**	 **12a,b**	80 80	> 20 : 1 > 20 : 1
7a (n = 1) 7b (n = 2)		**6** **6**	 **13a,b**	80 91	------ ------
8a (R^1 = H, R^2 = H) 8b (R^1 = H, R^2 = Br) 8c (R^1 = NO_2, R^2 = H)		**6** **6** **6**	 **14a,b,c**	92 80 68	> 20 : 1 > 20 : 1 > 20 : 1
9	 **15**	**6**[d]	 **16**	61	> 20 : 1
10		**6**[d]	 **17**	66	8 : 1
11	 **18**[e]	**6**[f]	 **19**	58	10 : 1
12	 **20**	**6**[f]	 **21**	65	15 : 1

[a] (1 equiv cross partner) 5 mol % **2**, 0.2 M in CH_2Cl_2, reflux. 0.2−0.4 mmol scale. [b] 1.0 equiv, unless otherwise indicated. [c] Determined by ^{1}H NMR. [d] 2.0 equiv. [e] E/Z = 1:16. [f] 2.5 equiv.

SCHEME 1



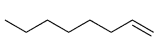
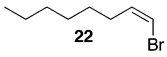
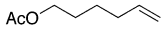
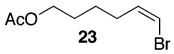
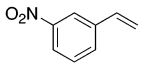
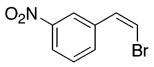
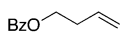
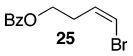
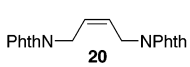
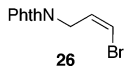
but **6** was isolated in significantly higher yields (80%) relative to **5** (60%).

The results of the cross-metathesis reaction between vinyl boron reagents **4**, **5**, or **6** and various olefins are summarized in Table 1.[19] Entries 1 and 2 show the first successful cross-metathesis reactions using an alkenyl boronic acid (i.e., **4**). Although reactions with **4** are highly *E*-selective, the resultant low isolated yields, due in part to the high polarity and cyclic trimerization[16] of the cross products, made pinacol boronic esters **5** and **6** more favorable reagents. While use of **5** and **6** affords cross-metathesis products in similar yields and *E*/*Z* selectivity (Table 1, entries 3 and 4), the ability to prepare **6** in higher yield and greater ease than **5** led us to primarily use **6** in further studies.

Boronate cross-metathesis is moderately to highly *E*-selective and is compatible with a variety of functional groups. As shown in Table 1, styrenes, allylsilanes, and protected alcohols and amines undergo efficient metathesis. Additionally, 1,1-disubstituted olefins are excellent cross partners, and their metathesis results in products (e.g., **13a** and **13b**) that cannot be prepared by

(19) Efficient vinyl boronate cross-metathesis can also be achieved with use of catalyst **1** when unhindered aliphatic terminal olefins are used, as we have previously reported (ref 13).

TABLE 2. In Situ Vinyl Boronate Cross-Metathesis/Bromination[a]

entry	cross partner	vinyl boronate[b]	product	isolated yield (%)	$E:Z$[c]
1		**6**	 **22**	73	1 : 9
2		**6**	 **23**	64	1 : 13
3a		**5**[d]	 **24**	93	< 1 : 20
3b		**6**[d]		87	< 1 : 20
4a		**5**	 **25**	65	1 : 10
4b		**6**		73	1 : 9
5a[e]	 **20**	**5**[f]	 **26**	85	1 : 8
5b		**6**[f]		68	1 : 8

[a] (1) (1 equiv cross partner) 5 mol % **2**, 0.2 M in CH_2Cl_2, reflux; (2) (1 equiv boronate) Br_2 (2 equiv), 0 °C; NaOMe (2 equiv), MeOH, 0 °C; 0.2−0.4 mmol scale, unless otherwise indicated. [b] 2.0 equiv, unless otherwise indicated. [c] Determined by ^{1}H NMR. [d] 2.0 mmol scale. [f] 2.5 equiv.

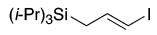
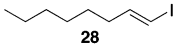
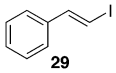
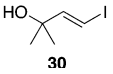
alkyne hydroboration. High levels of *E*-selectivity are achieved by using either styrenes or olefins that have secondary or tertiary allylic substitution.

Monitoring the boronate cross-metathesis reactions by ^{1}H NMR (CD_2Cl_2 solvent) reveals that nearly all of the terminal olefin cross partner is transformed into the desired cross product.[20] For example, we observed 86% conversion of **15** to the desired cross product **16**.[21] The lower isolated yield of **16** (i.e., 61%) indicates that some decomposition occurs during purification by column chromatography. This example is typical of the lower-yielding reactions reported in Table 1.

Vinyl halides, like vinyl boronates, are valuable components in Suzuki cross-coupling reactions. In addition, they have been designated as one of the most important building blocks of transition-metal-catalyzed syntheses in general.[22] The inability to synthesize alkenyl halides using olefin cross-metathesis has been a long-standing problem.[23] However, the ability to prepare vinyl boronates using cross-metathesis provides a unique route to vinyl halides, which employs the halogenation procedures reported by Brown[3] to stereoselectively convert the vinyl boronate cross-metathesis products into vinyl bromides and iodides.

Brominations (Br_2, NaOMe) can be performed in situ with the cross-metathesis reaction, resulting in a one-pot vinyl bromide synthesis (Table 2).[24,25] In agreement with Brown's observations,[3b] the olefin stereochemistry of the vinyl boronate is always inverted, resulting in predominantly *Z*-vinyl bromides. Surprisingly, in several cases the isolated yields of the vinyl halides were greater than the isolated yields of the corresponding vinyl boronate cross product, which provides a way to curb the purification losses that are encountered with some vinyl boronate cross products.

TABLE 3. Iodination of Vinyl Pinacol Boronates[a]

entry	vinyl boronate	$E:Z$[b]	product	isolated yield (%)	$E:Z$[b]
1	**9**	8 : 1	 **27**	99	8 : 1
2	**11**	9 : 1	 **28**	90	11 : 1
3	**14a**	> 20 : 1	 **29**	99	> 20 : 1
4	**16**	> 20 : 1	 **30**	82	> 20 : 1

[a] I_2 (2 equiv), NaOH (3 equiv), THF, rt; 0.4 mmol scale. [b] Determined by ^{1}H NMR.

We were unable to obtain high yields of the vinyl iodide product using one-pot cross-metathesis/iodination reactions (I_2, NaOH). However, vinyl iodides are obtained in high isolated yields when purified vinyl boronates are used as starting materials (Table 3). The olefin stereochemistry of the starting vinyl boronate is retained during these reactions.[3a]

The reaction of iodine with a vinyl boronate compound is more sensitive to steric bulk on the boron atom than that of bromine. Brown observed that iodinations were unsuccessful using boronate catechol esters and had to hydrolyze them prior to iodination, whereas brominations readily occurred for both the boronic acids and their catechol esters.[3] In addition, pinacol boronate esters have been reported to resist reaction with iodine.[26] In our studies, we observed little or no iodination using Brown's conditions (ether, 0 °C) and had to employ a more polar solvent and a higher temperature (THF, room temperature) to observe high product yields. It is possible that the sensitivity of the iodination reactions to solvent polarity contributed to the inefficiency of the one-pot cross-metathesis/iodination reactions, as these reactions had to be carried out in either CH_2Cl_2 or a CH_2Cl_2/THF mixed solvent system in order to allow efficient performance of the metathesis reaction.

In summary, we have generated both functionalized and β,β-disubstituted vinyl boronates using ruthenium-catalyzed olefin cross-metathesis of 1-propenyl pinacol boronate **6**, which is readily synthesized from commercially available reagents in significantly higher yield than its vinyl analogue **5**. We halogenated the boronate cross products to form predominantly *Z*-vinyl bromides and *E*-vinyl iodides. Thus, the components of Suzuki and numerous other metal-catalyzed coupling reactions were constructed out of alkenes. Brominations can be carried out in one-pot with the cross-metathesis reaction, resulting in the first examples of effective *Z*-vinyl bromide synthesis via olefin cross-metathesis.

(20) Using excess cross partner rather than excess boronate did not significantly affect the amount of cross product formed.

(21) Conversions were calculated relative to an anisole internal standard.

(22) Tsuji, J. Reactions of Organic Halides and Pseudohalides. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2000; pp 27−108.

(23) Grubbs group, unpublished results.

(24) Excess boronate is utilized in order to minimize the formation of homodimers, which form dibrominated side products.

(25) For ease of purification, it was sometimes advantageous to use **5** rather than **6**, as methylated side products were sometimes observed with **6**.

(26) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3929−3932.

Experimental Section

General Procedure for Cross-Metathesis of Compounds 4, 5, or 6. A solution of catalyst **2** (5 mol % relative to the cross partner) and dry dichloromethane (cross partner = 0.2 M) was added via cannula to a flame-dried, round-bottomed flask equipped with a reflux condenser and kept under slight argon pressure. The olefin cross partner and either **4**, **5**, or **6** were added to the flask via syringe. The brick red solution was refluxed for roughly 12 h. The mixture was then concentrated in vacuo, and the product(s) were purified by silica gel chromatography.

General Procedure for One-Pot Cross-Metathesis/Bromination of Compounds 5 or 6. After completion of the cross-metathesis reaction (carried out as described above), the reaction vessel was placed in an ice bath, and bromine (2 equiv relative to **5** or **6**) was added dropwise via syringe. The reaction was allowed to stir at 0 °C for 30 min, after which time a solution of 2 equiv (relative to **5** or **6**) sodium methoxide (roughly 0.6 M in anhydrous methanol) was added via syringe. The solution was allowed to stir at 0 °C for 30 min, after which time aqueous sodium thiosulfate was added. The aqueous layer was extracted three times with dichloromethane. The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo, and the product(s) were purified by silica gel chromatography.

General Procedure for Iodination of Vinyl Pinacol Boronates. The boronate and reagent-grade THF (boronate = 0.4 M) were added via syringe to a round-bottomed flask equipped with an addition funnel and kept under slight argon pressure. A solution of (3 equiv) sodium hydroxide (3 M in deionized water) was added via syringe, and the solution was stirred vigorously at room temperature for about 10 min. A solution of iodine (2 equiv, 0.2 M in THF) was added dropwise (via addition funnel) to the reaction mixture, waiting for the red-orange color of the reaction to turn to yellow before adding more iodine solution. As the reaction progressed, the red-orange color disappeared more slowly, and by the end of the reaction, it did not go away at all. Reaction times were, on average, about 2 h. At the end of the reaction, aqueous sodium thiosulfate was added, and the aqueous layer was extracted three times with diethyl ether. The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo, and the product(s) were purified by silica gel chromatography.

1-Propenylboronic Acid (4). A 4.5 mL (40 mmol) portion of trimethyl borate and 10 mL of diethyl ether were added via syringe to a flame-dried, round-bottomed flask kept under slight argon pressure. The flask was placed in a dry ice/acetone bath, and 100 mL of 1-propenylmagnesium bromide (0.5 M in THF, 50 mmol) was added dropwise, over about 30 min, to the solution using an addition funnel. After all the Grignard reagent had been added, the reaction was allowed to stir for 1 h at −78 °C, at which point the reaction was placed in an ice bath and 70 mL 30% aqueous HCl was added. After being stirred for 30 min, the solution was warmed to room temperature and extracted three times with 100 mL diethyl ether. The organic portion was dried with sodium sulfate and concentrated in vacuo, and purified **4** was obtained by recrystallization from benzene. ^{1}H NMR (300 MHz, CD_3CN, ppm): (cyclic trimer, *E*-isomer) δ 6.49 (3H, dq, J = 17.7, 6.0 Hz), 5.37 (3H, dq, J = 17.6, 1.7 Hz), 1.80 (9H, dd, J = 6.6, 1.8 Hz) ^{13}C NMR (300 MHz, CD_3CN, ppm): (cyclic trimer, *E*-isomer) δ 147.8, 22.1. HRMS (EI): calcd for $C_9H_{15}B_3O_3$ 204.1300, found 204.1301.

4,4,5,5-Tetramethyl-2-vinyl[1,3,2]dioxaborolane (5). The same procedure described above, only using vinylmagnesium bromide, was followed. After the ether extractions, the organic layer was dried with sodium sulfate, and the solution was concentrated in vacuo but was not allowed to become completely concentrated (which would lead to decomposition of the acid intermediate). The solution was added to a flask containing 50 mL of diethyl ether and 5 g of activated 4 Å molecular sieves. A 7 g portion of pinacol (59 mmol) was added, and the solution was allowed to stir (under argon flow) at room temperature for about 12 h, at which point the solution was passed through a filter and concentrated in vacuo using a weak-vaccuum rotovap (as **5** is somewhat volatile). The crude product was purified using column chromatography (9:1 pentane/diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.0 (3H, m), 1.29 (12H, s). ^{13}C NMR (300 MHz, $CDCl_3$, ppm): δ 137.1, 83.5, 25.1. HRMS (EI): calcd for $C_8H_{15}BO_2$ 154.1165, found 154.1165.

4,4,5,5-Tetramethyl-2-propenyl[1,3,2]dioxaborolane (6). A procedure identical to that described for compound **5** was followed, with less concern over decomposition of the boronic acid intermediate upon concentration. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): (*E*-isomer) δ 6.65 (1H, dq, J = 17.9, 6.5 Hz), 5.46 (1H, dq, J = 18.2, 1.7 Hz), 1.85 (3H, dd, J = 6.6, 1.8 Hz), 1.27 (12H, s); (*Z*-isomer) δ 6.5 (1H, m), 5.35 (1H, dq, J = 13.8, 1.5 Hz), 1.98 (3H, dd, J = 7.1, 1.7 Hz), 1.28 (12H, s). ^{13}C NMR (300 MHz, $CDCl_3$, ppm): (*E*-isomer) δ 149.8, 83.2, 25.1, 22.1; (*Z*-isomer) δ 149.8, 83.0, 25.2, 18.9. HRMS (EI): calcd for $C_9H_{17}BO_2$ 168.1322, found 168.1321.

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Noted Added after ASAP Posting. In the version posted ASAP on June 26, 2003, this paper was incorrectly formatted as an article. It was correctly formatted as a note in the version posted on July 7, 2003.

Supporting Information Available: General experimental methods and characterization data (^{1}H and ^{13}C NMR, HRMS) for compounds **7**−**14**, **16**, **17**, **19**, and **21**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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