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Boron-Directed Regio- and Stereoselective Enyne Cross Metathesis: Efficient Synthesis of Vinyl Boronate Containing 1,3-Dienes

Mansuk Kim and Daesung Lee*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

dlee@chem.wisc.edu

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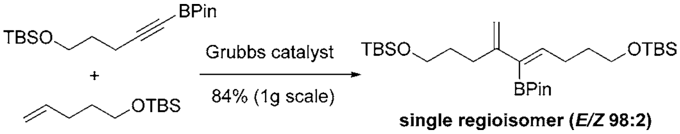
ABSTRACT



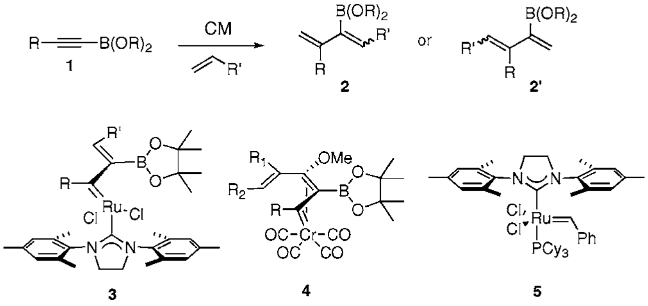
Regio- and stereoselective enyne cross metathesis reactions between borylated alkynes and terminal alkenes were realized to provide a variety of functionalized vinyl boronates. High chemical yield and regioselectivity was achieved irrespective of substituents on the alkyne and alkene counterparts, whereas *Z*/*E*-selectivity was found to be dependent upon the substituents both on the alkyne and alkene.

Vinylboronates are versatile building blocks in the synthesis of natural products and unnatural compounds of medicinal importance. Because they can serve as one of the most general substrates for transition-metal-mediated coupling reactions, such as the Suzuki−Miyaura coupling[1] and Heck-type reactions,[2] the efficient and stereocontrolled synthesis of this functional group constitutes an important goal in synthetic organic chemistry.

The ring closing metathesis (RCM)[3] of enynes possessing alkynyl boronate has been employed for the synthesis of vinyl boronates embedded in cyclic structures.[4] However, the tether between the alkene and alkyne counterparts imposes a significant limitation to structural diversification in this process. Recently, Grubbs and co-workers[5] utilized the cross metathesis (CM)[6] between terminal vinlyl boronate and alkene to generate more functionalized vinyl boronates.

To expand the scope and utility of enyne metathesis,[7] we envisioned using borylated alkyne **1** in CM, which would provide a straightforward access to vinyl boronate **2** or **2′** (Scheme 1). Having no precedent for enyne CM reaction of borylated alkynes, the regio- and stereochemical consequence providing **2** or **2′** cannot be predicted. However, the favored regiochemistry in the formation of a putative intermediate **3**

Scheme 1



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(1) Review: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

(2) Yoon, C. H.; Yoo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, *6*, 4037 and references therein. For reviews, see: (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(3) Reviews: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (e) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2.

(4) (a) Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995. (b) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101. (c) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272.

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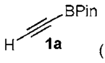
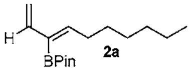
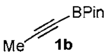
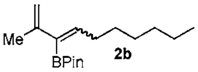
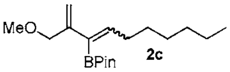
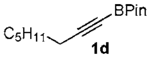
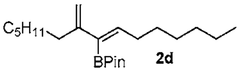
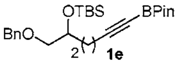
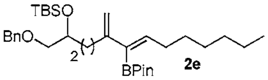
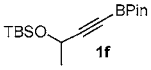
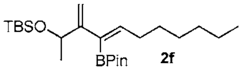
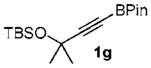
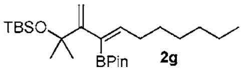
from the reaction between **1** and **5** leading to **2** might be inferred from a Fisher carbene complex **4** formed from borylated alkynes as an intermediate in the benzannulation reaction.[8]

Herein we report a highly regio- and stereoselective CM[9] of borylated alkyne **1**, showing a strong directing effect of the boron substituent, thereby providing a general and stereocontrolled synthesis of vinylboronates, providing selectively **2** over **2′**.

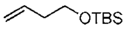
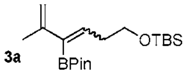
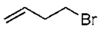
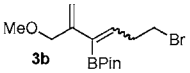
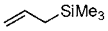
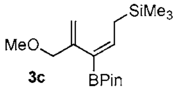
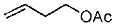
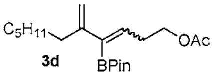
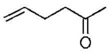
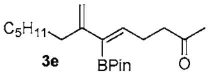
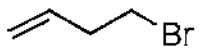
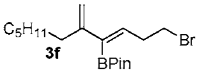
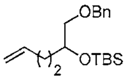
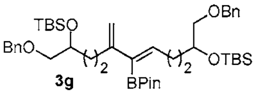
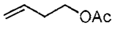
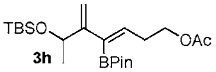
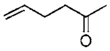
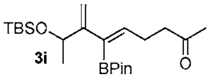
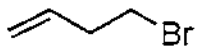
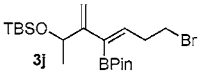
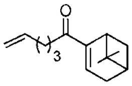
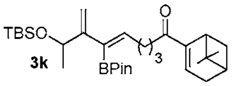
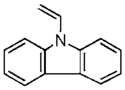
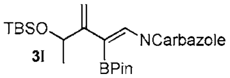
First, the reactivity and selectivity of borylated alkynes[10] possessing different substituents was examined by treating the mixture of alkynes **1a**−**g** and 1-octene (2 equiv) with 5 mol % of Grubbs catalyst **5**[11] at 40 °C (Table 1). The CM products **2b**−**f** were isolated in high yields as single regioisomers (entries 2−6).[12] However, both the sterically least hindered terminal alkyne **1a** and most hindered geminally substituted substrate **1g** did not afford the expected CM products **2a** and **2g**, giving only recovery of starting material (entries 1 and 7). The stereoselectivity of formation of **2b**−**f** is sensitive to the nature of substituents at the propargylic site, providing low selectivity with small substituents (entries 2 and 3) while giving high selectivity with larger substituents (entries 4−6).

Table 1. Cross Metathesis of Alkynyl Boronate with 1-Octene[a]

entry	alkyne	vinyl boronate	yield (%)[b]	E/Z[c]
1	 **1a** (Pin = pinacolate)	 **2a**	0	—[d]
2	 **1b**	 **2b**	82	43:57
3	 **1c**	 **2c**	81	41:59
4	 **1d**	 **2d**	96	98:2
5	 **1e**	 **2e**	90	97:3[e]
6	 **1f**	 **2f**	93	93:7
7	 **1g**	 **2g**	0	—[d]

[a] Alkyne **1** and 1-octene (2.5 equiv) with catalyst **5** (5 mol %) in CH_2Cl_2 (0.02 M) under reflux for 4−6 h. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR, and the stereochemistry was inferred from the NOE data of **2e**. [d] No reaction. [e] The stereochemistry of the major isomer was confirmed by NOE experiment.

Table 2. Cross Metathesis of Alkynyl Boronate with Various Alkenes[a]

entry	alkyne	alkene	vinyl boronate	yield (%)[b]	E/Z[c]
1	**1b**		 **3a**	79	43:57
2	**1c**		 **3b**	78	42:58
3	**1c**		 **3c**	59	1: 99[d]
4	**1d**		 **3d**	74	83:17
5	**1d**		 **3e**	80[e]	96:4
6	**1d**		 **3f**	94	>98:2
7	**1e**		 **3g**	86	>99:1
8	**1f**		 **3h**	60	93:7
9	**1f**		 **3i**	76	>99:1
10	**1f**		 **3j**	77	93:7
11	**1f**		 **3k**	74	93:7
12	**1f**		 **3l**	91	95:5[d]

[a] A solution of **1** and alkene (2−2.5 equiv) with catalyst **5** (5 mol %) in CH_2Cl_2 (0.02 M) was heated to reflux for 4−6 h. [b] Isolated yield. [c] Ratio was determined by ^{1}H NMR. [d] The stereochemistry was confirmed by NOE experiment. [e] Inseparable mixture of the desired product and the minor adduct resulting from the CM between styrene and alkene.

Noting the excellent CM reactivity of **1b**−**f** with 1-octene, we next explored the CM with heteroatom-containing alkenes (Table 2). The CM of alkynes **1b** and **1c** with alkenes possessing homoallylic substituents provided nearly 1:1 mixtures of *E*/*Z*-isomers in good yields (entries 1 and 2), whereas that of **1c** with allyltrimethylsilane gave only *Z*-isomer **3c** in moderate yield (59%, entry 3). The substituent effect can be seen more clearly in the CM of alkynes **1c** and

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(5) For acyclic vinyl boronate via CM, see, (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. (b) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

(6) Review of cross metathesis: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. A leading reference: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360 and references therein.

(7) Review on enyne metathesis: (a) Giessert, A. J.; Diver, S. T. *Chem. Rev.* **2004**, *104*, 1317. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (c) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176−204. (d) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154.

(8) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525.

(9) For regio- and stereoselective cross enyne metathesis with silylated alkynes, see: Kim, M.; Park, S.; Maifeld, S. V.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 10242.

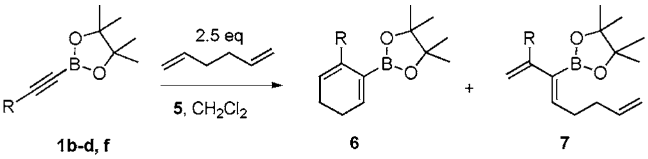
(10) For the preparation of alkynyl boronate, see Supporting Information.

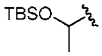
(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

1d with 3-butenyl-1-bromide (entries 2 and 6), providing an *E/Z*-mixture (42:58) of **3b** from the former and a 98:2 ratio of **3f** from the latter. Reactions of alkyne **1d** with two different alkenes also showed different *E/Z*-selectivity, providing marginal selectivity with an acetate substituent (87:13) but excellent selectivity with an acetyl group (96:4). The combination of more heavily functionalized alkyne **1e** and an alkene afforded high yield and selectivity (86%, >99:1) in the formation of **3g** (entry 7). Alkyne **1f** with a branched carbon at the propargylic site is well-tolerated[13] in the CM reaction with a diverse array of alkenes, providing good yields of the corresponding vinyl boronates **3h**−**l** with excellent regio- and *E/Z*-selectivity (entries 8−12). Even vinyl carbazole,[14] which would generate a Fisher carbene-like stable alkylidene intermediate provided high yield of **3l** with excellent *E*-selectivity (entry 12). However, CM between borylated alkynes and vinyl ethers gave low yield and selectivity accompanied with a significant amount of deborylated product.[15]

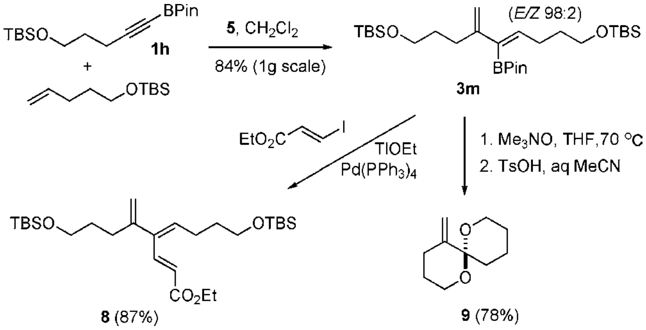
Not only acyclic 1,3-dienes but also cyclic dienes can be generated via enyne CM by employing an α,ω-diene. The CM of alkyne **1c** with 1,5-hexadiene (2.5 equiv) provided a 4:1 mixture of cyclic and acyclic vinyl boronates **6** and **7** (major, $n = 1$; minor, $n = 2$ and/or 3) in 67% yield (Scheme 2).[16] Interestingly, the ratio between cyclic dinene **6** and acyclic diene **7** does not change with respect to the change in the steric and stereoelectronic environment of borylated alkynes.

Scheme 2. Cross Metathesis of Alkyne with 1,5-Hexadiene



entry	alkyne	R	yield (%)	**6 : 7**
1	**1b**	Me		4 : 1
2	**1c**	$MeOCH_2$		4 : 1
3	**1d**	C_6H_{13}		4 : 1
4	**1f**	 TBSO		4 : 1

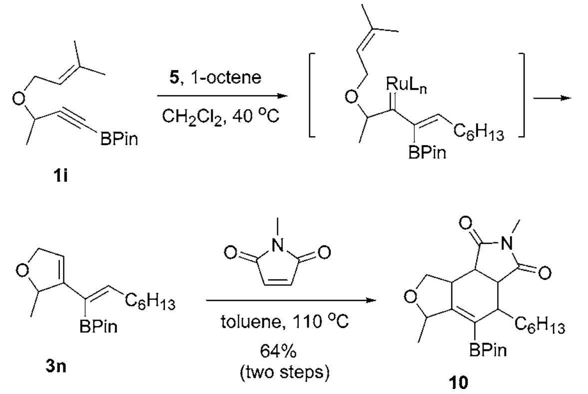
Scheme 3. Vinyl Boronate Functionalization



To demonstrate the utility of the vinyl boronates formed via the enyne CM, subsequent transformations of these vinyl boronates were explored. The CM reaction of alkyne **1h** with TBS-protected 4-penten-1-ol provided **3m** in 84% yield with high (98:2) *E/Z* ratio (Scheme 3). Under typical Suzuki coupling conditions ($Pd(PPh_3)_4$, TlOEt, wet THF),[17] vinyl boronate **3m** was converted into a cross conjugated triene **8** in 87% yield. Oxidation of the C═C−B(Pin) bond in **3m** under mild conditions ($Me_3NO{\cdot}2H_2O$, THF, reflux)[18] followed by acid treatment (TsOH, aq MeCN) induced spiroketalization, thereby providing spiroketal **9** in 78% yield (two steps).

To take advantage of the regio- and stereoselective nature of the cross enyne metathesis between borylated alkynes and alkenes, a tandem CM-RCM[19] sequence employing enyne **1i** and 1-octene was envisioned (Scheme 4). As expected, borylated 1,3-diene **3n** was generated as a single regio- and stereoisomer, which readily underwent Diels−Alder reaction with *N*-methyl maleimide to yield boronate **10**[20] as a single isomer in 64% overall yield (Scheme 4). This is a rare example of forming a 1,2,3,4-tetrasubstituted 1,3-diene with controlled double bond geometry via enyne metathesis.[21]

Scheme 4. Tandem CM-RCM Followed by Diels−Alder Reaction



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[12] The regiochemistry of **2c** was assigned after oxidation of the vinyl boronate to the corresponding enone (**2c′**; see Support Information). The regiochemistry of other compounds was assigned by analogy.

[13] The corresponding silylated alkyne showed no reactivity in CM; see ref 9.

[14] Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.

[15] CM of **1d** and ethyl vinyl ether gave low conversion, and the product obtained was only the protodeboronated compound as an *E/Z* mixture.

[16] For synthesis of monosubstituted 1,3-cyclohexadienes via enyne CM-RCM, see: (a) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171. (b) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110.

[17] Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.

[18] Kabalka, G. W.; Slayden, S. W. *J. Organomet. Chem.* **1977**, *125*, 273. Reference 4b.

[19] For related CM-RCM sequences with alkenes and diynes, see: Stragies, R.; Schuster, M.; Blechert, S. *Chem. Commun.* **1999**, 237.

[20] The preparation and Diels−Alder reaction of 2-borono-1,3-diene, see: Kamabuchi, A.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 4827.

In conclusion, we have developed an efficient enyne cross metathesis between borylated alkynes and terminal alkenes to generate functionalized vinyl boronates. High yields with excellent regioselectivity were obtained irrespective of substituents on the alkyne and alkene, whereas the *E/Z*-selectivity was found to be dependent upon the substituents both on the alkyne and alkene. Further investigation to elucidate the origin of the selectivity and the subsequent functionalization of the vinyl boronate are in progress.

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Supporting Information Available: General procedures and characterization of represented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For examples of the formation of 1,1,3,4-tetrasubstituted 1,3-diene synthesis via tandem RCM-CM sequence, see: Lee, H.-Y.; Kim, H. Y.; Tae, H. Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.