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Communication

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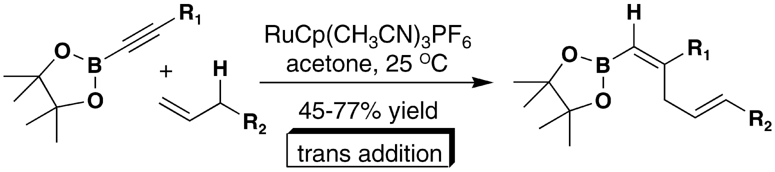

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COMMUNICATIONS

Synthesis of β,β-Disubstituted Vinyl Boronates via the Ruthenium-Catalyzed Alder Ene Reaction of Borylated Alkynes and Alkenes

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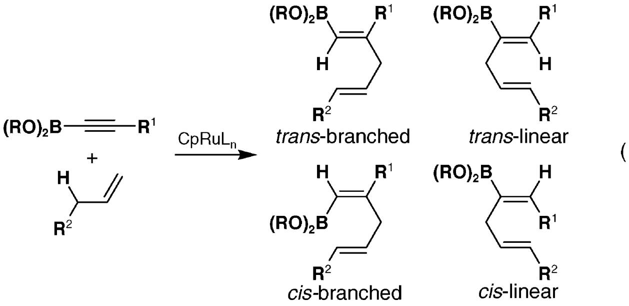
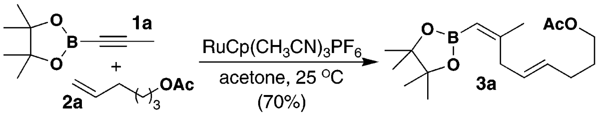
Vinyl boronates play a prominent role as versatile substrates for various coupling reactions such as the Suzuki−Miyaura[1] coupling and Heck-type reactions.[2] The development of efficient and stereocontrolled syntheses of vinyl boronates[3] is a prerequisite for applying these reactions toward complex natural product synthesis.[4] We envisioned the use of boronate-substituted alkynes in the ruthenium-catalyzed Alder ene reaction[5] as a means of rapidly generating substituted vinyl boronates. We anticipated that the boronate on the alkyne would have a directing effect in the Alder ene reaction, improving the selectivity between the branched and linear isomers (eq 1).[6] The trans stereochemistry of the vinyl boronate would be defined if the reaction proceeds by the generally accepted mechanism involving ruthenacyclopentene[5] formation; however, an alternate mechanism[7] could give rise to the cis isomer. Due to the lack of precedent involving borylated alkynes in this reaction, it is not possible, a priori, to predict which stereo- or regioisomer will be preferred.[8] Herein, we report a strong directing effect of the boronate substituent on the alkyne toward formation of the branched isomer with unusual cis stereochemistry.



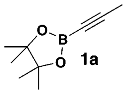
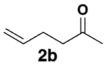
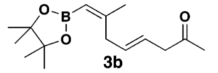
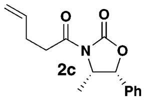
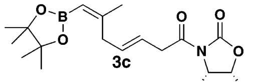
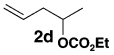
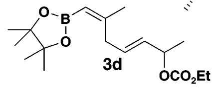
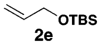
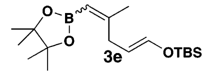
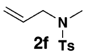
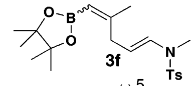
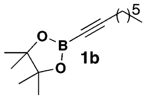
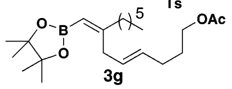
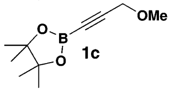
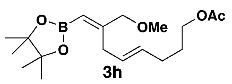
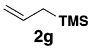
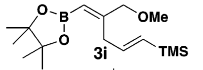
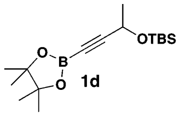
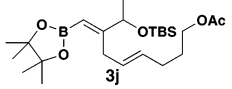
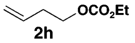
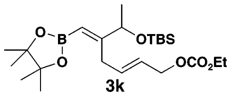
(1)

To test the reactivity and selectivity of alkynyl boronates[9] in the Alder ene reaction, alkynyl pinacol boronate **1a** and 1-hexenyl acetate **2a** in acetone was treated with a cationic ruthenium complex [RuCp(CH$_3$CN)$_3$PF$_6$][10] at 25 °C. The branched isomeric ene product **3a** was isolated in 70% yield after 2 h. Most surprising was the stereochemistry of the β,β-disubstituted vinyl boronate moiety, which was opposite to the normally observed stereochemical outcome in the Alder ene reaction of other internal alkynes.[11]



(2)

Table 1. Ruthenium-Catalyzed Alder Ene Reaction of Boronate−Substituted Alkynes[a]

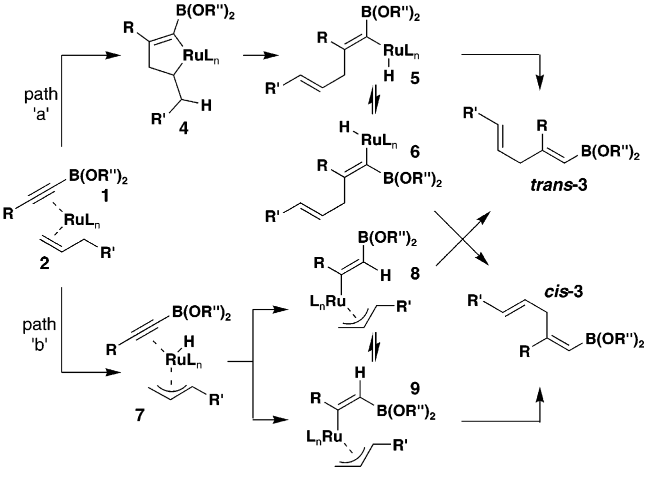
entry	alkyne	alkene	vinyl boronate	yield (%)[b]
1	 **1a**	 **2b**	 **3b**	72
2	**1a**	 **2c**	 **3c**	65[d]
3	**1a**	 **2d**	 **3d**	53[d]
4	**1a**	 **2e**	 **3e**	63[c]
5	**1a**	 **2f**	 **3f**	77[c]
6	 **1b**	**2a**	 **3g**	61
7	 **1c**	**2a**	 **3h**	64[d]
8	**1c**	 **2g**	 **3i**	45
9	 **1d**	**2a**	 **3j**	71
10	**1d**	 **2h**	 **3k**	57

[a] Reactions performed with 7−10 mol % of RuCp(CH$_3$CN)$_3$PF$_6$ at 25 °C. [b] Isolated yield. [c] Mixture of cis and trans isomers. [d] 9:1 cis/trans trisubstituted double bond isomers.

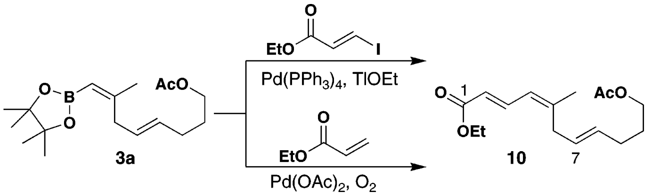
To investigate the generality of this reaction, alkynyl boronates **1a**−**d** and terminal alkenes **2b**−**h** were coupled to generate a variety of vinyl boronates **3b**−**k** (Table 1). Best results were achieved when a slight excess of the alkyne (1.2 equiv) was reacted with alkene in the presence of 10 mol % catalyst in acetone, although DMF, CH$_2$Cl$_2$, THF, and ClCH$_2$CH$_2$Cl gave similar results. Typically, vinyl boronate products could be isolated in moderate to good yields (45−77%), giving only the branched isomer in all cases. The nature of the alkyl substituents on alkynes **1a**−**d** did not affect the yield or the selectivity of the reaction. On the other hand, the substituents on the alkene counterparts have a strong influence on both the yields and stereoselectivity.[12] For example, the reaction of **1a** with alkenes possessing remote heteroatom substituents (**2b**−**c**) gave much higher yields (entries 1 and 2) than that with alkene **2d** bearing a homoallylic carbonate (53%, entry 3).[13] Consistently, the stereochemistry of β,β-disubstituted vinyl boronates **3a**−**d** is such that the alkyne substituents end up trans to the pinacol boronate moiety in the final products. Unexpectedly, the reactions of **1a** with alkenes **2e**−**f** that contain an allylic OTBS or N(Me)Ts group respectively provided stereoisomeric mixtures of **3e** and **3f**. It was found that the stereochemistry about the disubstituted double bond on both **3e** and **3f** is trans, but that of the β,β-disubstituted vinyl boronate

10.1021/ja0424629 CCC: $30.25

Scheme 1. Possible Mechanisms for the Formation of Vinyl Boronates **3**



Scheme 2. Suzuki Coupling and Heck Reaction of a Vinyl Boronate Derived from the Alder Ene Reaction



moiety is a 1:1 mixture of cis and trans (entries 4 and 5). Reactions of alkynes **1a**−**d** with alkene **2a** resulted in similar yields and selectivity (eq 2, entries 6 and 7). Sterically hindered allyltrimethylsilane **2g** lowers the reaction efficiency, providing only 45% yield of **3i** (entry 8). In contrast, steric congestion on the alkyne **1d** seems to be less detrimental, providing **3j** in good yield (entry 9). The marginal yield of **3k** (57%) is probably due to the deleterious effect of the carbonate at the homoallylic position (entry 10).

There are several speculative mechanisms which can be used to rationalize the observed stereochemistry of vinyl boronates **3a**−**k**. The Alder ene mechanism proposed by Trost et al. involves the formation of ruthenacyclopentene **4** followed by a rate-limiting β-hydride elimination, generating intermediate **5** (path a, Scheme 1).[5] The formation of *trans*-**3** is the consequence of a direct reductive elimination of **5** while *cis*-**3** would result only after an isomerization of **5** to **6**. It is difficult to justify the extent of isomerization of **5** using this mechanism as giving complete isomerization when R′ = alkyl and partial isomerization when R′ = OTBS or N(Me)Ts. An alternate mechanism involves the allylic C−H activation to form a π-allyl ruthenium hydride complex **7** (path b), which was also suggested by Trost et al. for the cyclization of certain 1,6-enynes.[7] There are two possible routes for **7** to lead to the observed products. The first involves a *cis*-hydroruthenation of **7** to generate **8**, which liberates *trans*-**3** upon reductive elimination. Isomerization of **8** to **9** followed by reductive elimination would provide *cis*-**3**. Alternately, a *trans*-hydroruthenation[14] of **7** would directly generate **9**. A more reasonable explanation of how the R′ substituent can affect the partitioning of the intermediates between **8** and **9** is obtained by invoking the interaction between R′ and the other substituents during the hydroruthenation step of the π-allyl mechanism.

The use of the vinyl boronate products for subsequent transition metal-catalyzed reactions was demonstrated. The Suzuki−Miyaura coupling of **3a** with *trans*-2-iodoacrylate provided dienoate product **10** in 60% yield, the C1−C7 segment of which is identical to subunits of zampanolide[15] and superstolide[16] (Scheme 2). The stereochemistry of the vinyl boronate **3a** was further confirmed by verification of the stereochemistry of **10**. This compound can also be obtained from **3a** by a boronate-mediated Heck reaction with ethyl acrylate under oxidative conditions.[2a]

In conclusion, we have developed a ruthenium-catalyzed Alder ene reaction that selectively generates the branched isomer with unusual stereoselectivity. Further investigation into the reaction mechanism and applications toward natural product synthesis are underway.

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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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