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Synthesis of tri-substituted vinyl boronates via ruthenium-catalyzed olefin cross-metathesis

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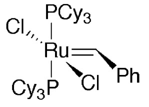
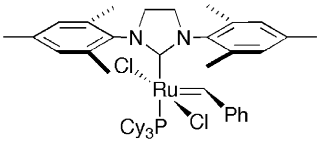
Abstract—Tri-substituted vinyl pinacol boronates, which are key reactive intermediates in a variety of transformations, are synthesized using ruthenium-catalyzed olefin cross-metathesis of α-substituted vinyl boronates and various alkenes. Cross-metathesis of 2-isopropenyl pinacol boronate proceeds with moderate yield and high *Z*-selectivity when sterically unhindered cross partners are used. Cross-metathesis of vinyl boronates that possess α-substitution larger than a methyl group is also achieved. Yield and *Z*-selectivity are lower in these cases, and the success of a cross-metathesis reaction is highly dependent on the steric bulk surrounding the double bond of the α-substituted vinyl boronate.

Vinyl boronates are important intermediates in organic synthesis.[1] The boronate moiety can be converted into various functionalities such as hydrogen,[1c] an aldehyde or ketone,[1c,2] a halide,[3] an amine,[2] or an alkyl group.[4] Most notably, these compounds are excellent components in Suzuki cross-coupling reactions.[5] Vinyl boronates are most commonly synthesized using alkyne hydroboration.[1c,6] While this method usually works well when forming 1,2-disubstituted vinyl boronates from terminal alkynes, the formation of tri-substituted vinyl boronates from unsymmetrical, internal alkynes is more difficult to achieve due to lack of regioselectivity in the hydroboration reaction.[7] Desirable results are only obtained when the two substituents on the starting alkyne are significantly different in steric bulk, and even then these results are highly dependent on the reaction conditions and the boron source.[8]

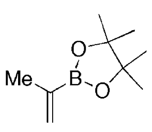
Olefin cross-metathesis has become a viable synthetic strategy for the synthesis of highly functionalized alkenes,[9,10] due to the development of ruthenium catalysts such as **1**[11] and **2**.[12] The more active catalyst, **2**, can be used to synthesize tri-substituted olefins.[13]



1 (Cy = cyclohexyl)



2



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Because cross-metathesis lacks the regioselectivity issues that arise in hydroboration reactions, it offers an attractive alternative for the synthesis of tri-substituted vinyl boronates. In addition, alkenes are more desirable starting materials than alkynes, because alkynes are often more challenging to install in a molecule[14] and are inherently more reactive than alkenes.[15] A variety of functionalized 1,2-disubstituted vinyl boronates were prepared using cross-metathesis catalyzed by **2**.[16] As discussed below, cross-metathesis of α-substituted vinyl boronates provides a route to selected tri-substituted vinyl boronates.

The initial studies examined the cross-metathesis of 2-isopropenyl pinacol boronate (**3**).[17] The results of these reactions are given in Table 1.[18] Tri-substituted vinyl boronates were obtained in moderate yield (ca. 60%) when relatively unhindered cross partners were used (entries 1–3). Unfortunately the product yield dropped significantly when more hindered cross partners were used (entries 4–6). Even a methyl group in the α-position

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Keywords: Olefin cross-metathesis; Vinyl boronates; Tri-substituted alkenes; Ruthenium catalysis.

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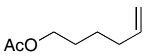
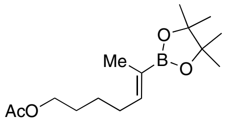
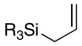
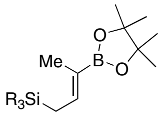
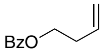
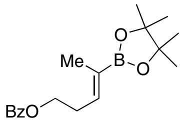
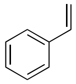
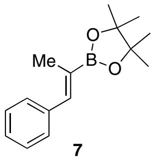
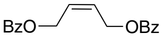
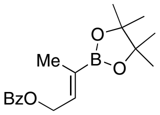
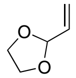
Table 1. Cross-metathesis of **3** with various alkenes[a]

Entry	Cross partner	Equiv	Cross product	Isolated yield (%)	Z:E[b]
1		0.5	 **4**	58	>20:1
2a (R = *i*-Pr)		1	 **5a**,**b**	59	>20:1
2b (R = Me)		1		59	>20:1
3		1	 **6**	46	>20:1
4		2	 **7**	30	>20:1
5	 **8**[c]	0.5	 **9**	30	2:1
6		1	—	N.R.	—

[a] (1 equiv **3**) 5 mol% **2**, 0.2 M in CH_2Cl_2, reflux, 12 h, 0.2–0.4 mmol scale.

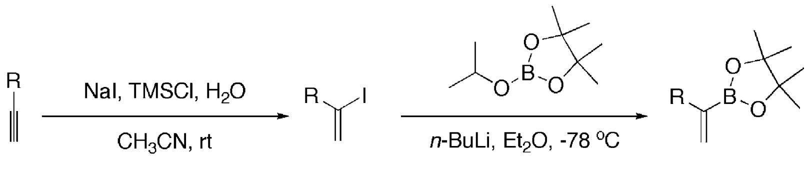
[b] Determined by ^1H NMR.

[c] Z:E = 16:1.

of an alkenyl boronate makes the substrate much more challenging for cross-metathesis than both vinyl and 1-propenyl boronate.[16] Although the yields were moderate, in most cases the cross-metathesis of **3** proceeded with high Z-selectivity. The tri-substituted vinyl boronate products shown in Table 1 would be challenging to synthesize regioselectively using alkyne hydroboration.

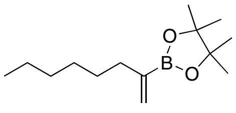
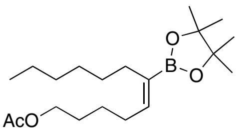
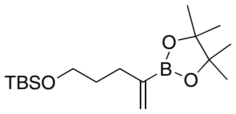
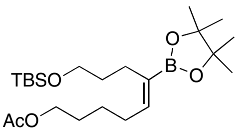
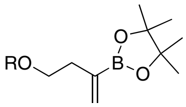
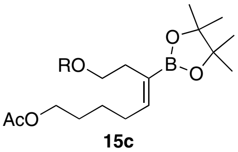
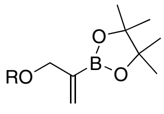
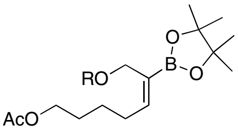
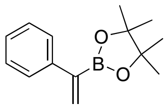
Vinyl boronates possessing α-substitution that was larger than a methyl group were synthesized in moderate-to-high yield according to the general procedure illustrated in Scheme 1.[19,20] Table 2 shows the results of the cross-metathesis reactions using these larger substrates. Unfortunately these α-substituted boronates were even more challenging substrates for cross-metathesis than boronate **3**, and thus the yields in these reactions were moderate at best, with several substrates exhibiting no cross-metathesis activity at all. The Z-selectivity in these reactions was only moderate as well, although the E- and Z-isomers could be separated by column chromatography, allowing the isolation of each stereoisomer.

Examination of the results shown in Table 2 reveals that the success of these cross-metathesis reactions is extremely dependent on the steric bulk surrounding the double bond of the α-substituted vinyl boronate starting materials. For example, when the α-substituent is an alkyl chain with a bulky silyloxy group at the end, decreasing the number of methylene units in the chain from three to two reduces the cross-metathesis yield by about half (Table 2, compare entries 2 and 3c). Furthermore, when the alkyl chain is reduced to only a single methylene unit, no cross-metathesis is observed (Table 2, entry 4c). Cross-metathesis yields also vary widely when the protecting groups are changed. For example,



Scheme 1.

Table 2. Cross-metathesis of α-substituted vinyl boronates with 5-hexenyl acetate[a]

Entry	α-Substituted vinyl boronate	Equiv	Cross product	Isolated yield (%)	*Z*:*E*[b]
1	 **10**	2	 **11**	40 54[c]	3:1 4:1[c]
2	 **12**	1.2	 **13**	35	4:1
3a (R = OH)	 **14a,b,c**	2	 **15c**	N.R.	—
3b (R = OAc)		2		N.R.	—
3c (R = OTBS)		1.3		17	5:1
4a (R = OH)	 **16a,b,c**	2	 **17b**	N.R.	—
4b (R = OAc)		2		40	1:1
4c (R = OTBS)		2		N.R.	—
5		2	—	N.R.	—

[a] (1 equiv 5-hexenyl acetate) 5 mol% **2**, 0.2 M in CH_2Cl_2, reflux, 12 h, 0.2–0.4 mmol scale.

[b] Determined by ^1H NMR.

[c] 20 mol% **2**.

in entry 4 of Table 2, the cross-metathesis product is isolated in 40% yield when the α-substituent of the vinyl boronate contains an acetate group (**16b**), but no cross-metathesis is observed when the acetate is replaced with a *t*-butyldimethylsilyloxy group (**16c**). These observations have led us to conclude that a metathesis catalyst that is more tolerant of sterically bulky olefins is needed in order for cross-metathesis of α-substituted vinyl boronates to provide a general route to tri-substituted vinyl boronates.

Cross-metathesis of α-substituted vinyl boronates can be used to generate tri-substituted vinyl boronates. When the α-substituent is a methyl group, the cross-metathesis products can be isolated in moderate yields (ca. 60%) and possess almost entirely *Z*-geometry as long as sterically unhindered cross partners are used. Cross-metathesis products can also be isolated when vinyl boronates possessing α-substitution larger than a methyl group are used. However, in these cases the yields and stereoselectivity drop significantly (ca. 40% yield and *Z*:*E* = 4:1 at best), and the success of a cross-metathesis reaction is highly substrate dependent. Most of the tri-substituted vinyl boronates reported in this paper would be difficult or impossible to generate regioselectively using conventional hydroboration procedures, and thus this cross-metathesis procedure has the potential to be extremely useful in organic synthesis. Both the yields and the stereoselectivities in these reactions have room for improvement, which we believe can be achieved through the development of new metathesis catalysts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.069. Information available: Experimental procedures and characterization for **4**–**7** and **9**–**17**.

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17. Boronate **3** was synthesized according to the procedure given in Ref. 16.
18. In the cross-metathesis reactions reported in both Tables 1 and 2, we sometimes observed the isomerization (ca. 5–20%) of the 1,1-disubstituted vinyl boronate starting material into its 1,2-isomer. In the case of boronate **3**, we also sometimes observed the cross-metathesis of its 1,2-isomer with the other olefins in solution, which resulted in various 1,2-disubstituted vinyl boronate side products.
19. Vinyl iodides were synthesized according to the procedure given in Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, *11*, 675–676. To obtain optimal results alcohols were protected as acetates during the reaction and subsequently deprotected. TBS protecting groups were not stable under these reaction conditions and thus had to be added after this reaction occurred.
20. Vinyl iodides were converted to vinyl boronates according to the procedure given in Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995–7996. Substrates containing free alcohols required 2.5 equiv. of *n*-butyllithium and pinacol borate reagent. In this procedure the pinacol borate was also added into the free alcohols but it was selectively removed by stirring the substrate in methanol (0.6 M) at room temperature for 4 h.