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Synthesis of Trisubstituted Alkenyl Boronic Esters From Alkenes Using the Boryl-Heck Reaction

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Abstract

The direct borylation of disubstituted alkenes is reported. These conditions allow for the conversion of a variety 1,1- and 1,2-disubstituted alkenes to trisubstituted alkenyl boronic esters with outstanding yields and excellent *E/Z* selectivities. The utility of this reaction has been demonstrated with several down-stream functionalization reactions, which allow access to diverse, stereodefined, functionalized olefins. Mechanistic studies are consistent with a boryl-Heck pathway.

Graphical Abstract:

Alkenyl boronic esters are important and versatile synthons in organic synthesis.¹ In particular, highly substituted alkenyl boronic esters have many synthetic applications, including in the synthesis of tri- and tetrasubstituted alkenes via the Suzuki reaction,² and are commonly employed in the total synthesis of natural products and pharmaceutical agents.³

Carboboration of alkynes⁴ or Miyaura borylation of alkenyl halides⁵ are common methods for the synthesis of highly substituted alkenyl boronic esters. These methods, however, are complicated by issues with regioselectivity with non-symmetric alkynes and the need for regio-defined alkenyl halide starting materials, respectively. Dehydrogenative borylation of disubstituted alkenes with HBpin or B2pin2 has been explored as a route to convert simple alkenes into highly substituted alkenyl boronic esters,⁶ but to date these reactions have not been developed into robust synthetic methods. For example, recently a high yielding and

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures, crystallographic and spectral data. This material is available free of charge on the ACS Publications website.

functional group tolerant method for the dehydrogenative borylation of 1,1-disubstituted alkenes has been reported,^{6b} but it is limited to styrenyl alkenes and requires the use of highly air-sensitive (glovebox) reagents. Even more notably, for 1,2-disubstituted alkenes only a few sporadic examples have been reported (all of which are limited to hydrocarbon alkenes),^{6c–e} and no general methods have been described.

Recently we reported a palladium-catalyzed boryl-Heck reaction that proved to be an efficient route to synthesize *trans*-1,2-disubstituted alkenyl boronic esters (Scheme 1).⁷ This reaction involves the coupling of *B*-chlorocatecholborane (catBCl) with a variety of terminal olefins, proceeding with excellent yields, high *E/Z* selectivities, and good functional group tolerance. Although this reaction is a competitive alternative to dehydrogenative borylation,^{6a, 6c, 6d, 8} the initial conditions were limited to terminal monosubstituted olefins.⁹ We recognized that boryl-Heck reactions tolerant of more substituted alkenes would allow for the direct synthesis of valuable highly substituted alkenyl boronic esters. Further, we envisioned developing a general set of reaction conditions for the incorporation of both 1,1- and 1,2-disubstituted alkenes.

We now report the development and utility of second-generation boryl-Heck reaction conditions that allow for the direct borylation of a variety of 1,1- and 1,2-disubstituted alkenes. This reaction enables the synthesis of a variety of stereodefined trisubstituted alkenyl boronic esters directly from simple alkenes without the need for pre-functionalization. The key to this success was the identification of both a new electrophilic borylation reagent and a more active catalyst. The relevance of this reaction is demonstrated with several one-pot and two-pot sequences synthesizing a variety of functionalized alkenes. Mechanistic studies support a Heck-like mechanism and show that formation of alkenyl boronic esters is kinetically favored over the allylic isomers.

We rationalized that the failure of disubstituted alkenes to participate in the previous boryl-Heck reaction conditions stemmed from the added steric repulsion imparted by the additional substitution during migratory insertion. Notably, related intramolecular carboboration reactions reported by Suginome also do not tolerate 1,1- or 1,2-disubstituted alkenes.¹⁰ A similar trend is observed in the classical bimolecular Heck reaction of aromatic halide electrophiles, where reactivity drops off dramatically with increased alkene substitution.¹¹ Recently, however, Sigman has shown that more highly substituted alkenes can participate in Heck reactions through the use of less coordinating counter-anions.¹² Similarly, we have recently found pronounced differences in reactivity with precatalysts bearing different ligand to metal ratios.¹³

Accordingly, using 1,1-disubstituted alkene **1** as a model substrate, we decided to investigate both the nature of the electrophilic boron reagent and the transition metal complex employed in the reaction. Consistent with our prior results, under our first-generation boryl-Heck or closely related conditions [catBCl, cat. (JessePhos)₂PdCl₂], only trace yield of the desired product was observed. For example, at 70 °C only 3% of **3** was found (Table 1, entry 1, ¹H NMR).^{14,15} In stark contrast, switching to *B*-bromocatecholborane (catBBr, which like catBCl is commercially available) showed a significant increase in reactivity, providing the desired product in 63% yield with minimal isomerization of **1** (entry 2).¹⁶ We attribute this

increase in reactivity to the longer and weaker Pd–Br bond resulting in a more cationic and less sterically encumbered palladium center.¹⁷ Importantly, in the absence of palladium, there is no reactivity, ruling out the possibility of a Lewis acid driven reaction (entry 3).

Next, we examined alternative single component precatalysts containing palladium and JessePhos. Prior studies of the silyl-Heck reaction have shown that catalytic efficiency is highly dependent on the ligand to metal ratio of the precatalyst used.¹⁸ We have recently found that (JessePhosPdI₂)₂, which bears a ligand to metal ratio of 1:1, is both bench stable and highly effective as a precatalyst for the silyl-Heck reaction.¹³ We rationalized that in the present boryl-Heck reaction, minimizing the amount of excess ligand would be highly important for increased reactivity. Such conditions should result in increased concentration of low-valent palladium intermediates, which should be less sterically demanding and more reactive towards migratory insertion. We were thus delighted to find that the use of (JessePhosPdI₂)₂ as the precatalyst resulted in a 95% yield of the desired product **3** (entry 4);¹⁹ demonstrating that both the nature of the halide leaving group *and* the nature of the catalyst are critical to the success of the reaction. The new catalyst does not produce satisfactory yields of the product when used in combination with catBCl (entry 5). Finally, by slightly increasing the equivalents of catBBr, excellent yields of **3** were obtained at shorter reaction times without detectable isomerization of the starting material (entry 6). Additionally, adding catBBr as a solution in toluene (~2 M) allowed for the entire reaction set-up to be performed *without the use of a glovebox*. This is an important practical consideration for the implementation of this reaction by non-specialist groups.

With optimal reaction conditions determined, we sought to explore the generality of this new procedure by examining the functional group tolerance and alkene substitution patterns. A variety of 1,1-disubstituted alkenes were subjected to these reaction conditions (Scheme 2). The model compound **3** was isolated in 94% yield with a 96:4 *E/Z* ratio. Symmetric exocyclic and acyclic alkenes gave excellent yields of **4** and **5** respectively. 2-Methylhexene also proved to be an excellent substrate, but *E/Z* selectivity in the product **6** was not as high (ca. 70:30). Naturally derived compounds such as limonene (**7**) and a pregnenolone derivative (**8**) can also be borylated with good yields and excellent *E/Z* selectivities, demonstrating that the borylation of feedstock chemicals is feasible. Notably, these examples also suggest that allylic stereocenters are not affected in the borylation reaction as no epimerization of the neighboring chiral carbon was observed. For example, product **7** retains absolute stereochemistry (98% ee (+)-limonene produces 98% ee product). We have previously demonstrated that related boryl-Heck reactions favor vinyl boronate products based upon thermodynamic selectivity.⁷ The results from **7** and **8** demonstrate that formation of the allylic isomer is not involved kinetically. In addition, with these second-generation reaction conditions, α -methyl styrene and related substituted aromatic alkenes could be borylated in very high yield (**9** and **10**).⁹

Next, several 1,2-disubstituted alkenes were examined under the optimized reaction conditions (Scheme 3). With the current reaction conditions, aryl substitution on the olefin is optimal to obtain good yields and selectivities. The borylation of *trans*- β -methyl styrene proceeded in 90% yield to a single *Z*-alkene isomer (**11**). When *cis*- β -methyl styrene was subjected to the reaction conditions, both stereoisomers of product are formed. In this case,

as with other *cis* alkenes, partial isomerization of the starting material to the *trans*-alkene was observed, explaining the erosion of the selectivity in the product.²⁰ Electron-rich styrenes including anisoles (**12**) and anilines (**13**) gave near quantitative yields also as single regio- and stereoisomers. Electron-deficient styrenes such as **14** and **15** were also well tolerated with 85% and 72% yield, respectively. Thiophenes are excellent substrates for this reaction; **16** was produced in superb yield. In addition to the displayed functional group tolerance, β -substitution with methyl (**11–12**), *n*-butyl (**13–16**), and cyclohexyl (**17**) groups is well tolerated all with good yields. Unfortunately, when non-aromatic internal alkenes, such as 4-octene, are subjected to the reaction conditions, multiple stereoisomers of the product are formed.²⁰ Likewise, higher-substituted alkenes failed to react.^{12c,21}

To illustrate the utility of this method in synthesis, several down-stream reactions of the products were briefly investigated. A tandem boryl-Heck/Suzuki reaction can be accomplished by the addition of aryl iodide and Cs₂CO₃ at the end of the reaction to form **19** in 92% yield (Scheme 4, top).¹ No additional palladium or ligand is required. Likewise, the addition of an oxidant, such as trimethylamine N-oxide, to the crude reaction mixture directly oxidized **18** to **20** in 71% overall yield as a mixture of diastereomers.²²

The stereodefined formation of C–O and C–X bonds can be a difficult task in organic chemistry. Using a procedure developed by Merlic,²³ allyl vinyl ether **21** was synthesized as a single stereoisomer in 69% yield (Scheme 4, bottom). Additionally, geometrically defined vinyl bromides can also be accessed using CuBr₂ (**22**).²⁴ In these latter cases, however, use of the isolated vinyl boronate is superior to *in situ* modification.

Finally, to further probe the mechanism of this reaction, we investigated the reactions of geometrically defined stilbenes (Scheme 5). When *trans*-stilbene (**23**) is subjected to these conditions, the *Z*-isomer is the major product (**24**). This is consistent with all the other β -substituted styrenes and is indicative of a Heck-like reaction pathway. In contrast, and although the yield was low, when *cis*-stilbene (**25**) was subjected to the reaction conditions, *trans*-**26** results as the major isomer. As discussed above, the reduced *E/Z* ratio is due to partial isomerization of the *cis* starting material. These results are consistent with sequential suprafacial migratory insertion and β -hydride elimination, and support a Heck-like mechanism.

In conclusion, we have developed boryl-Heck reaction conditions for the direct borylation of various disubstituted alkenes. Both 1,1- and 1,2-disubstituted alkenes are excellent substrates for these second-generation boryl-Heck reaction conditions, proceeding with excellent yields and *E/Z* selectivities. This reaction now provides access to highly substituted alkenyl boronic esters directly from alkenes. The key to this success was the identification of proper counter-ions and catalyst composition in order to access highly reactive catalytic species that can react with internal alkenes. The utility of these new reaction conditions has been demonstrated with several tandem one- and two-pot reactions leading to stereodefined functionalized olefins. Further support for a Heck-like mechanism was acquired from a series of mechanistic experiments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (15). As with our previous protocol, the reactions are worked up with the addition of pinacol to prepare the pinacol boronate esters. We have previously shown boronate products can also be accessed using varied workup conditions, see reference 7.
- (16). During the preparation of this manuscript, Tanaka and Hattori reported that BBr₃ can be used in the electrophilic borylation of alkenes, see: Tanaka S; Saito Y; Yamamoto T; Hattori T Org. Lett 2018, 20, 1828. [PubMed: 29527895]
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- (19). Supporting this notion, adding 1 equiv. of JessePhos compared to Pd precatalyst modestly suppresses the yield of product. See Supporting Information.
- (20). See Supporting Information.
- (21). We have also examined reactions of cyclic alkenes, such as cyclohexene. Consistent with a Heck-like mechanism, these substrates lead predominately to the allylic boronic ester product; however, the reactions are not yet sufficiently high-yielding to be of synthetic value. See Supporting Information for details.
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Previous Work: Alkene Borylation*Terminal Alkene Borylation*
General Conditions Established **This Work:** *Borylation of Disubstituted and Internal Alkenes* **Scheme 1.**

Methods for Direct Alkene Borylation

Scheme 2.
Scope of 1,1-Disubstituted Alkenes

^a Contains ~10% other alkene isomers

Scheme 3.
Scope of 1,2-Disubstituted Alkenes

Scheme 4.

Selected One and Two-Step Functionalization Reactions

Scheme 5.
Inversion of Alkene Geometry

Table 1.

Optimization of Reaction Conditions

entry	B-X (equiv)	precatalyst	2 ^a	3 ^a
1	catBCl (1.5)	(JessePhos) ₂ PdCl ₂	0%	3%
2	catBBr (1.5)	(JessePhos) ₂ PdCl ₂	2%	63%
3	catBBr (1.5)	none	0%	0%
4	catBBr (1.5)	(JessePhosPdI ₂) ₂	2%	95%
5	catBCl (1.5)	(JessePhosPdI ₂) ₂	12%	33%
6 ^b	catBBr (2.0)	(JessePhosPdI ₂) ₂	0%	94%

^aYield determined by NMR.^b4 h, isolated yield.