Synthesis of 1,1-Diboryl Alkenes Using the Boryl-Heck Reaction

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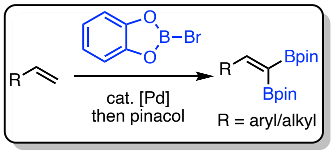
ABSTRACT: The synthesis of 1,1-diboryl alkenes from terminal alkenes is reported. 1,1-Regioselective addition is observed for both conjugated and unconjugated alkenes, allowing for a single method to prepare a wide range of 1,1-diboryl alkenes.



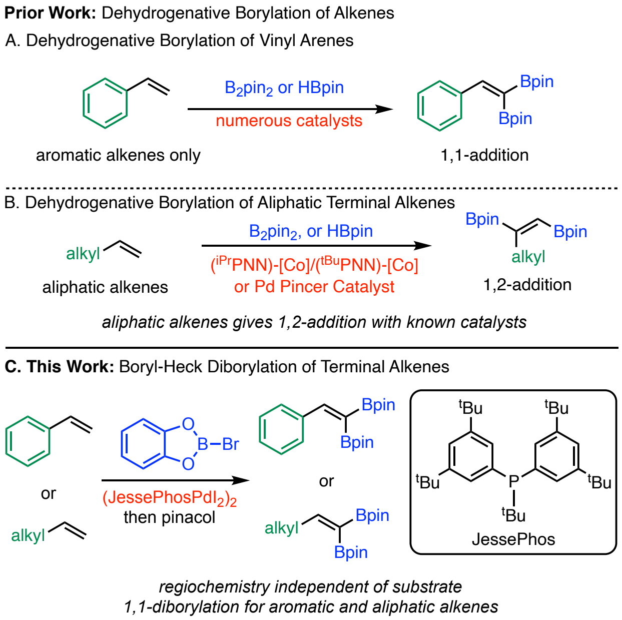
- **general conditions for aliphatic and conjugated alkenes**
- **selective for 1,1-diborylated product**
- **20 examples in up to 93% yield**

1,1-Diboryl alkenes are a highly useful class of vinyl boronic esters,[1] as they allow for stereoselective construction of polysubstituted alkenes via sequential stereoselective Suzuki-Miyaura cross-coupling reactions.[2] They can also serve as precursors to 1,1-dihaloolefins and 1,1-diboryl alkanes, can be oxidized to give the corresponding carboxylic acid,[3] and have found additional uses.[4]

Traditionally, 1,1-diborylalkenes have been accessed by stoichiometric lithiations of tetraborylmethane or vinyl halides.[5] In addition, multi-step methods involving the hydroboration of pre-formed alkynylboronates have also been reported.[6] Recently, milder and more efficient single-step catalytic entries into 1,1-diborylalkenes have been described. These include diborylation of acetophenones, vinyl ethers, vinyl sulfides, and conjugated alkynes using various catalysts.[7] While an improvement over other methods, these transformations are largely limited to the preparation of products bearing conjugated unsaturated groups adjacent to the diborylalkene. In 2017, Chirik reported a cobalt catalyzed diborylation of terminal alkynes.[3,8,9] This, and closely related processes,[4a, 10] currently provide the most general access to 1,1-diborylalkenes as they can operate on both conjugated and aliphatic alkynes. However, these latter processes require the use of alkyne starting materials.

Terminal alkenes present another highly useful class of potential starting materials, as they are widely available, generally inexpensive, and highly stable. While the diborylation of terminal alkenes is known via dehydrogenative borylation, most catalysts are limited to the use of aromatic alkenes (Scheme 1A).[11] Two catalysts have been described for the diborylation of terminal *aliphatic* alkenes, but both selectively lead to 1,2-diboryl products (Scheme 1B).[12] Thus, a general method for the 1,1-diborylation of terminal alkenes that tolerates both aromatic and aliphatic alkenes has remained unknown.

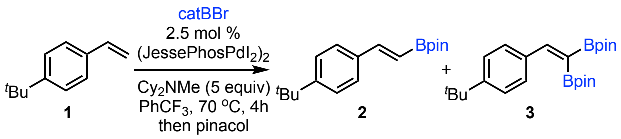
Scheme 1. Diborylation of Alkenes



Recently, we have developed a novel approach to alkene borylation using electrophilic boron reagents and palladium-catalysis via a boryl-Heck reaction. In our prior studies, we reported the mono-borylation of both terminal and internal alkenes to provide vinyl boronate esters.[13,14] In the latter work, we developed a highly active catalyst system that was capable of engaging more hindered alkenes. We postulated that this more reactive catalyst system might allow for polyborylation of less hindered terminal alkenes. Herein, we now report that terminal alkenes can be diborylated using boryl-Heck protocols (Scheme 1C). Importantly, the developed reaction conditions tolerate both aromatic and aliphatic mono-substituted alkenes, and in both cases, give exclusively 1,1-diborylalkenes in good yields. Mechanistic studies reveal that this process proceeds via two sequential mono-borylation events. This chemistry has been enabled by the identification of highly active reaction conditions that can be performed without the aid of a glovebox, making this an attractive and practical process for production of 1,1-diborylalkenes.

We began our investigation using 4-*tert*-butyl styrene (**1**) as the model substrate. Using the previously developed conditions [2.0 equiv of catBBr, 5 equiv Cy_2NMe, with 2.5 mol% $(JessePhosPdI_2)_2$, followed by workup with pinacol], we were pleased to see significant amounts of the desired diborylalkene **3** (65%), along with some of the mono-boryl product (**2**). Isolation and characterization revealed that both products resulted from exclusive borylation on the terminal carbon of the alkene. Gratifyingly, use of additional catBBr resulted in nearly quantitative yield of **3**. In no case, did we detect products resulting from additional borylation.

Table 1. Reaction Optimization[a]



entry	equiv catBBr	conditions	yield of **2** (%)	yield of **3** (%)
1	2.0	solid catBBr added	35	65
2	3.0	solid catBBr added	6	93
3	4.0	solid catBBr added	0	99
4[b]	4.0	catBBr added as aged solution in $PhCF_3$[c]	19	81
5	4.0	run with $PhCH_3$ in place of $PhCF_3$	12	88
6[b]	4.0	catBBr added as aged solution in $PhCH_3$	0	99

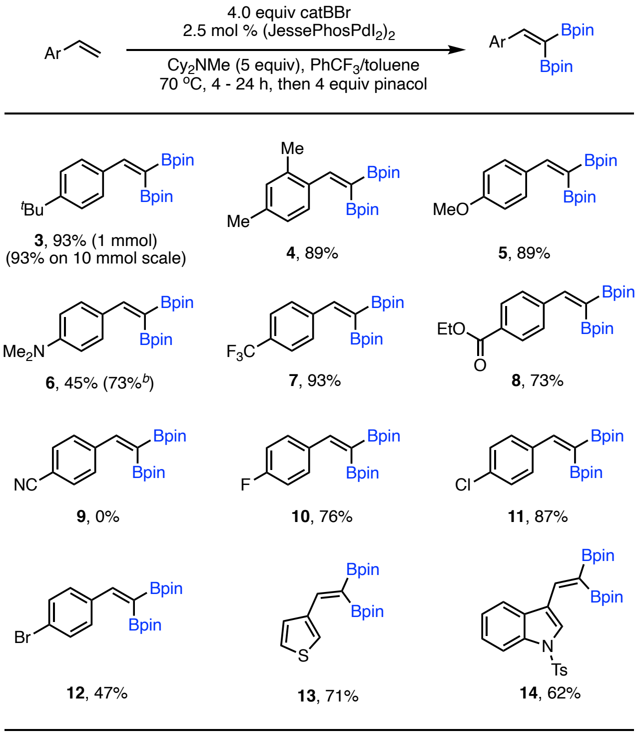
[a] Yields determined by ^1H NMR against a 1,3,5-trimethoxybenzene internal standard. [b] Using Schlenk-line conditions. [c] Solution prepared 6 h before use.

The initial optimization studies, however, had been conducted with the aid of a glovebox and had involved the addition of solid catBBr to the reaction mixture. In an effort to maximize the utility of the method, we wished to develop conditions that could be conducted under standard Schlenk conditions, without need for a glovebox, and that were compatible with the air-sensitive catBBr. Towards this end, we initially investigated such "bench-top" reactions using a solution of catBBr prepared in $PhCF_3$ (the reaction solvent). To our disappointment, however, unless the solution was used immediately after preparation, we found that the reactions were considerably less effective when setup in this manner, resulting significant amounts of mono-borylation product and variable yields (Table 1, entry 4). ^{11}B NMR studies revealed that catBBr decomposes in $PhCF_3$ over a period of hours at rt, and more rapidly at 70 °C, explaining the inconsistencies in our preliminary bench-top experiments. In contrast, similar studies revealed that catBBr solutions in toluene are much more stable; even after heating at 70 °C for 2 days, we could not detect decomposition via ^{11}B NMR.

Unfortunately, attempts to run the diborylation reaction using only toluene as the solvent was also met with suboptimal results (entry 5). Ultimately, we found that introduction of the toluene solution of catBBr to a reaction setup in $PhCF_3$ (final solvent ratio 1:1) provided the ultimate combination of reagent stability, bench-top accessibility, and productivity, providing the desired product **3** in 99% assay yield. Using this protocol, catBBr solutions could be stored for at least a week at rt without adversely affecting the outcome of the reaction. Further, we ultimately found that the mixed solvent system was important for high yield with aliphatic alkenes (see below), regardless of the setup conditions.[15]

With the optimized, bench-top conditions in hand, we explored the scope of the reaction (Scheme 1). The model product **3** was isolated in an average of 93% yield. Other electron-rich styrenes also underwent diborylation smoothly. These included those with other alkyl substituents (**4**), as well as stronger electron-donors (**5-6**). In the case of *N,N*-dimethylaniline **6**, we found that slow addition of the styrene to the reaction mixture provided superior results. We attribute this to reversible binding of the dimethylamino group of the starting material to the catBBr, which evidently impedes the reaction when present in high concentrations.[13a, 16] Product **4** also shows that increased steric bulk on the arene can be tolerated.

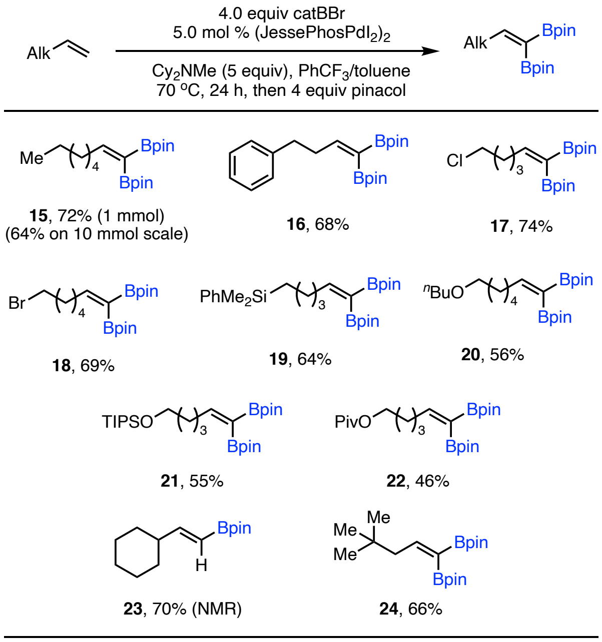
Scheme 1. Scope of Styrenyl Derivatives[a]



[a] Isolated yields, 1 mmol scale. [b] Alkene added over 2 h.

Electron-poor styrenes also generally performed well in the reaction (**7-8**). One exception was for cyanoarenes, which failed to provide product (**9**). We believe the nitrile group competitively binds either the catalyst or boron reagent. Finally, both aryl halides (**10-12**) and a variety of heterocycles (**13-14**) were tolerated in the reaction, allowing for highly functionalized products to be prepared.

Scheme 2. Scope of Aliphatic/Unconjugated Alkenes[a]



[a] Isolated yields, 1 mmol scale.

We next examined the use of aliphatic terminal alkenes in the reaction (Scheme 2). To our delight, not only did these compounds prove to be suitable substrates, but they also gave exclusively 1,1-diborylalkenes as products. This result makes the boryl-Heck approach to 1,1-diborylalkenes unique, as it is the only method that allows the use of both aromatic *and* aliphatic alkenes as substrates. Both simple alkenes (**15**) and those containing a variety of functional groups (**16**-**22**) could be used and resulted in good to excellent yields of products. Tolerated functional groups include aromatic groups (**16**), alkyl chlorides and bromides (**17**-**18**), alkyl silanes (**19**), ethers (**20**), silyl ethers (**21**), and non-enolizable esters (**22**). In general, these reactions were as efficient as for the aromatic alkenes, however the isolated yields were suppressed due to the slight sensitivity of the products to column chromatography.[17] We also investigated branched aliphatic substrates. For those with allylic branching, only mono-borylation was observed (**23**).[18] However, fully substitution at the homoallylic position was well tolerated (**24**). Finally, the reaction with both aromatic and aliphatic substrates could be scaled up to 10 mmol scale (10 times larger) and similar yields were achieved (see **3** and **15**; Scheme 1 and 2)

To probe the mechanism, we conducted a time course study using the model reaction (Figure 1).[15] Consistent with our optimization studies, we found that the reaction proceeds via initial monoborylation to provide **2**. Subsequently, **2** is then converted to the product **3** in a second, but slower boryl-Heck reaction. This time study is consistent with the proposed mechanism shown in Figure 2.[19]

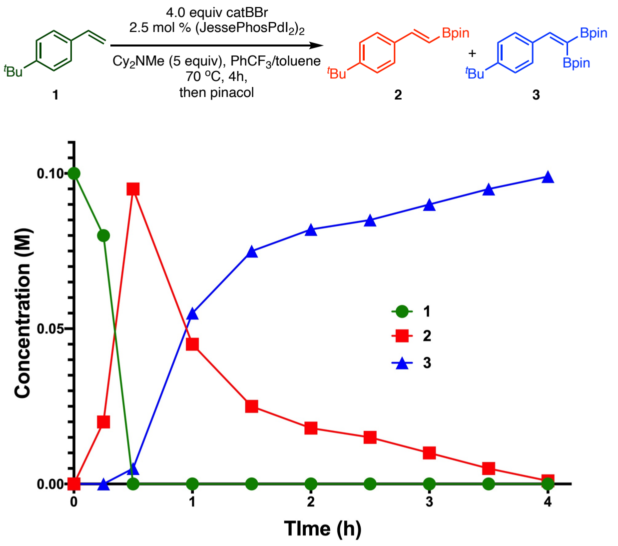


Figure 1. Time Study for the Diborylation of 4-*tert*-butyl styrene

In conclusion, we have shown that the boryl-Heck reaction is capable of diborylating terminal alkenes. Unlike previously reported systems for alkene diborylation, this reaction is capable of utilizing both aromatic and aliphatic alkenes and provides 1,1-diboryl products regardless of the nature of the substrate. Scope studies show that the process is tolerant of a wide array of functional groups under bench-top reaction conditions. Mechanistic studies demonstrate that the reaction proceeds via two sequential mono-boryl-Heck reactions and was enabled by the identification of a highly reactive catalyst system. Overall, this new methodology provides a unified strategy for the synthesis of 1,1-diboryl alkenes from inexpensive and readily available alkene starting materials.

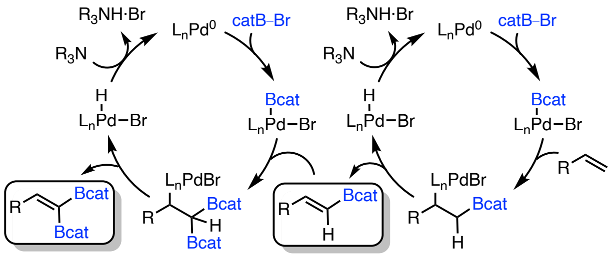


Figure 2. Proposed Mechanism for the Diborylation of Alkenes

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectral data (PDF).

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Notes

The authors declare no competing financial interest.

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17. In some cases, small amounts of the monoborylated products were observed as byproducts, however these could be removed using chromatography.
18. Compound **23** was prepared in an earlier study, see Ref 13a.
19. We also investigated the preparation of stereo-defined 1,1-diborylalkenes containing two different boronic esters. One-pot procedures led to complex mixtures, but we could borylate trans-1-styrenyl-(pinacolato)boronic esters with catBBr under the reaction conditions to deliver the mixed 1,1-diborylalkenes as single geometric isomers. However, because of instability of the catechol-containing 1,1-diborylalkenes and the inefficiency of this two-step process, and because the boryl groups of trisubstituted 1,1-diboryl alkenes already exhibit distinct reactivity (see Ref. 2), we did not pursue this further. See Supporting Information.