Direct Synthesis of Alkenyl Boronic Esters from Unfunctionalized Alkenes: A Boryl-Heck Reaction

William B. Reid, **Jesse J. Spillane**, **Sarah B. Krause**, and **Donald A. Watson**[*]

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

Abstract

We report the first example of a boryl-Heck reaction using an electrophilic boron reagent. This palladium-catalyzed process allows for the conversion of terminal alkenes to *trans*-alkenyl boronic esters using commercially available catecholchloroborane (catBCl). *In situ* transesterification allows for rapid access to a variety of boronic esters, amides, and other high value alkenyl boron adducts.

Graphical abstract
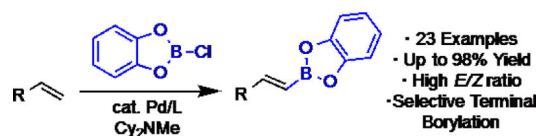
Organoboron compounds are among the most versatile reagents in synthetic chemistry.[1] Alkenyl boronic esters in particular have gained great interest in recent years, as they participate in a variety of transformations, including Suzuki cross-couplings[1] and Petasis reactions.[2] These reagents can also be used to forge C-O, C-N, C-F, C-Br and C-I bonds.[3] Traditionally, these intermediates are synthesized via hydroboration,[4] which requires access to the appropriate alkynes, or Miyaura borylation,[5] which requires prefunctionalized alkenes. Both of these classes of starting materials are significantly more expensive and less commercially abundant than the corresponding alkenes, making methods for direct borylation of alkenes highly attractive for both economical and efficiency reasons.

Alkene cross-metathesis provides one route to convert terminal alkenes into alkenyl boronic esters.[3a, 6,7] However, this method requires the preformed vinyl or 1-propenyl boronic esters, which require several steps to prepare from BCl_3 or $B(OMe)_3$ and are thus relatively expensive to buy or time-consuming to make.[3a]

[*]**Corresponding Author**, dawatson@udel.edu.

ASSOCIATED CONTENT

Supporting Information

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

A variety of rhodium- and palladium-catalyzed methods for direct borylation of terminal alkenes have also been explored using B_2Pin_2, HBPin, or related reagents.[8] These methods are typically limited in scope (particularly with respect to linear α-olefins[8a]) and frequently suffer from competitive over-borylation,[8b, 8d-f] or alkene reduction/hydroboration.[8c, 8g, 8h, 8i] As such, excess or sacrificial alkenes as hydrogen acceptors are often required.[8a, 8j-l] Many of these problems stem from the use of highly reduced boron reagents. In addition, although some are commercially available, diboranes require several synthetic steps to access - and thus are relatively expensive.[9]

An alternative approach involves the palladium-catalyzed borylation of alkenes using chloroborane reagents via a Heck-like reaction (Figure 1). Such a boryl-Heck process would be advantageous, as the use of a more highly oxidized reagent would eliminate problematic reduction byproducts. In addition, the required chloroboranes are prepared directly from inexpensive BCl_3 and diols.

Tanaka has established that oxidative addition of palladium to B-Cl bonds and subsequent migratory insertion into unsaturated C-C bonds (alkynes) is feasible.[10] Suginome has elegantly utilized these steps in multi-component cascade cyclizations of chloroaminoboranes that lead to complex borane-containing products,[11] and in one case has shown a bimolecular cascade involving alkynes.[12] However, to date, a complete boryl-Heck reaction that converts an alkene to an unsaturated boronic ester using an electrophilic borane has not been demonstrated.[13]
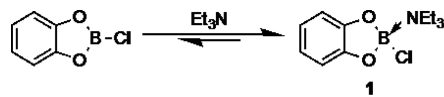
$$\tag{1}$$

In fact, Marder has previously suggested a boryl-Heck reaction.[14] However, his preliminary studies showed that catecholchloroborane (catBCl) and Et_3N (a common base in Heck reactions) form highly stable amine-borane adduct **1** (eq 1), which presumably prevents oxidative addition. He also showed that phosphines can both coordinate and decompose catBCl. Marder's results, along with Suginome's use of less electrophilic aminoboranes, illustrate the inherent difficulty of developing a boryl-Heck reaction to deliver a simple alkenyl boronic ester. Such a reaction requires both Lewis acidic chloroboronic esters and a base to turn over the catalytic cycle.

We have developed a palladium-catalyzed direct silylation of alkenes using electrophilic silanes (silyl-Heck reactions).[15] This work inspired us to reinvestigate the analogous boryl transformation. Herein, we report the successful palladium-catalyzed borylation of alkenes using readily available catBCl as an electrophilic boron source. This transformation converts a wide range of terminal mono-substituted alkenes into terminal *trans*alkenyl boronic esters with excellent regio- and stereoselectivity. The labile catechol group of the initial products allows facile transesterification to a variety of boronic acid derivatives. This reaction avoids problematic reduction and overborylation products, utilizes an inexpensive boron source,

and most importantly, demonstrates for the first time that electrophilic borylating agents are compatible with a Heck-like catalytic cycle.

CatBCl is an attractive reagent, as it is commercially available and readily synthesized from BCl_3 and catechol (both are abundant and inexpensive on-scale).[16,17] Using this reagent, we initially explored borylation of 1-decene using conditions similar to our silyl-Heck protocol (20 mol % Cy_3P, 10 mol % [(COD)Pd(CH_2SiMe_3)$_2$], Et_3N, $PhCF_3$, 80 °C).[15a] We did not observe the desired borane, but only the amine-borane adduct **1** previously reported by Marder (Table 1, entry 1).[14]

We hypothesized that formation of amine-borane adducts could be disrupted by the use of a different class of base or by a larger amine that might form a less stable adduct. Without base or with inorganic bases such as potassium carbonate, nearly full isomerization of the starting material to internal alkene isomers **3** was observed (entries 2 and 3). Weaker organic bases, such as pyridine or 2,6-lutidine, suppressed isomerization but did not lead to **4** (entries 4 and 5). In contrast, with the larger trialkylamine Hünig's base, 15% of *trans*-alkenyl boronic ester **4** was observed (entry 6). With *N,N*-dicyclohexylmethylamine (Cy_2NMe) even more of **4** (26%) was formed along with less starting material isomerization (entry 7). Importantly, in both entries 6 and 7, **4** was the only organoboron product; no internal alkenyl- or allyl-boronic esters were detected. In both cases, **4** was formed with high *E/Z* selectivity (ca. 90:10).

To optimize the reaction further, we turned our attention to the nature of the catalyst. In the absence of palladium and ligand, no product was observed (Table 2, entry 1). Using Cy_3P as ligand, a broad range of palladium precatalysts provided similar yields of **4**.[18] Pd_2dba_3 was selected for further study (entry 2). Interestingly, Pd_2dba_3 without added phosphine yielded a significant quantity of **4** (65%, entry 3). Numerous other phosphines were examined;[18] however, most were inferior to entry 3. For example, both Ph_3P and SPhos provided poor results (entries 4 and 5). In contrast, the use of $^tBuPPh_2$ led to less alkene isomerization, albeit in similar yield as entry 3 (entry 6). We next examined phosphine **L1**, a ligand designed in our group for silyl-Heck reactions.[15e,19] Somewhat unexpectedly, this ligand provided a notable increase in the production of **4** (82%, entry 7), even with only 5 mol % Pd (entry 8), and has proven to be the most effective to date.[20] Even with **L1**, alkene isomerization of the starting material continued to erode the yield. To suppress this, we investigated the use of additives. The addition of 1.5 equiv of LiOTf fully suppressed starting material isomerization.[21] With no competing isomerization, an increase in temperature was permissible, and a quantitative yield was achieved (entry 9). To further simplify the method, a single component catalyst (**L1**)$_2$$PdCl_2$ was developed.[18] Using this air and moisture stable complex, quantitative yield of **4** was observed as a 88:12 mixture of *E/Z* alkenyl boronate isomers with only 2.5 mol % catalyst. Further studies also revealed that the single component catalyst provided more consistent results on preparative scale (Tables 3 and 4).

The scope was next examined (Table 3). To facilitate isolation, pinacol (3 equiv) was added at the end of each reaction, resulting in rapid, quantitative conversion of the products to more easily isolated pinacol boronic esters. Under these conditions, the product from 1-

decene (**5**)was isolated in 93% yield with an *E/Z* ratio of 89:11. Other aliphatic alkenes were converted to alkenyl boronic esters with good yields and *E/Z* selectivities (**6-7**). Using 3 equivalents of catBCl, 1,7-octadiene was diborylated in 83% yield (**8**). A variety of functional groups were well tolerated, including silyl-protected alcohols (**9**), ethers (**10**), alkyl chlorides (**11**), silanes (**12**), and alkyl pinacol boronic esters (**13**). Although enolizable carbonyls interfered with the reaction (**14-15**, presumably due to competitive formation of boron enolates), non-enolizable carbonyls (**16-17**) did not. When allylbenzene was used as substrate, boronate **18** was observed as a mixture of alkene isomers. This is the only case where an allyl boronic ester was observed, which we attribute to the stability of a conjugated aromatic group.[18]

Substituted styrenes were also investigated (Table 4). Since starting material isomerization is not possible, LiOTf is not required. However, an examination of other additives showed that 5 mol % LiI accelerated the reactions, allowed for lower reaction temperature (70 °C), and led to improved yields.[22] In the case of styrenyl substrates (except for **29**), only *E*-alkenyl boronates were observed. 4-*tert*-Butylstyrene was converted to **19** in 92% yield. Sterically hindered (**20**), electron-rich (**21**-**22**), and electron-poor substrates (**23**-**24**) all gave good to excellent yields. Aryl fluorides (**25**) and chlorides (**26**) were well tolerated. Heterocyclic alkenes, such as indoles (**27**) and dioxolanes (**28**), were also excellent substrates. Significantly, α-methylstyrene was also borylated in good yield and with excellent *E/Z* selectivity (**29**).[8c, 8d] This product cannot be synthesized via hydroboration, and it demonstrates that increased substitution on the alkene may be accessible in future work.[23]

Different boronic esters provide different reactivity in a variety of transformations.[1] This boryl-Heck reaction is readily adapted to produce diverse boronate derivatives by simply changing the nucleophile added after the reaction, delivering various boronic esters (Table 5, **30-32**), amides (**33**), and trifluoroborates (**34**).

On-going studies are aimed at elucidating the mechanism. At present we favor the Heck-like pathway outlined in Figure 1. Preliminary studies have revealed two key observations. First, with regard to the role of the amine, although the combination of catBCl and Cy_2NMe (in $CDCl_3$) does reveal formation of an amine-borane adduct by ^{11}B NMR (Figure 2, **35**), it is distinct from that formed with Et_3N (**1**). The Cy_2NMe derived complex is broader and more downfield, both of which indicate a less tightly bound boron atom. Further, addition of 1 equiv of Et_3N to **35** results in complete conversion to **1**, providing additional evidence for a less stable Cy_2NMe complex. This data supports the notion that a greater concentration of free catBCl is available with the use of the larger base and explains our success when compared to earlier reports.

Second, selective formation of *E*-alkenyl boronates appears to be thermodynamic.[24] The observed *E/Z* ratio is similar to that of earlier rhodium-catalyzed processes[8l] and closely reflects the calculated thermodynamic ratio of all possible allyl and alkenyl isomers.[18] Experimental evidence for thermodynamic control was gained by spiking isomerically pure (*E*)-hexenylborane **36** into the boryl-Heck reaction of 4-phenylbutene (eq 2). Boronate **6** was formed with the expected *E/Z* selectivity, however **37** was found with only a 93:7 *E/Z* ratio.

This isomerization is not due to transesterification; erosion of alkene geometry is not seen without catalyst.[18] Future studies will be aimed at elucidating the kinetic product.
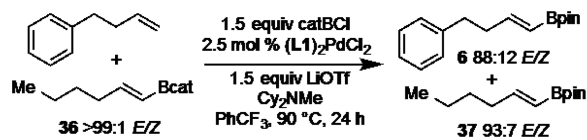
(2)

In conclusion, we have demonstrated the first example of a boryl-Heck reaction using an electrophilic boron reagent. This transformation converts terminal alkenes to alkenyl boronic esters and their derivatives in high yield and with good functional group tolerance. The reaction is compatible with both linear α-olefin and styrenyl substrates, and provides products with excellent E/Z ratios. This work demonstrates that identification of a bulky amine base, in combination with appropriate catalyst and additives, overcomes the previously observed incompatibility of chloroboranes with conditions that enable β-hydride elimination. By harnessing a Heck mechanism, this method enables use of an inexpensive, readily available borylating reagent and avoids formation of byproducts, two significant advantages over existing methods to deliver these valuable versatile synthetic intermediates.

Supplementary Material

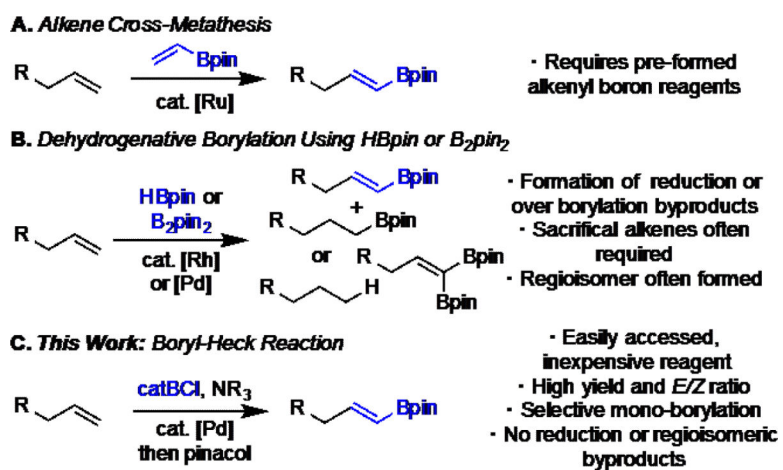Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

REFERENCES

1. Hall, DG. Boronic Acids. Wiley-VCH; Weinheim: 2011.

2. Candeias NR, Montalbano F, Cal PMSD, Gois PMP. Chem. Rev. 2010; 110:6169. [PubMed: 20677749]

3. a Morrill C, Grubbs RH. J. Org. Chem. 2003; 68:6031. [PubMed: 12868943] b Shade RE, Hyde AM, Olsen J-C, Merlic CA. J. Am. Chem. Soc. 2010; 132:1202. [PubMed: 20067245] c Furuya T, Ritter T. Org. Lett. 2009; 11:2860. [PubMed: 19507870] d Tao C-Z, Cui X, Li J, Liu A-X, Liu L, Guo Q-X. Tetrahedron Lett. 2007; 48:3525.

4. Barbeyron R, Benedetti E, Cossy J, Vasseur J-J, Arseniyadis S, Smietana M. Tetrahedron. 2014; 70:8431.

5. Ishiyama T, Miyaura N. Chem. Rec. 2004; 3:271. [PubMed: 14762827]

6. a Morrill C, Funk TW, Grubbs RH. Tetrahedron Lett. 2004; 45:7733.b Hemelaere R, Carreaux F, Carboni B. J. Org. Chem. 2013; 78:6786. [PubMed: 23772914] c Kiesewetter ET, O'Brien RV, Yu EC, Meek SJ, Schrock RR, Hoveyda AH. J. Am. Chem. Soc. 2013; 135:6026. [PubMed: 23586708]

7. Also see: Marciniec B, Jankowska M, Pietraszuk C. Chem. Commun. 2005:663.

8. a Selander N, Willy B, Szabó KJ. Angew. Chem., Int. Ed. 2010; 49:4051.b Westcott SA, Marder TB, Baker RT. Organometallics. 1993; 12:975.c Coapes RB, Souza FES, Thomas RL, Hall JJ, Marder TB. Chem. Commun. 2003:614.d Mkhalid IAI, Coapes RB, Edes SN, Coventry DN, Souza FES, Thomas RL, Hall JJ, Bi S-W, Lin Z, Marder TB. Dalton Trans. 2008:1055. [PubMed: 18274686] e Takaya J, Kirai N, Iwasawa N. J. Am. Chem. Soc. 2011; 133:12980. [PubMed: 21780822] f Kirai N, Iguchi S, Ito T, Takaya J, Iwasawa N. Bull. Chem. Soc. Jpn. 2013; 86:784.g Brown JM, Lloyd-Jones GC. J. Chem. Soc., Chem. Commun. 1992:710.h Brown JM, Lloyd-Jones GC. J. Am. Chem. Soc. 1994; 116:866.i Murata M, Watanabe S, Masuda Y. Tetrahedron Lett. 1999; 40:2585.j Murata M, Kawakita K, Asana T, Watanabe S, Masuda Y. Bull. Chem. Soc. Jpn. 2002; 75:825.k Iwadate N, Suginome M. Chem. Lett. 2010; 39:558.l Morimoto M, Miura T, Murakami M. Angew. Chem., Int. Ed. 2015; 54:12659.m Mkhalid IAI, Barnard JH, Marder TB, Murphy JM, Hartwig JF. Chem. Rev. 2010; 110:890. [PubMed: 20028025]

9. Anastasi NR, Waltz KM, Weerakoon WL, Hartwig JF. Organometallics. 2003; 22:365.

10. Onozawa, S.-y.; Tanaka, M. Organometallics. 2001; 20:2956. Also see: Braunschweig H, Gruss K, Radacki K, Uttinger K. Eur. J. Inorg. Chem. 2008; 2008:1462.

11. a Daini M, Suginome M. J. Am. Chem. Soc. 2011; 133:4758. [PubMed: 21391594] b Daini M, Yamamoto A, Suginome M. J. Am. Chem. Soc. 2008; 130:2918. [PubMed: 18278920] c Yamamoto A, Suginome M. J. Am. Chem. Soc. 2005; 127:15706. [PubMed: 16277504]

12. Daini M, Suginome M. Chem. Commun. 2008:5224.

13. In one case, a cascade cyclization has been reported that is terminated in a Heck-like process after capture of the organometallic intermediate with styrene. See: Nakada K, Daini M, Suginome M. Chem. Lett. 2013; 42:538.

14. Coapes RB, Souza FES, Fox MA, Batsanov AS, Goeta AE, Yufit DS, Leech MA, Howard JAK, Scott AJ, Clegg W, Marder TB. J. Chem. Soc., Dalton Trans. 2001:1201.

15. a McAtee JR, Martin SES, Ahneman DT, Johnson KA, Watson DA. Angew. Chem., Int. Ed. 2012; 51:3663.b Martin SES, Watson DA. J. Am. Chem. Soc. 2013; 135:13330. [PubMed: 23984876] c Martin SES, Watson DA. Synlett. 2013; 24:2177.d McAtee JR, Martin SES, Cinderella AP, Reid WB, Johnson KA, Watson DA. Tetrahedron. 2014; 70:4250. [PubMed: 24914247] e McAtee JR, Yap GPA, Watson DA. J. Am. Chem. Soc. 2014; 136:10166. [PubMed: 25003502] f McAtee JR, Krause SB, Watson DA. Adv. Synth. Cat. 2015; 357:2317.

16. Gerrard W, Lappert MF, Mountfield BA. J. Chem. Soc. 1959:1529.

17. For recent uses of catBCl see: Hirner JJ, Faizi DJ, Blum SA. J. Am. Chem. Soc. 2014; 136:4740. [PubMed: 24588331] Faizi DJ, Issaian A, Davis AJ, Blum SA. J. Am. Chem. Soc. 2016; 138:2126. [PubMed: 26849770]

18. See Supporting Infomation.

19. L1 is commerically avaliable from Aspira Scientific, Milpitas, CA.

20. The reason for the superiority of L1 is not immediately obvious. However, Marder has shown that highly nucleophilic phosphines complex catBCl, and less basic phosphines can decompose it: see reference 14. We suspect that L1 has the correct balance of electron donor ability to support a highly active palladium catalyst, but is sterically hindered enough to prevent decomposition or deactivation of the boron reagent in situ.

21. At present we do not understand the role of LiOTf in suppressing alkene isomerization, but suspect that the limited solubilty of LiCl in PhCF3 might be important in controlling unfavorable palladium hydride equilibria in the reaction.

22. Added LiI increases isomerization with non-styrenyl substrates.

23. To date, other disubstituted alkenes have provided much lower yield in this reaction. These substrates are the subject of current investigations.

24. Kondoh A, Jamison TF. Chem. Commun. 2010; 46:907.

A. Alkene Cross-Metathesis

- Requires pre-formed alkenyl boron reagents

B. Dehydrogenative Borylation Using HBpin or B_2pin_2

- Formation of reduction or over borylation byproducts
- Sacrifical alkenes often required
- Regioisomer often formed

C. This Work: Boryl-Heck Reaction

- Easily accessed, inexpensive reagent
- High yield and *E/Z* ratio
- Selective mono-borylation
- No reduction or regioisomeric byproducts

Scheme 1.
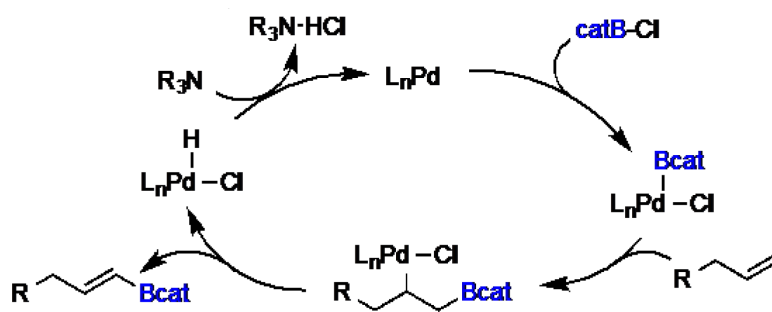Borylation of Mono-Substituted Terminal Alkenes
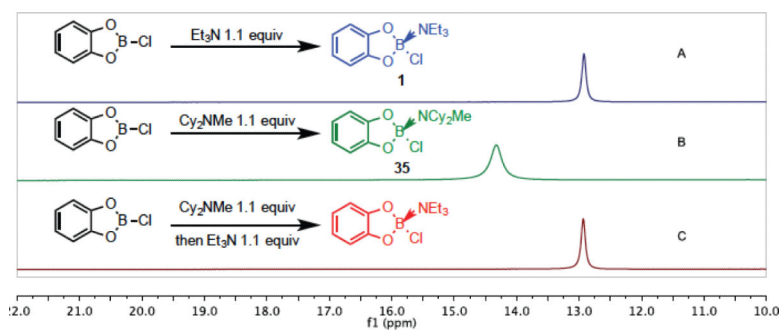
Figure 1.
Boryl-Heck Reaction

Figure 2.
^{11}B NMR spectra of coordination complexes.

Table 1
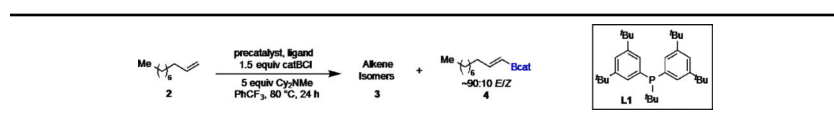
Identification of an Effective Base

entry	base	2 (%)^a	3 (%)^a	4 (%)^a	E/Z of 4
1	Et$_3$N	100	0	0	-
2	none	3	97	0	-
3	K$_2$CO$_3$	4	96	0	-
4	pyridine	91	9	0	-
5	2,6-lutidine	70	30	0	-
6	^{i}Pr$_2$NEt	52	33	15	~90:10
7	Cy$_2$NMe	65	9	26	~90:10

^{a}Yield determined by NMR.

Table 2

Optimization of Alkenyl Boronic Ester Formation

entry	precatalyst (mol %)	ligand (mol %)	additive	2 (%)[a]	3 (%)[a]	4 (%)[a]
1	none	none	none	100	0	0
2	Pd$_2$dba$_3$ (5 mol %)	Cy$_3$P (20 mol %)	none	53	15	32
3	Pd$_2$dba$_3$ (5 mol %)	none	none	0	35	65
4	Pd$_2$dba$_3$ (5 mol %)	Ph$_3$P (20 mol %)	none	65	10	25
5	Pd$_2$dba$_3$ (5 mol %)	SPhos (10 mol %)	none	0	56	44
6	Pd$_2$dba$_3$ (5 mol %)	^{t}BuPPh$_2$ (20 mol %)	none	19	19	62
7	Pd$_2$dba$_3$ (5 mol %)	**L1** (20 mol %)	none	2	16	82
8	Pd$_2$dba$_3$ (2.5 mol %)	**L1** (10 mol %)	none	0	18	82
9[b]	Pd$_2$dba$_3$ (2.5 mol %)	**L1** (10 mol %)	LiOTf[c]	0	0	>99
10[b]	(**L1**)$_2$PdCl$_2$ (2.5 mol %)	none	LiOTf[c]	0	0	>99

[a]Yield determined by NMR.

[b]90 °C.

[c]1.5 equiv.

Table 3

Scope of Linear α-Olefin Substrates[a]

5 93% (*E/Z* 89:11)[b]	**6** 89% (*E/Z* 88:12)	**7** 84% (*E/Z* 96:4)
8 83% (*E/Z* 90:10)[c]	**9** 90% (*E/Z* 90:10)	**10** 92% (*E/Z* 87:13)
11 86% (*E/Z* 88:12)[b]	**12** 89% (*E/Z* 89:11)	**13** 72% (*E/Z* 89:11)
14 R = Me, 0% **15** R = OEt, 0%	**16** 82% (*E/Z* 87:13)	**17** 91% (*E/Z* 88:12)
	18 72%	
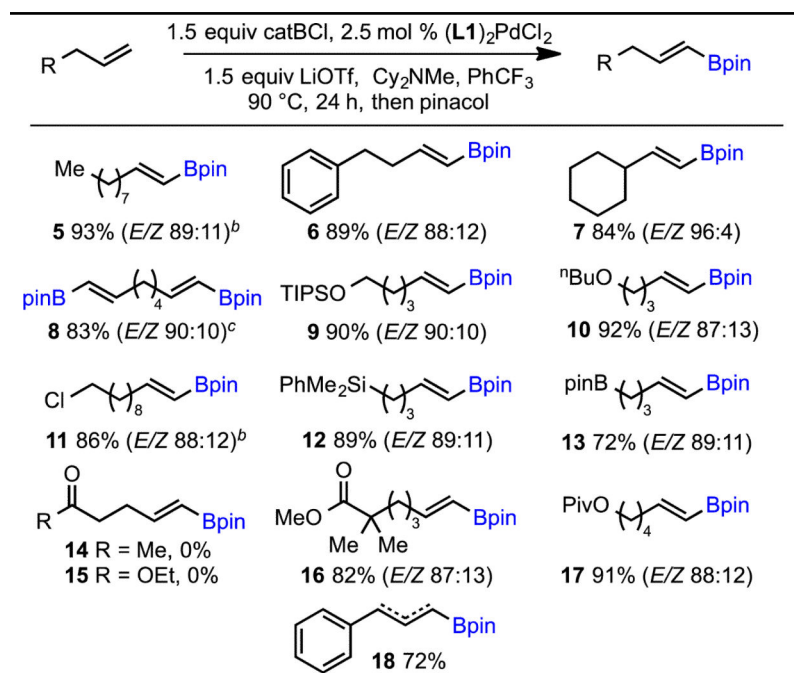
[a] Isolated yields, 3 mmol scale; [b]Average yield over two runs; [c] 3 equiv catBCl.

Table 4

Scope of Styrenyl Substrates

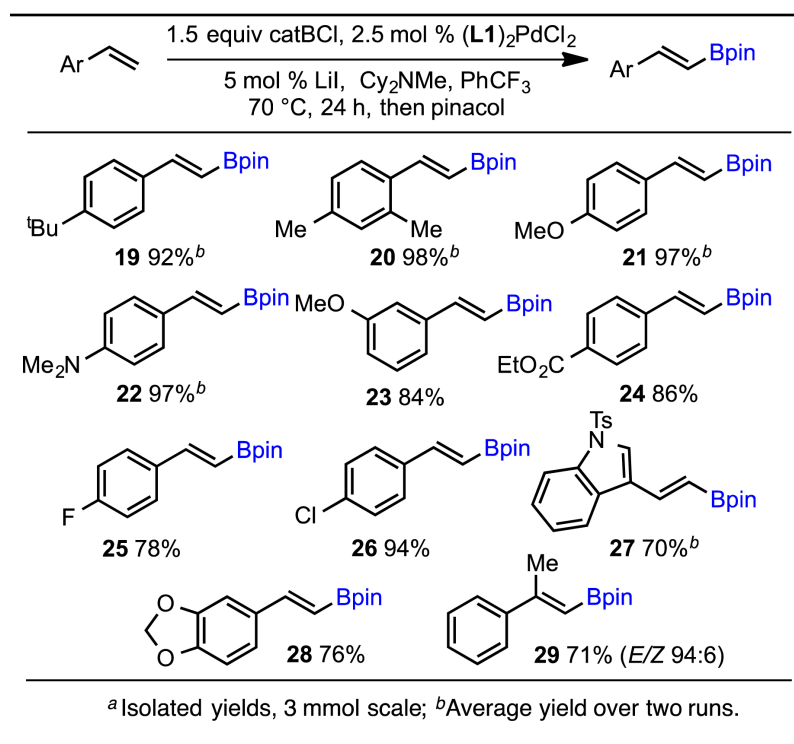^{a} Isolated yields, 3 mmol scale; ^{b}Average yield over two runs.

Table 5

Synthesis of Alternative Boronic Derivatives[a]

[a] Isolated yields, 3 mmol scale; [b] 1.5 equiv catBCl, 2.5 mol % (**L1**)$_2$PdCl$_2$, 5 mol % LiI, Cy$_2$NMe, PhCF$_3$, 70 °C, 24 h; [c] (RYH)$_2$ = aqueous KHF$_2$.