# Ni- and Pd-Catalyzed Synthesis of Substituted and Functionalized Allylic Boronates

**Ping Zhang**, **Ian A. Roundtree**, and **James P. Morken**[*]
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

## Abstract
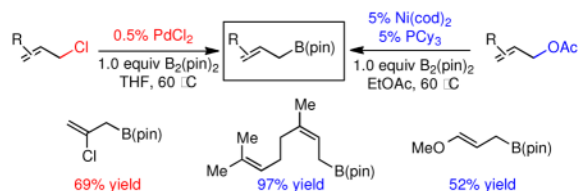
Two highly efficient and convenient methods for the synthesis of functionalized and substituted allylic boronates are described. In one procedure, readily available allylic acetates are converted to allylic boronates catalyzed by Ni/PCy$_3$ or Ni/PPh$_3$ complexes with high levels of stereoselectivity and in good yields. Alternatively, the borylation can be accomplished with commercially available Pd catalysts [e.g. Pd$_2$(dba)$_3$, PdCl$_2$, Pd/C] and starting with easily accessed allylic halides.

Organoboron reagents represent exceedingly versatile building blocks for organic synthesis. [1] Allylic boronates, [2] in particular, are well known for their additions to aldehydes,[3] ketones[4] and imines,[5] generating valuable homoallylic alcohols and amines, often with high levels of stereocontrol. More recently, allylic boronates have been used as partners for cross-coupling reactions with aryl[6] and allyl electrophiles.[7] Due to the importance of allylboronate building blocks in synthetic organic chemistry, their synthesis has been the subject of many studies. Besides stoichiometric substitution reactions that involve allyllithium [8] or allylmagnesium [9] reagents, homologation of vinyl boronates[10] has also been a practical route to many of these materials. Catalytic synthesis of allyl boronates has also received attention and is attractive because of its high level of functional group tolerance and mild reaction conditions. The preparation of allylic boronates through the cross-coupling of allyl electrophiles and boryl nucleophiles (Scheme 1), particularly B$_2$(pin)$_2$, was pioneered by Miyaura and represents a broadly useful strategy for construction of substituted allyl boronates. [11] While operable, the most commonly used Miyaura borylation, the C-B coupling between allyl acetates and bis(pinacolato)diboron [B$_2$(pin)$_2$] catalyzed by Pd(dba)$_2$, is occasionally accompanied with dimerization that generates 1,5-diene byproducts (**2**, Scheme 1). More recent contributions from Szabó and Aggarwal have expanded the electrophile scope to include allylic alcohols.[12] While this process is very attractive it does require the use of DMSO as a co-solvent, as well as the use excess B$_2$(pin)$_2$, both of which can complicate the purification. Lastly, Masuda reported that Pt(dba)$_2$ can catalyze the coupling between allylic halides and pinacolborane [HB(pin)].[13]

morken@bc.edu.

We have been interested in utilizing allylic boronates in allylation and cross-coupling reactions and our program required ready access to functionalized allyl boronate reagents. Ideally, the practical and efficient synthesis of allylic boronates should include the following features: (1) use commercially available catalysts and readily available electrophiles, (2) avoid using reagents in excess in order to reduce costs and simplify purification, (3) operate in a wide range of solvents such that tandem reaction sequences might be accessible. Herein, we report two practical and efficient syntheses of allylic boronates from commercially available $B_2(pin)_2$ and readily available allylic electrophiles. We demonstrate that allylic acetates are readily converted to allylic boronates by Ni-catalysis with a high level of functional group and substituent tolerance; we also demonstrate that allylboron reagents can be effectively synthesized through the borylation of allylic halides in the presence of a number of commercially available Pd sources without the assistance of a dry-box.

To initiate these studies, the borylation of methylallyl acetate (**3**) was examined (Table 1). In a preliminary experiment, conditions similar to those described by Miyaura (entry 1, Table 1) were modified: DMSO was replaced with THF, only 1 equivalent of $B_2(pin)_2$ was employed, and 10 mol% Pd was used. As depicted in entry 2 of Table 1, these changes dramatically decreased the catalyst activity with less than 5% of the starting material converted after 12 hours heating at 60 °C (*vs.* >99% conversion in entry 1). To improve the reaction, additives known to promote coupling reactions involving boronate nucleophiles were applied in the borylation. $Cs_2CO_3$ proved particularly beneficial and in a concentration-dependent manner. However, these modifications were not effective enough to deliver methallylB(pin) (**4**) with complete conversion. At this point, it should be noted that although 84% conversion (e.g. in entry 5) might provide the allyl boronate in acceptable yield, compounds **3** and **4** possess similar polarity thereby rendering their chromatographic separation a challenging task. Therefore, other catalysts were examined and we were pleased to find that Ni(cod)$_2$,[14] in the presence of phosphine ligands, provided remarkably effective catalysts delivering complete conversion as judged by ^{1}H NMR analysis of the unpurified material (entries 8–10). Importantly, it was also found that EtOAc could replace THF as the solvent for these processes. Lastly, since it proved difficult to remove PPh$_3$ from the allyl boronate product, PCy$_3$ was selected as the optimal ligand for these transformations.

The scope of the Ni-catalyzed allylic borylation was examined using a series of allylic acetates. As depicted in Table 2, the reaction was effective with a range of substrates, generally delivering terminal allylic boronate products with excellent selectivity towards *trans*-olefins (except entries 8 and 9). A variety of substitution and functional groups were tolerated and it should be noted that both internal and terminal allylic acetates (both *E* and *Z* isomers) could be used interchangeably in the reaction. Reactions of aromatic and aliphatic substrates proceeded in good yields, while more functionalized substrates can be converted smoothly into allylic boronates bearing oxygen (entry 7) and silicon (entries 8 and 9) groups on γ-carbon. Noteworthy, is that acetals are reactive substrates for the coupling, affording the *E* γ-oxygenated allyl boronate in excellent selectivity (entry 7).

Presumably due to isomerization of the Ni-π-allyl complex during the borylation reaction, terminal boronates bearing *trans* olefins are the favored product even when *cis* allylic acetates are employed (see entry 5, Table 2). However, it was found that when trisubstituted allylic acetates (e.g. *E*-**5** and *Z*-**5** in Scheme 2) were used as substrates, the olefin geometry was unchanged over the course of the reaction. As shown in Scheme 2, both *E* and Z allylic boronates were synthesized in excellent yield and in very high stereoisomeric purity from the corresponding geraniol and nerol derivatives.

Considering the ready availability of allylic chlorides, we considered whether these substrates might also be converted to the derived allyl boronates. While Ni catalysts proved

less effective it was found that Pd complexes were highly efficient in these transformations (Table 3). Attractive features of this Pd-catalyzed borylation are: (1) multiple commercially available Pd sources (e.g. $Pd_2(dba)_3$, $PdCl_2$, Pd/C) can be applied as catalysts equally; (2) the catalysts can give excellent turnover numbers such that only 0.5 mol % of catalyst was used in this reaction; (3) the reaction can be set up without the assistance of a dry box and can operate with a minimum of solvent ([substrate] = 2 M in THF), which is important for larger scale syntheses. It was also found that both allylic chlorides and bromides can be used as substrates in this reaction (entry 1), although the transformation using the bromide is not as clean as that of the corresponding chlorides. Importantly, as shown in entry 5 of Table 3, 2-chloro-allylB(pin) was prepared from 2,3-dichloropropene wherein the vinylic chloride was untouched during the allylic borylation. Lastly, it was found that executing the reaction on 10 mmol scale (entry 4), was equally effective as smaller scale experiments.

Ready access to functionalized and substituted allylboron reagents can facilitate the preparation of useful organic building blocks. As one example, benzaldehyde was directly added to unquenched Ni-catalyzed borylation mixtures. As depicted in Table 4, this strategy directly furnished allylation products in a highly diastereoselective fashion and in good yields.

In conclusion, we have presented Ni- and Pd-catalyzed allylic borylation reactions. Both processes employ readily available starting materials, catalysts, and furnish products in a readily usable form.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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R⎯⧸⎯⧹⎯X  +  B₂(pin)₂  —catalyst→  R⎯⧸⎯⧹⎯B(pin)  +  [ structure 2 ]

                                        **1**                    **2**
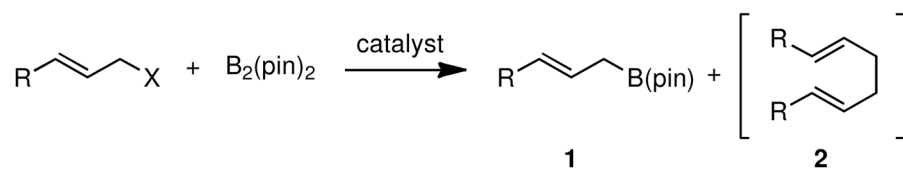
**Scheme 1.**
Catalytic Borylation of Allylic Electrophiles

$$\text{(1)}$$

$$\text{(2)}$$
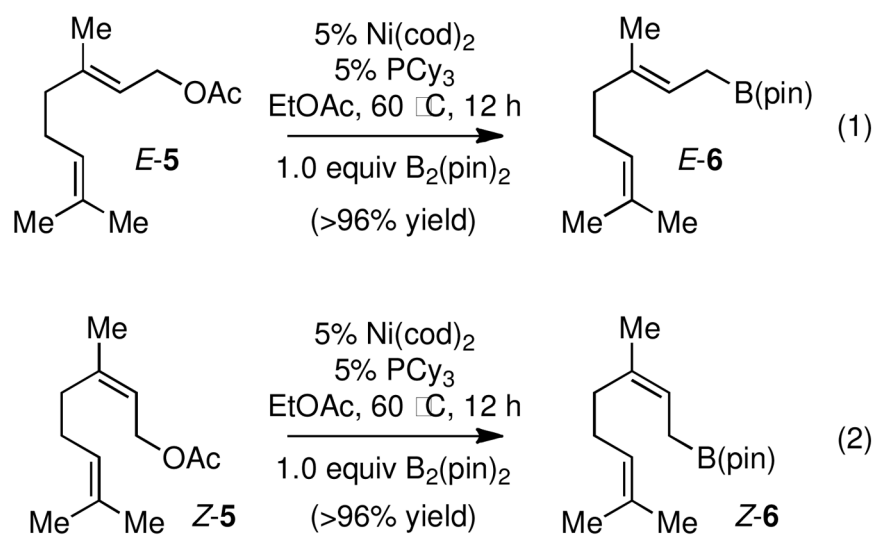
**Scheme 2.**
Ni-Catalyzed Synthesis of Trisubstituted Allylic Boronates with Retention of Configuration.

**Table 1**

Optimization of Reaction Conditions for the Conversion of Allylic Acetates to Allylic Boronates.



| entry | catalyst | additive | solvent | % conv[a] (yield)[b] |
|---|---|---|---|---|
| 1 | 2.5% $Pd_2(dba)_3$ | none | DMSO | 100[c] (62) |
| 2 | 5% $Pd_2(dba)_3$ | none | THF | <5 |
| 3 | 10% $Pd_2(dba)_3$ | none | THF | <5 |
| 4 | 5% $Pd_2(dba)_3$ | $Cs_2CO_3$[d] | THF | 56 |
| 5 | 5% $Pd_2(dba)_3$ | $Cs_2CO_3$[e] | THF | 84 |
| 6 | 5% $Pd_2(dba)_3$ | CsF | THF | 12 |
| 7 | 10% $Ni(cod)_2$ | none | THF | 75 |
| 8[f] | 10% $Ni(cod)_2/PPh_3$ | none | THF | 100 |
| 9[f] | 5% $Ni(cod)_2/PPh_3$ | none | EtOAc | 100 (84[g]) |
| 10[f] | 5% $Ni(cod)_2/PCy_3$ | none | EtOAc | 100 (80) |

[a]Determined by NMR analysis of unpurified reaction mixture.

[b]Isolated yield of purified material.

[c]Experiment employed 2.2 equiv of $B_2(pin)_2$.

[d]Employed 1.2 equiv of additive.

[e]Employed 3 equiv of additive.

[f]Employed 1:1 Ni/ligand.

[g]Contaminated with $PPh_3$.

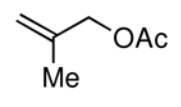**Table 2**

Ni-Catalyzed Allylic Boronate Synthesis from Allylic Acetates.



| entry | substrate | product | yield (%)[a] |
|-------|-----------|---------|--------------|
| 1 | Ph⌁OAc | Ph⌁B(pin) | 92 |
| 2 | Me⌁OAc | Me⌁B(pin) | 84[b] |
| 3 | Me⌁OAc | Me⌁B(pin) | 94 |
| 4 | Me⌁OAc | Me⌁B(pin) | 96 |
| 5 | heptyl⌁OAc | heptyl⌁B(pin) | 92 |
| 6 | ⌁OAc | ⌁B(pin) | 95 |
| 7 | OCH₃ / OCH₃ | H₃CO⌁B(pin) | 52[d] |
| 8 | OAc / Si(t-Bu)Me₂ | Me₂(t-Bu)Si⌁B(pin) | 70[e] |
| 9 | Et₃Si⌁OAc | Et₃Si⌁B(pin) | 93[c,e] |

[a] Isolated yield of purified material. Value is an average of two experiments.

[b] Contains ca. 5% impurity.

[c] Employed 10% catalyst and PPh3.

[d] Employed 10% catalyst.

[e] Product is a 2:1 ratio of *E:Z* isomers as established by NMR.

**Table 3**
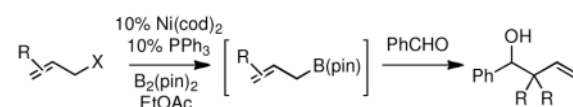
Pd-Catalyzed Allyl Boronate Synthesis from Allylic Halides.[a]
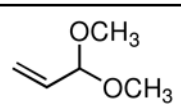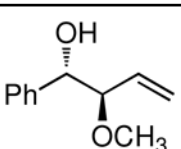


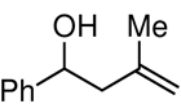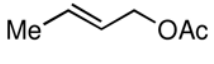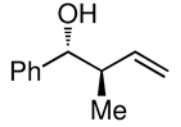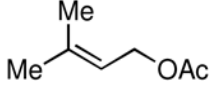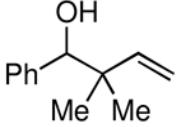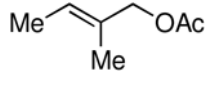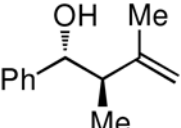| entry | substrate | product | Pd₂(dba)₃ yield (%) | PdCl₂ yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph⏤CH=CH⏤CH₂Cl | Ph⏤CH=CH⏤CH₂B(pin) | 90 (85[c]) | 97 |
| 2 | (CH₃CH(Cl)CH=CH₂) | Me⏤CH=CH⏤CH₂B(pin) | 77[d] | 81[d] |
| 3 | Me⏤CH=CH⏤CH₂Cl | Me⏤CH=CH⏤CH₂B(pin) | 70[d] | 70[d] |
| 4 | (CH₂=C(Me)CH₂Cl) | (CH₂=C(Me)CH₂B(pin)) | 67 | 70[e] |
| 5 | (CH₂=C(Cl)CH₂Cl) | (CH₂=C(Cl)CH₂B(pin)) | 69[f] | 69[f] |
| 6 | CH₂=CH⏤CH₂Cl | CH₂=CH⏤CH₂B(pin) | 79(74[g]) | 80 |

[a] Yields are isolated yields of purified material. Value is an average of two experiments.

[b] Experiments with PdCl2 were executed without the aid of a drybox; all reagents were weighed in air.

[c] Employed cinnamyl bromide as starting material.

[d] Product is a 6:1 mixture of E:Z isomers.

[e] Yield of 71% obtained on 10 mmol scale.

[f] Employed 1 equiv of KOAc.

[g] Employed Pd/C 10% wt as catalyst.

**Table 4**

One-pot Ni-Catalyzed Borylation/Allylboration.



| entry | substrate | product | % yield (dr)[a] |
|-------|-----------|---------|-----------------|
| 1 | | | 80 (20:1) |
| 2 | | | 88 |
| 3 | | | 80 (20:1) |
| 4 | | | 50 |
| 5 | | | 70 (15:1) |

[a]Isolated yield of purified material. Diastereomer ratio determined by ^{1}H NMR analysis.