Nickel-Catalyzed Enantioselective Hydroboration of Vinylarenes

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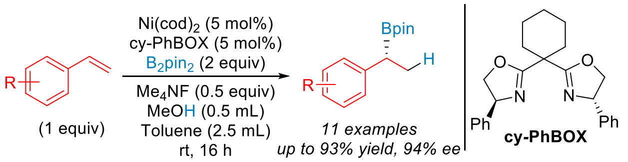
Supporting Information Placeholder

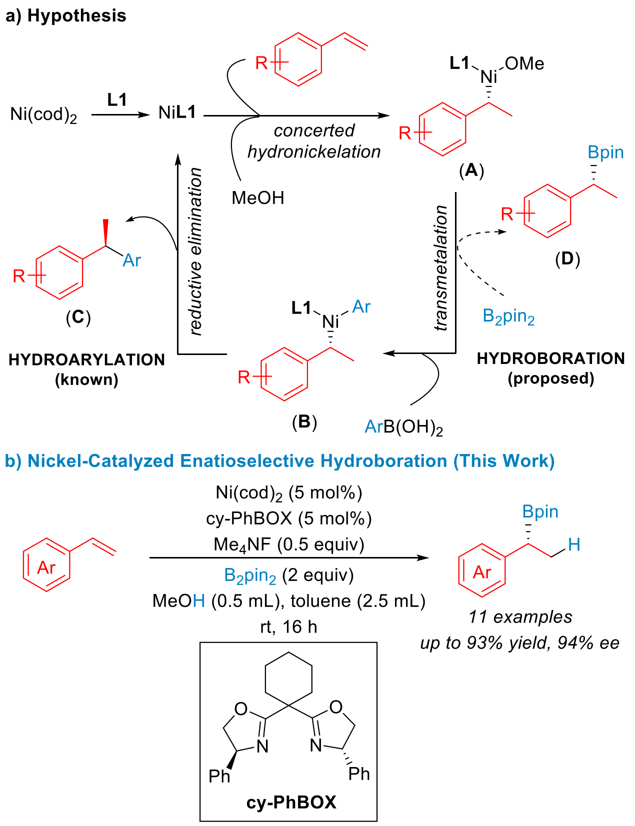


ABSTRACT: The enantioselective hydroboration of vinylarenes catalyzed by a chiral, non-racemic nickel catalyst is presented as a facile method to generate chiral benzylic boronate esters. Various vinylarenes react with bis(pinacolato)diboron (B_2pin_2) in the presence of MeOH as a hydride source to form the chiral boronate esters in up to 92% yield with up to 94% ee. The use of anhydrous Me_4NF to activate B_2pin_2 is crucial for ensuring fast transmetalation to achieve high enantioselectivities.

Chiral boronic esters are important building blocks in asymmetric synthesis since the carbon-boron bond can be readily transformed into new carbon-carbon or carbon-heteroatom bonds with the retention of configuration.[1] During the past decades, transition-metal catalyzed asymmetric hydroboration of vinylarenes has become a valuable method to synthesize chiral benzylic borylated products with control of regio- and enantioselectivity.[2-5] Rhodium complexes of chiral phosphorous ligands have been widely employed to achieve highly enantioselective hydroboration of vinylarenes.[3,4] In 2018, Aggarwal and co-workers reported the enantioselective rhodium(III)-catalyzed Markovnikov hydroboration of alkenes using a preactivated diboron reagent instead of the common boron reagents such as HBpin and HBcat.[4] These hydroboration reactions are catalyzed by a bisoxazoline-ligated rhodium complex under mild conditions. The application of earth-abundant metal catalysts containing cheap chiral ligands for catalytic, enantioselective hydroborations has the potential to render these reactions even more attractive to synthetic chemistry community. In 2009, Yun and co-workers reported enantioselective hydroborations of vinylarenes with HBpin that occur in the presence of copper catalysts.[5] In 2019, Lu and co-workers developed cobalt-catalyzed hydroboration of vinylarenes with HBpin using a chiral imidazoline phenyl picoliamide (ImPPA) ligand.[6] These reactions generate chiral boronic esters in high enantioselectivities and tolerate a variety of functional groups.

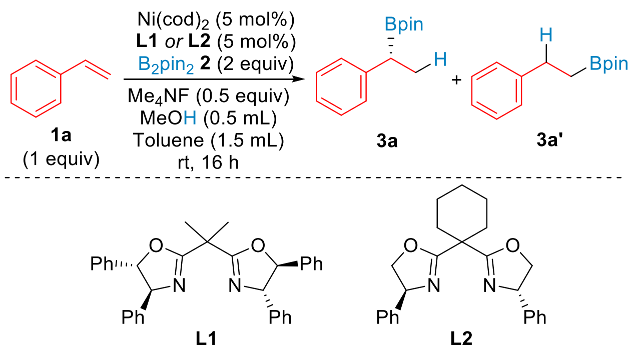
Recently, our group[7a] and others[7b,c] reported catalytic, enantioselective hydroarylations of vinylarenes in the presence of nickel complexes of bisoxazoline ligands[7a,c] or a spiroaminophosphine ligand.[7b] These reactions proceed via formation of chiral, non-racemic nickel benzyl intermediates (Scheme 1a). Subsequent transmetalation with arylboron nucleophiles and reductive elimination enable the formation of a variety of chiral 1,1-diarylethanes. We hypothesized that the chiral, non-racemic nickel benzyl intermediate can be intercepted with B_2pin_2 as a nucleophile to form a formal hydroboration product. Although the achiral nickel-catalyzed hydroboration of vinylarenes to synthesize racemic α-borylated products is well-established,[8] the enantioselective reaction has not been reported. Therefore, we sought to develop the first nickel-catalyzed asymmetric hydroboration of vinylarenes using a catalyst prepared from $Ni(cod)_2$ and a modified PhBOX ligand (Scheme 1b).

Scheme 1. Enantioselective Nickel-Catalyzed Hydroboration of Vinylarenes.


a) Hypothesis

b) Nickel-Catalyzed Enatioselective Hydroboration (This Work)

Table 1. Reaction Optimization[a]



Entry	Ligand	Deviation from standard conditions	Yield 3a/3a′ (%)[b]	ee (%)[c]
1	**L1**	2.5 equiv Me_4NF	60/5	90
2	**L1**	2.5 equiv $Bu_4NF\bullet H_2O$ instead of Me_4NF	56/3	90
3	**L1**	2.5 equiv $Me_4NF\bullet 4H_2O$ instead of Me_4NF	50/3	90
4	**L1**	2.5 equiv KOAc instead of Me_4NF	57/1	48
5	**L2**	2.5 equiv Me_4NF	58/0	93
6	**L2**	none	68/0	95
7[d]	**L2**	**2** as limiting reagent	63/0	87
8	**L2**	Benzene instead of toluene	60/3	92
9	**L2**	nBuOH instead of MeOH	16/1	-
10	**L2**	*i*PrOH instead of MeOH	0/0	-
11	**L2**	10 °C instead of rt	66/1	83
12	**L2**	40 °C instead of rt	75/0	92
13	**L2**	0.5 mL toluene	86/0	87
14	**L2**	**2.5 mL toluene**	**85(80)[e]/ 0**	**94**

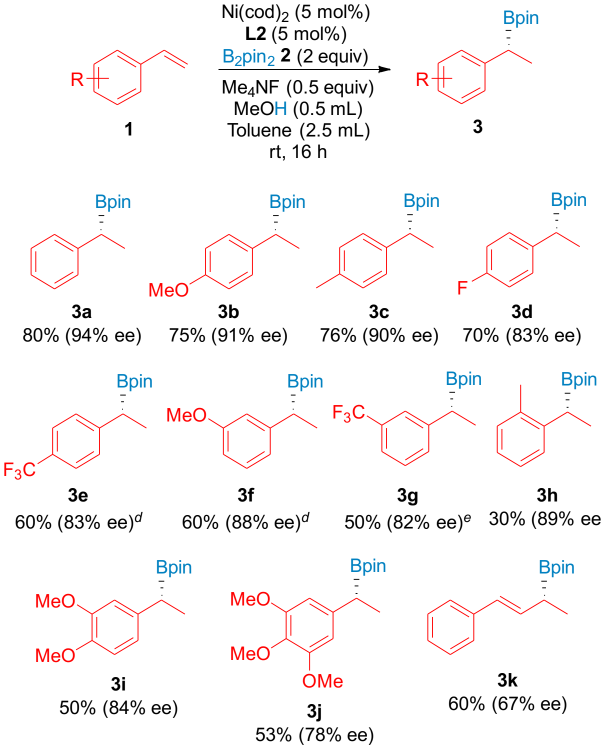
[a] Reaction condition: **1a** (0.25 mmol), **2** (0.5 mmol), Ni(cod)$_2$ (0.0125 mmol), ligand (0.0125 mmol) Me_4NF (0.125 mmol), MeOH (0.5 mL), and toluene (1.5 mL). [b] Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c] Enantioselectivities were determined by chiral HPLC. [d] **1a** (0.5 mmol), **2** (0.25 mmol). [e] Isolated yield in parentheses.

Initially, the reaction of styrene **1a** and B$_2$pin$_2$ **2** in the presence of MeOH as a hydride source was evaluated to identify suitable reaction conditions (Table 1). We found the nickel complex of *trans*-Ph$_2$BOX ligand **L1**, which was the most effective ligand in our previous hydroarylation chemistry,[7a] furnished the desired branched product **3a** in 60% yield with 90% ee, while the linear product **3a′** was produced in 5% yield (Table 1, entry 1). We found that fluoride sources sufficiently activate B$_2$pin$_2$[9] and lead to the formation of the hydroboration product in good yields and high enantioselectivity (entries 1-3). Reactions run in the presence of additional bases led to low yields or low enantioselectivities (Table S1). For example, the hydroboration run in the presence of KOAc led to the formation of **3a** in 57% yield and 48% ee (entry 4). As we observed in our asymmetric hydroarylation, fast transmetalation is key to generating products with high enantioselectivity.[7a] Although KOAc was shown to be effective in nickel-catalyzed racemic hydroborylation of styrenes,[8a,8c] mechanistic studies of Miyaura borylation reactions[10] show no coordination of the acetoxy anion to the boron reagent and no formation of a tetrahedral activated species.[10c] In contrast, the coordination of the fluoride ion with one of the boron centers transforms the hybridization of the boron moiety from sp^2 to sp^3, generating the anionic sp^2-sp^3 diboron adduct.[9b] This sp^2-sp^3 diboron adduct is proposed to provides more nucleophilic Bpin fragment capable of accelerating the transmetalation step. As a result, poor enantioselectivity was observed in the reaction with KOAc (48% ee, entry 4) whereas the reaction promoted by Me$_4$NF furnished the desired product in 90% ee (entry 1).

Next, we evaluated the impact of a variety of bisoxazoline ligands (Table S2). The nickel catalyst derived from cy-PhBOX ligand **L2** led to slightly improved yield and enantioselectivity of the product **3a** and completely shut down the production of the linear product **3a′** (Table 1, entry 5). Ligand **L2** allowed the amount of anhydrous Me$_4$NF to be reduced to 0.5 equiv (entry 6). Excess B$_2$pin$_2$ **2** is essential to achieve high enantioselectivity (entry 7). Performing the hydroboration reaction in the presence of different solvents and hydride sources did not improve the yield of the hydroboration product (entries 8-10 and Tables S3 and S4). Lowering the reaction temperature to 10 °C led to a decrease in the enantioselectivity of the reaction (entry 11). At 40 °C the reaction generated the product **3a** in 75% yield while maintaining high enantioselectivity (92% ee, entry 12 and Table S6). Increasing the concentration of the reaction led to lower enantioselectivity (entry 13 and Table S8). The reaction conditions leading to the highest yield and enantioselectivity were identified by diluting the concentration of the reaction, with the reaction generating the desired product **3a** in 85% yield with 94% ee when 2.5 mL of toluene and 0.5 mL of MeOH were used as the solvent and hydride source (entry 14).

With reaction conditions identified that lead to high yields and enantioselectivities in our model reaction, we sought to establish the scope of the reaction by evaluating hydroborations of a variety of vinylarenes (Scheme 2). Reactions of B$_2$pin$_2$ **2** with an array of substituted vinylarenes **1** generate chiral, benzylic boronic esters **3** in modest-to-high yields (30−80%) with good-to-excellent enantioselectivities (78−94%). Reactions of electron-rich vinylarenes generally occur with slightly higher enantioselectivities. Notably, slightly higher concentration is required to achieve high yield for the reaction of 4-trifluoromethylstyrene **1e**. Similarly, *meta*-substituted products **3f** and **3g** were formed in higher yields when using 1.5 and 0.5 mL of toluene as solvent, respectively. Reactions of 2-methylstyrene produced the corresponding hydroboration product **3h** in lower yield with high enantioselectivity. The high enantioselectivity observed for hydroboration of 2-methylstyrene contrasts the low enantioselectivity observed in our nickel-catalyzed asymmetric hydroarylation of this substrate.[7a] Moreover, polysubstituted styrenes **1i-1j** react to form the benzylic boronate esters in modest yields (50–53%) with good enantioselectivities (78–84% ee). In addition to reactions of vinylarenes, the hydroboration of 1-phenyl-1,3-butadiene formed the corresponding allylic boronate ester in modest yield with modest enantioselectivity. Hydroborations of vinylheteroarenes (e.g., 3-vinylindole and 4-vinylpyridine) and 4-(methoxycarbonyl)styrene generated the corresponding boronate ester products in <15% yields. Reactions of α- or β-substituted styrenes (e.g., α-methylstyrene or indalin) and unactivated alkenes (e.g., 1-octene) did not occur under our hydroboration reaction conditions.

Scheme 2. Substrate Scope[a,b,c]



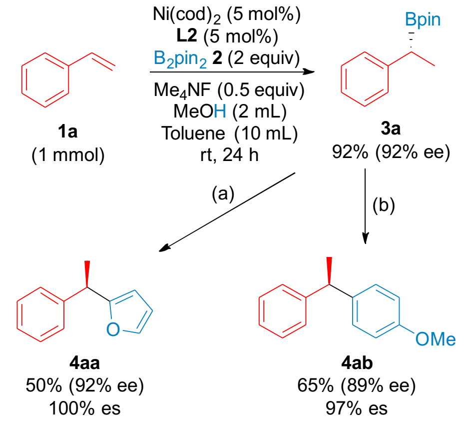
[a]Reaction condition: **1a-k** (0.25 mmol), **2** (0.5 mmol), Ni(cod)$_2$ (0.0125 mmol), **L2** (0.0125 mmol) Me$_4$NF (0.125 mmol), MeOH (0.5 mL), and toluene (2.5 mL). [b]Isolated yields. [c]Enantioselectivities were determined by chiral HPLC. [d] 1.5 mL toluene used. [e]0.5 mL toluene used.

In addition to the desired benzylic boronate ester products, we also observed alkylbenzenes in up to 20% yield in select cases (determined by ^{1}H NMR with CH$_2$Br$_2$ as an internal standard). For instance, the hydroboration of 3-methoxystyrene **1f** generated the desired product **3f** in 67% NMR yield and 3-ethylanisole in 20% yield. In the reaction of 3,4,5-trimethoxystyrene **1j**, we observed 64% NMR yield of the hydroboration product **3j**, 19% yield of 5-ethyl-1,2,3-trimethoxybenzene and 17% of the unreacted 3,4,5-trimethoxystyrene **1j**.

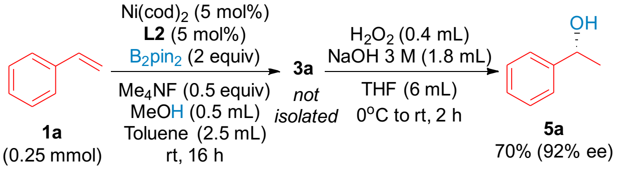
We examined the scalability of the hydroboration in a 1-mmol scale reaction of styrene **1a**. This reaction formed the desired product in 92% yield with 92% ee (Scheme 3A). In addition, the synthetic utility was demonstrated by subjecting the chiral boronate ester product to enantiospecific transformations.[11,12] The reaction of enantiomerically enriched **3a** with furan under transition-metal free cross-coupling conditions developed by Aggarwal and co-workers[12] furnished the product **4aa** in 50% yield with complete stereospecificity. Using the palladium-catalyzed enantiospecific Suzuki–Miyaura cross-couplings of benzylic organoboronic esters developed by Crudden and co-workers,[12] the chiral 1,1-diarylethane **4ab** was produced in 65% yield with 97% stereospecificity. Furthermore, a sequential hydroboration-oxidation of styrene **1a** afforded the corresponding chiral benzylic alcohol in 70% yield with 92% ee (Scheme 3B).

Scheme 3. 1-mmol Scale Reaction and Synthetic Applications[a,b,c]

A. Scalability and Enantiospecific Transformations



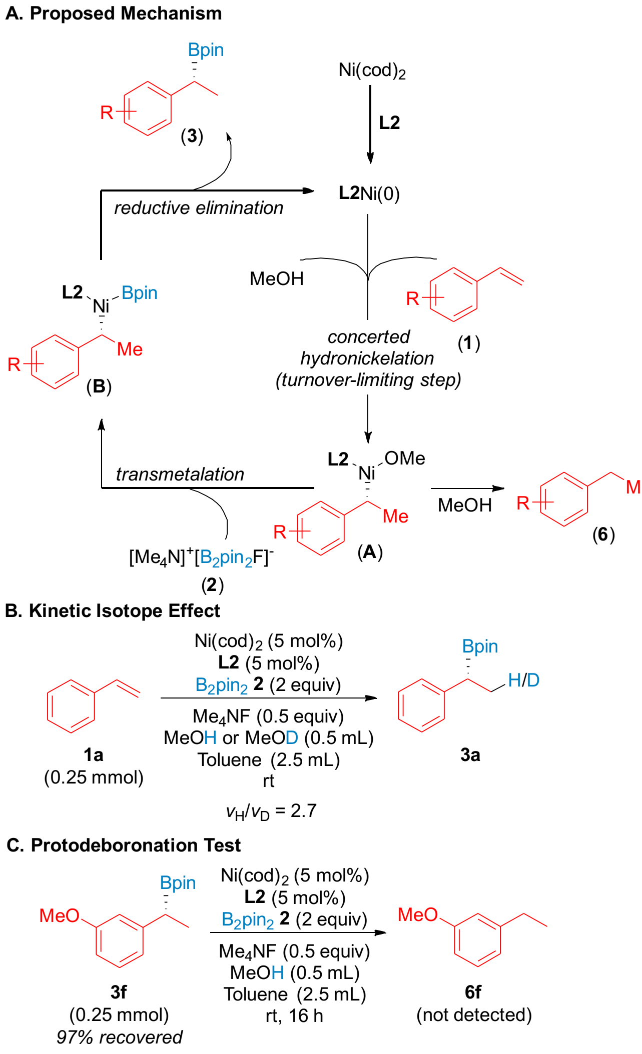
B. Sequential Hydroboration-Oxidation



[a]Isolated yields. [b]Enantioselectivities were determined by chiral HPLC. [c]See Supporting Information for detailed reaction conditions. Reaction condition for (a): **3a** (0.227 mmol), 4-iodoanisole (0.15 mmol), Pd(PPh$_3$)$_4$ (0.0117 mmol), PPh$_3$ (0.0470 mmol), Ag$_2$O (0.226 mmol), K$_2$CO$_3$ (0.232 mmol), DME (3 mL), 85 °C, 24 h. Reaction condition for (b): **3a** (0.25 mmol), furan (0.30 mmol), *n*BuLi (0.30 mmol), THF (1.5 mL), -78 °C, 2 h then NBS (0.30 mmol), THF (1 mL), -78 °C, 1 h.

Based on our previous study[7a] and computational studies[13] on nickel-catalyzed hydroarylation of vinylarenes, we propose the following mechanism for the nickel-catalyzed hydroboration of vinylarenes (Scheme 4A). The active catalyst **L2**Ni(0) undergoes hydronickelation with MeOH and a vinylarene to generate the benzylic nickel intermediate **A**. Subsequent transmetalation with a diboron species generated from B$_2$pin$_2$ and fluoride anion forms intermediate **B**,[9b] followed by reductive elimination to produce the chiral boronate ester product **3** and regenerate the active catalyst. We also determined the kinetic isotope effect by conducting parallel reactions with MeOH and MeOD to determine the rates of these reactions. These reactions gave a kinetic isotope effect of ν_H/ν_D = 2.7 for the nickel-catalyzed hydroboration reaction (Scheme 4B). These experiments suggest that the cleavage of the O-H bond is involved in the turnover-limiting step and hydronickelation of the vinylarene is likely the turnover-limiting step.[14] In addition, we conducted a control experiment to probe the formation of ethylbenzene byproducts **6**. We hypothesized the formation of the byproducts could be either from protodeboronation of the benzylic boronate ester products or the direct protonation of benzylic nickel species **A** by MeOH. To distinguish these possibilities, we subjected compound **3f** to the hydroboration reaction conditions (Scheme 4C). Compound **3f** was recovered in 97% and 3-ethylanisole **6f**, which is the product of the protodeboronation of **3f**, was not detected. This experiment suggests that the direct protonation of benzylic nickel species **A** by MeOH is likely responsible for the formation of the ethylbenzene byproducts.[15]

Scheme 4. Mechanistic Studies and Reaction Mechanism



In conclusion, we have developed an enantioselective hydroboration of vinylarenes catalyzed by a nickel complex prepared *in situ* from Ni(cod)$_2$ and cy-PhBOX ligand **L2** to generate chiral benzylic boronate esters under mild reaction conditions. The use of Me$_4$NF to activate B$_2$pin$_2$ leads to fast transmetalation and is critical to produce the chiral boronate ester products in high enantioselectivities. Additional studies on asymmetric, nickel-catalyzed hydrofunctionalization of alkenes are ongoing.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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