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Cobalt-Catalyzed Asymmetric Markovnikov Hydroboration of Styrenes

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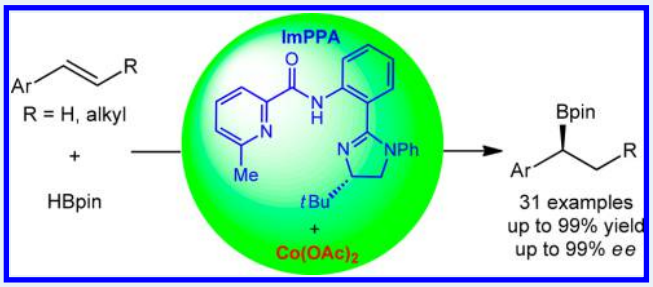
Supporting Information

ABSTRACT: A cobalt-catalyzed asymmetric hydroboration of styrenes using an imidazoline phenyl picoliamide (ImPPA) ligand was first reported to deliver the valuable chiral secondary organoboronates with good functional tolerance and high enantioselectivity (up to >99% ee). This protocol is operationally simple without any activator. Particularly, this method can be applied in the asymmetric hydroboration of allylamine to afford 1,3-amino alcohol, which is a key intermediate for the synthesis of fluoxetine and atomoxetine. Furthermore, control experiments, isotopic labeling experiments, and qualitative and quantitative kinetic studies were also conducted to figure out the primary mechanism.

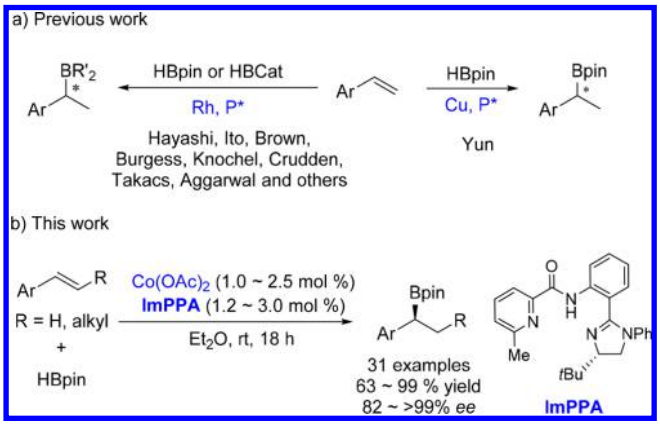


KEYWORDS: *cobalt, styrenes, asymmetric hydroboration, nitrogen ligand, chiral organoboronates*

Chiral boronic esters are important building blocks in asymmetric synthesis because their carbon−boron bond can be easily converted to a carbon−carbon or carbon−heteroatom bond in a stereospecific fashion.[1] Metal-catalyzed asymmetric hydroboration of alkenes has been shown to be one of the most powerful methods for the synthesis of chiral boronic esters.[2] To date, phosphine-ligated rhodium complexes[3] have dominated the catalyst landscape of highly enantioselective hydroboration of styrenes. However, they also suffer from some drawbacks in some cases, such as requiring a low reaction temperature (−78 °C)[3a,b] and a limited substrate scope with moderate selectivity using stable pinacol borane (HBpin).[3g] Because of the global emphasis on sustainable chemistry, the low abundance, high cost, and toxicity of precious metals has triggered chemists' interest in earth-abundant metal catalysis.[2f,4] Particularly, recent years have witnessed growing interest in using earth-abundant metals such as copper,[5] iron,[6] or cobalt[7] for catalytic asymmetric hydroboration of alkenes. However, only copper catalysts based on chiral phosphine ligands have been employed in the asymmetric hydroboration of simple styrenes (eight examples, 51−95% ee) with Markvonikov selectivity in which the functional group tolerance was not well investigated (Scheme 1).[5a] The chiral iron and cobalt catalysts have only been reported for the anti-Markvonikov selective asymmetric hydroboration of alkenes.[6,7] Thus, it is still highly desirable to develop an efficient earth-abundant-metal-catalyzed asymmetric hydroboration of styrenes with broad substrate scope and high enantioselectivity.

Recently, we have reported cobalt-catalyzed asymmetric isomerization/hydroboration of alkenes using imidazoline phenyl picoliamide (ImPPA) as a chiral ligand.[8] However, the cobalt-catalyzed asymmetric Markovnikov hydroboration of styrenes with high enantioselectivity has not been explored. On the basis of our previous studies on asymmetric hydrofunctionalization of alkenes,[6,8,9] we reported an activator-free, highly enantioselective cobalt-catalyzed hydroboration of simple styrene and β-substituted vinylarenes using an imidazoline phenyl picoliamide (ImPPA) ligand with broad substrate scope under mild reaction conditions (Scheme 1).

Scheme 1. Metal-Catalyzed Asymmetric Hydroboration of Monosubstituted Styrenes



On the basis of our study on the iron-catalyzed Markovnikov selective hydroboration of styrenes,[10] the combination of $Co(OAc)_2$ with chiral oxazolinylphenyl picolinamide ligand was tested for asymmetric transformation. The reaction of

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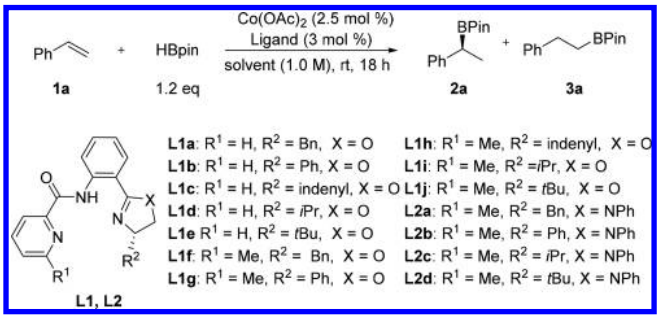
styrene **1a** with pinacolborane in the presence of **L1a** and $Co(OAc)_2$ as catalysts afforded product **2a** in 68% yield but only with 10% ee (Table 1, entry 1). A variety of amide-type

Table 1. Optimization Conditions[a]



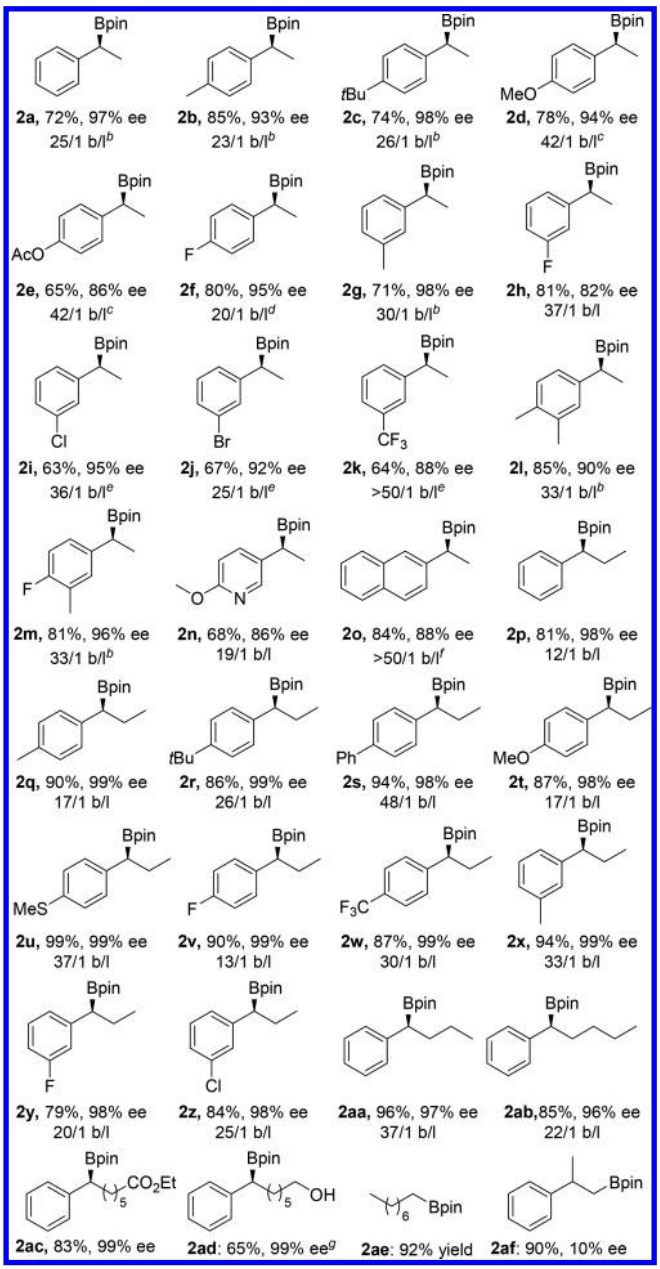
entry	ligand	solvent	2a/3a (%)[b]	ee/(%)[c]
1	**L1a**	dioxane	68/0.7	−10
2	**L1b**	dioxane	74/0.5	−11
3	**L1c**	dioxane	80/0.3	−5
4	**L1d**	dioxane	81/0.3	−5
5	**L1e**	dioxane	75/0.5	−4
6	**L1f**	dioxane	76/4.2	81
7	**L1g**	dioxane	88/2.2	87
8	**L1h**	dioxane	75/4.2	70
9	**L1i**	dioxane	78/3.2	79
10	**L1j**	dioxane	72/5.0	82
11	**L2a**	dioxane	87/2.2	94
12	**L2b**	dioxane	80/3.2	91
13	**L2c**	dioxane	89/2.5	96
14	**L2d**	dioxane	75/6.0	99
15	**L2d**	Et_2O	79/3.5	97
16	**L2d**	Et_2O	72/2.8	97[d]

[a]Reactions were conducted using **1a** (1.0 mmol), HBpin (1.2 mmol), $Co(OAc)_2$(2.5 mol %), and a ligand (3.0 mol %) in a solution of dioxane (1.0 mL) at room temperature under a N_2 atmosphere for 18 h. [b]Yields were determined using TMSPh as an internal standard. [c]ee values were determined by chiral HPLC analysis. [d]1 mol % catalyst.

ligands **L1b**−**L1e** were then evaluated; **2a** was obtained in 74−81% yields, however, with less than 11% ee (entries 2−5). The use of **L1f** bearing a methyl group at the 6-position on pyridine greatly enhanced the enantioselectivity of the reaction to 81% ee with no deterioration in yield and regioselectivity (entry 6). Ligands **L1g**−**L1j** containing different substituents on the oxazoline were then investigated, and no better result was found (entries 7−10). Surprisingly, when **L2a** containing a more electron-rich phenyl-protected imidazoline was used, the ee value of **2a** was increased to 94% (entry 11). Evaluation of a series of imidazoline ligands showed that the more bulky **L2d** was the best ligand to give product **2a** in 99% ee but with a slight decrease in regioselectivity (12/1 b/l; entries 12−14). Next, various solvents were investigated in which Et_2O was found to be the best solvent to give the product **2a** in 97% ee with 25/1 b/l (entry 15). The reaction could occur smoothly using 1 mol % of catalyst to give 72% yield and 97% ee (entry 16). The standard conditions are identified as 1 mmol of alkene, 1.2 mmol of HBpin, 2.5 mol % of $Co(OAc)_2$, and 3 mol % of **L2d** in 1.0 mL of Et_2O for 18 h.

With the standard conditions in hand, various styrenes were investigated (Table 2). Styrenes containing both electron-donating and electron-withdrawing groups could participate to give the corresponding chiral boronic esters in 63−85% yields

Table 2. Substrate Scope[a]



[a]Standard conditions: unless otherwise noted, $Co(OAc)_2$(2.5 mol %), **L2d** (3.0 mol %), alkene (1 mmol), HBPin (1.2 equiv), Et_2O (1 mL), rt, 18 h. Yields referred to the isolated yields ee values were determined by chiral HPLC analysis. Regioselectivities were determined by ^1H NMR analysis of a crude mixture of products. [b]$Co(OAc)_2$(1.0 mol %), **L2d** (1.2 mol %). [c]$Co(OAc)_2$(1.0 mol %), **L2c** (1.2 mol %), 36 h. [d]$Co(OAc)_2$(1.0 mol %), **L2d** (1.2 mol %), 36 h. [e]$Co(OAc)_2$(2.5 mol %), **L2d** (3.0 mol %), 36 h. [f]$Co(OAc)_2$(2.5 mol %), **L2c** (3.0 mol %). [g]Isolated yield for corresponding alcohol.

with high regioselectivity and 82−98% ee. Styrenes with acetoxyl, fluoro, chloro, bromo, and trifluoromethyl groups can be tolerated, which shows the good functional group tolerance of this reaction system. The styrenes containing a heterocycle and polycyclic ring, such as 3-pyridyl (**1n**) and 2-naphthyl (**1o**), could be converted to the correponding product in 68% yield with 86% ee and 84% yield with 88% ee, respectively. The moderate yields got in some cases attributed to the formation of the hydrogenated product. It should be noted that various β-

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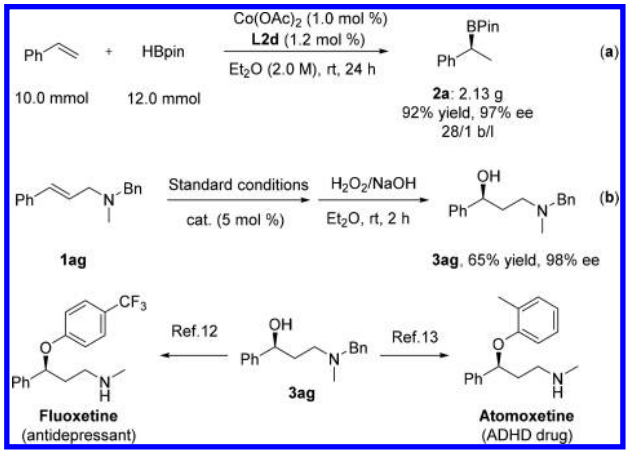
substituted vinylarenes can participate in the reaction to give the corresponding products in 65−99% yields with 96−99% ee. The electronic nature of the substituents on the aromatic ring has little effect on the enantioselectivity of this reaction. Particularly, alkene **1ad** with primary alcohol could also participate in the reaction to afford **2ad** in 65% yield with 99% ee. The reaction of oct-1-ene with HBpin afforded the linear product **2ae** in 92% yield, which indicated that the aromatic ring may contribute to the formation of a benzylic metal-complex and determine the regioselectivity and enantioselectivity.[11] When α-methylstyrene was subjected to this reaction system, the anti-Markovnikov addition product **2af** was obtained in 90% yield with 10% ee, and benzylic boronate was not observed.

A gram scale reaction of **1a** could be performed to afford **2a** in 92% yield with 97% ee using 1.0 mol % of $Co(OAc)_2$ and 1.2 mol % of ligand (Scheme 2a). Cinnamyl amine (**1ag**) could

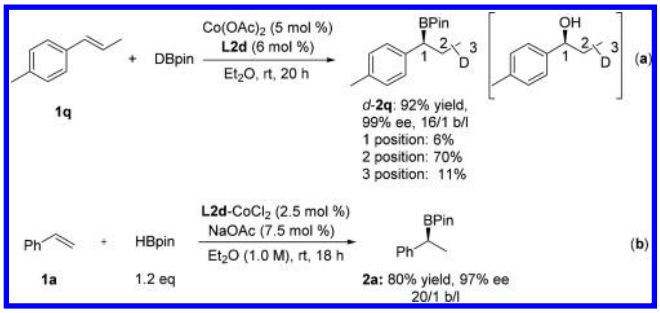
Scheme 2. Gram Scale Reaction and Synthesis of 1,3-Amino Alcohol



be converted to 1,3-amino alcohol **3ag** in 65% yield with 98% ee, which is a key intermediate for the synthesis of the antidepressant drug fluoxetine,[12] as well as the attention deficit hyperactivity disorder (ADHD) drug atomoxetine[13] (Scheme 2b). Traditionally, asymmetric hydrogenation of ketones is the main method for the synthesis of chiral 1,3-amino alcohol, which needs a noble-metal catalyst and the high pressure of a hydrogen atmosphere. This method embraces the benefits of earth-abundant metal catalysis and mild reaction conditions. To the best of our knowledge, this is also the first example of metal-catalyzed asymmetric hydroboration of cinnamyl amine.

To probe the mechanism of this hydroboration reaction, the deuterium experiment of alkene **1q** with DBpin was conducted to give *d*-**2q** in 92% yield with 70% D-incorporation in the 2-position and 6% D-incorporation in the 1-position (Scheme 3a). The 11% D-incorporation in the 3-position showed the occurrence of alkene isomeration during the process, which illustrated the formation of cobalt hydride species. Although the structure of **L2d**·$Co(OAc)_2$ was difficult to obtain, we got the X-ray crystal structure of **L2d**·$CoCl_2$,[14] which indicated that both pyridine and amide coordinated with cobalt (Figure 1). It should be noted that the proton on the amide was shifted to imidazoline, which inhibited the formation of a tridendate cobalt complex. The reaction of **1a** with HBpin using **L2d**·$CoCl_2$ did not occur. However, the reaction using cobalt complex **L2d**·$CoCl_2$ and NaOAc as an additive could give **2a**

Scheme 3. (a) Deuterium Experiment and (b) Reaction Conducted Using Complex L2d·$CoCl_2$.



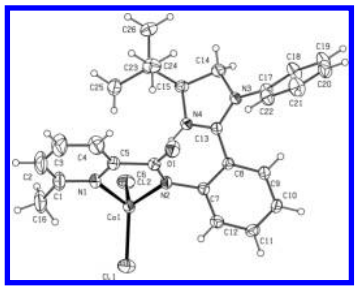


Figure 1. X-ray structure of **L2d**·$CoCl_2$.

in 80% yield with 97% ee (Scheme 3b). The control experiments demonstrated two possibilities: one was that a metal complex with a weak coordinated counterion from ligand exchange was easier to reduce; the other was that a weak base could deprotonate the proton from the metal complex to accelerate the formation of an active pincer-type metal complex.

Quantitative kinetic studies were also performed to determine the roles of HBpin, styrene, and a catalyst. Measurements of the initial rates (K_{in}) for the reaction of styrene with different concentrations of HBpin and the catalyst showed a corresponding rise in the rates of the reactions. Plots of K_{in} versus the concentrations of HBpin and the catalyst gave linear curves (slope = 1.24×10^{-5} M s^{-1}; 1.00×10^{-3} M s^{-1}) indicating a first order rate dependence on HBpin and the catalyst (Figure 2a,b). Similar kinetic studies on styrene showed that with a first-order rate dependence on styrene, however, the reaction rates were slightly affected negatively

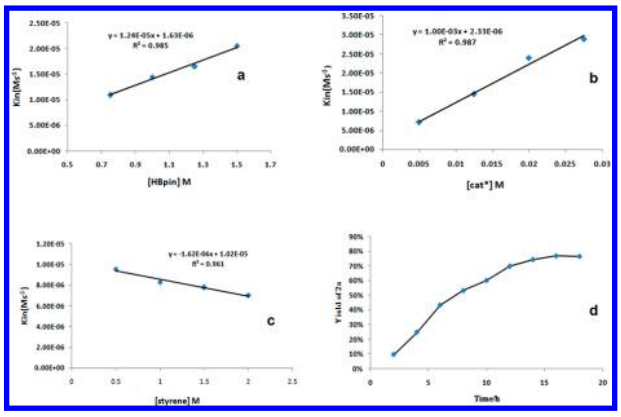


Figure 2. (a) A plot of K_{in} vs HBpin concentrations. (b) A plot of K_{in} vs catalyst concentrations. (c) A plot of K_{in} vs styrene concentrations. (d) Time course studies.

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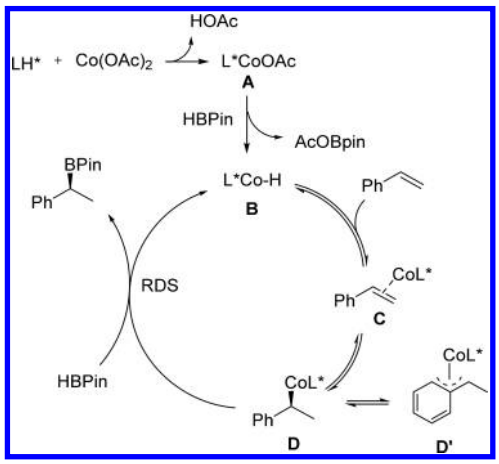
with the increasing concentrations of styrene (Figure 2c). These kinetic studies showed that the σ-bond metathesis with HBpin is a rate-limiting step. The phenomenon that the increased concentration of styrene decreased initial rates may attribute to the multiple ligation of alkene to the catalyst, which depletes the coordination sites of the catalyst and precludes it from approaching the HBpin.

On the basis of these mechanistic studies, a possible mechanism is illustrated in Scheme 4. First, ligand LH*

Scheme 4. Possible Mechanism



coordinates to cobalt(II) acetate to form cobalt(II) precatalyst **A** and releases a molecule of acetic acid.[15] Then, cobalt precursor **A** enters the catalytic cycle to generate cobalt(II) hydride species **B** through σ-bond metathesis with HBpin. Alkene undergoes coordination and insertion to a cobalt hydrogen bond to form cobalt(II) species **D** or **D′**.[11] Finally, species **D** undergoes a rate-limiting σ-bond metathesis with HBpin to regenerate cobalt(II) hydride species **B** and afford chiral organoboronic ester.

In summary, we have developed the cobalt-catalyzed highly enantioselective asymmetric hydroboration of styrenes and β-substituted vinylarenes using an imidazoline phenyl picoliamide (ImPPA) ligand. Various vinylarenes are subjected to this reaction system to afford the chiral secondary organoboronates in good to excellent enantioselectivity (up to >99% ee). Featuring an earth-abundant catalysis and additional activator-free, simple operation and good functional group tolerance, this protocol will be a practical method for preparing synthetic useful chiral organoboronates. The development of other cobalt-catalyzed asymmetric transformations is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b05135.

Experimental details, characterization data of all new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Associated crystallographic information file (CIF)

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Notes

The authors declare no competing financial interest.

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