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Cobalt-Catalyzed Asymmetric Markovnikov Hydroboration of Styrenes

Xu Chen, Zhaoyang Cheng, and Zhan Lu

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Cobalt-Catalyzed Asymmetric Markovnikov Hydroboration of Styrenes

Xu Chen, Zhaoyang Cheng, Zhan Lu*
Department of chemistry, Zhejiang University, Hangzhou 310058, China.

Supporting Information Placeholder

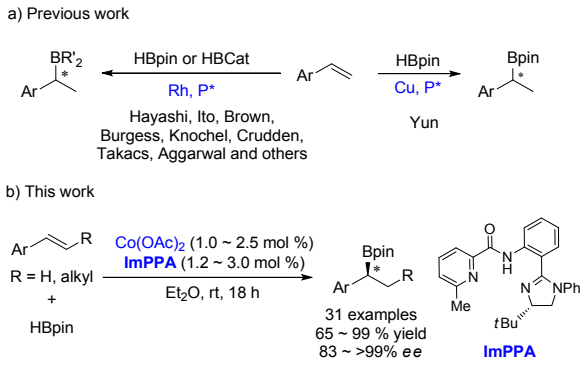
ABSTRACT: A cobalt-catalyzed asymmetric hydroboration of styrenes using imidazoline phenyl picoliamide (ImPPA) ligand was firstly reported to deliver the valuable chiral secondary organoboronates with good functional tolerance and high enantioselectivity (up to >99% ee). This protocol is operationally 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, the 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 for their carbon-boron bond can be easily converted to carbon–carbon or carbon–heteroatom bond in a stereospecific fashion.[1] Metal-catalyzed asymmetric hydroboration of alkenes has 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, it also suffered from some drawbacks in some cases such as, requiring low reaction temperature (- 78 °C),[3a, 3b] 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 on earth-abundant metal catalysis.[2f, 4] Particularly, recent years have witnessed the 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 catalyst based on chiral phosphine ligand have been employed in the asymmetric hydroboration of simple styrenes (8 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 alkene 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. Based on our previous studies on asymmetric hydrofunctionalisation of alkenes,[6, 8-9] we reported an activator free, highly enantioselective cobalt-catalyzed hydroboration of

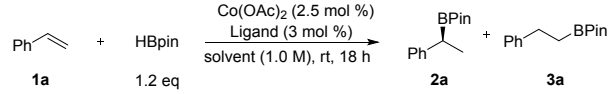
Scheme 1. Metal-catalyzed asymmetric hydroboration of monosubstituted styrenes



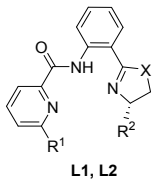
simple styrene and *β*-substituted vinylarenes using imidazoline phenyl picoliamide (ImPPA) ligand with broad substrate scope under mild reaction conditions (**Scheme 1**).

Based 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 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 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 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 were 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 serials of imidazoline ligands shown that the more bulky

Table 1. Optimization conditions.[a]



1a **2a** **3a**



L1, L2

L1a: R^1 = H, R^2 = Bn, X = O
L1b: R^1 = H, R^2 = Ph, X = O
L1c: R^1 = H, R^2 = indenyl, X = O
L1d: R^1 = H, R^2 = *i*Pr, X = O
L1e R^1 = H, R^2 = *t*Bu, X = O
L1f: R^1 = Me, R^2 = Bn, X = O
L1g: R^1 = Me, R^2 = Ph, X = O
L1h: R^1 = Me, R^2 = indenyl, X = O
L1i: R^1 = Me, R^2 = *i*Pr, X = O
L1j: R^1 = Me, R^2 = *t*Bu, X = O
L2a: R^1 = Me, R^2 = Bn, X = NPh
L2b: R^1 = Me, R^2 = Ph, X = NPh
L2c: R^1 = Me, R^2 = *i*Pr, X = NPh
L2d: R^1 = Me, R^2 = *t*Bu, X = NPh

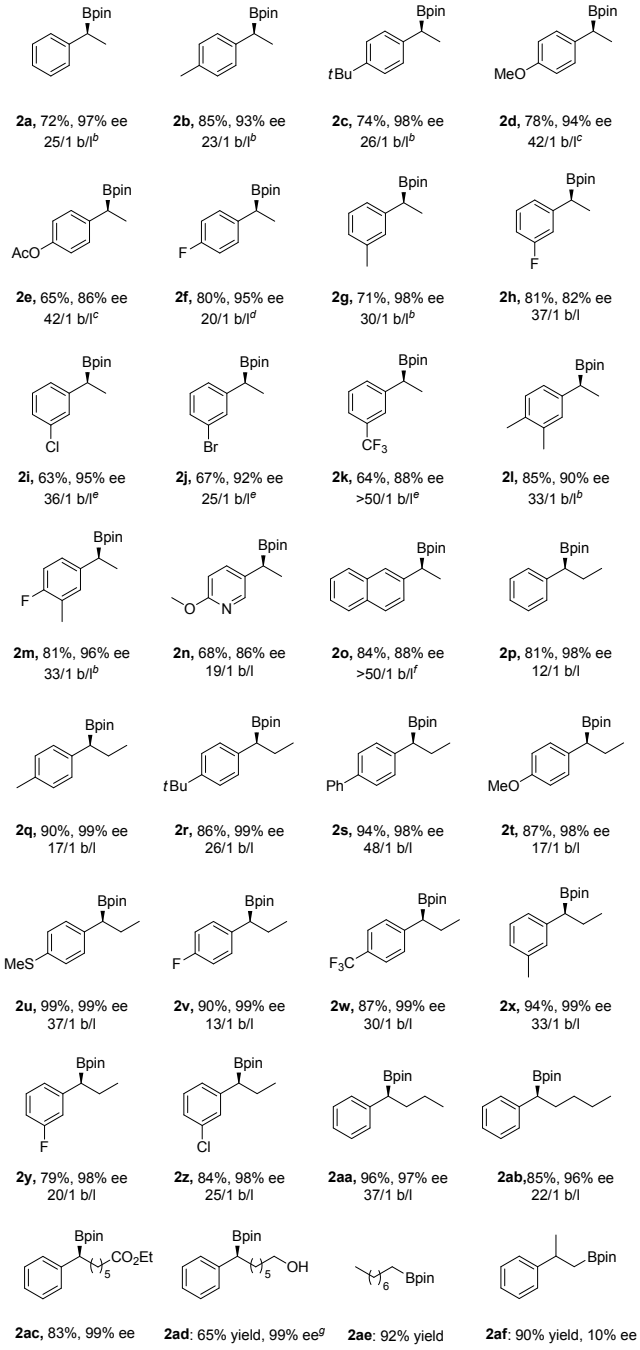
Entry	Ligand	Solvent	**2a**/**3a** (%)[b]	Ee/(%)[c]
1	**L1a**	dioxane	68/0.7	-10
2	**L1b**	dioxane	74/0.5	-11
3	**L1c**	dioxane	80/0.3	-5
4	**L1d**	dioxane	81/0.3	-5
5	**L1e**	dioxane	75/0.5	-4
6	**L1f**	dioxane	76/4.2	81
7	**L1g**	dioxane	88/2.2	87
8	**L1h**	dioxane	75/4.2	70
9	**L1i**	dioxane	78/3.2	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 ligand (3.0 mol %) in a solution of dioxane (1.0 mL) at rt under 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.

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 $Co(OAc)_2$, 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 with high regioselectivity and 82-98% *ee*. Styrenes with acetoxyl, fluro, chloro, bromo and trifluoromethyl group can be tolerated which show the good functional group tolerance of this reaction system. The styrenes containing 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-substituted vinylarenes can participate in the

Table 2. Substrate scope.[a]



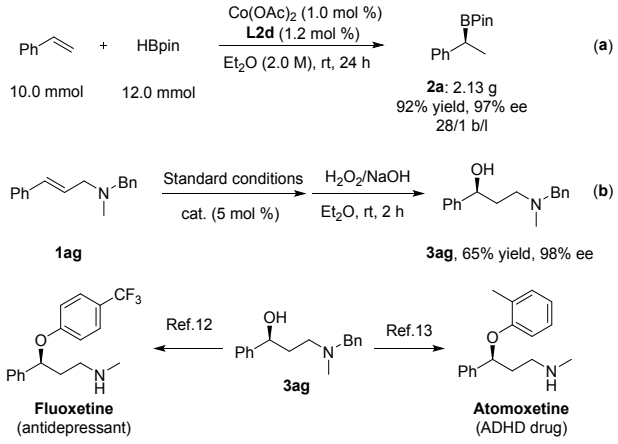
2a, 72%, 97% ee, 25/1 b/l[b]
2b, 85%, 93% ee, 23/1 b/l[b]
2c, 74%, 98% ee, 26/1 b/l[b]
2d, 78%, 94% ee, 42/1 b/l[c]
2e, 65%, 86% ee, 42/1 b/l[c]
2f, 80%, 95% ee, 20/1 b/l[d]
2g, 71%, 98% ee, 30/1 b/l[b]
2h, 81%, 82% ee, 37/1 b/l
2i, 63%, 95% ee, 36/1 b/l[e]
2j, 67%, 92% ee, 25/1 b/l[e]
2k, 64%, 88% ee, >50/1 b/l[e]
2l, 85%, 90% ee, 33/1 b/l[b]
2m, 81%, 96% ee, 33/1 b/l[b]
2n, 68%, 86% ee, 19/1 b/l
2o, 84%, 88% ee, >50/1 b/l[f]
2p, 81%, 98% ee, 12/1 b/l
2q, 90%, 99% ee, 17/1 b/l
2r, 86%, 99% ee, 26/1 b/l
2s, 94%, 98% ee, 48/1 b/l
2t, 87%, 98% ee, 17/1 b/l
2u, 99%, 99% ee, 37/1 b/l
2v, 90%, 99% ee, 13/1 b/l
2w, 87%, 99% ee, 30/1 b/l
2x, 94%, 99% ee, 33/1 b/l
2y, 79%, 98% ee, 20/1 b/l
2z, 84%, 98% ee, 25/1 b/l
2aa, 96%, 97% ee, 37/1 b/l
2ab,85%, 96% ee, 22/1 b/l
2ac, 83%, 99% ee
2ad: 65% yield, 99% ee[g]
2ae: 92% yield
2af: 90% yield, 10% ee

[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 analysis of 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.

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 aromatic ring may contribute to the formation of 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 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 noble-metal catalyst and the high pressure of 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.

Scheme 2. Gram scale reaction and synthesis of 1,3-amino alcohol



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 2-position and 6% D-incorporation in 1-position (**Scheme 3a**). 11% D-incorporation in 3-position showed that 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 be obtained, 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 amide was shifted to imidazoline which inhibited the formation of 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** in 80% yield with 97% ee (**Scheme 3b**). The control experiments demonstrated two possibilities: one was that metal complex with weak coordinated counter ion from ligand exchange was easier to be reduced, the other was that weak base could deprotonate the proton from metal complex to accelerate the formation of active pincer-type metal complex.

Scheme 3. (a) Deuterium experiment. (b) Reaction conducted using complex L2d·$CoCl_2$.

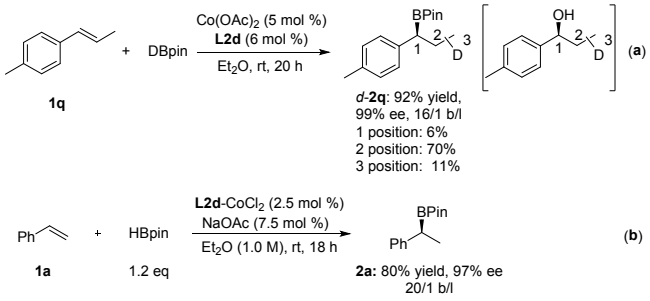


Figure 1. X-ray structure of L2d•$CoCl_2$.

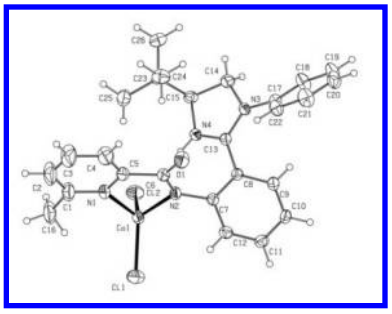
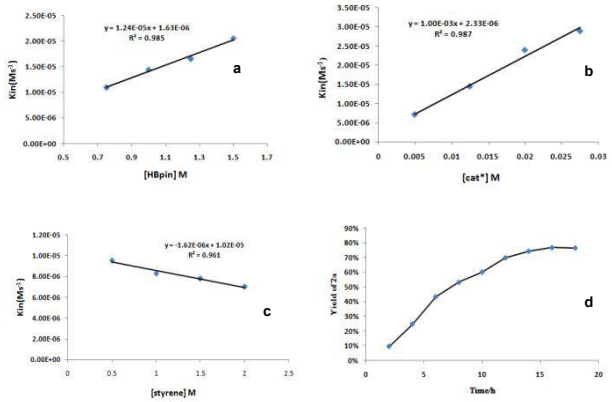


Figure 2. (a) A plot of K_{in} vs. HBpin concentrations. (b) A plot of K_{in} vs. catalyst concentrations. (c) A plot of K_{in} vs. styrene concentrations. (d) Time course studies.

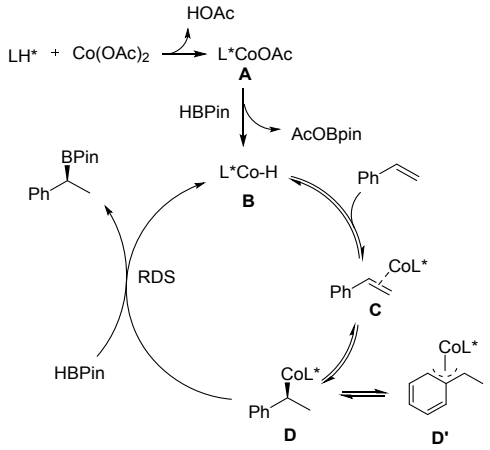


Quantitative kinetic studies were also performed to determine the roles of HBpin, styrene and catalyst. Measurements of the initial rates (K_{in}) for the reaction of styrene with different concentrations of HBpin and the catalyst showed a corresponding rise in the rates of the reactions. Plots of *K*in 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 (**Fig. 2a-b**). Similar kinetic studies on styrene showed that a first order rate dependence on styrene, however, the reaction rates were slightly affected negatively with the increasing concentrations of styrene (**Fig. 2c**). These kinetic studies showed that the σ-bond metathesis with HBpin is rate-limiting step. The phenomenon that the increased concentration of styrene decreased initial rates may attribute to the multiple ligation of alkene to catalyst, which depletes the coordination sites of catalyst and precluded it from approaching the HBpin.

Based on these mechanistic studies, a possible mechanism is illustrated in **Scheme 4**. First, ligand LH* 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 cobalt hydrogen bond to form cobalt(II) species **D** or **D'**.[15] Finally, species **D** undergoes a rate- limiting σ-bond metathesis with HBpin to regenerate cobalt (II) hydride species **B** and afford chiral organoboronic ester.

Scheme 4. Possible mechanism.



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 earth-abundant catalysis, additional activator free, simple operation and good functional group tolerance, this protocol will be a practical method for preparing synthetic useful chiral organoboronates. Developing 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.

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

AUTHOR INFORMATION

Corresponding Author

*E-mail: luzhan@zju.edu.cn.

Notes

The authors declare no competing financial interest.

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