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Dual Stereocontrol Asymmetric Cobalt-Catalyzed Hydroboration of Sterically Hindered Styrenes

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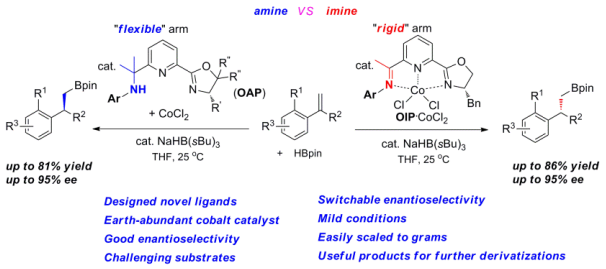


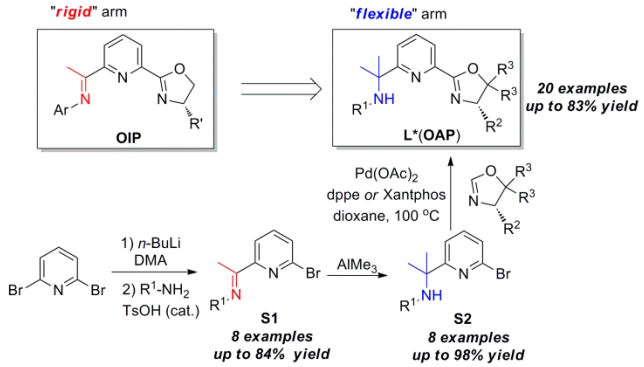
ABSTRACT: *An oxazoline aminoisopropyl pyridine (OAP) was designed and synthesized for cobalt-catalyzed asymmetric hydroboration of sterically hindered styrenes. A unique dual stereocontrol phenomenon was observed using rigid OIP·$CoCl_2$ complex or flexible OAP with $CoCl_2$ as precatalysts, respectively. The reaction could be easily carried out with gram scales to afford chiral alkylboronic esters which could be converted into diverse C-X (C, N and O) bond cross-coupling products. The mechanistically distinct pathways were proposed based on deuterium experiments.*

KEYWORDS: *ligand design, dual stereocontrol, hydroboration, cobalt-catalyzed, alkenes*

Chirality as an important and widely existing phenomenon in nature has been utilized in pharmaceutical and material science, as well as in organic synthesis, particularly in catalytical asymmetric reactions.[1] For traditional strategies, two enantiomers could be obtained with high enantioselectivities using two opposite chrial sources, however, many natural chiral sources are available in only one absolute configuration or unnatural chiral sources are very expensive. The ideal strategy is to obtain both enantiomers of the product by using a single chiral source.[2] Asymmetric reactions to afford both enantiomers with high enantioselectivities (>90% ee) are interesting, useful and challenging. Using effects of metals,[3] solvents,[4] additives and counteranions,[5] dual stereocontrol highly enantioselectivities in various types of reactions were observed. Change in catalyst substitutents is also a major effect which has been proven by Hou and Wu,[6] Takacs,[7] Ma,[8] and Liao.[9] However, changing functionalization groups in catalyst to achieve both high enantioselectivities has not been well explored.

Catatylical asymmetric hydroboration of alkenes is a direct, efficient, and atom-economic method for synthesis of chiral alkylboronic acid derivatives which are widely used in organic synthesis capable of being transferred to numerous functional groups via consecutive carbon-carbon and carbon-heteroatom bonds formation reactions.[10] Due to the difficulty in differentiating two enantiotopic faces in prochiral substrates, the asymmetric hydroboration of 1,1-disubstituted alkenes is still a challenge.[11] Since the pioneering works by Suzuki,[11a] Burgess,[11b,c] Ito and Hayashi[11d] on Rh-catalyzed asymmetric hydroboration of α-methylstyrene, Mazet,[11e] Hoveyda,[11f] Huang,[11g] Diéguez,[11j] and we,[11h,i] independently, developed

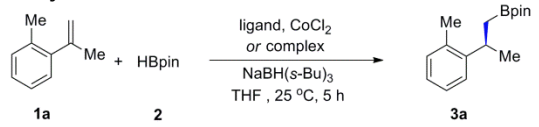
***Scheme 1*. Synthesis of Chiral Oxazoline Aminoisopropyl Pyridine (OAP)**



L_{Aa}, R^1 = 2,6-di*i*PrC_6H_3, R^2 = *t*Bu, R^3 = H
L_{Ba}, R^1 = 2,6-diEtC_6H_3, R^2 = *t*Bu, R^3 = H
L_{Ca}, R^1 = 2,6-diMeC_6H_3, R^2 = *t*Bu, R^3 = H
L_{Da}, R^1 = Ph, R^2 = *t*Bu, R^3 = H
L_{Ea}, R^1 = Bn, R^2 = *t*Bu, R^3= H

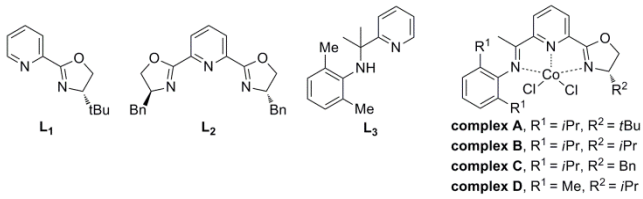
L_{Bb}, R^1 = 2,6-diEtC_6H_3, R^2 = *i*Pr, R^3 = H
L_{Cb}, R^1 = 2,6-diMeC_6H_3, R^2 = *i*Pr, R^3 = H
L_{Bc}, R^1 = 2,6-diEtC_6H_3, R^2 = Bn, R^3 = H
L_{Cc}, R^1 = 2,6-diMeC_6H_3, R^2 = Bn, R^3 = H
L_{Cc1}, R^1 = 2,6-diMeC_6H_3, R^2 = Bn, R^3 = Me
L_{Cc2}, R^1 = 2,6-diMeC_6H_3, R^2 = Bn, R^3 = Ph

Table 1. Optimization Studies for Asymmetric Hydroboration of Styrenes[a]



entry	ligand *or* complex	yield of **3a** (%)[b]	ee of **3a** (%)[c]
1	$\mathbf{L_{Aa}}$	(10)	58
2	$\mathbf{L_{Ba}}$	82	86
3	$\mathbf{L_{Ca}}$	78	92
4	$\mathbf{L_{Da}}$	(42)	79
5	$\mathbf{L_{Ea}}$	(36)	56
6	$\mathbf{L_{Bb}}$	60	75
7	$\mathbf{L_{Cb}}$	83	72
8	$\mathbf{L_{Bc}}$	63	84
9	$\mathbf{L_{Cc}}$	80	79
10	$\mathbf{L_{Cc1}}$	85	84
11	$\mathbf{L_{Cc2}}$	(71)	71
12	**L1**	(<5)	-
13	**L2**	(10)	27
14	**L3**	(<5)	-
15	**complex A**	80	-66
16	**complex B**	76	-82
17	**complex C**	81	-83
18	**complex D**	86	-59

[a]**1a** (1 mmol), HBpin (1 mmol), ligand (8 mol%), $CoCl_2$ (5 mol%), NaBH(*s*-Bu)$_3$ (15 mol%) in a solution of THF (0.5 M) at 25 °C for 5 hours. Or using cobalt **complex A-D** (5 mol%) instead of ligand and $CoCl_2$ (entries 15-18). [b]Isolated yields. NMR yields are in the parenthesis. [c]Enantioselectivities were determined by chiral HPLC analysis.



asymmetric transition-metal-catalyzed hydroboration of α-substituted styrenes. However, there is still a puzzle that the more sterically hindered substrate such as α-methyl (*ortho*-methyl)styrene in which two substitutions are quite easily differentiated[12] showed poor or moderate enantioselectivity in the asymmetric hydroboration. Otherwise, the very expensive unnatural D-valine should be used to give the opposite enantiomers. Herein, we designed and synthesized a novel oxazoline aminoisopropyl pyridine (OAP) ligand for highly enantioselective cobalt-catalyzed hydroboration of sterically bulky styrenes with an unexpected reversed absolute configuration.

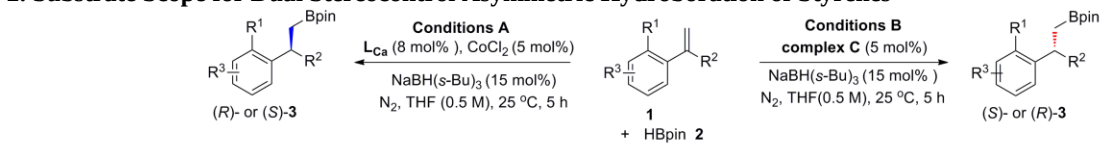
We proposed that sterically bulky styrenes could not easily coordinate the active metal center to set the right position due to steric hindrance of the oxazoline iminopyridine (OIP). Inspired by side arm strategy by Tang,[13] we designed to use *a more flexible amine group* instead of *a rigid imino group* for modification of oxazoline pyridine. The novel oxazoline aminoisopropyl pyridine ligand (OAP) (**Scheme 1**, also see SI) could be synthesized from commercially available 2,6-dibromopyridine. Acylation of 2,6-dibromopyridine followed by condensation with aniline or benzylic amine afforded 2-bromo-6-iminopyridine (**S1**) which underwent methylation with trimethylaluminum to give 2-aminoisopropyl-6-bromopyridine (**S2**). Using our previously reported palladium-catalyzed cross-coupling reactions of heteroaryl halide with oxazoline,[11i,14] the desired ligands (**L***) could be obtained up to 83% yields.

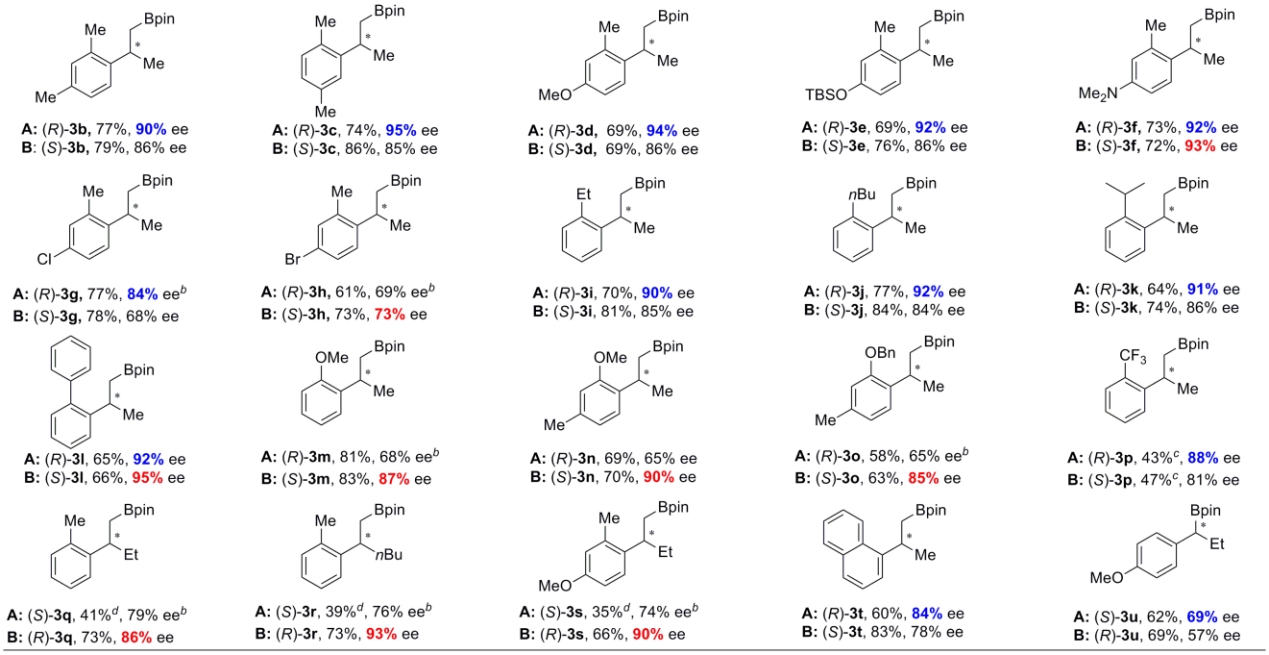
The first test reaction of 2-methyl(2'-methyl)styrene **1a** with HBpin in the presence of ligand ($\mathbf{L_{Aa}}$) and $CoCl_2$ using NaBH(*s*-Bu)$_3$ as a reductant in a solution of THF offorded the hydroboration product **3a** in 10% NMR yield with 58% ee (entry 1, **Table 1**). *Unexpectedly, the absolute configuration of major products is opposite to one obtained by using OIP·CoCl$_2$ precatalyst.* This unique phenomenon is beyond our design.

The 2,6-diethyl and 2,6-dimethyl aniline-derived ligands were quite suitable to afford **3a** up to 82% yield with up to 92% ee (entries 2 and 3). Further decreasing the steric hindrance on phenyl ring or using benzyl amine, either reactivities or enantioselectivities were diminished (entries 4 and 5). The valine-derived oxazoline with less sterically bulky anilines were able to promote hydroboration with moderate ee (entries 6 and 7). The phenylalamine-derived oxazolines with various anilines were investigated that $\mathbf{L_{Cc1}}$ (2,6-dimethylaniline with 5,5-dimethyl-4-benzyl oxazoline) was better to give **3a** in 85% yield with 84% ee (entries 8-11). Other OAP ligands, various solvents and reductants were also examined; however no further improvement was observed (SI). To identify the unique property of newly designed ligands, classic PyOx and PyBox ligands were used instead of OAP, either reactivity or enantioselectivity were deminished dramatically (entries 12 and 13). Simple aminoisopropyl pyridine was not efficient to inhabit the background reaction (entry 14). We also roughly reinvestigated the reactions using OIP·$CoCl_2$ complexes and found complex C to provide **3a** in 81% yield with reversed 83% ee (entries 15-18). Based on above ligand screen, the combination of $\mathbf{L_{Ca}}$ with $CoCl_2$ could efficiently catalyze the hydroboration of sterically bulky α-methyl styrene (conditions A). On the other hand, another enantiomer could be obtained by using OIP·$CoCl_2$ complexes from one single chiral source (conditions B).

With standard conditions in hands, a variety of sterically bulky α-substituted styrenes were investigated in **Table 2.** α-Methyl(2'-methyl)styrenes with electron-rich groups, such as methyl, methoxy, TBS-protected phenyl, dimethylamino groups were suitable for both conditions to produce the chiral boronates **3b-f** in 69-77% yields and 90-95% ee (*R*), 69-79% yields and 85-93% ee (*S*), respectively. With electron-poor subsitituent (Cl), the reaction under OAP conditions afforded (*R*)-**3g** with 84% ee. On the contrary, (*S*)-**3g** was obtained under OIP conditions with a slightly low ee (68%). With bromide on phenyl ring, moderate enantioselectivities were observed in both conditions (**3h**). Using more sterically bulky groups such as ethyl, *n*-butyl, *iso*-propyl instead of methyl group, OAP conditions showed better enantioselectivities than OIP conditions (**3i-k**). Interestingly, 2'-phenyl α-methylstyrene could participate both transformations to give **3l** in 92% and 95% ee, respectively, which is a suitable model to potentially construct axial chirality. With *ortho*-methoxy or *ortho*-benzyloxy group, (*R*)-**3m-o** were obtained under OAP conditions in 58-81% yields with moderate ee, relatively, en-

Table 2. Substrate Scope for Dual Stereocontrol Asymmetric Hydroboration of Styrenes[a]



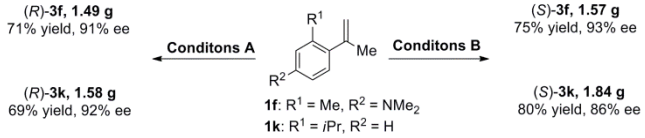


[a]Standard conditions A: Unless otherwise noted, **1** (1.0 mmol), HBpin (1.0 mmol), $\mathbf{L_{Ca}}$ (0.08 mmol), $CoCl_2$ (0.05 mmol), $NaBH(s\text{-}Bu)_3$ (0.15 mmol) in 2 mL of THF at 25 ℃ under nitrogen for 5 h. Standard conditions B: similar with conditions A, using **complex C** (0.05 mmol) instead of $\mathbf{L_{Ca}}$ and $CoCl_2$. [b]Using $\mathbf{L_{Cc1}}$ instead of $\mathbf{L_{Ca}}$. [c]12 h. [d]10 h.

antioselectivities under OIP conditions were up to 90% ee. Although *ortho*-trifluoromethyl group decreased the reactivities (**3p**), the enantioselectivities were still good (88% ee under conditions A). Increasing the α-substituent did affect the reactivity and selectivity of OAP-type reactions, however, high ees were observed under conditions B (**3q-s**). Sterically bulky 1-naphthyl derived (*R*)-**3t** was obtained with 84% ee which was better than that observed under conditions B. The reactions of 1,2-disubstituted styrene **1u** could be carried out to give exclusively regioselective **3u** in moderate yields and ees.

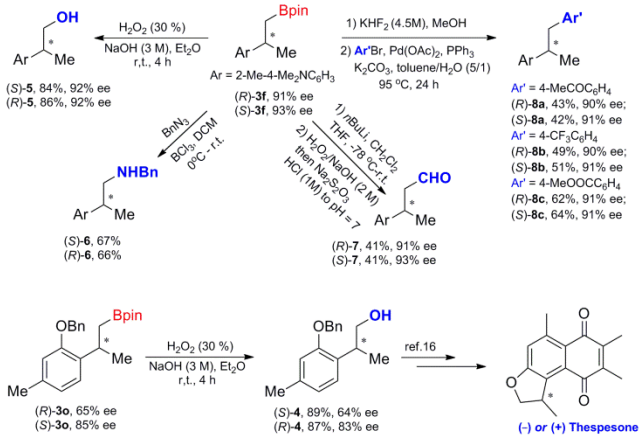
Gram scale reactions could be carried out smoothly to afford corresponding hydroboration products with good yields and high enantioselectivities (**Scheme 2**).

***Scheme 2*. Gram Scale Reactions**



The chiral boronates could be converted to diverse useful chiral compounds through oxidation, amination, dichloromethyllithium homologation and Suzuki-cross-coupling reactions (**Scheme 3**). The absolute configuration of hydroboration products was determined by the single crystal X-ray structural analysis of the derivative (*S*)-**8c** (**Scheme 3**).[15] The chiral alcohols **4** are the crucial precursors in synthesis of chiral Thespesone (**Scheme 3**),[16] which showed potential anticancer activities.

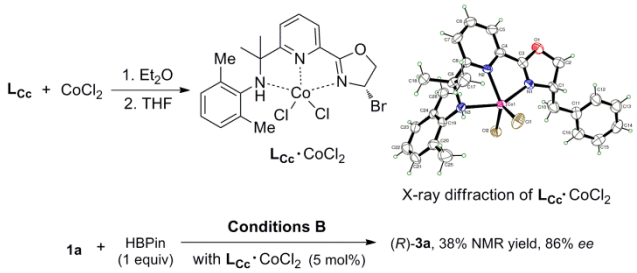
***Scheme 3*. Further Derivatizations**



To demonstrate the possibility of coordination with cobalt salts, the ligand and $CoCl_2$ were mixed in a solution of Et_2O to precipitate a dark blue solid whose structure was analyzed by single crystal X-ray diffraction (**Scheme 4**).[17] Using the $\mathbf{L_{Cc}}$·$CoCl_2$ as the precatalyst, the reaction could afford **3a** in a slightly low yield with good enantioselectivitiy.

Using methyl-protected fully substituted amine ligand $\mathbf{L_4}$, almost no reactivity was observed for hydroboration, which suggested that deprotonation of amine on the ligand might occur during activating the precatalyst (**Scheme 5**). Interestingly, removing the gem-dimethyl group on the link, the reactivity and enantioselectivity of the hydroboration reaction

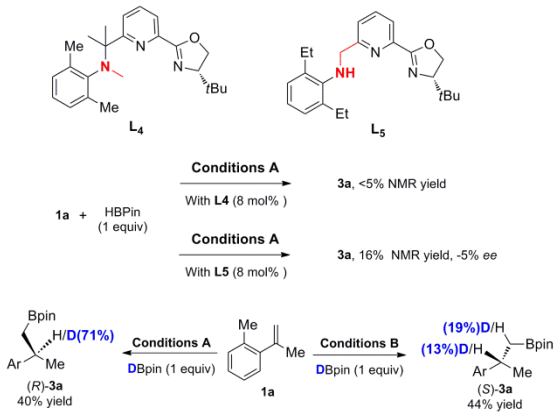
***Scheme 4*. Cobalt Complex and Its Catalytic Reaction**



were also diminished dramatically which was consistent with the Thrope-Ingold effect[18] (**Scheme 5**).

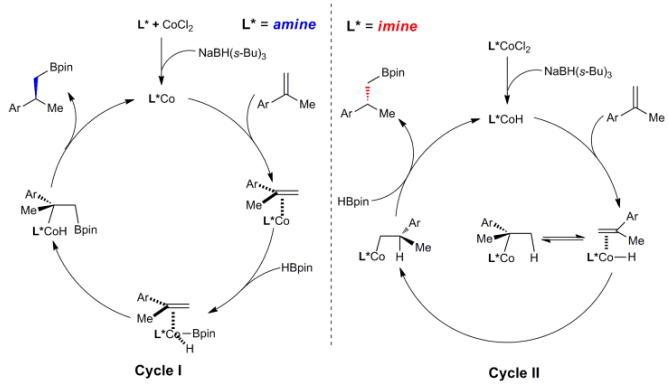
To explain the details of transformations, the deuterium experiments using DBpin were conducted (**Scheme 5**). Under conditions A, the deuterium atom was only observed at the benzyl position. Dissimilarly, under conditions B, 13% of deuterium atoms was observed at the benzyl position and also found on the borated carbon atom which indicated that the alkene insertion to a cobalt-hydride bond was a fast equilibrium.

***Scheme 5*. Control and Deuterium Experiments**



Using amine as a ligand (**cycle I** in **Scheme 6**), the ligand could undergo a deprotonation pathway to generate the active OAP cobalt species. The coordination of cobalt species with alkene might occur followed by oxidative addition of HBPin, insertion of alkene to cobalt-boron bond and reductive elimination to regenerate the active OAP cobalt species and give the hydroboration product. Based on the mechanism of the bis(imino)pyridine cobalt-catalyzed hydroboration of alkene with HBPin proposed by Chirik,[19] the OIP cobalt-catalyzed alkene hydroboration was proposed as **cycle II** in **Scheme 6**. An OIP cobalt hydride species might be the active catalyst which could coordinate with alkene followed by the insertion and ligand exchange to regenerate the catalyst and deliver the product. The stereochemistry might be determined at the coordination step. The primary models to predict the stereochemical outcome of products were shown in **Scheme S2** in SI, however, further studies should be carried out to prove the nature of the mechanism.

***Scheme 6*. Possible Mechanism**



In summary, we reported a dual stereocontrol asymmetric cobalt-catalyzed hydroboration of sterically hindered styrenes by ultilizing a novel flexible oxazoline aminoisopropyl pyridine ligand and a rigid oxazoline iminopyridine ligand, respectively. The more challenging styenes could easily undergo the enantioselective hydroboration to afford the chiral alkyl boronates in a gram-scale which are benefit for further derivatizations, such as oxidation, amination, lithium carbonation and Suzuki-cross-coupling reactions, to deliver diverse functional products. The primary mechanisms based on control and deuterium experiments were proposed that two reactions underwent mechanistically distinct pathways. Further studies on chiral ligand design is undergoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures for the experiments, synthesis and isolation of the hydroboration products, NMR and HPLC data and spectra of products (PDF). The cif documents of X-ray diffractions of compounds (*S*)-**8c** and $\mathbf{L}_{\mathbf{Cc}}$·$CoCl_2$.

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Notes

The authors declare no competing financial interest.

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