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Cobalt-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Aryl Alkenes

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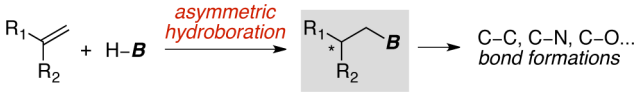
Supporting Information

ABSTRACT: We report the synthesis of cobalt complexes of novel iminopyridine−oxazoline (IPO) ligands and their application to the asymmetric hydroboration of 1,1-disubstituted aryl alkenes. The new catalysts afforded α-alkyl-β-pinacolatoboranes with exclusive regioselectivity in high yields with up to 99.5% ee. Furthermore, we have applied this method to an efficient synthesis of naproxen.

Enantioselective transformations of 1,1-disubstituted alkenes represent an ultimate challenge because of the difficulty in discriminating the enantiotopic faces of such substrates.[1] Until recently, high enantioselectivity (>90% ee) has been achieved only in asymmetric hydrogenation[2] and dihydroxylation[3] reactions. On the other hand, enantioselective hydroboration of 1,1-disubstituted alkenes is of especial interest because it can provide access to optically pure alkylboron compounds, which are vital intermediates in organic synthesis (Scheme 1).[4] Thus, an efficient method for asymmetric hydroboration of 1,1-disubstituted alkenes is highly desirable.

Scheme 1



There are two strategies for asymmetric alkene hydroboration: one involves the use of chiral organoborane agents, and the other involves asymmetric catalysis. Pioneered by Brown,[5] numerous chiral organoboranes have been developed for uncatalyzed asymmetric anti-Markovnikov hydroborations of alkenes.[6] Recently, Soderquist and co-workers developed chiral 9-borabicyclo[3.3.2]decanes that gave the best enantioselectivity of any chiral boron reagents investigated to date for hydroborations of 1,1-disubstituted alkenes. The reactions with α-deuterium-labeled styrene and α-methylstyrene gave 98% and 78% ee, respectively.[7]

To avoid using the expensive and difficult-to-access chiral organoborane reagents, several transition-metal catalysts have been developed for asymmetric hydroborations with common boron reagents.[8−10] The Rh- and Ir-catalyzed hydroborations of 1,1-disubstituted alkenes with catecholborane exhibit low regio- and enantioselectivity.[8c,11] Recently, Mazet and Gerard[12] reported an Ir complex of phosphinooxazoline for anti-Markovnikov hydroboration of 1,1-disubstituted aryl alkenes with pinacolborane (HBPin). While the reaction with α-methylstyrene afforded 93% ee, most reactions occurred with low to moderate enantioselectivity (<5 to 80% ee). Another attractive protocol was reported by Hoveyda and co-workers, where NHC−Cu complexes catalyze asymmetric hydroboration of 1,1-disubstituted aryl alkenes with bis(pinacolato)diboron (B_2Pin_2). The Cu-catalyzed processes afforded excellent site selectivity and ≥90% ee in the case of four α-alkyl aryl olefins (overall range of ee: 61−93%).[13]

Base-metal catalysts have received significant attention in the past decade not only because of their low cost, high earth abundance, and environmentally benign nature but also because they may supplant the traditional precious-metal catalysts in some catalytic processes.[14,15] As one manifestation of this phenomenon, Fe and Co complexes of tridentate bipyridyl phosphine (PNN) pincer ligands developed in our group have proven to be 2−4 orders of magnitude more active than the classical Rh and Ir catalysts for hydroborations of α-olefins with HBPin.[16] The PNN−iron complex was also found to be active for the anti-Markovnikov hydroboration of 1,1-disubstituted alkenes. We envisioned that asymmetric hydroboration of 1,1-disubstituted alkenes might be feasible through the use of base-metal catalysts containing suitable chiral ligands. Herein we report the preparation of Co complexes of new iminopyridine−oxazoline (IPO) ligands and the first Co-catalyzed asymmetric alkene hydroborations with HBpin. This system exhibits unprecedented levels of enantioselectivity for hydroborations of 1,1-disubstituted aryl alkenes (up to 99.5% ee). The reactions occur at ambient temperature with low catalyst loadings.

The synthesis of the new IPO ligands and their corresponding Co complexes is outlined in Scheme 2. Treatment of 2-acetyl-6-cyanopyridine with an arylamine bearing *i*Pr substituents at the 2,6-aryl positions formed iminopyridine compound **1**. The condensation of **1** with various amino alcohols in the presence of $Zn(OTf)_2$ produced the chiral IPO ligands (*S*)-**2a−c** and (*R*)-**2a** in moderate yields. The neutral Co(II) dichloride complexes [(*R*/*S*)-R-IPO]$CoCl_2$ (R = *i*Pr for (*S*)-**3a** or (*R*)-**3a**; R = *t*Bu for (*S*)-**3b**; and R = Bn for (*S*)-**3c**) were formed in high yields by the addition of the corresponding ligands to the anhydrous Co salt. These Co(II) complexes show broadened and paramagnetically shifted resonances in the ^{1}H NMR spectrum. Single-crystal X-ray diffraction analysis of (*S*)-**3c** revealed a distorted square-pyramidal geometry around the Co center (Figure 1).

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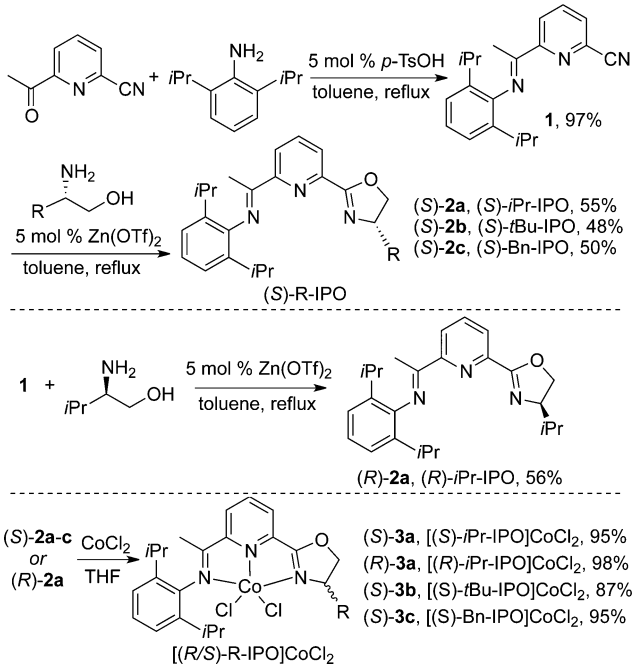
Scheme 2. Synthesis of the IPO Ligands and Their Corresponding Co Complexes



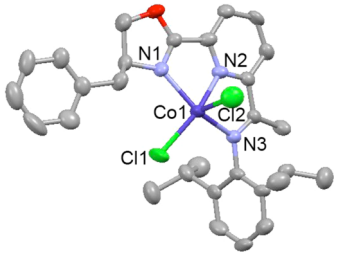
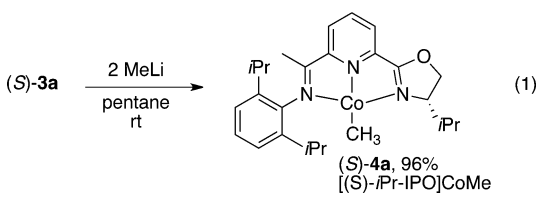


Figure 1. Crystal structure of complex (*S*)-**3c**. H atoms have been omitted for clarity. Ellipsoids are drawn at the 30% probability level. Selected bond distances (Å) and angles (deg): Co1–N1, 2.143(3); Co1–N2, 2.065(4); Co1–N3 2.200(3); Co1–Cl1, 2.2614(14); Co1–Cl2, 2.2998(12); N1–Co1–N2, 74.47(14); N2–Co1–N3, 73.61(14); N1–Co1–N3, 139.63(13); N2–Co1–Cl1, 151.80(9); N2–Co1–Cl2, 91.04(9); Cl1–Co1–Cl2, 117.13(5).

The Co dichloride complexes can be readily converted to the Co methyl species. The reaction of [(*S*)-*i*Pr-IPO]$CoCl_2$ (*S*)-**3a** with 2 equiv of MeLi formed the Co methyl complex [(*S*)-*i*Pr-IPO]CoMe (*S*)-**4a** in 96% yield (eq 1). (*S*)-**4a** is diamagnetic,

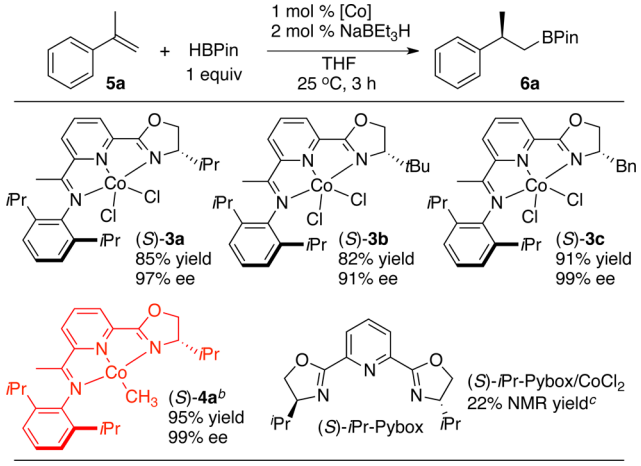


(1)

which facilitates its characterization by NMR spectroscopy. The characteristic Co–Me resonance appears at −2.34 ppm as a singlet in the ^{1}H NMR spectrum, which is consistent with that observed for the related bis(imino)pyridine Co methyl complexes.[2b]

The enantiopure C_1-symmetric (IPO)Co complexes were evaluated as precatalysts for the asymmetric hydroboration of α-methylstyrene (**5a**). The results are summarized in Table 1.

Table 1. Cobalt-catalyzed Asymmetric Hydroboration of α-Methylstyrene (5a) with HBPin[a]



[a]Reaction conditions: **5a** (0.5 mmol), HBPin (0.5 mmol), (*S*)-**3** or (*S*)-**4a** (0.5 mol %), and $NaBEt_3H$ (1 mol %) in THF (2 mL) at 25 °C. Isolated yields and ee's determined by HPLC analysis are shown. [b]Without the addtion of $NaBEt_3H$. [c]Reaction conditions: **5a** (0.5 mmol), HBPin (0.5 mmol), (*S*)-*i*Pr-Pybox (0.5 mol %), $CoCl_2$ (0.5 mol %), and $NaBEt_3H$ (1 mol %) in THF (2 mL) at 25 °C. The yield was determined by ^{1}H NMR analysis with mesitylene as an internal standard.

Upon activation with $NaBEt_3H$, the Co dichloride complex (*S*)-**3a** with an *i*Pr substituent on the oxazoline moiety is active for hydroboration of **5a** with HBPin. The process with 1 mol % (*S*)-**3a** in THF (3 h, 25 °C) formed the primary alkylboronate ester **6a** in 85% yield. The reaction gave exclusive regioselectivity and excellent enantioselectivity (97% ee). An increase in the steric bulk in going from (*S*)-**3a** to (*S*)-**3b** by replacing the *i*Pr substituent with *t*Bu led to a lower enantioselectivity (91% ee). However, the precatalyst (*S*)-**3c** with a Bn substituent afforded the product with 99% ee in 91% yield. When the Co methyl complex (*S*)-**4a** derived from (*S*)-**3a** was employed, the best results in terms of enantioselectivity and yield were obtained (99% ee, 95% yield). The high activity of (*S*)-**4a** allowed the reaction to occur with a lower catalyst loading (0.5 mol %) and a shorter reaction time (0.5 h), furnishing **6a** in 95% yield with 99% ee (Table 2). It should be noted that the reactions with (*S*)-**4a** do not need an activating reagent.

To probe whether the imino moiety of the IPO ligands is required for the asymmetric hydroboration reaction, the IPO ligand was replaced by (*S*)-*i*Pr-Pybox. Under otherwise identical reaction conditions, a combination of (*S*)-*i*Pr-Pybox and $CoCl_2$ led to a reduced yield of **6a** (22% NMR yield; Table 1). The preliminary results suggest that while the oxazoline unit of the IPO ligands induces the enantioselectivity, the imino group is essential for enhanced activity of the Co catalyst in alkene hydroborations.

To delineate the scope of the Co-catalyzed asymmetric hydroboration, (*S*)-**4a** was applied to the reactions of various 1,1-disubstituted aryl alkyl ethenes. The results are summarized in Table 2. All of the reactions proceeded smoothly at ambient temperature with low catalyst loadings (0.5–2 mol %). Most of the reactions provided high isolated yields with excellent enantioselectivity (95–99.5% ee) and complete regioselectivity. The method works efficiently for α-methylstyrene derivatives bearing both electron-donating and -withdrawing groups. Halogen-substituted α-methylstyrenes, including the *p*-iodo-

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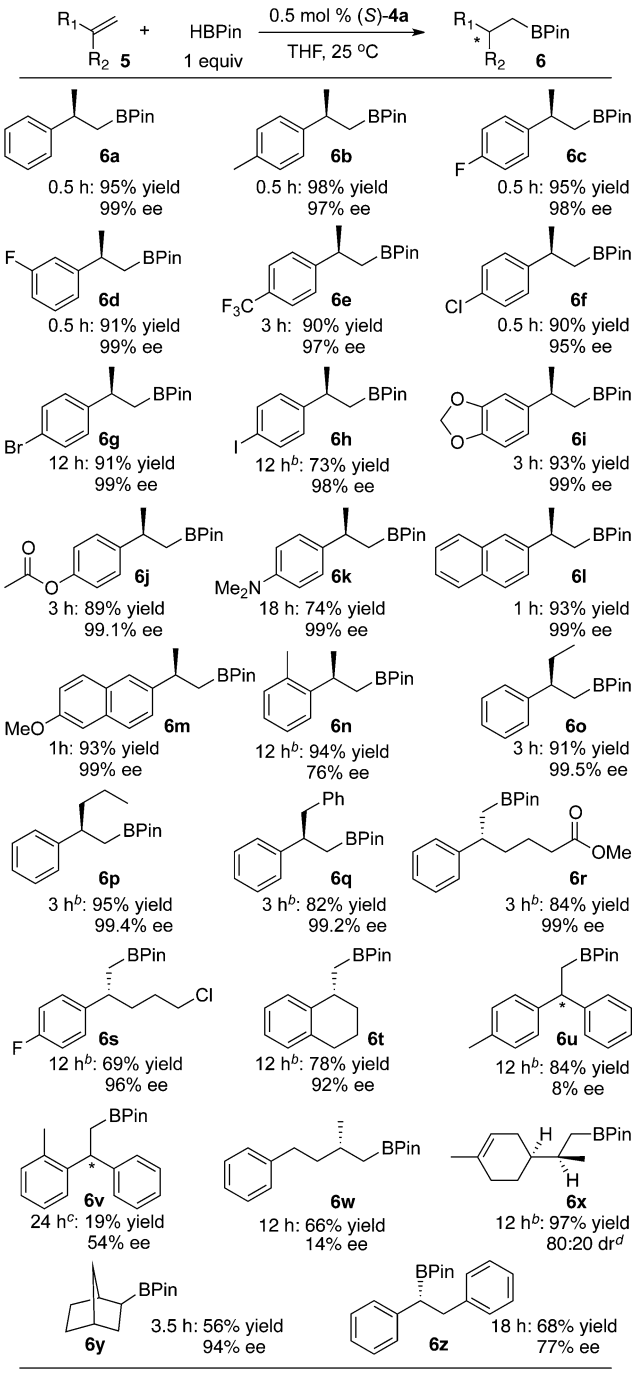
Table 2. Cobalt-catalyzed Asymmetric Hydroboration of 1,1-Disubstituted Alkenes[a]



[a]Reaction conditions: **5** (0.5 mmol), HBPin (0.5 mmol), and (*S*)-**4a** (0.5 mol %) in THF (2 mL) at 25 °C. Isolated yields and ee's determined by HPLC analysis are shown. The absolute configurations were assigned by comparison with reported optical rotations. [b]With 2.0 mol % (*S*)-**4a**. [c]With 3.0 mol % (*S*)-**4a**. [d]Determined by oxidation to the corresponding alcohol using 30% H_2O_2 and quantitative ^{13}C NMR analysis.

substituted one, were hydroborated in high yields with 95−99% ee. Ester and dimethylamine functionalities are tolerated, as shown by the isolation of **6j** and **6k** in high yields with high enantioselectivity. Substituents at the para and meta positions of the phenyl ring are tolerated under the reaction conditions, furnishing the hydroboration products in high yields with excellent enatioselectivity. Earlier work showed that the asymmetric hydroboration of ortho-substituted α-methylstyrene is very difficult (e.g., the Ir-catalyzed hydroboration of *o*-methyl-α-methylstyrene (**5n**) reported by Mazet gave <5% ee and 66% yield.[12]) To our delight, the Co-catalyzed hydroboration of **5n** afforded 76% ee and 94% yield. The substrates bearing naphthyl groups reacted smoothly to afford the desired products (**6l**, 93% yield, 99% ee; **6m**, 93% yield, 99% ee).

Increasing the steric demand in the vicinity of the benzylic position by using an Et, *n*Pr, or Bn group did not affect the enantioselectivity (**6o−q**). Ester and chloride functionalities in the alkyl chains were also tolerated, as demonstrated by the isolation of **6r** and **6s** with excellent enantioselectivity. Furthermore, the hydroboration of exocyclic 1,1-disubstituted alkene **5p** provided the product in 78% yield with 92% ee.

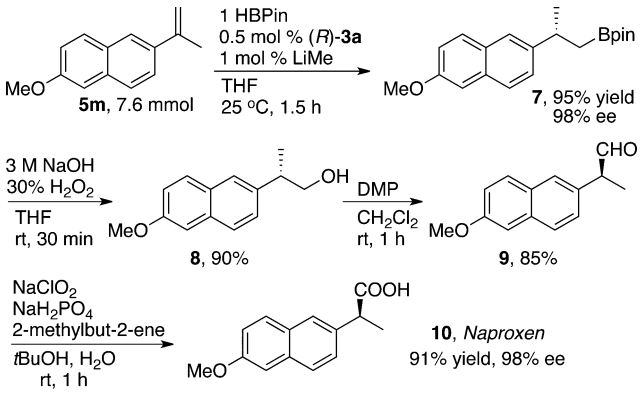
Asymmetric hydroboration of 1,1-diarylethenes is a significant challenge. Indeed, no catalyst systems for asymmetric hydroboration of this substrate type have previously been reported. The Co-catalyzed hydroboration of 1,1-diarylethene **5u** bearing a *p*-methyl substituent gave the product in 84% yield with 8% ee. Although the bulkier diarylethene **5v** with an *o*-methyl substituent was less reactive (24 h, 19% yield), the steric bias at the ortho position led to the formation of **6v** with 54% ee.

The hydroboration of the 1,1-dialkylethene 2-methyl-4-phenyl-1-butene (**5w**) gave the product **6w** with low enantioselectivity (14% ee). However, the reaction of chiral (*L*)-limonene (**5x**) with (*S*)-**4a** afforded the *S,R* diastereomer **6x** with 80:20 dr. The mismatched combination of **5x** with (*R*)-**3a** provided 68:32 dr in favor of the *S,S* diastereomer. It is noteworthy that the trisubstituted olefin in **5x** is unreactive under the Co-catalyzed hydroboration conditions.

Our preliminary results show that the (IPO)Co catalyst is also active for hydroboration of 1,2-disubstituted internal olefins. The asymmetric hydroboration of norbornene gave the exo product **6y** exclusively with an impressive 94% ee.[17] The reaction of (*E*)-1,2-diphenylethene formed **6z** in 77% ee.

Finally, the asymmetric hydroboration provided an efficient method for the synthesis of naproxen. Hydroboration of **5m** with (*S*)-**4a** as the catalyst precursor as shown above produced the *S* enantiomer selectively (see Table 2). We were pleased to find that a simple change of the precatalyst from (*S*)-**4a** to (*R*)-**3a** (0.5 mol %) resulted in the formation of the *R* enantiomer **7** in 95% yield with 98% ee. A three-step oxidation sequence converted **7** to naproxen without epimerization of the stereogenic center (98% ee, 66% overall yield) (Scheme 3).

Scheme 3. Synthesis of Naproxen



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In summary, we have prepared and characterized cobalt complexes ligated by chiral iminopyridine−oxazoline (IPO) ligands. The new cobalt catalyst system is highly efficient for asymmetric hydroboration of 1,1-disubstituted aryl alkenes, thus affording optically pure primary alkylboronate esters with unprecedented enantioselectivity. Additional studies of asymmetric transformations with the IPO ligands are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and crystallographic data (CIF) for complex (*S*)-**3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[†]L.Z. and Z.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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(17) As a comparison, the best enantioselectivity reported in early studies was obtained by Rh-catalyzed hydroboration of norbornene with catecholborane (64% ee). See ref 11b.