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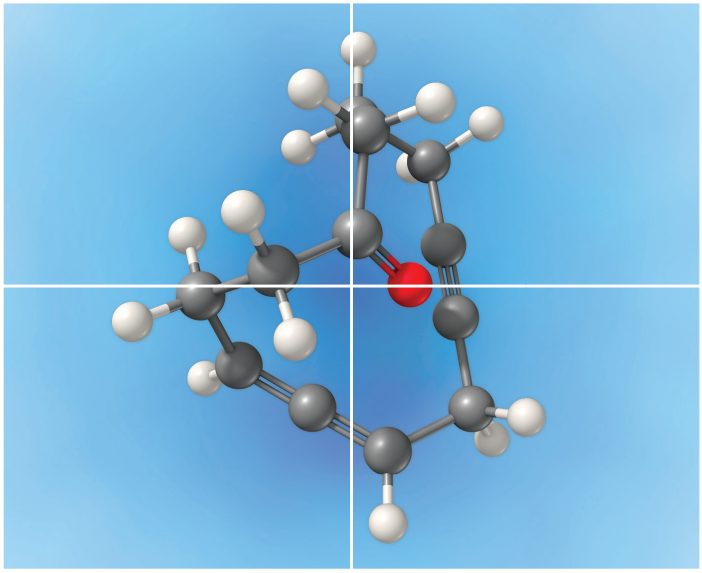

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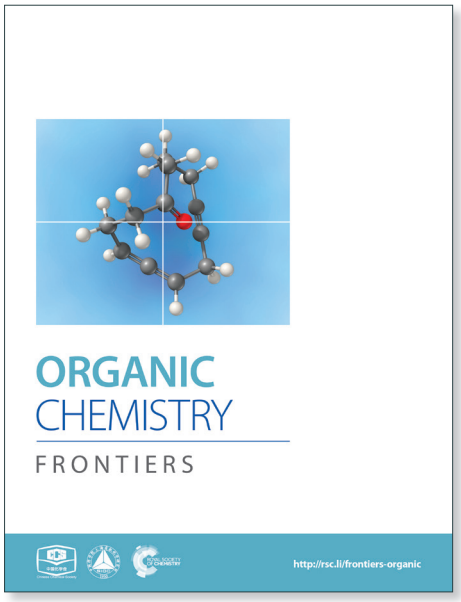

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ARTICLE TYPE

Asymmetric Cobalt Catalysts for Hydroboration of 1,1-Disubstituted Alkenes

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The chiral iminopyridine oxazoline (IPO) ligands were designed, synthesized and utilized for the first cobalt-catalyzed highly regio- and enantioselective *anti*-Markovnikov hydroboration of 1,1-disubstituted aryl alkenes. This novel IPO ligands will likely be of high value for asymmetric transformations with first-row transition metals.

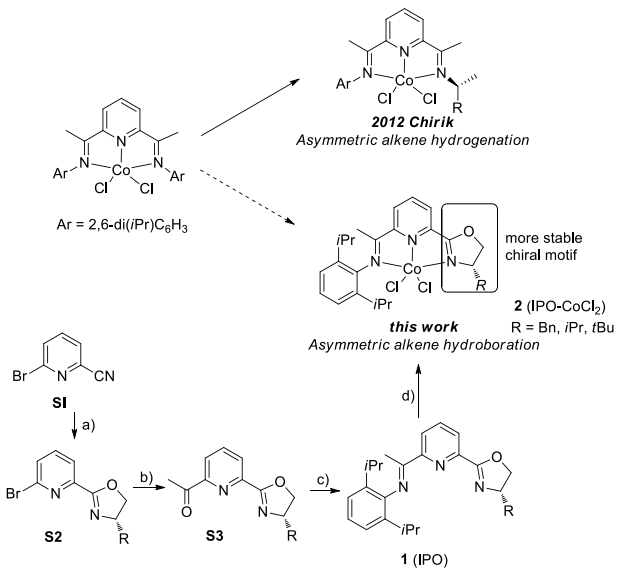
Introduction

Asymmetric hydroboration of alkenes is one of the most useful methods to form chiral alkylboronic acid derivatives which are widely used in organic synthesis.[1] Hydroboration of terminal alkenes catalyzed by chiral transition metals is more favored to Markovinov regioselectivity.[2] Catalytic asymmetric *anti*-Markovnikov hydroboration of 1,1-disubtituted alkenes remains a challenge.[3] Low enantioselectivity and in some case poor regioselectivity were obtained through Rh- and Ir-catalyzed reactions of 1,1-disubstituted alkenes with catecholborane.[4] Recently, two catalytic systems, Iridium with chiral PN-ligand[5] and copper with chiral NHC ligand,[6] were reported, respectively, to realize asymmetric hydroboration of 1,1-disubstituted alkenes. However, noble transition metal was used, or $B_2(pin)_2$ was used to provide more waste, a few case shows high enantioselectivity (≥90%ee). To the best of our knowledge,[7] there is no previous report on asymmetric cobalt-catalyzed *anti*-Markovnikov hydroboration of 1,1-disubtituted alkenes.[8]

Noble metals play a very important role of asymmetric organic transformations in academia and industry, such as asymmetric hydrogenation of alkenes,[9] however, earth-abundant metal catalysts often reacting via one-electron processes are limited in some type of reactions. Redox-active ligands which have been studies by the spectroscopy properties might provide the possibility for earth-abundant metals to go through two-electron redox processes to promote bond- breaking and making events.[10] The asymmetric applications of redox-active ligands are extremely rare. Recently, Chirik group reported highly enantioselective hydrogenation of alkenes[11] using *C1*-symmetric bis(imino)pyridine cobalt complexes[12] which show that chiral redox-active ligand is a potential good class of catalysis for asymmetric organic synthesis, however, the chiral imine on the catalyst is not stable and easily to release. Based on the bi(imino)pyridine ligands, we introduced the chiral oxazoline units as stereodirecting elements[13] and designed the new iminopyridine oxazoline (IPO) cobalt complexes, in which, the iminopyridine group is proposed to stabilize the cobalt and chiral oxazoline group to control enantioselectivity (**Scheme 1**).

Herein we report the synthesis of a series of chiral IPO ligands from the commercially available starting materials (**Scheme 1**). The cobalt complexes **2** could be synthesized by combining cobalt dichloride with the corresponding ligands and are bench-stable.

Scheme 1. Design and synthesis of chiral redox-acitve cobalt complexes.



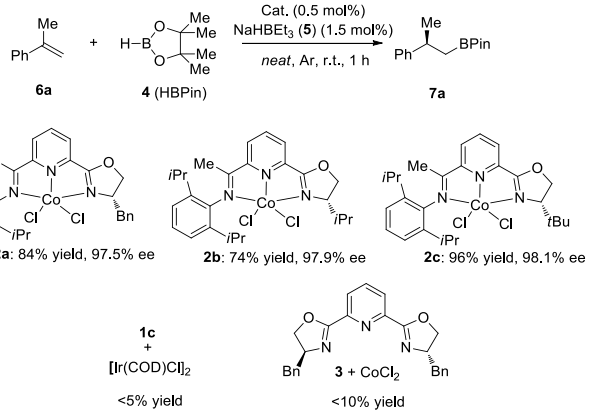
a) (*S*)-aminoalochol, $Zn(OTf)_2$, toluene, reflux, 70-93% yield; b) *n*BuLi, Et_2O, -78 °C, 2 h, then DMA, 35-40% yield; c) 2,6-diisopropylaniline, cat. HCOOH, MeOH, relux, 24 h, 32-41% yield; d) $CoCl_2$, THF, rt, then Et_2O, 86-95% yield.

Results and discussion

We chose the hydroboration of styrene **6a** with HBpin as the model reaction to test the reactive of our designed chiral cobalt complexes (IPO-$CoCl_2$). Using only 0.5 mol% cobalt complexes and 1.5 mol% of $NaHBEt_3$ (1 M in THF solution) as the reductant without any additive solvent, high reactivity and regio- and enantioselectivities were observed in all cases among which complex **2c** gave the excellent yield and highest enantioselectivity (**Scheme 2**). The reaction was really slow using **1c** with iridium catalyst which might illustrate that IPO ligands worked better with first-row transition metals than late-transition

metals. Poor reactivities were shown in using the bisoxazoline ligand instead of IPO ligands which the iminopyridine group is proposed to stabilize the cobalt.

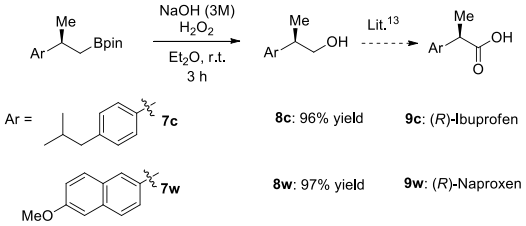
Scheme 2. Optimizations.



With the best complex **2c** in hands, studies exploring the scope of this process are summarized in Chart 1. The reactions were operated under schlenk line in 2.5 mmol scale, not necessarily in glove box. 1) The reaction represented high enantioseletivities with a variety of substituted α-methyl styrenes, including both electron-rich and electron-deficient styrene compounds; 2) Halides and protected heteroatoms can be tolerated at *para*, *meta* and *ortho*-position on the aryl rings; 3) Although a silghtly low ee were observed in the reaction of *ortho*-substituted styrenes, high yields were obtained; 4) Long alkyl chain on α-position of styrenes, even with functionalized alkyl chain, were tolerated to prepare the corresponding hydroboration products in high enantioselectivities; 5) The cyclic styrene with terminal alkene was also reacted to afford **7ab** in a slightly low yield with 95% ee; 6) Gratifyingly, 1,1-dialkyl substituted alkenes **6ac** and **6ad** also participated in this reaction to give the desired hydroboration products in 72% yield with 33% ee and 70% ee, respectively.

The compounds **7c** and **7w** can be easily oxidized and further derivatized[14] to (*R*)-naproxen and (*R*)-ibuprofen, which enantiomers are well-known non-steroid anti-inflammatory and analgesic drugs [15](**Scheme 3**).

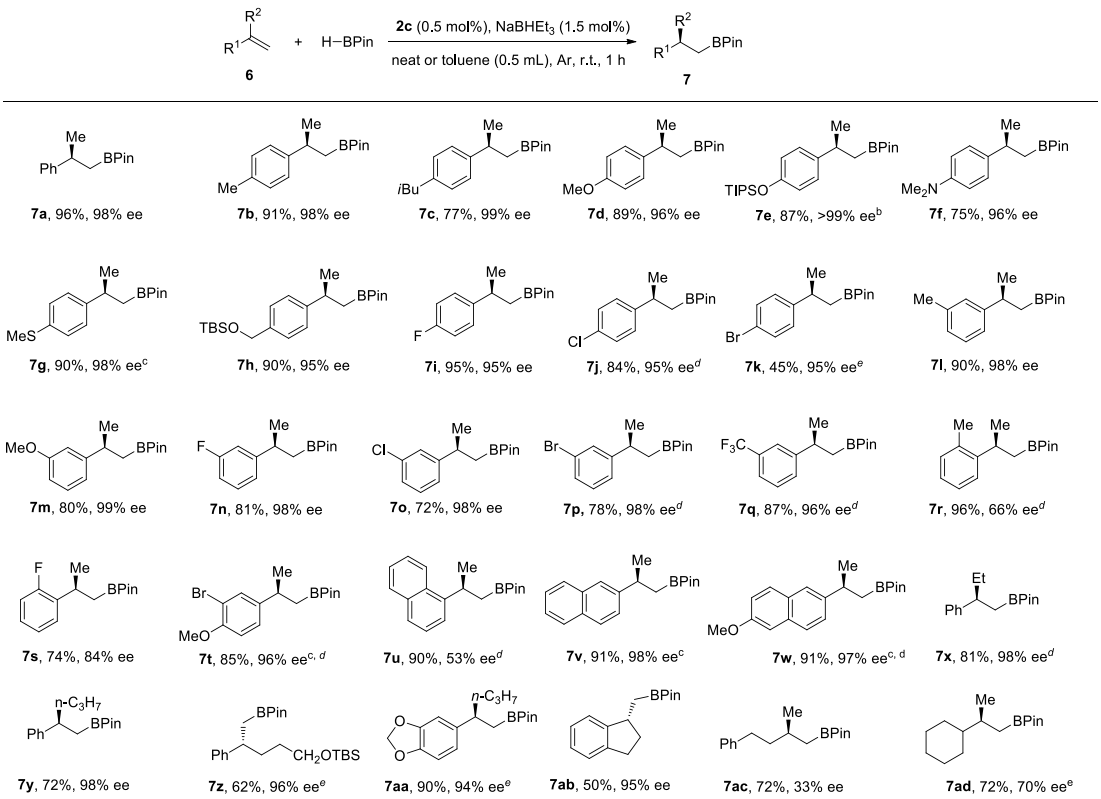
Scheme 3. Further derivatizations.



Conclusions

In conclusions, we have developed a novel iminopyridine oxazoline cobalt-catalyzed highly enantioselective and regioselective *anti*-Markovnikov hydroboration of 1,1-disubstituted alkenes with hydroborate. A series of useful highly enantiopure borate compounds were easily synthesized from the simple alkenes without any directing group. Current

Chart 1. Asymmetric *anti*-Markovnikov hydroboration of alkenes.[a]



[a] Standard condition: Unless otherwise noted, **6** (2.5 mmol), HBPin (2.5 mmol), **2c** (0.5 mol%), $NaBHEt_3$ (1.5 mol%) at room temperature for 1 h; [b] 2 mol% **2c**; [c] toluene (0.5 mL). [d] 1 mol% **2c**; [e] 5 mol% **2c**.

efforts in our lab are underway to explore the applications of IPO ligands in asymmetric reactions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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