This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Asymmetric Cobalt Catalysts for Hydroboration of 1,1-Disubstituted Alkenes

Jianhui Chen, Tuo Xi, Xiang Ren, Biao Cheng, Jun Guo and Zhan Lu

Received (in XXX, XXX) Xth XXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX
DOI: 10.1039/b000000x

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 alkyboronic acid derivatives which are widely used in organic synthesis. Hydroboration of terminal alkenes catalyzed by chiral transition metals is more favored to Markovnikov regioselectivity. Catalytic asymmetric anti-Markovnikov hydroboration of 1,1-disubstituted alkenes remains a challenge. Low enantioselectivity and in some case poor regioselectivity were obtained through Rh- and Ir-catalyzed reactions of 1,1-disubstituted alkenes with catecholborane. Recently, two catalytic systems, Iridium with chiral PN-ligand and copper with chiral NHC ligand, were reported, respectively, to realize asymmetric hydroboration of 1,1-disubstituted alkenes.

Noble metals play a very important role of asymmetric organic transformations in academia and industry, such as asymmetric hydrogenation of alkenes, 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. The asymmetric applications of redox-active ligands are extremely rare. Recently, Chirik group reported highly enantioselective hydrogenation of alkenes using C1-symmetric bis(imino)pyridine cobalt complexes 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 bis(imino)pyridine ligands, we introduced the chiral oxazoline units as stereoregulating elements 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-active cobalt complexes.

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-CoCl2). Using only 0.5 mol% cobalt complexes and 1.5 mol% of NaHBEt3 (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 2e 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.
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 enantioselectivities 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 slightly 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 to (R)-naproxen and (R)-ibuprofen, which enantiomers are well-known non-steroid anti-inflammatory and analgesic drugs (Scheme 3).

Scheme 3. Further derivatizations.

In conclusion, 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.

<table>
<thead>
<tr>
<th>R²</th>
<th>2c (0.5 mol%), NaH(0.5 mol%), H₂P(2.5 mmol), Me₆Si(0.5 mL), Ar, τ. 1 h</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>7a, 96%, 98% ee</td>
<td>7b, 91%, 98% ee</td>
</tr>
<tr>
<td>Me</td>
<td>7c, 77%, 99% ee</td>
<td>7d, 89%, 96% ee</td>
</tr>
<tr>
<td>Me</td>
<td>7e, 75%, 96% ee</td>
<td>7f, 75%, 96% ee</td>
</tr>
</tbody>
</table>

- Standard condition: Unless otherwise noted, 6 (2.5 mmol), HBPin (2.5 mmol), 2c (0.5 mol%), NaBHEt (1.5 mol%) at room temperature for 1 h; 2 mol% 2c; 5 mol% 2c; 1 mol% 2c.
efforts in our lab are underway to explore the applications of IPO ligands in asymmetric reactions.

Acknowledgements

Financial support was provided by the “Thousand Youth Talents Plan”, the Fundamental Research Funds for the Central Universities (2013QNA3022), the Starting Funds from Zhejiang University

Notes and references


8 Unfortunately, during we were submitting the manuscript on our independent work, a similar result was reported by Huang, Z. et al L. Zhang, Z.-Q. Zuo, X.-L. Wan, Z. Huang, J. Am. Chem. Soc. 2014, 136, 15501. However, we used the different strategy for synthesis of chiral iminopyridine oxazoline since November 14th, 2013.


