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Iminopyridine Oxazoline Iron Catalyst for Asymmetric Hydroboration of 1,1-Disubtituted Aryl Alkenes

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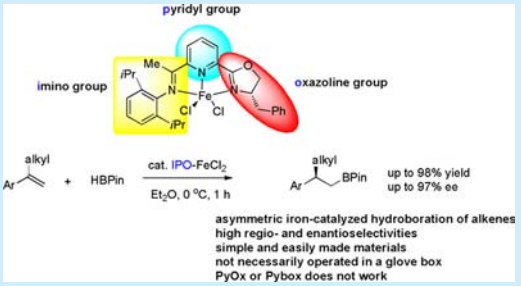
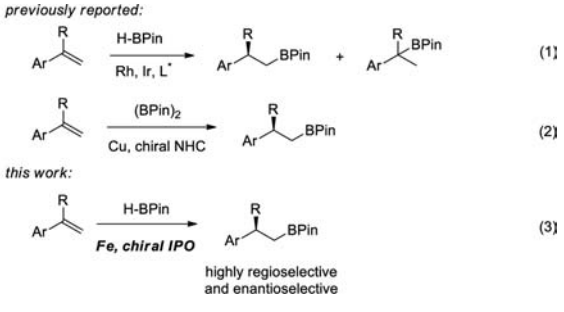
Supporting Information

ABSTRACT: The highly regio- and enantioselective iron-catalyzed anti-Markovnikov hydroboration of 1,1-disubstituted aryl alkenes is reported by using a novel chiral iminopyridine oxazoline (IPO) ligand, in which the iminopyridine group is proposed to stabilize the iron and chiral oxazoline group to control enantioselectivity. This distinct class of reactive IPO ligands will likely be of high value for a large variety of asymmetric transformations using first-row transition metals.



Hydroboration of alkenes is one of the most useful methods to access alkylboronic acid derivatives, which are widely used in modern organic synthesis.[1] Chiral boronic acid derivatives could be synthesized by hydroboration of alkenes with stoichiometric amounts of chiral hydroborating compounds.[2] A more efficient strategy is the transition-metal-catalyzed asymmetric hydroboration of alkenes with the boronic compounds using catalytic amounts of chiral ligands. Asymmetric hydroboration of terminal alkenes catalyzed by chiral transition metal complexes is primarily selective for Markovinov regioselectivity.[3] However, the enantioselective hydroboration of 1,1-disubstituted alkenes is still a challenge.[4−6] Low enantioselectivity and in some cases poor regioselectivity were obtained through rhodium- and iridium-catalyzed reactions of 1,1-disubstituted alkenes with catecholborane (eq 1).[4] Recently, an iridium-catalyzed asymmetric hydroboration of 1,1-disubstituted alkenes with HBPin was reported using a chiral Phox-ligand to achieve high regioselectivity (eq 1).[5] However, only moderate enantioselectivity was observed in most cases. Another work involves the chiral NHC-copper-catalyzed enantioselective hydroboration of 1,1-disubstituted alkenes with $(BPin)_2$ (eq 2).[6]



A long reaction time of 2 days at low temperature (−50 °C) is required to afford high regioselectivity and >90% ee, in the case of two acyclic α-substituted styrenes. Iron is a naturally abundant, minimally toxic, cheap, and commercially available base metal.[7] Although chiral iron catalysts have been used in several types of reactions thus far, asymmetric reductive reactions catalyzed using low valent iron catalysts were limited to the reduction of ketones and imines.[8,9] To our best knowledge, there has been no report on asymmetric hydroboration of carbon−carbon double bonds by chiral iron catalysts. Herein, we report a highly regio- and enantioselective iron-catalyzed *anti*-Markovnikov hydroboration reaction of 1,1-disubstituted aryl alkenes with HBPin using the newly designed chiral iminopyridine oxazoline (IPO) iron catalyst (eq 3).

To begin this study, we elected to study the hydroboration of α-methylstyrene with HBPin as the model reaction to test our hypothesis, based on the iron-catalyzed racemic hydroboration. Using biiminopyridine ligands, which can stabilize center

Scheme 1. Design, Synthesis, and X-ray Structure of Iron Compound 2

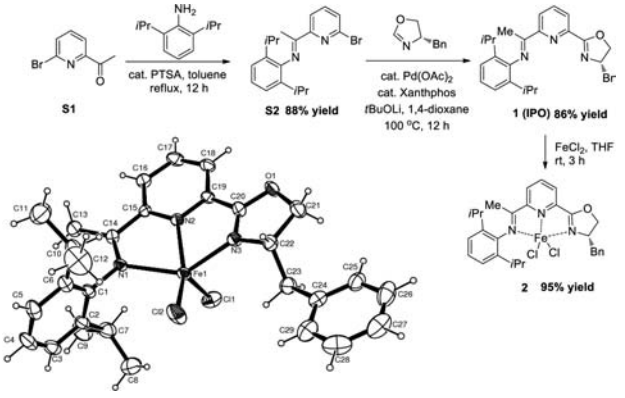


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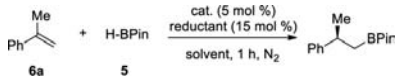
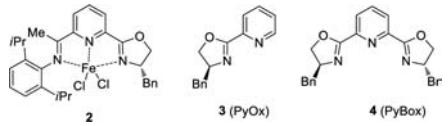
Table 1. Optimization Studies for Asymmetric Hydroboration of Alkenes

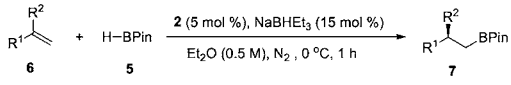


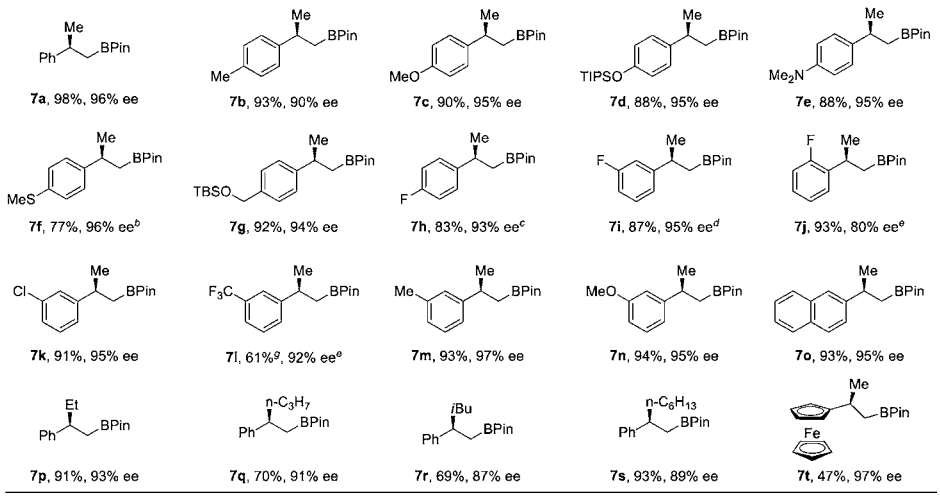
entry	cat.	solvent (M)	reductant	temp	yield (%)[a]	ee (%)[b]
1	**2**	THF (0.25)	Mg	rt	nr	–
2	**2**	THF (0.25)	Et_2Zn	rt	nr	–
3	**2**	THF (0.25)	EtMgBr	rt	nr	–
4	**2**	THF (0.25)	PhMgBr	rt	<20	83
5	**2**	THF (0.25)	$NaBHEt_3$	rt	26	92.9
6	**2**	toluene (0.25)	$NaBHEt_3$	rt	93 (85)	92.1
7	**2**	Et_2O (0.25)	$NaBHEt_3$	rt	88(81)	95
8	**2**	Et_2O (0.5)	$NaBHEt_3$	rt	98 (93)	95
9	**2**	Et_2O (1)	$NaBHEt_3$	rt	96 (83)	93.7
10	**2**	Et_2O (0.5)	$NaBHEt_3$	0	100(98)	96.0
11	**2**	Et_2O (0.5)	$NaBHEt_3$	−10	97(88)	95.7
12	**3**+$FeCl_2$	Et_2O (0.5)	$NaBHEt_3$	0	<5	–
13	**4**+$FeCl_2$	Et_2O (0.5)	$NaBHEt_3$	0	6	–
14	**1**+[Ru][c]	Et_2O (0.5)	$NaBHEt_3$	0	nr	–
15	**1**+[Ir][d]	Et_2O (0.5)	$NaBHEt_3$	0	nr	–

[a]Yields determined by ^1H NMR analysis using TMSbenzene as an internal standard. Isolated yield in parentheses. [b]ee values determined by chiral HPLC analysis. [c][Ru]: $Ru(PPh_3)_3Cl_2$. [d][Ir]: $[Ir(COD)Cl]_2$.



Scheme 2. Asymmetric *anti*-Markovnikov Hydroboration of Alkenes[a]





[a]Standard conditions: Unless otherwise noted, **6** (1 mmol), HBPin (0.5 mmol), **2** (0.025 mmol), $NaBHEt_3$ (0.075 mmol) in 1 mL of Et_2O at 0 °C under nitrogen for 1 h. [b] **2** (0.05 mmol), $NaBHEt_3$ (0.15 mmol). [c] Toluene instead of Et_2O at −10 °C. [d] Toluene instead of Et_2O. [e] **2** (0.05 mmol), $NaBHEt_3$ (0.15 mmol), toluene instead of Et_2O.

metals,[10] we used well-defined pyridylbisoxazoline (**4**) as the ligand. Unfortunately, the catalytic reactions did not work well. Subsequently, we attempted to combine the chiral oxazoline and imino group on the same molecule and designed a new type of chiral iminopyridine oxazoline ligand, in which the iminopyridine group is postulated to stabilize the iron and the chiral oxazoline group to control the enantioselectivity. The newly designed chiral iminopyridine oxazoline[11] ligand **1** can be easily synthesized from commercially available starting materials (Scheme 1). The iron complex **2** could be easily synthesized by combining iron dichloride with the corresponding ligand, identified by elemental analysis and X-ray,[12] and is stable under a nitrogen atomsphere up to a year.

We also studied the hydroboration of styrene **6a** with HBpin (**5**) to test the reactivity of our chiral iron complex **2** (IPO·$FeCl_2$). First, several reductants (entries 1−5, Table 1) were screened; Mg, Et_2Zn, and EtMgBr displayed poor reactivities (entries 1−3). The reaction using PhMgBr and $NaBHEt_3$ as reductants

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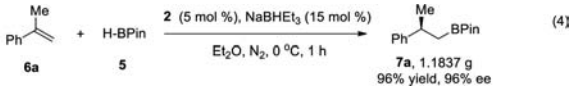
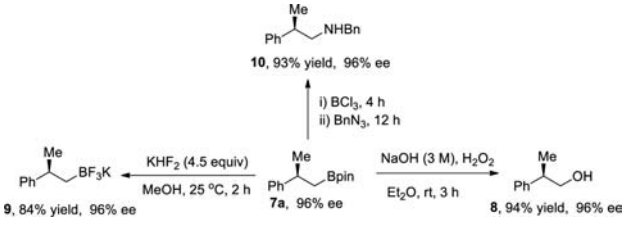
exhibited similar reactivities, but the latter displayed better enantioselectivity. To our delight, despite the modest reactivity, the regio- and enantioselectivity were excellent. Solvents play an important role in affecting reactivity (entries 5−7); good yields were obtained using both toluene and ether, and a slightly better enantioselectivity is observed in ether. The reaction concentration also had an effect on the reactivity with 0.5 M being the most optimal. The reaction at 0 °C increased the enantioselectivity; further decreasing the temperature did not lead to an improvement in the ee. The standard reaction conditions involve **6a** (1 mmol, 2 equiv), HBpin (0.5 mmol), **2** (5 mol %), and $NaBHEt_3$ (15 mol %) in Et_2O (1 mL) at 0 °C as the standard conditions. In addition, **7a** was observed in <5% or 6% yield when the catalyst was $FeCl_2$ with the Pyox ligand (entry 12) or Pybox ligand (entry 13); **7a** was not observed when the reaction was performed with ruthenium or iridium with the IPO ligand (entries 14 and 15), which shows iron with the novel IPO ligand is more efficient than noble transition metals.

With the optimal set of conditions, the scope of this reaction is shown in Scheme 2. We observed that the reaction can be successfully initiated with a variety of substituted styrenes, including electron-rich and -deficient styrenes. The reaction can tolerate protected phenol, aniline, thiophenol, and benzyl alcohol. *Para-*, *meta-*, or *ortho*-fluorinated α-methylstyrene can react in good yields and enantioselectivity. The reaction of chloro-styrene with HBpin gave exclusively hydroboration products without any dehalogenated sideproducts. Strongly electron-deficient substituents, such as the trifluoromethyl group, also led to high enantioselectivity (92% ee) and regioselectivity. Hydroboration of 2-(prop-1-en-2-yl)naphthalene gave **7o** in 93% yield with 95% ee. The reaction of α-alkyl-substituted styrenes proceeded smoothly to yield the corresponding products in good enantioselectivities (87−91% ee). Interestingly, ferrocenyl olefin **6t** can also undergo reaction to generate the chiral ferrocenyl derivative with excellent enantioselectivity.

This reaction can be easily scaled up smoothly to afford the desired product without compromising the yield (eq 4).



Scheme 3. Further Derivatizations



The chiral alkylboronic esters, which were easily isolated and bench-stable, can be further transformed into a variety of chiral compounds including alcohols, amines, and fluorated boronic derivatives (Scheme 3).

In conclusion, we have developed the iron-catalyzed, highly enantio- and regioselective *anti*-Markovnikov hydroboration of 1,1-disubstituted aryl alkenes with pinacolborane. This newly designed chiral iminopyridine oxazoline ligand, together with the environmentally benign iron catalyst, provides a highly efficient system compared to other noble transition metal catalytic systems in similar reactions. The reaction can be readily operated in a Schlenk line, not necessarily in a glovebox. A series of useful chiral borate compounds were easily synthesized and isolated with 100% atom efficiency under mild conditions. It is also an efficient way to construct a chiral carbon center at the benzyl position. Current efforts in our laboratory are underway to understand the mechanistic intricacies of this process and develop new base-metal-catalyzed asymmetric reactions based on the IPO ligand.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Unfortunately, during the time we were submitting the manuscript on our independent work, a similar result was reported by Zhang, L.; Zuo, Z.-Q.; Wan, X.-L.; Huang, Z. *J. Am. Chem. Soc.* **2014**, *136*, 15501. However, since November 14th, 2013, we used a different strategy for the synthesis of chiral iminopyridine oxazoline.
(12) CCDC number is 1029987.