

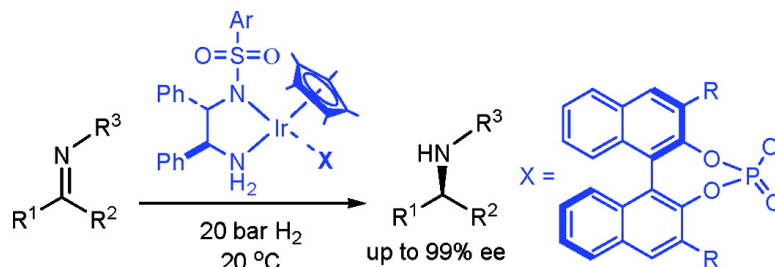
Communication

Chiral Counteranion-Aided Asymmetric Hydrogenation of Acyclic Imines

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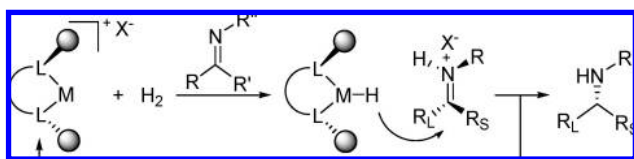
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Asymmetric hydrogenation of imines provides direct access to chiral amines, one of the most important functionalities in fine chemical, agrochemical, and pharmaceutical products.^{1,2} However, in terms of both enantioselectivity and substrate scope, this transformation remains challenging, particularly in the case of acyclic imines.^{1b,c} The vast majority of the transition metal catalysts reported thus far employ phosphorus-containing ligands, and it is generally believed that the reduction proceeds via imine nitrogen coordination to the metal center.^{1c} However, Norton recently showed that imines can be reduced through an ionic pathway, where a Ru(II)–H₂ complex is deprotonated by an amine and the resulting Ru(II)–H reduces preformed iminium salts.³ In more recent studies in organocatalysis,⁴ the groups of Rueping, List, and MacMillan reported highly enantioselective transfer hydrogenation with Hantzsch ester of imines^{4b,c} or imines in situ generated from ketones and amines;^{4d} the reduction is catalyzed by chiral phosphoric acids, which protonate the imines while the anion of which directs the facial attack of the hydride. Inspired by these discoveries, we envisioned that if a heterolitically hydrogen-activating catalyst⁵ is associated with a chiral counteranion, the latter may be exploited to influence the enantiodiscrimination of the chiral ligands by ion pairing with the resulting iminium cation (Scheme 1).⁶ We report herein that when combined with a chiral phosphate anion, diamine-ligated Ir(III) catalysts indeed enable highly enantioselective asymmetric hydrogenation of acyclic imines, affording up to 99% ee.

Scheme 1



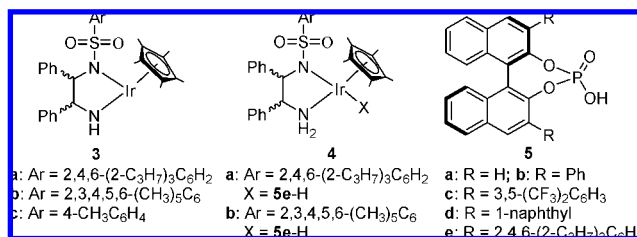
We recently found that the complex [Cp*Ir(TsDPEN-H)(H₂O)][SbF₆] acts as an excellent catalyst for asymmetric hydrogenation of cyclic imines.^{7–9} However, disappointing results were obtained with acyclic imines. Thus, in the reduction of the model imine 4-methoxy-*N*-(1-phenylethylidene)benzenamine **1a** at 20 bar H₂ in toluene, an ee of only 3% was observed at 20 °C. In contrast, the analogous Ir(III) complex led to encouraging results, affording a 22% ee. This prompted us to search for Cp*Ir(III) catalysts containing chiral phosphate anions. A quick way for accessing such catalysts is to protonate the 16e complex **3** with the phosphoric acid **5**,¹⁰ which is expected to in situ generate the catalyst **4**.¹¹ As can be seen from Table 1, while **3a** was inactive in hydrogenating **1a**, the combination of **3a** and **5a–e** delightfully led to conversions and enantioselectivities, which vary with the phosphoric acid used, with **5e** promoting an excellent ee of 97% (entry 6). The **3b–5e** and **3c–5e** couples were less enantioselective, however (entries 7–8). Remarkably, the phosphoric acids **5a,b** afforded the amine with the configuration opposite to that observed with **5c–e** (entries 2–3 vs 4–6), revealing the directing effect of phosphates on enantioselection. Still further, on changing the

Table 1. Optimization of Conditions for the Hydrogenation of **1a**^a

entry	catalyst	additive	conv. (%) ^b	ee (%) ^c
1	(<i>S,S</i>)- 3a	none	0	–
2	(<i>S,S</i>)- 3a	5a (6%)	53	17(<i>R</i>)
3	(<i>S,S</i>)- 3a	5b (6%)	57	26(<i>R</i>)
4	(<i>S,S</i>)- 3a	5c (6%)	40	20(<i>S</i>)
5	(<i>S,S</i>)- 3a	5d (6%)	43	38(<i>S</i>)
6	(<i>S,S</i>)- 3a	5e (6%)	60	97(<i>S</i>)
7	(<i>S,S</i>)- 3b	5e (6%)	76	92(<i>S</i>)
8	(<i>S,S</i>)- 3c	5e (6%)	30	81(<i>S</i>)
9	(<i>R,R</i>)- 3a	5e (6%)	47	38(<i>R</i>)
10	(<i>R,R</i>)- 3c	5e (6%)	27	3(<i>R</i>)
11	(<i>S,S</i>)- 4a	none	76	97(<i>S</i>)
12	(<i>S,S</i>)- 4a	5e (0.5%)	90	97(<i>S</i>)
13	(<i>S,S</i>)- 4a	5e (1%)	92	97(<i>S</i>)
14	(<i>S,S</i>)- 4a	5e (3%)	84	97(<i>S</i>)
15	(<i>S,S</i>)- 4a	5e (7%)	69	96(<i>S</i>)
16	(<i>S,S</i>)- 4a	5e (10%)	60	96(<i>S</i>)
17 ^d	(<i>S,S</i>)- 4a	5e (5%)	83	99(<i>S</i>)

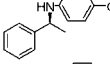
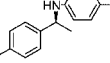
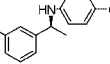
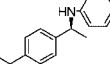
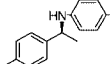
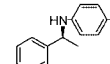
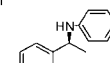
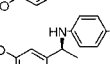
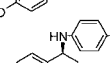
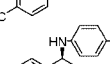
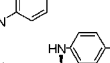
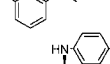
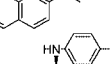
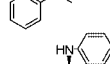
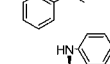
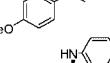
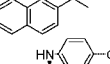
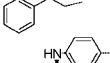
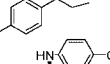
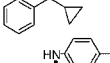
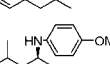
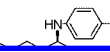
^a Reaction conditions: 0.5 mmol of **1a**, 1 mol% catalyst, 2 mL of toluene, 20 bar of H₂, 20 °C, 12 h. ^b Determined by ¹H NMR analysis of the crude product. ^c Determined by HPLC analysis; configuration assigned by comparison with the literature.^{2,4} ^d 10 °C, 18 h.

chirality of the diamine ligand, i.e. from (*S,S*)-**3a,c** to (*R,R*)-**3a,c**, a dramatic decrease in ee's (entries 6, 8 vs 9, 10) was recorded, showing the chirality of the catalyst needs to match that of its counteranion.



Having identified the bulky **5e** to be the best promoter for enantioselectivity among **5a–e**, we prepared the complex **4a**, which has the conjugate base of **5e** as the counteranion. Using **4a** as catalyst with no additional phosphoric acid, the hydrogenation of **1a** afforded the same ee as when the catalyst was in situ prepared from **3a** and **5e** (entries 6 vs 11). However, additional **5e** was found to affect the catalytic activity, with the highest conversion being observed at ca. 1 mol% **5e** (entries 12–16). A higher ee of 99% was obtained when the hydrogenation was performed at a lower temperature of 10 °C. As with reactions that involve ion-pairing intermediates,⁶ the hydrogenation is solvent-sensitive. Thus, lower ee's were observed in more polar solvents such as THF (92%) and MeCN (10%).

Table 2. Asymmetric Hydrogenation of Imines **1** to Amines **2**^a

Entry	imine	product	yield (%)	ee (%) ^b
1	1a		94	97
2	1b		93	97
3	1c		95	96
4	1d		94	98
5	1e		93	97
6	1f		94	96
7	1g		93	97
8	1h		92	97
9	1i		94	93
10	1j		93	92
11	1k		93	84
12	1l		96	98
13	1m		93	94
14	1n		94	95
15	1o		93	97
16	1p		94	95
17 ^c	1q		92	90
18 ^c	1r		93	91
19 ^c	1s		92	97
20 ^c	1t		88	95
21 ^{c,d}	1u		90	92
22 ^{c,d}	1v		91	94

^a Reaction conditions: 0.5 mmol of **1a**, 1 mol% **4a**, 1 mol% **5e**, 2 mL of toluene, 20 bar of H₂, 20 °C, 15–20 h. ^b Determined by HPLC analysis; *S* configuration, assigned by comparison with the literature.^{2,4} ^c *S,S*-**4b** as catalyst. With **4a**, the ee's were ca. 6% lower. ^d Configuration was assigned by analogy with entry 20.

Using the optimized conditions, i.e. 1 mol% **4a** or the analogous **4b** in the presence of 1 mol% **5e**, a range of acyclic imines were hydrogenated.¹² The results are given in Table 2. As can be seen, a wide spectrum of imines are hydrogenated with **4**, affording excellent yields and ee's in almost all the cases. Notably, the catalyst tolerates functional groups of diverse electronic properties (–OMe, –Br, –Cl, –CN, –NO₂, alkenyl, and cyclopropyl). Furthermore, it allows *N*-aryl ketimines with aryl ethyl groups (entries 17, 18) and with dialkyl substituents (entries 20–22) to be reduced with 90–97% ee's. In both metallo- and organocatalysis,^{1,2,4} such substrates have rarely proved to be viable. MacMillan,^{4d} List^{4c} and co-workers recently reported ee's of 81–94% for dialkyl-substituted *N*-aryl ketimines in organocatalytic reduction, but for related aryl alkyl ketimines with high enantioselectivities, the alkyl group appears to be restricted to a methyl.^{4d} Much lower enantioselectivities were reported for the dialkyl ketimines with homogeneous metal catalysts; in fact, none seems to give ee's higher than 80%.^{13,14}

In conclusion, we have developed an efficient catalytic system for asymmetric hydrogenation of the often-problematic acyclic imines. The catalyst is viable for a wide variety of imines and appears to operate via cooperative catalysis between a chiral metal catalyst and its chiral counteranion.

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Supporting Information Available: Experimental details and spectroscopy data (¹H, ¹³C NMR, and HPLC). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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