

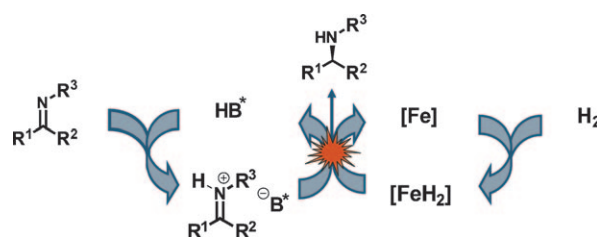
Cooperative Transition-Metal and Chiral Brønsted Acid Catalysis: Enantioselective Hydrogenation of Imines To Form Amines**

Shaolin Zhou, Steffen Fleischer, Kathrin Junge, and Matthias Beller*

Chiral amines are an integral part of numerous important bioactive compounds. This privileged structural motif is found in naturally occurring alkaloids and amino acid derivatives as well as in pharmaceuticals, herbicides, and insecticides.^[1] Typically, enantiomerically pure amines are key building blocks in the drug-discovery process, but they are also sold on a multi-hundred-ton-scale as kinetic-resolution reagents.^[2] With the growing importance of chiral compounds in the life-science industries, the development of efficient methodologies continues to be a topic of interest in organic chemistry and catalysis. Clearly, asymmetric hydrogenation has become a prime technology for the synthesis of chiral compounds.^[3–12] In this respect, the atom-efficient reaction of imines with inexpensive hydrogen to form amines has received much attention in recent years. The largest metal-catalyzed asymmetric process in industry today, the iridium-catalyzed hydrogenation in the production of metolachlor,^[3d] is a prime example of this methodology. Virtually all of the known catalyst systems employed for asymmetric hydrogenation are derived from precious late transition metals in combination with specific chiral phosphine ligands for the control of enantioselectivity.

An interesting alternative organocatalytic approach for the reduction of imines in the presence of chiral Brønsted acids was reported by the research groups of Rueping,^[13a–c] List,^[13d–g] MacMillan,^[13h] and Antilla.^[13i] Unfortunately, the requirement of stoichiometric amounts of expensive Hantzsch dihydropyridines as the hydrogen source has limited the application of this methodology. Over the past decade, the field of asymmetric Brønsted acid catalysis has grown at a dramatic pace. This form of catalysis provides new ways for the enantioselective preparation of various kinds of C–C, C–O, and C–N bonds.^[14] However, the majority of these methods are restricted to the generation of a stabilized carbocation and its direct reaction with active carbon- or heteroatom-based nucleophiles.

Herein, we describe a different approach involving the combination of a molecularly defined iron hydrogenation catalyst with a chiral Brønsted acid for the reduction of various imines with hydrogen to form the corresponding amines with high selectivity (Scheme 1).^[15] Conceptually, the



Scheme 1. Cooperative hydrogenation of imines with an iron/Brønsted acid catalyst system.

Brønsted acid catalyst and the organometallic center work together in a cooperative manner, in analogy with catalysis by iron-based hydrogenases.^[16] Notably, the levels of enantioselectivity observed with a simple iron catalyst rival those of the most efficient precious-metal-based systems.

To date, no catalytic hydrogenation of imines in the presence of nonchiral metal complexes has been reported to give the corresponding amines with high enantioselectivity.^[12–n,o,w] Potential problems with the envisioned reaction were the possible inadequate reactivity of the two components of the catalytic system: the organometallic complex and the Brønsted acid. The latter has to specifically activate the original substrate, whereas the former has to react with the activated intermediate. Furthermore, nonspecific deactivation reactions between the two components might compromise the desired overall process.

Owing to the industrial importance of 1-aryl ethylamines, our initial catalytic investigations were carried out on the hydrogenation of *N*-(1-phenylethylidene)aniline (**2a**) as a benchmark reaction (Table 1). According to our concept, we intended to use commercially available chiral 3,3'-bisaryl 1,1'-binaphthyl-2,2'-diyl hydrogen phosphates **1** for the induction of stereoselectivity.

Well-known homogeneous and heterogeneous hydrogenation catalysts were added to the reaction mixture to promote the desired catalytic reduction with hydrogen. Selected results are shown in Table 1. First experiments revealed that the desired *N*-(1-phenylethyl)aniline was formed in the presence of various Ru, Rh, Ir, and Pd catalysts (Table 1, entries 2–7). However, none of these established precious-metal hydrogenation catalysts in combination with chiral Brønsted acids, for example, 3,3'-bis(2,4,6-triisopropyl-

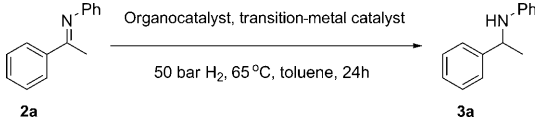
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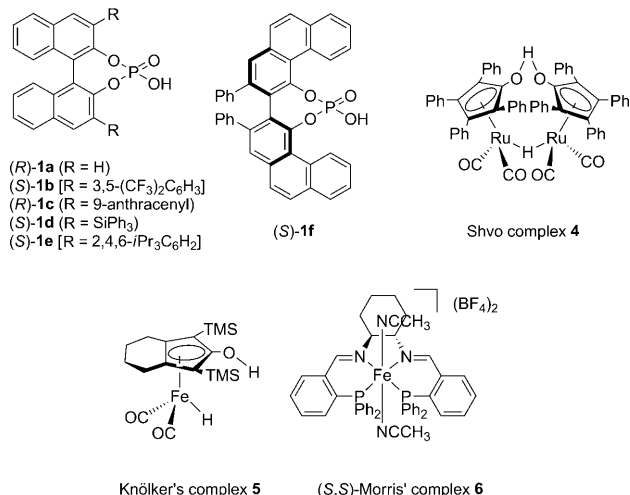
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Table 1: Initial investigations of the proposed asymmetric hydrogenation.^[a]

					
Entry	Brønsted catalyst (mol %)	Transition-metal catalyst (mol %)	Conv. ^[b] [%]	Yield ^[b] [%]	ee ^[c] [%]
1	1e (5)	—	80	0	—
2	1e (1)	4 (0.5)	> 99	71	8
3	1e (1)	[(Ph ₃ P) ₃ RhCl] (1)	> 99	45	0
4	1e (1)	[Rh(CO)H(PPh ₃) ₃] (1)	97	3	0
5	1e (1)	[{IrCl(C ₈ H ₁₂) ₂ } ₂] (0.5)	> 99	62	0
6	1e (1)	Rh/C (1)	> 99	16	0
7	1e (1)	Pd/C (1)	> 99	35	0
8	1e (1)	[Fe ₃ (CO) ₁₂] (1.67)	> 99	93	0
9	1e (1)	[(C ₈ H ₈)Fe(CO) ₃] (5)	> 99	0	—
10	1e (1)	6 (5)	85	0	—
11	1e (1)	5 (5)	> 99	81	94
12	1e (1)	FeCl ₃ (5)	98	0	—
13	1e (1)	Fe(OAc) ₂ (5)	98	0	—
14	1a (1)	5 (5)	76	35	0
15	1b (1)	5 (5)	54	40	47
16	1c (1)	5 (5)	23	12	41
17	1d (1)	5 (5)	25	6	30
18	1f (1)	5 (5)	15	8	4
19	1e (1)	5 (3)	> 99	63	94
20 ^[d]	1e (1)	5 (5)	98	71	94

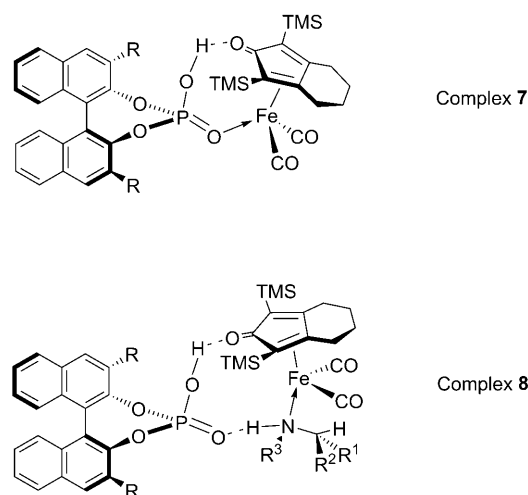
[a] Reaction conditions: **2a** (0.5 mmol), Brønsted catalyst (1–5 mol %), transition-metal catalyst (1–5 mol %), toluene (0.2 mL), H₂ (50 bar), 65 °C, 24 h. [b] The conversion and the yield were determined by GC methods with hexadecane as an internal standard. [c] The ee value was determined by HPLC on a chiral stationary phase. [d] H₂ (20 bar). TMS = trimethylsilyl.



phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP, **1e**), induced any significant enantioselectivity. This behavior is easily explained: the corresponding Ru-, Rh-, Ir-, and Pd-catalyzed hydrogenations of imine **2a** also took place without any Brønsted acid present (see Table S1 in the Supporting Information). Notably, the differences between conversion and product yield resulted from aldol condensation reactions, which are observed as unwanted side reactions in the presence of Rh, Ir, and Pd catalysts (Table 1, entries 3–7).

A number of active iron hydrogenation and transfer-hydrogenation catalysts have been developed in the last decade.^[17,18] We thus turned our interest to the performance of these biorelevant complexes.^[19] To our surprise, even simple triiron dodecacarbonyl generated an active catalyst with **1e** and provided the corresponding amine in 93 % yield. Unfortunately, again no stereoselectivity was observed. The use of other simple iron salts or the Morris complex **6** led to no amine at all. However, dicarbonylhydro[2,5-di(trimethylsilyl)-3,4-butylene-1-hydroxy(η⁵-cyclopentadienyl)]iron (**5**), which was first synthesized by Knölker et al.,^[20] yielded *N*-phenyl-1-phenylethylamine in 81 % yield with 94 % ee (Table 1, entry 11)! The combination of **5** with other chiral phosphates also created active catalysts; however, the reaction yields and enantioselectivities were lower (Table 1, entries 14–18). Excellent enantioselectivities were also observed at lower pressure (20 bar) and with a smaller amount of the iron catalyst **5** (3 mol %; Table 1, entries 19 and 20).

In situ NMR spectroscopic investigations of a 1:1 mixture of TRIP and the Knölker iron complex at the reaction temperature (65 °C) showed immediate formation of hydrogen and the coordinated species **7** (Scheme 2, Figure 1 d). This



Scheme 2. Proposed reaction intermediates. R = 2,4,6-*i*Pr₃C₆H₂.

reaction also proceeded slowly at room temperature and could be reversed by the addition of hydrogen. Upon the addition of *N*-(1-phenylethylidene)aniline (**2a**) to a 1:1 mixture of TRIP and the Knölker iron complex **5**, the corresponding iron–amine complex **8** was observed as the major reaction product alongside **7** (Figure 1 e). The TRIP–amine adduct and the Knölker iron complex **5** were observed upon hydrogenation (Figure 1 f). The ee value measured for the amine was 98 % both before and after hydrogenation.

Encouraged by these results, we studied the general use of this cooperative catalyst system in more detail. Various aromatic ketimines were hydrogenated smoothly in high yields and with excellent enantioselectivity (Table 2). Both electron-donating and electron-withdrawing substituents on the aromatic rings at *meta* or *para* positions had little impact

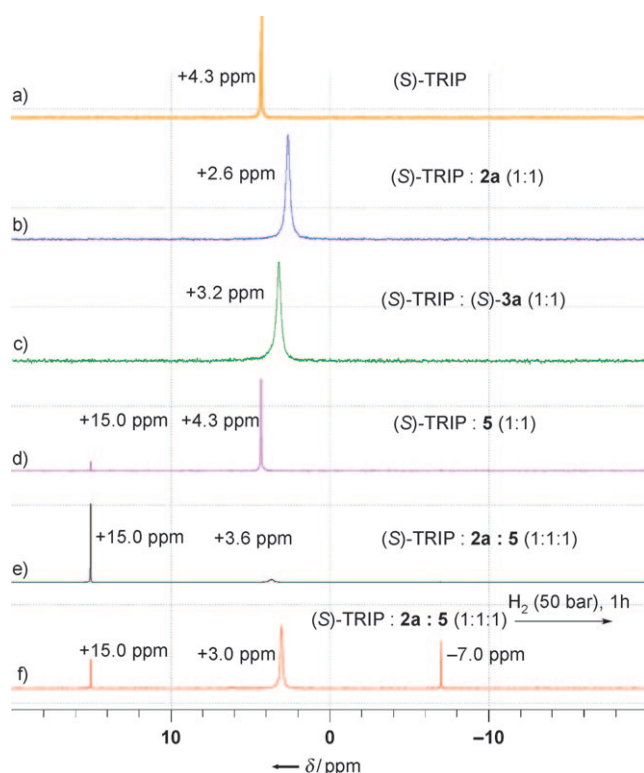


Figure 1. In situ ^{31}P NMR spectra of (S)-TRIP, iron complex **5**, imine **2a**, and amine **3a** in different ratios: a) pure (S)-TRIP; b) 1:1 mixture of (S)-TRIP and imine **2a** (spectrum shows the generation of an iminium phosphate salt); c) 1:1 mixture of (S)-TRIP and amine (S)-**3a** (spectrum shows the generation of an ammonium phosphate salt); d) 1:1 mixture of (S)-TRIP and iron complex **5** at room temperature (spectrum shows the generation of a small amount of intermediate **7** (3%)); e) 1:1:1 mixture of (S)-TRIP, imine **2a**, and complex **5** (spectrum shows the generation of intermediates **7** and **8**); f) reaction mixture after the hydrogenation reaction (spectrum shows the generation of an ammonium phosphate salt).

Table 2: Scope of the iron-catalyzed asymmetric hydrogenation of *N*-aryl imines.^[a]

$\text{R}^1\text{R}^2\text{C}=\text{N}-\text{R}^3 \xrightarrow[50 \text{ bar H}_2, \text{ toluene, } 65^\circ\text{C, } 24\text{h}]{1 \text{ mol\% (S)-TRIP, } 5 \text{ mol\% } \mathbf{5}} \text{R}^1\text{R}^2\text{CH}-\text{N}(\text{R}^3)$			
Entry	Imine	Yield ^[b] [%]	<i>ee</i> ^[c] (S) [%]
1		2a 3a : 82 (80)	94
2		2b 3b : 84 (82)	96
3		2c 3c : 84 (82)	95
4		2d 3d : 88 (60)	93

Table 2: (Continued)

Entry	Imine	Yield ^[b] [%]	<i>ee</i> ^[c] (S) [%]
5		2e 3e : 87 (70)	93
6		2f 3f : 99 (90)	92
7		2g 3g : 92 (68)	91
8		2h 3h : 70 (67)	93
9		2i 3i : 96 (86)	90
10		2j 3j : 94 (89)	88
11		2k 3k : 96 (86)	93
12		2l 3l : 80 (71)	91
13		2m 3m : 91 (91)	93
14		2n 3n : 80 (71)	91
15		2o 3o : 99 (93)	80
16		2p 3p : 87 (79)	98
17 ^[d]		2q 3q : 99 (91)	83
18 ^[d]		2r 3r : 99 (93)	81
19 ^[d]		2s 3s : 99 (94)	67
20 ^[d]		2t 3r : 89 (69)	70

[a] General reaction conditions: imine (0.5 mmol), (S)-TRIP (1 mol%), **5** (5 mol%), H_2 (50 bar), 65°C , 24 h. [b] The yield was determined by ^1H NMR spectroscopic analysis with dibromomethane as an internal standard. The yield of the pure isolated product is given in brackets. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] (S)-TRIP: 2 mol%, **5**: 2.5 mol%. PMP = *p*-methoxyphenyl.

on the hydrogenation activity; high enantioselectivity was observed for unsubstituted as well as *meta*- and *para*-substituted 2-aryl ethylamines (88–96% *ee*; Table 2, entries 1–12). Gratifyingly, heteroaromatic imines and *N*-heteroaryl-substituted imines were also reduced with excellent enantioselectivity (91–98% *ee*; Table 2, entries 13, 14, and 16).

Acetophenonimines are typical substrates for asymmetric hydrogenation. We were also interested in the behavior of our system with less common, more challenging substrates. The reduction of aliphatic imines occurred with high enantioselectivity (67–83% *ee*; Table 2, entries 17–20). Notably, in case of the α,β -unsaturated imine **2t**, no reduction of the conjugated double bond was observed.

In conclusion, we have demonstrated the possibility of performing enantioselective reduction reactions with hydrogen without the use of precious-metal catalysts and chiral ligands. Instead, the combination of an iron complex with chiral acids enabled smooth hydrogenation. It was shown that both components of the catalyst system act in a cooperative manner reminiscent of biocatalysis.

Experimental Section

All hydrogenation experiments were carried out in a Parr Instruments 4560 series autoclave (300 mL) containing an alloy plate with wells for seven 4 mL glass vials.

Typical procedure: In a glovebox under an argon atmosphere, imine **2a** (98 mg, 0.5 mmol), (*S*)-TRIP (3.7 mg, 0.005 mol), complex **5** (9.8 mg, 0.025 mmol), toluene (0.2 mL), and a magnetic stir bar were placed in a vial, which was then capped with a septum equipped with a syringe. The vial was placed in the alloy plate, which was then placed in the predried autoclave. Once sealed, the autoclave was purged three times with hydrogen, then pressurized to 50 bar and heated at 65 °C for 1 day. The autoclave was then cooled to 5 °C and depressurized, and the reaction mixture was transferred to a flask. A 1 M solution of KOH in methanol (0.1 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant: hexane/ethyl acetate 10:1) to give the corresponding amine **3a** (79 mg, 80%), which was analyzed by HPLC to determine the *ee* value.

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