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Towards a Zinc-Catalyzed Asymmetric Hydrogenation/Transfer Hydrogenation of Imines

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Abstract: The first asymmetric hydrogenation/transfer hydrogenation of imines to amines using zinc(II) triflate in combination with chiral ligands is described. The monodentate binaphthophosphepine ligand (**3g**) provided the highest enantioselectivities. Using different imines, the corresponding amines were obtained in moderate yields and enantioselectivities.

Keywords: asymmetric synthesis · amines · hydrogenation · imines · zinc

Introduction

The development of improved methods for the synthesis of enantiomerically pure amines is of continuing industrial and academic interest owing to their importance in agrochemicals, pharmaceuticals, chiral auxiliaries, and biological systems.[1,2] Notably, in 2010 more than 45% of the top 200 brand-name drugs by US retail sales contained at least one stereogenic center, and 20% of which represented chiral amines. Selected examples of these products are shown in Figure 1.[3]

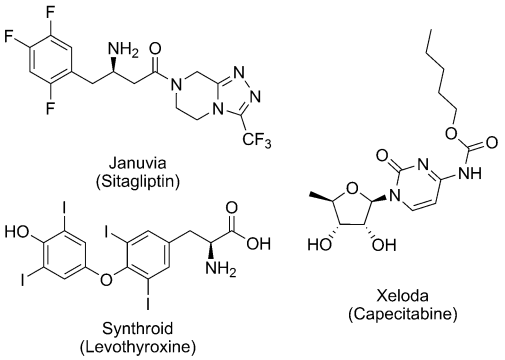


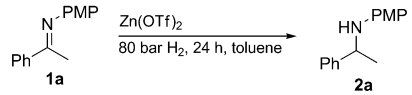
Figure 1. Selection of the top 200 brand-name drugs by US retail sales in 2010.

Among the different catalytic methods known for the asymmetric synthesis of amines, hydrogenation of imines/enamines is an important and environmentally friendly approach.[4–6] In the past decades, impressive progress has been achieved especially using precious metal-based catalysts, for example, Ir,[7] Ru,[8] Rh,[9] and Pd[10] complexes. However, catalytic hydrogenations with non-precious metal complexes are far less developed. During our investigations on iron-catalyzed enantioselective imine hydrogenations,[11] we discovered that similar reductions proceed in the presence of catalytic amounts of simple zinc(II) triflate.[12] Most recently, we were able to perform atom-efficient reductive hydroaminations of alkynes with this unique catalyst. However, to the best of our knowledge no asymmetric hydrogenations using zinc catalysts are known. Herein, we describe the first examples of both zinc-catalyzed hydrogenations and transfer hydrogenations of imines to amines.

Results and Discussion

While testing different Lewis acids for the hydrogenation of *para*-methoxy-*N*-(1-phenylethylidene)aniline **1a** (*p*-methoxyphenyl = PMP) to give the corresponding amine **2a**, to our surprise $Zn(OTf)_2$ was discovered as a suitable catalyst.[12] In Table 1, selected reactions from the previous optimization studies are shown. For example, using 5 mol% of simple $Zn(OTf)_2$ without any ligand at 100 °C afforded **2a** in 72% yield (Table 1, entry 1). By increasing the catalyst loading to 10 mol% **2a** was obtained in 95% yield (Table 1,

Table 1. Optimization of zinc triflate as a hydrogenation catalyst.[a]



Entry	$Zn(OTf)_2$ [mol%]	*T* [°C]	Conv. [%][b]	Yield [%][b]
1	5	100	83	72
2	10	100	95	95
3	**5**	**120**	**>99**	**92**
4	2	120	74	47
5	1	120	38	4

[a] Reaction conditions: **1a** (0.5 mmol), $Zn(OTf)_2$, toluene (0.5 mL), H_2 (80 bar), *T*, 24 h. [b] Conversion and yield were determined by GC methods using hexadecane as an internal standard.

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entry 2). On the other hand, at 120 °C in the presence of 5 mol % of $Zn(OTf)_2$, **1a** was converted into **2a** with a similar product yield of 92 % (Table 1, entry 3). To perform the enantioselective hydrogenation reactions,[13] we used $Zn(OTf)_2$ in combination with a variety of chiral nitrogen- and phosphorous-based ligands for the enantioselective reduction of *N*-(1-*p*henylethyl)aniline **1b**. As shown in Figure 2, we initially tested different chiral P-containing ligands, which are well-known for hydrogenation reactions.[13a,i,14] Without any ligand, the hydrogenation of **1b** to **2b** proceeded in 87 % isolated yield. However, employing chiral P-ligands such as **3a**–**3j** decreased the product yield significantly. The highest yield of 61 % was achieved with the bidentate ligand (*S,S*)-deguphos (**3b**), while the observed enantiomeric excess with this ligand was only 12 %. Increasing the ligand loading to 10 mol %, the desired amine **1b** was produced in 46 % yield and 17 % *ee*.

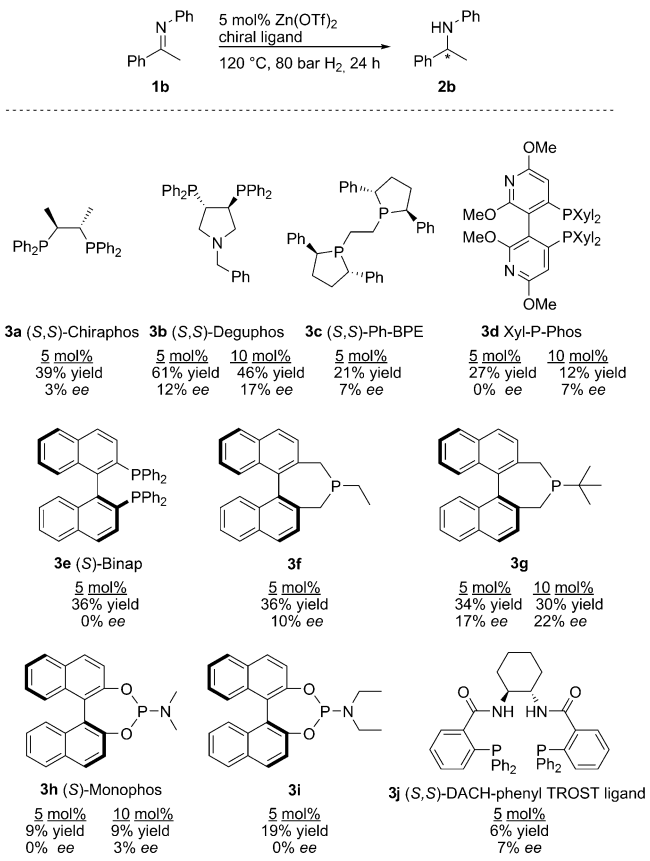

Figure 2. Zn-catalyzed hydrogenation of **1b** in the presence of different chiral P-containing ligands **3** (GC yields are presented).

In the presence of other chiral P-ligands such as **3a**, **3c**–**3f**, and **3h**–**3j**, low to moderate yields between 6 % and 39 % were observed as well as low enantioselectivities of up to 10 % *ee*. However, using 5 mol % of the monodentate binaphthophosphepine ligand **3g** gave a moderate yield of 34 % and 17 % *ee*. The enantiomeric excess could be increased to 22 % by using a higher concentration of the phosphepine ligand **3g**. Unfortunately, repeating the reaction with combinations of $Zn(OTf)_2$/**3g** or **3b** at 80 °C did not afford amine **2b**. Hence, a correlation between enantioselectivity and reaction temperature can therefore not be discussed. Temperatures >100 °C are required for the activation of molecular hydrogen mediated by $Zn(OTf)_2$. Furthermore, it should be noted that the low yields resulted mostly from aldol condensations of the imine **1b**, which were observed as side reactions.

Next, we tested different N-containing ligands such as pyridinebisoxazoline (pybox) and pyridinebisimidazoline (pybim; Figure 3); these ligands have recently been employed successfully for enantioselective zinc-catalyzed hydrosilylations and ruthenium-catalyzed transfer hydrogenations of ketones.[13a,15] Unfortunately, either traces or no amine **2b** was formed in the presence of **4a**–**e**, **5a,** and **5b**. Additionally, three different diamine ligands were tested. The product **2b** was obtained in 30 % yield with an enantioselectivity of 13 % using ligand **6a**. The reaction gave a similar yield (31 %) and *ee* (11 %) in the presence of **6c**. The hemilabile ligand **7a** gave a moderate yield of 22 %, however, the *ee* was significantly lower (5 %).

As none of the tested chiral ligands revealed satisfying results, we considered the use of chiral Brønsted acids as co-catalysts. Recently, chiral 1,1′-binaphthalene-2,2′-diol phosphoric acids have been used successfully in the enantioselective reduction of C=X bonds using Hantzsch esters as reducing agents.[16] Consequently, we combined zinc(II) triflate with different phosphoric acids **8** for the hydrogenation of imine **1b** (Table 2). The highest yield (31 %) of amine **2b** was obtained using (*R*)-TRIP **8d** as the ligand, albeit racemically. Notably, in the presence of H_8-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **8e** almost no hydrogenation took place. The chiral Brønsted acids **8a**–**8c** and **8f** led to low product yields between 10 % and 26 %; a chiral induction of up to 15 % *ee* was detected for **8a** (Table 2, entry 1). To prove the highest possible enantioselectivity with the tested ligands, we performed hydrogenation experiments of *N*-(1-phenylethylidene)-aniline (**1b**) using stoichiometric amounts of zinc(II) triflate with ligands **3b**, **3g**, and **3h**. As shown in Scheme 1, good yields between 72 % and 84 % of **2b** were achieved. In the presence of ligand **3b** only a slight increase in the *ee* from 17 % to 19 % was obtained, and **3h** produced amine **2b** as a racemate. However, the best enantioselectivity of 37 % *ee* was achieved with $Zn(OTf)_2$/**3g**. Reducing the temperature to 80 °C to obtain higher enantioselectivity

Abstract in German: Die ersten asymmetrischen Hydrierungen bzw. Transfer-hydrierungen von Iminen zu Aminen in Gegenwart von Zinktriflat und chiralen Liganden werden beschrieben. Beste Enantioselektivitäten werden mit dem Binaphthophosphepin-Liganden **3g** erhalten. Verschiedene Imine konnten so zu den entsprechenden Aminen mit moderaten Ausbeuten und Enantioselektivitäten umgesetzt werden.

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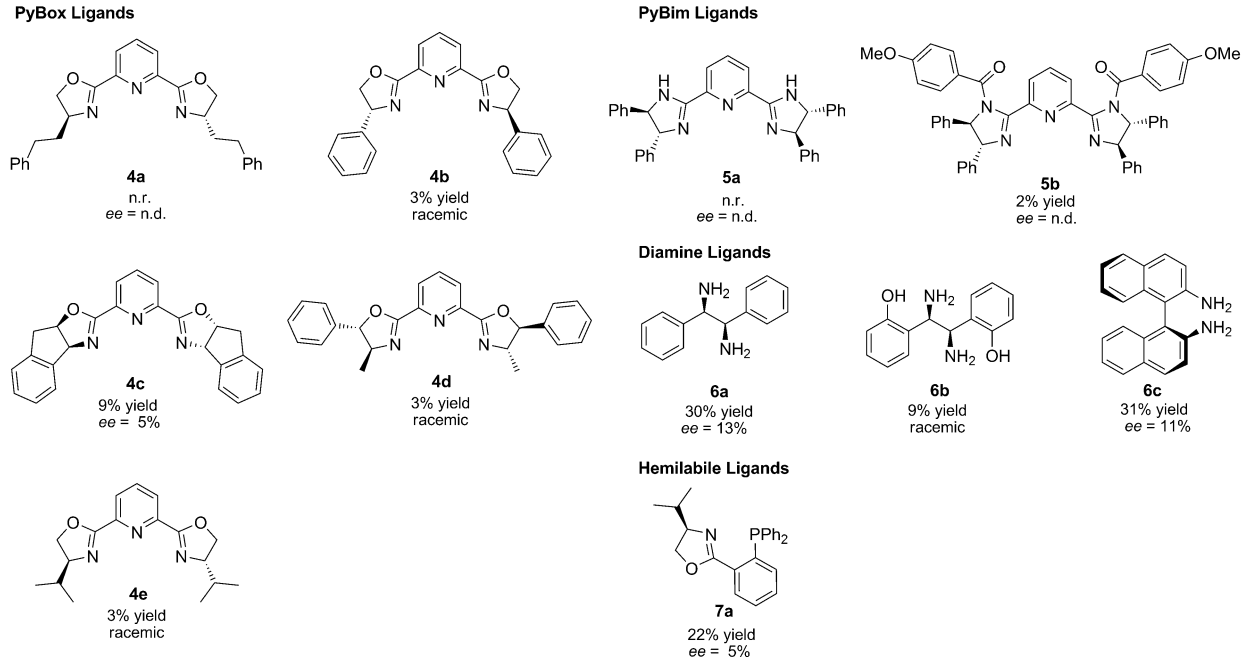
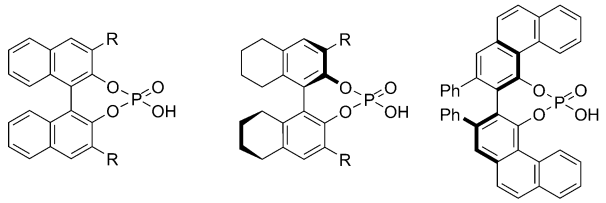


Figure 3. Different chiral N-containing ligands **4**, **5**, **6**, and **7** for imine hydrogenation reactions (GC yields are presented).

Table 2. Variation of different chiral Brønsted acids for the hydrogenation of imine **1b**.[a]



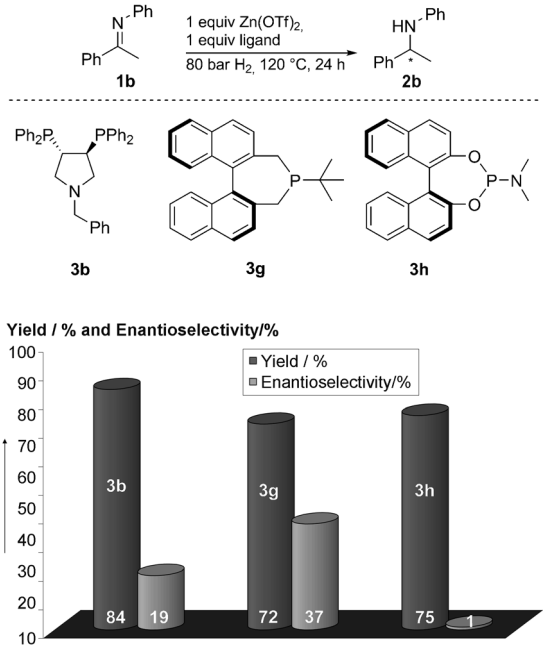
(*R*)-**8a** (R = 9-anthracenyl)
(*S*)-**8b** (R = 3,5-$(CF_3)_2$-C_6H_3)
(*S*)-**8c** (R = $SiPh_3$)
(*S*)-**8d** (R = 2,4,6-(*i*Pr)$_3C_6H_2$)

(*R*)-**8e** (R = 2-naphthyl)

(*R*)-**8f**

Entry	Brønsted acid [mol%]	Yield of **2b** [%][b]	*ee* [%][c]
1	**8a**	10	15
2	**8b**	26	5
3	**8c**	16	racemic
4	**8d**	31	racemic
5	**8e**	3	n.d.
6	**8f**	17	7

[a] Reaction conditions: **1b** (0.25 mmol), $Zn(OTf)_2$, Brønsted acid **8**, toluene (1 mL), H_2 (80 bar), 120 °C, 24 h. [b] The yield was determined by GC methods using hexadecane as an internal standard. [c] The *ee* was determined by chiral HPLC analysis. n.d. = not determined.



Scheme 1. Reduction of **1a** with stoichiometric amounts of $Zn(OTf)_2$ and selected ligands.

using $Zn(OTf)_2$/**3g** led to a lower yield (14%) of **2b** with an enantioselectivity of 34% *ee*. Noticeably, the lower temperature reduces the yield, whereas the enantiomeric excess remains nearly the same as that at 120 °C (37% *ee*).

These results indicate that a non-asymmetric reduction of the imine mediated by $Zn(OTf)_2$ takes place in parallel to the enantioselective hydrogenation catalyzed by $Zn(OTf)_2$/**3g**. Possibly, the former catalytic reaction proceeds at a similar rate or the chiral catalyst system $Zn(OTf)_2$/**3g** is not stable during the reaction.

Obviously, $Zn(OTf)_2$ is a unique hydrogenation catalyst. However, as already discussed in our previous work,[12] we analyzed $Zn(OTf)_2$ by inductively coupled plasma spectrometry, where no detectable amounts of Ru, Rh, Ir, and Pd were observed. Furthermore, several samples of $Zn(OTf)_2$

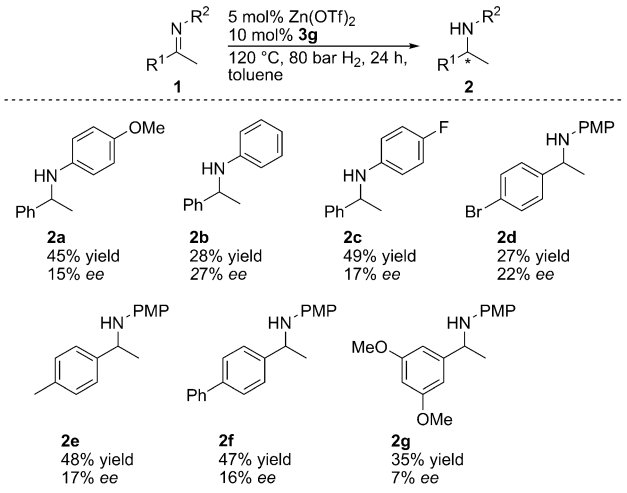


Figure 4. Substrate scope of the Zn/**3g**-catalyzed hydrogenation of imines.

from various suppliers showed identical results for the hydrogenation of **1a** to **2a**.

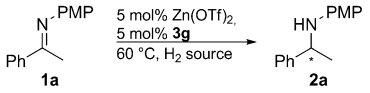
Finally, the optimized catalyst system was applied in the reduction of seven different imines **1** to the corresponding amines **2**. As shown in Figure 4, the hydrogenation of different *meta*- and *para*-substituted aromatic imines bearing electron-donating as well as electron-withdrawing groups gave the corresponding amines in low to moderate isolated yields between 28% and 49%.

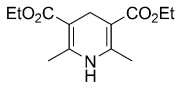
Furthermore, a disubstitued substrate was employed to furnish the desired amine **2g** (Figure 4). Notably, the achieved enantiomeric excesses (up to 27%) are not satisfying for synthetic applications. Nevertheless, to our knowledge, these reactions constitute the first examples of enantioselective zinc-catalyzed hydrogenations.

To perform the catalytic hydrogenation under milder reaction conditions, we also tested typical transfer hydrogenation reagents (Table 3). Besides, a typical Hantzsch ester, which gave nearly full conversion after 1 h (Table 3, entry 1), both *i*PrOH/KO*t*Bu and HCOOH/NEt_3 have been used as hydrogen donors. Using *i*PrOH as the hydrogen source and KO*t*Bu as the base resulted in no reaction (Table 3, entries 2 and 3). HCOOH/NEt_3 produced the amine **2a** in a low yield of 7% after 1 h and in 8% yield after 24 h (Table 3, entries 4 and 5), thus showing that the catalyst is not stable under these reaction conditions.

Unfortunately, no enantioselectivity was observed using the Hantzsch ester in the presence of zinc(II) triflate and different ligands (Table 4). Notably, in the absence of $Zn(OTf)_2$ and ligand, no reaction was observed.

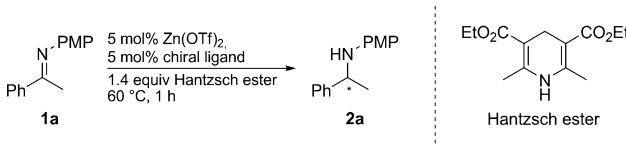
Table 3. Zn-catalyzed transfer hydrogenation of imine **1a**.



Entry	H_2 source	t [h]	Yield[c] [%]	ee[d] [%]
1[a]	 Hantzsch ester	1	95	racemic
2[b]	*i*PrOH/KO*t*Bu	1	–	n.d.
3[b]	*i*PrOH/KO*t*Bu	24	–	n.d.
4[b]	HCOOH/NEt_3	1	7	racemic
5[b]	HCOOH/NEt_3	24	8	racemic

[a] Reaction conditions: **1a** (0.5 mmol), 5 mol% $Zn(OTf)_2$, 5 mol% **3g**, Hantzsch ester (0.7 mmol, 1.4 equiv), toluene (1 mL), 60 °C for 1 h. [b] Reaction conditions: **1a** (0.5 mmol), 5 mol% $Zn(OTf)_2$, 5 mol% **3g**, *i*PrOH (1 mL)/10 mol% KO*t*Bu or HCOOH/NEt_3 (1 mL), 60 °C for 1 h. [c] Yield determined by GC methods using hexadecane as an internal standard. [d] The *ee* was determined by chiral HPLC analysis.

Table 4. Transfer hydrogenation of imine **1a** with Hantzsch ester.[a]



Entry	$Zn(OTf)_2$ [mol%]	Ligand [mol%]	T [°C]	Yield[b] [%]	ee[b] [%]
1	–	–	60	–	–
2	2	**3b** [5]	60	80	racemic
3	2	**3g** [5]	60	90	racemic
4	2	**6a** [5]	60	89	racemic
5	1	**3g** [5]	60	90	racemic
6	3	**3g** [5]	60	93	5
7	5	**3g** [5]	60	95	racemic
8	5	–	80	>99	–
9	5	**3g** [5]	80	97	racemic
10	5	**3g** [10]	80	98	racemic
11	2	**3g** [5]	80	93	racemic

[a] Reaction conditions: **1a** (0.25 mmol), $Zn(OTf)_2$ (5 mol%), chiral ligand, Hantzsch ester (0.7 mmol, 1.4 equiv), toluene (1.0 mL), 60 °C for 1 h. [b] Yield determined by GC methods using hexadecane as an internal standard. [c] The *ee* was determined by chiral HPLC analysis.

Conclusions

The first enantioselective zinc-catalyzed hydrogenations of imines are presented. Moderate to good yields are obtained in the presence of different Zn/phosphine catalyst systems, although the obtained enantioselectivities of up to 27% *ee* are too low to be synthetically useful. Nevertheless, our work demonstrates for the first time that such asymmetric hydrogenations are possible. We hope that this work will inspire other research groups to improve the stereoselectivity with improved ligands. In addition, zinc-catalyzed transfer hydrogenations of imines using a Hantzsch ester as a reducing agent are demonstrated.

Experimental Section

Unless otherwise stated, all reactions were carried out under an argon atmosphere with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. All isolated compounds were characterized by ^1H NMR and ^{13}C NMR spectrosco-

py, high resolution mass spectrometry (HRMS), and HPLC. NMR spectra were recorded on Bruker AV 300 or AV 400 spectrometers. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are related to solvent peaks (chloroform: 7.26 (^{1}H), 77.00 (^{13}C)). All measurements were carried out at room temperature unless otherwise stated. Mass spectra were generally recorded on a Finnigan MAT 95-XP (Thermo Electron) or on a 6210 Time-of-Flight LC/MS (Agilent). Gas chromatography was performed on a HP 6890 with a HP5 column (Agilent). The enantioselectivities were recorded with chiral HPLC on a HP 1100 (Hewlett Packard) or with a chiral GC on HP6890 (Hewlett Packard/Agilent).

General Information

Unless otherwise stated, commercial reagents were used without purification. All catalytic hydrogenation experiments using molecular hydrogen were carried out in a Parr Instruments 4560 series autoclave (300 mL) containing an alloy plate with wells for seven 4 mL glass vials.

Non-Asymmetric Hydrogenation of Imines with Hydrogen

Under an argon atmosphere, a glass vial was charged with $Zn(OTf)_2$ (9.1 mg, 0.025 mmol), imine **1a** (0.5 mmol), toluene (0.5 mL), and a magnetic stirring bar. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 80 bar and heated at 120 °C for 24 h to give the corresponding amine **2a**. After the reaction had finished, the autoclave was cooled to 25 °C, depressurized, and the reaction mixture was analyzed by GC.

Asymmetric Hydrogenation of Imines with Hydrogen

Under an argon atmosphere, a glass vial was charged with $Zn(OTf)_2$ (4.5 mg, 0.0125 mmol), chiral ligand **3**, **4**, **5**, **6**, **7**, or **8** (0.0125 or 0.025 mmol), imine **1** (0.25 mmol), toluene (1 mL), and a magnetic stirring bar. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 80 bar and heated at 120 °C for 24 h to give the corresponding amine **2**. After the reaction had finished, the autoclave was cooled to 25 °C, depressurized, and the yield was determined by GC and the *ee* by HPLC or chiral GC.

Asymmetric Hydrogenation of Imines with Hydrogen–Substrate Scope

Under an argon atmosphere, a glass vial was charged with $Zn(OTf)_2$ (4.5 mg, 0.0125 mmol), chiral ligand **3g** (0.025 mmol), imine **1** (0.25 mmol), toluene (1 mL), and a magnetic stirring bar. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 80 bar and heated at 120 °C for 24 h to give the corresponding amine **2**. After the reaction had finished, the autoclave was cooled to 25 °C, depressurized, and the reaction mixture was purified by column chromatography on silica gel (heptane/ethyl acetate = 9:1). The isolated compounds **2a**–**2f** were then analyzed by NMR spectroscopy, HRMS, and HPLC or chiral GC.

Asymmetric Hydrogenation of Imines with Hantzsch Ester

Under an argon atmosphere, a glass vial was charged with $Zn(OTf)_2$ (4.5 mg, 0.0125 mmol), chiral ligand **3b**, **3g**, or **6a** (0.0125 mmol), imine **1a** (0.25 mmol), Hantzsch ester (1.4 equiv, 0.7 mmol), toluene (1 mL), and a magnetic stirring bar. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate. The reaction mixture was heated up to 60 °C for 1 hour to give the corresponding amine **2a**. After the reaction had finished, the yield was determined by GC and the *ee* with chiral HPLC.

Asymmetric Hydrogenation of Imines with iPrOH/KOtBu or HCOOH/NEt_3

Under an argon atmosphere, a glass vial was charged with $Zn(OTf)_2$ (4.5 mg, 0.0125 mmol), chiral ligand **3g** (0.0125 mmol), imine **1a** (0.25 mmol), *i*PrOH (1 mL)/10 mol % KO*t*Bu or $HCOOH/NEt_3$ (1 mL), and a magnetic stirring bar. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate. The reaction mixture was heated up to 60 °C for 1 hour to give the corresponding amine **2a**. After the reaction had finished, the yield was determined by GC and the *ee* with chiral HPLC.

Acknowledgements

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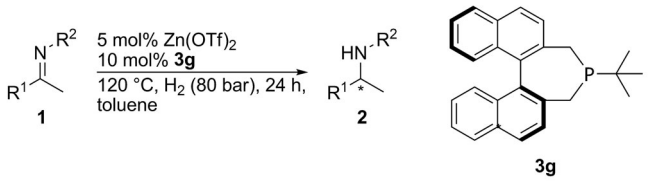

Let′s do it with Zinc: The first examples of zinc-catalyzed enantioselective hydrogenations of imines to amines are presented with moderate to good yields.

Hydrogenation

*Svenja Werkmeister, Steffen Fleischer, Kathrin Junge, Matthias Beller** _____ ▮▮▮▮–▮▮▮▮

Towards a Zinc-Catalyzed Asymmetric Hydrogenation/Transfer Hydrogenation of Imines

