

Leibniz-Institut für Katalyse e. V. an der Universität Rostock

# **Development of New Homogeneous (Enantioselective) Hydrogenation Catalysts Based on Bio-relevant Metals**

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Universität Rostock

Abstract

## **Development of New Homogeneous (Enantioselective) Hydrogenation Catalysts Based on Bio-relevant Metals**

by Shaolin Zhou

Leibniz-Institut für Katalyse e.V. an der Universität Rostock

This thesis presents the study and development of new catalysts based on first row transition metals for the (asymmetric) reduction of different C=O and C=N bonds. In addition, an unprecedented dehydration of primary amides to nitriles catalyzed by iron complexes or TBAF is presented.

An iron cluster catalyst with a chiral tetradentate  $P_2N_2$  ligand was discovered to catalyze the asymmetric transfer hydrogenation of *N*-diphenylphosphinylketimines. A variety of ketimines, including aromatic, heteroaromatic and cyclic imines were hydrogenated smoothly with high yields up to 98% and good to excellent enantioselectivities up to 98% *ee*.

The combination of a chiral Brønsted acid with a well-defined Shvo type iron complex (Knölker's Iron complex) creates an active catalyst which could hydrogenate a variety of *N*-aryl ketimines to amines using molecular hydrogen. Not only aryl alkyl ketimines but also more challenging dialkyl ketimines could be hydrogenated to corresponding amines with good yields and excellent *ee*'s.

An iron cluster catalyst catalyzes the reduction of secondary and tertiary amides with inexpensive PMHS. The new protocol proceeds with high selectivity and exhibits a broad substrate scope and functional group tolerance providing a variety of amines in good to excellent yields.

# Entwicklung Neuartiger (Enantioselektiver) Homogener Hydrierkatalysatoren auf Basis Biologisch Relevanter Metalle

von Shaolin Zhou

Leibniz-Institut für Katalyse e.V. an der Universität Rostock

Die vorgelegte Arbeit zeigt die Entwicklung neuartiger Katalysatoren auf der Basis von 3d-Übergangsmetallen zur Reduktion verschiedener C=O und C=N Bindungen. Darüber hinaus wird eine unerwartete Dehydratisierung von primären Amiden zu Nitrilen mit Hilfe von Eisenkomplexen und TBAF präsentiert.

Es wurde ein Eisenclusterkomplex mit einem chiralen P<sub>2</sub>N<sub>2</sub> Liganden entwickelt, der die asymmetrische Transferhydrierung von *N*-Diphenylphosphinylketiminen katalysiert. Eine Reihe von Ketiminen, darunter aromatische, heteroaromatische und zyklische Imine, wurden mit hohen Ausbeuten von bis zu 98% und guten bis exzellenten Enantioselektivitäten von bis zu 98% ee reduziert.

Die Kombination einer chiralen Brønsted-Säure mit einem definierten Eisenkomplex (Knölkers Eisenkomplex), welcher ähnlich dem rutheniumbasierten Shvo-Komplex ist, führt zu einem aktiven Katalysator, der eine Reihe von *N*-Aryl-Ketiminen zu Aminen hydriert. Es wurden nicht nur Aryl-Alkyl-Ketimine, sondern auch die schwerer zu reduzierenden Dialkyl-Ketimine zu den entsprechenden Aminen mit guten Ausbeuten und exzellenten Enantioselektivitäten hydriert.

Ein Eisenclusterkomplex katalysiert die Reduktion von sekundären und tertiären Amiden mit PMHS als preisgünstiges Reduktionsmittel. Die entwickelte Methode führt zu hohen Selektivitäten und zeigt eine hohe Substratanwendungsbreite sowie eine hohe Toleranz gegenüber funktionellen Gruppen. Eine Reihe von Aminen wurden in guten bis exzellenten Ausbeuten erhalten.

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## List of Abbreviations

Ac	acetyl
Ar	aryl
BINOL	1,1'-Bi-2-naphthol
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
bipy	bipyridine
Bn	benzyl
BTC	1,3,5-benzenetricarboxylate
<sup>t</sup> Bu	<i>tert</i> -butyl
CTAB	cetyltrimethylammonium bromide
cod	cycloocta-1,5-diene
Cy	cyclohexyl
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMPS	Dimethylphenylsilane
<i>ee</i>	enantiomeric excess
Et	ethyl

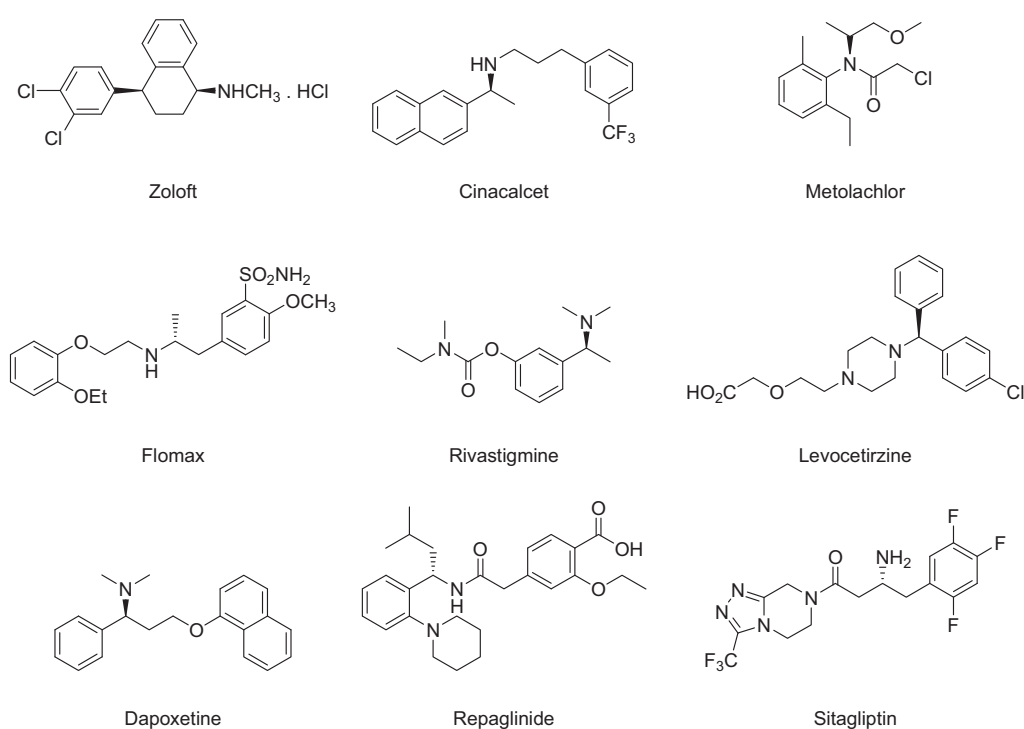


HPLC	high performance liquid chromatography
<i>i</i> -Pr	isopropyl
L	ligand
<i>m</i> -, <i>o</i> -, <i>p</i> -	<i>meta</i> -, <i>ortho</i> -, <i>para</i> -
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
NADH	nicotinamide adenine dinucleotide
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	acetate
OMe	methoxy
OMs	mesylate (methanesulfonate)
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate ( <i>p</i> -toluenesulfonate)
Ph	phenyl
PMHS	polymethylhydrosiloxane
PMP	<i>p</i> -methoxyphenyl
P(O)Ph <sub>2</sub>	Diphenylphosphinyl
Py	pyridine
rf	reflux
TBAF	tetra- <i>n</i> -butylammonium fluoride

TFA	trifluoroacetate	
THF	tetrahydrofuran	
TMDS	1,1,2,2-tetramethyldisilane	
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine	
TOF	turnover frequency; [TOF] = 1 h <sup>-1</sup>	
TON	turnover number	
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl phosphate	hydrogen
Xy	xylyl	

## 1 Introduction

Enantiomerically pure chiral amines are of increasing commercial value in the fine chemical and pharmaceutical areas in view of their application as resolving agents, chiral auxiliaries/chiral bases and catalysts for asymmetric synthesis. Moreover, chiral amines often possess pronounced biological activity in their own right, and hence are significant demand as intermediates for pharmaceuticals and agrochemicals (Fig. 1) in an expanding market where revenues due to chiral technologies are expected to reach US\$ 14.9 billion by 2009.



**Figure 1.** Selected pharmaceuticals and agrochemicals containing chiral amines.

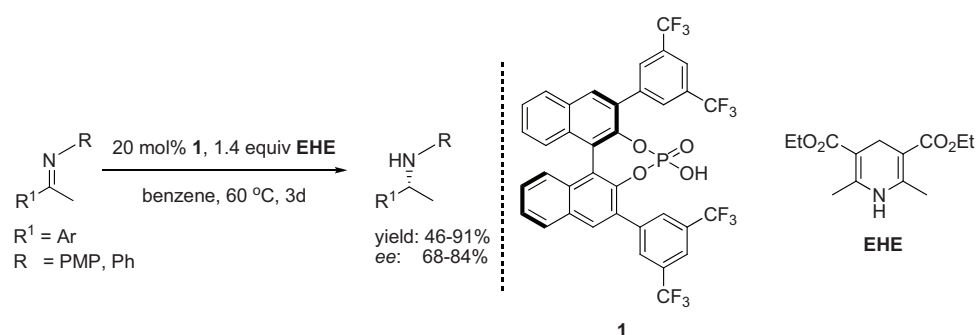
### 1.1 Asymmetric reduction of imines

The synthesis of enantiomerically enriched amines from prochiral ketimines is the most direct and efficient way.<sup>1</sup> Although significant progress has been made in the asymmetric hydrogenation of prochiral olefins and ketones over the last few decades, the asymmetric hydrogenation of prochiral ketimines remains a major challenge.

### 1.1.1 Organocatalytic asymmetric reduction of imines

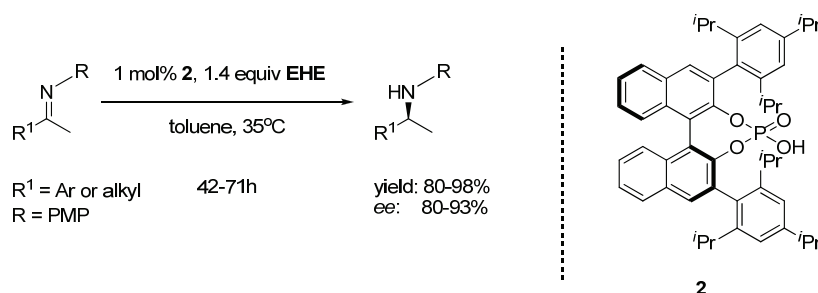
Living organisms employ organic dihydropyridine cofactors such as nicotinamide adenine dinucleotide (NADH) in combination with enzyme catalysts for the reduction of imines. Inspired by nature, List made the first proposal of asymmetric reduction of imines with Hantzsch esters in the presence of a chiral Brønsted acid catalyst in 2004. At the same year, the inventions of chiral Brønsted acid derived from BINOL by Akiyama and Tereda<sup>2</sup> paved the way for the asymmetric organocatalytic transformation.

In 2005, Rueping and co-workers demonstrated the first asymmetric transfer hydrogenation of ketimines using one Akiyama-Tereda catalyst **1** in combination with a Hantzsch ester (Scheme 1). A variety of ketimines derived from aryl methyl ketones and *p*-methoxyaniline were reduced to afford corresponding amines in 46-91% yield with 68-84% *ee*.<sup>3</sup>



**Scheme 1.** Organocatalytic asymmetric transfer hydrogenation of imines by Rueping.

Shortly after Rueping's report, List and co-workers reported a similar but significantly improved protocol using a sterically more hindered form of Akiyama-Tereda catalyst **2** (TRIP) (Scheme 2).<sup>4</sup> Remarkable features of List's process are shorter reaction times, higher yields

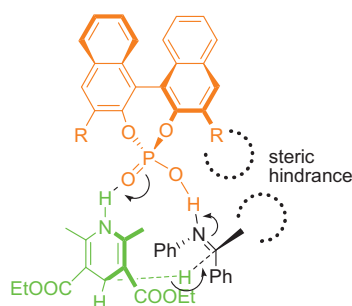


**Scheme 2.** Organocatalytic asymmetric transfer hydrogenation of imines by List.

## 1 Introduction

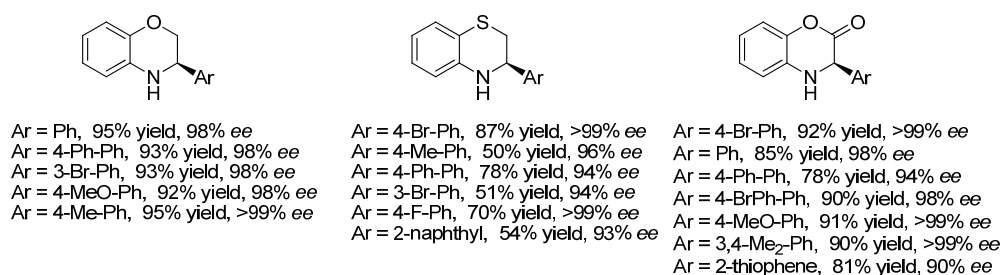
and *ees* based on substrate comparisons of the two studies. They also showed that one ketimine derived from isopropyl methyl ketone and *p*-methoxyaniline could be reduced to corresponding amine in 80% yield with 90% *ee*.

With regard to the mechanism of chiral Brønsted acid-catalyzed asymmetric transfer hydrogenation of ketimines with Hantzsch ester as hydrogen donor, Goodman and co-workers proposed “a three-point contact model” reaction mechanism based on calculations.<sup>5</sup> The model considers three interactions between the catalyst and the transition state structure: the phenylimine, in *Z* conformation if possible, is complexed to the catalyst (**first point interaction**) leaving the more sterical demanding groups towards the less hindered sites of the catalyst (**second point interaction**); the Hantzsch ester is then complexed to the other phosphoric acid oxygen of the catalyst (**third point interaction**), and hydride transfer takes place from this face (Fig. 2).



**Figure 2.** Goodman's three-point contact model.

Clearly, the asymmetric reduction of heterocyclic imines represents an attractive route to enantioenriched cyclic amines. A chiral Brønsted acid has been shown to catalyze the reduction of benzoxazines, benzothiazines, benzoxazinones with Hantzsch ester as hydride donor (Scheme 3).<sup>6</sup>

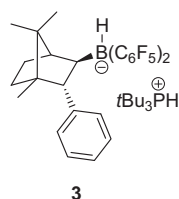


**Scheme 3.** Results of organocatalytic asymmetric transfer hydrogenation of cyclic imines.

## 1 Introduction

Notably, this protocol works well even with low catalyst loading (0.01 mol%). For the first time organocatalysis showed both high enantioselectivity and high activity and productivity in a process.

In 2010, Klankermayer and co-workers employed a chiral frustrated Lewis Pairs<sup>7</sup> **3** (Fig. 3) to catalyze the asymmetric hydrogenation of *N*-aryl ketimines.<sup>8</sup> Here, six ketimines were reduced with good *ee*'s (74-83% *ee*).

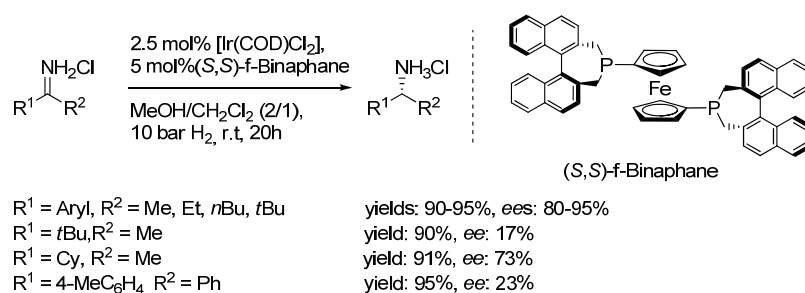


**Figure 3.** Klankermayer developed chiral frustrated Lewis Pairs for asymmetric hydrogenation of imines.

### 1.1.2 Transition metal catalyzed asymmetric reduction of imines

#### 1.1.2.1 Unprotected ketimines

In 2009, Zhang and co-workers developed the first highly enantioselective hydrogenation of unprotected *N*-H ketimines.<sup>9</sup> A variety of aryl alkyl imine hydrochloride salts were hydrogenated to afford corresponding primary amines in excellent enantioselectivities and high yields by using an Ir-binaphane catalyst. Other dialkyl imines and diaryl imine were reduced in low *ees* (Scheme 4).

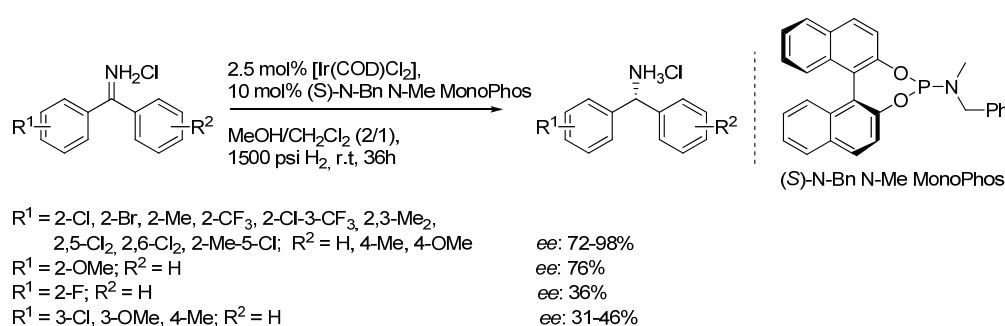


**Scheme 4.** Asymmetric hydrogenation of protect-free ketimines.

Interestingly, a negative impact on activity and enantioselectivities of the catalyst was observed, when the chloride in phenyl methyl imine hydrochloride salt was replaced with noncoordinating counterions, for example Cl<sup>-</sup> (99 conv., 95% *ee*), methanesulfonate (75%

## 1 Introduction

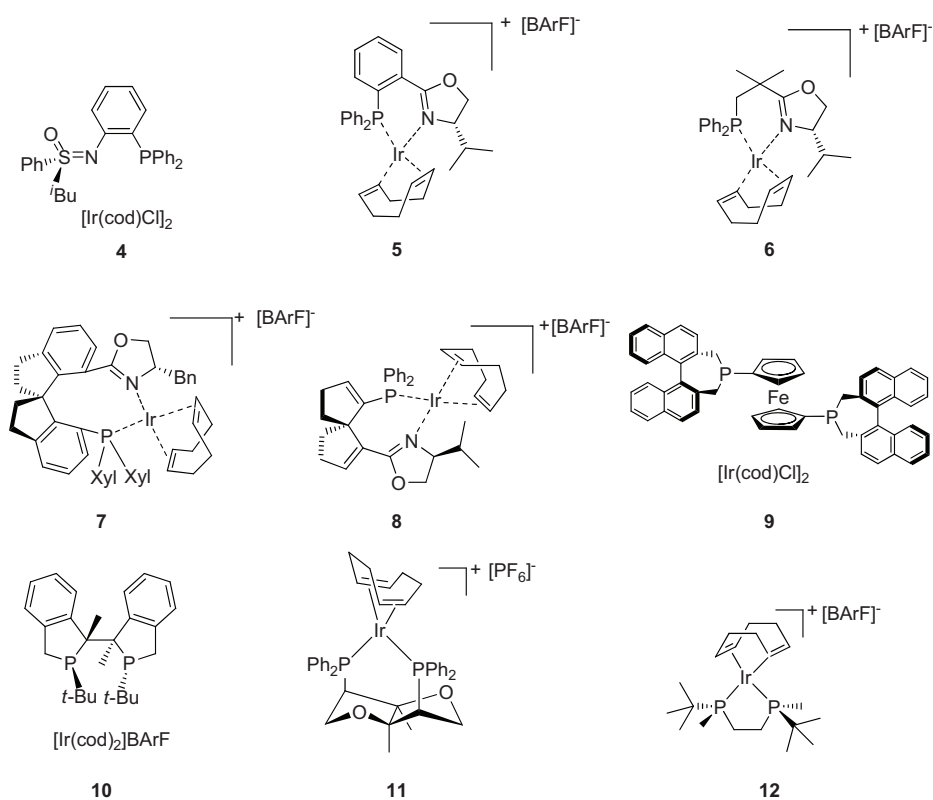
conv., 51% *ee*), PF<sub>6</sub><sup>-</sup> (90% conv., 91% *ee*), BF<sub>4</sub><sup>-</sup> (99 conv., 88% *ee*). Subsequently, the same group applied the protect-free strategy to diaryl imines using an [Ir(COD)Cl]<sub>2</sub> as iridium precursor with a monodentate BINOL-derived phosphoramidites ligand.<sup>10</sup> Excellent yields were obtained for all the benzophenone N-H imine hydrochloride salts (82-96%), but enantioselectivities were somewhat sensitive to the steric and electronic nature of the substituent at the *ortho* position. For example chloro, bromo, methyl, trifluoromethyl substituents at 2-position gave high enantioselectivities (82-98% *ee*). Decreased enantioselectivities were observed with coordinating 2-methoxy and smaller 2-fluoro substituents (76% and 36% *ee*, respectively). Substituents at the *meta* or *para* position led to significant decrease in enantioselectivities (31-46% *ee*) (Scheme 5).



**Scheme 5.** Asymmetric hydrogenation of substituted benzophenone N-H imines.

### 1.1.2.2 N-Arylimines

Since the chiral P,N ligands are successfully applied to Ir-catalyzed asymmetric hydrogenation of *N*-aryl ketimines by Pfaltz and co-workers,<sup>11</sup> the synthesis and applications of chiral P,N ligands in Ir-catalyzed hydrogenation of imines have attracted particular attention. An Ir-diphenylphosphanylsulfoximine catalyst **4** (Fig. 4) was introduced by Bolm for the asymmetric hydrogenation of *N*-arylimines in 2005.<sup>12</sup> High enantioselectivities (69-98% *ee*) were observed for a variety of *N*-(4-methoxy)phenylimines under optimized conditions. One of the interesting features of their system is the influence of iodide. No reaction occurred in the absence of iodine. Besides the substituent attached to nitrogen had a strong effect on the performance of the catalyst. For example, the introduction of a methoxy group at the 2-position of the *N*-aryl group led to lower enantioselectivity, and the introduction of 2,4,6-trimethyl groups on the *N*-aryl ring of the substrate resulted no reaction.



**Figure 4.** Catalysts for asymmetric hydrogenation of *N*-arylimines.

A new chiral phosphine-oxazoline ligand SIPHOX with a rigid and bulky spirobiindane scaffold were synthesized by Zhou and co-workers in 2006.<sup>13</sup> Cationic complexes of [Ir-SIPHOX]<sup>+</sup> [BArF]<sup>-</sup> **7**, a chiral analogues of the Crabtree catalyst were generated and examined in hydrogenation of *N*-arylimines. The Ir-SIPHOX complex could catalyze the hydrogenation of *N*-aryl ketimines with excellent enantioselectivities (90-97% *ee*) and full conversions.

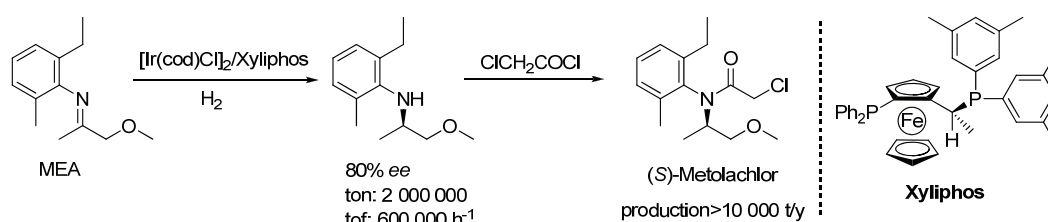
Inspired by the success of Pfaltz's PHOX ligands **5** and **6** and Zhou's SIPHOX **7** in Ir-catalyzed asymmetric hydrogenation of imines, Ding and co-workers developed a new class of chiral phosphine-oxazoline ligands (SpinPHOX) based on spiro[4,4]-1,6-nonadiene backbone. A cationic Ir-SpinPHOX complex **8** was found highly efficient in hydrogenation of a broad range of *N*-aryl ketimines.<sup>14</sup>

In industry, today's largest application of asymmetric hydrogenation of ketimines is the production of the herbicide (*S*)-metolachlor. An Ir/XyliPhos catalyst achieved unprecedented ton's of 2 000 000 and *tof* values around 600 000 h<sup>-1</sup> (Scheme 6).<sup>15</sup> Subsequently, several effective Ir/diphosphine catalysts were developed, such as Ir/*f*-binaphane **9** and Ir/Duanphos



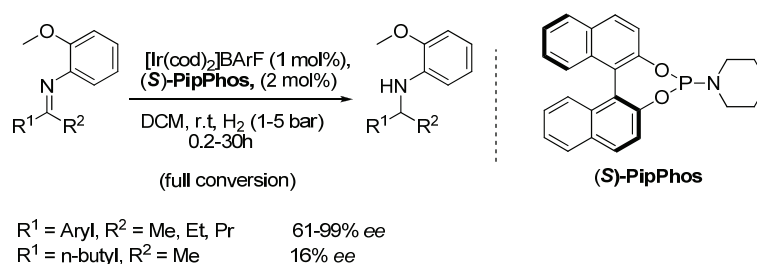
## 1 Introduction

**10** catalysts by Zhang,<sup>16</sup> Ir/<sup>t</sup>Bu-BisP catalyst **11** by Imamoto<sup>17</sup> and Ir/ddppm catalyst **12** by Dervisi.<sup>18</sup>



**Scheme 6.** Industrial process for synthesis of (S)-Metolachlor.

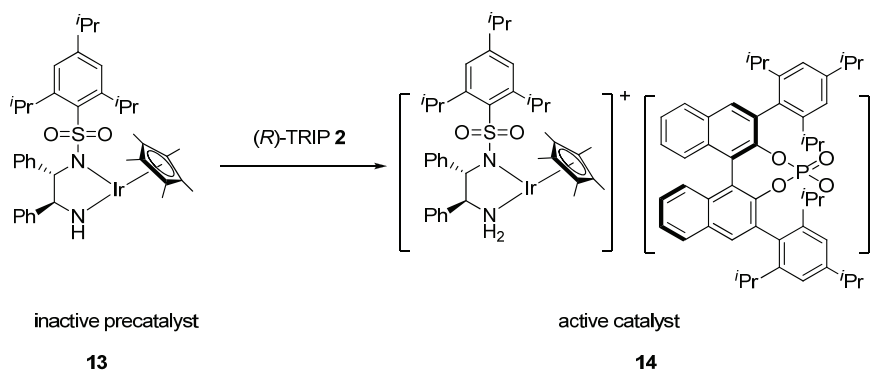
In 2009, de Vries and co-workers reported a highly enantioselective asymmetric hydrogenation of *N*-(2-methoxy)phenylimines using a readily available BINOL-derived (S)-PipPhos as chiral ligand and  $[\text{Ir}(\text{cod})_2]\text{BARf}$  as iridium precursor (Scheme 6).<sup>19</sup> Their initial experiments revealed that the nature of the counteranion on the iridium precursors and the *N*-aryl moiety of the imines influence the behavior of the catalyst. Compared to the neutral  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (no conv.), cationic precursors such as  $[\text{Ir}(\text{COD})_2]\text{PF}_6$  (>99% conv., 64% ee) and  $[\text{Ir}(\text{cod})_2]\text{BARf}$  (>99% conv., 87% ee) gave significantly higher enantioselectivity and conversions in the hydrogenation of phenyl methyl *N*-phenylimine. The introduction of a methoxy group in 2-position of *N*-aryl ring led to excellent enantioselectivity.



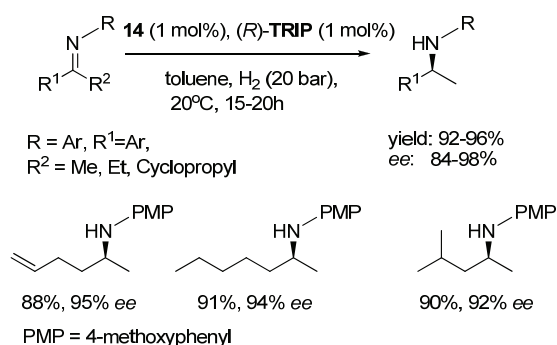
**Scheme 7.** Asymmetric hydrogenation of *N*-2-MeO-phenyl imines.

Xiao and coworkers used protonated diamine-Ir complexes by a chiral Brønsted acid such as (*R*)-TRIP **2** (Fig. 5) to facilitate the asymmetric hydrogenation of *N*-aryl ketimines (Scheme 8).<sup>20</sup> Not only aryl alkyl *N*-arylimines but also more challenging dialkyl *N*-arylimines could be hydrogenated to give corresponding amines in high yields with excellent enantioselectivities (84-98% ee).

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**Figure 5.** Activation of diamine-Ir catalyst by protonation from chiral Brønsted acid.

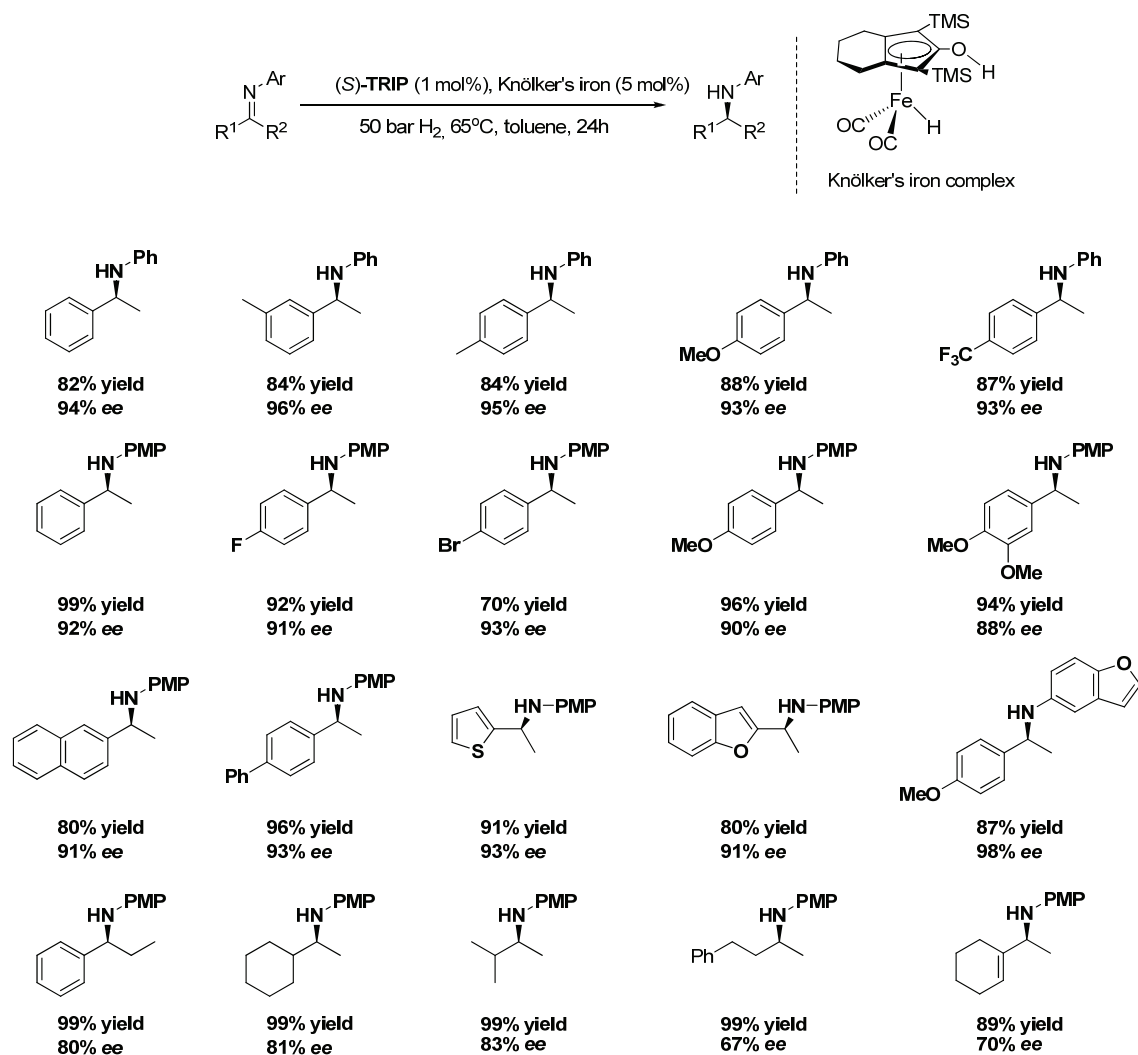


**Scheme 8.** Asymmetric hydrogenation of *N*-aryl imines.

In our group we described a different approach by combining a molecular-defined organometallic hydrogenation catalyst with chiral Brønsted acids for the hydrogenation of various imines to form highly selectively the corresponding amines. Conceptually, the Brønsted acid co-catalyst and the organometallic centre are working together in cooperative manner similar to iron-based hydrogenases. Until to date, no catalytic hydrogenations of imines in the presence of non-chiral metal complexes have been reported that give the corresponding amines with high enantioselectivity. Problems of the envisioned reaction are the adequate reactivity of the two components of the catalytic system: the organometallic complex and the Brønsted acid. While the latter acid has to react specifically with the original substrate, the former has to react with the activated intermediate. Furthermore, unspecific deactivation reactions between the two components might rival the desired activation processes. According to our concept we thought to realize the stereoselective induction by using chiral Brønsted acid catalysts. To achieve catalytic reduction, well-known homogeneous and heterogeneous hydrogenation catalysts were added to the reaction

## 1 Introduction

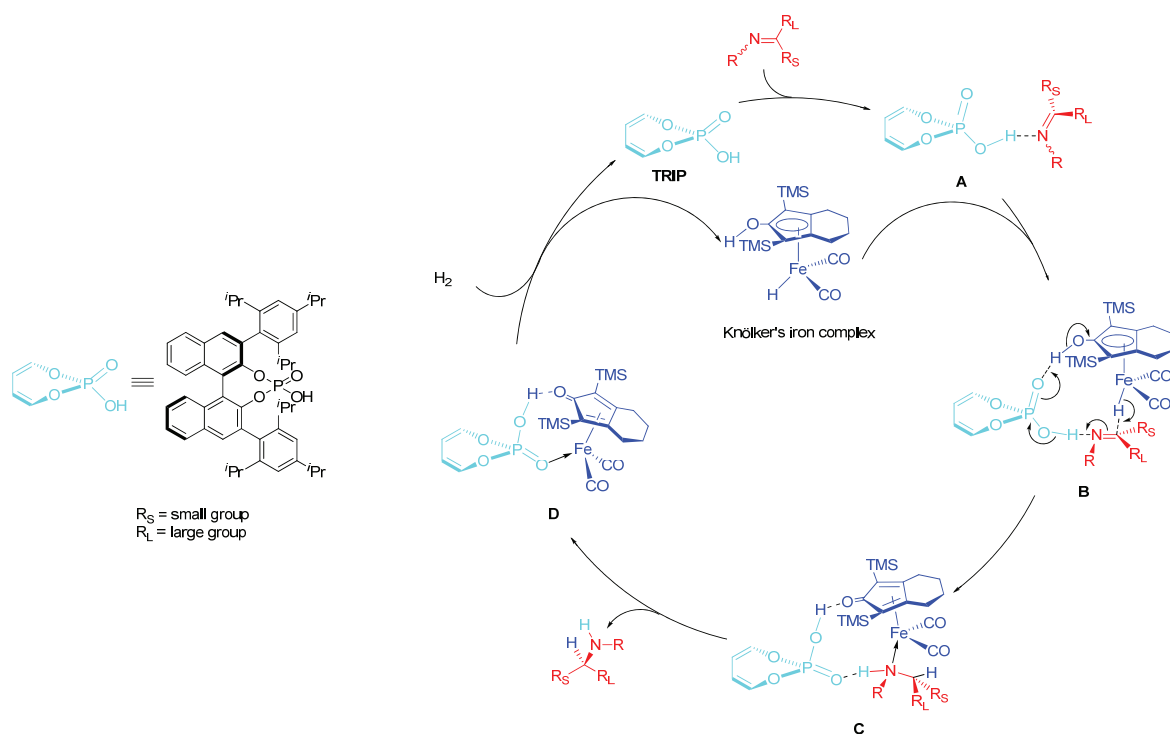
mixture. Finally, we found that the combination of chiral Brønsted acid **2** with a well defined Shvo type iron complex (Knölker's Iron complex) creates an active catalyst which could hydrogenate a variety of ketimines to amines. Not only aryl alkyl ketimines, but also more challenging dialkyl ketimines were hydrogenated to corresponding amines with good yields and excellent *ee*'s (Scheme 9).<sup>21</sup>



**Scheme 9.** Results of combining nonchiral iron hydrogenation catalyst with chiral Brønsted acids for the hydrogenation of *N*-arylimines.

We also proposed the mechanism based on our results and the previous studies of chiral Brønsted acids-catalyzed transfer hydrogenation of ketimines using Hantzsch ester, and the Goodman's "three point model". More specifically, it was postulated that the Knölker's iron complex behaves similar to Hantzsch ester, because both can coordinate to phosphoric acid oxygen via hydrogen bond followed by reduction of the C=N bond by adding hydride.

## 1 Introduction



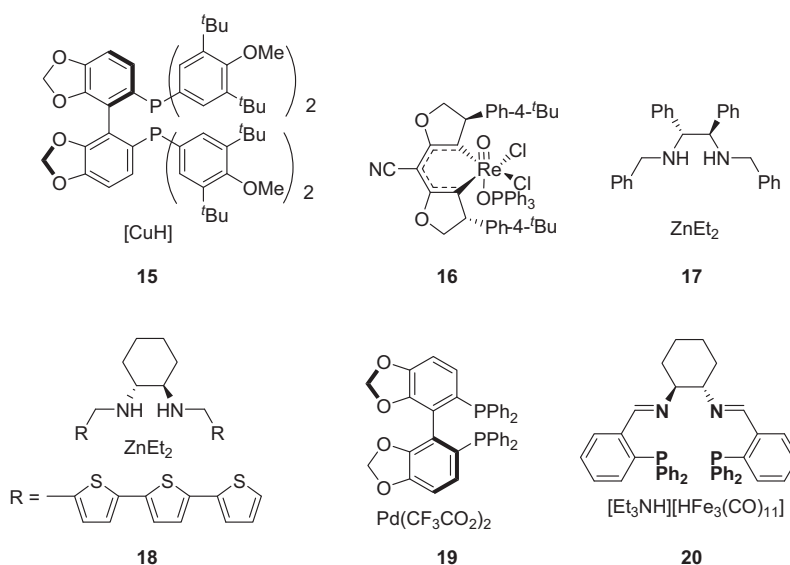
**Figure 6.** Proposed catalytic cycle of the cooperative iron catalysis and chiral Brønsted acid catalysis for imines hydrogenation.

At first, the imine in Z conformation, is complexed to the **TRIP** via hydrogen bond (first point interaction) leaving the more sterically demanding group towards the less hindered sites of the catalyst (second point interaction). Then the Knölker's iron complex is coordinated to the other phosphoric acid oxygen of the **TRIP** (third point interaction) via a second hydrogen bond to give the intermediate **B**. A subsequent hydride transfer takes place from this face to give the intermediate **C**, which is transferred to intermediate **D** by releasing the amine product. Finally, the intermediate **D** is hydrogenated to regenerate the **TRIP** and the Knölker's iron complex to finish the catalytic cycle. (Fig. 6).

In situ NMR investigations confirmed our proposal. NMR measurements of a 1:1-mixture of **TRIP** and Knölker's iron complex at reaction temperature (65°C) showed immediate formation of hydrogen and the coordinated species **D**. This reaction already slowly proceeded at room temperature and is reversible by adding hydrogen. Upon addition of the *N*-(1-phenylethylidene)aniline to a 1:1-mixture of **TRIP** and Knölker's iron complex the corresponding iron amine complex **C** is observed as the major reaction product in addition to **G**. **TRIP**-amine additive and Knölker's iron complex are observed by taking hydrogenation,

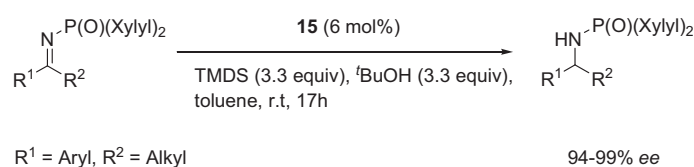
and the *ee*-values of amine are measured before and after hydrogenation giving 97% *ee* in both cases.

### 1.1.2.3 *N*-Phosphinylimines



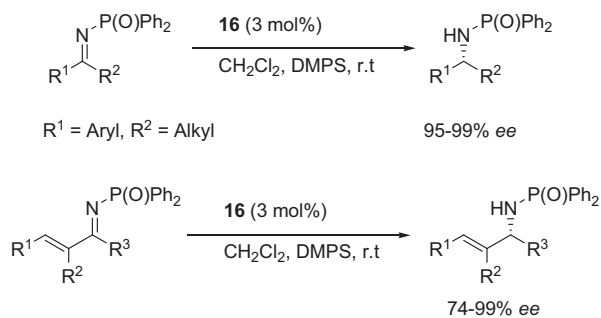
**Figure 7.** Catalysts for asymmetric reduction of *N*-phosphinylimines.

A process for an efficient asymmetric hydrosilylation of *N*-phosphinylimines based on cheap copper catalysts was developed by Lipshutz and coworker.<sup>22</sup> They used a ligated copper hydride prepared in situ from CuCl, NaOMe and DTMB-SEGPHOS with TMDS in the presence of <sup>t</sup>BuOH to effect the reduction of ten aryl alkyl ketimines (Scheme 10).



**Scheme 10.** Cu-catalyzed asymmetric hydrosilylation of *N*-phosphinylimines.

Toste and co-workers introduced the use of a high oxidation state chiral Rhenium(V)-oxo complex with DMPS to facilitate the reduction *N*-phosphinylimines.<sup>23</sup> Aryl alkyl *N*-phosphinylimines and  $\alpha,\beta$ -unsaturated *N*-phosphinylimines could be reduced to the corresponding amines with high *ee*'s (Scheme 11).



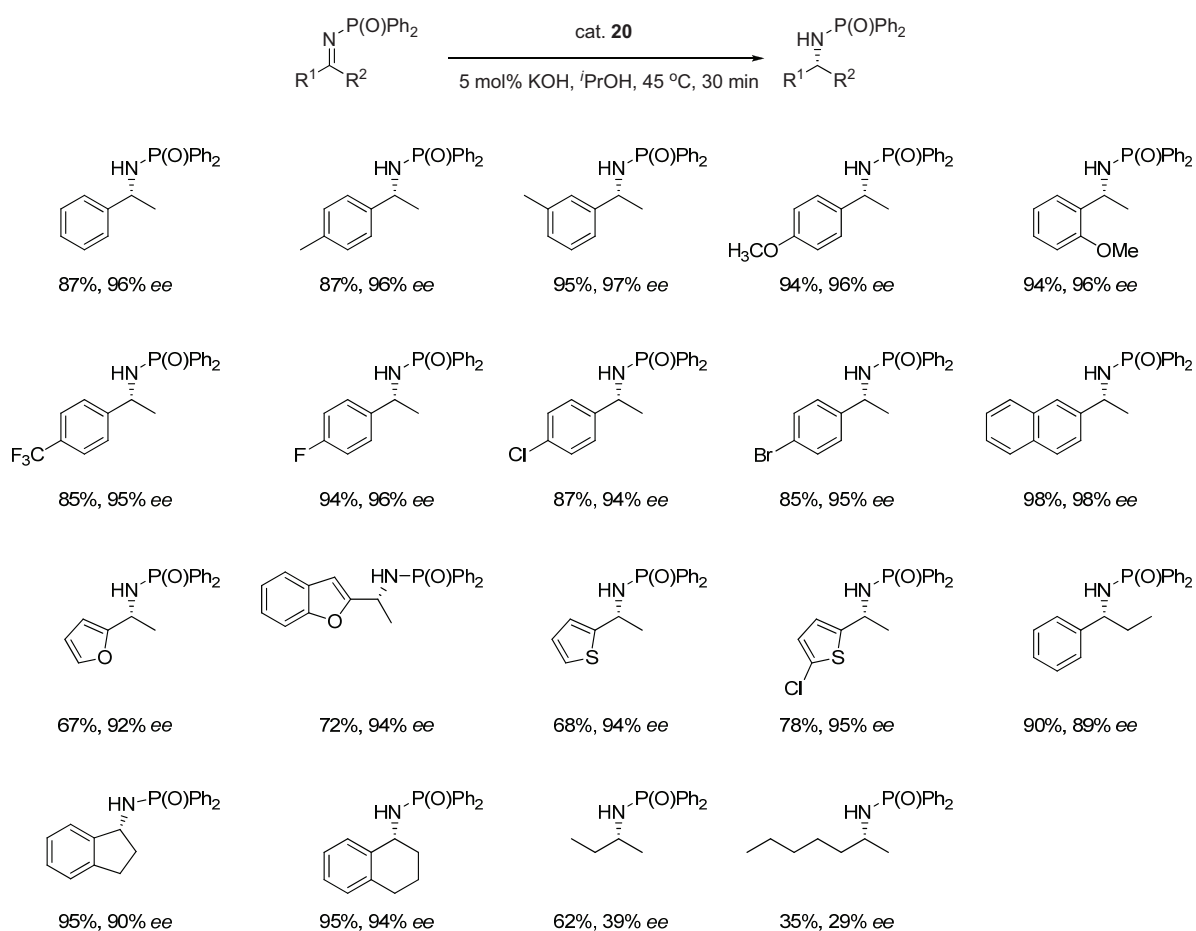
**Scheme 11.** Re-catalyzed asymmetric hydrosilylation of *N*-phosphinylimines.

In 2006, Yun and coworkers developed the Zn-diamine catalyst **17** with PMHS system for the asymmetric reduction of *N*-phosphinylimines.<sup>24</sup> Eight ketimines were reduced to give corresponding amines in high yields with good to excellent enantioselectivities. This process offers advantages such as the use of non-precious metal and inexpensive silanes or easy modification of chiral diamine ligands. Ronchi also reported a zinc-catalyzed asymmetric hydrosilylation of phenyl methyl *N*-phosphinylimine using a diamine-bis(*tert*-thiophene) as chiral ligand **18**.<sup>25</sup>

In addition, a Pd/SegPhos catalyst **19** was found to be very effective for the asymmetric hydrogenation of *N*-phosphinylimines.<sup>26</sup> A variety of aryl alkyl *N*-phosphinylimines could be reduced with excellent *ee*'s.

In 2010, again our group developed an iron-catalyzed asymmetric transfer hydrogenation of imines using isopropanol as the hydrogen donor.<sup>27</sup> We used an iron cluster catalyst with a chiral tetradentate P<sub>2</sub>N<sub>2</sub> ligand **20** to catalyze the asymmetric reduction of *N*-diphenylphosphinylketimines. A variety of ketimines, including aromatic, heteroaromatic and cyclic imines were hydrogenated smoothly with high yields up to 98% and good to excellent enantioselectivities up to 98% *ee* (Scheme 12). Both electron-donating and electron-withdrawing substituents on the aromatic ring at the *ortho*-, *meta*- or *para*-position had only a slight impact on the enantioselectivity (94-97% *ee*). On the other hand, the steric hindrance on aside of the C=N bond has a significant effect on the activity, but only a small effect on the enantioselectivity. Notable features of this protocol are the convenient formation of the active iron catalyst, the operational simplicity and the safe and mild reaction conditions.

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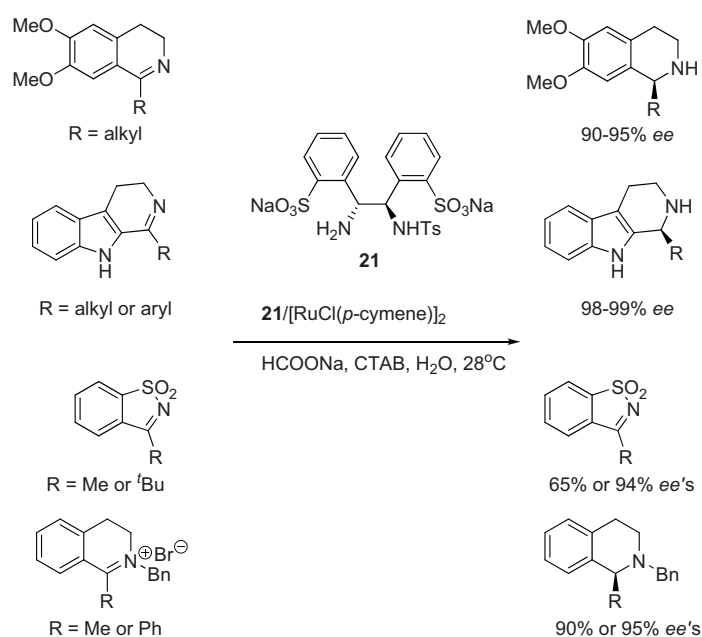


**Scheme 12.** Results of Fe-catalyzed asymmetric transfer hydrogenation of *N*-phosphenyl-imines.

### 1.1.2.4 Cyclic imines

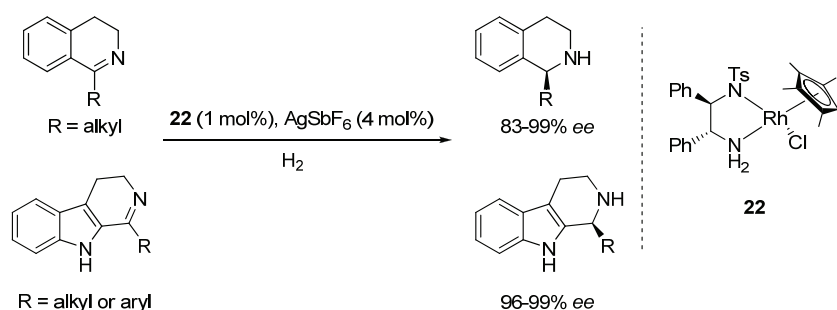
Deng and co-workers reported the catalytic asymmetric transfer hydrogenation for a series of cyclic imines, such as 1-alkyl-dihydroisoquinoline, 3,4-dihydro- $\beta$ -carboline derivatives and cyclic sulfonylimine derivatives, and 1-alkyl-dihydroisoquinoline iminium derivatives in water by using sodium formate as the hydrogen source and cetyltrimethylammonium bromide (CTAB) as the surfactant with a water-soluble ruthenium catalyst (Scheme 13).<sup>28</sup> Notably, in most cases, in water the enantioselectivities were superior to those obtained with formic acid-triethylamine as hydrogen source in organic solvent. In 2007, the same group developed a water-soluble rhodium catalyst, again with excellent enantioselectivities.<sup>29</sup>

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**Scheme 13.** Ir-catalyzed transfer hydrogenation of cyclic imines in water.

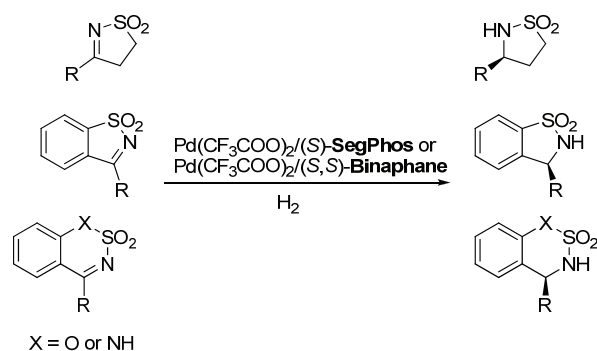
Xiao and Li disclosed a chiral cationic Rh-diamine catalyst that enabled cyclic imines to be hydrogenated.<sup>30</sup> Not only 1-alkyl-dihydroisoquinoline derivatives but also 3,4-dihydro- $\beta$ -carboline derivatives were able to be reduced with excellent *ee*'s (Scheme 14).



**Scheme 14.** Rh-catalyzed asymmetric hydrogenation of cyclic imines.

Enantioselective synthesis of cyclic sulfamidates was achieved via palladium-catalyzed asymmetric hydrogenation by Zhou and co-workers.<sup>23</sup> They found two Pd/diphosphine complexes to be very effective catalysts for the asymmetric hydrogenation of cyclic sulfonylimines (Scheme 15).




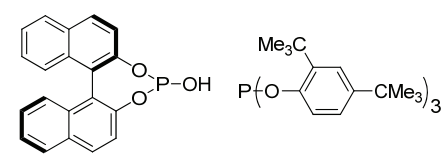


**Scheme 15.** Pd-catalyzed asymmetric hydrogenation of cyclic sulfonylimines.

### 1.1.2.5 *N*-Alkyl imines

Reetz reported the use of a BINOL-derived chiral phosphorous acid diester in combination with achiral phosphorus ligands leads to remarkably efficient catalyst systems in the Ir-catalyzed enantioselective hydrogenation of *N*-benzyl ketimines.<sup>31</sup> For example, in the Ir-catalyzed asymmetric hydrogenation of *N*-benzyl-(1-phenylethylidene)amine, ligand **23** alone leads to an *ee*-value of 45%, whereas in combination with non-chiral ligand **24** 88% enantiomeric excess was obtained (Table 1).

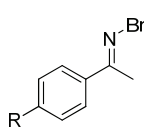
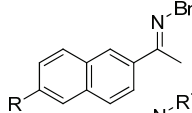
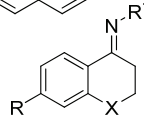
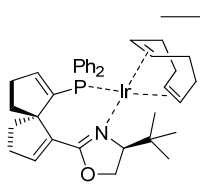
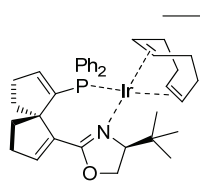
Imine	Catalyst system	Conv. [%]	Ee [%]	
Ar = ph	Ir: <b>23</b> = 1:4	21	45	
Ar = ph	Ir: <b>23:24</b> = 1:1.5:0.5	100	88	
	Ar = 4-Cl-C <sub>6</sub> H <sub>4</sub>	Ir: <b>23</b> = 1:4	36	
	Ar = 4-Cl-C <sub>6</sub> H <sub>4</sub>	Ir: <b>23:24</b> = 1:2:2	99	90
	Ar = 4-MeO-C <sub>6</sub> H <sub>4</sub>	Ir: <b>23</b> = 1:3	20	35
	Ar = 4-MeO-C <sub>6</sub> H <sub>4</sub>	Ir: <b>23:24</b> = 1:2:2	99	92
	Ar = 2-naphthyl	Ir: <b>23</b> = 1:2	100	7
	Ar = 2-naphthyl	Ir: <b>23:24</b> = 1:3:2	100	92



**23**                      **24**

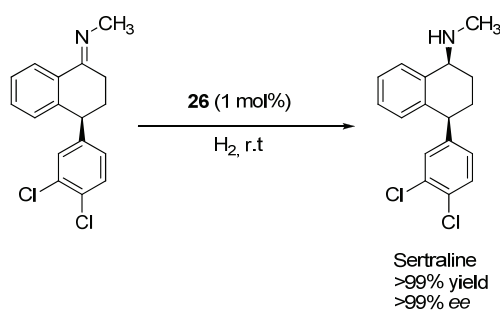
**Table 1.** Ir-catalyzed asymmetric hydrogenation of *N*-benzylimines.

Recently, very impressive results in the catalytic asymmetric hydrogenation of *N*-alkylimines have been achieved by Ding et al. When using their Ir/SpinPHOX complex catalysts, excellent enantioselectivities and yields are obtained (Table 2). The potential application of this methodology has been demonstrated by the asymmetric synthesis of Sertraline. Up to >99: 1

Imine	Catalyst	Conv. [%]	Ee [%]
 R = H R = OMe R = Me R = F R = Cl R = Br	<b>25</b>	>99	91
	<b>25</b>	>99	90
	<b>25</b>	>99	89
	<b>25</b>	>99	88
	<b>25</b>	87	91
	<b>25</b>	90	89
 R = H R = OMe	<b>26</b>	>99	92
	<b>26</b>	>99	93
 R = H, X = CH <sub>2</sub> , R <sup>1</sup> = Bn R = OMe, X = CH <sub>2</sub> , R <sup>1</sup> = Bn R = H, X = O, R <sup>1</sup> = Bn R = H, X = CH <sub>2</sub> , R <sup>1</sup> = Me R = H, X = CH <sub>2</sub> , R <sup>1</sup> = <i>i</i> Bu	<b>26</b>	99	96
	<b>26</b>	>99	95
	<b>26</b>	>99	98
	<b>26</b>	>99	98
	<b>26</b>	>99	96
 <b>25</b>			
 <b>26</b>			

**Table 2.** Asymmetric hydrogenation of *N*-alkylimines in the presence of **25** or **26**.

cis selectivity and up to >99% *ee* and quantitative yield are obtained in the hydrogenation of the imine precursor derived from methylamine and (*S*)-4-(3,4-dichlorophenyl)-1-tetralone (Scheme 16).



**Scheme 16.** Synthesis of Sertraline by asymmetric hydrogenation of its imine precursor in the presence of **26**.

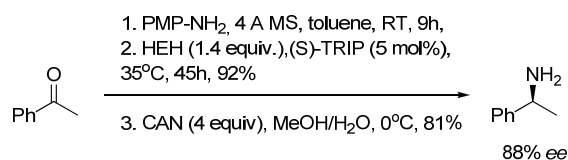
## 1.2 Direct asymmetric reductive amination (DARA)

### 1.2.1 Organocatalytic reductive asymmetric amination

In 2005, List and co-workers developed a practical two-step, one-pot synthesis of chiral amine based on their developed TRIP-catalyzed asymmetric transfer hydrogenation of ketimines with a Hantzsch ester as hydrogen donor. In the first part acetophenone and *p*-

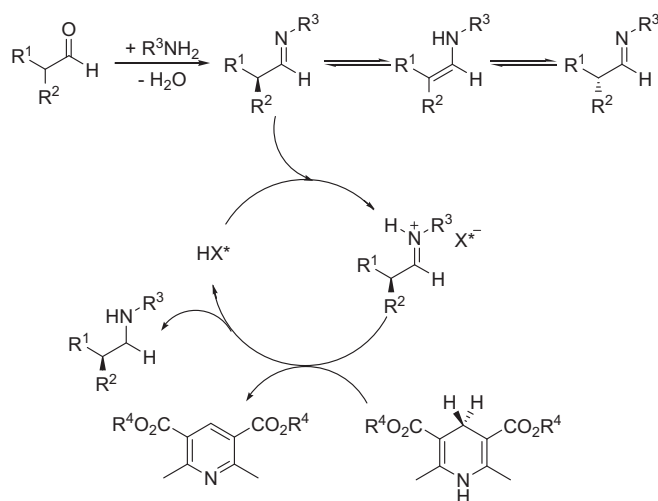
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anisidine react in toluene in the presence of 4 Å molecular sieves to form an imine. In the second step the chiral Brønsted acid TRIP and Hantzsch ester were added to catalyze the transfer hydrogenation of the ketimine giving the amine in 92% yield and 88% *ee* (Scheme 17).



**Scheme 17.** One-pot two-step, TRIP-catalyzed asymmetric reductive amination of acetophenone with Hantzsch ester.

Recently, List reported a chiral Brønsted acid catalyzed and Hantzsch ester mediated asymmetric reductive amination of aryl methyl ketones using benzylamine as the amine component.<sup>32</sup> Remarkable features of their protocol are the use of easily removable benzyl group as the protecting group and a Dean-Stark trap to remove the water.

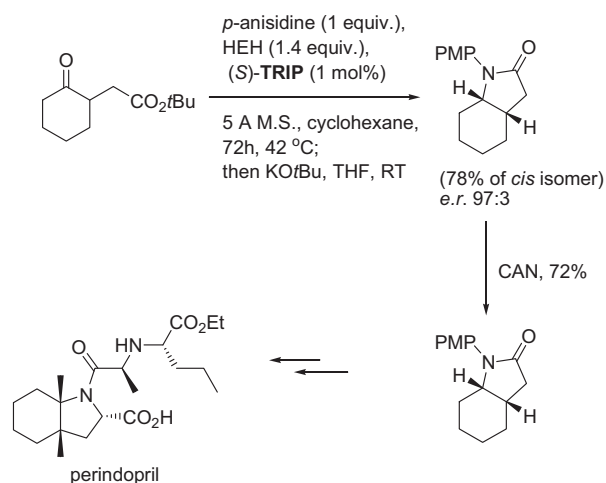


**Figure 8.** Proposed catalytic cycle of asymmetric reductive amination of  $\alpha$ -branched aldehydes by dynamic kinetic resolution.

List has extended his methodology to the reductive amination of  $\alpha$ -branched aldehydes by dynamic kinetic resolution (Fig. 8).<sup>33</sup> Both aromatic and aliphatic aldehydes could be converted into the corresponding  $\beta$ -chiral amines in good yields with good to excellent enantioselectivities.

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List also introduced his TRIP/*p*-anisidine system to the asymmetric reductive amination of racemic ketones by dynamic kinetic resolution.<sup>34</sup> A broad array of  $\alpha$ -branched ketones could be converted into their corresponding amines in good yields and diastereoselectivities, and high enantioselectivities. The synthetic utility of this protocol was demonstrated as a key step in the synthesis of perindopril, a long-acting ACE inhibitor (Scheme 18).



**Scheme 18.** Short total synthesis of perindopril by using organocatalytic asymmetric reduction of amination of  $\alpha$ -branched ketones as a key step.

A comprehensive study of enantioselective reductive amination of ketones with anilines was reported by MacMillan in 2006. A variety of ketones were transformed into the corresponding amines in good yields with excellent enantioselectivities by using a variant of Akiyama-Terada acid as the catalyst, Hantzsch ethyl ester as the hydride source, and aromatic amines as the amine component (Scheme 19).<sup>35</sup>

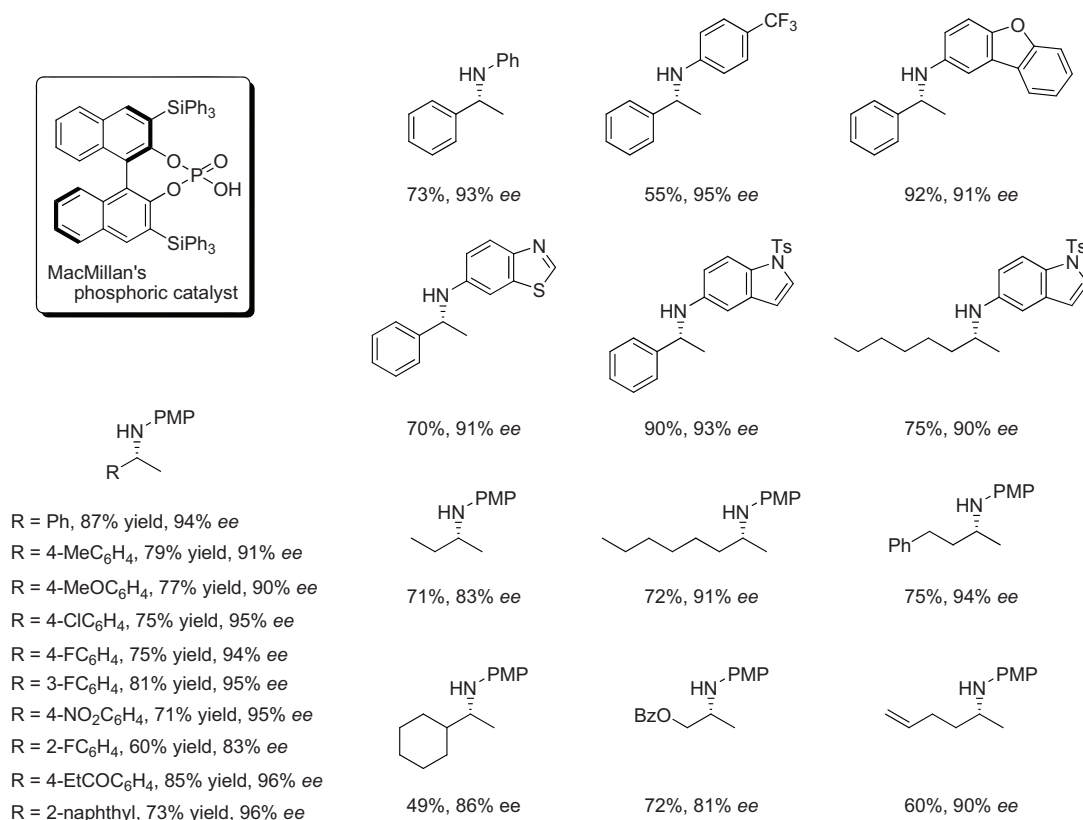
### 1.2.2 Transition metal-catalyzed asymmetric reductive amination

The first enantioselective reductive amination was reported by Blaser in 1999 for the synthesis of (*S*)-Metolachlor.<sup>36</sup> Since then, few studies on this area have been reported in the open literature.<sup>37</sup>

Xiao and co-workers used protonated chiral Ir- diamine complexes by a chiral Brønsted acid. In combination with or without additional chiral Brønsted acid catalyst the direct asymmetric reductive amination of ketones is realized using molecular hydrogen.<sup>38</sup> With respect to scope, yield and stereoselectivity, this protocol is greatly improved over existing transition metal-catalyzed asymmetric reductive amination of ketones. Not only aryl ketones but also more

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challenging dialkyl ketones (Scheme 20) could be used successfully. Especially for these dialkyl ketones, no additional chiral Brønsted acid catalyst was required and the enantioselectivities were generally >80%.

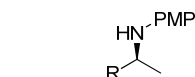
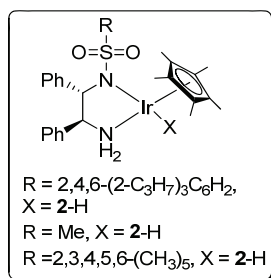



**Scheme 19.** Results of organocatalytic asymmetric reductive amination of ketones by MacMillan.

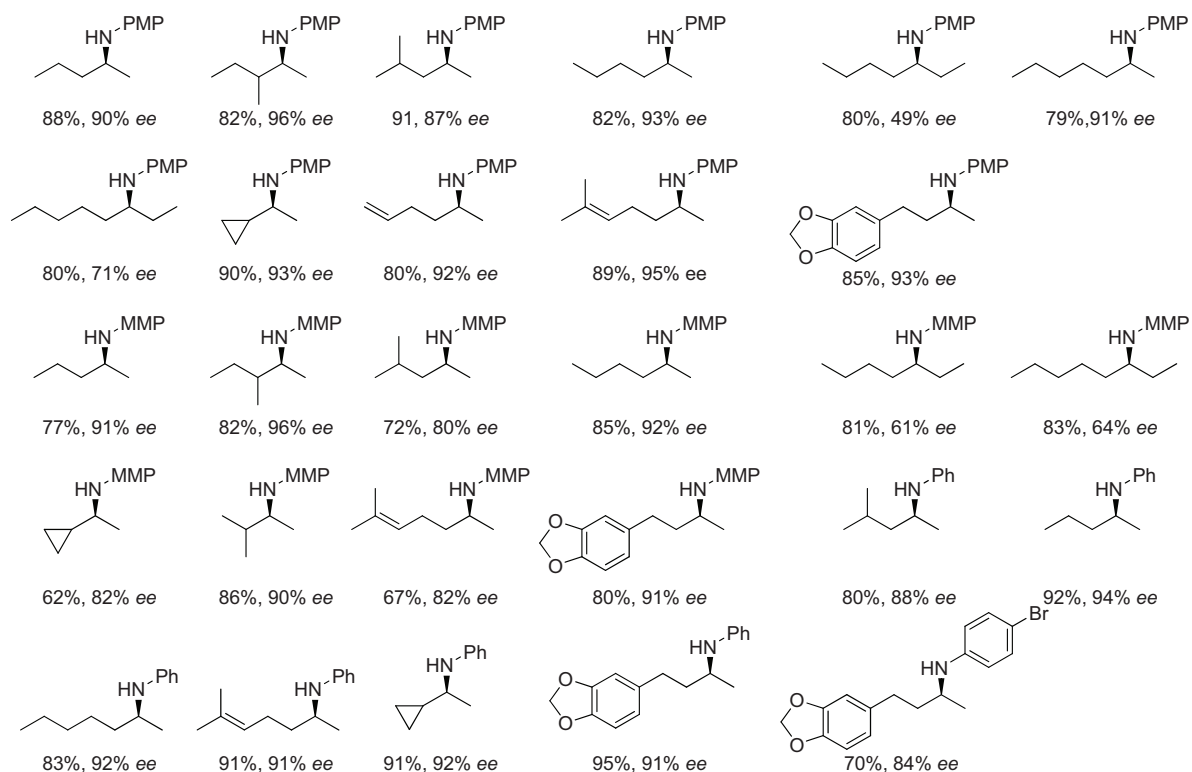
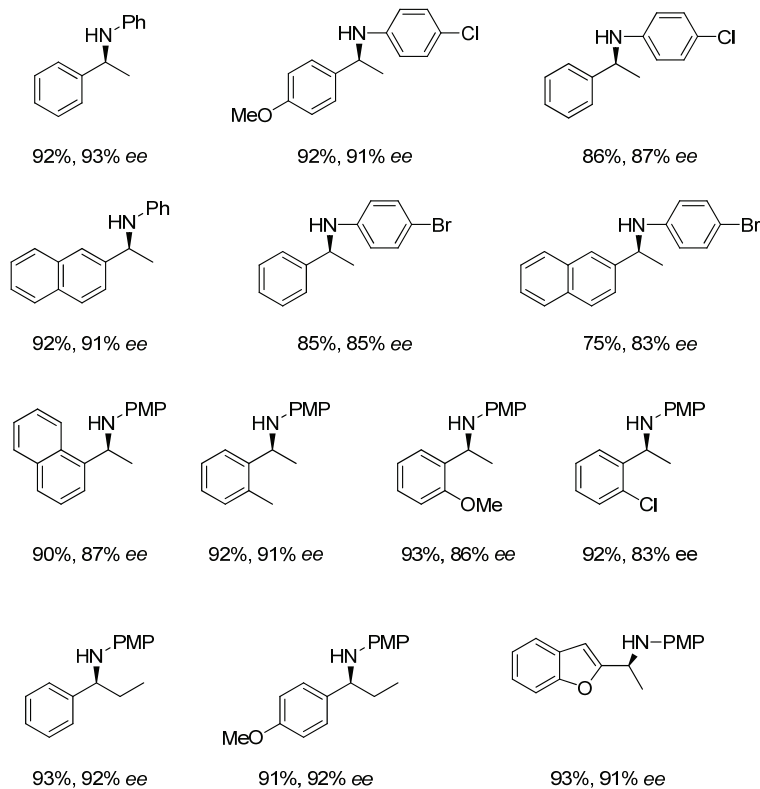
### 1.3 Conclusions

As described above, significant and impressive progress has been made over the past six years. Most remarkably are organocatalytic procedures, which proceed with high enantioselectivities. Unfortunately, in most cases expensive and non-atom efficient hydrogen donors have to be used. Clearly, the current procedures with regard to catalyst activity and productivity as well as the price of reagents still can not meet technical requirements. To this point, more efforts should be made.

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- R = Ph, 94% yield, 97% ee
- R = 4-MeC<sub>6</sub>H<sub>4</sub>, 93% yield, 97% ee
- R = 4-*i*-PrC<sub>6</sub>H<sub>4</sub>, 93% yield, 95% ee
- R = 4-MeOC<sub>6</sub>H<sub>4</sub>, 93% yield, 95% ee
- R = 4-BrC<sub>6</sub>H<sub>4</sub>, 94% yield, 94% ee
- R = 4-ClC<sub>6</sub>H<sub>4</sub>, 94% yield, 95% ee
- R = 4-FC<sub>6</sub>H<sub>4</sub>, 93% yield, 95% ee
- R = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 91% yield, 91% ee
- R = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 92% yield, 88% ee
- R = 4-CNC<sub>6</sub>H<sub>4</sub>, 92% yield, 86% ee
- R = 3-MeC<sub>6</sub>H<sub>4</sub>, 93% yield, 94% ee
- R = 3-MeOC<sub>6</sub>H<sub>4</sub>, 93% yield, 94% ee
- R = 3-BrC<sub>6</sub>H<sub>4</sub>, 93% yield, 94% ee
- R = 3-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 94% yield, 93% ee
- R = 2-naphthyl, 91% yield, 96% ee
- R = 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 92% yield, 95% ee
- R = , 93% yield, 95% ee



PMP = *p*-MeOC<sub>6</sub>H<sub>4</sub>, MMP = *m*-MeOC<sub>6</sub>H<sub>4</sub>

**Scheme 20.** Results of Ir-catalyzed asymmetric reductive amination of ketones.

## 1.4 Reference

1. For reviews, see: a) F. Spindler, H.-U. Blaser, in: *Transition Metals for Organic Synthesis*, 2nd Edn., Vol. 2, (Eds.: M. Beller, C. Bolm), WILEY-VCH, Weinheim, **2004**, p 113; b) H.-U. Blaser, F. Spindler, in *Handbook of Homogeneous Hydrogenation*, Vol. 3, (Eds: J. G. de Vries, C. J. Elsevier), WILEY-VCH, Weinheim, **2007**, pp 1193; c) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045-2061; d) H.-U. Blaser, C. Malan, B. Pugin, F. Spinder, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103-151; e) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3069; f) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819; g) M. Rueping, E. Sugiono, F. R Schoepke, *Synlett* **2010**, 852-865.
2. a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592-1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.
3. M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781-3783.
4. S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590-7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427.
5. L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741-8747.
6. M. Rueping, A. P. Antonchik, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765-3768; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751-6755.
7. For review see: D. W. Stephan, G. Erker, *Angew. Chem.* **2010**, *122*, 50-81; *Angew. Chem. Int. Ed.* **2010**, *49*, 46-76.
8. D. Chen, Y. Wang, J. Klankermayer, *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.201004525.
9. G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C.-Y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882-9883.
10. G. Hou, R. Tao, Y. Sun, X. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2010**, *132*, 2124-2125.
11. S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, *J. Am. Chem. Soc.* **1999**, *121*, 6421.
12. C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736-7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564-7567.
13. S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886-12891.
14. Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449-5453; *Angew. Chem. Int. Ed.* **2009**, *48*, 5435-5439.
15. H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 17-31.
16. Y. Chi, Y.-Z. Zhou, X. Zhang, *J. Org. Chem.* **2003**, *68*, 4120-4122.
17. A. Dervisi, C. Carcedo, L.-L. Ooi, *Adv. Synth. Catal.* **2006**, *348*, 175-183.
18. T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289-2292.
19. N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. deVries, *J. Am. Chem. Soc.* **2009**, *131*, 8358-8359.
20. C. Li, B. V.-M., J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967-6969.
21. S. Zhou, S. Fleischer, K. Junge, M. Beller, *manuscript in preparation*.
22. B. H. Lipshutz, H. Shimizu, *Angew. Chem.* **2004**, *116*, 2278-2280; *Angew. Chem. Int. Ed.* **2004**, *43*, 2228-2230.
23. K. A. Nolin, R. W. Ahn, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 12462-12463.

## 1 Introduction

- 24 B.-M. Park, S. Mun, J. Yun, *Adv. Synth. Catal.* **2006**, *348*, 1029-1032.
- 25 M. Bandini, M. Melucci, F. Piccinelli, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *Chem. Commun.* **2007**, *2007*, 4519-4521.
- 26 Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729-3734.
- 27 S. Zhou, S. Fleischer, K. Junge, S. Das, D. Addis, M. Beller, *Angew. Chem.* **2010**, *122*, 8298-8302; *Angew. Chem. Int. Ed.* **2010**, *49*, 8121-8125.
- 28 J. Wu, F. Wang, Y. Ma, X. Cui, L. Cun, J. Zhu, J. Deng, B. Yu, *Chem. Commun.* **2006**, 1766-1768.
- 29 L. Li, J. Wu, F. Wang, J. Liao, H. Zhang, C. Lian, J. Zhu, J. Deng, *Chem. Commun.* **2007**, 23-25.
- 30 C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208-13209.
- 31 M. T. Reetz, O. Bondarev, *Angew. Chem.* **2007**, *119*, 4607-4618; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523-4526.
- 32 V. N. Wakchaure, M. Nicoletti, L. Batjen, B. List, *Synlett* **2010**, *2010*, 2708-2710.
- 33 S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074-13075.
- 34 V. N. Wakchaure, J. Zhou, S. Hoffmann, B. List, *Angew. Chem.* **2010**, *122*, 4716-4718; *Angew. Chem. Int. Ed.* **2010**, *49*, 4612-4614.
- 35 R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84-86.
- 36 H. U. Blaser, H. P. Buser, H. P. Jalett, B. Pugin, F. Spindler, *Synlett* **1999**, 867-868.
- 37 a) Y. Chi, Y.-G. Zhou, X. Zhang, *J. Org. Chem.* **2003**, *68*, 4120-4122; b) R. Kadyroy, T. H. Riermeier, *Angew. Chem.* **2003**, *115*, 5630-5632; *Angew. Chem. Int. Ed.* **2003**, *42*, 5472-5474.
- 38 a) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *130*, 14450-14451; b) B. Villa-Marcos, C. Li, K. Mulholland, P. J. Hogan, J. Xiao, *Molecules* **2010**, *15*, 2453-2472.



## 2 Objectives of this work

Catalytic hydrogenations of organic compounds belong undoubtedly to the most studied methodologies of the entire class of organometallic reactions. Due to the limited availability and toxicity of precious transition metals, the development of more economical and environmental friendly alternatives based on first row transition metals is highly desirable. Especially iron offers significant advantages compared to precious metals. Since it is the second abundant metal in the earth crust (4.7% wt), various iron salts and iron complexes are commercially available on a large scale or easy to synthesize. Furthermore, iron compounds are relatively nontoxic and it takes part in various biological systems as essential key element. Clearly, the abundant availability and relative non-toxicity makes iron a highly attractive candidate for catalysis and a “cheap metal for noble tasks”.

Although significant achievements have been made in iron-based heterogeneous hydrogenation catalysts (e.g. Haber-Bosch process), homogeneous hydrogenation catalysts based on iron are almost ignored over the last century. However, in the last decade, organometallic iron hydrogenation catalysts received more attention. Compared to heterogeneous catalytic systems, homogeneous catalysts often show very attractive selectivities under very mild conditions. Moreover, homogeneous catalysis is generally better understood on a molecular level which leads to a more rational driven design and variation of homogeneous catalysts.

Having successfully developed iron and copper catalyzed (enantioselective) reduction of ketones and aldehydes (*Chem. Eur. J.* **2010**, *16*, 68-73; *Chem. As. J.* **2010**, *5*, 1687-1691), we turned our attention to more challenging unsaturated compounds, such as amides, esters and imines. In this work, the first iron catalyzed hydrosilylation of secondary and tertiary amides to amines was developed (*Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510). Also an improved zinc catalyzed variant was developed (*J. Am. Chem. Soc.* **2010**, *132*, 1770-1771). When we applied this protocol to primary amides, we found an unprecedented dehydration of primary amides to nitriles (*Chem. Commun.* **2009**, 4883-4885). Subsequently, iron and tetrabutylammonium fluoride-catalyzed dehydrations of primary amides to nitriles were

## *2 Objectives of this Work*

developed (*Org. Lett.* **2009**, *11*, 2461-2464). Based on the work of the iron-catalyzed hydrosilylation of amides to amines, an iron catalyzed asymmetric transfer hydrogenation *N*-phosphinylimines was disclosed (*Angew. Chem. Int. Ed.* **2010**, *49*, 8121-8125). Subsequently, a new protocol for enantioselective hydrogenation of *N*-aryl ketimines to amines was developed by combining a well-defined nonchiral iron complex and a chiral Brønsted catalyst (*Angew. Chem. Int. Ed.* **2011**, *50*, 5120-5124).

### 3 Publications

#### 3.1 Cooperative Transition-Metal and Chiral Brønsted Catalysis: Enantioselective Hydrogenation of Imines to Form Amines.

Shaolin Zhou, Steffen Fleischer, Kathrin Junge, Matthias Beller\* *Angew. Chem. Int. Ed.* **2011**, *50*, 5120-5124. (Featured on the cover, VIP paper)

**Contributions:** In this work, S. Z. developed the catalytic system, performed most of the experiments and analyzed the experimental data. His overall contribution is about approximately 70%.

### 3.2 Enantioselective Synthesis of Amines: General and Efficient Iron-Catalyzed Asymmetric Transfer Hydrogenation of Imines.

Shaolin Zhou, Steffen Fleischer, Kathrin Junge, Shoubhik Das, Daniele Addis, and Matthias Beller\* *Angew. Chem. Int. Ed.* **2010**, *49*, 8121-8125. (Featured on the inside cover, hot paper, highlighted by *Synfacts*)

**Contributions:** In this work, S. Z. developed the catalytic system, performed most of the experiments, analyzed the experimental data and wrote the manuscript. His overall contribution is about approximately 70%.

### 3.3 A Convenient and General Iron-Catalyzed Reduction of Amides to Amines

Shaolin Zhou, Kathrin Junge, Daniele Addis, Shoubhik Das, and Matthias Beller\* *Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510. (hot paper)

**Contributions:** In this work, S. Z. developed the catalytic system, performed most of the experiments, analyzed the experimental data and wrote the manuscript. His overall contribution is about approximately 75%.

### 3.4 A General and Convenient Catalytic Synthesis of Nitriles from Amides and Silane

Shaolin Zhou, Kathrin Junge, Daniele Addis, Shoubhik Das, and Matthias Beller,\* *Org. Lett.* **2009**, *11*, 2461-2464.

**Contributions:** In this publication, S. Z. developed the catalytic system, performed most of the experiments, analyzed the experimental data and wrote the manuscript. His overall contribution is about approximately 75%.

### 3.5 New catalytic properties of iron complexes: dehydration of amides to nitriles

Shaolin Zhou, Daniele Addis, Shoubhik Das, Kathrin Junge and Matthias Beller,\* *Chem. Commun.* **2009**, 4883-4885. (hot paper)

**Contributions:** In this publication, S. Z. developed the catalytic system, performed most of the experiments, analyzed the experimental data and wrote the manuscript. His overall contribution is about approximately 75%.

### 3.6 General and Efficient Synthesis of Sulfonamides Catalyzed by Nano Ru/Fe<sub>3</sub>O<sub>4</sub>

Feng Shi, Man Kin Tse, Shaolin Zhou, Marga-Martina Pohl, Jörg Radnik, Sandra Hübner, Klaus Jähnisch, Angelika Brückner, and Matthias Beller\*, *J. Am. Chem. Soc.* **2009**, *131*, 1775-1779.

**Contributions:** In this paper, S. Z. performed the catalytic reaction of various substrates. His overall contribution is about approximately 30%.



### 3.7 Selective Catalytic Reductions of Amides and Nitriles to Amines

Shoubhik Das, Shaolin Zhou, Daniele Addis, Stephan Enthaler, Kathrin Junge, and Matthias Beller\* *Topic in Catalysis* **2010**, 53, 979-984.

**Contributions:** In this paper, S. Z. participated in the preparation of the manuscript His contribution is approximately 25%.

### 3.8 Hydrosilylation of Ketones: From Metal Organic Framework to Simple Base Catalysts

D. Addis, S. Zhou, S. Das, K. Junge, H. Kosslick, A. Schulz,\* and M. Beller,\* *Chem. As. J.* **2010**, *5*, 2341-2345.

**Contributions:** In this paper, S. Z. performed the catalytic reaction of various substrates. His overall contribution is about approximately 25%.

### 3.9 Zinc-Catalyzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance

Shoubhik Das, Daniele Addis, Shaolin Zhou, Kathrin Junge, and Matthias Beller,\* *J. Am. Chem. Soc.* **2010**, *132*, 1770-1771.

**Contributions:** In this paper, S. Z. provided several tertiary amides substrates, analyzed some experimental data and participated in the preparation of the manuscript. His contribution is approximately 15%.

### 3.10 Chemo- and Stereoselective Iron-catalyzed Hydrosilylation of Ketones

Daniele Addis, Nadim Shaikh, Shaolin Zhou, Shoubhik Das, Kathrin Junge, and Matthias Beller, *Chem. As. J.* **2010**, 5, 1687-1691.

**Contributions:** In this paper, S. Z. performed the catalytic reaction of various substrates. His overall contribution is about approximately 15%.

### 3.11 Copper-catalyzed Enantioselective Hydrosilylation of Ketones by Using Monodentate Binaphthophosphepine Ligands

Kathrin Junge, Bianca Wendt, Daniele Addis, Shaolin Zhou, Shoubhik Das, and Matthias Beller\* *Chem. Eur. J.* **2010**, *16*, 68-73.

**Contributions:** In this paper, S. Z contributed to a significant amount of the argumentation. His contribution is approximately 10%.

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### Education

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- 5/2008 – today      **Leibniz-Institut für Katalyse e.V.**, Rostock, Germany  
  
PhD student in the research group of Prof. Dr. Matthias Beller  
  
*“Development of new catalysts for (asymmetric) hydrogenation”*  
  
Supervisors: Prof. Matthias Beller, Dr. Kathrin Junge.
- 9/2007 – 04/2008      **Leibniz-Institut für Katalyse e.V.**, Berlin, Germany  
  
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*“Application of catalytic reactions in microreactors”*  
  
Supervisors: Prof. Matthias Beller, Dr. habil. Klaus Jähnisch, Dr. Man-Kin Tse.
- 09/2000 – 07/2003      **Central China Normal University**, Department of Chemistry, Wuhan, China; Master thesis  
  
*“Synthesis and application of organic phosphorous and nitrogen based flame retardant”*  
  
Supervisor: Prof. Xingyu Yang.
- 09/1996 – 07/2000      China Three Gorges University, Department of Chemistry, Yichang City, China. Bachelor Degree.  
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- 03/2004 – 08/2007    **The Shanghai Institute of Organic Chemistry**, Chinese Academe of Sciences, Shanghai, China; research assistant.  
*“Development of Zirconium-Mediated New Organic Reactions”*  
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*“Transition-Metal Catalyzed C-C and C-N Coupling reactions”*  
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## **Scholarship**

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## **Selbstständigkeitserklärung**

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, 16<sup>th</sup>. November 2010