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Asymmetric Transfer Hydrogenation of Ketimines Using Well-Defined Iron(II)-Based Precatalysts Containing a PNNP Ligand

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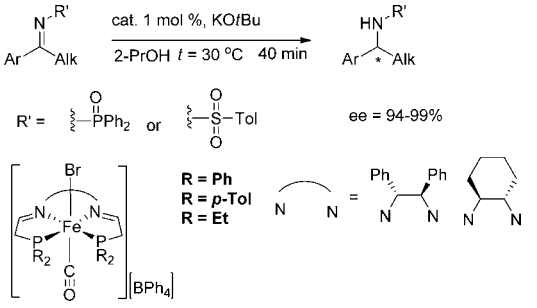
ABSTRACT



Well-defined iron(II)-based complexes containing PNNP ligands catalyze a highly enantioselective reduction of *N*-(diphenylphosphinoyl)- and *N*-(*p*-tolylsulphonyl)-ketimines. Under mild conditions and low catalyst loading, the ketimines are successfully reduced to the corresponding amines in enantiomeric excess ranging from 94 to 99%.

Chiral amines are commonly present in the structures of various pharmaceuticals, agrochemicals and other bioactive molecules. The importance of these molecules justifies why so much effort is devoted to the development of enantioselective and efficient methodologies for the synthesis of enantiopure amines.[1,2] The catalytic reduction of imines using chiral transition metal complexes with molecular hydrogen or cheap and safe 2-propanol as reducing agents is one of the most environmentally benign processes for the preparation of amines.[3−5] Although various catalytic systems based on Ru,[6−12] Rh,[12−20] Ir,[12,21−27] Ti,[28−30] Zn,[18,31] and Cu[32] were developed to be selective and efficient for the reduction of the C═N bond, they are less effective than the catalytic transfer- and H_2-hydrogenations of C═O and C═C bonds.[33] The challenges associated

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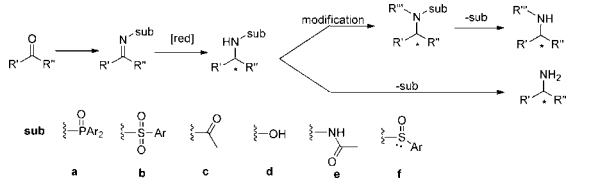
with the reduction of imines compared to other substrates are directly related to the intrinsic reactivity of these molecules:[34,35] they are sensitive to hydrolysis; they exist as anti/syn and enamine isomers, as hemiaminals and aminals when amines are present; as *N*,*O*-acetals, when an alcohol is present; their reactivity is highly dependent on the electronic and steric properties of the *N*-substituent; and products of the reduction (amines) may deactivate the catalyst via coordination. For this reason, the design of catalytic systems that are efficient for the reduction of imines with different structures is very challenging. This observation is supported by the fact that the catalytic systems are usually sensitive to the electronics and sterics of the imines.[36]

This issue can be resolved if imines are modified prior to the hydrogenation by the addition of a specific substituent that will provide the required steric and electronic properties for the successful reduction. Corresponding amines can be obtained when the substituent is removed (Scheme 1). This approach has the drawback of adding extra steps to the synthesis, but on the other hand, allows a controlled preparation of the primary, secondary and tertiary amines with the substituents of choice to be present in the structure. The most relevant functional groups to the proposed synthetic scheme are phosphinoyl (a) and sulfonyl (b) groups. Their syntheses[37−44] and efficient deprotection methods to corresponding amines,[39,45,46] which do not cause racemization, have been reported. Catalytic systems based on platinum group metals, which are active and enantioselective in the process of amine synthesis from such miscellaneous imines, are known.[14,43,45−51]

Although complexes containing platinum group metals are catalysts of choice for various catalytic transformations because of their exceptional activities, the toxicity and low availability of the metal make them undesirable for some applications.[52] Recently, several highly active and enantioselective catalytic systems for the reduction of prochiral ketones, which are based on more abundant and less toxic iron as a part of the catalyst, have been reported.[53−58] This activity led to the discovery that the iron-containing catalysts can also be efficiently employed for the reduction and for the reductive amination of aldehydes and ketones.[59−63]

Scheme 1. Chiral Amine Synthesis from Miscellaneous Imines



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Importantly, a catalytic system reported by Beller and co-workers that was generated *in situ* by the reaction of $(Et_3NH)[HFe_3(CO)_{11}]$, PNNP ligand and KOH (1:3:15) in 2-PrOH for 30 min at 45 °C, can be exceptionally enantioselective for the asymmetric transfer hydrogenation (ATH) of diphenylphosphinoyl imines giving the desired amine with 29−98% enantiomeric excess (ee).[60] These researchers also demonstrated that a well-defined precatalyst **(*S*,*S*)-1**, which was previously synthesized and utilized in our group for the catalytic transfer hydrogenation of ketones,[63] was also active for the reduction of diphenylphosphinoyl imine derived from the acetophenone, but was reproducibly less enantioselective compared to the reaction with the catalyst formed *in situ*.

We recently reported a versatile one pot template synthesis of iron(II) complexes containing various PNNP and *trans*-acetonitrile or Br/CO ligands (Figure 1).[64−66] These complexes are highly active (TOF up to 30000 h^{-1}) and enantioselective (ee up to 99%) in the ATH of ketones when activated with an excess of base at room temperature.[63,67−71] In this study we report the activity and selectivity of these precatalysts in the ATH of imines.

Initially it was important to investigate the effect of the *N*-substituent of the imine on the rate and selectivity of the reaction. The precatalyst (**(*S*,*S*)-3**), which is straightforward to make and very effective for the ATH of ketones, was tested first for the imine reduction reactions. Imine analogs of acetophenone were prepared using known protocols (see the Supporting Information for details) and were subjected to the ATH conditions. The results of the reactions are summarized in Table 1 and show that only the imines with bulky and strongly electron withdrawing *N*-substituents such as diphenylphosphinoyl or *p*-tolylsulphonyl (Table 1, entries 1−3) were successfully reduced to the corresponding amines. The reduction of the imine containing the *N*-diphenylphosphinoyl group is faster than the reduction of the imine with the *p*-tolylsulphonyl substituent. This indicates that both steric and electronic properties of *N*-substituent are important for the successful reaction. Exceptional enantioselectivities (up to 99%) were observed in the reduction of both imines.

The reduction of *N*-(diphenylphosphinoyl)-imines was conducted using various precatalysts (Figure 1). The results are summarized in Table 2. Complex **(*R*,*R*)-2**, which contains

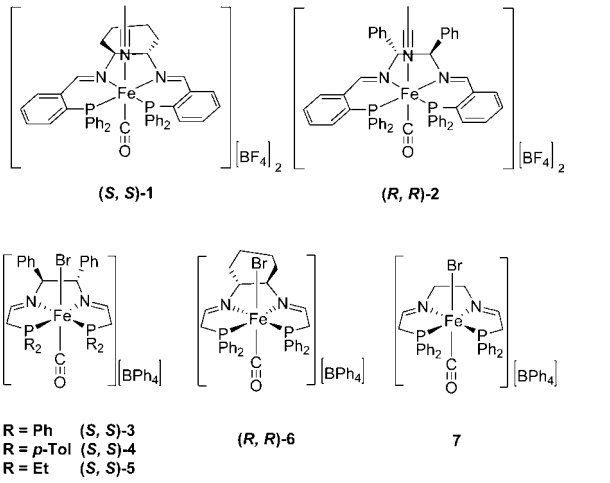

Figure 1. Structures of chiral complexes that were used as precatalysts for the asymmetric transfer hydrogenation reactions.

sterically demanding 1,2-diphenyl-(ethylenediamine) in the ligand backbone derived from *o*-phosphinobenzaldehyde compared to **(*S*,*S*)-1** showed reproducibly higher enantioselectivity in the formation of the amine but lower reactivity. Complexes **(*S*,*S*)-3**, **(*S*,*S*)-4**, **(*S*,*S*)-5** and **(*R*,*R*)-6,** which contain PNNP ligands originating from the phosphinoaldehyde $Ph_2PCH_2C(O)H$ and forming 5,5,5 membered rings with the metal, were highly enantioselective, giving the desired amine with ee from 94 to 99%. The activities of these complexes are strongly dependent on the substituents on the phosphorus and the type of the diamine incorporated into the ligand backbone. Complex **(*S*,*S*)-5** with electron donating substituents (Et) on the phosphorus displayed significantly lower activity (Table 2, entry 5) compared to the complexes **(*S*,*S*)-3** and **(*S*,*S*)-4** (Table 2, entries 3, 4), which have phenyl and *p*-tolyl substituents, respectively. Complexes with ethylenediamine and 1,2-diaminocyclohexane in the ligand backbone were only slightly active (Table 2, entries 6, 7) compared to the complexes with the 1,2-(diphenylethylene) diamine (Table 2, entries 3, 4). The behavior of these precatalyst in the reduction of imines is similar to their reactivity in the catalytic reduction of ketones.[69−71] The stereoselective formation of one stereoisomer of the amine over the other as expected is controlled by the stereoorientation of the diamine incorporated in the ligand backbone: (*R*,*R*)-diamine produces (*S*)-amine and vise versa.

The activity and selectivity of the most active and enantioselective complex **(*S*,*S*)-3** was further investigated in the reductions of *N*-(diphenylphosphinoyl) ketimines with various structures. The presence of the electron-withdrawing and -donating substituents in the *para*- and *meta*-positions on the aromatic ring of the ketimines has no substantial influence on the activity and selectivity of the reaction (Table 3, entries 1−4). The ketimine containing an ethyl group at the imine-carbon was reduced with exceptional ee but at a longer reaction time (Table 3, entry 5); this is expected taking into consideration the increased steric bulk

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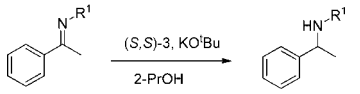
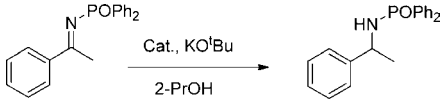
Table 1. Asymmetric Transfer Hydrogenation of *N*-Substituted Imines Catalyzed by the Complex **(*S*,*S*)-3**[a]



entry	R^1	cat/sub/base	time [hour]	conv [%]	ee [%]
1	-P(O)Ph_2	1/100/8	0.5	92	>99 (*S*)
2	-P(O)Ph_2	1/300/8[b]	0.5	62	>99 (*S*)
3	-S(O)$_2$-Tol	1/50/8	12	26	94 (*S*)
4	-Ph	1/100/8	1	<1	
5	-Bn	1/100/8	1	<1	
6	-C(O)CH_3	1/100/8	1	<1	

[a] Conditions: mol (cat.) = 0.0045 mmol (5.89×10^{-4} M), mol (imine) = 0.45 mmol (5.89×10^{-2} M), mol (KO*t*Bu) = 0.036 mmol (4.71×10^{-3} M), m (2-PrOH) = 6 g; temperature = 30 °C. [b] mol (imine) = 1.35 mmol.

Table 2. Asymmetric Transfer Hydrogenation of *N*-(Diphenylphosphinoyl)-acetophenimine[a]



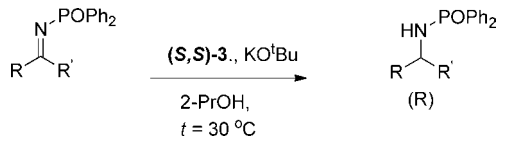
entry	cat.	conv [%]	ee [%]	conf
1	**(*S*,*S*)-1**	99	91	(*R*)
2	**(*R*,*R*)-2**	72	96	(*S*)
3	**(*S*,*S*)-3**	94	>99	(*R*)
4	**(*S*,*S*)-4**	70	>99	(*R*)
5	**(*S*,*S*)-5**	11	>98	(*R*)
6	**(*R*,*R*)-6**	15	94	(*S*)
7	**7**	17		

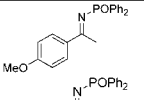
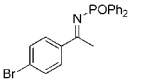
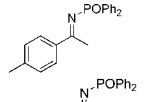
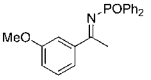
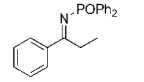
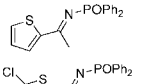
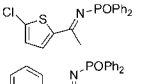
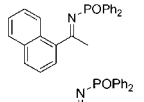
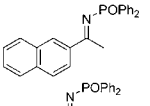
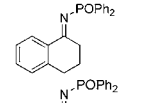
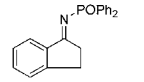
[a] Conditions: mol (cat.) = 0.0045 mmol, mol (imine) = 0.45 mmol, mol (KO*t*Bu) = 0.0036 mmol, m (2-PrOH) = 6 g; at 30 °C for 40 min.

of the substrate. Imines containing heteroaromatic groups (Table 3, entries 6 and 7) were also successfully reduced with exeptional enantioselectivities indicating that the sulfur atom does not coordinate to the active complex. Imines containing naphthyl substituents (Table 3, entries 8 and 9) were reduced with high enantioselectivity. A higher catalyst loading was required for the successful reduction of the imine group at the 1 position of naphthalene than for one at the 2 position due to the greater steric constraints of the imine carbon in the former compound. Low yields of the reaction were obtained for the cyclic imines (Table 3, entries 10 and 11) even at high catalyst loading possibly due to the rigidity of the imine carbon moiety. Nevertheless, the enantiomeric excess of the corresponding amines was high.

In conclusion, this study shows that well-defined iron(II) complexes containing PNNP ligands, which are highly active and enantioselective catalysts for the ATH of ketones, are also active and very enantioselective for the asymmetric reduction of *N*-(diphenylphosphinoyl)- and *N*-(*p*-tolylsulphonyl)-ketimines. Specifically, precatalyst

Table 3. Asymmetric Transfer Hydrogenation of *N*-(Diphenylphosphinoyl)-imines using Well-defined Precatalyst **(*S*,*S*)-3**[a]



entry	substrate	time (min)	(*S*,*S*)-3 [mol %]	conv [%]	ee [%]
1		40	1	91	98
2		40	1	92	95
3		40	1	90	>99
4		40	1	91	>99
5		120	1	91	>99
6		60	2	83	98
7		60	2	80	97
8		60	3	40	98
9		60	1	90	98
10		60	4	30	96
11		60	4	29	98

[a] General conditions: mol (cat.) = 0.0045 mmol (1 mol % loading), mol (imine) = 0.45 mmol, mol (KO*t*Bu) = 0.0036 mmol, m (2-PrOH) = 6 g; at *t* = 30 °C.

(*S*,*S*)-3 is the most selective and active well-defined system reported to date. The reactivity of the catalyst was found to be very sensitive to the sterics around the imine carbon but unresponsive toward variation of the electronic properties of the substrate.

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Supporting Information Available. General experimental procedure that was used for the catalytic reduction of imines, spectroscopic information and retention times observed for different stereoisomers of the amines. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.