

New P,N-Ferrocenyl Ligands for the Asymmetric Ir-Catalyzed Hydrogenation of Imines

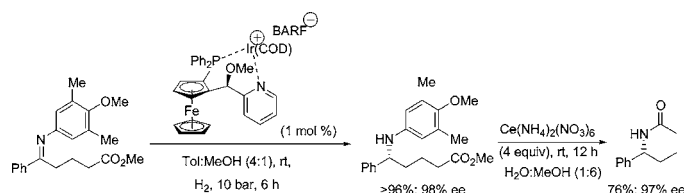
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ABSTRACT



The Ir-catalyzed enantioselective hydrogenation of various *N*-(3,5-dimethyl-4-methoxy)phenylimines was performed under mild conditions in the presence of new P,N-ferrocenyl iridium complexes leading to (*R*)-*N*-(3,5-dimethyl-4-methoxy)phenylamines in high yields and enantioselectivities (up to 99%). These chiral aryl amines can be readily deprotected using Ce(NH₄)₂(NO₃)₆.

The asymmetric synthesis of chiral amines is an important synthetic task since these structural units are part of numerous biologically relevant compounds.¹ In the past decade, the synthesis of chiral benzylic amines through asymmetric hydrogenation of imines received much attention.² Although many catalysts were developed for the asymmetric imine hydrogenation, most of them are only suitable for cyclic substrates. The reduction of acyclic imines with high enantioselectivities is still a major challenge in this field.³ Recently, chiral Ir complexes have been successfully used as catalysts for the highly enantioselective reduction of imines.⁴ Recent results on the Ir-catalyzed reduction of (*Z*)-

α -methylacetamidocinnamate using chiral terpene-derived ligands⁵ led us to study the use of readily available ferrocenyl ligands^{6,7} for the Ir-catalyzed imine reduction. Herein, we report a novel class of chiral P,N-ferrocenyl ligands and their use for the enantioselective reduction of imines (up to 99% ee). Thus, the treatment of (*S*)-ferrocenyl sulfoxide⁸ **1** with

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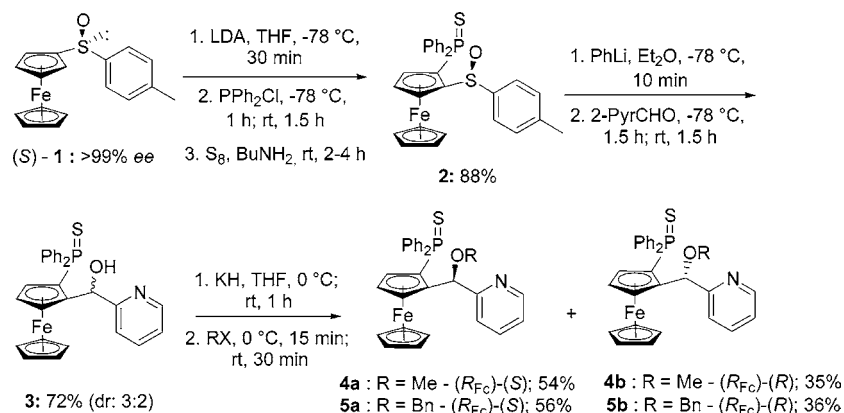
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Scheme 1



LDA ($-78\text{ }^{\circ}\text{C}$, 0.5 h) followed by the addition of ClPPh_2 ($-78\text{ }^{\circ}\text{C}$, 1 h, then $25\text{ }^{\circ}\text{C}$, 1.5 h) led to an air-sensitive

72% yield. This inseparable mixture of alcohols was alkylated with MeI or PhCH_2Br (KH, THF, $0\text{ }^{\circ}\text{C}$, 1 h then

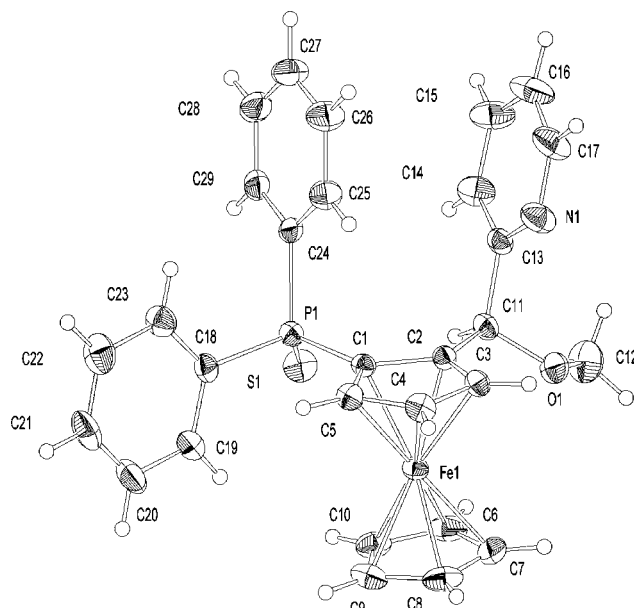


Figure 1. X-ray structure of the P,N-ligand **4b**.

diphenylphosphine derivative which was protected in situ with sulfur in BuNH_2 ($25\text{ }^{\circ}\text{C}$, 2–4 h) leading to the phosphinothioylferrocene **2** in 88% yield. The performance of a sulfoxide/lithium exchange^{8b} using phenyllithium⁹ (THF, $-78\text{ }^{\circ}\text{C}$, 10 min) followed by the addition of 2-pyridinecarboxaldehyde ($-78\text{ }^{\circ}\text{C}$, 1.5 h, then $25\text{ }^{\circ}\text{C}$, 1.5 h) leads to a 3:2 mixture of two diastereomeric ferrocenyl alcohols **3** in

Table 1. Asymmetric Hydrogenation of Imines **10a** Using the Catalysts **8a–9b**^a

entry	L*	solvent	conversion ^b (%)	ee ^c (%)
1	8b	toluene	96	11 (S)
2	8b	Tol/MeOH (1:1)	63	56 (S)
3	8b	MeOH	23	39 (S)
4	8b	Tol/MeOH (4:1)	72	67 (S)
5	8a	Tol/MeOH (4:1)	100	84 (R)
6	9a	Tol/MeOH (4:1)	100	84 (R)
7	9b	Tol/MeOH (4:1)	75	65 (S)
8 ^d	8a	Tol/MeOH (4:1)	100	84 (R)
9 ^e	8a	Tol/MeOH (4:1)	100	80 (R)

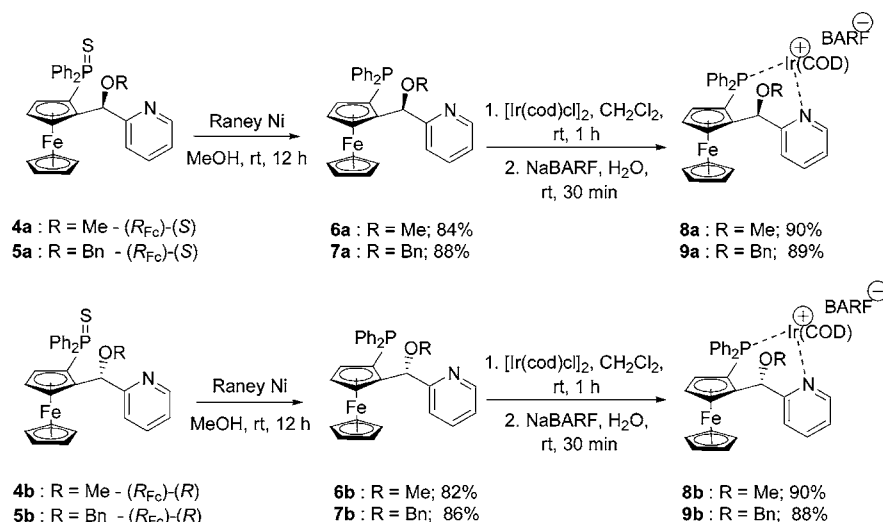
^a Reaction conditions: imine **10a** (0.5 mmol), catalyst (1 mol %), 10 bar, H_2 , rt. ^b Conversion was measured by Chiral GC or ^1H NMR after 2 h. ^c Enantioselectivity was determined by Chiral GC using a DEX-CB column. The configuration of amine **11a** is shown in parentheses. ^d Reaction was performed using 0.5 mol % of the catalyst, and full conversion was achieved in 3 h. ^e Reaction was performed using 0.25 mol % of the catalyst, and full conversion was achieved in 12 h.

MeI ($25\text{ }^{\circ}\text{C}$, 0.5 h) or PhCH_2Br ($25\text{ }^{\circ}\text{C}$, 0.5 h)) leading to readily separable ferrocenyl ethers **4a** (54%) and **4b** (35%)

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Scheme 2



or **5a** (56%) and **5b** (36%), respectively (Scheme 1). The relative stereochemistry of ferrocenes **4** and **5** was determined by X-ray analysis (Figure 1).¹⁰

Table 2. Asymmetric Hydrogenation of Imines **10a–h** and **12a** Using the Ir Complex **8a**

entry	imine	R	time ^a (h)	ee ^{b,c} (%)
1	10a	H	2	84 (84)
2	10b	4-MeO	2	85 (85)
3	10c	3,5-dimethyl	2	94 (93)
4	12a	3,5-dimethyl-4-methoxy	2	94 (92)

^a Time to achieve full conversion. ^b Enantioselectivity was determined by HPLC (Chiralcel OD-H) or by GC using a Chiral Dex-CB column. ^c Enantioselectivities obtained by using the catalyst **9a** are shown in parentheses.

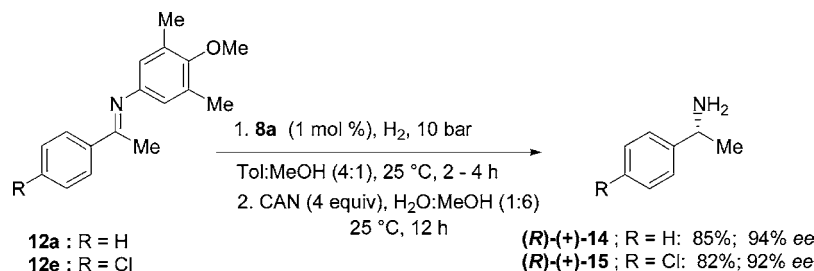
The four ferrocenyl derivatives **4a,b** and **5a,b** were smoothly desulfurized (Raney Ni, MeOH, 25 °C, 12 h)¹¹

leading to the air stable P,N-derivatives **6a,b** and **7a,b** in 82–86% yield. Their reaction with [Ir(COD)Cl]₂ in CH₂Cl₂ (25 °C, 1 h) followed by the addition of NaBARF¹² in water (25 °C, 0.5 h) led to the four chiral iridium complexes **8a,b** and **9a,b** in 88–90% yield (Scheme 2).

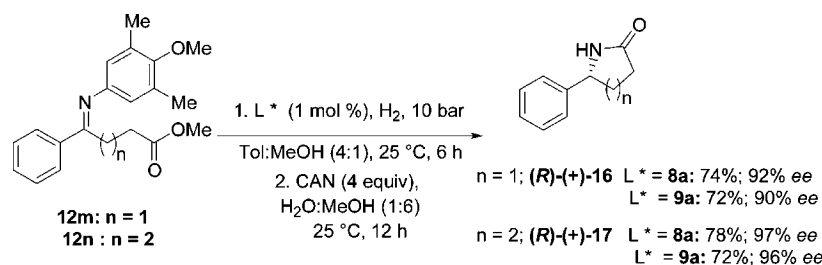
We have investigated the use of these readily available Ir catalysts **8a–9b** for the asymmetric reduction of aromatic imines using *N*-phenylethylideneamine **10a** as the model substrate. Preliminary studies indicate that catalysts **8a** and **9a** give the best enantioselectivities and reaction rates in the mixture of toluene and methanol (4:1) (Table 1).

To improve the asymmetric imine hydrogenation further, we have varied the aryl substituent attached to the imine nitrogen (Table 2). Whereas the hydrogenation of the imine **10a** (R = H) led to the chiral phenethylamine **11a** under mild conditions (10 bar, 25 °C, 2 h) in quantitative yield and 84% ee (entry 1 of Table 2), we noticed that the use of electron-rich imine **10b** (R = 4-MeO) led to an improved enantioselectivity of 85% ee (entry 2). Interestingly, hydrogenation of the imine **10c** (R = 3,5-dimethyl) gives the corresponding secondary amine **11c** in 93–94% ee (entry 3). However, due to difficulties for performing the deprotection of the phenylethylamine **11c**, we chose the second best imine (**12a** : R = 3,5-dimethyl-4-methoxy; entry 4), which leads to the phenylethylamine derivative **13a** in 92–

Scheme 3



Scheme 4



94% ee. It was anticipated that the deprotection of compounds like **13** would occur under mild conditions.

Table 3. Asymmetric Hydrogenation of Imines **12a–l** Using the Ir Complex **8a**

entry	imine	Ar	R	time ^a (h)	ee ^{b,c} (%)
1	12a	Ph	Me	2	94 (92)
2	12b	3-MeC ₆ H ₄	Me	2	93 (92)
3	12c	4-PhC ₆ H ₄	Me	2	92 (90)
4	12d	4-CF ₃ C ₆ H ₄	Me	2	89 (88)
5	12e	4-ClC ₆ H ₄	Me	4	92 (92)
6	12f	4-MeCO ₂ C ₆ H ₄	Me	4	94 (92)
7	12g	3-FC ₆ H ₄	Me	2	93 (91)
8	12h	2-MeC ₆ H ₄	Me	6	94 (93)
9	12i	2-naphthyl	Me	2	93 (93)
10	12j	Ph	Et	2	94 (92)
11	12k	Ph	Pent	4	95 (94)
12	12l	Ph	-(CH ₂) ₃ COPh	6	99 (98)

^a Time to achieve full conversion. ^b Enantioselectivity was determined by HPLC using Chiracel OD-H or by Chiracel-AD column. ^c Enantioselectivities obtained by using the catalyst **9a** are shown in parentheses.

We have prepared a range of imines of type **12** and have obtained uniformly high enantioselectivities (89–99% ee; Table 3) in asymmetric hydrogenation using the catalysts **8a** and **9a**. The catalyst **8a** generally provides slightly better results compared to the catalyst **9a** (Table 3). Both electron-donating (entries 2, 3, 8, and 9) as well as electron-withdrawing substituents (entries 4, 5, 6 and 7) gave good results. Extending this asymmetric imine hydrogenation with

catalysts **8a** and **9a** to various kinds of imines bearing a side chain at the α-position such as **12j** and **12k** led to the corresponding secondary amines **13j** and **13k** in 94 and 95% ee, respectively (entries 10 and 11). Interestingly, the reduction of the imine **12l** bearing a remote keto group proceeded quantitatively, yielding the corresponding amine **13l** in 99% ee (entry 12).

The deprotection of the 3,5-dimethyl-4-methoxyphenyl moiety of amines of type **13** occurs smoothly with cerium ammonium nitrate (CAN; Ce(NH₄)₂(NO₃)₆)¹³ in a 6:1 MeOH/H₂O mixture, providing the corresponding primary amines in good yields (Scheme 3).

Furthermore, we extended this protocol to the asymmetric synthesis of chiral γ and δ-lactams.^{14,15} Thus, the imines **12m** and **12n** bearing a remote ester group were subjected to the asymmetric hydrogenation, and after subsequent deprotection of the *N*-aromatic group, 5-phenyl-2-pyrrolidinone **16** and 6-phenyl-2-piperidinone **17** were obtained in 74% yield, 92% ee and 78% yield, 97% ee, respectively (Scheme 4).

In summary, we have prepared new ferrocenyl P,N-ligands which are effective for the Ir-catalyzed asymmetric hydrogenation of acyclic *N*-arylimines, providing various chiral phenylalkylamines with high enantioselectivities. This method can be used to prepare γ- and δ-lactams in 92–97% ee. Study of further applications of these ligands in asymmetric catalysis is currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Full details about atomic coordinates, bond lengths, and bond angles, can be obtained from The Cambridge Crystallographic Data Centre (CCDC 627426) via www.ccdc.cam.ac.uk/data-request/cif.

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