ORGANIC LETTERS

2007
Vol. 9, No. 16
3089−3092

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

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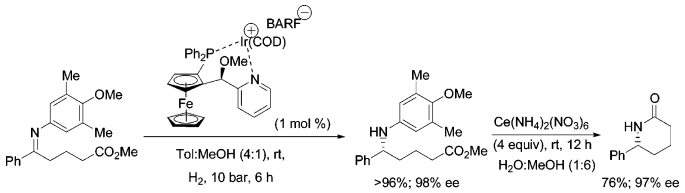
Received May 18, 2007

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 $Ce(NH_4)_2(NO_3)_6$.

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 ligands[5] 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 sulfoxide[8] **1** with

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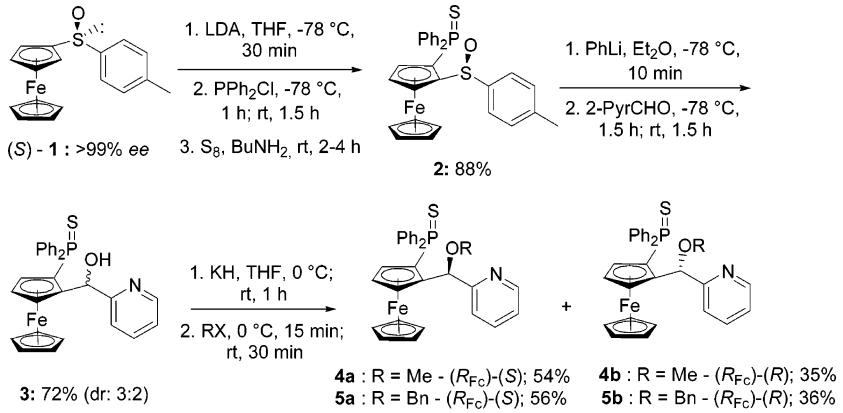
10.1021/ol071168t CCC: $37.00
Published on Web 07/07/2007

Scheme 1



LDA (−78 °C, 0.5 h) followed by the addition of $ClPPh_2$ (−78 °C, 1 h, then 25 °C, 1.5 h) led to an air-sensitive diphenylphosphine derivative which was protected in situ with sulfur in $BuNH_2$ (25 °C, 2−4 h) leading to the phosphinothioylferrocene **2** in 88% yield. The performance of a sulfoxide/lithium exchange[8b] using phenyllithium[9] (THF, −78 °C, 10 min) followed by the addition of 2-pyridinecarboxaldehyde (−78 °C, 1.5 h, then 25 °C, 1.5 h) leads to a 3:2 mixture of two diastereomeric ferrocenyl alcohols **3** in 72% yield. This inseparable mixture of alcohols was alkylated with MeI or $PhCH_2Br$ (KH, THF, 0 °C, 1 h then MeI (25 °C, 0.5 h) or $PhCH_2Br$ (25 °C, 0.5 h)) leading to readily separable ferrocenyl ethers **4a** (54%) and **4b** (35%)

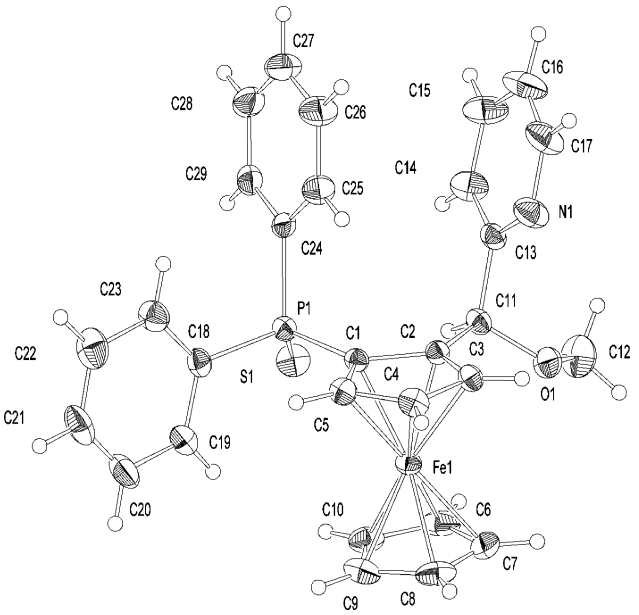
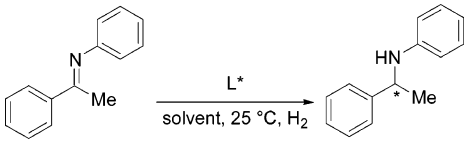


Figure 1. X-ray structure of the P,N-ligand **4b**.

Table 1. Asymmetric Hydrogenation of Imines **10a** Using the Catalysts **8a**−**9b**[a]



10a **11a**

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.

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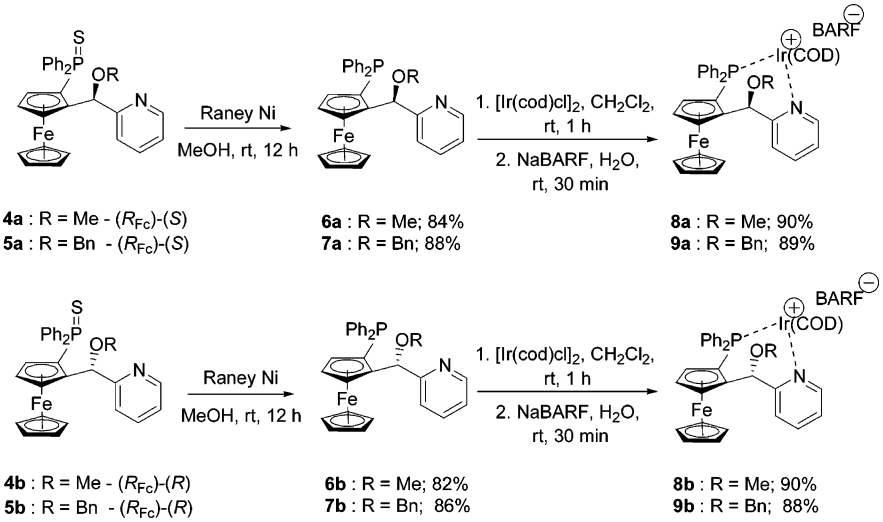
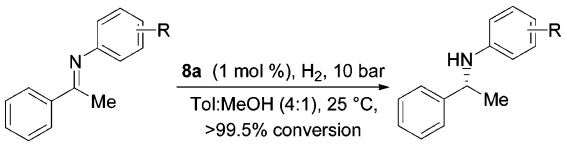
Scheme 2



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)

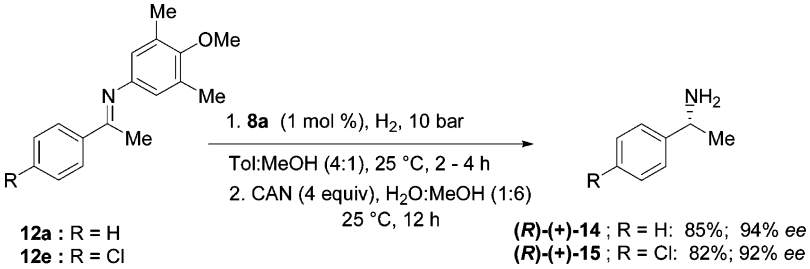
[a] Time to achieve full conversion. [b] Enantioselectivity was determined by HPLC (Chiralcel OD-H) or by GC using a Chiral Dex-CB column. [c] Enantioselectivities obtained by using the catalyst **9a** are shown in parentheses.

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 CH_2Cl_2 (25 °C, 1 h) followed by the addition of NaBARF[12] 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).

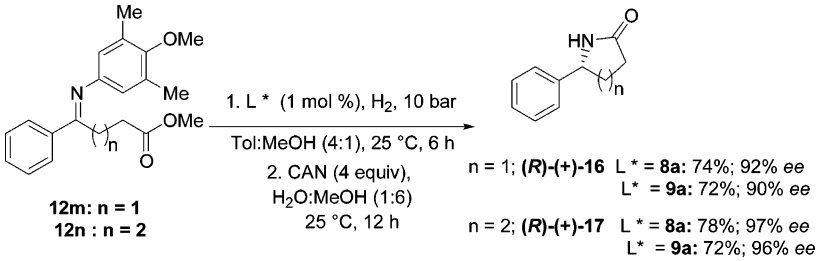
We have investigated the use of these readily available Ir catalysts **8a**−**9b** for the asymmetric reduction of aromatic imines using *N*-phenylethylideneamine **10a** as the model substrate. Preliminary studies indicate that catalysts **8a** and **9a** give the best enantioselectivities and reaction 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

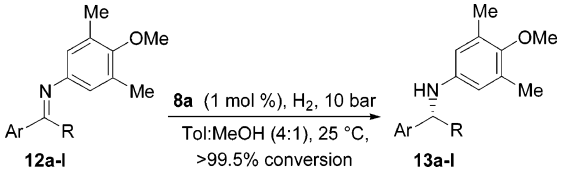


Scheme 4



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_6H_4	Me	2	93 (92)
3	**12c**	4-PhC_6H_4	Me	2	92 (90)
4	**12d**	4-$CF_3C_6H_4$	Me	2	89 (88)
5	**12e**	4-ClC_6H_4	Me	4	92 (92)
6	**12f**	4-$MeCO_2C_6H_4$	Me	4	94 (92)
7	**12g**	3-FC_6H_4	Me	2	93 (91)
8	**12h**	2-MeC_6H_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	$-(CH_2)_3COPh$	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; $Ce(NH_4)_2(NO_3)_6$)[13] in a 6:1 MeOH/H_2O 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.

Acknowledgment. We thank the Fonds der Chemischen Industrie for the financial support and Merck Research Laboratories (MSD), Chemetall GmbH (Frankfurt), and BASF AG (Ludwigshafen) for generous gift of chemicals.

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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