Asymmetric Hydrogenations

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Diphenylphosphanylsulfoximines as Ligands in Iridium-Catalyzed Asymmetric Imine Hydrogenations**

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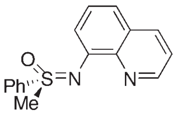
Chiral amines are ubiquitous in natural products and drugs, and their synthesis by asymmetric hydrogenation of carbon–nitrogen double bonds has attracted much attention.[1] However, the search for and development of efficient catalysts for enantioselective C–N double bond hydrogenations with high enantioselectivity at a reasonable catalyst loading proved much more difficult than for the reduction of C=C and C=O groups.[2–5] Furthermore, most of those catalysts are only suitable for asymmetric hydrogenations of cyclic substrates, whereas acyclic imines still represent challenging compounds.[6] In this case, one of the major problems for achieving a high enantiomeric excess is the equilibrium between the *E* and *Z* isomer of the imine,[7] which makes it difficult for the catalyst to convert all stereoisomers in a uniform and selective manner. Consequently, the first successful chiral catalysts for this important transformation have only recently been described. Among them, homogenous Ir complexes with chiral P,P- or P,N-ligands, which are structurally analogous to Crabtree's catalyst,[8] have attracted particular attention. For example, Zhang and co-workers reported enantioselective hydrogenations of *N*-aryl imines (with up to >99% *ee*) by applying an iridium catalyst bearing a chiral 1,1′-bisphosphanylferrocene (f-binaphane).[9] Phosphanyloxazoline complexes with noncoordinating anions have been used by several group to afford products with up to 90% *ee*.[10] Industrially relevant in this context is the asymmetric hydrogenation of an acyclic *N*-aryl imine as key step in the synthesis of the herbicide (*S*)-metolachlor by Syngenta.[11] Although only moderate enantioselectivities are achieved, the exceptionally high turnover numbers (TON) and turnover frequencies (TOF) of the iridium-ferrocenylphosphine catalyst allowed this imine reduction to become one of the largest catalytic enantioselective industrial processes to date.

Chiral sulfoximines are versatile ligands for asymmetric catalysis,[12] and highly enantioselective hetero-Diels–Alder reactions,[13] Mukaiyama-type aldol,[14] and carbonyl-ene reactions[15] with sulfoximine-based catalysts have recently been described. In all these catalytic reactions, dinitrogen chelates such as **1** or **2** with sulfoximine units linked to quinoline or aniline moieties were applied. We thus focused our attention on the synthesis and use of phosphine-substituted sulfoximines **3**, which on the basis of conclusions from solution and solid-state studies[13c,16] were expected to be good metal binders through their P and N donor sites.



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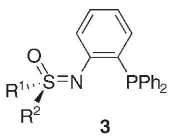

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For the preparation of diphenylphosphanyl sulfoximines **3**, phosphine oxide **4**, which can be obtained by palladium-catalyzed cross-coupling of 2-bromo-1-iodobenzene with diphenylphosphane, served as starting material.[17] Application of the newly developed copper-mediated *N*-arylation reaction[18] afforded products **6a–f** from **4** and sulfoximines **5a–f**, respectively, in moderate to good yields (Scheme 1). Reductive deoxygenation of **6** with trichlorosilane gave diphenylphosphanylsulfoximines **3** as solid, air-stable products in 55–81% yield.

Guided by the successful applications of other P,N-ligands as effective hydrogenation catalysts,[3–5,19] the novel sulfoximine derivatives **3** were tested in Ir-catalyzed asymmetric imine hydrogenations. For the initial screening and optimizing process, acetophenone-derived imine **7a** was selected as substrate. To our delight we found that the catalyst generated by mixing $[\{Ir(cod)Cl\}_2]$ (0.5 mol%) with sulfoximine **3a** (1.1 mol%) followed by the addition of iodine (2.0 mol%) led to full conversion of **7a** under H_2 into **8a** with rather encouraging 79% *ee* (Scheme 2).

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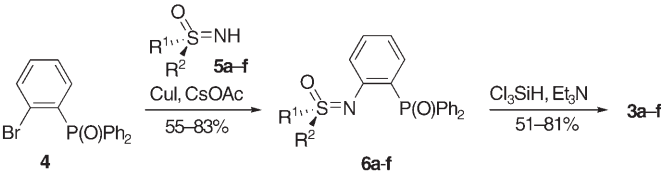
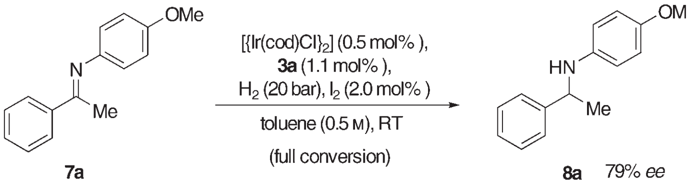


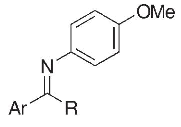
a: R^1 = Ph; R^2 = Me
b: R^1 = Ph; R^2 = *i*Pr
c: R^1 = Ph; R^2 = *c*Pent
d: R^1 = Ph; R^2 = *i*Bu
e: R^1 = Me; R^2 = 2-MeO-C_6H_4
f: R^1 = Me; R^2 = 3,5-xylyl

Scheme 1. Synthesis of the diphenylphosphanylsulfoximines **3**.



Scheme 2. Ir-catalyzed asymmetric imine hydrogenation.

Subsequent experiments revealed that no reaction occurred in the absence of iodine, which indicated that the $\mathrm{Ir^I}$ complex formed in situ was only a precatalyst, which most likely was further oxidized by iodine.[20] Hydrogenations of analogous substrates showed that the aryl group on the imine nitrogen atom had a strong effect on the reactivity and selectivity of the catalyst. The best result was achieved with the imine bearing the *N*-(*p*-methoxy)phenyl (PMP) group, which can easily be removed by oxidative methods. Use of the *N*-(*o*-methoxy)phenyl-protected substrate **9a** led to lower reactivity and enantioselectivity (58 % *ee* after 20 h). No reaction occurred with imine **10a** bearing the *N*-mesityl group.



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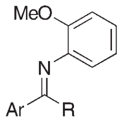

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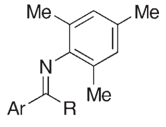

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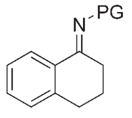
a: Ar = Ph, R = Me
b: Ar = Ph, R = Et
c: Ar = 2-MeC$_6$H$_4$, R = Me
d: Ar = 3-MeC$_6$H$_4$, R = Me
e: Ar = 4-MeC$_6$H$_4$, R = Me
f: Ar = 2-MeO-C$_6$H$_4$, R = Me
g: Ar = 3-MeO-C$_6$H$_4$, R = Me
h: Ar = 4-MeO-C$_6$H$_4$, R = Me
i: Ar = 4-Cl-C$_6$H$_4$, R = Me
j: Ar = 1-Naphtyl, R = Me
k: Ar = 2-Naphthyl, R = Me



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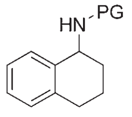

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PG = *p*MeOPh

Next, the influence of the ligand structure on the catalyst performance in the test reaction depicted in Scheme 2 was studied. Increasing the steric bulk of the alkyl substituent of the sulfoximine α to the sulfur atom drastically lowered both the activity and the enantioselectivity of the resulting catalysts. Thus, use of **3b** and **3c** bearing *S*-isopropyl or *S*-cyclopentyl groups resulted in low conversions of **7a** (<40 %), even after extended reaction times, to give **8a** with 66 and 10 % *ee*, respectively (Table 1, entries 2 and 3). Surprisingly, however, the effect of branching at the β position of the sulfoximine alkyl group was opposite, and the catalyst efficiency increased remarkably! Thus, with isobutyl-substituted sulfoximine **3d** an excellent conversion of **7a** was achieved after only 4 h, and the enantioselectivity of the resulting amine **8a** reached an unprecedented 96 % *ee* (Table 1, entry 4). Sulfoximines **3e** and **3f**, which have modified *S*-aryl groups, led to active catalysts as well (99 % conversion after 12 h; Table 1, entries 5 and 6), but in these cases the enantioselectivities were lower (50 and 88 % *ee*, respectively) than those attained with **3d**.

As the Ir catalyst with sulfoximine ligand **3d** performed exceptional well in the test reaction (Scheme 2), we briefly studied its catalytic behavior under modified reaction conditions. A decrease in the catalyst loading to 0.5 mol % did not result in any change in the enantioselectivity. With 0.1 mol % of catalyst, the hydrogen pressure had to be increased to 50 bar to achieve full conversion.[21] Toluene was the solvent of choice, and lowering the reaction temperature led to a slight increase in enantioselectivity (97 % *ee* at 0 °C).[22]

Table 1: Influence of the ligand structure on the asymmetric hydrogenation of imine **7a**.[a]

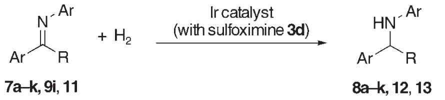
Entry	Sulfoximine	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*S*)-**3a**	4	99	79 (−)
2	(*S*)-**3b**	8	40	66 (−)
3	(*S*)-**3c**	20	<20	10 (−)
4	(*S*)-**3d**	4	99	96 (−)
5	(*R*)-**3e**	12	99	50 (+)
6	(*R*)-**3f**	12	99	88 (+)

[a] Reaction conditions: imine **7a** (0.5 mmol), [{Ir(cod)Cl}$_2$] (0.0025 mmol), sulfoximine **3** (0.0055 mmol), iodine (0.01 mmol), H$_2$ (20 bar), toluene (0.5 M), room temperature. [b] Determined by ^{1}H NMR spectroscopy. [c] The enantiomer ratios were determined by HPLC by using a column with a chiral stationary phase (Chiralcel OD-H). The direction of the optical rotation of **8a** is given in parenthesis.

To explore the scope of the Ir-catalyzed asymmetric hydrogenation with the catalyst based on sulfoximine **3d**, a series of imines with 4-methoxyphenyl groups on the imine nitrogen atom were reduced under the optimized reaction conditions (Table 2).

The data can be summarized as follows: Substrates with *meta-* or *para*-substituents on the arene (e.g. **7d**, **7e**, **7g–i**) reacted equally well as unsubstituted **7a** to afford the corresponding aryl-protected amines with enantioselectivities in the range 93–96 % *ee* (Table 2, entries 4, 5, 7–9). Although *ortho*-substituted imines **7c**, **7f**, and **7j** were applied as mixtures of double-bond isomers, they also gave products with excellent enantioselectivities (90–98 % *ee*; Table 2, entries 3, 6, and 10). Imine **7b**, which was derived from propiophenone (and isolated as a 7:1 mixture of *E*/*Z* isomers),

Table 2: Ir-catalyzed asymmetric hydrogenations of imines **7**.[a]



Entry	Imine	t [h]	ee [%][b]
1	**7a**	4	96 (−)
2	**7b**[c]	4	92 (−)
3	**7c**[c]	6	94 (+)
4	**7d**	4	93 (−)
5	**7e**	4	96 (−)
6	**7f**[c]	6	90 (+)
7	**7g**	4	96 (−)
8	**7h**	4	94 (−)
9	**7i**	4	95 (−)
10	**7j**[c]	6	98 (+)
11	**7k**	4	69 (−)
12	**9i**	12	75 (+)
13	**11**	4	91 (−)

[a] Reaction conditions: imine **7** (0.5 mmol), [{Ir(cod)Cl}$_2$] (0.0025 mmol), sulfoximine **3d** (0.0055 mmol), iodine (0.01 mmol), H_2 (20 bar), toluene (0.5 M), room temperature. In all cases, full conversion was achieved. [b] The enantiomer ratios were determined by HPLC using a column with a chiral stationary phase (Chiralcel OD-H). The directions of the optical rotations of amines **8** are given in parentheses. [c] Mixture of isomers; for details see the Supporting Information.

was hydrogenated to the corresponding amine with 92 % *ee* (Table 2, entry 2). Interestingly, the two isomeric naphthyl-substituted imines **7j** and **7k** afforded products with very different enantiomeric excesses. Whereas the first led to the corresponding amine with 98 % *ee*, the latter gave the product with only 69 % *ee* (Table 2, entries 10 and 11). Even when the alkyl group was incorporated into a cyclic structure, a high enantioselectivity was attained, as illustrated by the asymmetric hydrogenation of tetralone-derived imine **11** (91 % *ee*; Table 2, entry 13). Also with the catalyst bearing sulfoximine **3d** as ligand, switching the substituent at the imine nitrogen atom from the *para*- to the *ortho*-substituted arene led to a significant lower enantioselectivity (Table 2, entry 12).

In conclusion, we introduced a novel class of C_1-symmetric sulfoximines, which can effectively be used in Ir-catalyzed asymmetric hydrogenations of acyclic *N*-aryl imines. Under optimized reaction conditions, high enantioselectivities and reaction rates have been attained for a variety of *N*-(4-methoxy)phenyl imines. Currently, the application of these novel sulfoximines in other catalytic asymmetric processes is under investigation.

Experimental Section

3d: In an oven-dried Schlenk flask under an argon atmosphere sulfoximine **6d** (446 mg, 0.94 mmol) was dissolved in toluene (3 mL). The solution was cooled to 0 °C, and NEt_3 (655 μL, 4.70 mmol) and trichlorosilane (470 μL, 4.70 mmol) were added. The heterogenous mixture was stirred for 12 h at 105 °C. The reaction mixture was then cooled to room temperature, and degassed water (3 mL) was added. The solid was filtered through a small plug of celite and thoroughly rinsed with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to dryness. The pure product was obtained as a colorless solid (344 mg, 81 %) after flash chromatography (SiO_2; pentane/acetone 10:1). For analytical data, see the Supporting Information.

General procedure: Under an argon atmosphere [{Ir(cod)Cl}$_2$] (1.7 mg, 0.0025 mmol) and sulfoximine **3d** (2.5 mg, 0.0055 mmol) were placed in a 10-mL test tube equipped with a stirrer bar. After the addition of dry toluene (0.5 mL), the yellow solution was stirred for 30 min. Iodine (2.5 mg, 0.010 mmol) was then added, and the solution turned red within 30 min. To this catalyst solution was added the imine (0.5 mmol) and additional toluene (0.5 mL). The test tube was placed in an argon-filled steel autoclave, which was purged three times with hydrogen (5 bar) and finally pressurized to 20 bar. The reaction mixture was stirred for the indicated period of time. Then, the hydrogen gas was released and the reaction quenched by addition of pentane (3 mL). The product was filtered through a short plug of silica (3 cm) and eluted with pentane/acetone (20:1).

The conversions were determined by ^{1}H NMR spectroscopy, and the enantiomer ratio analyzed with analytical HPLC by using chiral columns. For details, see the Supporting Information.

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Keywords: amines · asymmetric catalysis · hydrogenation · imines · sulfoximines

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[21] With 0.5 mol% of the catalyst at 20 bar of H_2 pressure, the conversion of **7a** was > 99% after 4 h, and **8a** was obtained with 95% *ee*. Use of 0.1 mol% of the catalyst required 50 bar of H_2 pressure for full conversion after 4 h to obtain **8a** with 95% *ee*.

[22] For details, see the Supporting Information.