Chiral Phosphine−Phosphoramidite Ligands for Highly Efficient Ir-Catalyzed Asymmetric Hydrogenation of Sterically Hindered *N*-Arylimines
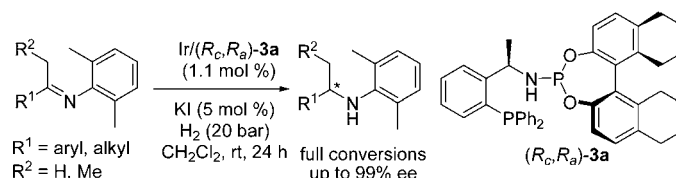
Chuan-Jin Hou,[†,‡] Ya-Hui Wang,[†] Zhuo Zheng,[†] Jie Xu,[†] and Xiang-Ping Hu*,[†]

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China, and School of Light Industry and Chemical Engineering, Dalian Polytechnic University, 1 Qinggongyuan, Dalian 116034, China

xiangping@dicp.ac.cn

ABSTRACT

A mild and general iridium-catalyzed, highly enantioselective hydrogenation of sterically hindered *N*-arylimines with a new H$_8$-BINOL-derived phosphine−phosphoramidite ligand has been developed. The present catalytic system features high turnover numbers (up to 100000) and good to perfect enantioselectivities (up to 99% ee) for the hydrogenation of a variety of sterically hindered *N*-arylimines.

Chiral amines are important synthetic intermediates in the preparation of many physiologically active compounds. As a result, significant efforts have been devoted to the asymmetric synthesis of these compounds via catalytic methods.[1] For its inherent efficiency and atom economy, catalytic asymmetric hydrogenation of prochiral imines has emerged as one of the most direct and convenient approaches to chiral amines and their derivatives.[2] To date, a variety of imine frameworks including cyclic and acyclic imines have proven to be suitable substrates.[3] However, asymmetric hydrogenation of sterically hindered

imines remains scarely explored,[4] despite the fact that the corresponding chiral amines are important building blocks in organic synthesis and agrochemistry. Except for a relevant example on the industrial production of the key intermediate for chiral herbicide (*S*)-metolachlor,[5] the most impressive example in this area was described by Zhang et al.,[6] in which high enantioselectivities were observed in the hydrogenation of some sterically hindered *N*-arylalkylarylimines employing an Ir catalyst with a ferrocenyldiphosphine ligand, (*R*,*R*)-f-binaphane. However, incomplete conversion was observed by using 2 mol % of a Ir−f-binaphane complex and under a H$_2$ pressure of 1000 psi. In addition, this catalytic system failed in the hydrogenation of sterically hindered *N*-aryldialkylimines. Therefore, the development of a highly efficient catalytic system that successfully addressed the challenges of low reactivity, narrow substrate scope, and harsh hydrogenation conditions encountered in the hydrogenation of

[†] Dalian Institute of Chemical Physics.

[‡] Dalian Polytechnic University.

(1) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010.

(2) Blaser, H.-U.; Spinder, F. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007.

(3) For main reviews, see: (a) Fleury-Bregeot, N.; de la Fuente, V.; Castillon, S.; Claver, C. *ChemCatChem* **2010**, *2*, 1346–1371. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713–1760.

(4) (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401. (b) Sablong, R.; Osborn, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3059–3062. (c) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Kruger, C.; Pfaltz, A. *Chem.—Eur. J.* **1997**, *3*, 887–892. (d) Blaser, H.-U.; Buser, H.-P.; Hausel, R.; Jalett, H.-P.; Spindler, F. *J. Organomet. Chem.* **2001**, *621*, 34–38.

(5) (a) Blaser, H.-U.; Buser, H.-P.; Loers, K.; Hanreich, R.; Jalett, H. P.; Jelsch, E.; Pugin, B.; Schneider, H. D.; Spindler, F.; Wagmann, A. *Chimia* **1999**, *53*, 275–280. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spinder, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151.

(6) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425–3428.

sterically hindered imines would represent a significant advancement.

Recently, we have developed a family of unsymmetrical hybrid phosphine—phosphoramidite ligands, (S_c,S_a)-PEA-Phos **1** and (R_c,R_a)-THNAPhos **2** (Figure 1), which are highly efficient for the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins.[7] A drive to further explore the potential of these ligands prompted us to investigate its application in the Ir-catalyzed asymmetric hydrogenation of imines, focusing on the challenging sterically hindered *N*-arylimines. Although phosphine—phosphoramidite ligands can generate highly active and enantioselective catalysts with different metal centers,[8−13] to the best of our knowledge, their application in the Ir-catalyzed asymmetric hydrogenation of acyclic imines has not yet been reported. Herein we described a mild and general iridium-catalyzed, highly enantioselective hydrogenation of sterically hindered *N*-arylimines with a new H_8-BINOL-derived phosphine—phosphoramidite ligand, in which high turnover numbers (up to 100000) and good to excellent enantioselectivities (up to 99% ee) were achieved.

With *N*-(2,6-dimethylphenyl)-1-phenylethylideneamine **4a** as a model substrate, an initial attempt at the Ir-catalyzed asymmetric hydrogenation was carried out
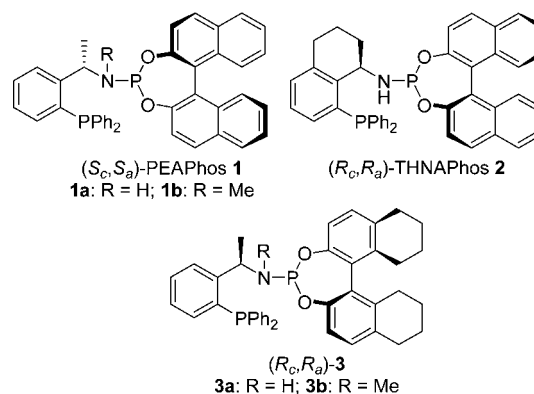
Figure 1. Chiral phosphine—phosphoramidite ligands (S_c,S_a)-PEAPhos **1**, (R_c,R_a)-THNAPhos **2**, and (R_c,R_a)-**3**.

in the presence of 1 mol % of catalyst prepared in situ from [Ir(COD)Cl]$_2$ and 2.2 equiv of chiral ligand with KI as an additive and under a H$_2$ pressure of 60 bar, and some representative results are shown in Table 1. To our delight, (S_c,S_a)-PEAPhos **1a** displayed a promising performance in this challenging hydrogenation, in which full conversion and 88% ee were achieved (entry 1). However, the use of (S_c,S_a)-PEAPhos **1b** and (R_c,R_a)-THNAPhos **2** gave incomplete conversion, although a slightly improved ee value was observed with (S_c,S_a)-PEAPhos **1b** (entries 2 and 3). These results suggested that the increased steric hindrance on the amino moiety and chiral carbon center of this ligand motif had a negative effect on the catalytic activity. We therefore decided to modify the binaphthyl backbone in a purpose to further improve the overall catalytic performance. New H_8-BINOL derived phosphine-phosphoramidite ligands, (R_c,R_a)-**3a** and (R_c,R_a)-**3b**, were then prepared and subjected to the model hydrogenation. The partially hydrogenated naphthalene rings contain sp^3 hybridized carbons that can increase the steric bulkiness of binaphthyl frameworks and change the biaryl dihedral angle, which may be beneficial to improve the enantioselectivity.[14] Using **3a** as the ligand, the substrate was fully converted with 97% ee (entry 4). Again, the introduction of a methyl group into the amino moiety of ligand led to a devastating decrease in catalytic activity (< 10% conversion) (entry 5). These results indicated that the presence of an *N*-H proton on the amino moiety and a H_8-binaphthyl moiety on this ligand motif is crucial for achieving high catalytic activity and enantioselectivity in this challenging hydrogenation. Better results obtained with the ligand bearing an *N*-H proton are presumably caused by the substrate orientation from a hydrogen bond between the ligand and the substrate as proposed by Reek et al.[15]

(7) (a) Huang, J.-D.; Hu, X.-P.; Duan, Z.-C.; Zeng, Q.-H.; Yu, S.-B.; Deng, J.; Wang, D.-Y.; Zheng, Z. *Org. Lett.* **2006**, *8*, 4367–4370. (b) Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Xu, X.-F.; Zheng, Z. *Angew. Chem., Int. Ed.* **2007**, *46*, 7810–7813.

(8) For Rh-catalyzed asymmetric reactions, see: (a) Franciò, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428–1430. (b) Jia, X.; Li, X.; Lam, W. S.; Kok, S. H. L.; Xu, L.; Lu, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2273–2278. (c) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585–3588. (d) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419–422. (e) Vallianatou, K. A.; Kostas, I. D.; Holz, J.; Boner, A. *Tetrahedron Lett.* **2006**, *47*, 7947–7950. (f) Zhang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5515–5518. (g) Zhang, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 1020–1023. (h) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198–7202. (i) Wassenaar, J.; Kuil, M.; Reek, J. N. H. *Adv. Synth. Catal.* **2008**, *350*, 1610–1614. (j) Wassenaar, J.; Reek, J. N. H. *J. Org. Chem.* **2009**, *74*, 8403–8406. (k) Yu, S.-B.; Huang, J.-D.; Wang, D.-Y.; Hu, X.-P.; Deng, J.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1862–1866. (l) Wassenaar, J.; Kuil, M.; Lutz, M.; Spek, A. L.; Reek, J. N. H. *Chem.—Eur. J.* **2010**, *16*, 6509–6517. (m) Wassenaar, J.; de Bruin, B.; Reek, J. N. H. *Organometallics* **2010**, *29*, 2767–2776. (n) Pullmann, T.; Engendahl, B.; Zhang, Z.; Holscher, M.; Zanotti-Gerosa, A.; Dyke, A.; Francio, G.; Leitner, W. *Chem.—Eur. J.* **2010**, *16*, 7517–7526. (o) Hintermair, U.; Hofener, T.; Pullmann, T.; Francio, G.; Leitner, W. *ChemCatChem* **2010**, *2*, 150–154. (p) Zhang, X.; Cao, B.; Yan, Y.; Yu, S.; Ji, B.; Zhang, X. *Chem.—Eur. J.* **2010**, *16*, 871–877. (q) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4047–4050. (r) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van der Vlugt, J. I.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 6607–6616.
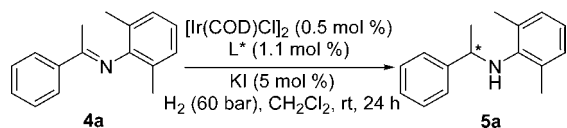
(9) For Ru-catalyzed asymmetric reaction, see: Burk, S.; Francio, G.; Leitner, W. *Chem. Commun.* **2005**, 3460–3462.

(10) For Ag-catalyzed asymmetric reaction, see: Yu, S.-B.; Hu, X.-P.; Deng, J.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 621–625.

(11) For Cu-catalyzed asymmetric reactions, see: (a) Boeda, F.; Rix, D.; Clavier, H.; Crevisy, C.; Mauduit, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2726–2729. (b) Hou, C.-J.; Guo, W.-L.; Hu, X.-P.; Deng, J.; Zheng, Z. *Tetrahedron: Asymmetry* **2011**, *22*, 195–199.

(12) For Pd-catalyzed asymmetric reactions, see: (a) Wassenaar, J.; van Zutphen, S.; Mora, G.; Le Floch, P.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Organometallics* **2009**, *28*, 2724–2734. (b) Wassenaar, J.; Jansen, E.; van Zeist, W.-J.; Bickelhaupt, F. M.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 417–421.

(13) For Rh-, Ru-, Ir-catalyzed asymmetric hydrogenation, see: Eggenstein, M.; Thomas, A.; Theuerkauf, J.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 725–732.

(14) For a review, see: Au-Yeung, T. L.-L.; Chan, S.-S.; Chan, A. S. C. *Adv. Synth. Catal.* **2003**, *345*, 537–555.

(15) Breuil, P.-A. R.; Patureau, F. W.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2162–2165.

Table 1. Ligand Screening[a]

entry	ligand	conv[b] (%)	ee[c] (%)
1	(S_c,S_a)-**1a**	>99	88
2	(S_c,S_a)-**1b**	84	90
3	(R_c,R_a)-**2**	86	51
4	(R_c,R_a)-**3a**	>99	97
5	(R_c,R_a)-**3b**	<10	[d]

[a] Hydrogenation was carried out with 5 mol % of KI and 1 mol % of Ir catalyst at rt for 24 h, unless otherwise specified. [b] Determined by GC. [c] Determined by HPLC using a chiral stationary phase. [d] Not determined due to low conversion.

The success of (R_c,R_a)-**3a** encouraged us to investigate the effects of the additive, solvent, and H_2 pressure to obtain optimal conditions, and some representative results are shown in Table 2. Initially, the additive was investigated because of its significant influence on the asymmetric catalysis.[16] In Zhang's report, the additive was deleterious to the Ir-catalyzed hydrogenation of sterically hindered imines, resulting in dramatically decreased conversion and enantioselectivity.[6] Our study disclosed, however, that the use of various I additives could significantly increase the reactivity and enantioselectivity. Thus, without any additives, the Ir/(R_c,R_a)-**3a** catalyst showed low activity and moderate enantioselectivity (entry 1). By use of KI, I_2, Bu_4NI, and NIS, significantly increased performance was obtained (entries 2−5). Among these I additives, KI and I_2 were optimal, by which perfect performance was achieved (entries 2 and 3). Except for I additives, however, other additives tested proved to have no positive effect on this hydrogenation (entries 6 and 7). H_2 pressure showed no apparent effect on the catalytic performance. Full conversions and 97% ee were achieved no matter the hydrogenation was performed under a H_2 pressure of 20, 60, or 90 bar (entries 2, 8, and 9). The effect of the solvent was next investigated, and an obvious solvent dependency was observed. However, no result surpassed that obtained in CH_2Cl_2 (entries 10−12). Lowering the catalyst loading to 0.1 mol % had no effect in the hydrogenation performance (entry 13). Good performance (>99% conversion and 93% ee) can be achieved even when the hydrogenation was performed at a catalyst loading of 0.01 mol % (entry 14), representing the most efficient catalytic system in the hydrogenation of sterically hindered *N*-arylalkylarylimines reported so far.

Having established the optimized hydrogenation conditions, we then examined the scope of this Ir/(R_c,R_a)-**3a** catalytic system by employing a range of sterically hindered *N*-arylimines. The results in Table 3 indicated that

(16) For a review, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

Table 2. Screening of Hydrogenation Conditions[a]
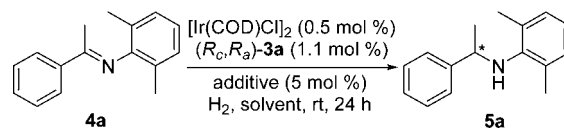
entry	additive	solvent	H_2 (bar)	conv[b] (%)	ee[c] (%)
1	none	CH_2Cl_2	60	33	61
2	KI	CH_2Cl_2	60	>99	97
3	I_2	CH_2Cl_2	60	>99	96
4	NIS	CH_2Cl_2	60	84	83
5	Bu_4NI	CH_2Cl_2	60	75	89
6	CSA	CH_2Cl_2	60	14	61
7	PA	CH_2Cl_2	60	24	59
8	KI	CH_2Cl_2	20	>99	97
9	KI	CH_2Cl_2	90	>99	97
10	KI	MeOH	20	<10	[d]
11	KI	toluene	20	12	80
12	KI	THF	20	46	91
13[e]	KI	CH_2Cl_2	60	>99	97
14[f]	KI	CH_2Cl_2	80	>99	93

[a] Hydrogenation was carried in CH_2Cl_2 with 5 mol % of KI and 1 mol % of Ir catalyst at rt for 24 h, unless otherwise specified. [b] Determined by GC. [c] Determined by HPLC using a chiral stationary phase. [d] Not determined. [e] Using 0.1 mol % of Ir catalyst. [f] Using 0.01 mol % of Ir catalyst at 90 °C for 36 h.

this catalytic system was efficient to a variety of *N*-arylalkylarylimines, *N*-aryldialkylimines, and α-imino esters, which were hydrogenated in good to excellent enantioselectivities. For *N*-arylalkylarylimines **4a**−**h**, the hydrogenations proceeded to completion and afforded the corresponding chiral amines in high yields (92−99%) and excellent enantioselectivities (95−99% ee) (entries 1−8). The electronic property of the substituent on the phenyl ring showed a limited influence on the enantioselectivity. Outstanding selectivity of up to 99% ee was achieved in the hydrogenation of 1-(3-nitrophenyl)ethylideneamine **4f** (entry 6). It is noteworthy that the hydrogenations of *N*-aryldialkylimines **4i**−**k** were conducted smoothly with good enantioselectivities (69%, 88% ee, and 96% ee, respectively), representing the best result reported so far (entries 9−11). More importantly, the present catalytic system was efficient for the hydrogenation of methyl 2-(2,6-dimethylphenylimino)propanoate **4l**, providing the corresponding amino acid derivative **5l** in 86% ee, which is the first successful example in the Ir-catalyzed asymmetric hydrogenation of α-imino ester substrates (entry 12). Methyl 2-(2,6-dimethylphenylamino)propanoate **5l** can be used as an intermediate for the preparation of the fungicide (*S*)-metalaxyl. The hydrogenation of the substrate bearing a β-substituent proved to be more difficult. Performing the hydrogenation at 60 °C and under a H_2 pressure of 80 bar for 36 h, the substrate **4m** with a β-methyl group could be hydrogenated completely in 90% ee (entry 13). These results demonstrated high efficiency of the present Ir/(R_c,R_a)-**3a** catalytic system in the hydrogenation of sterically hindered imines.

Table 3. Substrate Scope of Sterically Hindered Imines[a]

entry	imine	yield[b] (%)	ee[c] (%)
1	**4a**: R^1 = Ph, R^2 = H	98	97
2	**4b**: R^1 = 4-MeC$_6$H$_4$, R^2 = H	98	97
3	**4c**: R^1 = 4-ClC$_6$H$_4$, R^2 = H	98	98
4[d]	**4d**: R^1 = 4-BrC$_6$H$_4$, R^2 = H	98	96
5	**4e**: R^1 = 4-NO$_2$C$_6$H$_4$, R^2 = H	99	96
6	**4f**: R^1 = 3-NO$_2$C$_6$H$_4$, R^2 = H	98	99
7	**4g**: R^1 = 3-MeOC$_6$H$_4$, R^2 = H	98	98
8	**4h**: R^1 = 6-MeO-2-naphthyl, R^2 = H	92	95
9	**4i**: R^1 = Et, R^2 = H	94	69
10[d]	**4j**: R^1 = i-Pr, R^2 = H	97	88
11	**4k**: R^1 = MeOCH$_2$, R^2 = H	95	96
12	**4l**: R^1 = CO$_2$Me, R^2 = H	96	86
13[e]	**4m**: R^1 = Ph, R^2 = Me	97	90

[a] All hydrogenations were carried out with 5 mol % of KI and 1 mol % of Ir catalyst at rt for 24 h, unless otherwise specified. [b] Yields of isolated product. [c] Determined by HPLC or GC using a chiral stationary phase. [d] Performed at 60 °C under a H$_2$ pressure of 60 bar. [e] Performed at 60 °C under a H$_2$ pressure of 80 bar for 36 h.

A different *N*-aryl group on the imine substrates was also investigated under the optimized conditions, and some representative results are showed in Figure 2. No apparent effect on the catalytic activity and enantioselectivity was observed. Besides various sterically hindered *N*-aryl groups, the substrate **4q** with an *N*-phenyl substituent was also suitable to this hydrogenation, giving the hydrogenation product **5q** in 95% ee and 96% yield.

A practical application of this methodology as the key step in the enantioselective synthesis of the chiral herbicide (1*S*)-metolachlor was examined as shown in Scheme 1. The hydrogenation was performed on a 50 g scale at 100 °C for 18 h under a H$_2$ pressure of 80 bar with Bu$_4$NI as the additive by employing a catalyst loading of 0.001 mol % (S/C = 100000). MEA imine **6** was completely transformed into the corresponding MEA amine **7** in up to 80% ee. Restricted by the hydrogenation apparatus in our laboratory, we did not investigate the feasibility of the hydrogenation of MEA imine **6** under lower catalyst loading. Because of the ready availability and the low cost of chiral ligand, the present catalytic system should be a competent alternative for the use in the industrial production of chiral herbicide (1*S*)-metolachlor.

In conclusion, we have developed a mild, practical, and general iridium-catalyzed, highly enantioselective hydrogenation of sterically hindered *N*-arylimines with a new chiral phosphine−phosphoramidite ligand. The results
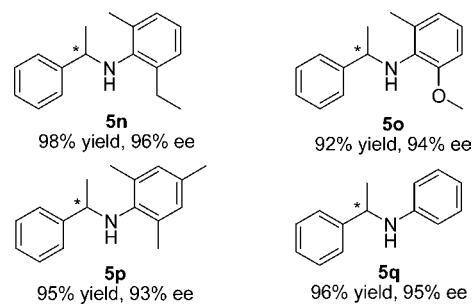
Figure 2. Effect of *N*-aryl group on the hydrogenation.

Scheme 1. Synthesis of Chiral Herbicide (1*S*)-Metolachlor
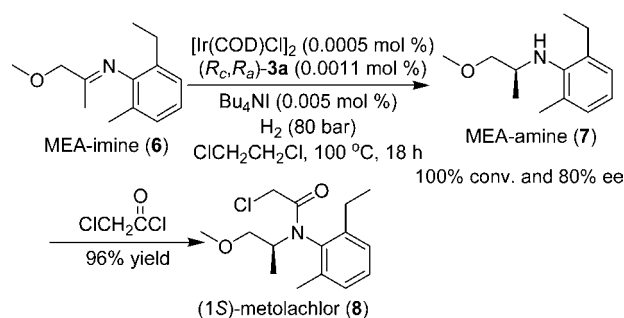
suggested that the presence of an *N*-H proton and a H$_8$-binaphthyl moiety on the ligand motif is crucial for this hydrogenation to obtain high catalytic activity and enantioselectivity. The present catalytic system features high turnover numbers (up to 100000) and good to perfect enantioselectivities (up to 99% ee) for the hydrogenation of a variety of sterically hindered *N*-arylimines, representing the most versatile catalyst in the hydrogenation of sterically hindered imines. The utility of this catalytic system was demonstrated by the synthesis of the chiral herbicide (1*S*)-metolachlor at a catalyst loading of 0.001 mol %. Further application of the present catalytic system is still underway.

Supporting Information Available. Experimental details, characterization data, NMR spectra, and HPLC or GC data for ee analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.