Well-Defined Chiral Spiro Iridium/Phosphine—Oxazoline Cationic Complexes for Highly Enantioselective Hydrogenation of Imines at Ambient Pressure

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · NOVEMBER 2006

Impact Factor: 12.11 · DOI: 10.1021/ja063444p · Source: PubMed

5 AUTHORS, INCLUDING:

Shou-Fei Zhu
Nankai University
109 PUBLICATIONS **2,507** CITATIONS

SEE PROFILE

J|A|C|S
ARTICLES
Published on Web 09/06/2006

Well-Defined Chiral Spiro Iridium/Phosphine−Oxazoline Cationic Complexes for Highly Enantioselective Hydrogenation of Imines at Ambient Pressure

Shou-Fei Zhu, Jian-Bo Xie, Yong-Zhen Zhang, Shen Li, and Qi-Lin Zhou*

Contribution from the State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received May 17, 2006; E-mail: qlzhou@nankai.edu.cn

Abstract: New chiral phosphine−oxazoline ligands (**7**, SIPHOX) with a rigid and bulky spirobiindane scaffold were synthesized, starting with optically pure 7-diphenylphosphino-7′-trifluoromethanesulfonyloxyl-1,1′-spirobiindane, in four steps in 40−64% overall yield. Iridium complexes of **7**, the chiral analogues of the Crabtree catalyst, were generated by coordination of ligands **7** and $[Ir(COD)Cl]_2$ in the presence of sodium tetrakis-3,5-bis(trifluoromethyl)phenylborate. The complexes were characterized by NMR, ESI-MS, and X-ray diffraction analysis. The Ir−SIPHOX complexes can catalyze the hydrogenation of acyclic *N*-aryl ketimines under ambient pressure with excellent enantioselectivities (up to 97% ee) and full conversions. This result represents the highest enantioselectivity and the first example of the hydrogenation of imines catalyzed by chiral analogues of the Crabtree catalyst at ambient pressure. Studies on the stability of the catalysts revealed that the catalysts Ir−SIPHOX are very stable and resistant to the formation of inactive trimers under hydrogenation conditions. On the basis of the X-ray diffraction analysis of the structures of catalysts and amine products, a rational explanation for the enantiocontrol of the chiral catalysts in the hydrogenation of imines is proposed.

Introduction

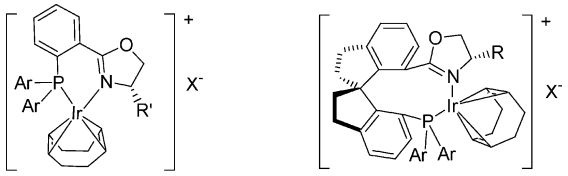
The catalytic asymmetric hydrogenation of imines has drawn much attention recently, since it provides one of the most efficient routes to the synthesis of chiral amines, which are widely used in pharmaceutical and agrochemical substances.[1] Although great efforts have been made in recent decades, catalytic asymmetric hydrogenation of imines remains a challenge in modern synthesis, in contrast to the relative ease of asymmetric hydrogenation of olefins and ketones.

In the past decade, several chiral transition metal complexes, such as Ti, Rh, Ru, and Ir complexes, have been investigated and exhibited promising results in the asymmetric hydrogenation of imines. The chiral titanocene developed by Buchwald et al.[2] was found to be highly enantioselective in the hydrogenation of a variety of cyclic imines. Rhodium complexes of chiral bidentate phosphines have proven to be effective catalysts in the asymmetric hydrogenation of benzylimines,[3] *N*-acylhydrazone,[4] and *N*-diphenylphosphinyl ketimines.[5] Ru−BINAP was successfully used in the hydrogenation of *N*-tosylimines[6] and cyclic sulfonamides.[7] The Ru−DuPhos−DACH complex was applied in the hydrogenation of acetophenone aniline imine with high enantioselectivity.[8] Since neutral $[Ir(COD)Cl]_2$/xyliphos was successfully applied in the industrial synthesis of the herbicide (*S*)-metolachlor,[9] a number of iridium complexes of chiral diphosphine ligands have been developed for the hydrogenation of cyclic and acyclic imines and quinolines in high enantioselectivities.[10] One of the most notable examples was reported by Zhang et al.[10b] in the hydrogenation of acyclic imines with up to >99% ee by using Ir/f-Binaphane catalyst. Very recently, neutral Ir complexes of P,N-ligands were also found to be highly enantioselective catalysts in the hydrogenation of *N*-aryl ketimines and quinolines with I_2 as an additive.[11]

In 1997, Pfaltz et al.[12] developed a chiral analogue of the Crabtree catalyst,[13] the cationic iridium/(*S*)-2-(2-(diphenylphos

(1) For reviews, see: (a) Blaser, H.-U.; Spinder, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 248. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spinder, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.
(2) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.
(3) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684.
(4) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.
(5) Spinder, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2001**, *343*, 68.
(6) Charette, A. B.; Giroux, A. *Tetrahedron Lett.* **1996**, *37*, 6669.
(7) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.
(8) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195.
(9) Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 17.
(10) (a) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661. (b) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (c) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 1053. (d) Vargas, S.; Rubio, M.; Suarez, A.; del Rio, D.; Alvarez, E.; Pizzano, A. *Organometallics* **2006**, *25*, 961. (e) Dervisi, A.; Carcedo, C.; Ooi, L. *Adv. Synth. Catal.* **2006**, *348*, 175. (f) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289.
(11) (a) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 909. (b) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564.
(12) (a) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887. (b) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897. (c) Kainz, S.; Brinkmann, A.; Leitner, W.; Pflatz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421.
(13) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

10.1021/ja063444p CCC: $33.50



Pfaltz's catalyst **1**

Figure 1. Cationic iridium catalysts with chiral P,N-ligands.

phino)phenyl)-4-alkyl-4,5-dihydrooxazole ((S)-PHOX) complex (Figure 1). There are three crucial features of Pfaltz's catalyst: (1) Simple synthesis and high stability make the purification and manipulation easier. (2) The ease of growing single crystals for X-ray diffraction analysis makes catalysts well-defined; this is beneficial to the study of the mechanism.[14] (3) High reactivity and enantioselectivity are observed in the hydrogenation of imines and unfunctionalized olefins.[15] Following Pfaltz's pioneering work, many chiral cationic iridium catalysts with different P,N-ligands[16] have been prepared and applied in the hydrogenation of imines, and some of them were proven to be efficient.[17] However, most of those catalysts gave only a modest enantioselectivity.

During our investigation of the chiral spirobiindane-backbone phosphorous ligands, we became aware that the spirobiindane scaffold is extremely rigid and bulky.[18] We therefore envisaged that the phosphine−oxazoline ligands bearing a spirobiindane scaffold would be crowded and perhaps could prevent the deactivation of their iridium complexes by inhibiting the formation of the inactive trimer, which was one of the drawbacks of the reported Ir/P,N catalysts. Herein we report the synthesis of chiral phosphine−oxazoline ligands containing a spirobiindane scaffold and their well-defined cationic iridium complexes **1**, and their application in asymmetric hydrogenation of acyclic *N*-aryl ketimines at ambient pressure with excellent enantioselectivities (up to 97% ee).

Results and Discussion

Synthesis of Chiral Spiro Phosphine−Oxazoline Ligands 7. Starting from the optically pure 1,1′-spirobiindane-7,7′-diol (SPINOL),[19] several routes can be considered to construct the chiral spiro phosphine−oxazoline ligands (abbreviated SIPHOX). As we have had intermediate **2** in the previous synthesis of chiral spiro diphosphine (SDP) ligands,[18d] two routes were advanced to synthesize ligands **7** from compound **2** (Scheme 1). The shorter route, including only two steps, was tried first. The palladium-catalyzed cyanation of **2** ran smoothly to provide compound **3** in 88% yield (step a). However, the next step, the condensation of cyano group with 2-amino alcohols catalyzed by anhydrous $ZnCl_2$ (step b), was completely suppressed. The alternative four-step route was then tested, and satisfying results were obtained. Compound **2** was converted to esters **4** by Pd-catalyzed carbonylation[20] in 85−91% yield (step c). The carboxylates **4** were hydrolyzed by aqueous KOH in methanol to provide acids **5** in 67−99% yield (step d). The condensation of acids **5** with enantiomerically pure 2-amino alcohols in the presence of 1-hydroxylbenzotriazole (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (THF) gave amides **6** in 87−100% yield (step e). Finally, the target ligands **7** were obtained by cyclization of the amides **6** in 69−76% yield (step f).[21] The phosphine−oxazoline ligands **7** are stable and can be purified by silica gel column chromatography.

Synthesis of Cationic Iridium Catalysts 1. In the Pfaltz procedure for the preparation of cationic iridium catalysts with chiral P,N-ligands, $[Ir(COD)Cl]_2$ was first reacted with P,N-ligands to form the complex [Ir(COD)(P,N)]Cl. The anion Cl^- was then exchanged to $BARF^-$ by treatment with aqueous solutions of NaBARF (BARF = tetrakis-3,5-bis(trifluoromethyl)-phenylborate).[12c] Although this procedure has been commonly used in the synthesis of cationic iridium catalysts and various P,N-ligands were reported to coordinate with $[Ir(COD)Cl]_2$ within several hours,[15b] the spiro phosphine−oxazoline ligand **7a** cannot completely coordinate to iridium under the standard conditions. When the mixture of $[Ir(COD)Cl]_2$ and ligand **7a** ($[Ir(COD)Cl]_2$/**7a** = 0.5:1) was refluxed in CH_2Cl_2 for 1 h (method A), ^{31}P NMR analysis (Figure 2) showed that the coordination of ligand **7a** to the iridium dimer was incomplete, leaving about 50% free ligand (δ −20.4 ppm). Two coordinated phosphorus signals at lower field (δ 22.2 and 16.4 ppm) indicated that two complexes were formed in the reaction. Prolonging the reaction time to more than 3 days, or carrying out the reaction in refluxing 1,2-dichloroethane (DCE) did not contribute to the complete coordination of ligand **7a** to iridium but rather induced decomposition of the ligand. However, as the ratio of $[Ir(COD)Cl]_2$/**7a** was increased to 1:1 (method B), a complete coordination of ligand **7a** to iridium was achieved in refluxing CH_2Cl_2, giving the same two complexes as those obtained via method A. The results from methods A and B clearly indicated that only one of two iridium atoms in the $[Ir(COD)Cl]_2$ was coordinated with ligand **7a**. It was found that, if $[Ir(COD)Cl]_2$, ligand **7a**, and NaBARF·$3H_2O$ ($[Ir(COD)Cl]_2$/**7a**/NaBARF = 0.5:1:1.5, method C) were mixed together, the coordination of ligand **7a** to iridium could be completed at room temperature. A compound with a ^{31}P NMR peak at 15.2 ppm was isolated in 85% yield, which was identified to be the

(14) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.
(15) For reviews, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.
(16) For reviews on chiral P,N-ligands, see: (a) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (b) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.
(17) (a) Cahill, J. P.; Lightfoot, A. P.; Goddard, R.; Rust, J.; Guiry, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 4301. (b) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40. (c) Cozzi, P. G.; Menges, F.; Kaise, S. *Synlett* **2003**, 833. (d) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159. (e) Ezhova, M. B.; Patrick, B. O.; James, B. R.; Waller, F. J.; Ford, M. E. *J. Mol. Chem. A: Chem.* **2004**, *224*, 71. (f) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825. (g) Solinas, M.; Pfaltz, A.; Cozzi, P. G.; Leitner, W. *J. Am. Chem. Soc.* **2004**, *126*, 16142. (h) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (i) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318.
(18) (a) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (c) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582. (d) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (e) Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2004**, *69*, 8157. (f) Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333. (g) Shi, W.-J.; Zhang, Q.; Xie, J.-H.; Zhu, S.-F.; Hou, G.-H.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 2780.
(19) (a) Birman, V. B.; Rheingold, A. L.; Lam, K.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 125. (b) Zhang, J.-H.; Liao, J.; Cui, X.; Yu, K.-B.; Deng, J.-G.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L.; Chung, L.-W.; Ye, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1363.
(20) Hotta, H.; Suzuki, T.; Miyano, S.; Inoue, Y. *J. Mol. Catal.* **1989**, *54*, L5.
(21) Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1779.

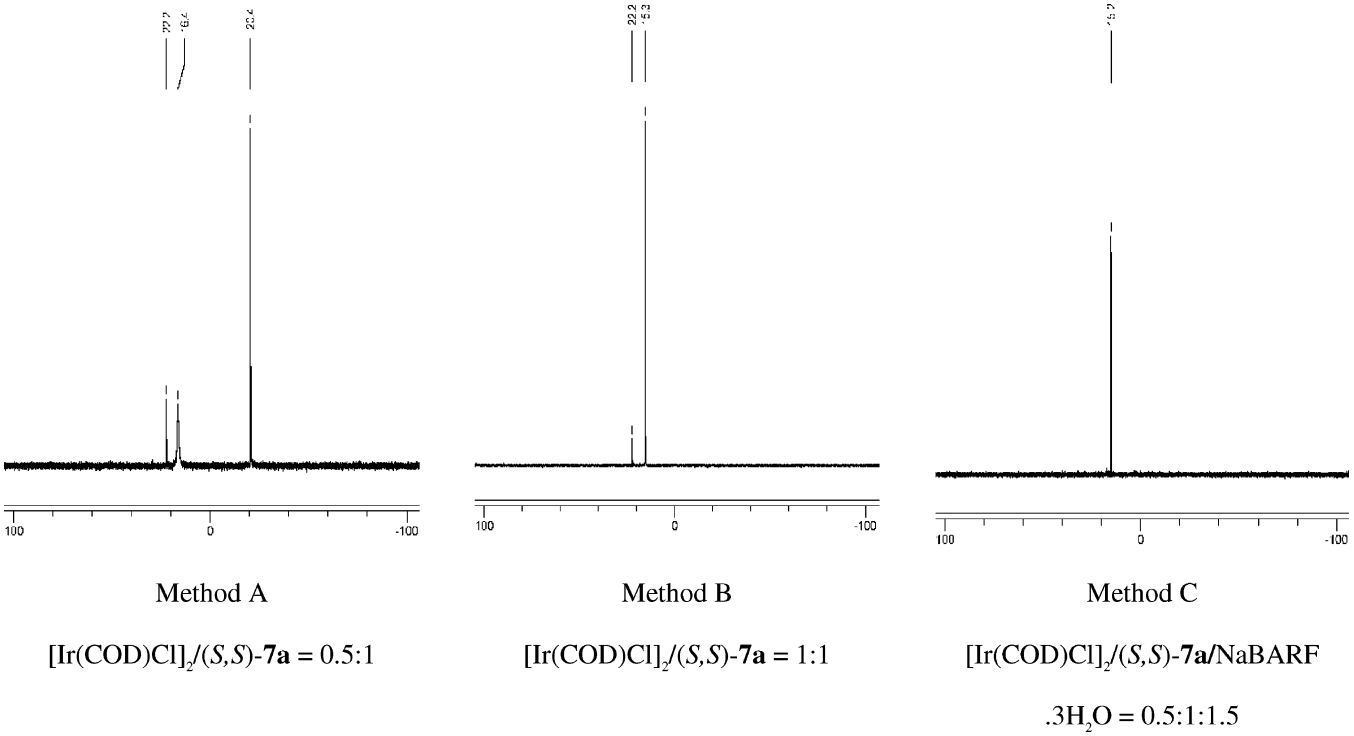
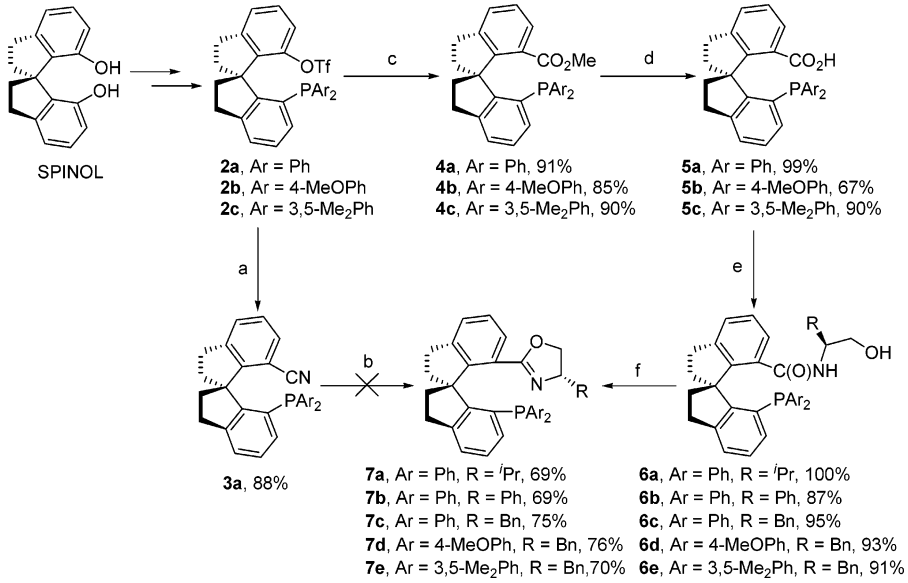


Figure 2. ^{31}P NMR studies on the coordination via three methods. (*S*,*S*)-**7a** reacted with $[Ir(COD)Cl]_2$ in dichloromethane for 1 h.

Scheme 1. Synthesis of Chiral Spiro Phosphine−Oxazoline Ligands **7**[a]

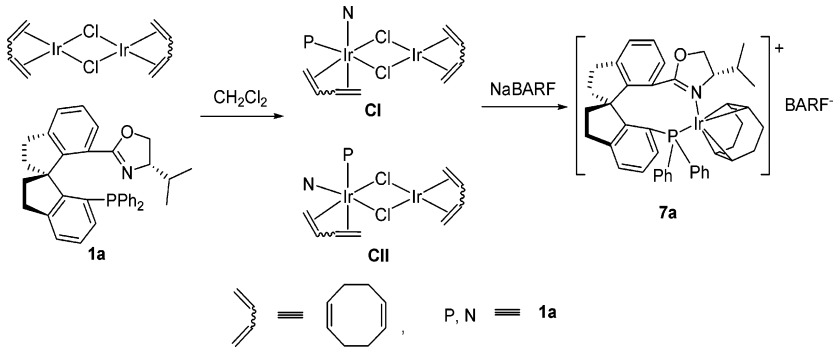


[a] Reagents and conditions: (a) 10 mol % $Pd(PPh_3)_4$, $Zn(CN)_2$, dimethylformamide, 130 °C; (c) 15 mol % $Pd(OAc)_2$, 15 mol % dppp, CO (1 atm), Et_3N, DMSO, MeOH, 70 °C; (d) 40−60% KOH, methanol, reflux; (e) 2-amino alcohol, DCC, HOBt, room temperature; (f) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature.

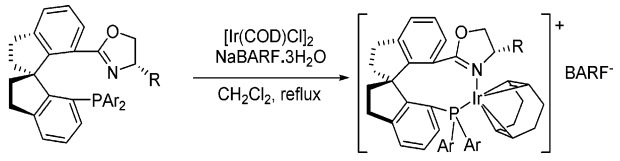
complex **1a**. Furthermore, by adding 1.5 equiv of NaBARF·$3H_2O$ to the mixtures in methods A and B, complex **1a**, identical to the authentic sample from method C, was produced in 80% yield.

On the basis of the experimental results, it was reasonable to assume that coordination of ligand **7a** to an iridium dimer cannot release the monomeric iridium complex; that is, the chlorine bridges still existed after a ligand was coordinated to one of the two iridium atoms in $[Ir(COD)Cl]_2$. Thus, a rational process for the coordination of ligand **7a** with $[Ir(COD)Cl]_2$ was proposed and is illustrated in Scheme 2. The two ^{31}P NMR peaks at lower field in methods A and B might represent the coordination modes **CI** and **CII**. Whenever the P,N-ligand is small or flexible enough, the second ligand can coordinate to the second iridium atom in $[Ir(COD)Cl]_2$, and the dimeric iridium complex will be scissioned into two monomeric iridium chlorides, as suggested in the literature.[12c] However, if the P,N-ligand was rigid and bulky, like SIPHOX, it would be very difficult for a second ligand to coordinate to the second iridium atom in $[Ir(COD)Cl]_2$, even under harsh conditions. In the presence of NaBARF, the complexes **CI** and **CII** were dechlorinated to release $[Ir(COD)]^+$ species, which was coordinated easily by P,N-ligand

Scheme 2. Proposed Coordination Pathway



Scheme 3. Synthesis of Cationic Iridium Complexes of SIPHOX Ligands



1a, Ar = Ph, R = ^{i}Pr
1b, Ar = Ph, R = Ph
1c, Ar = Ph, R = Bn
1d, Ar = 4-MeOPh, R = Bn
1e, Ar = 3,5-diMePh, R = Bn

7a, Ar = Ph, R = ^{i}Pr, 80%
7b, Ar = Ph, R = Ph, 85%
7c, Ar = Ph, R = Bn, 90%
7d, Ar = 4-MeOPh, R = Bn, 95%
7e, Ar = 3,5-diMePh, R = Bn, 92%

to yield the monomeric iridium complex. It should be pointed out that other coordination models, such as those with one P,N-ligand coordinated to two iridiums in $[Ir(COD)Cl]_2$, are also possible. Thus, all the Ir/SIPHOX complexes **1** were prepared in high yields according to the simple and efficient method C (Scheme 3). All the iridium complexes **1** were stable in the atmosphere.

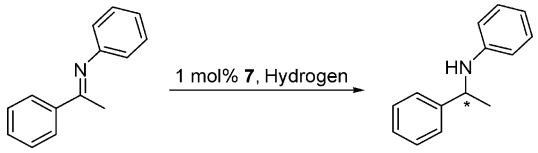
Structure Analysis of Chiral Iridium Complexes 1. The complexes (*S*,*S*)-**1a** and (*S*,*R*)-**1a** were easily crystallized from alcohol/water solvent and afforded crystals suitable for X-ray diffraction analysis. The X-ray diffraction analysis (Figure 3) revealed that the ligand **7a** coordinated iridium with phosphorus and nitrogen atoms. The ligand acted as a rigid pincer, and the iridium atom was clamped into a nine-membered heterometal ring. The spirobiindane backbone, *P*-phenyl groups, and isopropyl group on the oxazoline ring formed a relatively crowded and rigid environment around the central metal atom. The large chelate rings made the bite angle (P−Ir−N) values of both complexes (*S*,*S*)-**1a** and (*S*,*R*)-**1a** larger than those in the analogous Ir/(*S*)-PHOX complex [(*S*,*S*)-**1a**, 87.91°; (*S*,*R*)-**1a**, 92.20°; (*S*)-PHOX, 85.88° [12a]]. Although the Ir−N bond length in **1a** was in the normal range compared to Ir/(*S*)-PHOX complex [(*S*,*S*)-**1a**, 2.082 Å; (*S*,*R*)-**1a**, 2.109 Å; Ir/(*S*)-PHOX, 2.097 Å], the Ir−P bond in **1a** was apparently longer than that in the Ir/(*S*)-PHOX complex [(*S*,*S*)-**1a**, 2.349 Å; (*S*,*R*)-**1a**, 2.344 Å; Ir/(*S*)-PHOX, 2.305 Å]. This might be attributed to the steric hindrance of ligands and the electronic difference of the P atoms in the ligands. The SIPHOX ligands are more crowded and have a higher electronic density on the P atom than that in the PHOX ligand, which has an electron-withdrawing group (oxazoline) at the ortho position. The differences between complexes (*S*,*S*)-**1a** and (*S*,*R*)-**1a**, especially the difference in the bite angle, were mainly caused by the orientation of the isopropyl group on the oxazoline ring. The isopropyl in the complex (*S*,*S*)-**1a** departs from the biindane skeleton, while in the complex (*S*,*R*)-**1a** the isopropyl group is directed toward and repulsed by the biindane skeleton.

Asymmetric Hydrogenation of Imines with Catalysts 1. The hydrogenation of *N*-(1-phenylethylidene)aniline (**8a**) was chosen to test the reactivity and enantioselectivity of catalysts **1**. The reaction was performed in CH_2Cl_2 with 1 mol % of catalyst under 20 atm hydrogen pressure at 25 °C. The catalysts **1**, with different substituents on the oxazoline ring of the ligands, were compared first, and the results are listed in Table 1. By using catalyst (*S*,*S*)-**1a**, the imine **8a** was hydrogenated with 96% conversion, affording the product **9a** in 76% ee (Table 1, entry 1). The reaction catalyzed by (*S*,*R*)-**1a** gave a racemic product with a very low conversion, showing that the chiralities on the spirobiindane backbone and oxazoline ring in this catalyst are mismatched (entry 2). Catalyst **1b**, bearing a phenyl group on the oxazoline ring, also gave a good enantioselectivity (74% ee), although the conversion was only 18% (entry 3). A better result was achieved by using catalyst **1c**, which has a benzyl group on the oxazoline ring (entry 4, 98% conversion and 81% ee). The solvent effect was studied in the reaction catalyzed by **1c**. It was found that weakly polar solvents such as CH_2Cl_2, toluene, ether, and *tert*-butyl methyl ether (TBME) were suitable for obtaining high conversion and enantioselectivity.

By introducing substituents into the *P*-phenyl ring of the catalyst **1c**, another two catalysts, **1d** and **1e**, were synthesized. It can be seen from the data in Table 1 that the substituent on the *P*-phenyl ring had a negligible effect on the enantioselectivity of the catalyst (entries 9−11). However, the reactivity of the catalyst was remarkably increased in the case of **1e**, which bears 3,5-dimethyl groups on the *P*-phenyl ring. By using **1e**, the catalyst loading could be reduced to 0.5 mol % (entry 12) and the hydrogenation could be performed under ambient hydrogen pressure at 10 °C (entry 14). Catalyst **1e** was one of the few efficient chiral catalysts that could hydrogenate imines at ambient pressure.[10e,f]

Under the optimal reaction conditions, a variety of *N*-aryl ketimines can be hydrogenated at ambient hydrogen pressure in excellent enantioselectivities (>90% ee) with full conversions. From the data in Table 2, it can be seen that the introduction of an electron-donating group on the α-phenyl ring of ketimine slightly increased the enantioselectivity (entries 2, 3, and 8). However, an electron-withdrawing substituent on the *N*-phenyl ring led to higher enantioselectivity (entries 10, 11, and 13). The highest enantioselectivity (97% ee) was achieved in the hydrogenation of *N*-(1-phenylethylidene)-4-chloroaniline (**8j**, entry 10). This result represents, to the best of our knowledge,

Table 1. Asymmetric Hydrogenation of *N*-(1-Phenylethylidene)aniline Catalyzed by **1**[a]

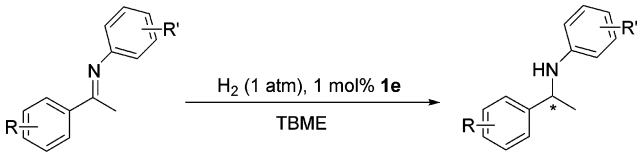


8a **9a**

entry	catalyst	solvent	conversion (%)[b]	ee (%)[c]
1	(*S*,*S*)-**1a**	CH_2Cl_2	96	76
2	(*S*,*R*)-**1a**	CH_2Cl_2	7	0
3	(*S*,*S*)-**1b**	CH_2Cl_2	18	74
4	(*S*,*S*)-**1c**	CH_2Cl_2	98	81
5	(*S*,*S*)-**1c**	THF	65	79
6	(*S*,*S*)-**1c**	toluene	98	82
7	(*S*,*S*)-**1c**	EtOAc	40	74
8	(*S*,*S*)-**1c**	MeOH	8	nd[d]
9	(*S*,*S*)-**1c**	ether	99	87
10	(*S*,*S*)-**1d**	ether	99	88
11	(*S*,*S*)-**1e**	ether	>99	90
12[e]	(*S*,*S*)-**1e**	ether	>99	89
13[f]	(*S*,*S*)-**1e**	ether	70	90
14[g]	(*S*,*S*)-**1e**	ether	>99	93
15[g,h]	(*S*,*S*)-**1e**	^{t}BuOMe	>99	93

[a] Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 M, 1 mol % catalyst, 20 atm H_2 pressure, 25 °C, 20 h. [b] Determined by GC using an HP-5 column. [c] Determined by chiral HPLC using a Chiracel AS or OD-H column. The absolute configuration is *R*.[22] [d] Not determined. [e] With 0.5 mol % catalyst. [f] With 0.1 mol % catalyst. [g] Under ambient hydrogen pressure at 10 °C. [h] 80 mg of 4 Å MS was added.

Table 2. Asymmetric Hydrogenation of *N*-Aryl Ketimines Catalyzed by **1e** under Ambient Hydrogen Pressure[a]



8 **9**

entry	substrate	R	R′	product	ee (%)[b]
1	**8a**	H	H	**9a**	93 (*R*)
2	**8b**	4-MeO	H	**9b**	94 (−)
3	**8c**	4-Me	H	**9c**	94 (−)
4	**8d**	4-Cl	H	**9d**	90 (−)
5	**8e**	4-Br	H	**9e**	91 (*R*)
6	**8f**	3-Cl	H	**9f**	93 (−)
7	**8g**	3-Br	H	**9g**	92 (−)
8	**8h**	3,4-diMe	H	**9h**	94 (−)
9	**8i**	H	4-Me	**9i**	93 (−)
10	**8j**	H	4-Cl	**9j**	97 (−)
11	**8k**	H	4-Br	**9k**	96 (+)
12	**8l**	H	3-Me	**9l**	91 (−)
13	**8m**	H	3-Br	**9m**	94 (−)

[a] Reaction conditions: 0.2 mmol of substrate, 1 mL of TBME, 80 mg of 4 Å MS, 1 mol % catalyst, ambient H_2 pressure, 10 °C, 20 h. Conversions were >99.5% in all reactions. [b] Determined by chiral HPLC using a Chiracel OD-H column.

the highest enantioselectivity in the asymmetric hydrogenation of ketimines using chiral cationic iridium catalysts.

Study on the Stability of Catalysts under a Hydrogen Atmosphere and Explanation of Stereochemistry in the Hydrogenation of Imines with Catalysts 1. It was reported that the cationic iridium catalysts deactivate easily under a hydrogen atmosphere by forming inactive trimers.[13,23] To measure whether the trimerization also takes place in our Ir−

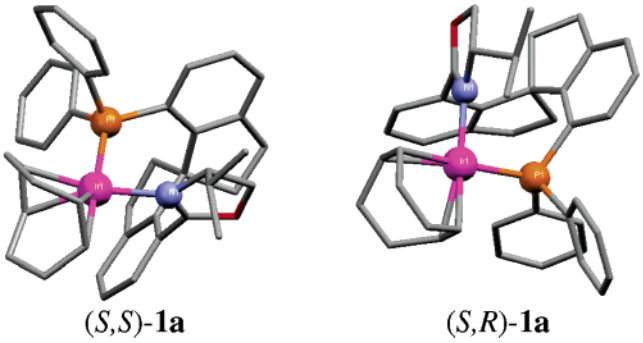


Figure 3. Crystal structures of (*S*,*S*)-**1a** and (*S*,*R*)-**1a**; the anion BARF$^-$ and hydrogen atoms are omitted for clarity.

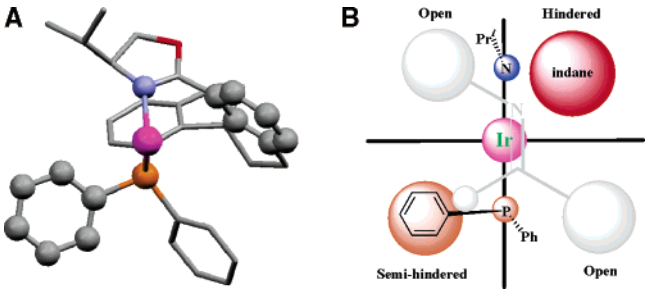


Figure 4. Structure of complex (*S*,*S*)-**1a** and proposed model for the stereochemistry in the asymmetric hydrogenation of imines (the hydrogen atoms, anion, and COD are omitted for clarity). (A) View from the front side of catalyst **1a**. (B) Selectivity model for hydrogenation of imines.

SIPHOX catalysts, we investigated the stability of **1a** under hydrogen pressure. After treatment of catalyst **1a** under 50 atm of hydrogen for 3 h, ESI-MS analysis showed only the monomer (**7a** + Ir, m/z = 708), and no trimeric molecule (with two positive charges,[23] m/z = 1066) was formed. This pre-hydrogenated catalyst was taken to catalyze the hydrogenation of *N*-(1-phenylethylidene)aniline (**8a**), giving the product **9a** in 74% ee with a full conversion, which was similar to that obtained by using the original catalyst, (*S*,*S*)-**1a**. This experiment clearly demonstrated that the iridium complex with SIPHOX ligand was resistant to the formation of inactive trimer even when exposed to a high pressure of hydrogen, which was consistent with what we expected in the catalyst design.

To explain the stereochemistry in the asymmetric hydrogenation of *N*-aryl ketimines catalyzed by Ir−SIPHOX complexes **1**, a model for the coordination of substrate to the catalyst was proposed, based on the crystal structure of catalyst **1a**. As shown in Figure 4, the iridium atom in the catalyst **1a** is surrounded by the ligand. In the four quadrants in front of iridium, the upper-right quadrant is strongly hindered by the spirobiindane backbone, the low-left quadrant is semi-hindered by one of the *P*-phenyls, and the other two quadrants are relatively open. The ketimine substrate must coordinate to iridium with the *Si* face so that its two bulky aryl groups can be located in the two open quadrants, as illustrated in Figure 4. According to this model, hydrogen was added to the substrate from its *Si* face, leading to the formation of amine product with *R* configuration, which was consistent with the experimental results (see Supporting Information).

(22) Kanth, J. V. B.; Periasamy. M. *J. Org. Chem.* **1993**, *58*, 3156.
(23) Smidt, S. P.; Pfaltz, A.; Martinez-Viviente, E.; Pregosin, P. S.; Albinati, A. *Organometallics* **2003**, *22*, 1000.

Conclusion

In conclusion, novel chiral phosphine−oxazoline ligands SIPHOX with a rigid and bulky spirobiindane scaffold were synthesized in good yields. The coordination behavior of the SIPHOX toward $[Ir(COD)Cl]_2$ was studied for development of the corresponding cationic iridium catalysts. Comparison of three different coordination methods indicated that formation of $[Ir(COD)(SIPHOX)]^+$ catalyst occurred only in the presence of NaBARF. X-ray diffraction analysis showed that the SIPHOX constructed a crowded and efficient chiral environment around the iridium metal in the Ir−SIPHOX catalysts. The Ir−SIPHOX catalysts were highly efficient for the hydrogenation of acyclic *N*-aryl ketimines under ambient hydrogen pressure, providing chiral amines in excellent enantiomeric excesses (up to 97% ee) and full conversions. NMR and ESI-MS analysis of catalysts revealed that the Ir−SIPHOX catalysts are stable under the reaction conditions by preventing the formation of inactive trimer. The excellent reactivity and enantioselectivity of these Ir−SIPHOX complexes in the hydrogenation of imines showed a high potential for wide application of this rigid and bulky P,N-ligand in transition metal-catalyzed asymmetric reactions.

Experimental Section

Synthesis of Phosphine−Oxazoline Ligands 7. General Procedure for the Synthesis of 4. A mixture of triflates **2** (11.3 mmol), $Pd(OAc)_2$ (381.7 mg, 1.70 mmol), dppp (701.1 mg, 1.70 mmol), MeOH (60 mL), dimethyl sulfoxide (DMSO, 90 mL), and Et_3N (24 mL) was saturated with CO and stirred under a CO atmosphere at 70 °C. The reaction mixture was monitored by TLC for full conversion. After cooling to room temperature, the mixture was concentrated at reduced pressure. The residue was chromatographed on silica gel with ethyl acetate/petroleum ether to afford esters **4**.

General Procedure for the Synthesis of 5. A mixture of esters **4** (6.49 mmol), MeOH (75 mL), and 40−60% KOH (15 mL) was heated to 100 °C under an argon atmosphere and monitored with TLC for full conversion. Concentrated hydrochloric acid was carefully added with vigorous stirring to pH 2. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, washed with saturated brine, and dried over anhydrous Na_2SO_4. After evaporation under reduced pressure, the residue was subjected to chromatography on silica gel with ethyl acetate/petroleum ether to give acids **5**.

General Procedure for the Synthesis of 6. A mixture of acids **5** (1.12 mmol), amino alcohol (3.50 mmol), HOBt (380 mg, 2.48 mmol), and DCC (664 mg, 3.22 mmol) in THF (60 mL) was stirred under an argon atmosphere at room temperature. The reaction mixture was monitored by TLC for a full conversion. After the solvent was evaporated under reduced pressure, the residue was subjected to chromatography on silica gel with ethyl acetate/petroleum ether to afford amides **6**.

General Procedure for the Synthesis of Ligands 7. To a solution of **6** (1.13 mmol), triethylamine (0.34 mL), and 4-methylaminopyridine (5 mg, 0.041 mmol) in dichloromethane (70 mL) was added methanesulfonyl chloride (130 μL) at 0 °C. The mixture was stirred for 30 min, and another portion of triethylamine (1.45 mL) was added. The resulting mixture was warmed to room temperature. The reaction was monitored with TLC for a complete conversion. The crude product was purified by chromatography on a silica gel column with ethyl acetate/petroleum ether and 2% (v/v) of triethylamine to give ligands **7**.

Preparation of Iridium Complexes 1. Method A. A mixture of ligand **7a** (62 mg, 0.12 mmol) and $[Ir(COD)Cl]_2$ (40 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) was stirred in a Schlenk tube under an argon atmosphere to a homogeneous solution. The solution was heated at the reflux temperature for 1 h. TLC and NMR showed that free ligand was still present. After the solution cooled to room temperature, $NaBARF{\cdot}3H_2O$ (170 mg, 0.18 mmol) was added, and the mixture was stirred vigorously for 1 h. TLC indicated that coordination of the ligand to iridium was complete. Next, 2 mL of water was added, and the mixture was stirred for 30 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel with CH_2Cl_2/petroleum ether to afford the orange-yellowish catalyst **1a** in 80% yield.

Method B. A mixture of ligand **7a** (62 mg, 0.12 mmol) and $[Ir(COD)Cl]_2$ (80 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) was stirred in a Schlenk tube under an argon atmosphere to a homogeneous solution. The solution was refluxed for 1 h. TLC and NMR showed no free ligand remained. $NaBARF{\cdot}3H_2O$ (340 mg, 0.36 mmol) was added at room temperature, and the mixture was stirred vigorously for 1 h. Catalyst **1a** was isolated in 80% yield by flash column chromatography on silica gel with CH_2Cl_2/petroleum ether.

Method C. A mixture of ligand **7a** (62 mg, 0.12 mmol), $[Ir(COD)Cl]_2$ (40 mg, 0.06 mmol), and $NaBARF{\cdot}3H_2O$ (170 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was stirred in a Schlenk tube under an argon atmosphere at room temperature for 1 h. TLC and NMR showed no free ligand remained. Catalyst **1a** was isolated in 85% yield by flash column chromatography on silica gel with CH_2Cl_2/petroleum ether.

Asymmetric Hydrogenation of Imines. General Procedure. A mixture of catalyst **1e** (3.8 mg, 2 μmol), substrate **8a** (39 mg, 0.2 mmol), 4 Å molecular sieves (MS, 80 mg), and TBME (1 mL) in a Schlenk tube was stirred under argon at room temperature for 10 min. The mixture was degassed with three freezing/vacuum cycles and finally filled with hydrogen in a balloon. The hydrogenation was performed with stirring at 10 °C for 20 h and monitored with GC (HP-5 column) for full conversion. The crude product was purified by column chromatography on a silica gel column with ethyl acetate/petroleum ether (1:12, v/v) to give pure amine **9a** in 99% yield.

Acknowledgment. We thank the National Natural Science Foundation of China, the Ministry of Education of China, and the Committee of Science and Technology of Tianjin City for financial support.

Supporting Information Available: Analytical data and spectra of the ligands, complexes, imines; determination of enantiomeric excesses and graphic for amine products; and selective X-ray diffraction analysis data, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA063444P