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Asymmetric Hydrogenation of Heteroaromatic Compounds Mediated by Iridium−(*P-OP*) Complexes

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Summary: A library of modular iridium complexes derived from P-OP ligands has been evaluated in iridium-mediated asymmetric hydrogenations of heteroaromatic compounds. The "lead" catalysts efficiently catalyzed the hydrogenation of several substituted quinolines and one quinoxaline (10 examples, up to 92% ee).

Chiral amines and N-containing compounds are key synthetic intermediates for many biologically and physiologically active products.[1] Asymmetric hydrogenation of C=N-containing functional groups[2] (e.g., imines,[3] C=N−X compounds,[4] and heteroaromatic compounds[5−7]) is one of the most important methodologies for stereoselective formation of C−N single bonds, enabling construction of diverse carbon frameworks for both natural and non-natural products.

We recently reported the preparation of a library of highly modular *P-OP* ligands (phosphine−phosphites and phosphine−phosphinites) for Pd-mediated allylic substitution[8] and for Rh-mediated asymmetric hydrogenation of functionalized C=C bonds.[9] Having found that literature precedent on the use of *P-OP* ligands in the Ir-catalyzed hydrogenation of C=N bonds was very limited, we felt that studying their application in this transformation was the next logical step in assessing their utility in asymmetric catalysis.[10] We envisioned that modular ligand design should enable catalyst optimization via systematic variation of the catalytic system components (R and G, Figure 1). Herein, we report synthesis of the structurally diverse Ir−(*P-OP*) complexes **1** and subsequent evaluation of them as catalysts for asymmetric hydrogenation of C=N bonds.

Our initial set of precatalysts comprised Ir(I) complexes with the general formula **1** that contain phosphine−phosphinite (**2**) or phosphine−phosphite (**3**) ligands, which we chose in order to evaluate the effect of sterically and/or electronically diverse phosphorus functionalities on the catalytic performance of their corresponding iridium(I) complexes.

Before running any catalytic assays, we first evaluated the ability of our bidentate *P-OP* ligands to form stable, well-defined iridium(I) complexes, which could be used as precatalysts in C=N hydrogenations. Complexation studies of related phosphine−phosphites with $[\{Ir(\mu\text{-Cl})(cod)\}_2]$ have been reported by Pizzano et al.[3j−l] However, to the best of

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(1) See, for example: (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605. (b) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162. (c) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (d) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556. (e) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603.

(2) See, for example, for general reviews on C=N hydrogenations: (a) Blaser, H.-U.; Spindler, F. Hydrogenation of Imino Groups. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, Germany, 1999; Vol. *I*, p 247. (b) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (c) Fleury-Brégeot, N.; de la Fuente, V.; Castillón, S.; Claver, C. *ChemCatChem* **2010**, *2*, 1346.

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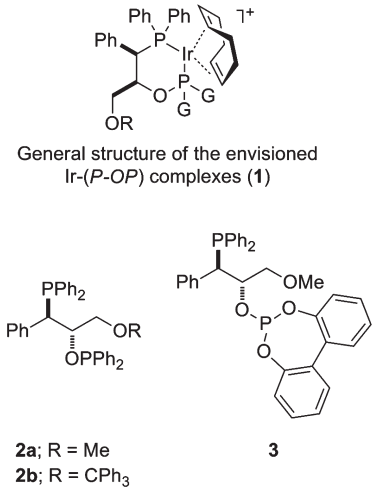
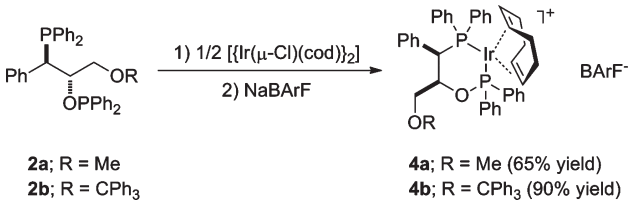


Figure 1. General structure of the Ir−(*P-OP*) complexes (top) and initial set of *P-OP* ligands (bottom).

our knowledge, no examples of iridium complexes derived from enantiomerically pure phosphine−phosphinites have been reported to date. Neutral complexes derived from our phosphine−phosphinites **2a**,**b** were prepared in good yields by reacting stoichiometric amounts of phosphine−phosphinites **2a**,**b** with [{Ir(μ-Cl)(cod)}$_2$] in DCM (Scheme 1). The $^{31}P\{^1H\}$-NMR spectrum of the reaction mixtures revealed that complexation had been very clean, showing disappearance of the *P-OP* signals and formation of one doublet for the phosphinite group arising from $^{31}P-^{31}P$ couplings (for example, for the complex derived from ligand **2a**: 92.0 ppm, J = 44.2 Hz) and another doublet for the phosphine moiety (for example, for the complex derived from ligand **2a**: 14.0 ppm, J = 44.2 Hz),[11] as expected for a 1/1 Ir/ligand complex.

Scheme 1. Preparation of [Ir(cod)(*P-OP*)]$^+$ Complexes Derived from Phosphine−Phosphinites



Iridium complexes containing BArF$^-$ (BArF = [B((3,5-$(CF_3)_2$)$C_6H_3)_4$]$^-$) have been reported as usually being more stable toward moisture and catalyst deactivation during hydrogenation[12] than iridium complexes containing other ligands (e.g., Cl$^-$). Exchange of Cl$^-$ by BArF$^-$ was attempted by adding stoichiometric amounts of NaBArF. Precipitation of NaCl in the reaction media (DCM) indicated that the exchange had occurred, and after filtration of the generated salts, followed by chromatographic purification, cationic iridium complexes **4a**,**b** were obtained as highly pure red solids (Scheme 1).

The complexation of [{Ir(μ-Cl)(cod)}$_2$] and phosphine−phosphite **3** was similar to that for **2a**,**b** and to that reported by Pizzano et al.[3k] for other phosphine−phosphites. Stoichiometric amounts of the iridium precursor and **3** in THF gave a very clean reaction, as indicated by $^{31}P\{^1H\}$ NMR, which showed one sharp doublet for the phosphite group and another doublet for the phosphine moiety, thus indicating the formation of a 1/1 Ir/ligand complex.[11] Attempts to isolate these complexes were unsuccessful. We hypothesized that the neutral complex **5** is the complexation product (Scheme 2).[13] This compound was subjected to ligand exchange (chloride to iodide) by reaction with excess lithium iodide. The corresponding iodo complex **6** was isolated in good yield (48% overall yield from the phosphine−phosphite **3**). Crystals of **6** suitable for X-ray analysis could be grown in a DCM/Et$_2$O mixture; using this technique, coordination of the iodo ligand to the iridium center

(6) For asymmetric hydrogenations of isoquinolines, see, for example: (a) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. For asymmetric hydrogenations of quinoxalines, see, for example: (b) Murata, S.; Sugimoto, T.; Matsuura, S. *Heterocycles* **1987**, *26*, 763. (c) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308. (d) Bianchini, C.; Barbaro, P.; Scapacci, G. *J. Organomet. Chem.* **2001**, *621*, 26. (e) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (f) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300. (g) Mrsic, N.; Jerphagnon, T.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2009**, *351*, 2549. (h) Cartigny, D.; Nagano, T.; Ayad, T.; Genet, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2010**, *352*, 1886. For asymmetric hydrogenations of quinolines, see, for example, ref 5a and: (i) Yang, P.-Y.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145. (j) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 909. (k) Xu, L.; Lam, K. H.; Ji, J.; Wu, J.; Fan, Q.-H.; Lo, W.-H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390. (l) Lam, K. H.; Xu, L.; Feng, L.; Fan, Q.-H.; Lam, F. L.; Lo, W.-h.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1755. (m) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W. Y.; Li, Y. M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955. (n) Reetz, M. T.; Li, X. *Chem. Commun.* **2006**, 2159. (o) Tang, W.-J.; Zhu, S.-F.; Xu, L.-J.; Zhou, Q.-L.; Fan, Q.-H.; Zhou, H.-F.; Lam, K.; Chan, A. S. C. *Chem. Commun.* **2007**, 613. (p) Wang, Z.-J.; Deng, G.-J.; Li, Y.; He, Y.-M.; Tang, W.-J.; Fan, Q.-H. *Org. Lett.* **2007**, *9*, 1243. (q) Chan, S. H.; Lam, K. H.; Li, Y.-M.; Xu, L.; Tang, W.; Lam, F. L.; Lo, W. H.; Yu, W. Y.; Fan, Q.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 2625. (r) Deport, C.; Buchotte, M.; Abecassis, K.; Tadaoka, H.; Ayad, T.; Ohshima, T.; Genet, J.-P.; Mashima, K.; Ratovelomanana-Vidal, V. *Synlett* **2007**, 2743. (s) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *J. Organomet. Chem.* **2007**, *692*, 3065. (t) Mrsic, N.; Lefort, L.; Boogers, J. A. F.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2008**, *350*, 1081. (u) Lu, S.-M.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1101. (v) Wang, X.-B.; Zhou, Y.-G. *J. Org. Chem.* **2008**, *73*, 5640.

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(11) See the Supporting Information for full details.

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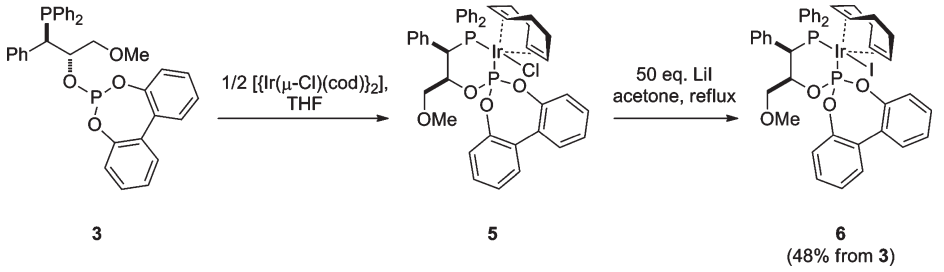
(13) This assumption was made on the basis of the coincidental NMR data (see the Supporting Information for details) for **5** and for **6** (whose structure was unequivocally elucidated by X-ray analysis).

Scheme 2. Preparation of Iridium Complexes Derived from Phosphine−Phosphites



3 5 6 (48% from 3)

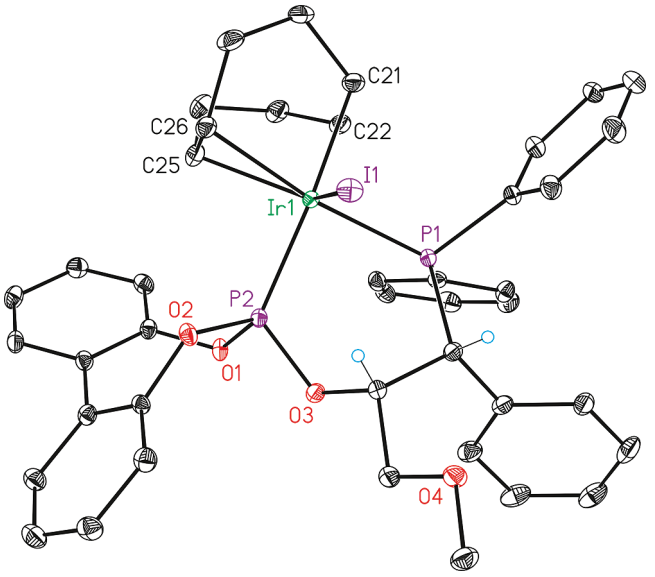
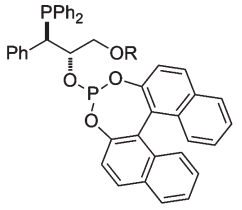


Figure 2. ORTEP view of **6**. Selected bond lengths (Å) and angles (deg): Ir−P(1) = 2.3194(6), Ir−P(2) = 2.2283(7), Ir−C(21) = 2.178(3), Ir−C(22) = 2.168(3), Ir−C(25) = 2.258(3), Ir−C(26) = 2.234(2), Ir−I = 2.8132(3); P(2)−Ir−P(1) = 86.99(2), P(1)−Ir−C(21) = 94.51(7), P(1)−Ir−C(22) = 85.54(7), P(2)−Ir−C(26) = 100.62(8), P(2)−Ir−C(25) = 87.08(8), P(1)−Ir−I = 90.80(2), P(2)−Ir−I = 98.57(2).

was determined. Figure 2 shows an ORTEP diagram of this complex, along with selected bond distances and angles. The complex **6** displays distorted-square-pyramidal coordination geometry, with the iodo ligand located in the apical position. Furthermore, this ligand forms two roughly right I−Ir−P angles with the phospino group and phosphite unit (90.8 and 98.6°, respectively). The angles between the mutually cis ligands in the base of the pyramid range from 85.5 to 100.6°. As previously observed by other groups for related complexes,[3k] the Ir−P(phosphite) distance (2.228 Å) is appreciably shorter than the Ir−P(phosphine) distance (2.319 Å). The greater π-acceptor character of the phosphite is also reflected in the Ir−C bond values of **6**, with longer bonds for the olefinic carbons trans to phosphine (C(25) and C(26)) than for those trans to the phosphite (C(21) and C(22); mean difference in distance 0.07 Å).

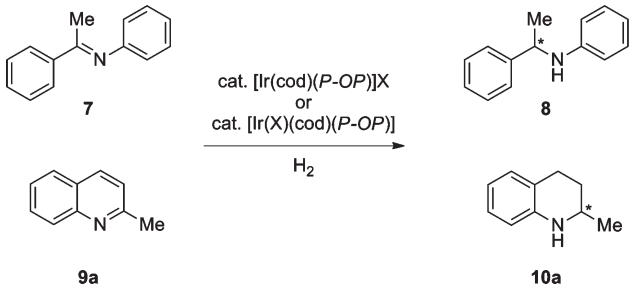
With a synthetic methodology for the preparation of [Ir(cod)(*P-OP*)]X or [Ir(X)(cod)(*P-OP*)] complexes, we began evaluating their activity and selectivity in iridium-mediated asymmetric hydrogenations of C=N bonds. In the first set of experiments, we examined their use in the reduction of *N*-(1-phenylethylidene)aniline (**7**) and 2-methylquinoline (**9a**). Hydrogenations were performed using either preformed iridium precatalysts or in situ generated complexes from



11a; R = Me, (S_a)-BINOL
11b; R = CPh_3, (S_a)-BINOL
11c; R = Me, (R_a)-BINOL
11d; R = CPh_3, (R_a)-BINOL

Figure 3. *P-OP* Ligands with configurationally stable biaryl moieties at the phosphite group.

Scheme 3. Asymmetric Hydrogenation of Two Model Substrates: *N*-(1-Phenylethylidene)aniline (7) and 2-Methylquinoline (9a)



0.5 mol % of [{Ir(μ-Cl)(cod)}$_2$] and 1.1 mol % of the *P-OP* ligand (Scheme 3).

The enantioselectivities obtained with the two substrates were low (see Table 1 in the Supporting Information), regardless of the ligand type (i.e., phosphine−phosphite or phosphine−phosphinite), the nature of the iridium precursor (cationic (**4a**) or neutral (**5** and **6**)), or the reaction conditions. However, the high conversions encouraged us to continue optimizing the ligand and to consider the phosphine−phosphites **11a−d**, which feature configurationally stable biaryl moieties at the phosphite group and substituents of varying size at the R-oxy position (Figure 3). The preparation of ligands **11a**,**c** has already been reported by us.[9] Ligands **11b**,**d** are reported for the first time here and were readily synthesized using our standard route of epoxide ring opening followed by *O*-phosphorylation (see the Supporting Information for details).[8,9]

Although all the iridium complexes gave good conversions in the reduction of **7** and **9a** (in MeOH and THF), the enantioselectivities varied greatly (see Table 1). The iridium precatalysts that contain the phosphites derived from (S_a)- and (R_a)-BINOL (**11a**,**c**, respectively) provided only moderate selectivities in the reduction of **7** (entries 1 and 2 in Table 1). However, these same iridium complexes and those featuring the same phosphite moieties as well as a trityl group at the R-oxy position (**11b**,**d**) gave high enantioselectivities in the

Table 1. Asymmetric Hydrogenation of C=N Bonds Mediated by Iridium Complexes of Ligands 11a−d[a]

entry	ligand	substrate	solvent	pressure (bar)	conversn (%)[b]	ee (%)[c] (confign)[d]
1	**11a**[e]	**7**	MeOH	50	>99	39 (*R*)
2	**11c**[e]	**7**	MeOH	50	>99	29 (*S*)
3	**11a**	**9a**	THF	80	69	62 (*R*)
4	**11a**	**9a**	toluene	80	19	68 (*R*)
5	**11b**	**9a**	THF	80	75	70 (*R*)
6	**11b**	**9a**	toluene	80	44	76 (*R*)
7	**11c**	**9a**	THF	80	87	83 (*S*)
8	**11c**	**9a**	toluene	80	53	86 (*S*)
9	**11d**	**9a**	THF	80	64	79 (*S*)
10	**11d**	**9a**	toluene	80	16	90 (*S*)

[a] All reactions were run with the iridium precatalyst generated in situ using a substrate/ligand/Ir precursor ratio of 100/1.1/0.5, at room temperature for 20 h, unless otherwise cited. [b] Conversion was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by HPLC. [d] The absolute configuration was assigned by comparison with published data. [e] A substrate/ligand/Ir precursor ratio of 100/2.2/1 was used.

Table 2. Effects of the Temperature, Solvent, Catalyst Loading, and Additive in the Asymmetric Hydrogenation of 9a Mediated by Iridium Complexes Containing Ligands 11c,d

entry	reacn conditions[a]	solvent	conversn (%)[b]	ee (%)[c] (confign)[d]
1	ligand **11c**, 1 mol % precatalyst, 10 mol % HCl, room temp, 20 h	THF	>99	84 (*S*)
2	ligand **11c**, 1 mol % precatalyst, 10 mol % HCl, 0 °C, 20 h	THF	11	83 (*S*)
3	ligand **11c**, 0.2 mol % precatalyst, 10 mol % HCl, 40 °C, 20 h	THF	>99	82 (*S*)
4	ligand **11c**, 1 mol % precatalyst, 10 mol % HCl, room temp, 20 h	toluene	63	90 (*S*)
5	ligand **11c**, 1 mol % precatalyst, 10 mol % HCl, room temp, 65 h	toluene	>99	91 (*S*)
6	ligand **11c**, 0.5 mol % precatalyst, 10 mol % HCl, 40 °C, 20 h	toluene	90	89 (*S*)
7	ligand **11d**, 1 mol % precatalyst, 10 mol % HCl, room temp, 20 h	THF	98	85 (*S*)
8	ligand **11d**, 1 mol % precatalyst, 10 mol % HCl, room temp, 20 h	toluene	47	93 (*S*)
9	ligand **11d**, 1 mol % precatalyst, 10 mol % HCl, room temp, 65 h	toluene	85	93 (*S*)

[a] All reactions were run with the iridium precatalyst generated in situ using a substrate/ligand/Ir precursor ratio of 100/1.1/0.5 and under 80 bar of H_2 unless otherwise stated. [b] Conversion was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by HPLC. [d] The absolute configuration was assigned by comparison with published data.

reduction of heteroaromatic compound **9a** in THF (62−83% ee; entries 3, 5, 7, and 9 in Table 1). Furthermore, better enantioselectivities were obtained for the same precatalysts in toluene than in THF (compare entries 3, 5, 7, and 9 with 4, 6, 8, and 10 in Table 1), although at the expense of lower conversions. Finally, we did not observe any clear relationship between enantioselectivity and the size of the R-oxy group.[14] In previous work on rhodium-mediated hydrogenations, we observed that as the size of the ligand's R group increased,[9] the enantioselectivity slightly decreased. In the iridium-catalyzed hydrogenation of C=N bonds, the same trend is observed in THF when switching from methyl to trityl in the (R_a)-BINOL-containing ligands **11c**,**d** (enantioselectivity dropped from 83% ee to 79% ee; entries 7 and 9 in Table 1, respectively). In contrast, the enantioselectivity increased, in THF or toluene as solvent, when changing from methyl to trityl in the (S_a)-BINOL-containing ligands **11a**,**b** (compare entry 3 with 5 and entry 4 with 6 in Table 1). Interestingly, the binaphthyl moiety strongly influences the stereochemical outcome of the reaction: an opposite configuration of products **8** and **10a** were obtained with (S_a)-BINOL-containing ligands (**11a**,**b**) and (R_a)-BINOL-containing ligands (**11c**,**d**).

Several authors have reported that additives[15] can improve catalytic activity. Thus, we explored several additives in the reduction of **9a** catalyzed by an iridium complex of one of our highest performing ligands (**11c**). We used 10 mol % (relative to **9a**) of NBS,[15a] iodine,[15b] methanol, TFA,[15c] *p*-toluenesulfonic acid,[15c] triflic acid[15c] or (+)- or (−)-camphorsulfonic acid.[15d] However, none of these provided any noticeable improvement in conversion or in enantioselectivity. Remarkably, addition of 10 mol % of anhydrous HCl[16] afforded complete conversion in the hydrogenation of **9a** in THF with iridium complexes derived from ligands that incorporate the (R_a)-BINOL fragment (for ligand **11c**, compare entry 1 in Table 2 with entry 7 in Table 1; for ligand **11d**, compare entry 7 in Table 2 with entry 9 in Table 1). Better conversions and enantioselectivities (entries 5 and 9 in Table 2) were achieved with toluene, although this required longer reaction times (65 h). We sought to further increase the enantioselectivity by reducing the temperature, but this strategy turned out to be ineffective, as it led to dramatically lower conversion (entry 2 in Table 2). We were able to use a lower catalyst loading with almost no loss in catalytic activity: down to 0.2 mol % in THF (entry 3 in Table 2) and to 0.5 mol % in toluene (entry 6 in Table 2).

(14) The steric environment at this position has proven critical to the catalytic activity of other chiral ligands derived from Sharpless epoxy alcohols, in several asymmetric transformations. See, for example: (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (b) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773. (c) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (d) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902. (e) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164. (f) Jimeno, C.; Vidal-Ferran, A.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 3895. (g) Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2007**, *349*, 2265. (h) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 1539.

(15) For a general reference on additive effects, see: Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570. For details on specific additives, see: (a) References 6u and 7c, for NBS. (b) Reference 5a, for iodine. (c) Reference 7b, for TFA and *p*-toluenesulfonic and triflic acids. (d) Reference 5t, for camphorsulfonic acids.

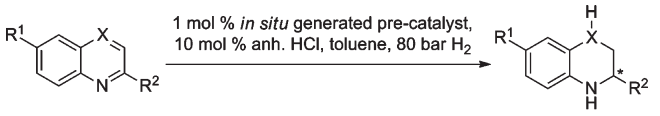
(16) The use of ammonium or quinolinium chloride as additive has been reported by Feringa[6t] and Zhou.[7l] We chose adding anhydrous HCl (10 mol %) to generate in situ the corresponding hydrochloride of each substrate. Greater amounts of HCl (up to stoichiometric quantity) did not provide any improvement.

Table 3. Hydrogenations of a Structurally Diverse Array of Heteroaromatic Substrates Mediated by the Iridium Complex Containing Ligand 11c[a]

entry	substrate	substituents on the substrate	conversn (%)[b]	ee (%)[c] (config)[d]
1	**9a**	R^1 = H; R^2 = Me; X = CH	>99	91 (*S*)
2	**9b**	R^1 = H; R^2 = *n*-Pr; X = CH	98	71 (*S*)
3	**9c**	R^1 = H; R^2 = *n*-Bu; X = CH	99	85 (*S*)
4	**9d**	R^1 = H; R^2 = *i*-Bu; X = CH	>99	88 (*S*)[e]
5	**9e**	R^1 = F; R^2 = Me; X = CH	92	88 (*S*)
6	**9f**	R^1 = Me; R^2 = Me; X = CH	74	92 (*S*)
7	**9g**	R^1 = MeO; R^2 = Me; X = CH	38	89 (*S*)
8	**9h**	R^1 = MeO; R^2 = Et; X = CH	23	87 (*S*)[e]
9	**9i**	R^1 = H; R^2 = Ph; X = CH	>99	84 (*R*)
10	**9j**[f]	R^1 = H; R^2 = Me; X = N	97	70 (*R*)

[a] All reactions were run with the iridium precatalyst generated in situ using a substrate/additive/ligand/Ir precursor ratio of 100/10/1.1/0.5, at room temperature for 65 h. [b] Conversion was determined by ^{1}H NMR. [c] Enantiomeric excess was determined by HPLC. [d] The absolute configuration was assigned by comparison with published data. [e] Configuration was tentatively assumed to be *S* by analogy. [f] Iridium complex containing ligand **11a** was used as the precatalyst in this case.

Scheme 4. Asymmetric Hydrogenation of Heteroaromatic Compounds Mediated by the Iridium Complex Containing Ligand 11c



Iridium complexes derived from **11c**,**11d** both enabled efficient reduction of 2-methylquinoline: although slightly higher enantioselectivities were obtained for ligand **11d** in toluene (93% ee vs 91% ee; entries 5 and 9, respectively, in Table 2), ligand **11c** gave the hydrogenated product in quantitative conversion. Thus, we chose **11c** for studying the hydrogenation of structurally diverse heteroaromatic substrates (mostly quinolines; see Scheme 4). The results of these hydrogenations are summarized in Table 3.

The chain length of the R^2 group barely influenced the catalytic activity, since enantioselectivities remained high for R^2 = Me, *n*-Bu, *i*-Bu (91%, 85%, and 88% ee, respectively; entries 1, 3, and 4 in Table 3) and good for R^2 = *n*-Pr (71% ee, entry 2 in Table 3). Replacing the alkyl R^2 group with a phenyl substituent did not affect the catalytic activity, and the enantioselectivity remained high (84% ee; entry 9 in Table 3). Regardless of the electronic nature of the substituent R^1, substrates were hydrogenated with high enantioselectivity (88−92% ee; entries 5−7 in Table 3), although conversion decreased dramatically in the case where R^1 is an electron-donating group (**9g**,**h**, R^1 = MeO; entries 7 and 8 in Table 3). Fluoro-substituted 1,2,3,4-tetrahydroquinoline **10e** was obtained in high conversion and enantioselectivity (entry 5 in Table 3), and this compound is a key building block in the preparation of the antibacterial agent flumequine.[17] The iridium complex derived from ligand **11a** was preferably used for the hydrogenation of substituted quinoxaline **9j** (entry 10 in Table 3).

In conclusion, catalytic screening revealed that the iridium complexes of chiral phosphine−phosphite ligands **11c**,**d** are excellent catalysts in the reduction of various aromatic compounds that contain C=N bonds. In contrast, these complexes failed to give high enantioselectivity in the reduction of imine **7** and quinoxaline **9j**. The "lead" precatalyst of the series (derived from ligand **11c**) in combination with catalytic amounts of anhydrous HCl exhibits excellent catalytic properties in this transformation and tolerates a wide range of substituents in the 2- and 6-positions of the quinoline scaffold. Furthermore, we have validated our chiral catalyst discovery strategy, which entails modifying the steric and electronic properties of the molecular fragments or modules of a catalyst to generate higher performing analogues. We are currently screening these ligands in new asymmetric transformations and will report on this work in due course.

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Supporting Information Available: Text, figures, tables, and a CIF file giving experimental details, characterization data, NMR spectra (for compounds **4**−**6** and **11b**,**d**), crystallographic data for **6**, and details on catalytic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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