Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2049–2052

Asymmetric hydrogenation of imines catalyzed by iridium complexes with phosphine–phosphite ligands: importance of backbone flexibility

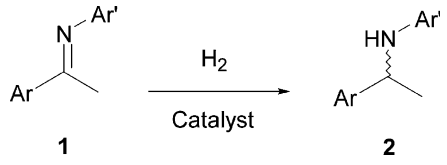
Sergio Vargas, Miguel Rubio, Andrés Suárez and Antonio Pizzano*

Instituto de Investigaciones Químicas, Consejo Superior de Investigaciones Científicas-Universidad de Sevilla, Avda Américo Vespucio s/n, Isla de la Cartuja, 41092 Sevilla, Spain

Received 30 November 2004; revised 25 January 2005; accepted 26 January 2005

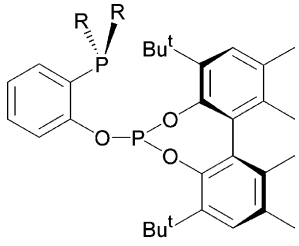
Abstract—Chiral phosphine–phosphites provide an alternative class of ligands for the iridium catalyzed enantioselective hydrogenation of imines. Optimization of ligand structure has afforded enantioselectivities up to 84% ee in the reduction of *N*-aryl imines. A significant influence of backbone nature on enantioselectivity has also been observed.

Asymmetric catalytic hydrogenation of imines is a very attractive approach to the synthesis of chiral amines due to simplicity and efficiency often associated to enantioselective hydrogenation.[1] However, despite the great advances achieved in the reduction of ketones and olefins, the hydrogenation of prochiral imines is at a substantially lower maturity.[2] For instance, good to excellent results have been obtained in the hydrogenation of several *N*-alkyl, -benzyl[3] and cyclic imines,[4] while the hydrogenation of *N*-aryl imines (Eq. 1), a transformation of great interest due to the importance of corresponding chiral amines,[5] has offered significant difficulties. Thus, intense efforts have been dedicated to the study of this reaction and only few catalysts have been able to surpass the 80% ee level.[6,7] The latter values are often acceptable for agrochemical applications,[8] while enantioselectivities in the 95–99% ee range have only been reached with an iridium catalyst bearing a strong donor ferrocenyl diphosphine described by Xiao and Zhang.[9] Upon this background, it looks clear that both the examination of new catalytic systems and the identification of suitable ligand properties for this reaction are of great interest.



1 2 (1)

Chiral phosphine–phosphites form a group of ligands receiving a growing interest in asymmetric catalysis.[10] They have been applied successfully in a variety of catalytic processes, but to the best of our knowledge they have not been investigated in the hydrogenation of imines. We have recently described a straightforward synthesis of a family of modular phosphine–phosphites and its application in the highly enantioselective hydrogenation of several olefins.[11] In this contribution we report preliminary results pointing to the usefulness of phosphine–phosphites in the hydrogenation of *N*-aryl



R = Ph (**3a**), Pr^i (**3b**), Me (**3c**)

Keywords: Asymmetric hydrogenation; Chiral amines; Phosphine–phosphites.
* Corresponding author. Tel.: +34 9544 89556; fax: +34 9544 60565; e-mail: pizzano@iiq.csic.es

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.144

imines. In addition, the high modularity of the corresponding catalysts have allowed to identify backbone mobility as an important variable in this reaction.

Initially, we have performed a screening with some catalyst precursors of formulation $[Ir(COD)(\mathbf{3})]BF_4$ (COD = 1,5-cyclooctadiene) as well as with those prepared from $[Ir(Cl)(COD)]_2$ and **3**, at a metal to ligand ratio of 1, in the hydrogenation of model substrate *N*-(1-phenylethylidene)aniline **1a** (Ar = Ar′ = Ph).[12] This exploration indicated that neutral precursors were more active than cationic ones. For instance, under reaction conditions depicted in Table 1, conversions with **3b** were 100% and 45%, respectively. Thus, all catalysts mentioned below were prepared in situ from the iridium dimer and the appropriate phosphine–phosphite at a Ir–ligand ratio of 1.

Use of compounds **3a**–**e** led to active catalysts that completed the reaction under relatively mild conditions (Table 1).[13] Enantioselectivities were low in all cases, thus indicating the need of a substantial structural modification in order to improve catalyst performance. Inspired by the mentioned study on a ferrocenyl based catalyst,[9] we envisioned ligand flexibility as a plausible variable for catalyst optimization. As ligands **3** possess a rather rigid backbone, it is of interest the investigation of more flexible derivatives. For that purpose we have prepared ethane bridged phosphine–phosphites **6** (Scheme 1). As a requisite for the latter, hydroxy-phosphines **4** are required. Procedure described in the literature for 2-diphenylphosphinoethanol[14] proved suitable for the preparation of the rest of compounds **4**. Subsequent condensation with chiral chlorophosphite **5**, in the presence of NEt_3, led to ligands **6**.[15]

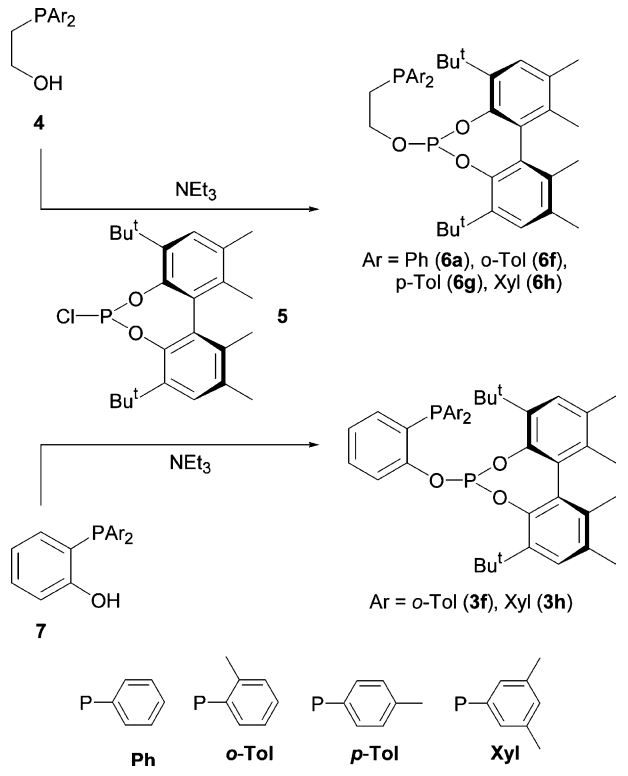
Interestingly, catalyst derived from **6a** completed the reaction under our standard conditions. The reaction was faster than expected and was actually completed in less than 6 h. Most noteworthy, this ligand produced a significant increase on the enantioselectivity of the reaction up to 81% ee (Table 2). With the intention to further optimize the enantioselectivity of the reaction, we have also examined other phosphine aryl substituents.[16] Unfortunately, ligands **6f**–**h** did not provide a significant improvement and the best result was 82% ee

Table 1. Hydrogenation of **1a** with precatalysts 1/2 $[Ir(Cl)(COD)]_2$ + **3**[a]

Entry	Ligand	% Ee (conf.)
1	**3a**	36 (*S*)
2	**3b**	25 (*S*)
3	**3c**	20 (*S*)

Conversion was determined by ^{1}H NMR and enantiomeric excess (ee) by chiral HPLC (Chiralcel OJ, 30 °C, hexane–Pr^{i}OH (97:3), 1.0 mL/min). Configuration was determined by comparison of optical rotation with literature value.[6a]

[a] All hydrogenations were completed under conditions specified. Reactions were carried out at room temperature with an initial hydrogen pressure of 30 bar, in methylene chloride at a S/C = 100. Reaction time 24 h.



Scheme 1.

Table 2. Hydrogenation of **1** with precatalysts 1/2 $[Ir(Cl)(COD)]_2$ + ligand[a]

Entry	Substrate	Ligand	% Ee (conf.)
1	**1a**	**6a**	81 (*S*)
2	**1a**	**6f**	70 (*S*)
3	**1a**	**6g**	76 (*S*)
4	**1a**	**6h**	82 (*S*)
5[b]	**1a**	**6h**	84 (*S*)
6	**1b**	**6h**	83 (*S*)
7	**1a**	**3a**	36 (*S*)
8	**1a**	**3f**	47 (*S*)
9	**1a**	**3h**	42 (*S*)

Compound **2b**: Chiralpak AD, 30 °C, hexane–Pr^{i}OH (99:1), 1.0 mL/min. Configuration was determined by comparison of optical rotation with literature value.[6a]

[a] All hydrogenations were completed under conditions specified. Reactions were carried out at room temperature with an initial hydrogen pressure of 30 bar, in methylene chloride at a S/C = 100. Reaction time 24 h. Conversion was determined by ^{1}H NMR and enantiomeric excess (ee) by chiral HPLC (**2a**: Chiralcel OJ, 30 °C, hexane–Pr^{i}OH 97:3, 1.0 mL/min).

[b] Hydrogenation performed at 0 °C, reaction time 10 h.

obtained with the xylyl derivative **6h**, which could be increased to 84% ee at 0 °C. In addition, *p*-anisyl imine **1b** (Ar = Ph, Ar′ = 4-MeO–C_6H_4) of interest due to its easy conversion into the primary amine,[9] was hydrogenated to give **2b** with 83% ee (entry 6).

The notable increase on enantioselectivity (Δee = 45%) obtained with **6a**, regarding to **3a**, have prompted us to investigate if this positive influence of the backbone is more general. For that purpose *o*-tolyl (**3f**, Scheme 1)

and xylyl (**3h**) have also been prepared.[17] Most noteworthy, the latter ligands produced amine **2a** with significantly lower enantiomeric excesses than their ethane counterparts **6f** and **h**. Then, values of Δee in the three couple of ligands investigated ranged from 23% to 45% ee indicating a general positive influence of the ethane backbone.[18]

In conclusion, we have demonstrated that chiral phosphine–phosphites are appropriate ligands for the iridium catalyzed asymmetric hydrogenation of imines. Ligand optimization have led to efficient catalysts, as well as it has identified the nature of the backbone as an important variable in catalyst design. Studies regarding optimization and scope of this catalytic system are currently under progress.

Acknowledgments

We gratefully acknowledge Ministerio de Educación y Ciencia for financial support (BQU-2000-1167). S.G. and M.R. thank CSIC (I3P Program) and Ministerio de Educación y Ciencia (FPU Program), respectively, for fellowships.

References and notes

1. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1.
2. (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.
3. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952; (b) Lensink, C.; deVries, J. G. *Tetrahedron: Asymmetry* **1992**, *3*, 235; (c) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *Chem. Commun.* **1991**, 1684.
4. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703; (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536; (c) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308; (d) Ringwald, M.; Stürmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, *121*, 1524.
5. (a) Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 17; (b) Blaser, H.-U.; Spindler, F. *Top. Catal.* **1997**, *4*, 275.
6. (a) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195; (b) Dorta, R.; Broggini, D.; Stoop, R.; Rüegger, H.; Spindler, F.; Togni, A. *Chem. Eur. J.* **2004**, *10*, 267; (c) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887; (d) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159; (e) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825; (f) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem. Eur. J.* **2004**, *10*, 4198.
7. The racemization of a *N*-aryl amine by an Ir C–H activation has recently been demonstrated. This transformation would difficult the achievement of high enantioselectivities in the hydrogenation of *N*-aryl imines. See: Dorta, R.; Broggini, D.; Kissner, R.; Togni, A. *Chem. Eur. J.* **2004**, *10*, 4546.
8. Blaser, H.-U.; Pugin, B.; Spindler, F. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 3.
9. Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3425.
10. (a) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413; (b) Nozaki, K.; Sato, N.; Tonomura, Y.; Yasutomi, M.; Takaya, H.; Hiyama, T.; Matsubara, T.; Koga, N. *J. Am. Chem. Soc.* **1997**, *119*, 12779; (c) Deerenberg, S.; Pàmies, O.; Diéguez, M.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 7626; (d) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810; (e) Pàmies, O.; Diéguez, M.; Net, G.; Ruiz, A.; Claver, C. *J. Org. Chem.* **2001**, *66*, 8364; (f) Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H.-G. *Adv. Synth. Catal.* **2002**, *344*, 868; (g) Yan, Y.; Chi, Y.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2173; (h) 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.
11. (a) Suárez, A.; Pizzano, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2501; (b) Suárez, A.; Méndez-Rojas, M. A.; Pizzano, A. *Organometallics* **2002**, *21*, 4611; (c) Rubio, M.; Suárez, A.; Alvarez, E.; Pizzano, A. *Chem. Commun.* **2005**, 628.
12. General procedure for asymmetric hydrogenation. To a solution of $[Ir(Cl)(COD)]_2$ (3 mg, 0.004 mmol) in CH_2Cl_2 (1 mL) was added **6a** (6 mg, 0.009 mmol) dissolved in CH_2Cl_2 (1 mL). The mixture was stirred for 15 min and added to a solution of imine **1a** (174 mg, 0.9 mmol) in CH_2Cl_2 (8 mL). The mixture was transferred to an autoclave, purged three times with hydrogen and finally pressurized at 30 bar. The reaction was stirred for 24 h, reactor was depressurized and resulting solution evaporated to dryness. The residue was redissolved in a hexanes–ethyl acetate mixture (1:1) and passed through a short pad of silica. Evaporation of solvent yielded amine **2a** in quantitative yield. Enantiomeric excess was determined by chiral HPLC (Chiralcel OJ, 30 °C, hexane–Pr^{i}OH (97:3), flow 1.0 mL/min, $t_1 = 15.1$ min (*S*), $t_2 = 16.9$ min (*R*)).
13. As ligands **3** are considerably poor donor than diphosphines, this observation emphasizes that it is possible to get active iridium catalysts with P–P ligands possessing broad electronic properties. Accordingly, there have appeared reports on the literature of catalysts bearing from electron rich diphosphines[9] to poor donating diphosphites, see: Guiu, E.; Muñoz, B.; Castillón, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169.
14. Chantreux, D.; Gamet, J.-P.; Jacquier, R.; Verducci, J. *Tetrahedron* **1984**, *40*, 3087.
15. Representative procedure for the synthesis of ligands. Over a solution of **5** (0.354 g, 0.84 mmol) and NEt_3 (0.24 mL, 1.68 mmol) in toluene (30;mL) was added a solution of 2-(diphenylphosphino)ethanol (0.195 g, 0.84 mmol) in toluene (20 mL). The reaction was stirred for 12 h and the resulting suspension filtered. The solvent was evaporated, the residue redissolved in Et_2O and filtered through neutral alumina. Evaporation of the solution obtained led to compound **6a** as a white foamy solid (0.34 g, 70%). $[\alpha]_{20}^{D}$ 117 (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 9H, CMe_3), 1.47 (s, 9H, CMe_3), 1.77 (s, 6H, 2Me), 2.19 (s, 3H, Me), 2.26 (s, 3H, Me), 2.29–2.36 (m, 2H, 2CHH), 3.36 (m, 1H, CHH), 3.92 (m, 1H, CHH), 7.04 (s, 1H, H arom), 7.07 (s, 1H, H arom), 7.30 (m, 10H, H arom). ^{31}P{^{1}H} NMR ($CDCl_3$, 121.5 MHz): δ −24.4 (s, PC), 128.9

(s, PO). HRMS (EI): *m*/*z* 612.2908, $[M]^+$ (exact mass calculated for $C_{38}H_{46}O_3P_2$: 612.2922).

16. For catalyst improvements by aryl optimization see for instance: Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Cagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.
17. Compounds **3f** and **h** have been prepared from corresponding phenol-phosphines **7** as described for **1a**–**e**.[11]
18. The improvement produced by ligands **6**, in comparison with **3**, can be ascribed to the expected higher flexibility of the former or, in addition, to the adoption of a more efficient conformation by coordinated **6**.