Asymmetric hydrogenation of quinolines catalyzed by iridium complexes of BINOL-derived diphosphonites

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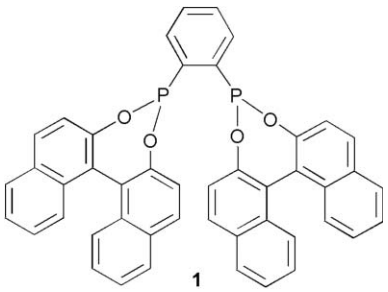
A chiral diphosphonite, derived from BINOL and with an achiral diphenyl ether backbone, is an excellent ligand for the Ir-catalyzed asymmetric hydrogenation of quinolines; achiral P-ligands serving as possible additives (ee = 73–96%).

The asymmetric hydrogenation of quinoline derivatives constitutes a convenient route to chiral tetrahydroquinolines, compounds which are not only useful synthetic intermediates but also the structural units of a number of alkaloids.[1] Inspite of a fair amount of effort,[2] only four ligand systems are known to provide ee values greater than 90%. Zhou *et al.* reported that Ir complexes generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-Biphep[3] or a ferrocenyl-oxazoline-derived P,N-ligand[4] are effective in the asymmetric hydrogenation of 2-substituted quinolines (maximum ee = 96 and 92%, respectively). Similar results were subsequently described by Chan[5a] using his previously prepared family of chiral dipyridyl-phosphane ligands[6] (P-Phos) (maximum ee = 92%) and more recently H8-BINAPO.[5b] In our own earlier work, we showed that readily accessible and therefore cheap BINOL-derived diphosphonites of the type **1–5** are highly efficient ligands in Rh-catalyzed olefin hydrogenation,[7] Rh-catalyzed conjugate addition reactions of arylboronic acids[8] and Ru-catalyzed transfer reductions of ketones.[9] In each case, success depends upon the appropriate choice of achiral backbone, *i.e.*, among compounds such as **1–5**, there is no universal ligand that is most suited to all reaction types. We now report that this class of chiral ligands is also well suited to the asymmetric Ir-catalyzed hydrogenation of quinoline derivatives, and that, once again, the nature of the backbone is crucial.



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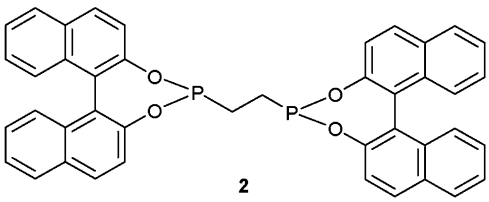

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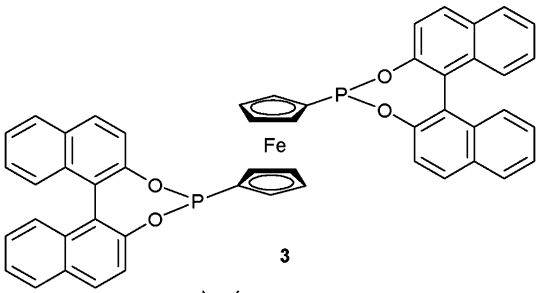

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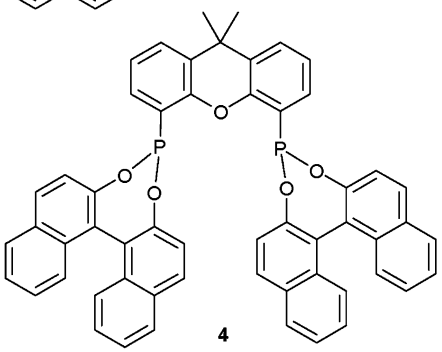

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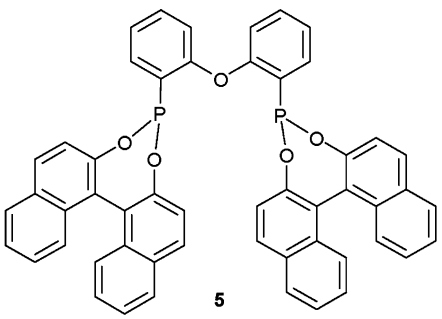

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Ligands **1–5**, all prepared from (*S*)-BINOL, were first screened in the asymmetric hydrogenation of **6a**, with the formation of tetrahydroquinoline **7a** under non-optimized conditions using I_2 as an additive[10] (substrate : $[Ir(COD)Cl]_2$: ligand : I_2 = 100 : 1 : 2 : 20; 15 bar H_2; toluene; 20 h). The ee values for **7a** resulting from the use of ligands **1**, **2**, **3**, **4** and **5** were 45% (*R*), 50% (*R*), 16% (*R*), 43% (*S*) and 88% (*S*), respectively. The reaction conditions using the diphenyl ether-derived ligand **5** were then optimized (substrate : $[Ir(COD)Cl]_2$: **5** : I_2 = 200 : 1 : 2 : 2; 60 bar H_2; toluene; 20 h), resulting in an ee value of 92% (>96% conversion). At 0 °C, enantioselectivity increased to ee = 96% (>96% conversion).

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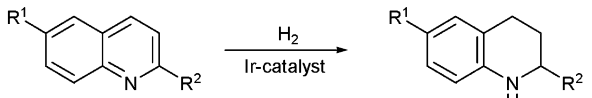
Table 1 Ir-catalyzed asymmetric hydrogenation of quinoline derivatives **6a–g** using ligand (*S*)-**5**, with and without achiral P-additives[a]

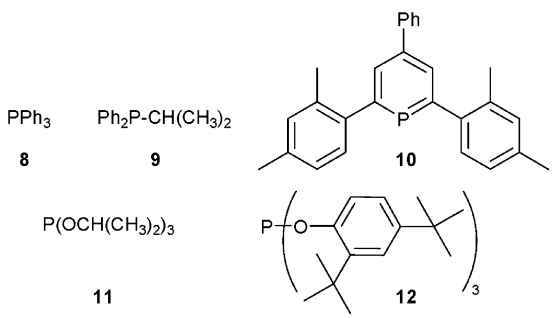
Entry	Quinoline	Achiral ligand	Conversion (%)	ee (%)
1	**6a**	None	>96	92(*S*)
2	**6a**[b]	None	>96	96(*S*)
3	**6a**[b]	**10**	>96	96(*S*)
4	**6a**[c]	**10**	>96	94(*S*)
5	**6a**[c]	**11**	66	94(*S*)
6	**6a**[c]	**12**	73	94(*S*)
7	**6b**	None	>96	85(*S*)
8	**6b**	**10**	>96	91(*S*)
9	**6c**	None	>96	88(*S*)
10	**6c**	**10**	>96	91(*S*)
11	**6d**[b]	None	42	73(*S*)
12	**6e**	**10**	>96	80(*S*)
13	**6f**	None	>96	82(*R*)
14	**6f**	**10**	>96	90(*R*)
15	**6g**	**10**	>96	92(*R*)

[a] Substrate : $[Ir(COD)Cl]_2$: (*S*)-**5** : I_2 = 200 : 1 : 2 : 2; 60 bar H_2; toluene; 23 °C; 20 h. [b] Substrate : Ir = 50 : 1 at 0 °C. [c] 15 bar H_2.



6a R^1 = H; R^2 = CH_3 **e** R^1 = R^2 = CH_3
b R^1 = H; R^2 = C_2H_5 **f** R^1 = F; R^2 = CH_3
c R^1 = H; R^2 = *n*-C_4H_9 **g** R^1 = H; R^2 = $CH_2C(CH_3)_2OH$
d R^1 = H; R^2 = C_6H_5

Previously we have shown that monodentate BINOL-derived phosphites and phosphonites are excellent ligands in a variety of Rh-catalyzed olefin hydrogenation reactions, and that mixtures of such ligands and achiral monodentate P-ligands[11] can lead to further improvements. So far, we have not been able to reach ee values of >80% in the Ir-catalyzed hydrogenation of quinolines using this strategy. Nevertheless, we decided to test possible effects when using mixtures of ligand **5** and achiral P-ligands such as **8–12** (**5** : achiral ligand = 1 : 2). Again, substrate **6a** was used in the model reaction. Generally, no positive effects resulted, but in some cases small improvements were observed, depending upon the nature of the achiral ligand (**8**, 92% ee; **9**, 90% ee; **10**, 94% ee; **11**, 94% ee; **12**, 94% ee).



Following these exploratory experiments, the optimized protocol was applied to the other substrates. The results of the hydrogenation experiments using compounds **6a–g** are summarized in Table 1. It can be seen that in all cases, with the exception of **6d** and **6e** (Table 1, entries 11 and 12), enantioselectivities in the range 90–96% ee were achieved, although in some cases this required the use of an appropriate achiral ligand in combination with **5**. The ee values were determined by HPLC (OJ, AS-H or OD-H columns), similar to Zhou's procedure.[3,4]

In summary, we have developed an efficient catalyst system for the asymmetric Ir-catalyzed hydrogenation of quinoline derivatives. The ligand comprises a diphosphonite derived from BINOL and an achiral backbone originating from diphenyl ether. Due to the ready accessibility of this ligand, the process is likely to attract the interest of industrial chemists. Illuminating the source of the enantioselectivity and the possible role of the achiral P-ligand (new Rh-complexes or O_2-scavengers?) are goals for the future.

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Notes and references

1 (*a*) J. G. Keay, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 8, pp. 579–601; (*b*) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031–15070; (*c*) *Comprehensive Natural Products Chemistry*, ed. D. H. Barton, K. Nakanishi and O. Meth-Cohn, Elsevier, Oxford, 1999, vol. 1–9.

2 Reviews of asymmetric hydrogenation of heteroaromatic compounds: (*a*) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.*, 2003, **345**, 103–151; (*b*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029–3069; (*c*) *Principles and Applications of Asymmetric Synthesis*, ed. G. Q. Lin, Y. M. Li and A. S. C. Chan, Wiley-Interscience, New York, 2001. For some recent publications, see: (*d*) J. P. Henschke, M. J. Burk, C. G. Malan, D. Herzberg, J. A. Peterson, A. J. Wildsmith, C. J. Cobley and G. Casy, *Adv. Synth. Catal.*, 2003, **345**, 300–307; (*e*) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa and Y. Ito, *Org. Lett.*, 2004, **6**, 2213–2215; (*f*) C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966–8967; (*g*) F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehmann, *Angew. Chem.*, 2004, **116**, 2910–2913, (*Angew. Chem., Int. Ed.*, 2004, **43**, 2850–2852) and references cited therein.

3 W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 10536–10537.

4 S.-M. Lu, X.-W. Han and Y.-G. Zhou, *Adv. Synth. Catal.*, 2004, **346**, 909–912.

5 (*a*) L. Xu, K. H. Lam, J. Ji, J. Wu, Q.-H. Fan, W.-H. Lo and A. S. C. Chan, *Chem. Commun.*, 2005, 1390–1392; (*b*) K. H. Lam, L. Xu, L. Feng, Q.-H. Fan, F. L. Lam, W.-H. Lo and A. S. C. Chan, *Adv. Synth. Catal.*, 2005, **347**, 1755–1758.

6 (*a*) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan and W. T. Wong, *J. Am. Chem. Soc.*, 2000, **122**, 11513–11514; (*b*) J. Wu, H. Chen, Z.-Y. Zhou, C. H. Yeung and A. S. C. Chan, *Synlett*, 2001, 1050–1054; (*c*) J. Wu, H. Chen, W. H. Kwok, K. H. Lam, Z. Y. Zhou, C. H. Yeung and A. S. C. Chan, *Tetrahedron Lett.*, 2002, **43**, 1539–1543; (*d*) J. Wu, H. Chen, W. Kwok, R. Guo, Z.-Y. Zhou, C.-H. Yeung and A. S. C. Chan, *J. Org. Chem.*, 2002, **67**, 7908–7910; (*e*) J. Wu, X. Chen, R. Guo, C. Yeung and A. S. C. Chan, *J. Org. Chem.*, 2003, **68**, 2490–2493; (*f*) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung and A. S. C. Chan, *Chem.–Eur. J.*, 2003, **9**, 2963–2968.

7 (*a*) M. T. Reetz, A. Gosberg, R. Goddard and S.-H. Kyung, *Chem. Commun.*, 1998, 2077–2078; (*b*) M. T. Reetz, *Pure Appl. Chem.*, 1999, **71**, 1503–1509.

8 M. T. Reetz, D. Moulin and A. Gosberg, *Org. Lett.*, 2001, **3**, 4083–4085.

9 M. T. Reetz and X. Li, *J. Am. Chem. Soc.*, 2006, **128**, 1044–1045.

10 (*a*) A. Togni, *Angew. Chem.*, 1996, **108**, 1581–1583, (*Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1475–1477); (*b*) D. Xiao and X. Zhang, *Angew. Chem.*, 2001, **113**, 3533–3536), (*Angew. Chem., Int. Ed.*, 2001, **40**, 3425–3428).

11 (*a*) M. T. Reetz and X. Li, *Angew. Chem.*, 2005, **117**, 3019–3021, (*Angew. Chem., Int. Ed.*, 2005, **44**, 2959–2962); (*b*) R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *Angew. Chem.*, 2005, **117**, 4281–4284, (*Angew. Chem., Int. Ed.*, 2005, **44**, 4209–4212).

