# Biaryl phosphite-oxazolines from hydroxyl aminoacid derivatives: highly efficient modular ligands for Ir-catalyzed hydrogenation of alkenes†

**Montserrat Diéguez,*[a] Javier Mazuela,[a] Oscar Pàmies,[a] J. Johan Verendel[b] and Pher G. Andersson*[b]**

*Received (in Cambridge, UK) 23rd April 2008, Accepted 20th May 2008*
*First published as an Advance Article on the web 3rd July 2008*
**DOI: 10.1039/b806891g**

**High enantioselectivities and activities are achieved in the Ir-catalyzed hydrogenation of several unfunctionalized olefins using modular biaryl phosphite-oxazoline ligands from hydroxyl aminoacid derivatives; the presence of a biaryl phosphite group is crucial to this success.**

The asymmetric hydrogenation of olefins has been widely used in stereoselective organic synthesis and some processes have found industrial applications. In this respect, the asymmetric hydrogenation of unfunctionalized olefins still represents a challenging class of substrates.[1] Iridium complexes with chiral P,N ligands have become established as efficient catalysts for the hydrogenation of unfunctionalized olefins, with scope complementary to that of Rh- and Ru-diphosphine complexes.[2] Unlike Rh- and Ru-catalysts, they do not require a coordinating polar group adjacent to the C=C group. The first chiral ligands developed for this process were the phosphine-oxazolines, which are chiral mimics of Crabtree's catalyst. These ligands have been used successfully for the asymmetric hydrogenation of a limited range of alkenes.[3] Recently, the composition of the ligands has been extended by the discovery of new mixed P,N ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation.[4] Of them all, the most successful ligands contain a phosphinite moiety as P-donor group and either an oxazoline, oxazole or pyridine as N-donor group.[4b–d,g]

In the last few years, phosphite-containing ligands have demonstrated that they are potentially extremely useful in many transition-metal catalyzed reactions.[5] Their highly modular construction, facile synthesis from readily available chiral alcohols, greater resistance to oxidation than phosphines and π-acceptor capacity have proved to be highly advantageous. Despite this, they have rarely been used in the Ir-catalyzed hydrogenation of olefins. So far only two reports have been published that use phosphite ligands.[6] One of these reports described the application of TADDOL-based phosphite-oxazoline ligands **1** (Fig. 1).[6a] However, their substrate range was more limited and their enantioselectivities and activities were lower than those of related phosphinite/phosphine-oxazoline ligands. They also required higher catalyst loadings (4 mol%) and higher pressures (100 bar) to achieve full conversions. The second report was published recently and presented the successful application of pyranoside phosphite-oxazoline ligands **2** (Fig. 1).[6b] However it is unclear whether this success is due to the pyranoside-sugar backbone or the introduction of a biaryl phosphite moiety.

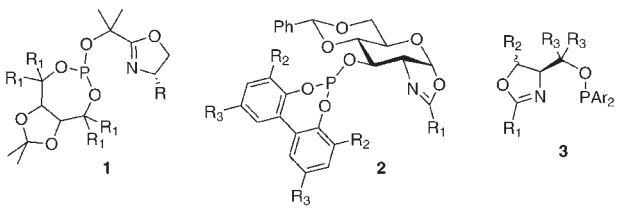



**Fig. 1** Phosphite-oxazoline ligands **1** and **2** and phosphinite-oxazoline ligands.

To address this point, we took one of the most successful ligand families for this process (ligands **3**, Fig. 1) and replaced the phosphinite moiety with a biaryl phosphite moiety (ligands **L1–L6a–e**, Fig. 2). In this communication we present the application of this phosphite-oxazoline ligand library (**L1–L6a–e**, Fig. 2)[7] in the asymmetric Ir-catalyzed hydrogenation of several unfunctionalized olefins. Another advantage of this new ligand library design is that it enables more ligand parameters to be studied than in our first phosphite-oxazoline ligand library **2**. These parameters are important for the hydrogenation reactions, and because they are easy to introduce they are easy to study. With this library (Fig. 2), we investigated the effect of systematically varying the substituents in the oxazoline moiety ($R^1$) and the alkyl backbone chain ($R^3$). We also studied the presence of a second stereogenic

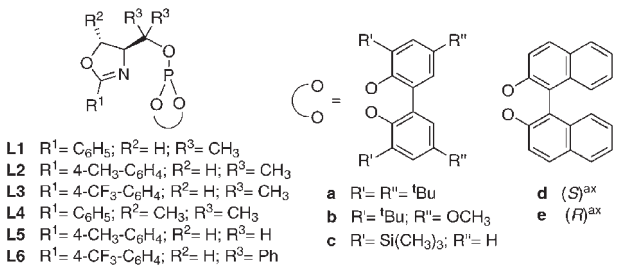


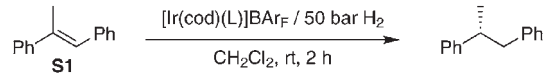

**Fig. 2** Phosphite-oxazoline ligands **L1–L6a–e**.

[a] *Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/ Marcelli Domingo, s/n. 43007 Tarragona, Spain. E-mail: montserrat.dieguez@urv.cat; Fax: +34-977559563; Tel: +34-977558780*
[b] *Department of Biochemistry and Organic Chemistry, Uppsala University, BOX 576, 751 23 Uppsala, Sweden. E-mail: pher.andersson@kemi.uu.se*

† Electronic supplementary information (ESI) available: Experimental procedures and characterization of [Ir(cod)(L)]$BAr_F$ (L = **L1–L6a–e**) complexes. See DOI: 10.1039/b806891g

**Table 1** Ir-catalyzed asymmetric hydrogenation of **S1** using ligands **L1–L6a–e**[a]




| Entry | L | mol% Ir | % Conv.[b] | % ee[c] |
|---|---|---|---|---|
| 1 | **L1a** | 2 | 100 | 97 (*R*) |
| 2 | **L1b** | 2 | 100 | 94 (*R*) |
| 3 | **L1c** | 2 | 100 | 98 (*R*) |
| 4 | **L1d** | 2 | 100 | 99 (*R*) |
| 5 | **L1e** | 2 | 100 | 94 (*R*) |
| 6 | **L2a** | 2 | 100 | 95 (*R*) |
| 7 | **L3a** | 2 | 100 | 90 (*R*) |
| 8 | **L4a** | 2 | 100 | 92 (*R*) |
| 9 | **L5a** | 2 | 100 | 91 (*R*) |
| 10 | **L6a** | 2 | 80 | 81 (*R*) |
| 11 | **L1d** | 0.2 | 100 | 99 (*R*) |

[a] Reactions carried out using 1 mmol of **S1**. [b] Conversion measured by $^1$H-NMR. [c] Enantiomeric excesses determined by chiral HPLC.

centre in the heterocycle ring ($R^2$) and the substituents and configurations in the biaryl phosphite moiety (**a–e**). By carefully selecting these elements, we achieved high enantioselectivities and activities in a wide range of substrates.

To make the initial evaluation of this new type of ligands (**L1–L6a–e**), we chose the Ir-catalyzed hydrogenation of *trans*-α-methylstilbene **S1** (Table 1). As this reaction was carried out with a wide variety of ligands carrying different donor groups, we were able to compare the efficacy of the various ligand systems.

The catalyst precursors [Ir(cod)(L)]$BAr_F$ (L = **L1–L6a–e**) were prepared following a standard protocol[3d] and used without further purification. The results (Table 1) indicate that enantioselectivity is affected by the substituents at the oxazoline and in the alkyl backbone chain, the presence of a second stereogenic centre in the oxazoline ring and the substituents/configuration in the biaryl phosphite moiety. The best result (100% conversion; 99% ee) was therefore obtained with ligand **L1d** (entry 4), which contains the optimal combination of ligand parameters. These results show the efficiency of using highly modular scaffolds in the ligand design.

We also performed the reaction at low catalyst loading (0.2 mol%) using ligand **L1d** (entry 11). The excellent enantioselectivity (99% (*R*) ee) and activity (100% conversion after 2 h at room temperature) were maintained.

The subsequent screening of other potential substrates showed that these catalysts also allow the asymmetric hydrogenation of several other trisubstituted unfunctionalized linear **S2–S4** and cyclic **S5** olefins, α,β-unsaturated ester **S6**, allylic alcohol **S7** and acetate **S8** (Fig. 3). The enantioselectivities are among the best observed for these substrates.[2] It should be noted that if ligands are appropriately tuned, high enantioselectivities can also be obtained for the more demanding *Z*-isomer **S4**, which usually reacts with a lower enantioselectivity than that of the corresponding *E*-isomer **S3**. These phosphite-oxazolines also provided higher enantioselectivities in a wider range of substrates at lower catalyst loadings than their related phosphinite-oxazoline counterparts **3**, one of the most successful ligand classes.[8]

To further study the potential of these readily available ligands, we also tested the Ir-**L1d** catalyst in the asymmetric

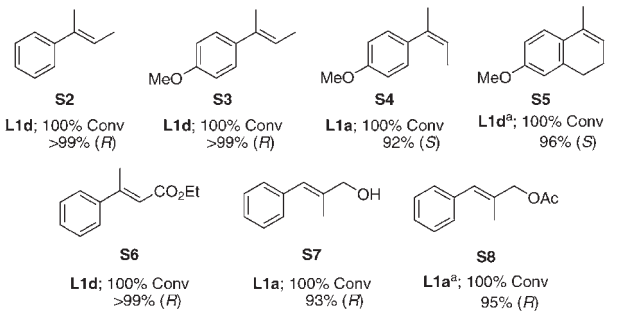



**Fig. 3** Selected hydrogenation results. *Reaction conditions*: 0.2 mol% catalyst, $CH_2Cl_2$ as solvent, 50 bar $H_2$, 2 h. [a]1 mol% catalyst.

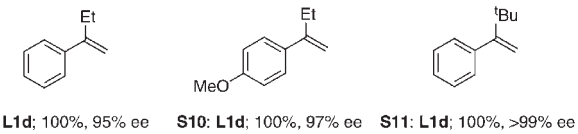



**Fig. 4** Selected hydrogenation results. *Reaction conditions*: 0.2 mol% catalyst, $CH_2Cl_2$ as solvent, 1 bar $H_2$, 30 min.

hydrogenation of terminal olefins **S9–S11** (Fig. 4). The enantioselectivity in this substrate class is more difficult to control than for the *E* trisubstituted olefins **S1–S3**. Therefore, few catalytic systems have provided high enantioselectivities.[9] Interestingly, we achieved high activities and enantioselectivities at low catalyst loadings (0.2 mol%) under mild reaction conditions (1 bar of $H_2$). Enantiomeric excesses for substrates **S9** and **S10** are among the best values reported to date.[9] Of particular note is the excellent enantioselectivity (>99% ee) obtained for the most sterically hindered substrate **S11**, which surpasses the best values obtained to date.[6b] Again, the replacement of a phosphinite moiety by a phosphite group in the ligand design leads to higher enantioselectivity (*i.e.* 97% ee *vs.* 94% ee[9a] for **S10**).

In summary, we have described the successful application of modular phosphite-oxazoline ligands in the Ir-catalyzed asymmetric hydrogenation of several unfunctionalized olefins. We have demonstrated that the introduction of a biaryl phosphite moiety into the ligand design is highly adventitious in terms of catalytic activity and substrate versatility. Therefore, they provided higher enantioselectivities and activities for a wider range of di- and tri-substituted substrates than their phosphinite-oxazoline counterparts. We have also found that the effectiveness at transferring the chiral information in the product can be tuned by suitably choosing the ligand components (phosphite, oxazoline and backbone substituents). This means that these catalyst systems are extremely attractive for further research. Because of the modular construction of these phosphite-oxazoline ligands, structural diversity is easy to achieve, so activities and enantioselectivities can be maximized for each new substrate as required. Studies of this kind, as well as mechanistic studies, are currently under way.

We thank the Spanish Government (CTQ2007-62288/BQU), the Catalan Government (2005SGR007777, 2006BE-210167 and Distinction to M.D.), COST D40, Vetenskapsrådet (VR)

and Astra Zeneca for support. We are grateful to Päivi Kaukoranta for assistance with chiral analyses.

## Notes and references


1 (*a*) I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley-VCH, New York, 2nd edn, 2000; (*b*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*c*) H.-U. Blaser and E. Schmidt, *Asymmetric Catalysis on Industrial Scale*, Wiley, New York, 2004; (*d*) J. M. Brown, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999, vol. 1.

2 For recent reviews, see: (*a*) K. Källström, I. Munslow and P. G. Andersson, *Chem.–Eur. J.*, 2006, **12**, 3194; (*b*) S. J. Roseblade and A. Pfaltz, *Acc. Chem. Res.*, 2007, **40**, 1402; (*c*) T. L. Church and P. G. Andersson, *Coord. Chem. Rev.* 2008, **252**, 513; (*d*) X. Cui and K. Burgess, *Chem. Rev.*, 2005, **105**, 3272.

3 See for instance: (*a*) W. Tang, W. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2003, **42**, 943; (*b*) D.-R. Hou, J. Reibenspies, T. J. Colacot and K. Burgess, *Chem.–Eur. J.*, 2001, **7**, 5391; (*c*) P. G. Cozzi, F. Menges and S. Kaiser, *Synlett*, 2003, 833; (*d*) A. Lighfoot, P. Schnider and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 3897; (*e*) F. Menges, M. Neuburger and A. Pfaltz, *Org. Lett.*, 2002, **4**, 4713; (*f*) D. Liu, W. Tang and X. Zhang, *Org. Lett.*, 2004, **6**, 513; (*g*) W. J. Drury III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2004, **43**, 70.

4 (*a*) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies and K. Burgess, *J. Am. Chem. Soc.*, 2003, **125**, 5391; (*b*) J. Blankestein and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2001, **40**, 4445; (*c*) S. Kaiser, S. P. Smidt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2006, **45**, 5194; (*d*) K. Källström, C. Hedberg, P. Brandt, P. Bayer and P. G. Andersson, *J. Am. Chem. Soc.*, 2004, **126**, 14308; (*e*) M. Engman, J. S. Diesen, A. Paptchikhine and P. G. Andersson, *J. Am. Chem. Soc.*, 2007, **129**, 4536; (*f*) A. Trifonova, J. S. Diesen and P. G. Andersson, *Chem.–Eur. J.*, 2006, **12**, 2318; (*g*) F. Menges and A. Pflatz, *Adv. Synth. Catal.*, 2002, **334**, 4044; (*h*) T. T. Co and T.-J. Kim, *Chem. Commun.*, 2006, 3537.

5 For some representative examples see: (*a*) C. Claver, M. Diéguez, O. Pàmies and S. Castillón, in *Catalytic Carbonylation Reactions*, ed. M. Beller, Springer-Verlag, Berlin, 2006, pp. 35–64; (*b*) M. Diéguez, O. Pàmies, A. Ruiz and C. Claver, in *Methodologies in Asymmetric Catalysis*, ed. S. V. Malhotra, ACS, Washington, 2004, pp. 161–174; (*c*) M. Yan, Z.-Y. Zhou and A. S. C. Chan, *Chem. Commun.*, 2000, 115; (*d*) O. Pàmies, M. Diéguez and C. Claver, *J. Am. Chem. Soc.*, 2005, **127**, 3646; (*e*) Y. Mata, O. Pàmies and M. Diéguez, *Chem.–Eur. J.*, 2007, **13**, 3296.

6 (*a*) R. Hilgraf and A. Pfaltz, *Adv. Synth. Catal.*, 2005, **347**, 61; (*b*) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel and P. G. Andersson, *J. Am. Chem. Soc.*, 2008, **130**, 7208.

7 Ligands **L1–L6a–e** have been successfully used in Pd-catalyzed allylic substitution, see: M. Diéguez and O. Pàmies, *Chem.–Eur. J.*, 2008, **14**, 3653.

8 The related phosphinite-oxazoline ligands **3** afforded >99% ee for **S3**, 92% ee for **S4**, 85% ee for **S5**, 94% ee for **S6** and 92% ee for **S7** at 1 mol% Ir-catalyst. See: (*a*) ref. 4*g*; (*b*) S. P. Smidt, F. Menges and A. Pflatz, *Org. Lett.*, 2004, **6** 2023. There are no data reported for substrates **S2** and **S8**.

9 For successful applications, see: (*a*) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt and A. Pfaltz, *Adv. Synth. Catal.* 2005, **347**, 282 (ee's up to 94% for **S10**); (*b*) ref. 4*d* (ee's up to 97% for **S10**); (*c*) ref. 6*b* (97% ee for **S11**).