J|A|C|S
COMMUNICATIONS

Published on Web 05/16/2008

Chiral Pyranoside Phosphite−Oxazolines: A New Class of Ligand for Asymmetric Catalytic Hydrogenation of Alkenes

Montserrat Diéguez,*,† Javier Mazuela,† Oscar Pàmies,† J. Johan Verendel,‡ and Pher G. Andersson*,‡

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Campus Sescelades, C/ Marcel·lí Domingo, s/n 43007 Tarragona, Spain, and Department of Biochemistry and Organic Chemistry, Uppsala University, BOX 576, 751 23 Uppsala, Sweden

Received March 7, 2008; E-mail: montserrat.dieguez@urv.cat; pher.andersson@kemi.uu.se

The enantioselective hydrogenation of olefins is one of the most powerful transformations in asymmetric catalysis for preparing optically active compounds. Although ruthenium- and rhodium-catalyzed asymmetric hydrogenation of chelating olefins has a long history, unfunctionalized olefins are still a challenge, because they lack an adjacent polar group.[1] Iridium complexes with chiral P,N ligands have become established as efficient catalysts for the hydrogenation of unfunctionalized olefins.[2] In this context, Pflatz and others have used phosphine−oxazoline ligands as chiral mimics of Crabtree's catalyst. They have been successfully used for the asymmetric hydrogenation of a limited range of alkenes.[3] Recently, the composition of the ligands has been extended by replacing the phosphine moiety with a phosphinite or a carbene group and the oxazoline moiety with other N-donor groups (such as pyridine, thiazole, and oxazole). The structure of the chiral ligand's backbone has also been modified.[4] These modifications have led to the discovery of three main ligand structures: phosphinite−oxazoline **1**,[4b,g] phosphinite−oxazole **2**,[4d] and phosphinite−pyridine **3**,[4c] which have considerably broadened the scope of Ir-catalyzed hydrogenation.

In the past few years, a group of less electron-rich phosphorus compounds, phosphite containing ligands, have demonstrated their huge potential utility in many transition-metal catalyzed reactions.[5] Their highly modular construction, facile synthesis from readily available chiral alcohols and greater resistance to oxidation than phosphines have proved to be highly advantageous. Despite the successful early use of phosphite ligands in the Rh-catalyzed hydrogenation of dehydroaminoacid derivatives,[6] only one report has been published on phosphite ligands, TADDOL-based phosphite−oxazoline ligands, in the Ir-catalyzed hydrogenation of alkenes.[7] However, their substrate range limitation was higher and enantioselectivities and activities lower than their related phosphinite/phosphine−oxazoline ligands. They also required higher catalyst loadings (4 mol %) and higher pressures (100 bar) to achieve full conversions. More research is therefore needed to study the possibilities of phosphite−oxazoline ligands in this process. In this Communication we present the application of a phosphite−oxazoline ligand library (**L1**−**L4a**–**g**, Figures 1,2)[8] in the asymmetric Ir-catalyzed hydrogenation of several unfunctionalized olefins. For comparative purposes, we also evaluated phosphinite−oxazoline analogue **L1h**. These ligands are derived from natural D-glucosamine so they also have the advantages of carbohydrates: that is to say, they are cheap and can be easily constructed in modules. With this library we therefore investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituents (**L1**−**L4**) and different substituents/configurations in the biaryl phosphite moiety (**a**−**g**). By carefully selecting these elements, we achieved high enantioselectivities and activities in a wide range of substrates.

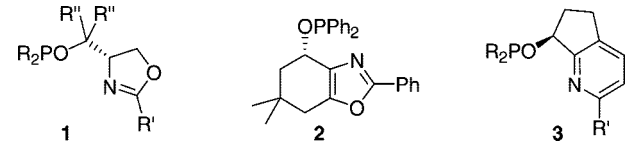


Figure 1. Privileged P,N ligands for Ir-catalyzed hydrogenation of alkenes.

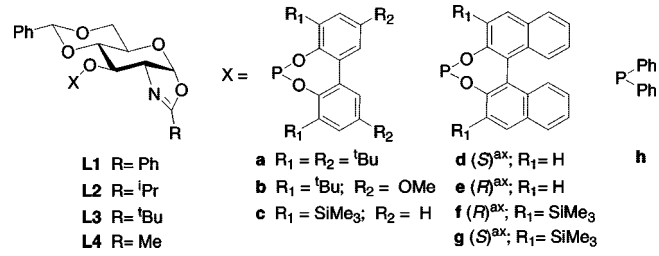
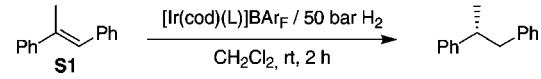


Figure 2. Phosphite−oxazoline ligands **L1**−**L4a**−**f** and phosphinite−oxazoline ligand **L1h**.

Table 1. Ir-Catalyzed Asymmetric Hydrogenation of **S1** Using Ligands **L1**−**L4a**−**h**[a]



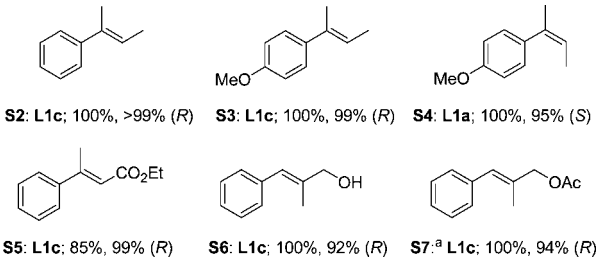
entry	L	mol % Ir	% conversion[b]	% ee[c]
1	**L1a**	2	100	99 (*R*)
2	**L1b**	2	100	98 (*R*)
3	**L1c**	2	100	>99 (*R*)
4	**L1d**	2	50	20 (*R*)
5	**L1e**	2	45	98 (*R*)
6	**L1f**	2	100	99 (*R*)
7	**L2a**	2	98	95 (*R*)
8	**L3a**	2	40	99 (*R*)
9	**L4a**	2	100	92 (*R*)
10	**L1c**	0.2	100	>99 (*R*)
11	**L1h**	2	100	95 (*R*)

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

In the first set of experiments, we used the Ir-catalyzed hydrogenation of *trans*-α-methylstilbene **S1** to scope the potential of ligands **L1**−**L4a**−**g**. The results are summarized in Table 1. The reaction proceeded smoothly at room temperature. The catalyst precursors [Ir(cod)(L)]BAr_F (L= **L1**-**L4a**–**h**) were prepared with a standard protocol[3d] and used without further purification. The results indicate that enantioselectivity is affected by the electronic and steric properties of the substituents at the oxazoline moiety and by the substituents/configuration in the biaryl phosphite moiety. However,

† Universitat Rovira i Virgili.
‡ Uppsala University.

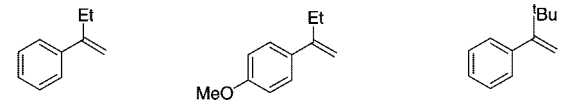
10.1021/ja801706s CCC: $40.75



S2: **L1c**; 100%, >99% (*R*) **S3**: **L1c**; 100%, 99% (*R*) **S4**: **L1a**; 100%, 95% (*S*)

S5: **L1c**; 85%, 99% (*R*) **S6**: **L1c**; 100%, 92% (*R*) **S7**:[a] **L1c**; 100%, 94% (*R*)

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



S8: **L1c**; 100%, 99% (*S*) **S9**: **L1c**; 100%, >99% (*S*) **S10**: **L1c**; 100%, 97% (*S*)

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

activity is mainly affected by the steric properties of the oxazoline substitutent and by the substituents at the ortho positions of the biaryl phosphite moiety. The presence of bulky substitutents in the biaryl phosphite and less-sterically demanding substituents in the oxazoline is necessary if activities are to be high. The best result (100% conversion; >99% ee) was therefore obtained with ligand **L1c** (entry 3), which contains the optimal combination of the substituent in the oxazoline and in the biaryl phosphite moieties.

We also performed the reaction at low catalyst loading (0.2 mol %) using ligand **L1c** (entry 10). The excellent enantioselectivity (>99% (*R*) ee) and activity (100% conversion after 2 h at room temperature) were maintained.

Interestingly, these phosphite−oxazoline ligands showed higher enantioselectivities than its corresponding phosphinite−oxazoline analogue **L1h** (entry 3 vs 11) .

To study the potential of these readily available ligands further, we also tested them in the asymmetric hydrogenation of several trisubstituted unfunctionalized olefins **S2**−**S4** (Figure 3). The enantioselectivities are among the best observed for these substrates.[2,9] It should be noted that if ligands are appropriately tuned, high enantioselecitvities 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**. Ir-**L1c** also proved to be an excellent catalyst for the hydrogenation of α,β-unsaturated ester **S5**, allylic alcohol **S6**, and acetate **S7** (Figure 3).

Encouraged by the excellent results, we also tested the Ir-**L1c** catalyst in the asymmetric hydrogenation of more demanding substrates: the terminal olefins **S8**−**S10** (Figure 4). For these substrates, the development of highly enantioselective Ir-catalysts is still a challenge. Therefore few catalytic systems have provided high enantioselectivities.[10] The enantiomeric excesses obtained for this substrate class surpass the best values reported to date. Note also the high activities obtained at low catalyst loadings (0.2 mol %) under mild reaction conditions (1 bar of H_2). Interestingly, Ir-**L1c** is also capable of hydrogenating substrate **S10**, which contains an sterically hindered ^{t}Bu group, in high activities and enantioselectivities.

In summary, we have described the first successful application of phosphite containing ligands in the Ir-catalyzed asymmetric hydrogenation of several unfunctionalized olefins. The advantage of these phosphite−oxazoline ligands is that they are easily prepared in a few steps from commercial D-glucosamine, an inexpensive natural chiral feedstock. In addition, they can be easily tuned in the oxazoline and biaryl phosphite moieties so that their effect on catalytic performance can be explored. By carefully selecting the ligand components, we obtained high activities and enantioselectivities under unoptimized reaction conditions. Of particular note are the excellent activities and enantioslectivities at low catalyst loadings obtained with simple disubstitued olefins. So, this is an exceptional ligand family that competes favorably with a few other ligand series that also provide high ee values for tri- and disubstituted substrate types. The introduction of a bulky biaryl phosphite moiety in the ligand design is highly advantageous in the product outcome. Therefore, these ligands provides higher enantioselectivities than its phosphinite−oxazoline analogue. These results provide a new class of ligands for the highly active and enantioselective Ir-catalyzed hydrogenation of a wide range of substrates. Mechanistic studies are currently under way and further applications are being looked into.

Acknowledgment. We thank the Spanish (CTQ2007−62288/BQU) and Catalan (2006BE-210167 and Distinction to M.D.) Government, COST D40, Vetenskapsrådet (VR), and Astra Zeneca for support. We are grateful to Päivi Kaukoranta for assistance with chiral analyses.

Supporting Information Available: Experimental procedures and characterization of new ligands **L1f** and **L1g** and [Ir(cod)(L)]BAr_F (*L*= **L1**−**L4a**−**h**) complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

References

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

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

(3) See for instance: (a) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943. (b) Hou, D.-R.; Reibenspies, J.; Colacot, T. J.; Burgess, K. *Chem.*−*Eur. J.* **2001**, *7*, 5391. (c) Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833. (d) Lighfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3897. (e) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (f) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513. (g) Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70. (h) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659.

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

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

(6) See for instance: (a) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179. (b) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702.

(7) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.

(8) Ligands **L1**−**L4a**−**e** have been successfully used in Pd-catalyzed allylic substitution and Heck reactions, see: (a)(a) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943. (b) Reference 5e.

(9) The best enantioselectivities obtained so far are: >99% ee for **S3** (ref 4c), 98% ee for **S4**(ref 4c), 99% ee for **S5** (ref 3g), 98% ee for **S6** (ref 4d) and 99% ee for **S7** (ref 4d) at 1 mol % Ir-catalyst.

(10) For successful applications, see: (a) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282. (ee values up to 94% for **S9**). (b) Reference 4d (ee values up to 97% for **S9**).

JA801706S