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COMMUNICATIONS

Published on Web 10/13/2004

Rationally Designed Ligands for Asymmetric Iridium-Catalyzed Hydrogenation of Olefins

Klas Källström,[†] Christian Hedberg,[†] Peter Brandt,[‡] Annette Bayer,[§] and Pher G. Andersson*[,†]

Organic Chemistry, Department of Chemistry, Uppsala University, Box 599, 751 24, Uppsala, Sweden, Department of Structural Chemistry, Biovitrum AB, 112 76 Stockholm, Sweden, and Department of Chemistry, Faculty of Science, University of Tromsø, 9037, Tromsø, Norway

Received June 17, 2004; E-mail: pher.andersson@kemi.uu.se

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis. While ruthenium- and rhodium-catalyzed asymmetric hydrogenations of chelating olefins have a long history,[1] unfunctionalized olefins still represent a challenging class of substrates. During the past few years, Pfaltz and others[2a−h] have developed chiral mimics of Crabtree's catalyst,[3] which have been used successfully for asymmetric hydrogenation of arylalkenes. However, iridium-catalyzed asymmetric hydrogenation is still highly substrate dependent, and the development of new efficient chiral ligands that tolerate a broader range of substrates remains a challenge.

In this Communication, we report a new class of phosphinite−oxazole iridium complexes **1a**−**c**, which are highly enantioselective for a wide range of substrates. Moreover, one single complex, **1b**, was able to reduce a large variety of substrates and gave results in the range of the best ever reported.[4]

Since very little was known about the mechanism and the enantioselectivity-determining factors of asymmetric iridium-catalyzed hydrogenations, our group recently undertook a kinetic and computational study of the hydrogenation of (*E*)-1,2-diphenyl-1-propene **6** with the Pfaltz iridium-PHOX complex.[5] Our findings encouraged us to design a new class of N,P-ligands with the following specifications: the ligand should (i) contain a nitrogen atom and a phosphorus atom to get a significant trans effect and reaction site discrimination, (ii) be able to form a six-membered chelate ring upon complex formation, (iii) contain a rigid backbone fused to the aromatic heterocycle to reduce conformational flexibility, and (iv) form a chiral environment to the substrate, as depicted in Figure 1.

With these criteria in mind, we envisioned the ligand structure in Figure 2. Retrosynthetic analysis of the structure in Figure 2 resulted in a four-step synthesis from readily available starting materials (Scheme 1).

Following this synthetic scheme, we prepared complexes **1a**−**c** with different aromatic groups on the phosphorus atom. Rhodium-catalyzed conversion of diazodimedone[6] **2** in the presence of benzonitrile gave the keto oxazole[7] **3** in 52% yield. Catalytic enantioselective reduction of keto oxazole **3** with (*R*)-Me-CBS-borane provided the (*S*)-alcohol[8] **4** in 91% yield and 90% ee. One single recrystallization with 85% recovery of the alcohol increased the ee to >99%. The phosphinites were prepared according to a published procedure,[2b] and **5a**−**c** were obtained in good yields (60−80%). Due to the lability of **5a**−**c**, these compounds were filtered through a short plug of silica and subjected to complex formation[2a] without further purification. The resulting iridium complexes **1a**−**c**

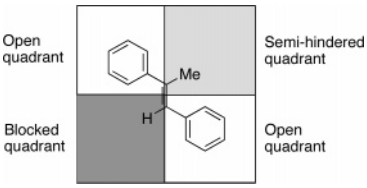


Figure 1. Selectivity model applied in ligand design.

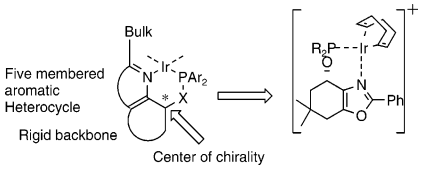
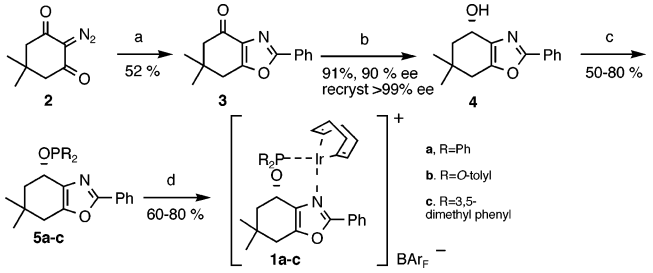


Figure 2. General ligand structure.

Scheme 1. Synthesis of Complex **1a**−**c**[a]



[a] Conditions and reagents: (a) benzonitrile, $Rh_2(OAc)_4$ (0.17 mol %), 60 °C, 2 h. (b) BH_3·Me_2S, (*R*)-Me-CBS-oxazaborolidine (10 mol %), THF, 2 h, room temperature. (c) TMEDA, BuLi, THF, −78 °C to room temperature, 1 h, then R_2PCl, room temperature, 16 h. (d) $[IrCl(COD)]_2$, CH_2Cl_2, reflux, 30 min, then $NaBAr_F$, H_2O, room temperature, 30 min; BAr_F = (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).

are stable, crystalline compounds and can be stored for months without detectable decomposition.

Hydrogenation of **6** using 0.5 mol % of **1a** under standard conditions[2a] at different pressures showed 30 bar to be optimal for this substrate. At 1 bar, no conversion could be detected after 2 h. For substrate **13** the ee increased slightly, from 91% ee to 93% ee, on going from 30 to 50 bar. The standard pressure was therefore set to 50 bar.

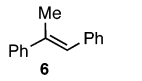
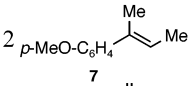
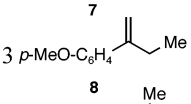
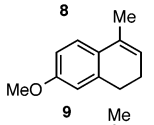
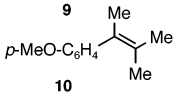
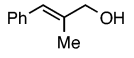
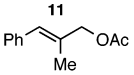
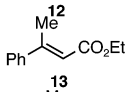
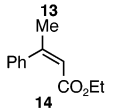
These new complexes also proved to be highly efficient in the hydrogenation of other substrates (Table 1, entries 2−9), with complex **1b** as the overall best. As expected, 2-*p*-methoxyphenyl-3-methylbut-2-en **10** (entry 5) showed poor enantioselectivity.

The success of these catalysts for enantioselective reduction of substituted styrenes could be rationalized in terms of the selectivity model in Figure 1. To get a firmer hold of the catalyst−ligand interactions in the selectivity-determing transition state, we optimized the coupled migratory insertion/oxidative addition for

[†] Uppsala University.
[‡] Biovitrum AB.
[§] UiT.

10.1021/ja0464241 CCC: $27.50

Table 1. Iridium-Catalyzed Hydrogenation of Substrates **3**−**10**[a]

entry	substrate	1a conv.	1a *ee*	1b conv.	1b *ee*	1c conv.	1c *ee*	abs. config.
1	 **6**	**>99**	**>99**	**>99**	**>99**	**>99**	**>99**	*S*
2	 **7**	>99	90	**>99**	**96**	93	97	*S*
3	 **8**	>99	95	**>99**	**97**	>99	97	*S*
4	 **9**	>99	92	**>99**	**94**	>99	90	*R*
5	 **10**	37	15	46	rac.	47	rac.	*S*
6		96	92	**95**	**98**	40	97	*S*
7	 **11**	>99	99	**>99**	**>99**	>99	99	*S*
8	 **12**	>99	66	**>99**	**93**	>99	72	*S*
9	 **13** **14**	50	rac.	50	33	48	38	*R*

[a] Conditions: pressure, 30 bar (entry 1), 50 bar (entries 2−4, 6−9), 100 bar (entry 5); all reactions were run at room temperature for 2 h, except for entries 5 and 6, where the reaction was run overnight instead; catalyst loading, 0.5 mol %, except for entries 5 and 6, where 1 mol % was used instead; all reactions were run in CH_2Cl_2 as 0.25 M solutions.

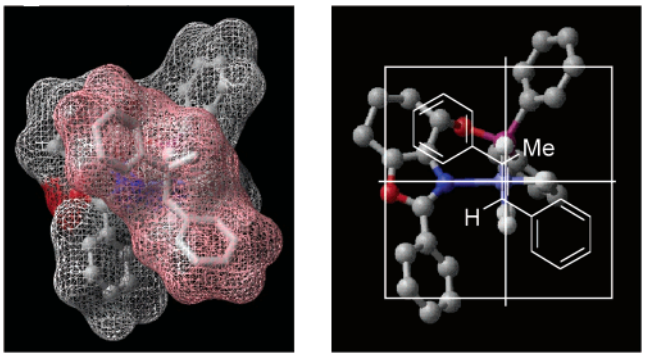


Figure 3. (Left) Structure of the selectivity-determining transition state of the coupled migration insertion/oxidative addition of dihydrogen. (Right) Selectivity model using the ligand structure of the optimized transition state and a schematic substrate molecule.

substrate **6** being hydrogenated by catalyst **1a** (Figure 3).[9] The calculated structure, being very similar to those previously reported,[5] clearly shows a chiral pocket well suited to accommodate an alkene with large trans substituents. The enantiofacial selectivity is primarily based on discrimination between a larger and a smaller geminal substituent. Thus, due to the pseudo-C_2 symmetry of the reactive site, only one large substituent is required on the alkene, but two large substituents in trans configuration will perform better. The nonsubstituted position on the alkene will preferentially be oriented toward the bulky phenyl substituent of the oxazole part in the catalyst. Thus, tetra-substituted alkenes are poor substrates for this catalyst, i.e., alkene **10**. For alkenes with the most bulky substituents cis, such as **9**, the selectivity could be compromised. α,β-Unsaturated esters add a complicating electronic effect to the selectivity. B3LYP/LACVP calculations on *trans*-methyl crotonate suggest a strong preference for β-addition of the hydride (5 kcal/mol). This results in low converversion and poor enantioselectivity in the reduction of methyl α-methyl cinnamate.

In conclusion, we have used a computationally derived selectivity model to design new catalysts for hydrogenation of disubstituted styrenes. This new class of catalysts is highly selective and applicable to a wide range of substrates. The enantioselectivities reported here are in the range of the best previously reported.

Acknowledgment. This work was supported by grants from the Swedish Research Council (VR) and SELCHEM graduate program. A.B. thanks the Norwegian Research Council (grant 151722/V30) and NorFA for financial support. We are also very grateful to Professor Lars Kristian Hansen (University of Tromsø) for performing the X-ray analysis.

Supporting Information Available: Experimental procedures for the preparations of the ligands, complexes, hydrogenation procedures, characterization data, and chiral separation data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Brown J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp 121−182.
(2) (a) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew.* Chem., Int. Ed. **1998**, *37*, 2897−2899. (b) Blankenstein, J.; Pfaltz, A. *Angew.* Chem., Int. Ed. **2001**, *40*, 4445−4447. (c) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett*. **2002**, *4*, 4713−4716. (d) Durry, W. J., III; Zimmerman, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew.* Chem., Int. Ed. **2004**, *43*, 70−74. (e) Perry, M. C.; Cui, X.; Powell, M.; Hou, D.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc*. **2003**, *125*, 113−123. (f) Tang, W.; Wang, W.; Zhang, X. *Angew.* Chem., Int. Ed. **2003**, *42*, 943−946. (g) Xu, G.; Gilbertson, S. R. *Tetrahedron Lett*. **2003**, 953−955. (h) Bunlaksananurson, T.; Polborn, K.; Knochel, P. *Angew.* Chem., Int. Ed. **2003**, *42*, 3941−3943.
(3) Crabtree, R. H. *Acc. Chem. Res*. **1979**, *12*, 331−338.
(4) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal*. **2003**, *345* (Nos. 1+2), 33−43.
(5) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. Eur. J*. **2003**, 339−347.
(6) Parakash, I.; Parakash, O.; Bailey, B. R., III; Moriarty, R. M. *J. Am. Chem. Soc*. **1985**, *107*, 1345−1378.
(7) Rok, L.; Yup, Y. S. J. *Heterocycles* **1998**, *48*, 875−884.
(8) Absolute configuration of alcohol **4** was determined by X-ray analysis of the corresponding (*S*-1-phenylethyl)carbamic acid 6,6-dimethyl-2-phenyl-4,5,6,7-tetrahydrobenzooxazol-4-yl ester (**15**). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 237031. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, UK (fax +44-(0)1223−336033 or e-mail deposit@ccdc.cam.ac.uk).
(9) Transition-state optimization was performed at the B3LYP/LACVP level of theory in the Jaguar program. For details, see ref 5.

JA0464241