Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

© Wiley-VCH 2007

69451 Weinheim, Germany

High Enantioselectivity induced by a Single Monodentate Phosphoramidite Ligand in Iridium-Catalyzed Asymmetric Hydrogenation

Francesca Giacomina, Auke Meetsma, Lavinia Panella, Laurent Lefort,* André H. M. de Vries, and Johannes G. de Vries*

DSM Pharmaceutical Products-Advanced Synthesis, Catalysis and Development, P.O. Box 18, 6160 MD Geleen, The Netherlands

General Procedure.

All reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques or in the glove box.

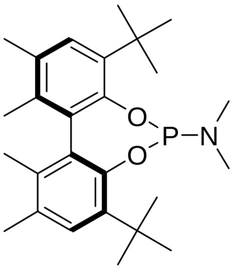
Anhydrous solvents over molecular sieve purchased from Fluka were systematically used. $[Ir(COD)Cl]_2$ and Biphen were used as provided by Strem. The Binol-based phosphoramidites were prepared according to a published procedure.[1] The hydrogenation substrates, methyl 2-acetamido-cinnamate **(1)**, and the *p*-methoxy and *p*-Cl derivatives[2], methyl 2-formamido-acrylate and 2-formamido-4-methyl-pent-2-enoic acid methyl ester[3] were synthesized following published procedures. 2-acetamido-cinnamic acid and methyl 2-acetamido-acrylate were purchased from Aldrich and used as such.

The hydrogenation reaction is carried out in the Endeavor^{TM}[4]. The Endeavor is an autoclave with eight reactors equipped with glass reaction vessels.

31P NMR spectra were recorded at room temperature in dry undeuterated toluene on a Bruker Avance 300 (300MHz).

Conversion and enantiomeric excesses were determined by capillary GC analysis with a CP-Chirasil-L-Val (25m, 0.25mm, 0.12μm, 175°C) for reaction with substrate.

Synthesis of L4, (S)-(3,3’-Di-*tert*-butyl-5,5’, 6,6’-tetramethyl-1,1’-biphenyl-2,2’-diyl)-N,N-dimethylphosphoramidite



To a solution of (S)-3,3’-di-*tert*-butyl-5,5’, 6,6’-tetramethyl-1,1’-biphenyl-2,2’-diol (500 mg, 1.4 mmol) in toluene (8 ml), a catalytic amount of NH_4Cl (10 mg) and hexamethylphosphorus triamide (0.38 ml, 2.1 mmol) were added. The resulting mixture was stirred at 100°C for 16h. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated *in vacuo* to afford a crude solid. The solid was purified by column chromatography on silica gel (pretreated with a solution of toluene:Et_3N=95:5) to give the product as white solid (237 mg, 40% yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 1.44 (s, 9H), 1.77 (s, 3H), 1.88 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.30-2.53 (br, 6H), 7.08 (s, 1H), 7.13 (s, 1H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 141.1.

NMR data of 2-Formamido-4-methyl-pent-2-enoic acid methyl ester

The synthesis has been performed exactly as described in the litterature.[3]
The crude mixture was purified by flash chromatography on silica gel (heptanes-ethyl acetate 1:1). Both isomers are oils, Z/E 2.2:1, 1.38 g, 8.0 mmol, 73% yield.

E isomer: Rf (E)= 0.33; trans:cis = 3:1. 1H-NMR (300 MHz, CDCl3) d 8.31 (s, 1H, trans), 8.23 (d, J= 11.1 MHz, 1H, cis), 7.41 (bs, 1H), 7.13 (d, J= 9.9 MHz, 1H, trans), 5.85 (d, J= 9.9 MHz, 1H, cis), 3.86 (s, 3H, trans), 3.84 (s, 3H, cis), 3.52-3.25 (m, 1H), 1.09 (s, 3H), 1.07 (s, 3H). 13C-NMR (300 MHz, CDCl3) d 164.5 (s), 162.2 (d, cis), 159.1 (d, trans), 141.0 (s, trans), 140.7 (s, cis), 122.2 (d), 52.5 (q, trans), 52.4 (q, cis), 27.7 (d, trans), 27.3 (d, cis), 23.0 (q, 2C, trans), 22.8 (q, 2C, cis).

Z isomer: Rf (Z)= 0.31; trans:cis = 1.3:1. 1H-NMR (300 MHz, CDCl3) d 8.27 (s, 1H, trans), 8.17 (d, J= 11.5 MHz, 1H, cis), 7.06-6.75 (bs, 1H), 6.59 (d, J= 10.3 MHz, 1H, trans), 6.49 (d, J= 10.7 MHz, 1H, cis), 3.81 (s, 3H, cis), 3.79 (s, 3H, trans), 2.83-2.53 (m, 1H), 1.10 (d, J= 6.5 MHz, 3H), 1.08 (d, J= 6.5 MHz, 3H). 13C-NMR (300 MHz, CDCl3) d 165.0 (s), 163.8 (d, cis), 159.3 (d, trans), 146.2 (s, trans), 142.1 (s, cis), 123.2 (d, cis), 121.2 (d, trans), 52.7 (q, cis), 52.5 (q, trans), 28.4 (d, trans), 27.3 (d, cis), 22.3 (q, 2C, cis), 21.5 (q, 2C, trans).

General procedure for the preparation of the cationic Iridium complexes: $[Ir(COD)LL’]^+X^-$

$[Ir(COD)Cl]_2$ was placed in a 10 ml Schlenk flask. The entire apparatus was evacuated and back filled with N_2 three times to establish an inert atmosphere. DCM and L (1eq/Ir) were added and the reaction mixture stirred at r.t. for 10 min. The reaction mixture was then reduced to dryness under vacuum giving an orange solid. The solid was then dissolved in DCM or MeOH and L’(1eq/Ir) was added. After stirring the reaction mixture for 30 min, MX (1eq/Ir) was added. The obtained complex was then tested in hydrogenation without further purification.

Example: Preparation of **[Ir(COD)Monophos(Pyridine)]** $[Ir(COD)Cl]_2$ (12.3 mg, 0.018 mmol) was placed in a 10 ml Schlenk flask. The entire apparatus was evacuated and back filled with N_2 three times to establish an inert atmosphere. DCM (2 ml) and (*S*)-Monophos (12.9 mg, 0.036 mmol) were added and the reaction mixture stirred at r.t. for 10 min. The reaction mixture was then reduced to dryness under vacuum giving an orange solid. The obtained solid was dissolved in MeOH (1 ml) and pyridine (Py) (0.036 mmol) was added. After stirring the reaction mixture for 30 min, KPF_6 (0.036 mmol) was added and the reaction stirred for 20 min then the substrate was added for the catalytic test.

General procedure for the preparation of the neutral Iridium complexes: [Ir(COD)(L)Cl]

$[Ir(COD)Cl]_2$ was placed in a 10 ml Schlenk flask. The entire apparatus was evacuated and back filled with N_2 three times to establish an inert atmosphere. DCM and L (1eq/Ir) were added and the reaction mixture stirred at r.t. for 10 min. The reaction mixture was then reduced to dryness under vacuum to give the desired compound as an orange solid.

Preparation of **[Ir(COD)(L_4)Cl]**: [Ir(COD)Cl]2 (65mg, 0.096mmol) was placed in a 10 ml Schlenk flask. The entire apparatus was evacuated and back filled with N2 three times to establish an inert atmosphere. Dry degassed DCM (1mL) and (S)-L4 (82mg, 0.192mmol) were added and the reaction mixture was stirred at r.t. for 10 min. X-ray quality crystal were obtained upon layering and slow diffusion with n-heptane. 1H NMR (300 MHz) δ: 7.22 (s, 1H), 7.09 (s, 1H), 5.40-5.29 (m, 1H), 5.13-5.24 (m, 1H), 3.57-3.47 (m, 1H), 2.83-2.74 (m, 1H), 2.61 (b, 3H), 2.58 (b, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H), 1.65 (s, 9H), 1.37 (s, 9H). 31P NMR (121.5 MHz, CDCl3) δ: 107.8. Elem. Anal.: calcd: C 53.49, H 6.60, N 1.83; found: C 53.4, H 6.8, N 1.8.

Hydrogenation Experiments

Hydrogenation experiments were both performed in Schlenk tube (at atmospheric pressure) and in the Endeavor reactor (at 5 Bar H_2)

Procedure in a Schlenk tube:

In a Schlenk tube equipped with a septum the Ir complex was dissolved in 3 ml of solvent (DCE or DCM) and 50 eq of the hydrogenation substrate were added. The inert atmosphere was replaced by 1 bar of hydrogen, causing an immediate colour change of the solution to pale yellow. The reaction was stirred overnight at room temperature and samples were taken and analyzed by GC.

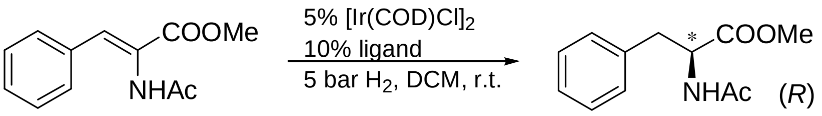
Procedure in the Endeavor:

The Endeavor is an autoclave with eight reactors equipped with glass reaction vessels, with independent P and T. 0.5 mmol of substrate, 0.01 mmol of [Ir(COD)Cl]2 and 0.02 mmol of ligand were weighed in these reaction vessels. The vessels were placed in the reactors and 5 ml of DCM were added. The reactors were purged for 30 minutes with N_2 before applying a hydrogen atmosphere of 5 bar. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken which were subjected to e.e. determination by GC.

Results

a) For methyl (*Z*)-2-acetamido-cinnamate, with the different phosphoramidite ligands:

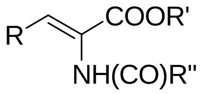
Reaction conditions: $[Ir(COD)Cl]_2$=0.01 mmol/vessel, L=0.02 mmol/vessel, S/C=50, DCM, 5 bar, 25°C



Entry	**Ligand**	**Conv. (%)**	**E.e. (%)**	**Time (min)**
1	(S)-Monophos	24	28	720
2	(R)-3,3’-diBrMonophos	100	87	90
3	(R)-3,3’-diMeMonophos	100	67	180
4	(S)-3,3’-diPhMonophos	100	93	45
5	(S)-BiphenMonophos	100	99	15

b) Substrate scope:

Reaction conditions: $[Ir(COD)Cl]_2$=0.01 mmol/vessel, $\mathbf{L_4}$=0.02 mmol/vessel, S/C=50, DCM, 5 bar, 25°C

	Substrate = 			Conv. (%)	ee (%)
	R	R’	R”		
1	Ph	Me	Me	100	98.8
2	(p)MeO-Ph	Me	Me	100	98.2
3	(p)Cl-Ph	Me	Me	100	97.8
4	Ph	H	Me	50	97.6
5	H	Me	Me	100	50
6	H	Me	H	89	39.4
7	iPr	Me	H	89	88.4

General procedure to prepare the NMR sample

In a Schlenk tube, $[Ir(COD)Cl]_2$ was placed. After evacuating and back filling with N2 three times, the ligand was added and CDCl3. The Schlenk tube as brought into a glovebox and, after stirring the solution for 20 min, the solution was transferred in a NMR tube.

	L	**eq/Ir**	**^{31}P NMR**
1	(S)-Monophos	1	s 117.6 ppm
2	(S)-Monophos	2	s 117.6 ppm d 94.5 ppm J=38.6Hz d 88.6 ppm J=38.6Hz
3	(R)-3,3’-diPhMonophos	1	s 116.8 ppm
4	(R)-3,3’-diPhMonophos	2	s 148.8 ppm s 116.8 ppm
5	(S)-BiphenMonophos	1	s 107.8 ppm
6	(S)-BiphenMonophos	2	s 141.1 ppm s 107.8 ppm

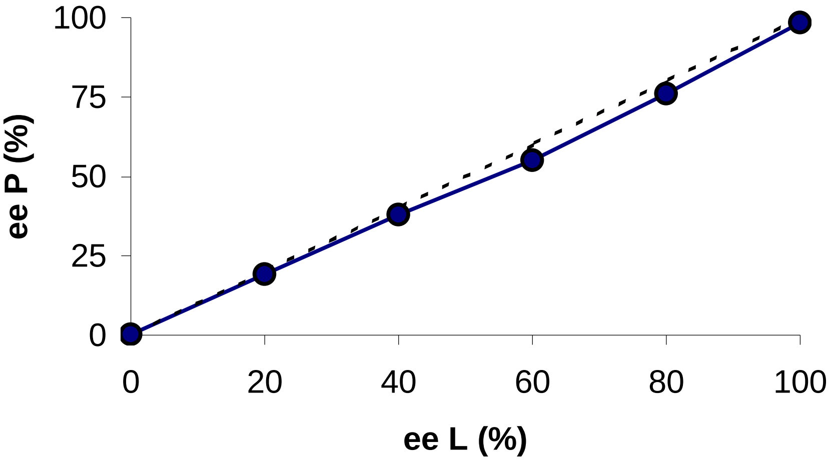
Non Linear Effect (NLE) experiment

The hydrogenation experiments for the NLE study were performed in the Endeavor with dehydrophenylalanine methyl ester as a substrate. The enantiomeric purity of the ligand $\mathbf{L_4}$, was varied from 100% to 0%, in two different ways:

1) by using both hands of the ligand in different ratio.
2) by using the racemate and adding different amounts of the S-enantiomer.

Reaction conditions: $[Ir(COD)Cl]_2$=0.01 mmol/vessel, $\mathbf{L_4}$=0.02 mmol/vessel ((*S*)/(*R*) ratio varies from 100 to 0), S/C=50, THF, 5 bar, 25°C, 2h.

The following curve represents the ee of the product vs the ee of the ligand. The deviation from the theoretical curve is within the error of measurement.



---

[1] de Vries, A.H.M.; Pineschi, M.; Arnold, L.A.; Imbos, R.; Feringa, B.L. *Angew. Chem Int. Ed*. **1997**, 36, 2620.

[2] For **1**, see Laneman, S.A.; Froen, D.E.; Ager, D.J. *Chem. Ind.* **1998**, *75 (Catalysis of Organic Reactions, F.E. Herkes, Ed., Marcel Dekker, Inc.)*, 525. For **2**, see Ovenden, S.B.P.; Capon, R.J.; Lacey, E.; Gill, J.H.; Friedel, T.; Wadsworth, D. *J. Org. Chem.* **1999**, *64*, 1140.

---

[3] Panella, L.; Marco Aleixandre, A.; Kruidhof, G.J.; Robertus, J.; Feringa, B.L.; de Vries, J.G.; Minnaard, A.J. *J. Org. Chem.* **2006**, *71*, 2026.

[4] van den Berg, M.; Minnaard, A. J.; Haak, R.M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, E.P.; Willans, C.E.; Hyett, D.; Boogers, J.A.F.; Henderickx H.J.W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308.