Advanced Synthesis & Catalysis

Supporting Information

Asymmetric Synthesis of the Roche Ester and its Derivatives by Rhodium-INDOLPHOS Catalyzed Hydrogenation

Jeroen Wassenaar,[a] Mark Kuil,[b] and Joost N. H. Reek[a,]*

[a] *Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands.*
E-mail: reek@science.uva.nl; Fax: +31 20 5256422; Tel: +31 20 5256437
[b] *BASF Nederland B.V. Catalysts, Strijkviertel 67, 3454 PK De Meern, The Netherlands*

Supplementary Material

I General Remarks

All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. With exception of the compounds given below, all reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: phosphorochloridite of (*S*)-(-)-2,2'-bisnaphthol,[1] methyl 2-hydroxymethylacrylate (**2a**),[2] benzyl 2-hydroxymethyl-acrylate (**2b**),[3] and methyl (2*E*)-3-phenyl-2-hydroxymethylacrylate (**2d**).[4] THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl; CH_2Cl_2, isopropanol and methanol were distilled from CaH_2, and toluene was distilled from sodium under nitrogen. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra (^1H, ^{31}P and ^{13}C) were measured on a Varian INOVA 500 MHz or a Varian MERCURY 300 MHz. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer; for FAB-MS 3-nitrobenzyl alcohol was used as matrix. Chiral GC separations were conducted on an Interscience Trace GC Ultra (FID detector) with a Chiralsil DEX-CB column (internal diameter 0.1 mm, 5 m column, film thickness 0.1 μm) and an Interscience HR GC Mega 2 apparatus (split/splitless injector, carrier gas 70 kPa He, FID detector) with a Supelco BETA DEX column (0.25 mm x 30 m). Chiral HPLC separations were conducted on a Shimadzu 10A HPLC, equipped with a UV-detector.

II Spectroscopic and analytical data of ligands

Ligands **4a-f** and indolylphosphines **3a-d** are prepared according to the general procedure given in the experimental section. Spectroscopic and analytical data for **3a-b**, **4a-b**, and **4e-f** are available in the literature.[5] Analytical data for **3c-d** and **4c-d** are given below.

Dicyclohexyl(3-methyl-2-indolyl)phosphine (3c). Yield: 2.84 g (64 %). Mp = 118 °C. ^1H NMR ($CDCl_3$, 499.8 MHz, 298 K): δ (ppm) 7.89 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 2.45 (s, 3H), 1.99-1.89 (m, 4H), 1.81-1.78 (m, 2H), 1.70-1.62 (m, 6H), 1.38-1.08 (m, 10H). ^{13}C NMR ($CDCl_3$, 125.7 MHz, 298 K): δ (ppm) 137.94 (C_q), 129.17 (C_q, J_{CP} = 5.9 Hz), 127.81 (C_q, J_{CP} = 27.9 Hz), 123.51 (C_q, J_{CP} = 24.9 Hz), 122.88 (CH), 119.25 (CH), 119.18 (CH), 110.76 (CH), 33.44 (CH, J_{CP} = 9.3 Hz), 30.85 (CH_2, J_{CP} = 17.7 Hz), 29.93 (CH_2, J_{CP} = 6.3 Hz), 27.36 (CH_2, J_{CP} = 16.5 Hz), 27.28 (CH_2, J_{CP} = 10.6 Hz), 26.54 (CH_2), 10.39 (CH_3, J_{CP} = 12.7 Hz). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 202.3 MHz, 298 K): δ (ppm) −26.95 (s). HRMS (FAB) calcd for $[M + H]^+$ $C_{21}H_{31}NP$, 328.2194; found, 328.2193.

Di-(*o*-Tolyl)-(3-methyl-2-indolyl)phosphine (3d). Yield: 3.88 g (83 %). Mp = 194 °C. ^1H NMR ($CDCl_3$, 499.8 MHz, 298 K): δ (ppm) 7.64 (d, J = 7.5 Hz, 1H), 7.36 (br s, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.26-7.18 (m, 4H), 7.15-7.10 (m, 3H), 6.86 (m, 2H), 2.48 (s, 3H), 2.38 (s, 6H). ^{13}C NMR ($CDCl_3$, 125.7 MHz, 298 K): δ (ppm) 142.35 (C_q, J_{CP} = 25.8 Hz), 138.40 (C_q), 134.30 (C_q, J_{CP} = 9.3 Hz), 132.49 (CH), 130.65 (CH, J_{CP} = 4.7 Hz), 129.53 (C_q, J_{CP} = 6.4 Hz), 129.17 (CH), 126.58 (CH), 125.90 (C_q, J_{CP} =

17.2 Hz), 123.06 (CH), 122.45 (C$_q$, J_{CP} = 28.3 Hz), 119.45 (CH), 119.37 (CH), 111.14 (CH), 21.24 (CH$_3$, J_{CP} = 20.6 Hz), 9.94 (CH$_3$, J_{CP} = 11.3 Hz). ^{31}P{^{1}H} NMR (CDCl$_3$, 202.3 MHz, 298 K): δ (ppm) −46.53 (s). HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{23}NP$, 344.1568; found, 344.1571.

Dicyclohexyl{1-[(*S*)-3,5-dioxa-4-phospha-cyclohepta(2,1-*a*;3,4-*a*')dinaphtalen-4-yl]-3-methyl-2-indolyl}phosphine (4c). Yield: 553 mg (59 %). Mp = 255 °C. $[\alpha]_D^{27}$ = +286.6 (c = 1.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz, 298 K): δ (ppm) 8.06 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.85 (br d, J = 7.5 Hz, 1H), 7.59 (br d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.51-7.46 (m, 4H), 7.39 (d, J = 8.0 Hz, 1H), 7.36-7.32 (m, 2H), 6.87 (t, J = 7.5 Hz, 1H), 6.83 (br s, 1H), 6.42 (br s, 1H), 6.20 (t, J = 8.0 Hz, 1H), 2.61 (br s, 2H), 2.48 (s, 3H), 2.00 (m, 2H), 1.86-1.55 (m, 8H), 1.43-1.20 (m, 10H). ^{13}C NMR (CDCl$_3$, 125.5 MHz, 298 K): δ (ppm) 150.68 (C$_q$), 148.90 (C$_q$), 140.29 (C$_q$), 133.09 (C$_q$, J_{CP} = 33.8 Hz), 131.97 (C$_q$), 131.76 (C$_q$, J_{CP} = 67.1 Hz), 131.07 (CH), 128.66 (CH, J_{CP} = 10.1 Hz), 127.36 (CH), 126.99 (CH), 126.69 (CH, J_{CP} = 20.0 Hz). 125.60 (CH), 125.17 (CH), 124.91 (C$_q$, J_{CP} = 5.9 Hz), 122.92 (C$_q$), 121.84 (CH), 121.57 (CH), 121.13 (CH), 32.64 (CH, J_{CP} = 21.1 Hz), 31.07 (CH$_2$), 30.88 (CH$_2$, J_{CP} = 9.3 Hz), 27.40 (CH$_2$, J_{CP} = 7.54 Hz), 27.03 (CH$_2$, J_{CP} = 14.7 Hz), 26.50 (CH$_2$, J_{CP} = 7.7 Hz), 11.45 (CH$_3$, J_{CP} = 17.3 Hz). ^{31}P{^{1}H} NMR (CDCl$_3$, 202.3 MHz, 233 K): δ (ppm) 144.24 (d, J_{PP} = 249.2 Hz, 0.3P), 141.50 (s, 0.7P), −19.91 (d, J_{PP} = 251.9 Hz, 0.3P), −22.17 (s, 0.7P). HRMS (FAB) calcd for $[M + H]^+$ $C_{41}H_{42}NO_2P_2$, 642.2691; found, 642.2697.

Di-(*o*-Tolyl)-{1-[(*S*)-3,5-dioxa-4-phospha-cyclohepta(2,1-*a*;3,4-*a*')dinaphtalen-4-yl]-3-methyl-2-indolyl}phosphine (4c). Yield: 749 mg (78 %). Mp = 175 °C. $[\alpha]_D^{20}$ = +207.2 (c = 1.1, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz, 298 K): δ (ppm) 7.98 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.50-7.42 (m, 5H), 7.38-7.21 (m, 8H), 7.19-7.12 (m, 3H), 6.88 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 6.24 (t, J = 7.8 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (CDCl$_3$, 125.5 MHz, 298 K): δ (ppm) 150.29 (C$_q$, J_{CP} = 5.5 Hz), 148.76 (C$_q$), 142.52 (C$_q$, J_{CP} = 26.5 Hz), 142.22 (C$_q$, J_{CP} = 26.1 Hz), 140.45 (C$_q$, J_{CP} = 5.5 Hz), 133.61 (CH), 133.10 (C$_q$), 132.95 (C$_q$), 132.47 (CH), 132.24 (C$_q$), 131.95 (C$_q$), 131.49 (C$_q$), 130.83 (CH), 130.61 (CH), 130.53 (CH, J_{CP} = 4.5 Hz), 130.08 (C$_q$, J_{CP} = 6.3 Hz), 129.86 (C$_q$, J_{CP} = 6.8 Hz), 129.18 (CH), 128.96 (CH), 128.63 (CH), 128.57 (CH), 127.49 (C$_q$), 126.92 (CH), 126.61 (CH), 126.55 (CH, J_{CP} = 4.7), 126.39 (CH), 126.11 (CH), 125.47 (CH), 125.12 (CH), 124.76 (C$_q$, J_{CP} = 5.9 Hz), 123.58 (CH), 123.16 (C$_q$), 123.04 (CH), 121.98 (CH), 121.62 (CH), 121.07 (CH), 119.39 (CH, J_{CP} = 8.9 Hz), 118.31 (CH), 116.13 (CH), 111.13 (CH), 21.67 (CH$_3$, J_{CP} = 19.9 Hz), 21.51 (CH$_3$, J_{CP} = 19.4 Hz), 9.88 (CH$_3$, J_{CP} = 3.4 Hz). ^{31}P{^{1}H} NMR (CDCl$_3$, 202.3 MHz, 298 K): δ (ppm) 144.11 (d, J_{PP} = 210.2 Hz), −40.08 (d, J_{PP} = 211.6 Hz). HRMS (FAB) calcd for $[M + H]^+$ $C_{43}H_{33}NO_2P_2$, 658.2065; found, 658.2063.

III ^{1}H and ^{13}C NMR spectra of new ligands

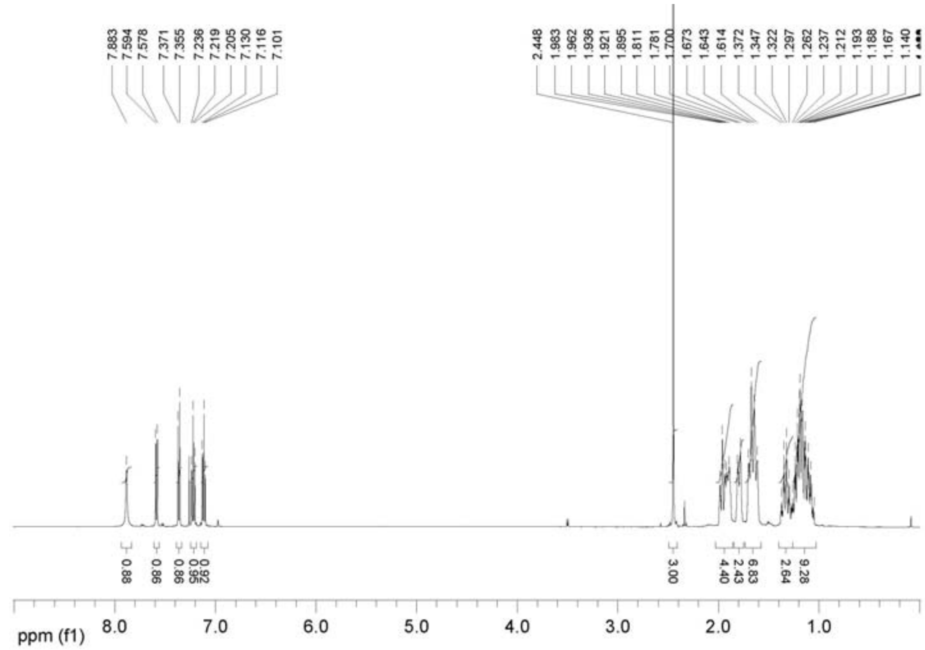


Fig. S1 ^{1}H NMR spectrum of **3c** in $CDCl_3$

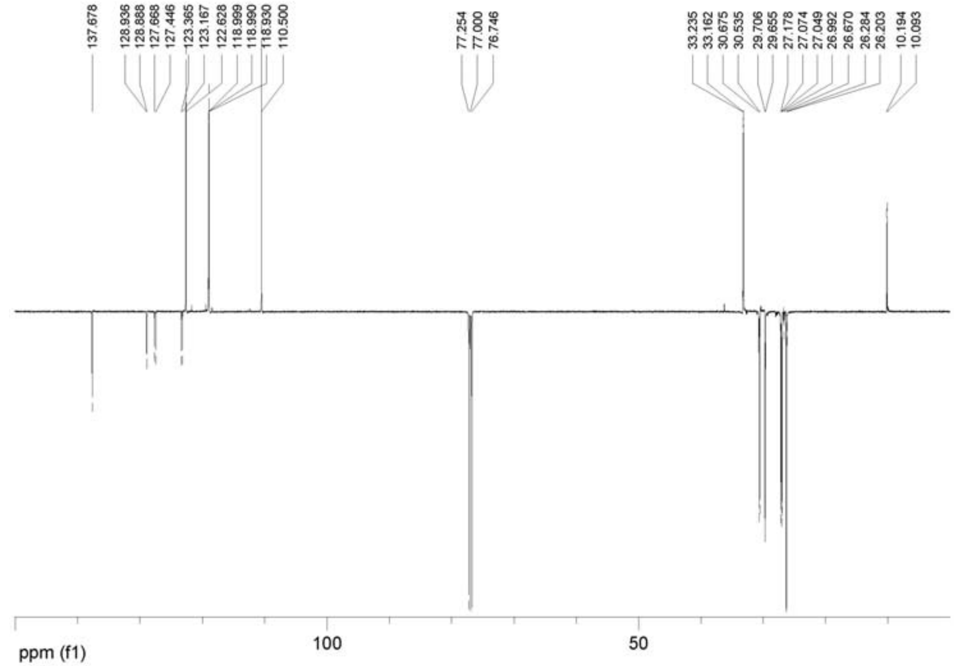


Fig. S2 ^{13}C NMR spectrum of **3c** in $CDCl_3$

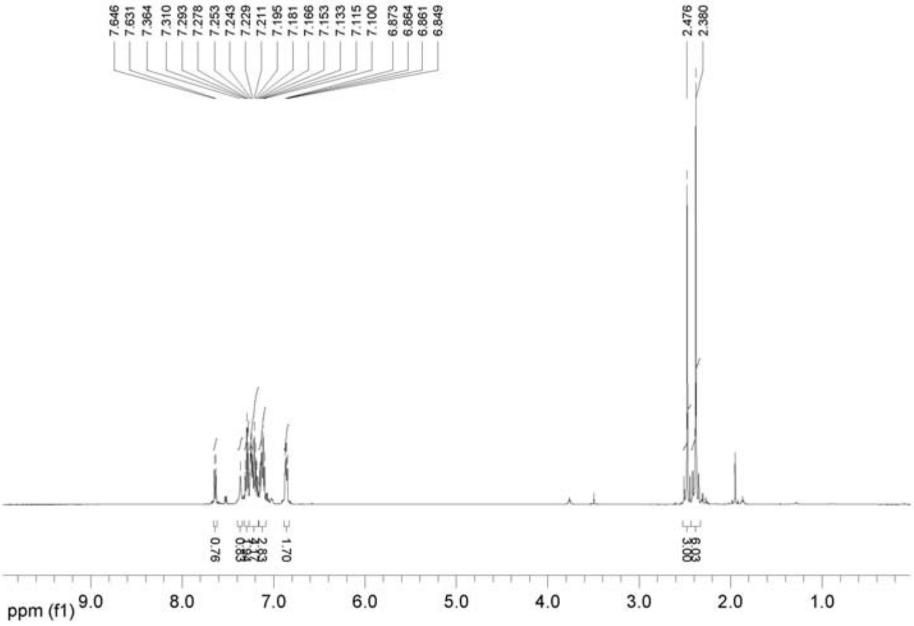


Fig. S3 ^{1}H NMR spectrum of **3d** in $CDCl_3$

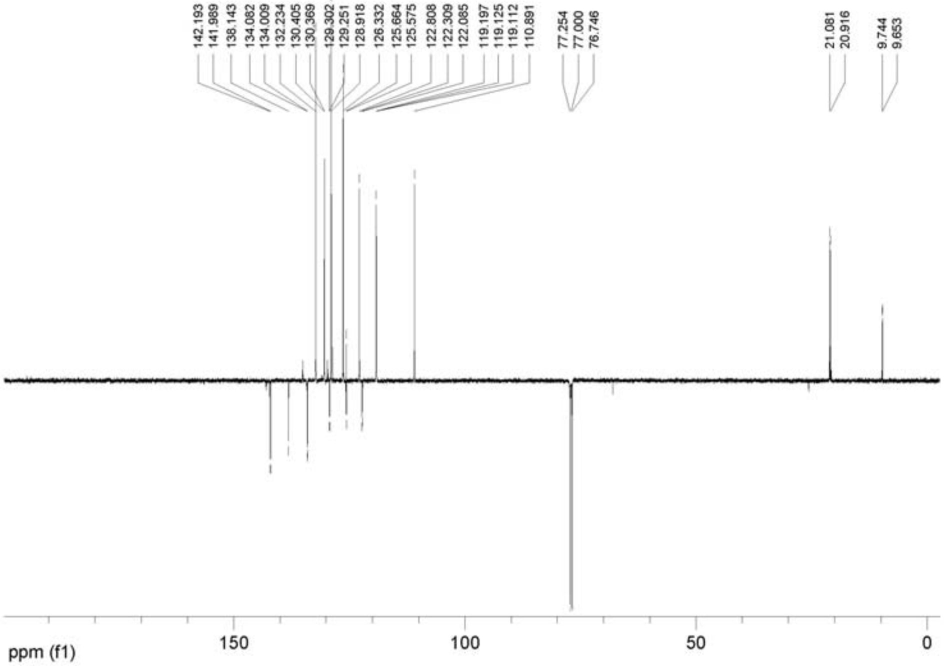


Fig. S4 ^{13}C NMR spectrum of **3d** in $CDCl_3$

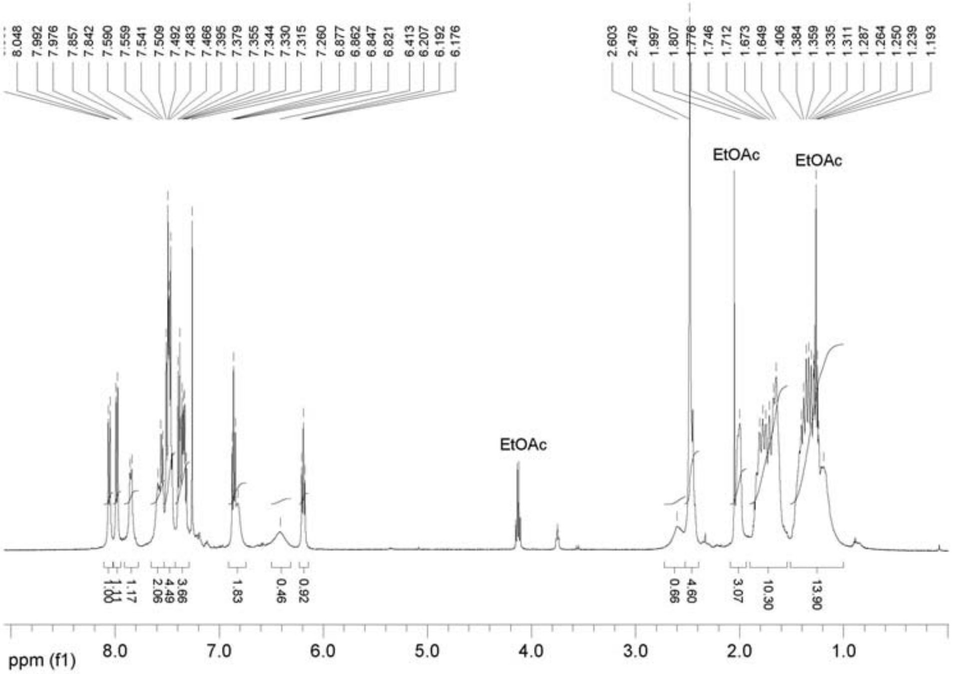


Fig. S5 ^{1}H NMR spectrum of **4c** in CDCl$_3$

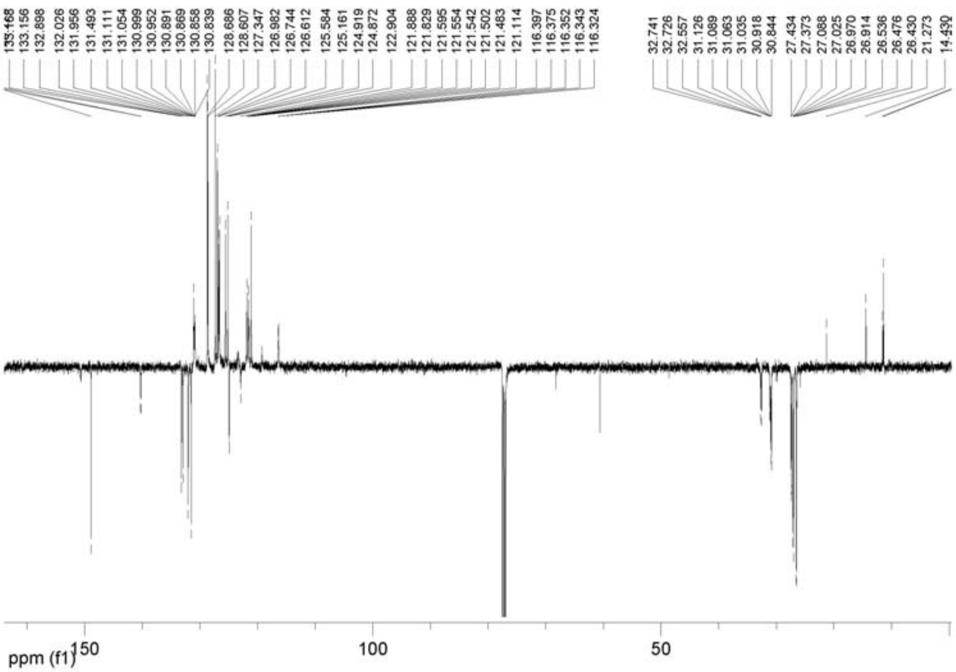


Fig. S6 ^{13}C NMR spectrum of **4c** in CDCl$_3$

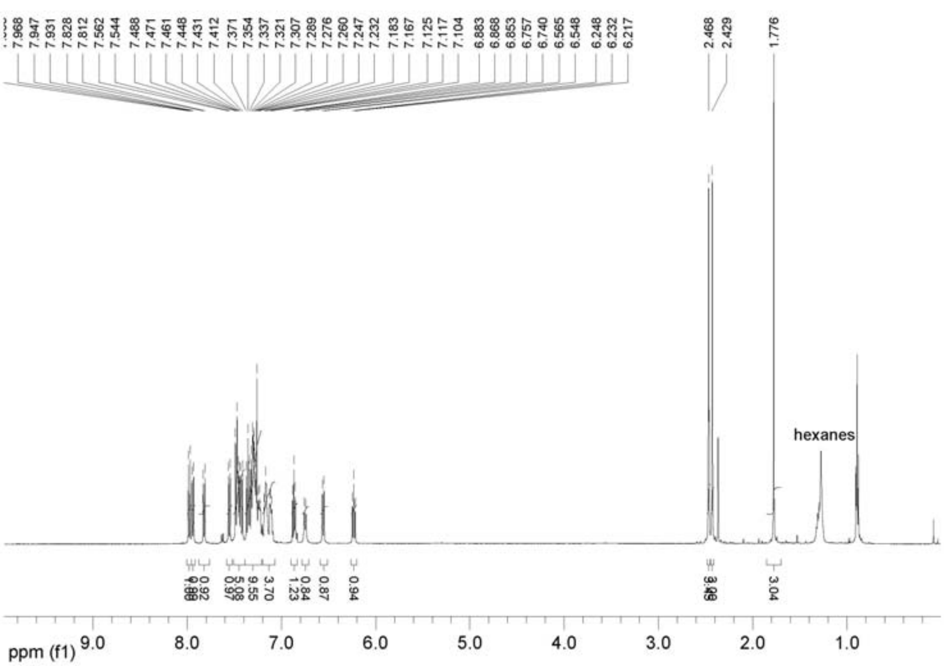


Fig. S7 ^{1}H NMR spectrum of **4d** in CDCl$_3$

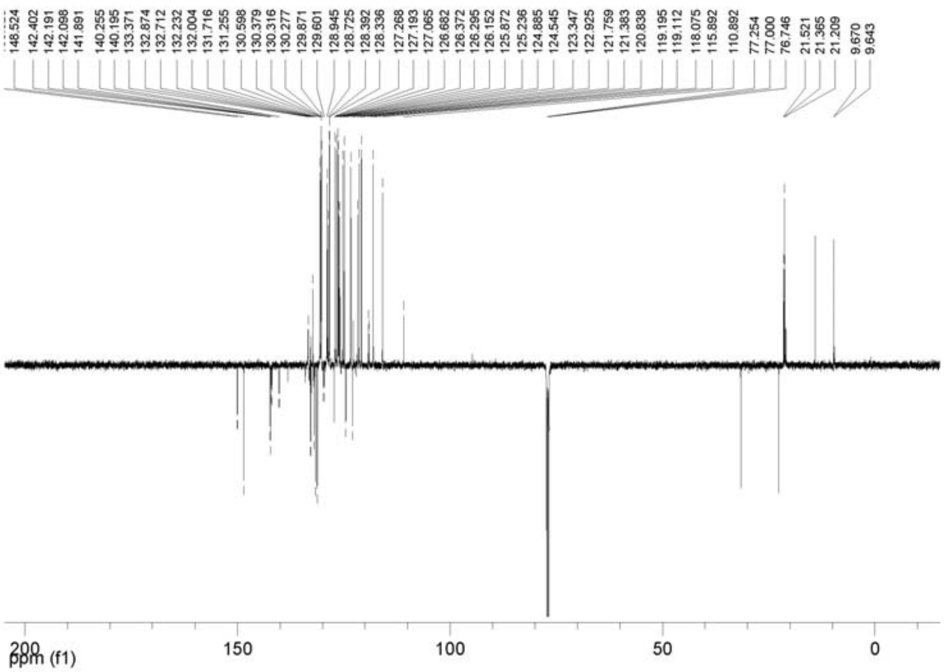


Fig. S8 ^{13}C NMR spectrum of **4d** in CDCl$_3$

IV Synthesis of substrates

Methyl 2-hydroxymethylacrylate (**2a**),[2] Benzyl 2-hydroxymethylacrylate (**2b**),[3] and (2*E*)-3-phenyl-2-hydroxymethylacrylate (**2d**)[4] were prepared according to literature procedures.

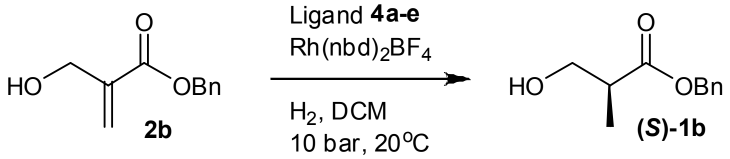
Methyl 2-acetoxymethylacrylate (2c). To a solution of methyl 2-hydroxymethylacrylate (2.24 g; 19.3 mmol) and pyridine (1.87 mL; 23.1 mmol) in Et_2O (20 mL) was added dropwise a solution of acetyl chloride (1.65 mL; 23.1 mmol) in Et_2O (10 mL). The resulting white suspension was stirred at room temperature for 0.5 h. To the suspension, 10 % aq. HCl (30 mL) was added and the aqueous phase was removed. The organic phase was washed subsequently with 2 % aq. HCl (30 mL), H_2O (30 mL), sat. aq. $NaHCO_3$ (30 mL), and H_2O (30 mL). After drying over $MgSO_4$ and filtration the solvent was removed by rotary evaporation to obtain a colourless liquid. Yield: 1.34 g (44 %). ^1H NMR ($CDCl_3$, 300.1 MHz, 298 K): δ (ppm) 6.36 (m, 1H), 5.85 (m, 1H), 4.80 (m, 2H), 3.78 (s, 3H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz, 298 K): δ (ppm) 170.68 (C_q), 165.91 (C_q), 135.37 (C_q), 127.86 (CH_2), 62.69 (CH_2), 52.31 (CH_3), 21.12 (CH_3).

V Additional catalysis results

General procedure for screening experiments.

The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 8 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with 1.0 μmol of $[Rh(nbd)_2]BF_4$, 1.1 μmol of ligand and 0.10 mmol of alkene substrate in 1.0 mL of CH_2Cl_2. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurized at 10 bar H_2. The reaction mixtures were stirred at 20 °C for the appropriate reaction time. After catalysis the pressure was reduced to 1.0 bar and the conversion and enantiomeric purity was determined by chiral GC or HPLC.

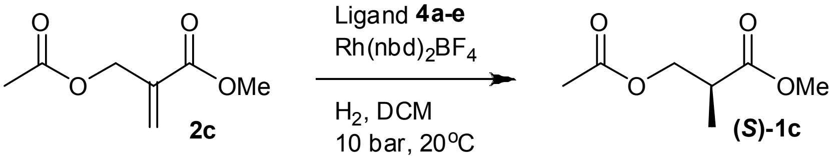
Table S-1. Ligand screening in the rhodium catalyzed asymmetric hydrogenation of benzyl 2-hydroxymethylacrylate.[a]



Entry	Ligand	% conv.	% ee[b]
1	**4a**	61	11
2	**4b**	100	89
3	**4c**	100	81
4	**4d**	100	70
5	**4e**	88	45
6	**4f**	100	72
7	**(*S*)-Monophos**[c]	90	48

[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, [Rh] = 1.0 mM, 10 bar of H_2, at 20°C for 20 h using $[Rh(nbd)_2]BF_4$ as metal precursor. [b] The (*S*)-enantiomer was obtained in all cases. [c] (*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine.

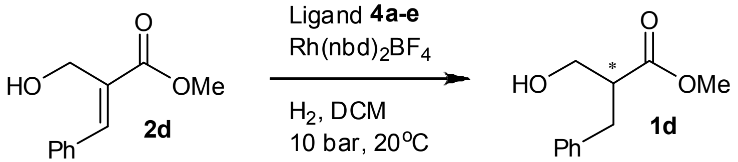
Table S-2. Ligand screening in the rhodium catalyzed asymmetric hydrogenation of methyl 2-acetoxymethylacrylate.[a]



Entry	Ligand	% conv.	% ee[b]
1	**4a**	97	3
2	**4b**	34	35
3	**4c**	41	32
4	**4d**	36	27
5	**4e**	21	22
6	**4f**	10	19
7	**(*S*)-Monophos**[c]	50	0

[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, [Rh] = 1.0 mM, 10 bar of H_2, at 20°C for 20 h using $[Rh(nbd)_2]BF_4$ as metal precursor. [b] The (*S*)-enantiomer was obtained in all cases. [c] (*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine.

Table S-3. Ligand screening in the rhodium catalyzed asymmetric hydrogenation of (2*E*)-3-phenyl-2-hydroxymethylacrylate.[a]



Entry	Ligand	% conv.	% ee[b]
1	**4a**	33	0
2	**4b**	0	-
3	**4c**	0	-
4	**4d**	0	-
5	**4e**	0	-
6	**4f**	0	-
7	**(*S*)-Monophos**[c]	23	0

[a] Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, [Rh] = 1.0 mM, 10 bar of H_2, at 20°C for 20 h using $[Rh(nbd)_2]BF_4$ as metal precursor. [b] The absolute configuration was not determined. [c] (*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine.

VI AMTEC experimental details

The experiments were carried out in the AMTEC SPR16[6] consisting of 16 parallel reactors equipped with temperature and pressure sensors, and a mass flow controller. The apparatus is suited for monitoring gas uptake profiles during the catalytic reactions.

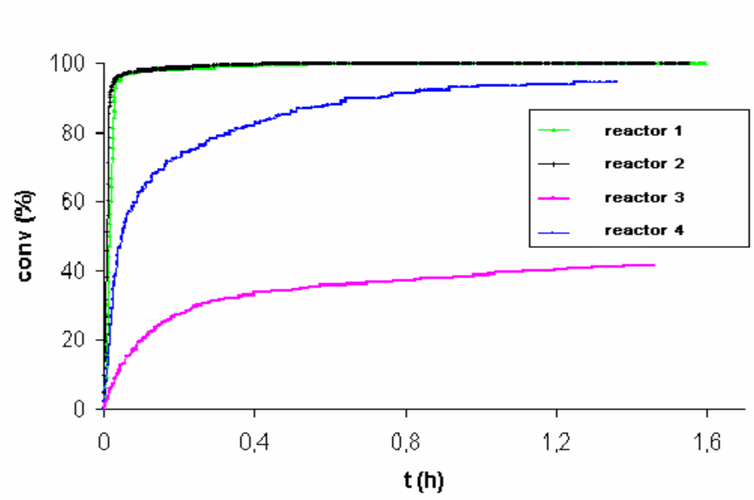
Four autoclaves were heated to 110 °C and flushed with argon (22 bar) five times. Next the reactors were cooled to 25 °C and flushed again with argon (22 bar) five times. The autoclaves were charged with the appropriate amount of $[Rh(nbd)_2(BF_4)]$, ligand **4b** and methyl 2-hydroxymethylacrylate in 8.00 ml of CH_2Cl_2 under argon. The reactors were pressurized with 5 (reactor 1) or 10 (reactors 2-4) bar H_2 and the pressure was kept constant during the whole reaction. The reaction mixtures were stirred at 25 °C for 1.5 h and the hydrogen uptake was monitored and recorded for every reactor. After catalysis the pressure was reduced to 2.0 bar and samples (0.2 ml) were taken.

VII Gas-uptake profiles

Table S-4. Hydrogenation of methyl 2-hydroxymethylacrylate (**2a**) under various conditions in AMTEC parallel reactor.

reactor	ligand	Rh[a] (µmol)	**2a** (µmol)	P_{H_2} (bar)	t (h)	conv (%)	ee (%)
1	**4b**	8.00	800	5	1.6	100	93
2	**4b**	8.00	800	10	1.5	100	93
3	**4b**	0.80	800	10	1.5	46	92
4	**4b**	0.80	320	10	1.4	95	93

[a] $[Rh(nbd)_2BF_4]$



Graph S-1. Gas-uptake profile for the hydrogenation of methyl 2-hydroxymethylacrylate

VIII Chiral GC and HPLC separation data for products 1a-d and 2-methyl-3-phenylpropanoic acid

Methyl 3-hydroxy-2-methylpropionate (1a). The conversion and ee were determined by chiral GC analysis (Chiralsil DEX-CB, isothermal at 75 °C for 2.0 min., 5 °C/min to 90 °C, 50 °C/min to 220 °C; t_R (*R*) = 5.42 min., t_R (*S*) = 5.52 min., and t_R (substrate) = 5.62 min.).

Benzyl 3-hydroxy-2-methylpropionate (1b). Conversion was determined by GC analysis (Chiralsil DEX-CB, isothermal at 110 °C for 30.0 min., 2 °C/min to 140 °C; t_R (substrate) = 20.94 min., t_R (*S*) = 41.16 min., and t_R (*R*) = 41.38 min.). The ee was determined by chiral HPLC analysis (Chiralcel OJ-H, flow rate: 1.0 mL/min, eluent: hexane/isopropanol (90/10), detection at 254 nm; t_R (*S*) = 12.01 min., and t_R (*R*) = 12.87 min.). For HPLC analyses, the crude reaction mixture was concentrated *in vacuo*, extracted with the corresponding eluent and filtered through a pad of neutral alumina.

Methyl 3-acetoxy-2-methylpropionate (1c). The conversion and ee were determined by chiral GC analysis (Supelco BETA DEX, isothermal at 70 °C for 30.0 min., 25 °C/min to 220 °C; t_R (*R*) = 28.19 min., t_R (*S*) = 28.78 min., and t_R (substrate) = 32.27 min.).

Methyl 3-hydroxy-2-benzylpropionate (1d). The conversion and ee were determined by chiral GC analysis (Chiralsil DEX-CB, isothermal at 115 °C for 30.0 min., 2 °C/min to 150 °C; t_R (enantiomer 1) = 44.13 min., t_R (enantiomer 2) = 44.61 min., and t_R (substrate) = 46.36 min.).

2-methyl-3-phenylpropanoic acid. Prior to analysis, the product from the hydrogenation of α-methylcinnamic acid (**5**) was converted to the methyl ester using trimethylsilyldiazomethane in MeOH. The conversion and ee were determined by chiral HPLC analysis (Chiralcel OD-H, flow-rate: 1.0 mL/min, eluent:

hexane/isopropanol (99.5/0.5), detection at 210 nm, t_R (*R*) = 9.1 min., t_R (*S*) = 10.7 min., and t_R (substrate) = 15.0 min.).

IX References

[1] G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Organometallics* **1997**, *16*, 2929-2939.
[2] C. Z. Yu, B. Liu, L. Q. Hu, *J. Org. Chem.* **2001**, *66*, 5413-5418.
[3] B. M. O'Leary, T. Szabo, N. Svenstrup, C. A. Schalley, A. Lûtzen, M. Schäfer, J. Rebek Jr., *J. Am. Chem. Soc.* **2001**, *123*, 11519-11533.
[4] D. Basavaiah, K. Padmaja, T. Satyanarayana, *Synthesis* **2000**, 1662-1664.
[5] J. Wassenaar, J. N. H. Reek, *Dalton Trans.* **2007**, 3750-3753.
[6] www.amtec-chemnitz.de