Screening of a Supramolecular Catalyst Library in the Search for Selective Catalysts for the Asymmetric Hydrogenation of a Difficult Enamide Substrate

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Robotic screening of a supramolecular catalyst library in the search for selective catalysts for the asymmetric hydrogenation of a difficult enamide substrate

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General:

Reagents were purchased from Aldrich, Acros, Fluka, Merck, Strem and used as received without any further purification unless stated otherwise. Most solvents were analytical grade and purified according to standard procedures, if necessary. ^{1}H NMR (300 MHz), ^{13}C NMR (75.4 MHz) and ^{31}P NMR (121.4 MHz) spectra were recorded on a Varian Mercury 300 spectrometer in $CDCl_3$. Chemical shifts were recorded in d units (ppm) relative to the residue deuterated solvent signals of $CHCl_3$ (^{1}H: 7.25 ppm, ^{13}C: 77.0 ppm); the splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants (*J*) are recorded in Hertz (Hz). The spectra recorded were consistent with the proposed structures of final compounds. Mass spectra were measured on an AEI-MS-902 mass spectrometer using FAB ionization. The hydroxyl porphyrins and L1-L2, L4-L7, L'1, L'3-L'5, L'7 were prepared according to literature procedure.[1] L3 was purchased from Aldrich. L12 was prepared according to published procedure.[2]

Typical synthetic procedure for the preparation of porphyrin-phosphites:

In a 100 ml 3-necked round flask, was placed 5-(2-hydroxyphenyl)-10, 15, 20-tris(phenyl) porphyrin (630, 2 mmol, 1.26 g), dipea (3ml) and dry DCM 20 ml under N_2. The mixture was cooled to 0^{o}C and to this mixture was added a solution of freshly prepared (*R, R*)-taddol-PCl [3](531, 2 mmol, 1.06 g) [or (*S*)-binol-PCl, bis(3,5-di-*t*-Bu)biphenyl-PCl] in 5 ml dry DCM. Subsequently, it was allowed to come to RT and the mixture was stirred for 30 mins after which Me_2Zn (2 M in toluene, 1.5 ml, 3 mmol) was added. After stirring for another 30 mins, the reaction went to completion as judged by TLC. The solvent was removed under vacuum; the crude mixture was dissolved in 20 ml dry DCM and filter through basic Al_2O_3 (DCM) under N_2. The filtrate was evaporated to dryness under vacuum and a purple solid was isolated (typical yield 70%, over 2 steps).

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[1] V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056-4057.
[2] a) P. H. Dussault, K. R. Woller, *J. Org. Chem.* **1997**, *62*, 1556-1559; b) M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889-3890.
[3] 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.

Characterization

(*R*, *R*)-(taddol)-[5-(phenyl-2-yl)-10, 15, 20-tris(phenyl)-zinc(II) porphyrin] phosphite **L'2**

^{31}P NMR d 132.5; ^{1}H NMR d 0.33 (s, 3H), 0.63 (s, 3H), 4.87 (d, 1H, *J* = 7.4 Hz), 6.01 (d, 1H, *J* = 7.3 Hz), 6.68-6.85 (m, 2H), 6.89-6.95 (m, 1H), 6.99-7.17 (m, 4H), 7.29-7.58 (m, 12H), 7.65-7.75 (m, 3H), 7.77-8.05 (m, 11H), 8.10-8.22 (m, 1H), 8.25-8.55 (m, 6H), 8.92-9.18 (m, 7H); ^{13}C NMR d 26.1, 27.1, 79.6, 81.6 (d), 83.8 (d), 86.9 (d), 113.7, 119.6, 121.4, 121.6, 122.5, 126.4, 126.9, 127.3, 127.8, 128.1, 128.6, 129.0, 129.6, 132.3, 132.5, 134.9, 136.3, 140.3, 141.4, 143.4, 145.3, 150.3, 150.5 HRMS (FAB$^+$, M+1) $C_{76}H_{60}O_5N_4PZn$, calcd. 1203.3593, found 1203.3579.

(*R*, *R*)-(taddol)-[5-(phenyl-3-yl)-10, 15, 20-tris(phenyl)-zinc(II) porphyrin] phosphite **L'6**

^{31}P NMR d 127.1; ^{1}H NMR d 0.80 (s, 3H), 0.97 (s, 3H), 5.26 (d, 1H, *J* = 7.3 Hz), 5.81 (d, 1H, *J* = 7.1 Hz), 6.87-6.96 (m, 1H), 6.98-7.07 (m, 1H), 7.08-7.27 (m, 4H), 7.28-7.52 (m, 9H), 7.54-7.76 (m, 11H), 7.79-7.96 (m, 9H), 7.99-8.06 (m, 1H), 8.32-8.48 (m, 4H), 8.92-9.14 (m, 7H); ^{13}C NMR d 26.8, 27.1, 80.8, 82.7 (d), 85.3 (d), 86.9 (d), 113.4, 119.2, 120.5, 121.5, 126.9, 127.4, 127.7, 127.8, 128.1, 128.2, 128.5, 129.0, 129.5, 130.3, 132.4, 134.9, 141.7, 143.4, 144.4, 146.3, 150.4, 150.6; HRMS (FAB$^+$, M+1) $C_{76}H_{60}O_5N_4PZn$, calcd. 1203.3593, found 1203.3593.

Typical synthetic procedure for the preparation of **L5**:

In a 100 ml 3-necked round flask, was placed imidazole (68, 5.3 mmol, 0.36 g), (para)formaldehyde (30, 0.24 g, 8 mmol) and dry toluene 10 ml under N_2. After stirring for 20 mins, Ph_2PH (1.02 g, 5.4 mmol) was added. The mixture was heated to 60^{o}C for 2 h. After cooling to RT, the mixture was filtered through Celite and the solvent was removed under vacuum. It was further purified through flash basic Al_2O_3 column (DCM, degassed) and the solvent was evaporated to dryness to result in **L5** as colorless oil (0.78 g, 2.9 mmol, 55% yield). ^{31}P NMR d –12.4; ^{1}H NMR d 4.42 (d, 2H, *J* = 7.1 Hz), 6.98 (s, 2H), 7.32 (m, 6H), 7.51 (m, 4H); ^{13}C NMR d 62.9 (d, *J* = 8.8 Hz), 121.9, 128.8, 128.9, 129.1, 131.6, 131.8, 132.8, 133.3, 133.5, 136.5, 136.7

Typical synthetic procedure for the preparation of *N*-containing phosphites:

In a 100 ml 3-necked round flask, was dissolved 2-pyridinol (95, 5 mmol, 0.48 g) [or 3-pyridinol, phenol, (*R*)-tropine, (*R*)-3-qunucidinol] in 10 ml dry THF under N_2. The mixture was cooled to 0^{o}C and to this mixture was NaH (60% in oil, 0.15 g, 6 mmol) slowly added. Subsequently, the mixture was allowed to warm to room temperature and heated to reflux for 2 h. After cooling to -40^{o}C, a solution of freshly prepared (*R*, *R*)-taddol-PCl [3](531, 5 mmol, 2.66 g) [or (*S*)-binol-PCl, bis(3,5-di-*t*-Bu)biphenyl-PCl] in 10 ml dry DCM was added. The obtained reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed under vacuum and the crude mixture was extracted with

20 ml dry toluene and subsequently with 60 ml *n*-hexane (twice). After filtration, the solvent was removed under vacuum and a white to off-white solid was isolated (65%-70% yield).

Characterization

(*R*, *R*)-(taddol)-(3-pyridyl) phosphite **L8**

^{31}P NMR d 124.9; ^{1}H NMR d 0.53 (s, 3H), 0.89 (s, 3H), 5.12 (d, *J* = 7.8 Hz, 1H), 5.73 (d, 1H, *J* = 8.1 Hz), 6.68-6.79 (m, 1H), 6.89-6.97 (m, 1H), 7.09-7.40 (m, 16H), 7.41-7.68 (m, 4H), 7.78-7.83 (m, 1H), 8.12-8.19 (m, 1H); ^{13}C NMR d 26.5 (d), 27.1 (d), 80.1 (d), 82.5 (d), 85.8 (d), 87.6 (d), 113.5, 123.9, 126.6 (d), 127.3, 127.8, 128.3, 128.5, 128.7, 129.2, 141.2, 141.5, 141.8 (d), 144.4, 145.9, 146.1, 149.1; HRMS (FAB^{+}, M+1) $C_{36}H_{33}O_5NP$, calcd. 590.2096, found 590.2093.

Catechol-(3-pyridyl) phosphite **L9**

^{31}P NMR d 125.4; ^{1}H NMR d 6.57-6.68 (m, 2H), 6.73-6.80 (m, 3H), 6.98-7.01 (m, 1H), 7.99 (d, 1H, *J* = 4.6 Hz), 8.11 (d, 1H, *J* = 2.3 Hz); ^{13}C NMR d 112.5, 123.2, 123.9, 124.3, 128.2, 144.6, 144.7, 145.9, 147.0; HRMS (FAB^{+}, M+1) $C_{11}H_9O_3NP$, calcd. 234.0320, found 224.0318.

Bis(3,5-di-*t*-Bu)biphenyl-(2-pyridyl) phosphite **L10**

^{31}P NMR d 138.0; ^{1}H NMR d 1.55 (s, 18H), 1.76 (s, 18H), 6.84 (d, 1H, *J* = 8.2 Hz), 7.01-7.05 (m, 1H), 7.31 (d, 1H, *J* = 2.3 Hz), 7.36 (d, 1H, *J* = 2.3 Hz), 7.58 (d, 1H, *J* = 2.3 Hz), 7.61 (d, 1H, *J* = 2.1 Hz), 7.64-7.67 (m, 1H), 8.26-8.29 (m, 1H); ^{13}C NMR d 30.1, 31.5, 31.8, 35.0, 35.1, 35.8, 112.3, 119.2, 124.7, 125.4, 126.8, 127.0, 131.0, 133.3, 139.7, 140.8, 140.9, 145.9, 146.9, 147.5, 148.6, 160.8; HRMS (FAB^{+}, M+1) $C_{33}H_{45}O_3NP$, calcd. 534.3137, found 534.3103.

(*S*)-(1,1'-binaphthyl-2,2')-(2-pyridyl) phosphite **L11**

^{31}P NMR d 144.2; ^{1}H NMR d 6.79 (d, 1H, *J* = 8.2 Hz), 7.01-7.05 (m, 1H), 7.24-7.31 (m, 1H), 7.34-7.49 (m, 6H), 7.59-7.66 (m, 1H), 7.88-8.04 (m, 5H), 8.31-8.32 (m, 1H); ^{13}C NMR d 112.8, 119.8, 120.5, 121.2, 122.1 (d), 125.4 (d), 126.4 (d), 127.3 (d), 128.7 (d), 130.2, 130.8, 131.3, 131.7 (d), 132.0, 132.1, 132.5, 132.9, 133.1, 135.0, 140.1, 142.0, 147.7, 148.2, 160.5, 165.8; HRMS (FAB^{+}, M+1) $C_{25}H_{16}O_3NP$, calcd. 410.0946, found 410.0937.

(*S*)-(1,1'-binaphthyl-2,2')-(3-tropinly) phosphite **L13**

^{31}P NMR d 143.8; ^{1}H NMR d 1.43-2.28 (m, 8H), 2.06 (s, 3H), 2.98 (m, 2H), 4.38 (m, 1H), 7.02-7.61 (m, 8H), 7.63-7.97 (m, 4H); ^{13}C NMR d 25.1, 37.9, 38.3, 39.5, 60.4, 68.1, 115.5, 121.7, 122.1, 125.1, 125.2, 126.6, 127.2, 128.6, 130.0, 130.7, 131.2, 131.7, 132.8, 133.0, 134.6, 148.7, 153.8; HRMS (FAB^{+}, M+1) $C_{28}H_{27}O_3NP$, calcd. 456.1729, found 456.1718.

(*S*)-(1,1'-binaphthyl-2,2')-3-quinuclidinly phosphite **L14**

^{31}P NMR d 140.0, 142.3; ^{1}H NMR d 1.24 (m, 2H), 1.52 (m, 1H), 1.98 (m, 2H), 2.42-2.98 (m, 6H), 4.30 (m, 1H), 7.11-7.16 (m, 1H), 7.22-7.25 (m, 1H), 7.26-7.29 (m, 1H), 7.32-7.48 (m, 4H), 7.51 (d, 1H, *J* = 8.8 Hz), 7.76 (dd, 1H, *J* = 4.4, 8.8 Hz), 7.84-7.93 (m, 2H), 7.97 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR d 18.9, 24.1, 27.5, 27.8, 46.2, 47.3, 56.8 (d), 71.9, 121.8, 122.0, 123.2, 125.2, 125.4, 126.6, 127.2, 128.2, 128.6, 129.0, 129.8, 130.1 (d), 130.7, 131.2, 131.8, 133.4 (d), 134.5, 147.7, 148.7, 153.5; HRMS (FAB$^+$, M+1) $C_{27}H_{25}O_3NP$, calcd. 442.1572, found 442.1551.

(*S*)-(1,1'-binaphthyl-2,2')-(*R*)-3-quinuclidinly phosphite **L15**

^{31}P NMR d 141.4. ^{1}H NMR d 1.25 (m, 2H), 1.54 (m, 1H), 1.96 (m, 1H), 2.05 (m, 1H), 2.72-2.90 (m, 2H), 3.46-3.62 (m, 2H), 3.82-3.92 (m, 1H), 3.97-4.10 (m, 1H), 4.78 (m, 1H), 7.20-7.25 (m, 3H), 7.32-7.50 (m, 4H), 7.57 (d, 1H, *J* = 8.8 Hz), 7.88 (s, 1H), 7.91 (s, 1H), 7.94 (s, 1H), 7.97 (s, 1H); ^{13}C NMR d 19.2, 24.0, 25.2, 30.1, 46.4, 47.3, 55.2, 70.8, 121.9, 122.2, 123.0, 124.4, 125.2, 125.4, 126.3, 126.6, 127.2, 128.2, 128.7 (d), 129.7, 130.2 (d), 130.8, 131.6 (d), 133.0 (d), 134.5, 148.0, 149.2, 154.1; HRMS (FAB$^+$, M+1) $C_{27}H_{25}O_3NP$, calcd. 442.1572, found 442.1558.

Typical procedure for asymmetric hydrogenation of **1** (Scheme 4)

In the HTE-96[4] reaction plate, 96 of 5 ml glass vials provided with 96 magnetic stirrers, the stock solution of porphyrin-phosphites (L'n, 0.003 mmol / vial), dipea (0.06 mmol / vial), *N*-containing phosphorus ligands (Ln, 0.0024 mmol / vial) in dry DCM was transferred to these vials via the robot in the glove box. After stirring at RT for 15 mins, a stock solution of $Rh(COD)_2BF_4$ (0.002 mmol / vial) was introduced and stirred for another 15 mins. The stock solution of substrate **1** (0.04 mmol / vial) in DCM was transferred to these vials. After capping in the glove box, these 96 vials were transferred outside the glove box and placed in an autoclave, which was closed, purged 3 times with N_2 and 3 times with H_2. The autoclave was pressurized with H_2 to 12 bar and the reactions were magnetically stirred at 40^{o}C. After the desired time, it was cooled to RT and the autoclave was opened. After filtration on a short silica gel column, the filtrate was analyzed by chiral GC (Chiralsil-DEXCB column) for the determination of conversion and enantiomeric excess (ee). The absolute configuration was assigned by comparing with the data reported in the literature.[5] Racemic sample was prepared by the hydrogenation of **1** with $Rh(PPh_3)_2Cl_2$ as catalyst in DCM for 14 hrs at 10 bar H_2.
Hydrogenation experiments carried out at larger scale (Table 2 of the paper) were carried in the Endeavor, [6] using 1 mmol **1** dissolved in 5 ml DCM at room temperature. The reactions were monitored independently by the pressure drop. After the reaction, the solvent was removed and the residue was dissolved MeOH and filter through basic Al_2O_3, and crystallized from CH_2Cl_2/*n*-hexane = 1/3, isolated yield 92% (light yellow needles).

[4] For a description of the apparatus, see: www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten.
[5] J. L. Renaud, P. Dupau, A. -E. Hay, M. Guingouain, P. H. Dixneuf, C. Bruneau, *Adv. Synth. Catal.* **2003**, *345*, 230-238.
[6] The Endeavor is the equipment that has 8 parallel vessels and could be used at the same time under high pressure with the monitor of the gas-uptake profiles.

The conversion and enantiomeric excess (e.e.) of the product were measured by chiral GC (Chiralsil-DEXCB, 170^{o}C, 45 mins, t_R = 18.9 min, t_S = 19.6 min, t_{sm} = 40.6 min).

Results of the hydrogenation of **1** in the high through-put equipment (HTE-96)

For *Table 1a and 1b*, see manuscript.

Table 2a: The conversion (%) of **2** induced by the rhodium catalysts based on various SUPRAphos ligands using achiral porphyrin-phosphites and chiral co-ligands

	L6	L8	L11	L12	L13	L15
L'3	9	100	100	100	100	100
L'7	3	15	98	49	34	80

Table 2b: The ee's (%) of **2** induced by the rhodium catalysts based on various SUPRAphos ligands using achiral porphyrin-phosphites and chiral co-ligands

	L6	L8	L11	L12	L13	L15
L'3	8	8	4	11	8	9
L'7	-4	6	10	14	13	18

Table 3 The hydrogenation results (conversions and ee's (%) of **1**) of control experiments [a]

Entry	Ligands	Conv. (%) [b]	e.e. (%) [b]
1	L'1	100	12 (+)
2	L'2	51	1 (+)
3	L'5	100	29 (+)
4	L'6	100	8 (-)
5	L6	0	0
6	L8	0	0
7	L11	73	9 (+)
8	L13	49	14 (+)
9	L15	96	11 (+)
10	L'1/L15	100	17 (+)

[a] Unless noted, reaction was performed under a condition of $Rh(COD)_2BF_4$, Rh/L'n or Rh/Ln = 1/2.1, 5 mol%, DCM, 12 bar H_2, 40^{o}C, 0.04 mmol of substrate **1**, 20 eqs. dipea (diisopropyl ethyl amine) as base contrast to porphyrin-phosphites, 14 hrs. [b] Conversion and ee were determined by chiral GC (Chiralsil-DEXCB). The optical signs are compared with the data in literature,[5] (-) means the opposite major enantiomer of the products.

All results of the hydrogenation of **1** obtained from experiments using the Endeavor

Table 4: Different combinations and ratios of **L'n/Ln** in the Endeavor [a]

Entry	Ligands	Rh/L'n/Ln	(L'n+Ln)/Rh	t (h)	Conv.(%) [c]	ee (%) [c]
1	L'1/L2	1/1.5/1.2	2.7	4 [b]	100	94 (+)
2 [d]	L'1/L2	1/1.5/1.2	2.7	14	86	93 (+)
3 [e]	L'1/L2	1/1.5/1.2	2.7	14	100	91 (+)
4	L'1/L3	1/1.5/1.2	2.7	4	20	17 (+)
5	L'1/PPh_3	1/1.5/1.2	2.7	4	56	24 (+)
6	L'4/L2	1/1.5/1.2	2.7	14	19	10 (+)
7	L12	1/0/2.1	2.1	4	85	1 (-)
8	L2	1/0/2.1	2.1	14	4	0
9	BINAPHOS	f	1.1	14	100	60 (+)
10	L'1/L2	1/1.5/1.5	3.0	14	100	92 (+)
11	L'1/L2	1/1.5/1	2.5	14	100	92 (+)
12	L'1/L2	1/2/1	3.0	14	100	93 (+)
13	L'1/L2	1/1.2/1	2.2	14	100	64 (+)
14	L'1/L2	1/0.5/0.5	1.0	14	100	9 (+)
15	L'2/L3	1/1.5/1.2	2.7	4	5	3 (+)
16	L12/L2	1/0/1.5/1.2	2.7	4	5	8 (+)
17	L12/L2	1/0/1.2/0.2	1.4	14	100	6 (+)

[a] Reaction conditions: 1 mmol of substrate **1**, 5 mol% $Rh(COD)_2BF_4$, CH_2Cl_2, 12 bar H_2, 25 °C, 20 eq. dipea (diisopropyl ethyl amine). [b] The time required for the reaction to go to completion based on H_2 uptake and GC analysis. [c] Conversion and ee were determined by chiral GC (Chiralsil-DEXCB); The optical signs in brackets are referenced to literature data.[5 a] [d] 1 mol% catalyst. [e] 1in the absence of 20 eq. dipea. [f] 1.1 eq. with respect to Rh.

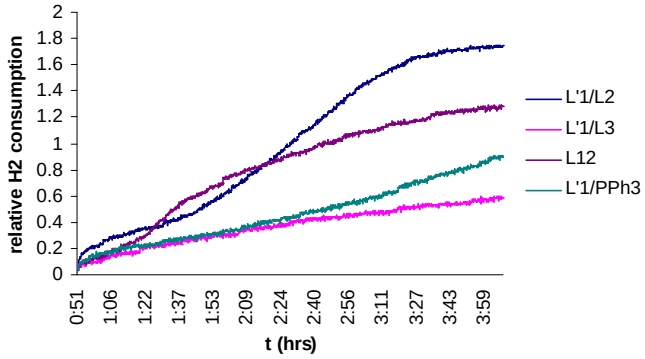


Chart 1 Kinetic profiles (relative H_2 consumption in time) of the hydrogenation experiments comparing catalysts based on SURPRAphos ligands L'1/L2, L'1/L3 with those based on L1/PPh_3 and L12. After 4 hrs the conversion was measured by GC, see table 4

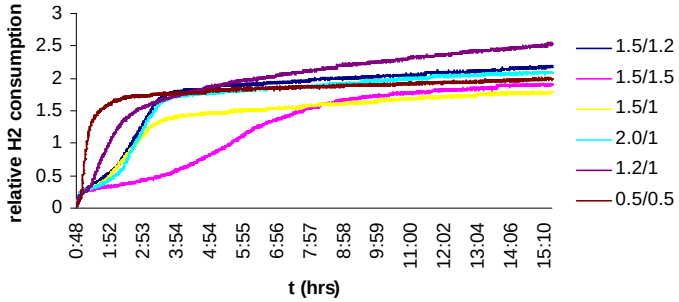


Chart 2 Kinetic profiles (relative H_2 consumption in time) of the hydrogenation experiments comparing catalysts based on SURPRAphos ligands L'1/L2 using different ratio of L'1/L2. After 14 hrs, the conversion was measured by GC, see table 4

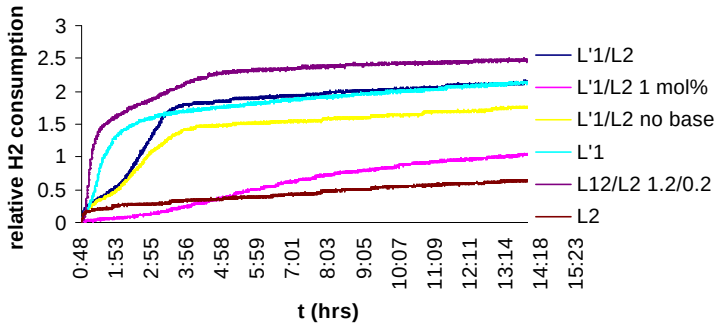
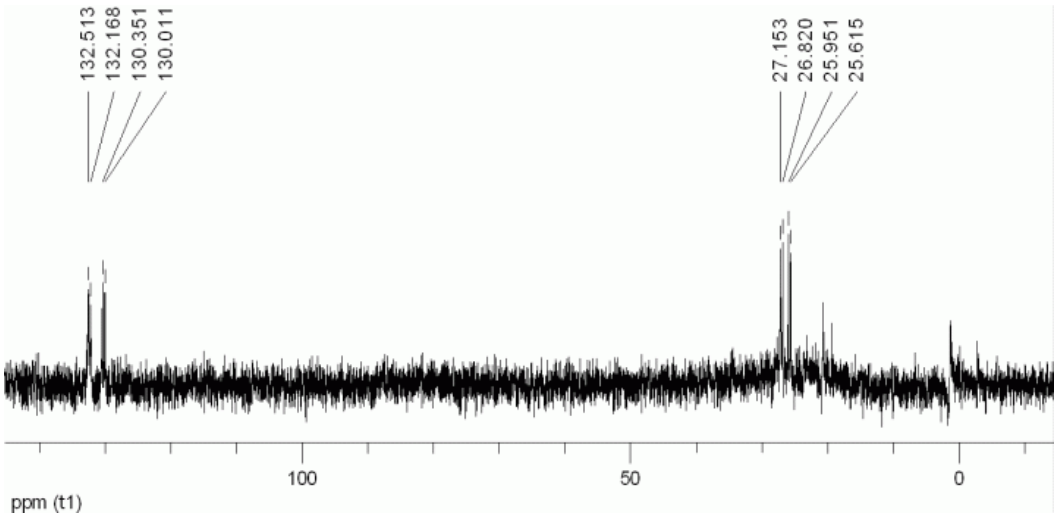


Chart 3 Kinetic profiles (relative H_2 consumption in time) of the hydrogenation experiments comparing catalysts based on SURPRAphos ligands L'1/L2 (various conditions) with control experiments. After 14 hrs the conversion was measured by GC, see table 4.

^{31}P NMR of $Rh(COD)_2BF_4$/L'1/L2 = 1/1.5/1.2 in CD_2Cl_2



For phosphite: $J_{P\text{-}P}$ = 41Hz, $J_{Rh\text{-}P}$ = 263 Hz; for phosphine: $J_{P\text{-}P}$ = 41 Hz, $J_{Rh\text{-}P}$ = 146 Hz.