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Rh-catalyzed linear hydroformylation of styrene†‡

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Usually the Rh-catalyzed hydroformylation of styrene predominantly yields the branched, chiral aldehyde. An inversion of regioselectivity can be achieved using strong π-acceptor ligands. Binaphthol-based diphosphite and bis(dipyrrolyl-phosphorodiamidite) ligands were applied in the Rh-catalyzed hydroformylation of styrene. High selectivities up to 83% of 3-phenylpropanal were obtained with 1,1-bi-2-naphthol-based bis(dipyrrolyl-phosphorodiamidite) with virtually no hydrogenation to ethyl benzene. The coordination chemistry of those ligands towards Rh(I) was investigated spectroscopically and structurally.

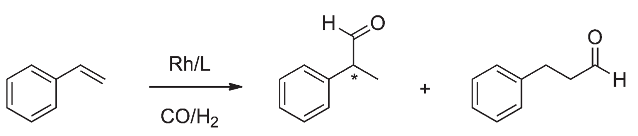
Introduction

The hydroformylation reaction is an atom efficient route for the functionalization of alkenes towards aldehydes.[1] Aldehydes are versatile intermediates for the synthesis of various fine chemicals.[2] Styrene is an often applied model substrate in the hydroformylation reaction of vinylarenes and usually the branched product that contains a stereogenic center is formed predominantly (Scheme 1). Especially, using rhodium catalysts with sigma-donating ligands such as triphenylphosphine (or without phosphorus ligands) the branched product is predominantly formed.[3,4]

However, especially in pharmaceutical chemistry, catalysts that selectively produce the linear aldehyde gain more and more interest, also because their synthesis *via* other routes is often cumbersome. The linear 3-phenylpropanal is also accessible *via* selective hydrogenation of the C–C double bond in cinnamaldehyde or *via* oxidation of the hydroxyl moiety in 3-phenylpropanol with *e.g.* CrO_3.

A few examples concerning hydroformylation of styrene towards the linear product exist in the literature. Sémeril *et al.* showed *l*/*b* ratios of about 3 in the Rh-catalyzed hydroformylation of styrene with calixarene-based diphosphites.[5] Reek and co-workers used a small library of SUPRAPhos phosphine–phosphoroamidite ligands and obtained 72% of the linear aldehyde (*l*/*b* = 2.6).[6] The catalyst that shows the highest selectivity towards 3-phenylpropanal was recently described by Zhang *et al.* Their substituted tetraphosphorus/Rh catalyst shows *l*/*b* ratios of up to 96% (*l*/*b* = 22) in this reaction.[7a]

Relatively few studies on the mechanism of the hydroformylation of styrene to the linear product have appeared in the literature.[7b] The proposed catalytic cycle is depicted in Fig. 1. Lazzaroni and co-workers have shown that at lower temperatures



Scheme 1 Hydroformylation of styrene.

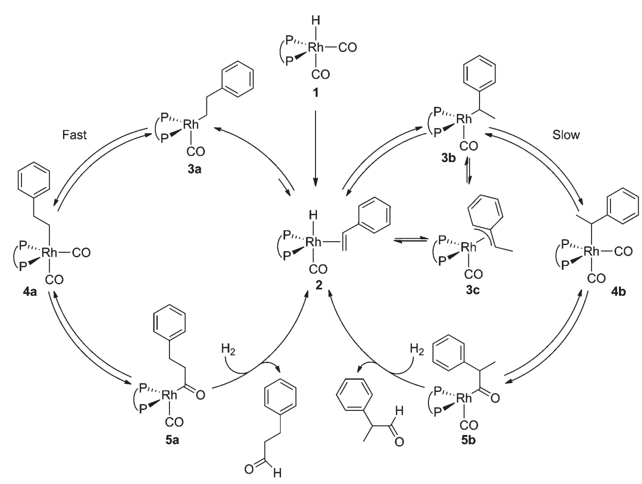


Fig. 1 Generally accepted mechanism for the hydroformylation of styrene.

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†Dedicated to Professor David Cole-Hamilton on the occasion of his retirement and for his outstanding contribution to transition metal catalysis.

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(room temperature) the kinetic, branched product is predominantly formed and deuterium labeling studies prove that the formation of both the linear and the branched alkyl species **3** is not reversible at low temperatures.[4] At higher temperatures, the insertion into the Rh–H bond becomes reversible. The branched alkyl species **3b** can convert back to complex **2** under β-hydrogen elimination, whereas this happens to a far lesser extent for the linear alkyl species **3a**. Complexes **3a** and **3b** are coordinatively and electronically (16 VE) unsaturated. However, complex **3b** can also become saturated by forming the 18 VE η^3-complex **3c**. This equilibrium slows down the formation of complex **4b**. On the other hand, complex **3a** can only form an 18 electron complex *via* coordination of CO. Therefore, the coordination of CO (**3a** to **4a**) is very fast.[8]

Here we report a group of π-accepting bidentate phosphorus ligands in the selective Rh-catalyzed styrene hydroformylation reaction and the tunability of the reaction outcome either to the branched or to the linear aldehyde.

Results and discussion

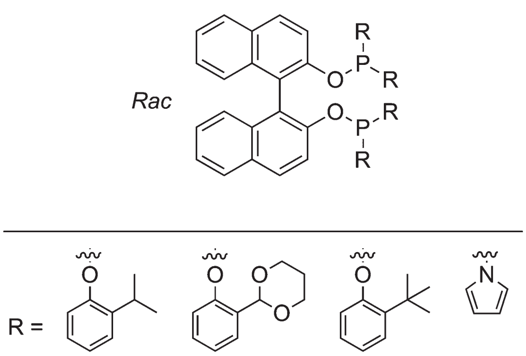
Synthesis

Binaphthol-based ligands have been applied in various homogeneously catalyzed reactions.[9a,b] Diphosphite ligands based on binaphthol, for example, have been applied in the hydrocyanation of styrene and 1,3-cyclohexadiene.[10,11] Bini *et al.* used binaphthol-based diphosphites in the hydrocyanation of styrene towards the linear product.[12]

Reaction of 2 equiv. of the appropriate substituted phenol or pyrrole with PCl_3 in the presence of Et_3N and subsequent reaction with half an equivalent of binaphthol resulted in the ligands **L1–L4** in reasonable to good yields (Fig. 2).[10] Ligands **L5**[7] and **L6**[13] are among the best performing ligands reported in the literature for the hydroformylation of respectively styrene and 1-octene and are used for comparison purposes (Fig. 3).

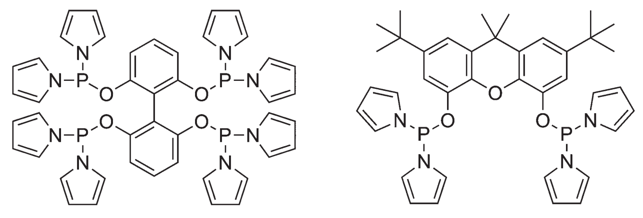
In order to obtain structural information for the precatalysts, attempts to crystallize the selected complexes were made. Crystals of [Rh(acac)**L4**] were obtained from a mixture of toluene and methanol at room temperature. Fig. 4 shows the molecular structure of [Rh(acac)L4] in the crystal as well as selected bond lengths and angles. The coordination geometry around the Rh center is square planar (angle sum 360.04(9)°) with both enantiomers of the complex present in the crystal, since racemic 1,1′-bi-2-naphthol was used in the synthesis.

Crystals of [Rh(acac)L6] were obtained from acetonitrile. The molecular structure in the crystal is depicted in Fig. 5,



L1 **L2** **L3** **L4**

Fig. 2 Binaphthol-based ligands **L1–L4**.



L5 **L6**

Fig. 3 Phosphorodiamidite ligands **L5** and **L6**.

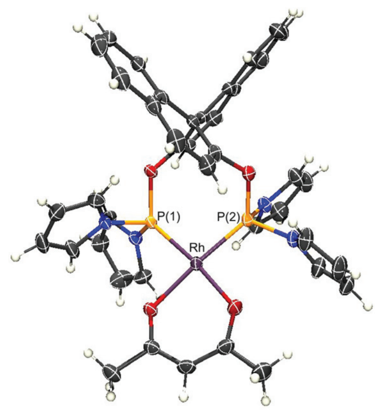


Fig. 4 The molecular structure of [Rh(acac)L4] in the crystal. Displacement ellipsoids are drawn at a 50% probability level. Only one of two independent molecules is shown. Disordered toluene solvent molecules have been omitted for clarity. Selected bond lengths (Å): Rh1–P11 = 2.1674(6), Rh1–P21 = 2.1490(6), Rh1–O31 = 2.0478(16), Rh1–O41 = 2.0587(16). Bite angle (°): P11–Rh1–P21 = 99.00(2).

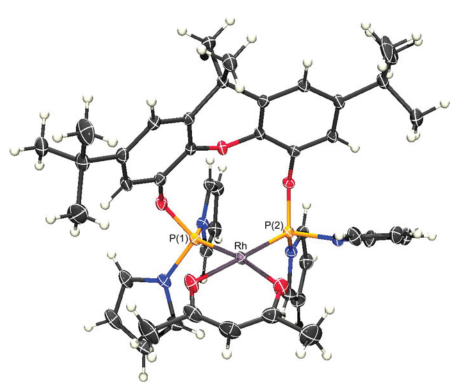


Fig. 5 The molecular structure of [Rh(acac)L6] in the crystal. Displacement ellipsoids are drawn at a 50% probability level. Selected bond lengths (Å): Rh1–P1 = 2.1489(4), Rh1–P2 = 2.1635(4), Rh1–O4 = 2.0434(10), Rh1–O5 = 2.0523(10). Bite angle (°): P1–Rh1–P2 = 93.183(14).

along with selected bond lengths. The coordination geometry around the central Rh atom is square planar (angle sum 359.91(6)°) and the bite angle is 93.183(14)°, which is relatively small.

Electronic properties

Ni carbonyl complexes are well known to be generated quantitatively from diphosphines and CO as shown in Fig. 6 and their IR spectra are a useful probe for the electronic properties. For this reason, Ni carbonyl complexes were prepared *in situ* with ligands **L1–L6**. Reaction of 1 equiv. of the bidentate ligands depicted in Fig. 2 and Fig. 3 with [Ni(cod)$_2$] in toluene led to the corresponding [Ni(cod)L] complexes. Purging the toluene solutions with carbon monoxide for 30 s, during which the color of the solution turned from yellow to colorless, afforded the corresponding [Ni(CO)$_2$L] complexes (Fig. 6).[14]

The Ni(0) complexes were investigated by means of IR spectroscopy in the ATR mode. By evaluating the A_1 and B_1 frequencies of the CO ligands, the electronic properties of the phosphorus ligands can be compared.[14] An overview of these frequencies is given in Table 1.

Ligands **L1–L6** show relatively high values for the A_1 and B_1 frequencies as compared to phosphine and also phosphite ligands.[14b] This means that ligands **L1–L6** have pronounced π-acceptor character.

In situ HP-IR spectroscopy

The coordination mode of ligands to the metal center is of high importance for the selectivity and activity of the corresponding catalyst. The resting state of the rhodium hydroformylation catalyst, HRh(L)(CO)$_2$, shows trigonal bipyramidal geometry. A bidentate ligand can coordinate either in equatorial–equatorial (ee) or equatorial–axial mode (Fig. 7).

The coordination mode of the ligand was studied by means of *in situ* high pressure IR spectroscopy, which enables investigation of the catalyst resting state under 'real' reaction conditions (*i.e.* catalytic Rh concentration, *T*, *p*). Complexes in which the bidentate ligand coordinates in an ee fashion show CO stretch frequencies at higher wave numbers

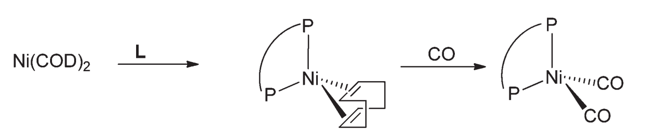


Fig. 6 Synthesis of [Ni(CO)$_2$L] complexes.

Table 1 ATR IR frequencies of the A_1 and B_1 vibrations of CO in [(L)Ni(CO)$_2$]

Entry	Ligand	A_1 (cm^{-1})	B_1 (cm^{-1})
1	**L1**	2041	1987
2	**L2**	2044	1990
3	**L3**	2049	2001
4	**L4**	2048	1993
5	**L5**	2050	1998
6	**L6**	2041	1989

(2075–1970 cm^{-1}) than the corresponding ea coordinated complexes (2030–1920 cm^{-1}).[15]

Fig. 8 shows the carbonyl region of the IR spectrum of the resting states for the three ligands bearing pyrrole substituents. [RhHL4(CO)$_2$] shows absorptions with maxima at 2080 and 2022 cm^{-1} and [RhHL5(CO)$_2$] at 2081 and 2027 cm^{-1}, indicative of an ee coordination mode. [RhHL6(CO)$_2$] shows four absorption maxima at 2070, 2031, 2009, and 1992 cm^{-1}. This suggests that there is more than 1 species present, which might be a mixture of ee and ea complexes. For comparison reasons, the IR data of the bidentate phosphine ligand Xantphos [HRh(Xantphos)(CO)$_2$] are 2039, 1996, 1974 and 1949 cm^{-1}, evidence for the coexistence of both the ee and ea isomers.[16] Application of this ligand showed low linearity in the hydroformylation of styrene with an *l*/*b* ratio of 0.88.[17]

NMR spectroscopy of the resting state complex can give complementary evidence for the coordination mode of the bidentate dipyrrolyl-phosphorodiamidite ligands. These Rh-complexes turned out to be stable when the syngas pressure was released. The hydride resonances observed for the complexes [HRhL4(CO)$_2$] and [HRhL5(CO)$_2$] show a broad singlet (Table 2, and ESI‡), whereas the ^{31}P NMR spectra show a broad

Fig. 7 Coordination mode of a bidentate ligand in the catalyst resting state.

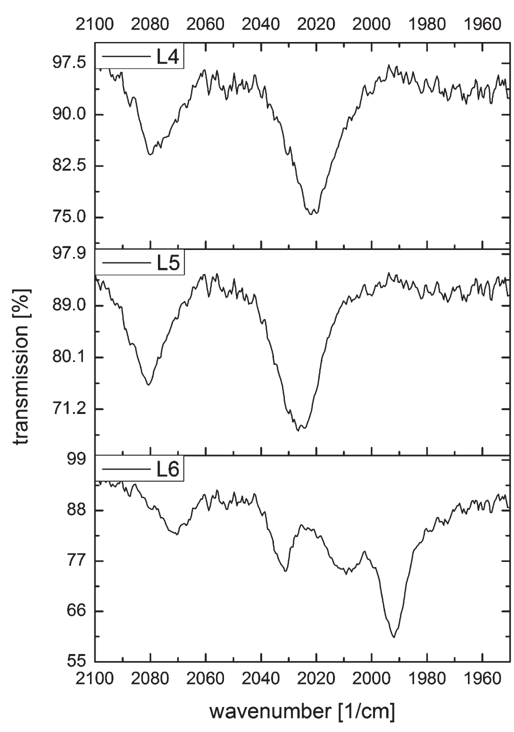


Fig. 8 HP-IR spectra of [HRhL(CO)$_2$], the resting state of the catalyst in the hydroformylation reaction, in 2-methyltetrahydrofuran.

Table 2 Spectroscopic data of [HRhL(CO)$_2$] complexes at room temperature

Complex	δ ^{1}H^a (ppm)	δ ^{31}P^a (ppm)	J_{HP} (Hz)	J_{HRh} (Hz)	J_{RhP} (Hz)	$\nu_{CO}{}^b$ (cm^{-1})
HRhL4(CO)$_2$	−10.18 (s)	140.8 (d)	n.d.	n.d.	216.3	2080, 2022
HRhL5(CO)$_2$	−10.72 (s)	141.5 (d)	n.d.	n.d.	212.3	2081, 2027
HRhL6(CO)$_2$	−9.48 (dt)	135.5 (dd)	33.0	4.8	203.7	2070, 2031, 2009, 1992

[a] Measured in toluene-d$_8$. [b] Measured in 2-methyltetrahydrofuran, s = singlet, d = doublet, dt = doublet of triplets.

Table 3 Results of the Rh-catalyzed hydroformylation of styrene at full conversion

Entry	Ligand	*T*	TOF (h^{-1})	Hydrogenation (%)	*l*/*b* ratio	Selectivity to linear (%)
1	**L1**	80	325	<1	0.37	27
2	**L2**	80	1010	<1	0.97	49
3	**L2**	140	13 874	14	7.1	88
4	**L3**	80	—	—	—	—
5	**L4**	80	3900	1	4.9	83
6	**L4**	60	653	<1	2.9	74
7	**L4**	140	11 657	10	4.7	82
8	**L5**	80	2300	<1	5.8	85
9	**L6**	80	7730	<1	2.5	71

Conditions: Rh : L : S = 1 : 2 : 2000, T_{pref} = 80 °C, *p* = 10 bar syn gas (CO/H$_2$, 1 : 1), Rh precursor = Rh(acac)(CO)$_2$, [Rh] = 0.9 mM, solvent = toluene, *l*/*b* ratio is determined by GC after gas-uptake ceased, turnover frequencies (TOF) were determined at 20% conversion and are given in (mol aldehyde)(mol Rh)-1h^{-1}.

doublet. Due to these broad signals we were unable to determine the J_{HP} and J_{HRh} coupling constants. J_{PP} coupling constants were also not observed because the phosphorus atoms are equivalent at room temperature. Complex HRhL6(CO)$_2$ shows a doublet of triplets in the hydride region of the ^{1}H NMR spectrum, with J_{HP} = 33 Hz and J_{HRh} = 4.8 Hz. The corresponding ^{31}P NMR spectrum shows a double doublet, because of phosphorus coupling with both Rh (J_{RhP} = 203.7 Hz) and hydride (J_{PH} = 33 Hz). From these *J* coupling constants in combination with HP-IR data it can be concluded that **L6** exists as both the ee and ea-isomers.

Catalysis: hydroformylation of styrene to the linear aldehyde

The binaphthol-based ligands, depicted in Fig. 2, were applied in the Rh-catalyzed hydroformylation of styrene. Their performance in terms of activity and regioselectivity towards the linear product was compared with ligands **L5** and **L6** (Fig. 3).

After initial screening of the diphosphite ligands **L1–L3** and bis(phosphorodiamidite) ligands **L4** at 80 °C and 10 bar of syngas pressure, the difference in performance was rather pronounced. Whereas catalysts based on ligands **L1**, **L2** and **L4** showed good activity in the reaction (Table 3, entries 1, 2 and 5), the catalyst based on ligand **L3** did not show any conversion (entry 4). The poor activity of the latter might be caused by the sterically demanding *tert*-butyl groups in the *ortho* position of the phenoxy moiety of the ligand. Indeed, ^{31}P NMR of the precatalyst did not show any coordination, *i.e.* only the phosphorus signal of the free ligand was observed (130.3 ppm). For **L2**, a remarkable increase in *l*/*b* from 0.97 to 7.1 was observed when the reaction temperature was increased to 140 °C. Although consequently, an increased hydrogenation of styrene was observed, yielding the by-product ethyl benzene. The pyrrole substituted ligand **L4** clearly shows a significantly higher regioselectivity, with an *l*/*b* ratio of 4.9 at 80 °C. However, the increased regioselectivity at increased temperature does not occur in the catalytic systems with **L4** and **L5**.[7] This is mainly due to the increased hydrogenation of styrene at elevated temperatures. For comparison, two other bis(phosphorodiamidite) ligands (**L5** and **L6**) were tested under the same conditions, with comparable selectivities compared to the catalytic system with **L4**. Remarkably, ligands with more pronounced π-acceptor properties (see Tables 1 and 2) lead to higher selectivities to the linear product under the same conditions. Especially for bis(phosphorodiamidites) **L4–L6**, the trend in π-acceptor properties (Fig. 7) correlates to the achieved regioselectivity. Moreover, the bidentate ee-coordination of **L4** and **L5** in trigonal bipyramidal [HRhL(CO)$_2$] seems to be the preferred isomer in the catalytic cycle to achieve high 3-phenylpropanal selectivity.

Fig. 9a shows that styrene is consumed with pseudo-first order kinetics. A steady increase of 3-phenylpropanal, 2-phenylpropanal and ethyl benzene is illustrated over the first 30 min. Fig. 9b shows that the product distribution remains constant over time. This demonstrates that the hydrogenation activity is not caused by a deactivated hydroformylation catalyst and that the catalyst is stable during the course of the reaction. As a result, the hydrogenation of the olefin is most likely in direct relation with temperature.

The reaction mechanism of the Rh-catalyzed hydroformylation, discussed in the introduction, can explain the increased regioselectivity for the strongly π-accepting ligands **L4–L6**. When applying strong π-acceptor ligands the 16 VE σ-alkyl complexes **3a** and **3b** (see Fig. 1) are destabilized and a higher activity should be observed. For species **3b** (the branched 1-phenyl ethyl species), the unsaturation can also be overcome by forming η^3-stabilized species **3c**. The regioselectivity is now determined by the rate of CO coordination. This causes the exceptionally high *l*/*b* ratios for this kind of ligand, and explains why the *l*/*b* ratio increases when ligands with stronger π-acceptor character are applied.

Conclusions

The Rh-catalyzed hydroformylation of styrene usually yields predominantly the branched product. By careful choice of the ligand, this regioselectivity can be inversed. It was demonstrated that ligands with pronounced π-acceptor properties show both enhanced activity and linearity in this reaction.

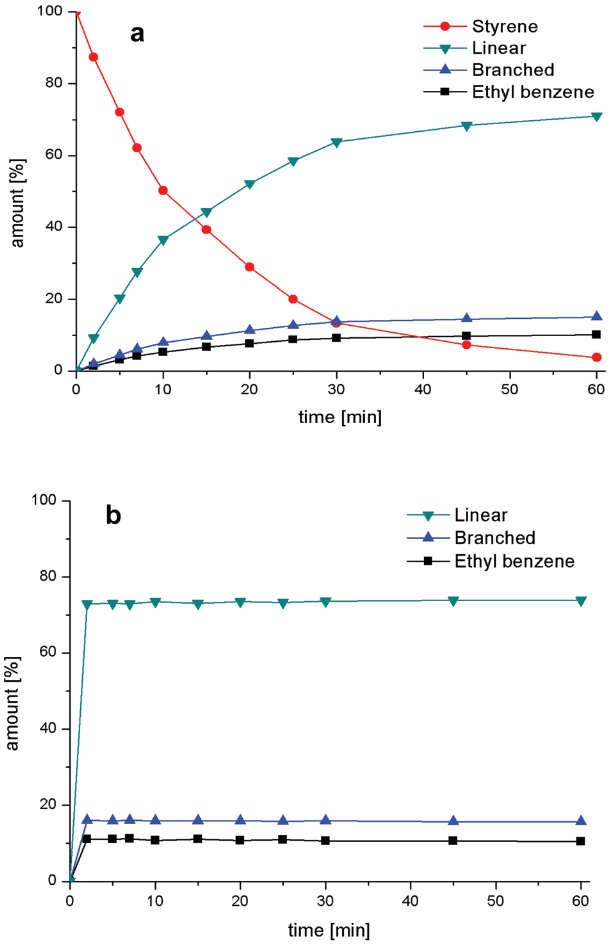


Fig. 9 The hydroformylation of styrene with $[HRhL4(CO)_2]$ monitored in time (a) and the distribution of products in time (b), conditions: T = 140 °C; p = 10 bar CO/H_2 (1 : 1), corresponding to entry 7.

NMR and *in situ* high pressure IR (HP-IR) spectroscopy once more proved to be powerful tools in determining the coordination mode and electronic properties of ligands. IR data show higher CO stretch frequencies for strongly π-accepting ligands on $[Ni(CO)_2L]$ or $[HRhL(CO)_2]$, because electron density is withdrawn from the metal centre. Bis(phosphorodiamidite) ligands (**L4–L6**), being better π-acceptor ligands than diphosphites, show higher regioselectivities to the linear aldehyde already at lower temperatures. Binaphthol-based ligand **L4** (l/b = 4.9) showed a selectivity of 83% towards the linear product with almost no hydrogenation of styrene (and no polymerization), which is very close to the best performing reference ligand **L5** (85%). Further investigation of $[HRhL(CO)_2]$ showed that ligands **L4** and **L5** coordinate in an equatorial–equatorial (ee) fashion to the trigonal bipyramidal rhodium, which seems to be required to obtain high linearity in hydroformylation. For $[HRhL6(CO)_2]$ both the ee and ea-isomers were detected by infrared spectroscopy. Furthermore, the catalytic system with *e.g.* the diphosphites can be tuned by simply increasing the reaction temperature, although more hydrogenation is typically observed at higher temperatures. Ligand **L2** showed an l/b increase from 0.97 to 7.1 when increasing the reaction temperature from 80 °C to 140 °C.

Experimental section

General procedure for the hydroformylation reactions

$[Rh(acac)(CO)_2]$ (1 equiv., 14.4 μmol, 3.7 mg) and the ligand (2 equiv., 28.8 μmol) were dissolved in 15 ml toluene for the preformation of the catalyst (1 h, 10 bar syngas, 80 °C). Then styrene (2000 equiv., 28.8 mmol) was diluted with toluene to 5 ml and added to the catalyst solution. Catalytic conversions were determined by gas chromatography (GC) on an ULTRA 2 column (25 m × 0.20 mm) using decane as an internal standard. Retention times were compared with authentic samples.

Acknowledgements

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