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Novel rhodium catalyst for asymmetric hydroformylation of styrene: Study of electronic and steric effects of phosphorus seven-membered ring ligands

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Abstract

The asymmetric hydroformylation of styrene catalysed by rhodium complexes modified by monodentate phosphepine ligands has been investigated. The effects of a systematic variation of the phosphorus substituent on catalytic activity and selectivity are reported as well as the outcome of a combinatorial approach for the formation of mixed ligands complexes with several commercially available ligands. Effective catalytic systems have been devised for the reaction that provide for full conversion within 24 h and regioselectivity up to 96% in the branched aldehyde and enantioselectivities up to 48%. The use of bidentate ligands built up by binaphthyl-supported seven-membered phosphacyclic units does not allow for further improvement in the reaction outcome.
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Keywords: Asymmetric hydroformylation; Rhodium; Monodentate phosphines

1. Introduction

Transition metal-catalysed hydroformylation is a powerful and efficient homogenous catalytic reaction, which provides for the one-carbon chain elongation of an alkene with the simultaneous introduction of a versatile aldehyde group with 100% atom efficiency. On the industrial level, hydroformylation has found several applications, most importantly the production of linear aldehydes or plasticiser alcohols (over six million tonnes per year of oxo products produced worldwide) [1]. In contrast to that, its asymmetric version has not yet reached general accessible applications, in spite of being highly valuable for pharmaceutical and agrochemical manufacturers as well as for academic research. Enantioselective hydroformylation (AHF) has been extensively studied mainly on some common terminal olefins, such as styrene, vinyl acetate and allyl cyanide [2]. Styrene is one of the benchmark substrates for this version since it provides a straightforward method for the preparation of aryl propionic acids, an important class of non-steroidal anti-inflammatory agents (Scheme 1) [3].

Nevertheless, highly enantioselective hydroformylation has been obtained with only few catalytic systems. The most successful catalysts are based on rhodium complexes activated by chiral bidentate phosphorus ligands. At variance of Pt/Sn complexes, which are highly enantioselective but produce a high share of hydrogenated products, rhodium complexes are able to react very selectively in hydroformylation. Hence, the challenge in the Rh-catalysed AHF is to couple the high chemo- and regioselectivities with an elevated stereoselection. In mid-1990s, the discovery of bis-phosphites [4] and of the phosphine–phosphite Binaphos **8** [5] led to a breakthrough in this field, allowing to reach up to 95% ee for the AHF of many olefins. More recently, several ligands based on rigid bisphosphacycles [6], phosphine–phosphoramidites [7], bis(diazaphospholidine) [8], and diphospholane [9] ligands have been found to deliver excellent enantioselection.

Most significant advances in this field are summarised in Fig. 1. It is apparent that all the best performing chiral ligands are

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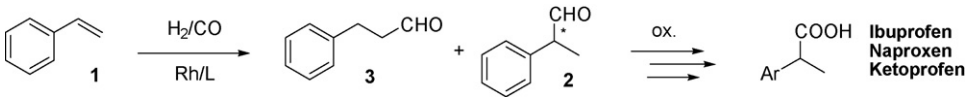


Scheme 1. Rhodium-catalysed hydroformylation of styrene.

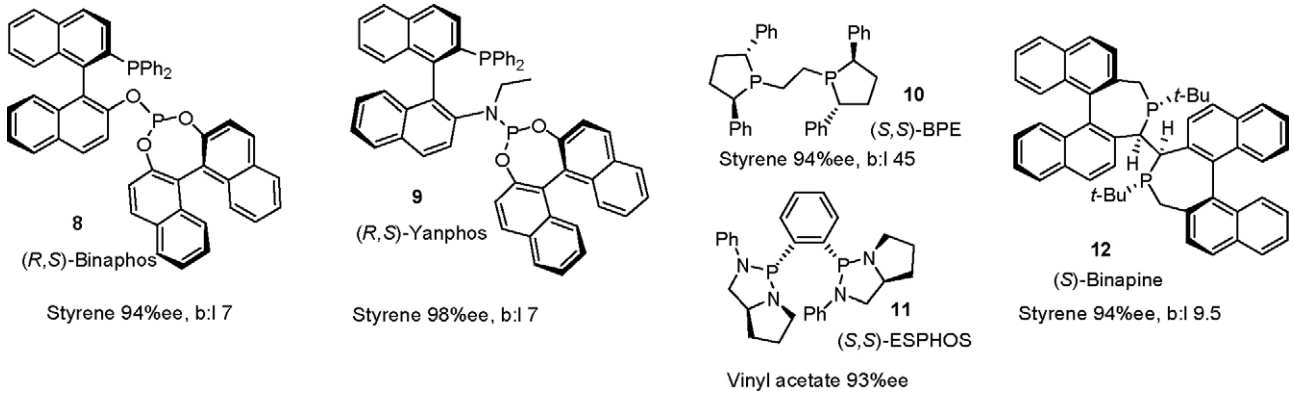


Fig. 1. Selected important ligands for asymmetric hydroformylation.

bidentate and feature two P-donors, which allow for the chelate binding to the metal. The use of monodentate chiral modificators in asymmetric hydroformylation has been much less explored and their scope in this reaction is substantially unknown.

During our ongoing research on enantioselective hydrogenation, we have developed a convenient synthesis of new ligands based on a 2,2′-dimethyl-1,1′-binaphthyl scaffold, such as amino phosphinite [10], phosphepine [11] and chelating ligands [12] (Fig. 2). Recently, many chiral ligands useful in asymmetric hydrogenation were also successfully employed in hydroformylation and *vice versa* [6]. This prompted us to assess our ligand toolbox based on this structure in the enantioselective hydroformylation of styrene. The electronic effect of the substituent was also investigated as well as the possibility to exploit commercially available ligands in a combinatorial approach aimed at improving catalyst selectivity.

2. Results and discussion

Pioneering research done by Gladiali et al. [13] in the 1990s reported the activity of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **4a** in the asymmetric hydroformylation of styrene in the presence of $Rh(CO)_2(acac)$ as the catalyst precursor. The best ee obtained at that time (20%) is apparently still now the highest for a monodentate ligand in this reaction. Having a variety of ligands with this structure on hand, we thus decided to investigate this catalytic system more in detail.

Initially, we set out to identify the optimal conditions for our ligand system, based on the preliminary study mentioned above. The catalyst was prepared *in situ* by mixing $Rh(CO)_2(acac)$ in the solvent of choice with 8 equiv. of ligand **4a**. Some representative results are given in Table 1. As already reported for other hydroformylation catalysts, the best activities and selectivities were obtained in apolar solvents such as toluene or CH_2Cl_2

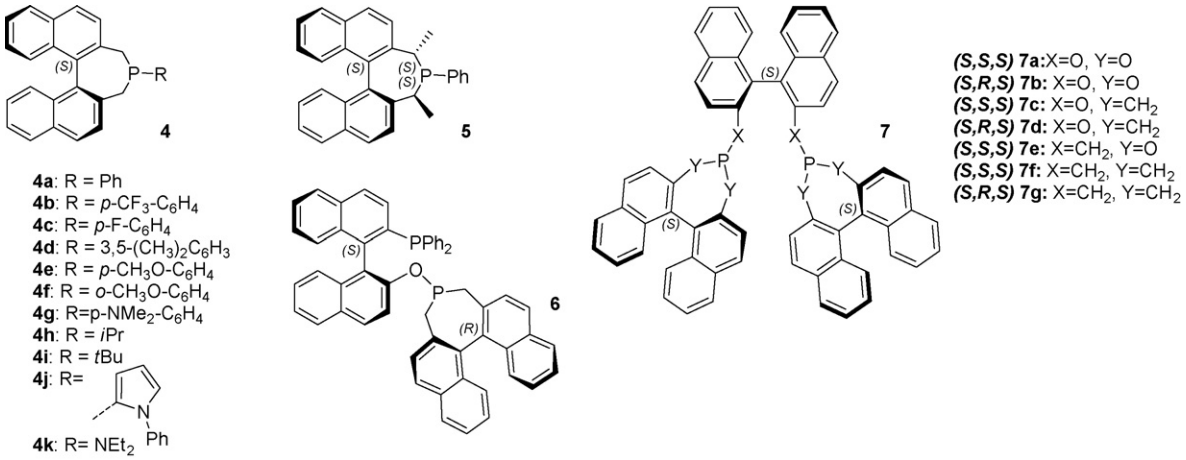


Fig. 2. Ligands based on 2,2′-dimethyl-1,1′-binaphthyl.

Table 1
Styrene AHF—parameters influence

Entry	Solvents	T (°C)	pH_2/CO (bar)	Rh/L	Time (h)	Conversion (%)	*Iso*/*n*	ee (%)
1	Toluene	60	60	1/8	24	87	13.6	29
2	CH_2Cl_2	60	60	1/8	24	90	14.0	26
3[a]	THF	60	60	1/8	24	81	11.2	17
4	Acetone	60	60	1/8	24	48	10.6	19
5	Toluene	25	60	1/8	24	13	18.4	32
6	Toluene	45	60	1/8	24	44	15.6	28
7	Toluene	80	60	1/8	24	99	26.5	24
8	Toluene	60	10	1/8	24	58	7.5	14
9	Toluene	60	20	1/8	24	82	10.8	21
10	Toluene	60	40	1/8	24	85	12.6	29
11	Toluene	60	80	1/8	24	80	14.5	31
12	Toluene	60	40	1/4	24	>99	16.0	30
13	Toluene	60	40	1/2	24	>99	14.4	20
14[b]	Toluene	60	40	1/4	2	20	69	30

All reactions were performed on 1.5 mmol of styrene in 1.5 mL solvent with appropriate amount of $Rh(CO)_2(acac)$ and ligand **4a**, pressurised with gas mixture H_2/CO 1:1. The enantiomeric excess is expressed as excess of the (*R*) enantiomer. No hydrogenation or other byproducts were observed.
[a] 15% hydrogenated product formed at 30 bar H_2/CO pressure.
[b] TOF = 146 h^{-1}.

(Table 1, entries 1 and 2), while more polar solvents showed low conversion (Table 1, entry 4) and/or low chemoselectivity (Table 1, entry 3). An increase in the temperature from 60 °C to 80 °C led to improved activity and regioselectivity, but to a lower enantioselectivity (Table 1, entry 7). In contrast to that, a reduction in temperature impaired the catalytic activity and was accompanied by only slight increase of regio- and enantioselectivity (Table 1, entries 5 and 6). The pressure dependency of the catalytic system is not pronounced, since activity and selectivity did not change that much in between 20 bar and 80 bar (Table 1, entries 9–11 and 1). Gas pressure lower than 20 bar does not allow to achieve full conversion and the selectivity is negatively affected. A lower ligand loading was also investigated and interestingly 4 equiv. of ligand with respect to rhodium were able to convey the same transfer of chirality, while increasing the activity of the catalyst. Full conversion within 24 h was also achieved with a lower ratio of ligand/rhodium, but this was accompanied by a remarkable loss of enantioselection

In summary, the hydroformylation of styrene with an *in situ* formed rhodium catalyst of **4a** under optimal conditions (toluene, 60 °C, 40 bar H_2/CO, [substrate]/L/Rh = 2000/4/1) leads to the branched aldehyde **2** in excellent yields but in modest enantioselectivity.

In the recent years several ligands based on the 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine structure **4a** have been synthesised and/or employed in asymmetric hydrogenation from our group: alkyl (**4h** and **4i**) and aryl (**4a**–**g** and **4j**) phosphorus-substituted [11] and α,α′-alkylated [14] (**5**) monodentate phosphepines as well as bidentate phosphine (**7f** and **7g**), phosphonite (**7e**), phosphinite (**7c** and **7d**) and phosphite (**7a** and **7b**) ligands [12]. Additionally, following the success of Binaphos **8** in the asymmetric hydroformylation of a broad range of olefins [5], a new ligand with this structure motif has been synthesised, the bidentate phosphino-phosphinite binaphthylphosphepine (**6**).

Based on the best conditions for ligand **4a**, diverse monodentate ligands were tested in the reaction and the effect of the

Table 2
Styrene hydroformylation catalysed by rhodium complexes of monodentate phosphorus ligands

Entry	Ligand	L/Rh	Conversion (%)	Yield (%)	*Iso*/*n* (%)	ee (%)
1	**4a**	8	85	85	12.6	29(*R*)
2	**4b**	8	88	83	11.9	14(*R*)
3	**4c**	8	99	99	14.2	22(*R*)
4	**4d**	8	>99	92	13.9	20(*R*)
5	**4e**	8	99	94	18.2	28(*R*)
6	**4f**	8	95	95	11.6	16(*R*)
7[a]	**4g**	8	>99	95	21.5	38(*R*)
8	**4h**	8	94	93	6.7	16(*R*)
9	**4i**	8	89	86	6.0	17(*R*)
10	**4j**	8	>99	99	10.5	12(*R*)
11[a]	**4k**	4	>99	87	17.4	23(*R*)
12[a]	**5**	8	>99	>99	25.0	15(*R*)
13[b]	**4g**	4	17	17	nd	48(*R*)

All reactions were performed at 60 °C in toluene with 40 bar 1:1 H_2/CO gas mixture, substrate/Rh = 2000, 1.0 M styrene concentration and 24 h reaction time. No hydrogenation or other byproducts were observed.
[a] TOF (after 2 h) = 381 h^{-1} (**4g**), 362 h^{-1} (**4k**) and 493 h^{-1} (**5**).
[b] 25 °C.

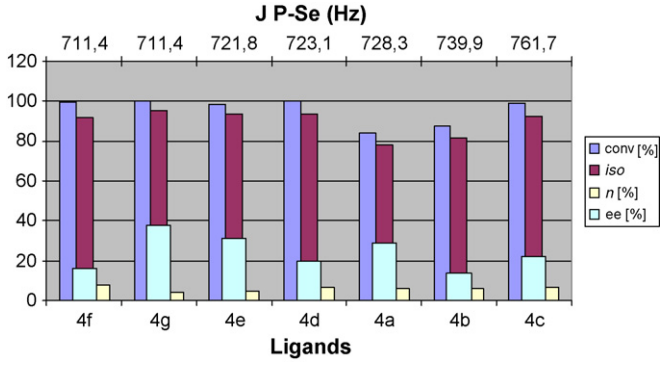


Fig. 3. Graphical representation of activity and selectivity in hydroformylation of styrene in relation to the coupling constant $^1J_{P-Se}$ of the aryl binaphthophosphepines.

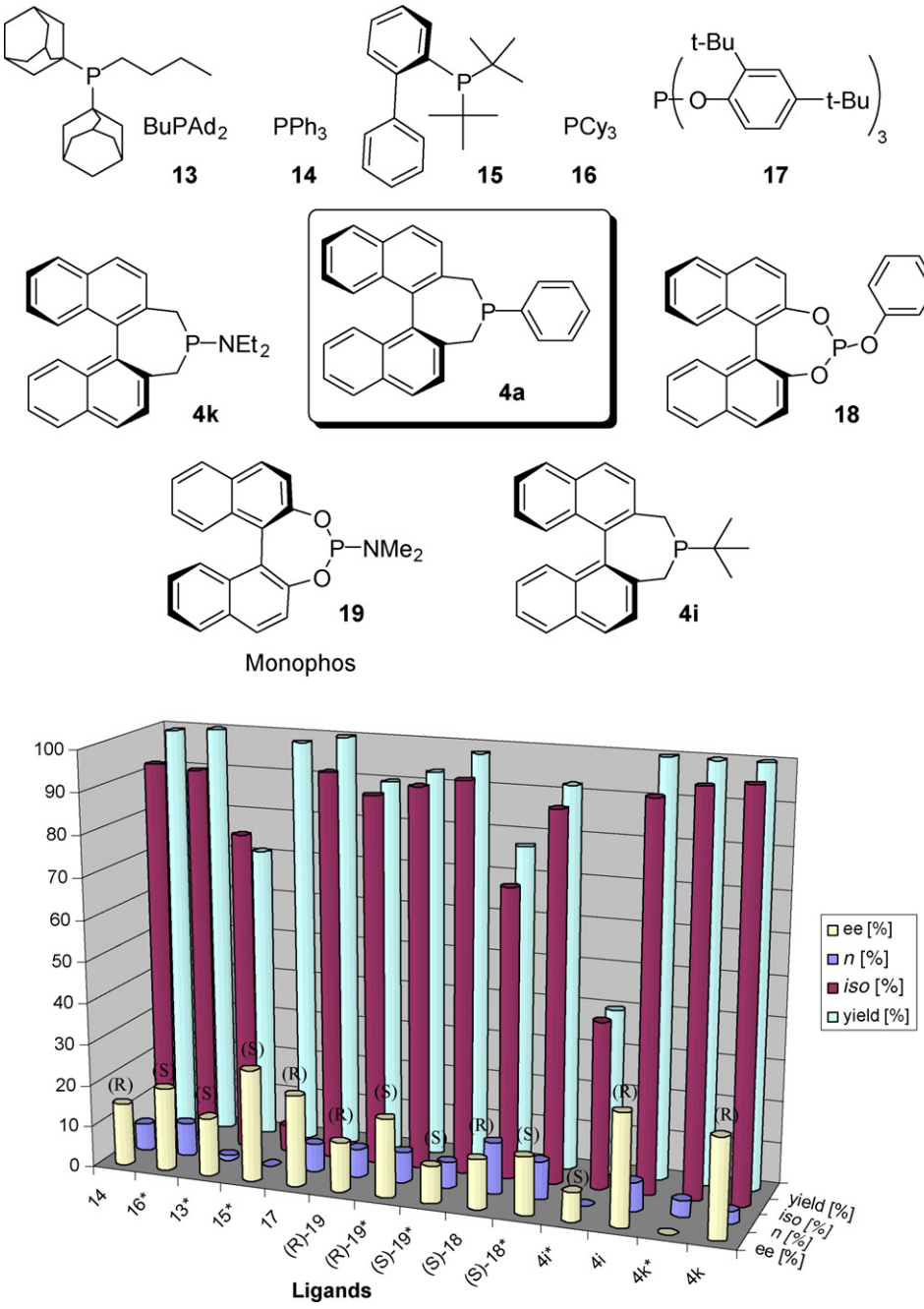
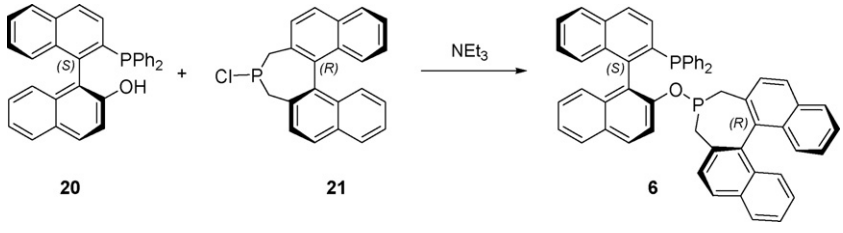


Fig. 4. Monodentate ligands for combinatorial approach and graphical representation of hydroformylation of styrene using combination of those ligands with **4a**. All reactions were performed at 60 °C in toluene with 40 bar 1:1 H_2/CO gas mixture, L_1/L_2/Rh = 2/2/1, substrate/Rh = 2000, 1.0 M styrene concentration and 24 h reaction time. L_1 is (*S*)-Binepine **4a** if not differently stated. *L_1 is (*R*)-Binepine **4a**.



Scheme 2. Synthesis of enantiopure (*S*,*R*)-4-(2′-(diphenylphosphino)-1,1′-binaphthyl-2-yloxy)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepine **6**.

substitution pattern was monitored. The electronic properties of those ligands have been examined in detail by measuring the amplitude of the first order coupling between P and Se of the corresponding selenides. This method has been already proved very reliable for assessing the donating ability of the phosphorus lone-pair orbital (smaller coupling constant corresponding to a more basic phosphine and *vice versa*) [15]. The selenides were readily prepared by mixing the phosphine and elemental selenium in refluxing deuterated chloroform, and the coupling constant $^{1}J_{P–Se}$ was measured without isolation of the product. The results are summarised in Table 2 and Fig. 3. In the case of lower electron density on the phosphorus (**4b**) the catalyst activity is unaltered and the enantioselection significantly decreased (**4b** and **4c**). Strong donating (**4e** and **4g**) substituents on the phenyl rest boosted the regioselectivity in the branched aldehyde (Table 2, entries 5 and 7) and tend to improve the transfer of chirality (Table 2, entries 7 and 13, ligand **4g**). A comparison of *para*- and *ortho*-substitution of methoxy-substituted aryl phosphepine (**4e** and **4f**) showed a negative steric influence on the enantioselectivity of the *ortho*-substitution. As shown in Fig. 3, there is no linear correlation between basicity of the phosphorus and activity or selectivity of the catalysts for this class of ligands. Alkyl-substitution at phosphorus (**4h** and **4i**) induced similar lower ee's and a remarkable loss of regioselectivity. Substitution on the phosphepine ring with methyl groups in the (*S*,*S*)-configuration led to an improvement in the regioselectivity and in the catalytic activity, but to a decrease in the enantioselectivity. *N*-Phenyl pyrrole ligand **4j** [16] showed comparable regio- and enantioselectivity to the deactivated ligands such as **4b** and **4f**.

The obtained results clearly indicate that the 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligand structure is optimal to convey high activity and regioselectivity in the hydroformylation of styrene, but fails in reaching the level of enantioselection of bidentate ligands like Binaphos **8** [5], Yanphos **9** [17] or BPE **10** [6b].

Nevertheless, the intrinsic advantage of monodentate ligands resides not only in their easier synthesis, but also in the possibility of obtaining mixed ligands complexes. The potential of this approach was for the first time documented by Reetz et al. [17] and Feringa and co-workers [18] for asymmetric hydrogenation of olefins and was later extended to hydroformylation [19]. On the basis of first promising results, we decided to investigate the applicability of our ligands in a combinatorial study. Among the variety of monodentate ligands at our disposal, we chose a subset of ligands, both achiral and chiral, which possess different steric and electronic properties (Fig. 4). Inspired by the structure of the most successful bidentate ligands in asymmetric hydroformylation, combinations of phosphine–phosphite as well as phosphine–phosphoramidite were favoured.

Combinations of ligand **4a** in (*S*) or (*R*) configuration with ligands in Fig. 4 were employed in AHF under the same optimised conditions as mentioned above, with a ligand ratio of 1:1. Unfortunately, none of the mixtures of chiral and achiral ligands led to a significant improvement. The majority of mixtures with achiral ligands like triphenylphosphine **14**, tricyclohexylphosphine **16**, and phosphite **17** left the outcome of the reaction almost unaffected. In comparison to that the chiral combinations with **19** (configurations (*R*,*S*), (*R*,*R*) or (*S*,*R*)) **18** (for the (*S*,*R*) combination) and **4k** ((*S*,*R*) combination) performed slightly worse on average. Achiral ligand **15** and the chiral (*S*)-**4i** and (*S*)-**4k** were found to form the best ligand combination tested, however the results were in the same range observed with ligand **4a** alone (see Table 1). Notably, a remarkable enhancement of regioselectivity was observed in combination with $BuPAd_2$ **13** [20], albeit the activity was impaired and a low enantioselectivity was recorded. The use of (*S*)-**18** and *S*-**4i*** led to significant reductions in all measures.

Table 3
Styrene hydroformylation catalysed by rhodium complexes of bidentate phosphorus ligands

Ligand	L/Rh	Conversion (%)	Yield (%)	*Iso*/*n*	ee (%)
7a (*S*,*S*,*S*)	4	41	40	3.0	25(*S*)
7b (*S*,*R*,*S*)	4	16	14	3.4	23(*S*)
7c (*S*,*S*,*S*)	4	88	83	10.1	16(*R*)
7d (*S*,*R*,*S*)	4	87	84	12.3	3(*R*)
7e (*S*,*S*,*S*)	4	91	91	6.7	2(*R*)
7f (*S*,*S*,*S*)	4	99	97	12.4	12(*R*)
7g (*S*,*R*,*S*)	4	>99	93	3.5	2(*S*)

All reactions were performed at 60 °C in toluene with 40 bar 1:1 H_2/CO gas mixture, substrate/Rh = 2000, 1.0 M styrene concentration and 24 h reaction time.

We moved then our attention to try to achieve higher enantioselectivity via a chelating strategy. Recently, we have reported the synthesis of some novel binaphthyl-derived phosphorus ligands **7c–g** [12]. Additionally, enantiomerically pure (*S*,*R*)-**6** was prepared from (*S*)-(−)-2-(diphenylphosphino)-2′-hydroxy-1,1′-binaphthyl **20** [21] and 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **21** [10] (Scheme 2). Given the similar phosphorus environs to known active ligands in AHF, several bidentate ligands of type **7** and the Binaphos-analogue **6** were also tested in the catalytic reaction. Representative results are displayed in Table 3.

In general the catalyst activity was lower than for the monodentate ligands and in all cases a significant loss of regioselectivity was observed. Applying ligand **6** we did not obtain reproducible results, probably due to decomposition of the ligand.

3. Conclusion

Monodentate ligands based on 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine template have been tested in rhodium-catalysed asymmetric hydroformylation of styrene, where they have proven to form highly active catalysts. Critical reaction parameters that influence the catalyst activity and stereoselectivity were examined in detail. In particular, it was observed that aryl-substitution on the phosphorus is beneficial to the reaction as well as the presence of electron donating substituents on the P-phenyl (i.e. *p*-NMe_2 ligand **4g**), which increase the basicity of the phosphorus, even though such a general correlation have not been confirmed. Moreover, the possibility of a combinatorial approach for improving the system was studied. Contrary to our expectations, bidentate ligands assembled with the dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine unit

did not result in improved enantioselectivity. The best ee reported with ligand **4g** (48%), albeit modest, is the highest ever recorded in the asymmetric hydroformylation of styrene with a monodentate chiral inducer.

4. Experimental

4.1. General

All the reactions were carried out in oven-dried glassware using standard Schlenk techniques under argon atmosphere. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker Spectrometer AVANCE 400 and 300 (^{1}H: 400.13 MHz, and 300.13 MHz; ^{13}C: 100.6 MHz, and 75.5 MHz; ^{31}P: 162.0 MHz). The calibration of ^{1}H and ^{13}C spectra was carried out on solvent signals (δ ($CDCl_3$) = 7.25 and 77.0). The ^{31}P chemical shifts are referenced to 85% H_3PO_4. Mass spectra were recorded on an AMD 402 spectrometer. Optical rotations were measured on a Gyromat-HP polarimeter. IR spectra were recorded as KBr pellets or Nujol mulls on a Nicolet Magna 550. Toluene was distilled from sodium benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Ethanol and 2-propanol were distilled from Na under argon. Methylene chloride was distilled from CaH_2 under argon. Ligands **4a**–**i**, **4k**, **5**, **7c** and **7d** were synthesised according to our previously published protocols [10–12,14]. Ligands (*S,S,S*)-**7** and (*S,R,S*)-**7** were easily prepared according to literature protocols [10,22]. (*S*)-2′-(Diphenylphosphino)-1,1′-binaphthyl-2-ol **20** [21] and 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **21** [10] were obtained by the synthetic route described in the literature.

4.2. Ligand synthesis

4.2.1. (S)-4-(2-(1-Phenyl)-pyrrol)-4,5-dihydro-3H-dinaphtho[2,1-c;1′,2′-e]phosphepine (4j)

To a cooled (0 °C) solution of *N*-phenylpyrrol (6.98 mmol) in *n*-hexane (25 mL) was dropwise added *n*-butyllithium (1.6 M in *n*-hexane, 6.98 mmol) in *n*-hexane (10 mL) subsequently followed by *N,N,N′,N′*-tetramethylethylendiamine (7.2 mmol). The obtained yellow solution was stirred for 1 h at room temperature, while some precipitate was formed. The flask was stored for 2 days at −30 °C until crystals were formed. The supernatant solution was removed via a tube and the crystals were washed two times with *n*-hexane (5 mL). After drying in vacuum colourless crystals were obtained in a yield of 63%. The complex of *N*-phenyl-2-lithiumpyrrol and *N,N,N′,N′*-tetramethylethylendiamine (4.37 mmol) was dissolved in THF (40 mL) and added to a solution of (*S*)-4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine **21** (4.37 mmol) in THF (25 mL) at −78 °C during a period of 2 h. The obtained red solution was slowly warmed to room temperature (12 h) and refluxed for 2 h. After removal of the solvent, the residue was dissolved in toluene (25 mL) and water (15 mL). The aqueous layer was separated via a syringe and the organic layer was dried over $MgSO_4$. The obtained crude product, after solvent removal, was dissolved in CH_2Cl_2 (40 mL) and H_2O_2 (1 mL) was added and stirred for 24 h. Afterwards the aqueous layer was removed and the organic layer was washed with water (2× 20 mL) and dried over Na_2SO_4. The crude product obtained after removal of the solvent was purified by flash column chromatography (*n*-hexane:ethyl acetate 1:1, $R_f = 0.11$) to yield a colourless foam. Subsequently, it was dissolved in toluene and reacted with triethylamine (1.9 mmol) and trichlorosilane (2.05 mmol) under refluxing conditions for 6 h. The solution was cooled to room temperature and sodium hydroxide (12.5 mmol) in degassed water (20 mL) was added. The aqueous layer was separated via syringe and the organic phase was dried over Na_2SO_4. After removal of the solvent, colourless foam was obtained (yield: 76%).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$–6.68 (m, 17H); 6.08 (dd, 1H, $J = 3.57$ Hz, $J = 2.83$ Hz); 5.77 (dd, 1H, $J = 3.77$ Hz, $J = 1.51$ Hz); 2.74 (dd, 1H, $J = 11.68$ Hz, $J = 1.51$ Hz); 2.47 (dd, $J = 16.58$ Hz, $J = 11.68$ Hz); 2.26 (t, 1H, $J = 14.17$ Hz); 2.09 (dd, 1H, $J = 14.11$ Hz, $J = 4.52$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 140.7$; 135.6; 129.5; 135.9; 128.9; 128.2; 127.9; 127.5; 127.45; 127.41; 126.7; 126.6; 126.0; 125.7; 125.61; 125.68; 124.9; 124.8; 120.5; 119.3; 110.4; 109.3; 31.4 (d, $J = 20.98$ Hz, CH_2); 31.0 (d, $J = 20.98$ Hz, CH_2). ^{31}P NMR (121.5 MHz, C_6D_6): $\delta = -18.5$. IR (KBr): 3044 w; 2913 w; 1635 m; 1596 m; 1508 m; 1497 s; 1456 w; 1422 m; 1359 w; 1320 m; 1261 m; 1248 m; 1225 m; 1208 m; 1159 m; 1094 m; 1074 m; 1040 m; 1026 m; 935 w; 866 w; 827 s; 805 m; 752 s; 728 m; 696 s; 671 m; 659 m; 621 m; 605 m; 568 m; 552 m; 526 m; 504 m; 477 m; 455 m; 403 s. MS (ES, 70 eV): *m/z* (%) = 453 ([M^+], 100); 311 (12); 282 (42); 279 (32); 276 (36); 265 (50); 252 (16); 172 (24); 156 (68); 69 (17); 28 (23). HRMS calculated for $C_{32}H_{24}NP$: 453.1641; found: 453.163.

4.2.2. 4-(2′-(Diphenylphosphino)-1,1′-binaphthyl-2-yloxy)-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]phosphepine (6)

2.7 mmol (*S*)-**20** and 1.5 equiv. NEt_3 (distilled from CaH_2) were solved in 40 mL toluene and 2.7 mmol (*R*)-**21** in 20 mL toluene were added. After refluxing for 5 h the reaction mixture was filtrated and the solvent was evaporated. The crude product was cleaned by flash chromatography in ethyl acetate/hexane/NEt_3 (16:80:4).

Pale yellow solid, 50% yield. mp: 236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$–7.94 (m, 3H); 7.91–7.88 (t, 3H); 7.85 (d, 1H, $J = 8.3$ Hz); 7.81 (d, 1H); 7.75 (d, 1H, $J = 8.3$ Hz); 7.57–7.49 (m, 4H); 7.45 (d, 1H); 7.42 (d, 1H); 7.41–7.36 (m, 3H); 7.32 (d, 1H); 7.25–7.1 (m, 9H); 7.06–7.02 (m, 3H); 6.9–6.88 (m, 2H); 6.8 (d, 1H, $J = 8.3$ Hz); 6.27 (d, 1H, $J = 8.3$ Hz); 2.44 (d, 1H, CH_2, $J = 14.9$ Hz); 2.42 (d, 1H, CH_2, $J = 17.5$ Hz); 2.24 (dd, 1H, CH_2, $J = 22.2$ Hz); 2.17 (d, 1H, CH_2, $J = 11.5$ Hz). Selected data: ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 37.7$ (d, CH_2, $J = 25.7$ Hz), 37.3 (d, CH_2, $J = 26.7$ Hz). ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = -14.2$ (d, $J = 11.1$ Hz); 153.6 (d, $J = 9.7$ Hz). IR (KBr, cm^{-1}): 3432 s; 3051 m; 2959 m; 2929 m; 1724 w; 1619 m; 1590 m; 1508 m; 1464 m; 1433 m; 1348 m; 1264 m; 1225 s; 1064 m; 1026 m; 979 m; 814 s; 774 m; 744 s; 695 s; 673 m; 659 w; 621 w; 565 w; 540 w; 517 m; 488 m; 434 w; 417 w. MS (FAB): *m/z* (%) = 765 ([$M^+ + 1$], 25); 720 (3); 641 (2);

580 (75); 454 (31); 437 (100); 375 (6); 311 (35); 299 (23); 281 (50); 265 (78); 252 (25); 207 (22); 183 (48); 147 (96).

4.3. Catalytic experiments

All hydroformylation reactions were carried out in an 8-fold parallel reactor array with 3.0 mL reactor volume.[1] In a typical experiment 1.5 mmol styrene, 0.75 μmol $Rh(CO)_2(acac)$, appropriate ligand amount and 0.3 mmol diglyme as internal standard in 1.5 mL toluene were placed under argon in a Schlenk tube. The autoclave was filled with the solution, purged with syngas (CO/H_2 1:1), allowed to reach the desired temperature (typically 60 °C) and then pressurised to the appropriate initial pressure of the reaction gas. The solution was stirred magnetically at an agitation speed of 300 rpm using a magnetic stirring bar. At the end of the reaction, the autoclave was cooled down and depressurised. The reaction mixture was analysed by gas chromatography. Conversions and composition of the reaction mixture (branched, linear aldehyde and unreacted styrene) were determined by GC (30 m HP5, 35 °C/10 min–8 °C/min–280 °C/30 min, constant flow 1.0 mL/min). The enantiomeric excess was determined by GC analysis on a Lipodex E 50m (85 °C/40 min–4 °C/min–180 °C, constant flow 0.4 mL/min). Absolute configuration of 2-phenylpropionaldehyde **2** was assigned in accordance to literature.

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