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Probing new classes of π-acceptor ligands for rhodium catalyzed hydroformylation of styrene

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Abstract

Three hitherto unexplored classes of strong π-acceptor ligands for use in homogeneous catalysis—phospha-π-aromatic compounds (class **A**), pyrrolyl phosphines (class **B**) and phosphenium cations (class **C**)—have been evaluatated for rhodium catalyzed hydroformylation of styrene. When testing monodentate ligands, the *ortho/ortho′*-disubstituted phosphabenzene derivative **1b** provided a rhodium-catalyst endowed with the highest catalytic activity. Based upon these results a first series of bidentate phosphabenzene ligands have been tailored employing the concept of an electronic differentiation of the two binding sites. An oxazoline/phosphabenzene system **8** which is capable of forming an eight-membered chelation ring gave the best results. Thus, a quantitative conversion of styrene at ambient temperature afforded the desired 2-phenylpropanal in high regioselectivity (25:1).

Keywords: Hydroformylation; π-acceptor ligands; Phosphabenzene-rhodium-catalysts

1. Introduction

Since its discovery in 1938 by O. Roelen, hydroformylation has developed into one of the most important homogeneous catalytic processes [1]. Even though 60 years of intensive research on all aspects of hydroformylation chemistry have passed, the simultaneous control of reactivity and selectivity in the course of the hydroformylation reaction is still a major challenge (for reviews see Refs. [2–4]). A breakthrough was achieved by Wilkinson in 1968 with the discovery of rhodium-phosphine complexes as extraordinarily reactive and selective hydroformylation catalysts [5]. Subsequent extensive studies of these catalysts provided an understanding of the factors that govern reactivity and selectivity [6]: σ-donor ligands may inhibit the reaction completely, switching to stronger π-acceptor ligands such as phosphites leads to more active and more selective hydroformylation catalysts [7–11]. [1] These findings of a ligands π-acceptor ability as a control element of reactivity and selectivity in rhodium catalyzed hydroformylations induced us to explore new classes of strong π-acceptor ligands as modifying ligands for the rhodium catalyzed hydroformylation reaction.

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[1] For the introduction of other interesting classes of new ligands for rhodium catalyzed hydroformylation see Refs. [12–18].

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To be a good π-acceptor ligand, the system should possess either π^* or σ^* orbitals which are well suited in symmetry and energy to overlap efficiently with occupied transition-metal d orbitals. This holds for $\lambda^3\sigma^2$ phosphorus compounds, e.g., phosphabenzenes **1** and phosphaindolizines **2** (class **A**), pyrrolyl-substituted phosphines **3** (class **B**) as well as phosphenium cations **4** (class **C**).

All three classes of compounds are known to form σ-transition metal complexes [19,20], [2, 3] in particular σ-rhodium-complexes are known for class **A** and **B** systems [19,23,24]. A quantitative description of a ligands π-acceptor ability can be made by the electronic parameter χ introduced by Tolman [25]. This would require the IR-spectral data for the $LNi(CO)_3$-complexes of the ligands **1**, **2** and **3**. Whereas these complexes are unknown, their CO-stretching frequencies may be estimated from the IR spectra of the known $LCr(CO)_5$ complexes for **1** [26] and **2** [27] and a $LFe(CO)_4$-complex of **4** [20,22] according to Strohmeier and Müller [28]. For representatives of class **A** ligands, the phosphabenzenes **1** and phosphaindolizines **2**, this parameter χ can be determined to be 23 and 29, respectively. The π-acceptor ability of these systems therefore should be comparable to that of phosphites. The pyrrolylphosphine-based systems (class **B**) show enhanced π-acceptor ability with $\chi = 36$ for **3** [19], which is comparable to that of the per-fluorine substituted $P(C_6F_5)_3$. However, the strongest π-acceptor systems are the phosphenium cations (class **C**) with a χ of 59 for **4**, i.e., their π-acceptor ability is therefore similar to that of phosphorus trifluoride ($\chi = 55$).

Thus, the π-acceptor ability of these three classes of ligands increases from class **A** to **C** and covers a range in electronic properties from phosphites to phosphorus trifluoride. Such hitherto unexplored classes of strong π-acceptor ligands could have beneficial effects in homogeneous catalysis in general and in hydroformylation chemistry in particular.

As a test reaction we investigated the hydroformylation of styrene, a potentially useful reaction for the preparation of the antiinflammatory 2-arylpropionic acids [29,30]. In this particular reaction regioselectivity favoring the branched aldehyde combined with high reactivity is important.

Herein we report in full detail on the preparation and use of representative ligands of classes **A**, **B** and **C** in a highly regioselective hydroformylation of styrene under mild conditions [31]. Based upon these results we tailored new electronically differentiated bidentate ligands which gave hydroformylation catalysts that combine high regioselectivity with high reactivity.

2. Experimental

2.1. General

Reactions were performed in flame-dried glassware either under argon (purity > 99.998%) or under nitrogen. The solvents were dried by standard procedures, distilled and stored under nitrogen. All temperatures quoted are not corrected. ^1H, ^{13}C NMR spectra: Bruker ARX-200, Bruker AC-300, Bruker WH-400, Bruker AMX-500 with tetramethylsilane (TMS), chloroform ($CHCl_3$) or benzene (C_6H_6) as internal standards. ^{31}P NMR spectra: Bruker WH 400 (161.978 MHz) with 85% H_3PO_4 as external standard. Melting points: melting point apparatus by Dr. Tottoli (Büchi). Optical rotations: Perkin Elmer 241. Mass spectra: MAT CH7A, MAT 711. Elemental analyses: CHN-rapid analyzer (Heraeus). Flash chromatography: Silica gel Si 60 E. Merck, Darmstadt, 40–63 μm. Hydroformylation reactions were performed in a 200 ml stainless steel autoclave equipped with a magnetical stirrer. Gases: Carbon monoxide 2.0

[2] The formation of $Ni(\eta^1\text{-}PC_5H_5)_4$ clearly demonstrates the ability of a phosphabenzene to function as a π-acceptor-ligand [21].

[3] For a review on phosphenium cations see Ref. [22].

(Messer-Griesheim), hydrogen 3.0 (Messer-Griesheim). Compounds **1a** [32], **1b** [33], **2** [27] **3** [19], **4a** [34], **5** [35], (*R,R*)-**10** [36], **11** [37], **13** [38], **16** [39], and L-**17** [40] were prepared by published methods.

2.2. Synthesis of **4b**

2.2.1. 1,3-Di[(1S)-1-phenyl-ethyl]-[1,3,2]diazaphopholidin-2-ium trifluoromethan sulfonate (**4b**)

To a solution of 246 mg (1.04 mmol) **5** in 3 ml of CH_2Cl_2 were added dropwise at room temperature 231 mg (1.04 mmol) trimethylsilyl triflate. The reaction mixture was stirred for 16 h at room temperature. All volatile components were removed in vacuo to give 464 mg (99%) **4b** as a highly viscous yellow oil. This compound was stored as a 0.5 M stock solution in CH_2Cl_2 and used as such for catalysis experiments.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.8$ (d, $J = 6.3$ Hz, 6H, CH_3), 3.6 (m, 4H, NCH_2), 4.64 (pseudo t, $J = 6.5$ Hz, 2H, CH), 7.39 (m, 10H, ArH).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 23.01$ (d, $J_{PC} = 15.3$ Hz, 2C), 52.25 (d, $J_{PC} = 8.8$ Hz, 2C), 60.29 (d, $J_{PC} = 13.6$ Hz, 2C), 121.05 (d, $J_{FC} = 319.8$ Hz), 127.77 (4C), 129.58 (2C), 129.97 (4C), 140.14 (d, $J_{PC} = 4.2$ Hz, 2C).

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = 265.4$.

2.3. Synthesis of **6**

2.3.1. (1R,2R)-(+)-1,2-Dicyclohexyl-2-hydroxyethyl 2-(diphenylphosphanyl)benzoate (**12**)

To a solution of 452 mg (2 mmol) (*R,R*)-1,2-dicyclohexylethylen-1,2-diol (**10**) in 10 ml of CH_2Cl_2, 613 mg (2 mmol) *ortho*-diphenylphosphanylbenzoic acid (**11**), 12 mg (0.1 mmol) DMAP and 413 mg (2 mmol) DCC were successively added and the resulting mixture was stirred at room temperature for 18 h. Subsequently, the reaction mixture was filtered through a plug of CH_2Cl_2-wetted Celite and washed with additional CH_2Cl_2. An appropriate amount of silica gel was added to the filtrate and evaporated to dryness. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (9:1) provided 770 mg (75%) of **12** as a colorless glass.

$[\alpha]_D^{20} = +95.7°$ ($c = 2.1$, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.67$–2.0 (m, 22H, *c*Hex), 2.8 (s, br, 1H, OH), 3.41 (d, $J = 6.2$ Hz, 1H, HCO), 5.11 (dd, $J = 8.2$, 2.6 Hz, 1H, HCO), 6.8 (ddd, $J = 7.4$, 4.2, 1.1 Hz, ArH), 7.2–7.5 (m, 12 H, ArH), 8.26 (m, 1H, ArH).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 25.33$, 25.82, 25.89, 25.92, 26.11, 26.37, 28.31, 28.61, 29.39, 29.45, 37.91, 40.63, 74.07, 80.14, 128.43, 128.56 (d, $J_{PC} = 6.6$ Hz, 2C), 128.68 (d, $J_{PC} = 6.1$ Hz, 2 C), 128.92 (2C), 131.99 (d, $J_{PC} = 3.8$ Hz), 132.12, 133.49 (d, $J_{PC} = 19.6$ Hz, 2C), 134.19 (d, $J_{PC} = 20.3$ Hz, 2 C), 134.83, 134.9 (d, $J_{PC} = 22$ Hz), 136.78 (d, $J_{PC} = 6.6$ Hz), 137.19 (d, $J_{PC} = 10.3$ Hz), 138.2 (d, $J_{PC} = 22.4$ Hz), 166.6.

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = -4.2$.

2.3.2. (1R,2R)-(−)-1,2-Dicyclohexyl-[2-(diphenylphosphanyl)benzoyloxy]ethyl 6-oxo-6H-pyran-2-oate (**15**)

To a suspension of 147 mg (1.05 mmol) α-pyrone carboxylic acid **13** in 3 ml benzene were added at room temperature one drop DMF and 0.29 ml (4 mmol) thionylchloride. The mixture was heated to reflux for 3 h. Subsequently, all volatile components were removed in vacuo. The remaining solid was dissolved in 3 ml CH_2Cl_2 and subsequently added at room temperature to a mixture of 514 mg (1 mmol) of **12** in 6 ml of CH_2Cl_2 and 1 ml of pyridine. After stirring for 1 h at room temperature, the reaction mixture was diluted with 20 ml of CH_2Cl_2 and washed successively each with 20 ml of sat. aqu. $NaHSO_4$, sat. aqu. $NaHCO_3$, water and brine. The organic layer was separated and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by flash chromatogra-

phy with petroleum ether/*tert*-butyl methyl ether (9:1) to furnish 350 mg (55%) of **15** as a pale yellow glass.

$[\alpha]_D^{20} = -6.1°$ ($c = 0.7$, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.76–1.7$ (m, 22H, *c*Hex), 5.18 (m, 2H, HCO), 6.44 (dd, $J = 9.3$, 1.0 Hz, 1H), 6.85 (ddd, $J = 7.7$, 4.0, 1.2 Hz, 1H), 7.02 (dd, $J = 6.5$, 0.9 Hz, 1H), 7.12–7.42 (m, 13H), 8.1 (ddd, $J = 7.7$, 3.8, 1.5 Hz, 1H).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 25.6$ (2C), 25.86, 25.79, 25.91 (2C), 27.49, 27.73, 29.17, 29.33, 38.52, 38.59, 75.67, 78.39, 110.07, 120.79, 128.24–128.46 (7 ArC), 130.79 (d, $J_{PC} = 1.9$ Hz), 132.06, 133.29 (d, $J_{PC} = 17.6$ Hz), 133.82 (d, $J_{PC} = 20.8$ Hz, 2C), 133.86 (d, $J_{PC} = 20.8$ Hz, 2 C), 134.15, 137.99 (d, $J_{PC} = 12.5$ Hz), 138.01 (d, $J_{PC} = 10.2$ Hz), 141.32 (d, $J_{PC} = 28.2$ Hz), 141.64, 149.14, 158.83, 159.58, 165.6 (d, $J_{PC} = 2.8$ Hz).

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = -3.7$.

*2.3.3. (1R,2R)-(−)-1,2-Dicyclohexyl-[2-(diphenylphosphanyl)benzoyloxy]ethyl 6-tert-butyl-phosphinin-2-oate (**6**)*

A Schlenk pressure vessel was charged with a solution of 324 mg (0.51 mmol) α-pyrone **15** and 61 mg (0.61 mmol) phosphaalkyne **16** in 2 ml of toluene and subsequently pressurized with 5 bar of argon. The reaction mixture was heated for 3 days at 140°C. After cooling, all volatile components were removed in vacuo and the residue was purified by flash chromatography with petroleum ether/*tert*-butyl methyl ether (9:1) to afford 231 mg (66%) **6** as a pale yellow glass.

$[\alpha]_D^{20} = -30.0°$ ($c = 0.6$, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.8–1.8$ (m, 22H, *c*Hex), 1.48 [s, 9H, $C(CH_3)_3$], 5.2 (dd, $J = 7.6$, 2.9 Hz, 1H, HCO), 5.3 (dd, $J = 7.5$, 2.8 Hz, 1H, HCO), 6.86 (m, 1H, ArH), 7.17–7.41 (m, 12H, ArH), 7.51 (d pseudo t, $J = 8.4$, 3.9 Hz, 1H, PArH), 7.98 (dd, $J = 8.4$, 6.0 Hz, 1H, PArH), 8.38 (m, 2H, ArH + PArH).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 25.72$ (2C), 25.84, 26.03, 26.09 (2C), 28.04, 28.31, 29.13, 29.26, 32.76 (d, $J_{PC} = 12.5$ Hz, 3C), 38.73, 38.80, 38.97 (d, $J_{PC} = 26.1$ Hz), 76.13, 76.65, 128.07, 128.28 (d, $J_{PC} = 7.2$ Hz, 4C), 128.42 (2C), 129.27 (d, $J_{PC} = 13.7$ Hz), 131.28, 131.91, 133.29 (d, $J_{PC} = 16.3$ Hz, 133.87 (d, $J_{PC} = 20.9$ Hz, 2C), 133.94, (signal for 1 aryl carbon atom is hidden by the signals between 138.7–134.0), 134.0 (d, $J_{PC} = 21.7$, 2C), 134.63 (d, $J_{PC} = 13.4$ Hz), 138.15 (d, $J_{PC} = 11.0$ Hz), 138.3 (d, $J_{PC} = 12.1$ Hz), 141.77 (d, $J_{PC} = 28.8$ Hz), 155.83 (d, $J_{PC} = 53.5$ Hz), 165.52 (d, $J_{PC} = 3.1$ Hz), 167.81 (d, $J_{PC} = 26.6$ Hz), 185.38 (d, $J_{PC} = 60.3$ Hz).

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = -2.9$ (s), 220.16 (s).

*2.4. Synthesis of **7***

*2.4.1. 6-Oxo-6H-pyran-2-carboxylic acid [(1S)-1-hydroxymethyl-2-methyl-propyl]-amide (**18**)*

To a solution of 280 mg (2 mmol) carboxylic acid **13** in 4 ml benzene were added at room temperature two drops of DMF and 0.58 ml (8 mmol) thionylchloride. The mixture was heated to reflux for 4 h. Subsequently, all volatile components were removed in vacuo. The remaining residue was dissolved in 4 ml CH_2Cl_2 and subsequently added at 0°C to a mixture of 206 mg (2 mmol) of L-valinol (**17**) in 6 ml of CH_2Cl_2 and 0.35 ml of triethylamine. After additional stirring for 1 h at room temperature, the reaction mixture was diluted with 50 ml of CH_2Cl_2 and washed with 50 ml sat. aqu. NH_4Cl. The organic phase was separated and the aqueous phase was reextracted three times with 20 ml of CH_2Cl_2 each. The combined organic phases were washed successively with 50 ml of 5% diluted aqu. HCl and 50 ml sat. aqu. $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed in vacuo to give 327 mg (73%) **18** as a brown oil, which was used directly in the subsequent Mitsunobu cyclization.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 7.2$ Hz, 3H, CH_3), 0.91 (d, $J = 7.2$ Hz, 3H, CH_3), 1.92 (m, 1H, CH), 3.3 (s, br, 1H, OH), 3.7 (m, 3H), 6.39 (d, $J = 9.4$ Hz, 1H), 7.03 (d,

$J = 6.6$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 1H, NH), 7.42 (dd, $J = 9.4$, 6.8 Hz, 1H).

^{13}C NMR (50.329 MHz, $CDCl_3$): $\delta = 18.64$, 19.26, 28.84, 57.21, 62.36, 106.74, 118.78, 143.05, 152.21, 158.53, 159.78.

*2.4.2. 6-[(4S)-4-Isopropyl-4,5-dihydro-oxazol-2-yl]-pyran-2-one (**19**)*

To a solution of 160 mg (0.71 mmol) carbonamide **18** in 7 ml THF were added at room temperature successively 186 mg (0.71 mmol) triphenylphosphine and 124 mg (0.71 mmol) DEAD. The reaction mixture was allowed to stir for further 60 min at room temperature. Subsequently an appropriate amount of silica was added and the mixture was evaporated to dryness. Flash chromatography with petroleum ether/*tert*-butyl methyl ether furnished 50 mg (34%) **19** as pale yellow crystals.

M.p. 101°C. $[\alpha]_D^{25} = -49.9°$ ($c = 1.05$, CH_2Cl_2).

Elemental analysis $C_{11}H_{13}NO_2$, $M = 207.23$. Calc.: C 63.76, H 6.32, N 6.76%. Found: C 63.93, H 6.17, N 6.76%.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.7$ Hz, 3H, CH_3), 0.95 (d, $J = 6.7$ Hz, 3H, CH_3), 1.8 (m, 1H, CH), 4.07 (m, 2H, OCH_2), 4.36 (dd, $J = 13.3$, 12.1 Hz, 1H, CH), 6.38 (dd, $J = 9.5$, 1.0 Hz, 1H), 6.81 (dd, $J = 6.6$, 0.9 Hz, 1H), 7.32 (dd, $J = 9.3$, 6.6 Hz, 1H).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 18.1$, 18.75, 32.55, 70.81, 73.08, 107.34, 118.95, 141.99, 149.25, 156.51, 159.75.

*2.4.3. (4S)-(3-tert-Butyl-2-phosphinin)-4-isopropyl-2-yl-4,5-dihydro-oxazole (**7**)*

A solution of 227 g (1.1 mmol) α-pyrone **19**, 400 mg (4 mmol) *tert*-butyl phosphaalkyne **16** in 3 ml toluene was heated for 4 days to 140°C. Subsequently, all volatile components were removed in vacuo and the residue was purified by Kugelrohr destillation to give 190 mg (65%) **7** as a yellow oil. This material contained about 20% unreacted starting material, which could not be separated.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.7$ (d, $J = 6.7$ Hz, 3H, CH_3), 0.88 (d, $J = 6.7$ Hz, 3H, CH_3), 1.21 [d, $J = 1.5$ Hz, 9H, $C(CH_3)_3$], 1.56 (m, 1H, CH), 3.74 (m, 2H, CH_2O), 3.94 (dd, $J = 8.6$, 7.0 Hz, 1H, CH), 7.1 (d pseudo t, $J = 8.4$, 4.0 Hz, 1H, ArH), 7.52 (dd, $J = 8.5$, 6.1 Hz, 1H, ArH), 8.5 (dd, $J = 8.2$, 4.5 Hz, 1H, ArH).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 18.73$, 18.97, 32.91 (d, $J_{PC} = 12.6$ Hz, 3C), 33.45, 39.0 (d, $J_{PC} = 21.9$ Hz), 70.63, 73.31, 129.53 (d, $J_{PC} = 14.1$ Hz), 132.62 (d, $J_{PC} = 10.9$ Hz), 133.12 (d, $J_{PC} = 13.1$ Hz), 154.4 (d, $J_{PC} = 52.5$ Hz), 165.2 (d, $J_{PC} = 27$ Hz), 185.09 (d, $J_{PC} = 59.5$ Hz).

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = 210.4$.

*2.5. Synthesis of **8, 9***

*2.5.1. (4S)-2-(Hydroxymethyl)-isopropyl-2-oxazolin (**20**)*

A solution of 10.3 g (0.1 mol) L-valinol (**17**) and 7.6 g (0.1 mmol) hydroxy acetic acid in 150 ml xylene were heated for 62 h to reflux with a Dean Stark trap. The solvent was removed in vacuo and the residue was purified by fractional distillation to give 8.15 g (57%) **20** at 57–64°C/0.01 mbar as a colorless oil, which solidified on standing at room temperature.

M.p. 57°C. $[\alpha]_D^{25} = -48.5°$ ($c = 2.0$, CH_2Cl_2).

Elemental analysis $C_7H_{13}NO_2$, $M = 143.19$. Calc.: C 58.72, H 9.15, N 9.78%. Found: C 58.76, H 9.22, N 9.55%.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 7.8$ Hz, 3H, CH_3), 0.96 (d, $J = 6.8$ Hz, 3H, CH_3), 1.74 (m, 1H, CH), 3.8–4.07 (m, 2H, CH_2OC), 4.21 (bs, 2H, CH_2OH), 4.28–4.37 (m, 1H, NCH), 5.26 (bs, 1H, OH).

^{13}C NMR (50.329 MHz, $CDCl_3$): $\delta = 18.1$, 18.7, 32.5, 57.2, 71.1, 71.5, 168.0.

*2.5.2. (4S)-(−)-(4-Isopropyl-4,5-dihydro-oxazol-2yl)methyl 6-oxo-6H-pyran-2-oate (**21**)*

To a suspension of 1.4 g (10 mmol) α-pyrone carboxylic acid **13** in 15 ml benzene were added at room temperature three drops of DMF and

2.9 ml (40 mmol) thionylchloride. The mixture was heated to reflux for 3 h. Subsequently, all volatile components were removed in vacuo. The remaining solid was dissolved in 10 ml CH_2Cl_2 and subsequently added at room temperature to a mixture of 1.43 g (10 mmol) of **20** in 25 ml of CH_2Cl_2 and 3 ml of pyridine. After stirring for 1 h at room temperature, the reaction mixture was diluted with 100 ml of CH_2Cl_2 and washed successively with 30 ml of sat. aqu. $NaHSO_4$, sat. aqu. $NaHCO_3$, water and brine each. The organic layer was separated and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by Kugelrohr destillation to give 1.22 g (41%) **21** as a brown highly-viscous oil.

$[\alpha]_D^{25} = -26.9°$ ($c = 2.0$, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.8$ (d, $J = 6.8$ Hz, 3H, CH_3), 0.88 (d, $J = 5.7$ Hz, 3H, CH_3), 1.7 (m, 1H, CH), 3.9 (m, 2H, OCH_2), 4.26 (dd, $J = 9.2$, 7.8 Hz, 1H, NCH), 4.88 (s, 2H, OCH_2), 6.5 (dd, $J = 9.4$, 1.0 Hz, pyrone CH), 7.12 (dd, $J = 6.6$, 1.0 Hz, pyrone CH), 7.41 (dd, $J = 9.4$, 6.6 Hz, pyrone CH).

^{13}C NMR (50.329 MHz, $CDCl_3$): $\delta = 17.57$, 18.22, 31.92, 58.96, 70.39, 71.75, 110.41, 120.96, 141.41, 148.14, 158.1, 159.12, 160.43.

$C_{13}H_{15}NO_5$: calcd. 265.0950; found 265.0953 (HRMS).

2.5.3. (4S)-(−)-(4-Isopropyl-4,5-dihydrooxazol-2yl)methyl 2-tert-butyl-phosphinin-2-oate (8)

A solution of 1.22 g (4.12 mmol) α-pyrone **21**, 450 mg (4.5 mmol) *tert*-butyl phosphaalkyne **16** in 5 ml toluene was heated for 24 h to 130°C. Subsequently, all volatile components were removed in vacuo and the residue was purified by flash chromatography with petroleum ether/ethyl acetate (4:1) to give 406 mg (31%) **8** as a yellow oil.

$[\alpha]_D^{25} = -13.3°$ ($c = 1.6$, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (d, $J = 6.8$ Hz, 3H, CH_3), 0.89 (d, $J = 6.8$ Hz, 3H, CH_3), 1.4 [d, $J = 1.6$ Hz, 9H, $C(CH_3)_3$], 1.7 (m, 1H, CH), 3.92 (m, 2H, OCH_2), 4.23 (dd, $J = 9.0$, 7.8 Hz, 1H, CH), 4.95 (dd, $J = 14.3$, 1.1 Hz, 2H, OCH_2), 7.49 (d, pseudo t, $J = 8.4$, 4.1 Hz, 1H, ArH), 7.94 (dd, $J = 8.4$, 6.3 Hz, 1H, ArH), 8.35 (dd, $J = 8.2$, 4.3 Hz, 1H, ArH).

^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 17.97$, 18.60, 32.38, 32.70 (d, $J_{PC} = 12.4$ Hz, 3 C), 38.97 (d, $J_{PC} = 21.6$ Hz), 58.79, 70.56, 72.21, 129.21 (d, $J_{PC} = 14.0$ Hz), 133.94 (d, $J_{PC} = 10.0$ Hz), 134.85 (d, $J_{PC} = 13.4$ Hz), 154.67 (d, $J_{PC} = 53.3$ Hz), 161.81, 167.45 (d, $J_{PC} = 27.5$ Hz), 185.3 (d, $J_{PC} = 59.7$ Hz).

^{31}P NMR (161.978 MHz, $CDCl_3$) $\delta = 221.3$.

Mass spectrum *m/e* 321 (M^+, 9.7), 306 (M^+–CH_3, 15.7), 278 (M^+–C_3H_7, 17.8), 179 ($tBuPC_5H_3CO$, 100).

$C_{17}H_{24}NO_3P$: calcd. 321.1494; found 321.1477 (HRMS).

2.5.4. (4S)-(−)-(4-Isopropyl-4,5-dihydrooxazol-2yl)methyl 3-tert-butyl-benzoate (9)

To a solution of 400 mg (2.24 mmol) 3-*tert*-butyl carboxylic acid [41] in 5 ml benzene were added at room temperature two drops of DMF and 0.654 ml (8.96 mmol) thionylchloride. The mixture was heated to reflux for 4 h. Subsequently, all volatile components were removed

Table 1
Regioselective hydroformylation of styrene with novel monodentate π-acceptor ligands[a]

Entry	Ligand	χ [25]	Rh:L	Conv. (%)[b]	b:l[b]
1	PPh_3	13	1:20	31	25.8:1
2	**1a**	23	1:20	–	–
3	**1b**	23	1:5	51	23.2:1
4	**1b**	23	1:2	80	26.6:1
5	**2**	29	1:20	–	–
6	**3**	36	1:20	8	6:1
7	**4a**	59	1:2	4	100:–
8	**4a**	59	1:1	20	31.5:1
9[c]	**4b**	59	1:2	10	29.8:1

[a] Reactions were carried out in toluene (0.65 mol/l) in a 200 ml stainless-steel autoclave under an atmosphere of H_2 and CO (1:1), 50 bar initial total pressure for 22 h at 20°C.

[b] Conversions and b:l ratios were determined by GC on a 0.25 mm × 30 m Supelcowax column with *n*-pentadecane as internal standard. In all cases aldehyde selectivity was 100%.

[c] No significant ee (> 5%) could be detected by oxidizing the crude product with $KMnO_4$ to the corresponding carboxylic acids followed by separation of the enantiomers by GC on a β-cyclodextrin column.

Table 2
Regioselective hydroformylation of styrene with bidentate phosphabenzene ligands[a]

Entry	Ligand	Rh:L	Conv. (%)[b]	b:l[b]
1[c]	**6**	1:2	42	21.4:1
2[c]	**7**	1:2	5	100:–
3[c]	**8**	1:2	98	24.8:1
4[c]	**9**	1:2	29	46.7:1

[a,b,c] See Table 1.

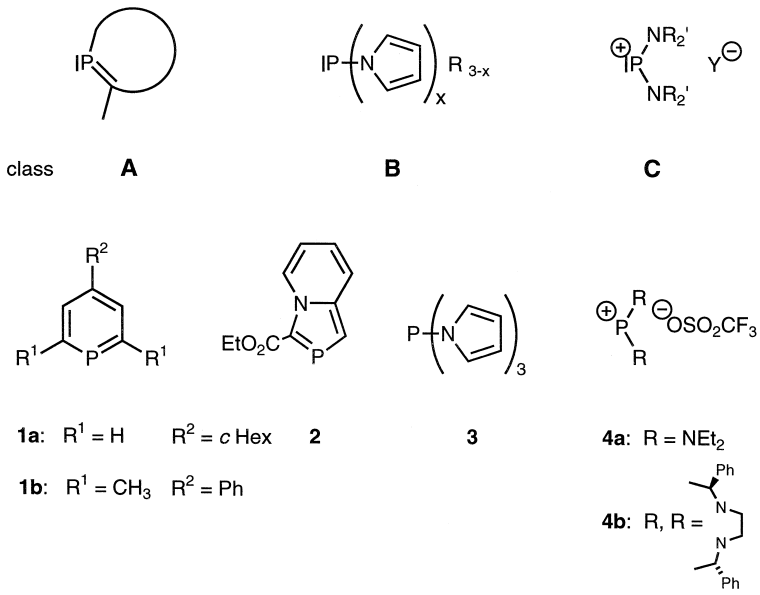
in vacuo. The remaining residue was disolved in 10 ml CH_2Cl_2 and subsequently added at room temperature to a mixture of 320 mg (2.24 mmol) **20** in 10 ml of CH_2Cl_2 and 1 ml of pyridine. After stirring for 1 h at room temperature, the reaction mixture was diluted with 50 ml of CH_2Cl_2 and washed successively with 30 ml of sat. aqu. $NaHSO_4$, sat. aqu. $NaHCO_3$, water and brine each. The organic layer was separated and dried (Na_2SO_4). Flash chromatography with petroleum ether/ethyl acetate (7:3) furnished **9** as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.83$ (d, $J = 6.4$ Hz, 3H, CH_3), 0.87 (d, $J = 6.1$ Hz, 3H, CH_3), 1.24 [s, 9H, $C(CH_3)_3$], 1.75 (m, 1H, CH), 4.25 (m, 2H), 4.75 (m, 3H), 7.4 (m, 2H, ArH), 7.9 (m, 2H, ArH).

2.6. Hydroformylation experiments

To a solution of 6.1 mg ($2.36 \cdot 10^{-2}$ mmol) of [$Rh(CO)_2$acac] in 5 ml of toluene at 20°C (exclusion of air and moisture) the indicated amount of ligand (see Tables 1 and 2) was added and the mixture was stirred for 30 min at 20°C. Subsequently, 689 mg (6.62 mmol) styrene was added and the resulting solution transferred by cannula with rinsing (toluene, 5 ml) into a carefully evacuated and argon filled stainless-steel autoclave (200 ml). The hydroformylation reaction was started by pressurizing successively with carbon monoxide (25 bar) and hydrogen (25 bar), and the reaction solution was stirred magnetically under these conditions for 22 h. The autoclave was depressurized and the reaction mixture analysed by GC.

Determination of enantiomeric excess: 3 ml of the reaction mixture was diluted in 50 ml of acetone and treated with 300 mg of potassium permanganate and 320 mg of magnesium sulfate to effect oxidation of the product aldehydes to



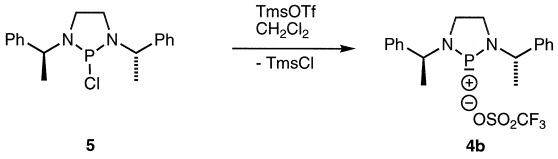
Scheme 1.

their respective acids. The mixture was stirred at room temperature for 0.5 h. Subsequently the solvent was removed under reduced pressure, the residue was extracted three times with 50 ml of hot water. The three aqueous solutions were then combined, filtered and washed with 50 ml of CH_2Cl_2. The aqueous layer was then acidified with concentrated HCl to a pH of 2 and extracted with 50 ml of CH_2Cl_2. The solvent was removed in vacuo, the resulting residue was dissolved in 0.5 ml of toluene, and this solution was analyzed by gas chromatography on a chiral β-cyclodextrin column.

3. Results and discussion

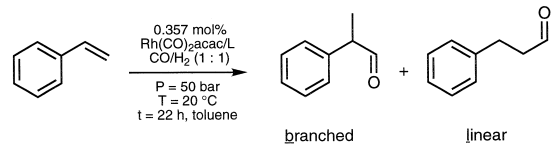
3.1. Monodentate π-acceptor ligands—ligand synthesis and catalysis

In a first series of experiments we explored rhodium catalysts modified with monodentate π-acceptor ligands. The monodentate ligands used are displayed in Scheme 1. Phosphabenzenes **1a, b** have been prepared according to Märkl et al. [32,33]. The phosphaindolizine **2** was obtained following a procedure developed by Bansal et al. [27]. Trispyrrolylphosphin **3** was prepared according to Moloy and Petersen [19]. Synthesis of phosphenium cation **4a** followed a method reported by Mazieres et al. [34]. Based upon this method we developed a synthesis of the first chiral phosphenium cation **4b** to explore its ability to induce asymmetry in the course of rhodium catalysed hydroformylation of styrene [42]. Thus, treatment of the known chlorophosphine **5** [35] with trimethylsilyl triflate provided the chiral phosphenium cation **4b**



5 **4b**

Scheme 2.

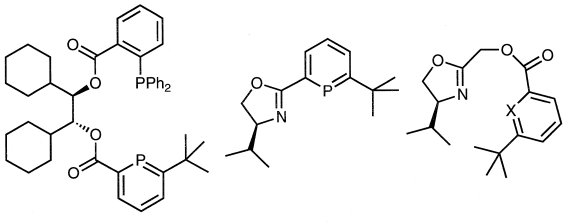


Scheme 3.

in quantitative yield. The ^{31}P chemical shift of $\delta = 200$ is in the range expected for a diamino substituted phosphenium cation system [34]. ^{13}C NMR data confirmed the C_2 symmetry of this ligand (Scheme 2).

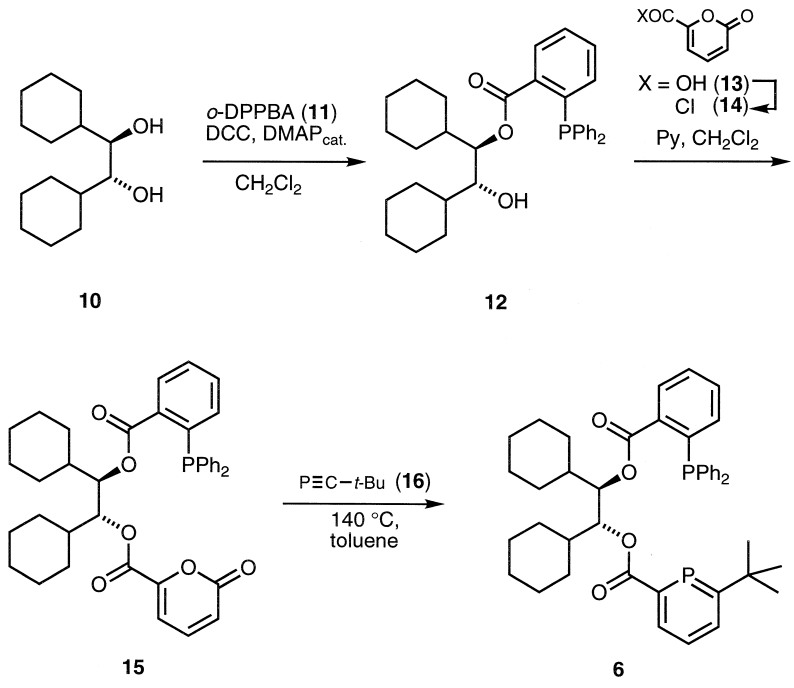
The catalysts were prepared in situ by reacting the catalyst precursor $Rh(CO)_2acac$ with the corresponding monodentate ligand in toluene followed by hydroformylation at ambient temperature (20°C) and 50 bar of H_2/CO (1:1) (Schemes 1 and 3, Table 1).

As a reference system the $Rh–PPh_3$ catalyst was chosen. This catalyst showed conversion of 31% after 22 h at 20°C, and a b:l ratio of 25.8:1 (Table 1, entry 1). Unexpectedly, the phosphabenzene **1a** and the phosphaindolizine **2** ligands both inhibited hydroformylation completely compared to the $Rh–PPh_3$ reference. However, using a phosphabenzene with two additional methyl substituents in *ortho/ortho′* positions of the phosphabenzene system (**1b**) resulted in the formation of a hydroformylation catalyst that performed with an activity more than twice as high as the standard $Rh–PPh_3$ catalyst (see entry 4). Thus, 80% conversion were obtained, while regioselectively maintained the high level of the reference system (26.6:1, b:l). Such activating effects have been



6 **7** **8**: X = P
9: X = CH

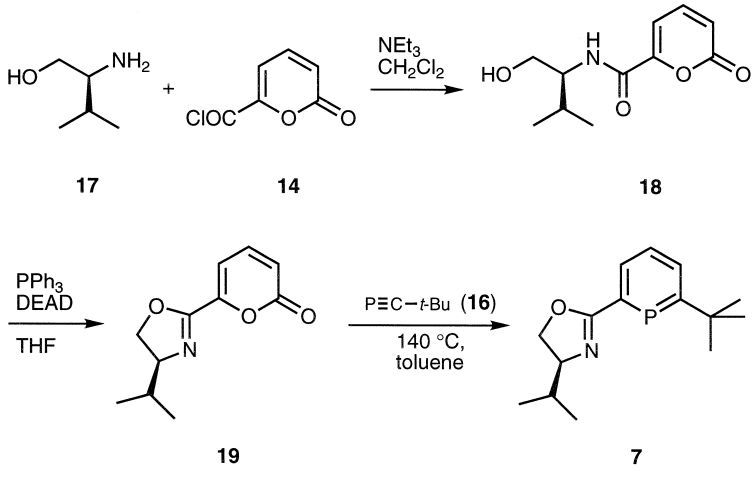
Scheme 4.



Scheme 5.

observed also with phosphite ligands when employing ligand systems with increased steric demand [7,8].

As a class **B** ligand the trispyrrolylphosphine **3** was examined. Thus, only low conversion and poor regioselectivity could be observed (Table 1, entry 6). To examine ligands with maximum π-acceptor ability, the phosphenium cation **4a** was chosen. Although regioselectivity with this system was excellent (entries 7, 8, 9), catalyst activity was low. The hydroformylation experiment with the chiral phosphenium cation ligand



Scheme 6.

4b revealed a similar result as that obtained for ligand **4a**, however enantioselectivity was low (< 5% ee).

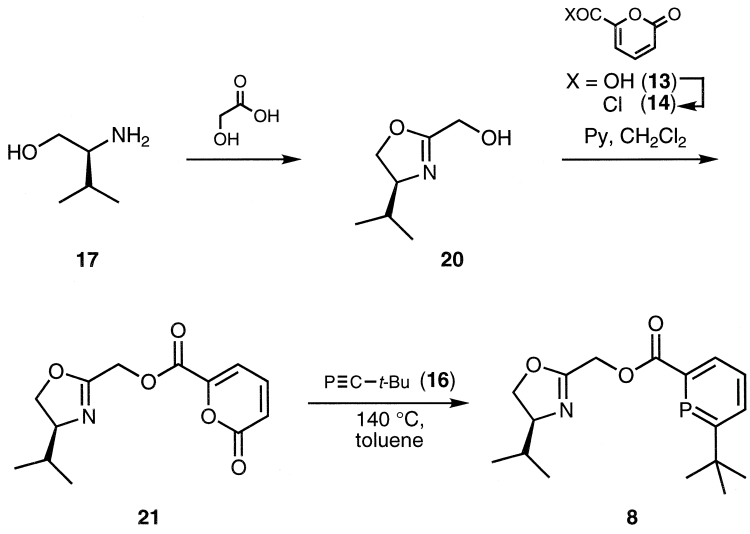
3.2. Bidentate ligands—ligand synthesis and catalysis

We next attempted to improve the performance of our π-acceptor catalysts. When studying the most selective ligand systems known, Takaya's BINAPHOS, a phosphine–phosphite ligand, two characteristic structural features appeared to be of great importance to control selectivities: first, a chelating bidentate binding mode, and secondly, an electronic differentiation of the two binding sites [43,44]. Taking these criteria into account we next modified the most active of our monodentate ligands, the 2,6-substituted phosphabenzene system. The bidentate ligand systems, which have been approached are displayed in Scheme 4.

As a first test system we became interested in a phosphine–phosphabenzene combination as represented by ligand **6**. Such a combination of donor sites should be electronically similar to a phosphine–phosphite combination. The synthesis of system **6** started from the known *R*,*R*-diol **10**. Esterification of **10** with one equivalent of *ortho*-diphenylphosphinobenzoic acid (*o*-DPPBA) (**11**) [37] furnished the monoester **12**. A second esterification with the α-pyrone carboxylic acid chloride gave pyrone **15** [38]. When **15** was reacted with the phosphaalkyne **16** according to a procedure developed by Becker et al. [39] and Rösch and Regitz [45] the phosphabenzene ligand **6** was obtained in 66% yield (Scheme 5).

In order to increase the electronic differentiation of the two coordinating elements, we attempted to introduce an oxazoline functionality as a hard σ-donor coordination site. As a first target ligand **7** capable of forming a five-membered chelate ring was envisioned. Synthesis of **7** was achieved starting with a carbonamide formation between L-valinol (**17**) and the α-pyrone-carboxylic acid chloride **14** (→ **18**). Condensation of **18** employing Mitsunobu conditions afforded the oxazoline **19**. Reaction of **19** with the phosphaalkyne **16** provided the desired ligand system **7** (Scheme 6).

To investigate an oxazoline/phosphabenzene system capable of forming a larger chelation ring, we turned to system **8**. Such a ligand should in principle allow for an eight-membered



Scheme 7.

chelating binding mode to a catalytically active rhodium center. [4] Thus, L-valinol (**17**) was transformed into the oxazoline **20**. Esterification of **20** with the acid chloride **14** and subsequent reaction of the ester **21** with the phosphaalkyne **16** provided the desired ligand system **8**. The control system **9** was obtained in an analogous manner employing the corresponding 3-*tert*-butyl benzoic acid chloride (Scheme 7).

When testing the bidentate ligands we employed exactly the same hydroformylation reaction conditions as have been used for the monodentate ligands (Table 2). Thus, the phosphine–phosphabenzene system **6** gave a 42% conversion (somewhat higher than for the PPh_3/Rh-system) and a good regioselectivity of 21.4:1 (b:l).

To explore ligands with an increased electronic differentiation of the two binding sites the oxazolin–phosphabenzene systems **7** and **8** were tested. While ligand **7** (Table 2, entry 2) did not improve the catalyst properties, the results with ligand **8** were the best. Standard hydroformylation reaction at ambient temperature (20°C) provided a quantitative conversion of styrene to 2-phenylpropionaldehyde with a regioselectivity of about 25:1. Thus, a rhodium catalyst modified with ligand **8** displays a reactivity three times as high as that for the Rh–PPh_3 system, while regioselectivity maintains the same high level. This is a clear advantage of our system compared to the most active catalyst for hydroformylation known in the literature for the hydroformylation of styrene, a phosphanorbornadiene–Rh system reported by Neibecker and Reau [16]. The high reactivity in this case however compromises regioselectivity, which decreased in the above-mentioned reaction to 11:1 (b:l).

To clarify the role of the phosphabenzene system in **8** during catalysis, control system **9**, which lacks the phosphabenzene unit, was tested. Standard hydroformylation with **9** clearly showed a much reduced catalytic activity (only 29% conversion, entry 4, Table 2) compared to the quantitative conversion of the phosphabenzene moiety in ligand **8** for the rhodium-catalyzed hydroformylation of styrene. This experiment clearly demonstrates the activating effect of a phosphabenzene nucleus for the rhodium catalyst. It is presumably an η^1-coordination of a phosphabenzene to a rhodium center which is responsible for this catalysts performance [23].

[4] For the effect of a bidentate ligand's bite angle on selectivity for Rh-catalyzed hydroformylation, see Ref. [46].

Acknowledgements

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