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Retaining Catalyst Performance at High Temperature: The Use of a Tetraphosphine Ligand in the Highly Regioselective Hydroformylation of Terminal Olefins

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Abstract: A new tetraphosphine ligand has been developed and applied in the highly regioselective hydroformylation of terminal olefins. The ligand retains high performance at high temperature when compared with its bisphosphine analogue.

Keywords: hydroformylation; phosphines; regioselectivity; rhodium

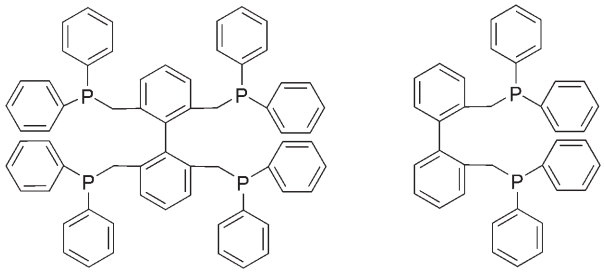
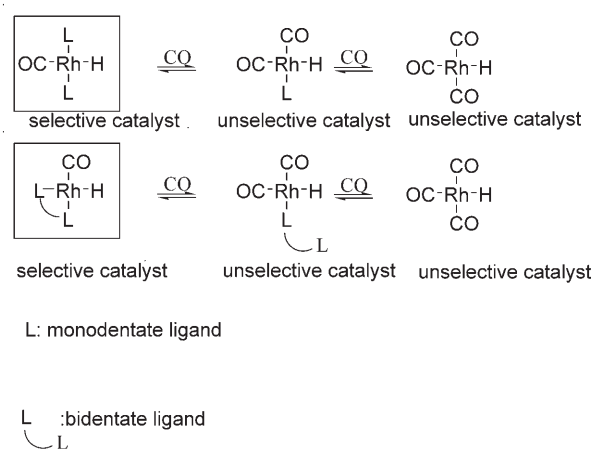


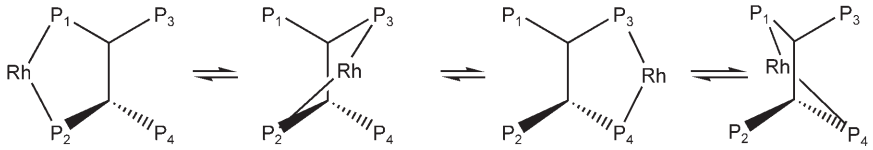
Figure 1. Tetraphosphine ligand **1** and bisphosphine Bisbi.

Hydroformylation of olefins is one of the most important homogeneous catalytic industrial processes.[1] The enormous amount of hydroformylation products (over 6 million tons) produced per year reflects its importance. One of the key issues in the hydroformylation process is the control of regiochemistry. Although commercial hydroformylation processes use monodentate ligands, their regioselectivities are not high. To address this issue, a number of catalysts based on bisphosphorus ligands has been developed. Some elegant examples include Bisbi,[2] Xantphos,[3] Biphephos,[4] calix[4]arene bisphosphite,[5] pyrrole-based bisphosphoramidite[6] and self-assembled bisphosphine.[7] Hydroformylation with these catalytic systems generally are carried out at relatively low temperature (below 125 °C) to ensure high regioselectivities. Since the hydroformylation reaction at high temperature affords a higher reaction rate, from the point of view of industrial applications, it is highly desirable to develop a regioselective ligand for high temperature hydroformylation. Herein, we report the design and synthesis of a biphenyl backbone-based tetraphosphine ligand **1** (Figure 1), as well as its applications in the highly regioselective hydroformylation of terminal olefins. Compared with its biphosphine analogue, Bisbi, tetraphosphine ligand **1** affords much higher regioselectivity at high temperature (linear: branched ratio $n{:}i = 45.2$ for the hydroformylation of 1-octene at 140 °C, whereas with Bisbi $n{:}i = 2.4$).

One of the reasons for the eroded regioselectivity in Rh-catalyzed hydroformylation at high temperature is the formation of unselective catalytic species, due to the dissociation of phosphorus ligands from the metal center (Scheme 1). We envision that tetraphosphine ligand **1** can solve this problem and afford better regioselectivity at high temperature than its bisphosphine analogue Bisbi for the following reasons: (1) Ligand **1** has enhanced chelating ability due to multiple chelating modes. When a phosphine in the bidentate ligand dissociates from the metal, an inter-



Scheme 1. Ligand dissociation in hydroformylation.



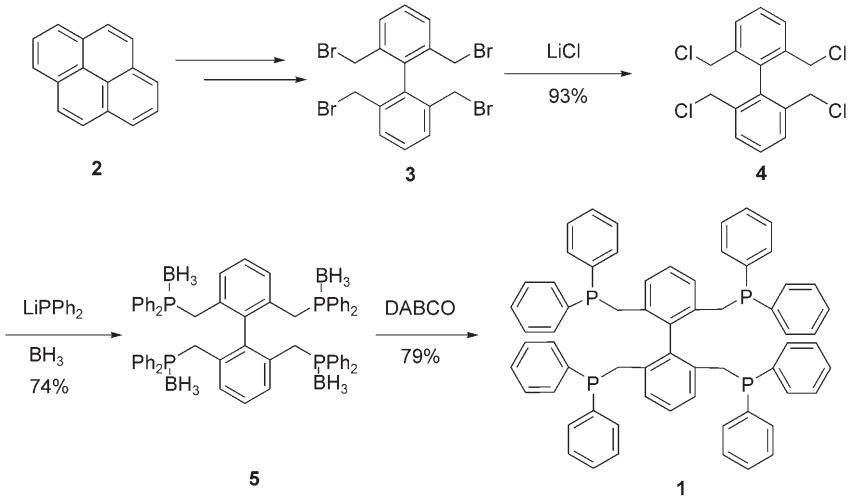
Scheme 2. Enhanced chelating ability of tetraphosphine ligand **1** through multiple chelating modes and increased local phosphorus concentration.

mediate with two different phosphines will form. One of these two phosphines can recoordinate to Rh and reform the bidentate system. (2) When ligand **1** is coordinated with the metal to form a bidentate system, the existing free phosphorus atoms can effectively increase the local phosphorus concentration around the metal center and enhance the chelating ability (Scheme 2). Based on this strategy, we recently developed a new pyrrole-based tetraphosphoramidite ligand for the highly regioselective hydroformylation of internal olefins.[8] However, when this ligand was applied in the hydroformylation of terminal olefins, a high level of isomerization (over 15%) was observed, which indicates that it is more suitable for the hydroformylation of internal olefins. Since terminal olefins are less likely to undergo isomerization when an electron-donating bisphosphine such as Bisbi is used, we envision that tetraphosphine ligand **1** could be a good candidate for the regioselective hydroformylation of terminal olefins with low isomerization.

Starting from pyrene **2**, tetrabromide **3** was prepared in high yields according to literature procedures.[9] Whereas the literature reported the synthesis of Bisbi by reaction of lithium diphenylphosphine with 2,2′-bisbromomethyl-1,1′-biphenyl in high yield,[2a] the reaction of tetrabromide **3** with lithium diphenylphosphine gave very complex products under the same reaction conditions. The reaction was monitored by *in situ* ^{31}P NMR and a messy spectra was observed. The reactivity of tetrabromide **3** was very different from its corresponding dibromide, 2,2′-bisbromomethyl-1,1′-biphenyl. To overcome this problem, we transformed tetrabromide **3** to the less reactive tetrachloride **4** by reaction of the tetrabromide with LiCl in DMF at room temperature. The tetrachloride **4** was obtained in high yield (93%). We were then pleased to find that the reaction of tetrachloride **4** with lithium diphenylphosphine cleanly afforded the desired tetraphosphine as indicated by a single peak in *in situ* ^{31}P NMR. Since tetraphosphine **1** is an air-sensitive compound, the tetraphosphine **1** was protected *in situ* with borane for work-up. A simple deprotection with DABCO afforded the desired tetraphosphine ligand **1** in 79% yield. The overall synthetic route is outlined in Scheme 3.

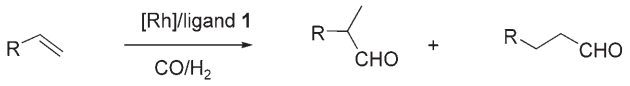
The hydroformylation of terminal olefins with the new tetraphosphine ligand **1** was then investigated. The hydroformylation reaction was conducted in toluene with 1-octene as the standard substrate and decane as an internal standard. The rhodium catalyst was prepared *in situ* by mixing the tetraphosphine ligand **1** with $Rh(acac)(CO)_2$. The substrate:catalyst ratio was 2000 and the catalyst concentration was 1.0 mM. The reaction was terminated after 1 h.

The effects of ligand:metal ratio on hydroformylation of terminal olefins with the tetraphosphine ligand **1** were first evaluated. As shown in Table 1 (entries 1–4), slight decreases of both *n*:*i* ratio and isomerization



Scheme 3. The synthesis of tetraphosphine ligand **1**.

Table 1. Optimization of reaction conditions for the hydroformylation of 1-octene.[a]



Entry	L/Rh	T [°C]	CO/H_2 [atm]	$n:i$[b]	Linear [%][c]	Isomerization [%][d]	TON[e]
1	1:1	100	10/10	53.7	98.2	7.9	1.8×10^3
2	2:1	100	10/10	53.4	98.2	7.3	1.8×10^3
3	4:1	100	10/10	50.5	98.1	5.6	1.8×10^3
4	6:1	100	10/10	48.9	98.0	5.6	1.8×10^3
5	4:1	140	10/10	45.2	97.8	6.5	1.8×10^3
6	4:1	120	10/10	49.8	98.0	5.8	1.8×10^3
7	4:1	80	10/10	34.2	97.2	3.4	1.4×10^3
8	4:1	100	30/30	16.5	94.3	2.9	1.2×10^3
9	4:1	100	20/20	22.3	95.7	3.0	1.2×10^3
10	4:1	100	5/5	66.7	98.5	17.3	1.6×10^3

[a] S/C = 2000, [Rh] = 1.0 mM, reaction time = 1 h, toluene as solvent, decane as internal standard.
[b] Linear/branched ratio, determined based on GC.
[c] Percentage of linear aldehyde in all aldehydes.
[d] Isomerization to internal olefins.
[e] Turnover number, determined based on GC.

were observed when the ligand:metal ratio increased from 1:1 to 6:1. The effects of reaction temperature on the hydroformylation reaction were also investigated (entries 3, 5–7). To our delight, only a slight decrease in *n:i* ratio was observed when the reaction temperature increased from 100 °C to 140 °C. As expected, hydroformylation at lower temperatures led to less olefin isomerization. Finally, the effects of CO/H_2 pressure were tested (entries 3, 8–10). At high CO/H_2 pressure, the regioselectivities were low. The regioselectivities could be increased by lowering the CO/H_2 pressure. The highest regioselectivity (*n:i* ratio of 66.7) was obtained under a CO/H_2 pressure of 5/5 atm. However, a high percentage of isomerization was observed under this pressure, indicating that low CO/H_2 pressures facilitate the olefin isomerization.

For comparison, the bisphosphine ligand Bisbi was prepared and employed in the hydroformylation of terminal olefins under identical reaction conditions. The results are summarized in Table 2. As can be seen clearly, tetraphosphine ligand **1** always afforded higher regioselectivity than bisphosphine ligand Bisbi under the same reaction conditions. It should be noted that, at high temperature, a dramatic decrease of regioselectivity and a high percentage of isomerization have been observed with bisphosphine ligand Bisbi (entries 1, 2, 7 and 8). For example, in the hydroformylation of 1-octene, the regioselectivity was significantly low (*n:i* = 2.4) and isomerization was significantly high (24 %) at 140 °C with Bisbi as ligand; whereas the regioselectivity remained high (*n:i* ratio = 45.2) and the isomerization remained low (6.5 %) using tetraphosphine ligand **1** at the same temperature. At lower temperature (100 °C), both tetraphosphine **1** and bisphosphine Bisbi afford high regioselectivity and low isomerization with *n:i* ratios >40 and isomerization $<10\,\%$ (entries 5,6, 11, and 12). The *similar* performances with both ligands at low temperature and *dramatic difference* at high temperature suggest that the better performance at high temperature with ligand **1** is indeed due to the enhanced chelating ability of tetraphosphine ligand **1**. This result is also important from the practical point of view because highly regioselective hydroformylation can now be carried out at higher temperature to gain a high reaction rate.

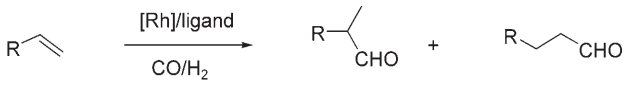
In conclusion, tetraphosphine ligand **1**, has been designed, synthesized and successfully applied in highly regioselective hydroformylations of terminal olefins. Compared with its bisphosphine analogue Bisbi, tetraphosphine ligand **1** retains high performance at high temperature.

Experimental Section

General Methods

All reactions and manipulations were performed in a nitrogen-filled glove-box or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200–400 mesh silica gel supplied by Natland International Corporation. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AM-300 and AMX-360 spectrometers. GC analysis was carried on Helwett-Packard 6890 gas chromatography using capillary columns.

Table 2. Comparison of tetraphosphine and bisphosphine ligands.[a]



Entry	Substrate	T [°C]	Ligand	*n*:*i*[b]	Linear [%][c]	Isomerization [%][d]	TON[e]	TOF[f] [h^{-1}]
1	1-octene	140	**1**	45.2	97.8	6.5	1.8×10^3	9.3×10^3
2	1-octene	140	Bisbi	2.4	70.6	24	1.5×10^3	6.2×10^3
3	1-octene	120	**1**	49.8	98.0	5.8	1.8×10^3	7.3×10^3
4	1-octene	120	Bisbi	29.5	96.7	8.7	1.8×10^3	5.7×10^3
5	1-octene	100	**1**	50.5	98.1	5.6	1.8×10^3	2.5×10^3
6	1-octene	100	Bisbi	45.2	97.8	6.7	1.6×10^3	3.4×10^3
7	1-hexene	140	**1**	43.8	97.8	7.7	1.8×10^3	9.5×10^3
8	1-hexene	140	Bisbi	4.9	83.1	20	1.6×10^3	8.7×10^3
9	1-hexene	120	**1**	48.5	98.0	7.1	1.8×10^3	6.6×10^3
10	1-hexene	120	Bisbi	35.8	97.3	9.1	1.8×10^3	6.0×10^3
11	1-hexene	100	**1**	48.6	98.0	6.6	1.8×10^3	3.3×10^3
12	1-hexene	100	Bisbi	43.2	97.7	9.4	1.7×10^3	2.6×10^3

[a] S/C = 2000, [Rh] = 1.0 mM, ligand/Rh ratio = 4:1, CO/H_2 = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard.
[b] Linear/branched ratio, determined based on GC.
[c] Percentage of linear aldehyde in all aldehydes.
[d] Isomerization to internal olefins.
[e] Turnover number, determined based on GC.
[f] Turnover frequency, determined based on GC, reaction time = 10 min.

Synthesis of 4

To a solution of **3** (2.2 g, 4.2 mmol) in DMF (80 mL) was added LiCl (2.82 g, 67.2 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 °C and 5% aqueous HCl solution (30 mL) was added carefully. After stirring for 5 min, the mixture was extracted with ether (4×40 mL) and washed with saturated aqueous NaCl solution (80 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to dryness. Pure product was obtained by recrystallization from CH_2Cl_2/hexanes as a white solid; yield: 1.35 g (93%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.74–7.62 (m, 4H), 7.59–7.56 (m, 2H), 4.28 (s, 8H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 137.0, 135.8, 131.2, 130.2, 45.0; HR-MS (EI^+): *m/z* = 345.9850, calcd. for $C_{16}H_{14}Cl_4$ [M^+]: 345.9853.

Synthesis of 5

To a cooled (−78 °C) solution of diphenylphosphine (2.32 mL, 13.2 mmol) in THF (10 mL) was added *n*-BuLi (5.28 mL, 2.5 M solution in hexane, 13.2 mmol) dropwise. After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was cooled to −78 °C and **4** (1.05 g, 3 mmol) in THF (10 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was cooled to 0 °C and a cold 1.0 M THF solution of BH_3 (132 mL, 132 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 °C and water was added carefully to quench the excess BH_3. The volatile material was removed under vacuum. To the residue were added CH_2Cl_2 (50 mL) and water (50 mL). The mixture was stirred for 10 min until all residues had dissolved. The organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2×25 mL). The combined organic phase was washed with saturated aqueous NaCl solution (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain an off-white solid. To the crude solid was added EtOAc (10 mL). The resulting suspension was stirred for 30 min and filtered. The residue was washed with cold EtOAc (2×5 mL) to give the pure borane-protected title compound as a colorless solid; yield: 2.5 g (73.8%). ^{1}H NMR (300 MHz, $CDCl_2$): δ = 7.58–7.52 (m, 16H), 7.45-.39 (m, 8H),7.36–7.31 (m, 16H), 7.03–6.97 (m, 2H), 6.87–6.84 (m, 4H), 3.16 (d, *J* = 13.4 Hz, 8H), 1.53–0.75 (bs, 12H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 133.1, 132.5 (d, *J* = 9.1 Hz), 131.5, 131.3, 130.6, 130.4, 129.2 (d, *J* = 9.9 Hz), 127.5, 30.2 (d, *J* = 30 Hz); ^{31} P NMR (146 Hz, CD_2Cl_2): δ = 15.2; HR-MS (ES^+): *m/z* = 1025.4431, calcd. for $C_{64}H_{66}NaP_4B_4$ [M + Na^+]: 1025.4385.

Synthesis of Ligand 1

To a solution of DABCO (448 mg, 4 mmol) in toluene (10 mL) was added **5** (501 mg, 0.5 mmol) in portions. The resulting suspension was stirred for 30 min at room temperature and slowly heated to 60 °C. The stirring was continued for 6 h at 60 °C. The reaction mixture was cooled to room temperature and additional toluene (10 mL) was added. The diluted solution was charged on a short silica gel column through cannula and eluted with toluene (40 mL). The solvent was removed under vacuum to give the desired ligand as a white solid; yield: 376 mg (79.4%). ^{1}H NMR (300 MHz, $CDCl_2$): δ = 7.32–7.22 (m, 40H), 6.91–6.86 (m, 2H), 6.76–6.74 (m, 4H), 3.24 (s, 8H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 139.6, 139.3, 137.1, 137.0, 133.5, 133.3, 128.9, 128.7, 127.4,

35.0 (d, $J=25.8$ Hz); ^{31}P NMR (146 Hz, CD_2Cl_2): $\delta=-15.3$; HRMS (ES^+): $m/z=947.3237$, calcd. for $C_{64}H_{55}P_4$ $[M+H^+]$: 947.3254.

General Procedure for the Regioselective Hydroformylation of Terminal Olefins with Tetraphosphine Ligand 1

To a 2-mL vial with a magnetic stirring bar was charged tetraphosphine ligand **1** (4 μmol) and $Rh(acac)(CO)_2$ (1 μmol in 0.1 mL toluene). The mixture was stirred for 5 min. Then 1-octene (2 mmol) was added followed by decane (0.1 mL) as internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was transferred to an autoclave. The autoclave was sealed and purged with nitrogen for three times and subsequently charged with CO (10 bar) and H_2 (10 bar). The autoclave was then heated to 100 °C (oil bath). After 1 h, the autoclave was taken out of the oil bath and cooled in ice/water. The pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.

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