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A Tetraphosphorus Ligand for Highly Regioselective Isomerization−Hydroformylation of Internal Olefins

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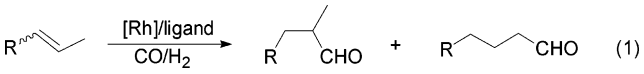
Abstract: A new pyrrole-based tetraphosphorus ligand capable of forming multiple chelating modes has been prepared. Higher regioselectivity has been achieved in the rhodium-catalyzed isomerization−hydroformylations of internal olefins compared with its bisphosphorus analogue.

Introduction

Hydroformylation is one of the most important industrial homogeneous catalytic processes, and over 6 million tons of oxo products are produced every year. Most commercial hydroformylation processes use rhodium catalysts modified with monophosphorus ligands. A number of catalysts based on bisphosphorus ligands have been developed to address the issue of regioselectivity. When coordinated with metal, bisphosphorus ligands can form chelating structures and afford better regioselectivities than monophosphorus ligands. To date, high regioselectivity in the hydroformylation of terminal olefins has been achieved by employing some bidentate bisphosphorus ligands.[1] Since internal olefins are cheaper and more readily available feedstock than terminal olefins, the development of highly selective and active isomerization−hydroformylation catalysts for internal olefins is of great importance from economic and energy points of view (eq 1). Recently, some progress has been



(1)

made in this area using van Leeuwen's Xantphos derivatives (linear/branched ratio $n:i = 9.5$ for 2-octene),[2] Beller's electron-withdrawing Naphos-type ligands ($n:i = 10.1$ for 2-octene),[3] Börner's acylphosphite ligands ($n:i = 2.2$ for mixtures of octene isomers),[4] and bulky phosphite ligands[5] of UCC ($n:i = 19$ and 17 for 2-hexene and 2-octene, respectively) and DuPont/DSM ($n:i = 36$ for 2-hexene). Highly regioselective isomerization−hydroformylation of internal olefins has also been reported in a biphasic system using a sulfonated Naphos derivative through careful control of pH and CO partial pressure ($n:i = 99:1$ for 2-octene).[6] Herein, we report the design and synthesis of a conceptually new tetraphosphorus ligand, **1** (Figure 1), with enhanced chelating ability for the regioselective homogeneous isomerization−hydroformylation of internal olefins. To the best of our knowledge, this catalytic system provided the highest regioselectivity in homogeneous isomerization−hydroformylation of internal olefins ($n:i$ values up to 80.6 for 2-hexene and up to 51.7 for 2-octene have been achieved with this catalytic system).

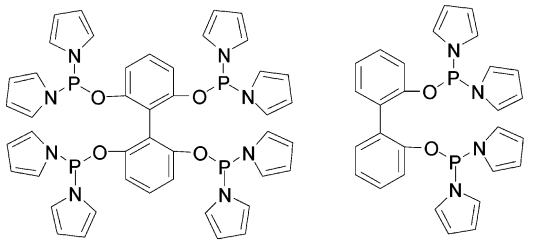


Figure 1. Tetraphosphorus ligand vs bisphosphorus ligand.

Results and Discussions

A goal of this new ligand design is to solve the issue of ligand dissociation, a major problem encountered in achieving high regioselectivity in hydroformylation (Scheme 1). In commercial oxo processes which are based on monophosphorus ligands, the catalytic species with two phosphines coordinated to the metal center is the desired regioselective catalytic species. The dissociation of phosphorus ligands from the metal center followed by replacement with CO leads to the formation of highly reactive yet unselective catalytic species. In order to prevent the formation of unselective catalytic species and achieve high regioselectivities, large excesses of ligands are employed. For known bidentate bisphosphorus ligands capable

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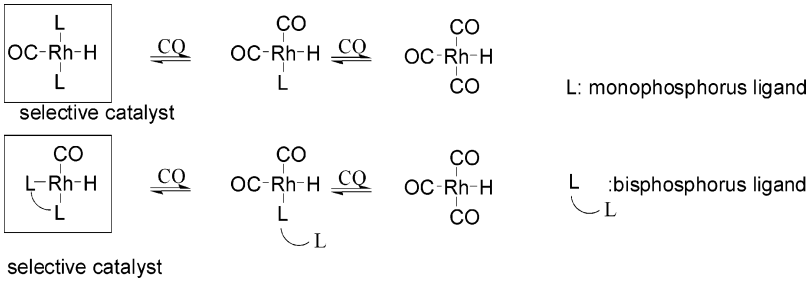
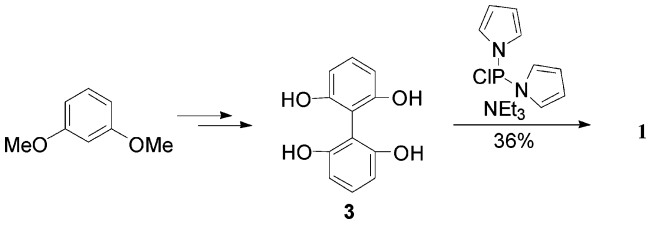
Scheme 1. Ligand Dissociation in Rh-Catalyzed Hydrodroformylation



Scheme 2. Enhanced Chelating Ability of Tetraphosphorus Ligand **1** through Multiple Chelating Modes and Increased Local Phosphorus Concentration

of affording high regioselectivities in hydroformylation, typically eight- or nine-membered ring chelations are formed. The chelating effects of eight- or nine-membered ring chelations are weaker compared with those of five- and six-membered chelations. We reason that the dissociation of bisphosphorus ligands from metal in eight- or nine-membered ring chelations can also happen under some hydroformylation conditions. To facilitate the isomerization of internal olefins, isomerization−hydroformylation of internal olefins is generally conducted at higher temperature than hydroformylation of terminal olefins, which may make the ligand dissociation problem even worse. In order to achieve high regioselectivity in the isomerization−hydroformylation of internal olefins, a new strategy to enhance the chelating ability of ligands is needed. We envision that chelating ability could be enhanced by using ligands capable of forming multiple chelating modes. As illustrated in Scheme 2, there are four identical chelating modes when tetraphosphorus ligand **1** is complexed with metal. On the other hand, when the tetraphosphorus ligand **1** is coordinated with metal, the existing free phosphorus atoms can effectively increase the local phosphorus concentration around the metal center and enhance the coordination ability of the tetraphosphorus ligand compared with the corresponding bisphosphorus ligand **2**. To achieve high regioselectivity in the isomerization−hydroformylation of internal olefins, a high isomerization rate of internal olefin to terminal olefin as well as high regioselectivity of terminal olefin is required. Recently, *N*-pyrrolylphosphorus ligands such as bisphosphorus ligand **2**[7] have been used for rhodium-catalyzed hydroformylation reactions. A fast isomerization rate and high regioselectivities of terminal olefins have been reported with ligand **2**. A detailed mechanistic study and a comparison study[7b] with a structurally closely related diphenyl-substituted bisphosphinite ligand suggest that the high regioselectivity achieved with ligand **2** was due to its high electron-withdrawing property and not to bite angle and steric hindrance. With electron-withdrawing ligand **2**, branched rhodium−alkyl complexes prefer exclusive β-hydride elimination (leading to the formation of 2-olefins) to carbon monoxide insertion (leading to the formation of branched aldehydes), whereas linear rhodium−alkyl complexes undergo carbon monoxide insertion to form

Scheme 3. Synthesis of Ligand **1**



linear aldehydes. On the basis of the enhanced chelating ability of tetraphosphorus ligand **1** and the unique electronic properties of *N*-pyrrolylphosphorus ligand, we envision that tetraphosphorus ligand **1** could serve as an effective ligand for isomerization−hydroformylation of internal olefins.

One of the key requirements of a ligand for practical applications is that the ligand synthesis has to be simple. The symmetric nature of tetraphosphorus ligand **1** makes its synthesis straightforward (Scheme 3). Following known literature procedures,[8] tetraol **3** can be synthesized in two steps starting from inexpensive 1,3-dimethoxybenzene. Reaction of chlorodipyrrolylphosphine with tetraol **3** in the presence of NEt_3 afforded the desired tetraphosphorus ligand **1** in 36% unoptimized yield. The resulting ligand is an air-stable crystalline solid which can be stored in air and handled easily in hydroformylation reactions (manipulation can be conducted in air before charging CO and H_2).

The isomerization−hydroformylation of internal olefins was then investigated using ligand **1**. Since the hydroformylation reaction is highly dependent on the reaction conditions, effects of ligand/metal ratio, temperature, and pressure on regioselectivity were first evaluated using 2-octene as the standard substrate. The catalyst were prepared in situ by mixing ligand **1** with $Rh(acac)(CO)_2$ at certain ratios. The reactions were carried out in toluene with decane as the internal standard. The rhodium concentration was 0.57 mM, and typically a substrate/catalyst ratio of 10 000 was used. The isomerization−hydroformylation results are summarized in Table 1. The ligand/metal ratio has a dramatic effect on the isomerization−hydroformylation reaction (Table 1, entries 1−3). At lower ratios, low regioselectivity was observed. A minimum ligand/metal ratio of 2 is essential to achieve high regioselectivity. Further increasing the ligand/metal ratio did not significantly improve the regioselectivity. On the other hand, higher ligand/metal ratio resulted in a slightly lower reaction rate. The reaction temperature also plays a key role in isomerization−hydroformylation (Table 1, entries 4−7). At low temperature, though high regioselectivity was observed, the reaction rate was low. To

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Table 1. Isomerization−Hydroformylation of 2-Octene with Ligand **1** under Different Reaction Conditions[a]

entry	L/Rh	T (°C)	CO/H_2 (atm)	n:i[b]	linear[c] (%)	TON[d]
1	1:1	100	10/10	17.7	94.7	1.8×10^3
2	2:1	100	10/10	43.4	97.7	1.5×10^3
3	4:1	100	10/10	46	97.9	1.5×10^3
4	3:1	120	10/10	30.4	96.8	3.4×10^3
5	3:1	100	10/10	46	97.9	1.6×10^3
6	3:1	80	10/10	47.7	97.9	7.7×10^2
7	3:1	60	10/10	53.7	98.2	1.4×10^2
8	3:1	100	30/30	24.3	96	3.1×10^2
9	3:1	100	20/20	30	96.8	5.1×10^2
10	3:1	100	5/5	51.7	98.1	1.5×10^3

[a] S/C = 10 000, [Rh] = 0.57 mM, t = 1 h, toluene as solvent, decane as internal standard. [b] Linear/branched ratio, determined on the basis of GC analysis. [c] Percentage of linear aldehyde in all aldehydes. [d] Turnover number, determined on the basis of GC.

Table 2. Isomerization−Hydroformylation of Internal Olefins with Ligands **1** and **2**[a]

entry	substrate	L	t (h)	n:i[b]	linear[c] (%)	TON[d]
1	2-octene	**1**	1	51.7	98.1	1.5×10^3
2	2-octene	**1**	12	38	97.4	7.7×10^3
3	2-octene	**2**	1	10.1	91	2.3×10^3
4	2-octene	**2**	12	5.49	84.6	8.4×10^3
5	2-hexene	**1**	1	80.6	98.8	1.7×10^3
6	2-hexene	**1**	12	56	98.2	6.0×10^3
7	2-hexene	**2**	1	15	93.8	2.1×10^3
8	2-hexene	**2**	12	13.5	93.1	6.8×10^3

[a] S/C = 10 000, [Rh] = 0.69 mM (for 2-hexene) or 0.57 mM (for 2-octene), ligand/Rh ratio = 3:1, temperature = 100 °C, CO/H_2 = 5/5 atm, toluene as solvent, decane as internal standard. [b−d] See Table 1.

facilitate the olefin isomerization and hydroformylation, a high temperature (100 °C) is preferred to achieve a high reaction rate as well as acceptable regioselectivity. The CO/H_2 total pressure also influences the reaction (Table 1, entries 8−10). Under high pressure, both reaction rate and regioselectivity were low. Lowering the pressure generally resulted in higher reaction rate and regioselectivity. Decreasing the CO/H_2 pressure from 10/10 atm to 5/5 atm did not change the reaction rate very much; however, the regioselectivity was improved to some extent.

Isomerization−hydroformylation of internal olefins was conducted under optimized reaction conditions (100 °C, CO/H_2 = 5/5 atm, ligand/metal ratio = 3). No 3-formylalkane products were formed under these reaction conditions. Very high initial *n*:*i* ratios (ratio after 1 h of reaction time) have been achieved in the isomerization−hydroformylation of 2-olefins (Table 2, entries 1 and 5). For the isomerization−hydroformylation of 2-octene, the initial ratio is 51.7, while this value increases to 80.6 for 2-hexene. Though elongating the reaction time to 12 h resulted in lower *n*:*i* ratios (38 for 2-octene and 56 for 2-hexene), the linear percentage remained high: a *n*:*i* ratio of 38 corresponds to 97.4% linear aldehyde in all aldehyde products, while a *n*:*i* ratio of 56 corresponds to 98.2% linear aldehyde (Table 2, entries 2 and 6). The *n*:*i* ratios of aldehydes from 2-hexene are greater than those from 2-octene. This can be explained on a statistical basis: there are more internal alkenes possible for octene, so the amount of 1-hexene at equilibrium will be greater than the amount of 1-octene at equilibrium. Isomerization−hydroformylation of *trans* 4-octene was also tested. However, no hydroformylation product was detected after 1 h, probably due to the slow isomerization of

Table 3. Hydroformylation of 1-Octene with Ligand **1** under Different Reaction Conditions[a]

entry	T (°C)	CO/H_2 (atm)	n:i[b]	linear[c] (%)	isomerization[d] (%)	TON[e]
1	100	10/10	236	99.6	21.6	7.6×10^3
2	80	10/10	372	99.7	15.3	6.9×10^3
3	60	10/10	442	99.8	5.4	3.5×10^3
4	40	10/10	461	99.8	3.9	0.64×10^3
5	80	30/30	242	99.6	8	7.7×10^3
6	80	5/5	405	99.8	28.3	6.2×10^3

[a] S/C = 10 000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, reaction time = 1 h, toluene as solvent, decane as internal standard. [b,c] See Table 1. [d] Isomerization to 2-olefin. [e] See Table 1.

Table 4. Hydroformylation of Terminal Olefins with Ligands **1** and **2**[a]

entry	substrate	L	n:i[b]	linear[c] (%)	isomerization[d] (%)	TON[e]
1	1-octene	**1**	372	99.7	15.3	6.9×10^3
2	1-octene	**2**	74.1	98.7	10	8.4×10^3
3	1-hexene	**1**	382	99.7	18.7	6.7×10^3
4	1-hexene	**2**	80.8	98.8	12.2	7.9×10^3

[a] S/C = 10 000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, temperature = 80 °C, CO/H_2 = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. [b,c] See Table 1. [d] See Table 3. [e] See Table 1.

4-octene (three consecutive double bond isomerizations need to be precede hydroformylation) under the current reaction conditions (100 °C, CO/H_2 = 5/5 atm, ligand/metal ratio = 3). For comparison, isomerization−hydroformylation with bisphosphorus ligand **2** has been conducted under the identical reaction conditions (Table 2, entries 3, 4, 7, and 8). In the literature,[7b] ligand **2** was also investigated in the isomerization−hydroformylation of 2-octene at 120 °C. However, only a few turnovers were reported, and the regioselectivity was only 1. Under our reaction conditions, ligand **2** catalyzed isomerization−hydroformylation of 2-olefins with high reactivity and regioselectivity. Our results demonstrated that the isomerization−hydroformylation reaction is sensitive to reaction conditions, and a previously "bad ligand" could be a "good ligand" under different reaction conditions. We attribute the difference to the high substrate/rhodium ratio employed in our experiments. At high substrate/rhodium ratios, the isomerization rates of internal olefins are much faster than at low ratios. From Table 2, it also can be seen clearly that tetraphosphorus ligand **1** always afforded better regioselectivities than bisphosphorus ligand **2** in the isomerization−hydroformylation of 2-olefins.

Hydroformylation of terminal olefins with tetraphosphorus ligand **1** was then investigated. As in the case of isomerization−hydroformylation of internal olefins, the optimization of reaction condition was first conducted with 1-octene as the standard substrate. The results are summarized in Table 3. To investigate the temperature effects, the hydroformylation reactions were first carried out at various temperatures ranging from 40 to 100 °C under otherwise identical conditions. High temperatures generally led to high reaction rates and high isomerization. Even though the results indicate that hydroformylation at higher temperatures resulted in lower regioselectivity, the regioselectivity remained very high. For example, the linear/branched ratio (*n*:*i*) at 40 °C was 461, whereas this number decreased to 236 (still a very high value) at 100 °C. Since hydroformylation of terminal olefins at high temperatures resulted in the formation of a high percentage of isomerization products, a low temper-

ature (80 °C) was preferred in the hydroformylation of terminal olefins. The effects of total pressure of CO/H_2 (pressure ranging from 5/5 to 30/30 atm) were also evaluated. Low pressure generally resulted in slightly decreased reactivity. An opposite trend between regioselectivity and isomerization was observed: whereas decreasing the pressure leads to high regioselectivity, the isomerization increased dramatically. For comparison, hydroformylation of terminal olefins with bisphosphorus ligand **2** was also conducted (Table 4). As in the case of hydroformylation of internal olefins, tetraphosphorus ligand **1** always afforded higher regioselectivity than bisphosphorus ligand **2**.

Conclusion

In conclusion, a new pyrrole-based tetraphosphorus ligand, **1**, capable of forming multiple chelating modes, has been prepared and applied in the regioselective isomerization−hydroformylation of internal olefins. To the best of our knowledge, the regioselectivities achieved with this new ligand in the homogeneous isomerization−hydroformylations of 2-hexene and 2-octene are the highest reported in the literature. Our results clearly indicate that tetraphosphorus ligand **1** has and enhanced ability to coordinate to metal and thus afforded better regioselectivity in isomerization−hydroformylation compared with the corresponding bisphosphorus ligand **2**. Such an approach represents a new concept in ligand design for highly regioselective isomerization−hydroformylation. Further ligand developments based on this new concept are now under investigation and will be reported in due course.

Experimental Section

General Methods. All reactions and manipulations were performed in a nitrogen-filled glovebox 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 Corp. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25-mm silica 60-F plates. ^1H, ^{13}C,and ^{31}P NMR spectra were recorded on Bruker AM-300 and AMX-360 spectrometers. MS spectra were recorded on a KRATOS MS 9/50 mass spectrometer. GC analysis was carried out on a Hewlett-Packard 6890 gas chromatograph using capillary columns. Tetraol **3** was synthesized according to the literature procedure.[8] Chlorodipyrrolylphosphine was prepared according to the literature procedure.[7] Hydroformylation reactions were repeated several times to ensure reproducibility (see Supporting Information).

Synthesis of Ligand 1. To a solution of chlorodipyrrolylphosphine (4.4 mmol, 0.87 g) in THF (10 mL) was added dropwise triethylamine (1 mL) and a solution of tetraol **3** (1 mmol, 0.218 g) in THF (5 mL) at room temperature. The triethylamine·HCl salts were formed immediately after the addition. The reaction mixture was stirred for 6 h at room temperature. The triethylamine·HCl salts were then filtered off, and the solvent was removed under vacuum. The crude product was purified by flash chromatography on basic aluminum oxide, eluted with hexane/EtOAc/NEt_3 (6:1:0.01), to afford the pure ligand **1** (0.31 g, 36%) as an air-stable colorless solid: ^1H NMR (300 Hz, CD_2Cl_2) δ 7.23 (t, 2H, $J = 8.3$ Hz), 6.68 (m, 20H), 6.21 (m, 16H); ^{13}C NMR (75 Hz, CD_2Cl_2) δ 152.86 (d, $J = 12.2$ Hz), 131.0, 121.4 (d, $J = 16.8$ Hz), 118.1, 115.3 (d, $J = 13.7$ Hz), 112.7; ^{31}P NMR (146 Hz, CD_2Cl_2) δ 107.3; HRMS (ES+) calcd for $C_{44}H_{39}N_8O_4P_4$ [MH^+] 867.2045, found 867.2021.

General Procedure for the Regioselective Isomerization−Hydroformylation of Internal Olefins with Ligand 1. A 2-mL vial with a magnetic stirring bar was charged with ligand **1** (3 μmol, 2.6 mg) and $Rh(acac)(CO)_2$ (1 μmol, 0.1 mL of 10 mM solution in toluene) under air. The mixture was stirred for 5 min. 2-Octene (10 mmol, 1.56 mL) was then added, followed by decane (0.1 mL) as internal standard. The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen three times and subsequently charged with CO (5 bar) and H_2 (5 bar). The autoclave was then heated to 100 °C (oil bath). After 12 h, the autoclave was cooled in icy water, and the pressure was carefully released in a well-ventilated hood. The reaction mixture was immediately analyzed by GC to determine the turnover number and regioselectivity.

General Procedure for the Regioselective Hydroformylation of Terminal Olefins with Ligand 1. A 2-mL vial with a magnetic stirring bar was charged with ligand **1** (0.6 μmol in 0.2 mL of toluene) and $Rh(acac)(CO)_2$ (0.2 μmol in 0.2 mL of 1 mM toluene) under air. The mixture was stirred for 5 min. 1-Octene (2 mmol) was then 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 purged with nitrogen three times and subsequently charged with CO (10 bar) and H_2 (10 bar). The autoclave was then heated to 80 °C (oil bath). After 1 h, the autoclave was cooled in icy water, and the pressure was carefully released in a well-ventilated hood. The reaction mixture was immediately analyzed by GC.

Supporting Information Available: Ligand NMR spectra and repeated hydroformylation reaction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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