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A Novel Triphosphoramidite Ligand for Highly Regioselective Linear Hydroformylation of Terminal and Internal Olefins

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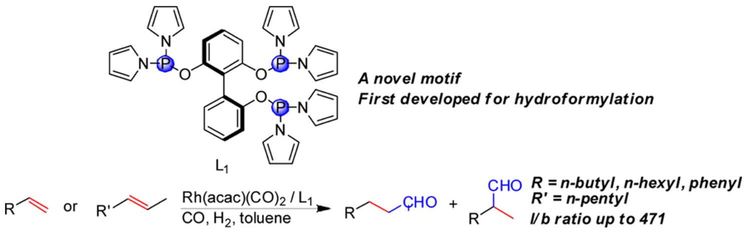
ABSTRACT



The first triphosphorus ligand has been designed and synthesized for highly regioselective linear hydroformylations. A very high *l*/*b* ratio (up to 471, 99.8% linear selectivity) was obtained in the linear hydroformylation of representative terminal and internal olefins. For the range of substrates tested, the regioselectivities achieved utilizing the novel triphosphoramidite ligand were much better than those of the bisphosphoramidite ligand and close to those of the tetraphosphoramidite ligand.

Regioselective hydroformylation represents a powerful C–C bond forming reaction converting alkenes and syngas into synthetically useful aldehydes in a perfect atom economic way.[1] Due to the great importance of aldehydes as versatile intermediates and building blocks, hydroformylation has been intensively applied in industry since its first discovery by Otto Roelen in 1938.[2,3] Oxo products produced *via* a hydroformylation process are estimated at over 10 million tons per year now.[2c]

In order to achieve high regioselectivities, efforts have been made in designing new types of phosphorus ligands for rhodium-catalyzed hydroformylation processes. As one of the key factors determining the regioselectivity, bisphosphorus ligands with a much stronger chelating ability afford higher regioselectivities in the hydroformylation of simple olefins compared with the corresponding monophosphorus ligands. Numerous catalysts and ligands have been developed based on bisphosphorus ligands, which were heavily patented by companies in Oxo Chemicals in the past decades (Scheme 1). As elegant examples, Bisbi type ligands,[4] Xantphos,[5] Biphephos,[6] Naphos,[7] calix[4]arene bisphosphite,[8] and self-assembled bisphosphane[9] showed very good regioselectivities. Extraordinarily,

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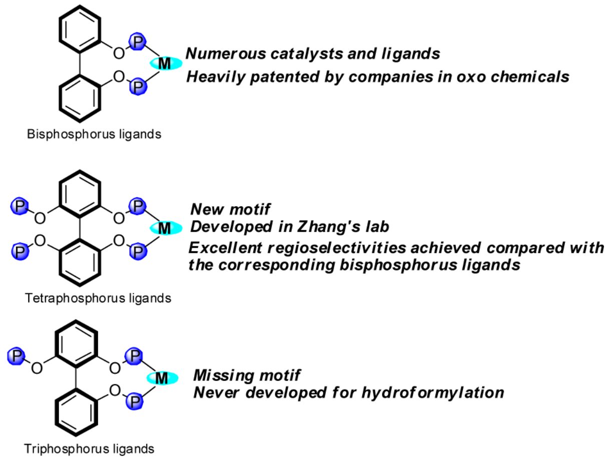
van Leeuwen's pyrrole-based bisphosphoramidite ligand exhibited excellent activity and regioselectivity due to the strong electron-withdrawing ability of the pyrrole moiety.[10] Furthermore, the spiroketal-based bisphosphorus ligands developed recently by Ding also afforded very good regioselectivities.[11] Besides bisphosphorus ligands, by incorporating four chelating sites our group developed two classes of tetraphosphorus ligands with a new motif which achieved unprecedented regioselectivities (Scheme 1).[12]

Scheme 1. Ligands Developed for Regioselective Hydroformylation



Although a number of ligands were developed, high catalyst loadings, low reaction rates, poor selectivity, and a narrow substrate scope are still challenging problems in the hydroformylation process. Further development of new efficient ligands for highly regioselective hydroformylation is still highly desirable. Although bis- and tetra-phosphorus ligands have been well developed for regioselective hydroformylation, as a missing motif, a triphosphorus ligand has never been developed (Scheme 1). We herein report the synthesis and application of a novel triphosphoramidite ligand **1** (Figure 1) for highly regioselective hydroformylation of terminal and internal olefins. To the best of our knowledge, this is the first example of triphosphorus ligands developed for highly regioselective linear hydroformylation.

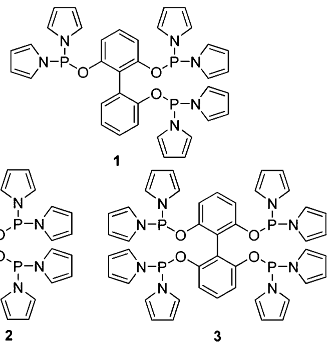
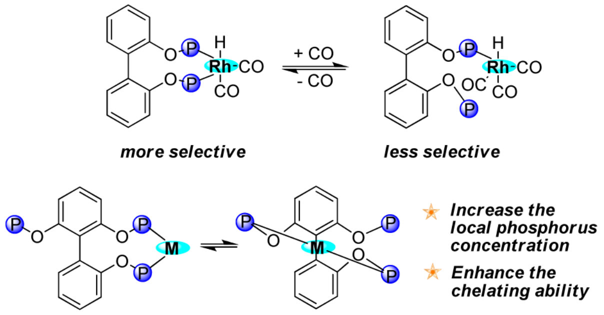


Figure 1. Triphosphoramidite and the corresponding bis- and tetra-phosphoramidite ligands.

Scheme 2. Coordination Modes of the Triphosphorus Ligand and the Corresponding Bisphosphorus Ligands



Generally, the nine-membered ring chelations of the bisphosphorus ligands are much weaker than the corresponding five- or six- membered ring chelations. Thus dissociation of the chelating phosphorus atom from the metal center by replacement of carbon monoxide at a relatively high temperature is possible, resulting in the formation of the less selective catalytic species which leads to worse linear selectivity (Scheme 2). One of the key goals of designing the novel triphosphoramidite ligand **1** is to enhance the chelating ability to form more selective catalytic species. As we rationalized, there are two identical chelating modes in the complex of ligand **1** with rhodium (Scheme 2). Dissociation of one phosphorus atom from the rhodium center is readily accompanied by the other free one; thus the local phosphorus concentration of rhodium center is increased and the chelating ability is greatly enhanced compared with the corresponding bisphosphorus ligand. In this case, more selective catalytic species will be generated and better linear selectivity will be obtained.

This novel triphosphorus ligand **1** can be easily synthesized in three steps (Figure 2). Using a known procedure, a ligand skeleton 2,6,2′-trimethoxybenzene **6** can be synthesized in one step from readily available materials **4** and **5**.[13] Reduction of the methoxy group of **6** gave **7** as a white solid. The air stable ligand **1** was obtained by treating **7**

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with dipyrrolylchlorophophine **8** in 62% unoptimized yield which is much higher than that of the tetraphosphorus ligand **3** (36% yield). The corresponding bis- and tetraphosphorus ligands **2** and **3** (Figure 1) were synthesized simultaneously following literature procedures in order to compare the regioselectivities of ligands **1**, **2**, and **3**.[10,12a]

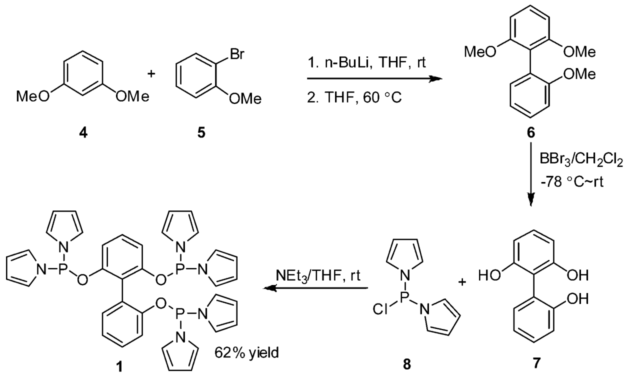

Figure 2. Synthesis of the triphosphoramidite ligand **1**.

Utilizing the newly synthesized triphosphoramidite ligand **1**, rhodium-catalyzed regioselective linear hydroformylations of terminal and internal olefins were explored. Screening of the reaction conditions was conducted by varying the ligand/metal ratio, temperature, syngas pressure, and reaction time using 1-octene as the standard substrate. The hydroformylation catalyst was prepared *in situ* by mixing $Rh(acac)(CO)_2$ with ligand **1** while the reaction was performed utilizing 1:1 CO/H_2 syngas and a typical substrate/catalyst loading of 10 000. Not surprisingly, the results fluctuated dramatically under different reaction conditions as summarized in Table 1. The ligand/metal ratio plays a key role in determining the regioselectivity (Table 1, entries 1–5). Only an *l*/*b* ratio of 4 was observed when the ligand/metal ratio was 1 (Table 1, entry 1). The minimum ligand/metal ratio was 2 to ensure high regioselectivity (Table 1, entry 2). A very high *l*/*b* ratio of 289 was achieved when the ligand/metal ratio was 3; however, increasing the ligand/metal ratio further did not distinctly improve the regioselectivity (Table 1, entries 4–5). As shown in Table 1, a high ligand/metal ratio gave a smaller TON value and resulted in a higher isomerization percentage of the alkene substrate. Temperature is also momentous in determining the regioselectivity and isomerization percentage of the alkene substrate. High temperatures generally facilitate the reaction rate at the cost of selectivity; as a result, increasing the reaction temperature to 100 °C reduced the regioselectivity distinctly (Table 1, entry 7). In contrast, an improved *l*/*b* ratio of 321 and a much smaller isomerization percentage were observed when lowering the reaction temperature to 60 °C (Table 1, entry 6). The syngas pressure also influences the regioselectivity significantly. Lowering the syngas pressure to 5:5 bar distinctly improved the *l*/*b* ratio to 399 *albeit* with a smaller TON value; in contrast, both a smaller *l*/*b* ratio and TON value were observed when the syngas pressure was increased to 20:20 bar (Table 1, entries 8–9). In order to improve the TON value, the reaction time was prolonged to 2 h, affording a higher TON value of 9200 while maintaining the *l*/*b* ratio to as high as 394 (Table 1, entry 10).

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

entry	L1/Rh	*T* (°C)	CO/H_2 (atm)	*l*/*b*[b]	linear (%)[c]	isomerization (%)[d]	TON[e]
1	1:1	80	10/10	4	80.3	17.7	9.5×10^3
2	2:1	80	10/10	280	99.7	16.8	9.4×10^3
3	3:1	80	10/10	289	99.7	17.7	9.3×10^3
4	4:1	80	10/10	297	99.7	18.0	9.3×10^3
5	8:1	80	10/10	298	99.7	18.2	9.1×10^3
6	3:1	60	10/10	321	99.7	6.8	4.0×10^3
7	3:1	100	10/10	247	99.6	18.6	9.4×10^3
8	3:1	80	5/5	399	99.8	12.1	5.3×10^3
9	3:1	80	20/20	235	99.6	8.3	6.8×10^3
10[f]	3:1	80	5/5	394	99.8	20.6	9.2×10^3

[a] S/C = 10 000, [Rh] = 0.2 mM, reaction time = 1 h, toluene as solvent, decane as internal standard. [b] Linear/branched ratio, determined by GC analysis. [c] Percentage of linear aldehyde. [d] Percentage of the isomerized alkene. [e] Turnover number, determined on the basis of the alkene conversion by GC analysis. [f] Reaction time was prolonged to 2 h.

In an effort to compare the regioselectivities of ligands **1**–**3**, ligands **2** and **3** were also tested in the hydroformylation of alkenes under the optimized reaction conditions of ligand **1** (80 °C, CO/H_2 = 5/5 bar, ligand/metal ratio = 3, reaction time = 2 h, Table 1, entry 10). Using 1-octene as a substrate, ligand **2** afforded an *l*/*b* ratio of only 117 *albeit* with a slightly higher TON value of 9400 while ligand **3** gave a higher *l*/*b* ratio of 559 but a lower TON value of 9200 (Table 2, entries 2–3), respectively. Regioselective linear hydroformylation of other terminal alkenes was also conducted under the optimized reaction conditions. As listed in Table 2, a very high *l*/*b* ratio of 471 accompanied by a high TON value of 7400 was achieved utilizing ligand **1** in the hydroformylation of 1-hexene (Table 2, entry 4). In contrast, an *l*/*b* ratio of only 125 was obtained using ligand **2** while ligand **3** afforded a higher *l*/*b* ratio of 618 (Table 2, entries 5–6). Ligand **1** was also subjected to the regioselective isomerization/hydroformylation of 2-octene. A high *l*/*b* ratio of 47 was achieved utilizing ligand **1** (Table 2, entry 7). Due to the much lower reactivity compared to the corresponding terminal alkene, the TON value achieved employing ligand **1** in the isomerization/hydroformylation of 2-octene was much smaller (TON = 2400, Table 2, entry 7). With ligand **2**, only an *l*/*b* ratio of 16 was obtained although the TON value is higher (Table 2, entry 8). Ligand **3** afforded a slightly higher regioselectivity (*l*/*b* ratio = 59, Table 2, entry 9) but a lower TON value compared with ligand **1**. As can be concluded from the above results, the regioselectivities achieved utilizing the novel triphosphoramidite ligand **1** are much better than those of ligand **2** and close to those of ligand **3**.

In order to further explore the substrate scope, the novel triphosphoramidite ligand **1** was also subjected to

Table 2. Hydroformylation of 1-Octene, 1-Hexene, and 2-Octene with Ligands **1**–**3**[a]

entry	substrate	L[b]	*T* (°C)	time (h)	*l*/*b*[c]	linear (%)[d]	isomerization (%)[d]	TON[e]
1	1-octene	L1	80	2	415	99.8	20.6	9.2×10^3
2	1-octene	L2	80	2	117	99.2	12.2	9.4×10^3
3	1-octene	L3	80	2	559	99.8	22.2	9.2×10^3
4	1-hexene	L1	80	2	471	99.8	22.3	7.4×10^3
5	1-hexene	L2	80	2	125	99.2	14.2	9.0×10^3
6	1-hexene	L3	80	2	618	99.8	24.5	7.5×10^3
7	2-octene	L1	100	1	47	98.0	n.d.	2.4×10^3
8	2-octene	L2	100	1	16	94.0	n.d.	2.8×10^3
9	2-octene	L3	100	1	59	98.3	n.d.	2.0×10^3

[a] S/C = 10 000, [Rh] = 0.2 mM, toluene as solvent, decane as internal standard, ligand/metal ratio = 3, CO/H_2 = 5:5 bar. [b] L1 = ligand **1**, L2 = ligand **2**, L3 = ligand **3**. [c] Linear/branched ratio, determined by GC analysis. [d] Percentage of linear aldehyde. [e] Turnover number, determined on the basis of the alkene conversion by GC analysis.

Table 3. Hydroformylation Results of Styrene with Ligands **1**–**3**[a]

entry	L[b]/Rh	*l*/*b*[c]	linear (%)[d]	TOF[e] (h^{-1})
1	L1/Rh = 1:1	2.5	71.7	840
2	L1/Rh = 2:1	3.3	76.6	570
3	L1/Rh = 3:1	3.2	76.4	430
4	L1/Rh = 4:1	3.2	76.2	360
5	L1/Rh = 5:1	3.2	76.2	280
6	L1/Rh = 6:1	3.2	76.0	270
7	L1/Rh = 8:1	3.1	75.8	200
8	L2/Rh = 4:1	1.1	52.3	680
9	L3/Rh = 4:1	5.0	83.4	470

[a] S/C = 1000, [Rh] = 0.1 mM, toluene as solvent, decane as internal standard, CO/H_2 = 5:5 bar, reaction time = 30 min. [b] L1 = ligand **1**, L2 = ligand **2**, L3 = ligand **3**. [c] Linear/branched ratio, determined by GC analysis. [d] Percentage of linear aldehyde. [e] Turnover frequency, determined on the basis of the alkene conversion by GC analysis.

the regioselective hydroformylation of styrene which is prevalently considered as a standard substrate for asymmetric hydroformylation due to its inherent preference to generate branched aldehyde. Ligand **1** also exhibited good regioselectivity affording a linear product percentage of 76.6% (Table 3, entry 2) while employing a ligand/metal ratio of only 2. A further increase in the ligand/metal ratio led to a slight drop in the regioselectivity and dramatic decline in the TON value (Table 3, entries 2–7). For comparison, the hydroformylation of styrene was also conducted with ligand **2** and **3** under the identical reaction conditions reported in the literature.[12a] As shown in Table 3, ligand **2** furnished an *l*/*b* ratio of only 1.1 even when employing a high ligand/metal ratio of 4 while ligand **3** afforded a higher *l*/*b* ratio of 5.0 (Table 3, entries 8–9).

In conclusion, a novel triphosphoramidite ligand **1** has been developed, which is the first example of a triphosphorus ligand for highly regioselective linear hydroformylation. Very high *l*/*b* ratios and TON values were obtained in the linear hydroformylation of simple terminal olefins (for 1-octene, *l*/*b* = 415, TON = 9200; for 1-hexene, *l*/*b* = 471, TON = 7400). The novel triphosphoramidite ligand **1** also exhibited excellent regioselectivities in the isomerization/hydroformylation of an internal alkene. As an example, ligand **1** afforded a typical *l*/*b* ratio of 47 in the isomerization/hydroformylation of 2-octene, giving 98.0% synthetically useful terminal aldehyde. It is noteworthy that ligand **1** also exhibited good regioselectivities in the linear hydroformylation of styrene which is generally considered as a standard substrate for asymmetric hydroformylation, affording 76.7% phenylpropanal. For the range of substrates listed above, the novel triphosphoramidite ligand **1** always displayed much better regioselectivities than those of the corresponding bisphosphoramidite ligand **2** and afforded comparable regioselectivities to those of the tetraphosphoramidite ligand **3**.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.