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New tetraphosphite ligands for regioselective linear hydroformylation of terminal and internal olefins†

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We successfully developed new tetraphosphite ligands **L1–L5** and applied them to the rhodium-catalyzed hydroformylation of terminal and internal olefins. High catalytic reactivities and excellent regioselectivities for linear aldehydes were obtained in the rhodium-catalyzed hydroformylation of simple olefins (l/b ratio up to 90, 98.9% linear selectivity, 99.2% conversion) using the tetraphosphite ligand **L2**. And the tetraphosphite ligand **L2** also displayed moderate to good linear regioselectivities for challenging substrates styrene and internal olefin 2-octene.

Introduction

Since its discovery by Otto Roelen in 1938,[1] the hydroformylation reaction is one of the most efficient routes for the functionalization of olefins to approach aldehydes now.[2] It has been developed into one of the most important homogeneous catalytic processes with rhodium-based catalysts in the field of industrial chemistry.[3] The corresponding aldehyde products are very important compounds and valuable intermediates for the synthesis of various chemicals, such as alcohols, amines and esters *etc.*[4] They are widely applied to construct blocks for pharmaceuticals, agrochemicals, commodities and fine chemicals.[5]

Ligand is one of the most significant factors to access high activity and selectivity of hydroformylation reaction catalyzed by the rhodium-based catalysts. Therefore, much attention has been paid to designing efficient and privileged ligands for the formation of industrially important aldehydes. A variety of excellent bisphosphorous ligands have been successfully developed for Rh-catalyzed hydroformylation reactions in the past decades, such as bisbi,[6] biphephos,[7] naphos,[8] xantphos,[9] calix[4] arene-based bisphosphites,[10] pyrrole-based bisphos-phoramidites,[11] and self-assembled bisphosphanes.[12] In addition, some new tetraphosphorus ligands were developed in our lab.[13] These ligands owned outstanding catalytic properties for their unique four identical coordination modes.[13a,b] Importantly, due to much higher local phosphine concentration around the metal center, the tetraphosphorus ligands afforded better chelating ability and thus exhibited much better regioselectivities compared with the corresponding bisphosphorus ligands. Latter we also successfully developed new triphosphorus ligands.[14] Similar to the tetraphosphorus ligands, the triphosphorus ligands also have better chelating ability with two identical coordination modes with rhodium and exhibited better regioselectivities compared with the corresponding bisphosphorus ligands. Although great efforts have been made to develop new ligands for linear hydroformylation, new ligands are still highly desirable to further resolve the problems of catalytic efficiency and selectivity.

Based on our long standing interest of tetraphosphorus ligands in hydroformylation,[13] our efforts were devoted to further developing new phosphorus ligands with excellent performance. Extensive research shown that the phosphines were typical-donors ligands and phosphites were strong-acceptors ligands. The phosphite ligands can facilitate the CO dissociation from the metal centers in the catalytic species. Therefore, it is helpful to greatly improve the reactivity by using the phosphite ligands in Rh-catalyzed hydroformylation reaction. We believe that the new tetraphosphite ligands **L1–L5** with four identical coordination modes with rhodium will show good reactivities and regioselectivities in the linear hydroformylation (Fig. 1). Importantly, ligands **L1–L5** are very concise and can be facilely synthesized. Herein, we present the synthetic route of new tetraphosphite ligands **L1–L5**, and the application in Rh-catalyzed hydroformylation reaction of simple and unfunctionalized olefins, providing the desired products in high conversions with moderate to excellent regioselectivities.

Results and discussion

The new tetraphosphite ligands **L1–L5** were efficiently synthesized from readily available starting materials (Scheme 1).[15] The

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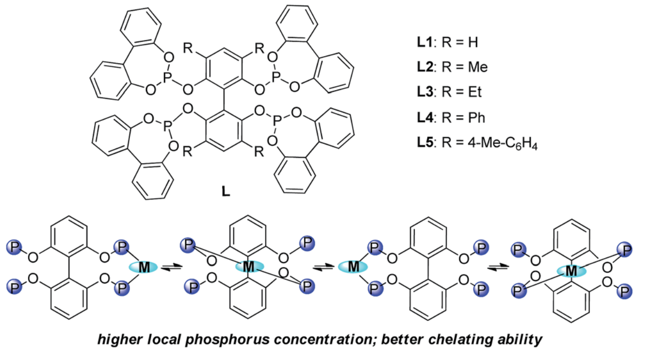


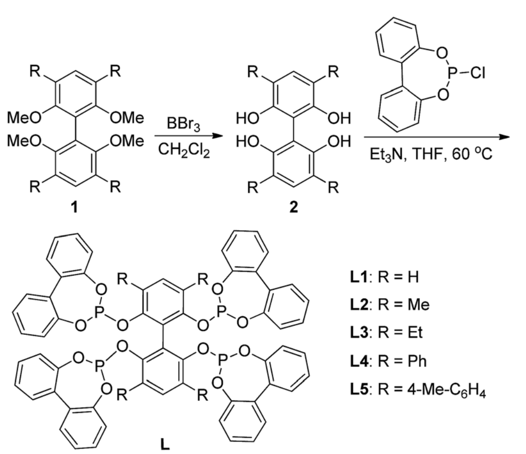
Fig. 1 Tetraphosphite ligands **L1–L5** and four identical coordination modes with rhodium.

ligand backbone 2,6,2′,6′-tetramethoxybenzene **1** was smoothly deprotected with BBr_3,[15a] formed the key intermediate [1,1′-biphenyl]-2,2′,6,6′-tetraol **2**. The condensation of compound **2** with the preformed phosphorochloridite in the presence of the triethylamine as hydrogen chloride scavenger provided the desired tetraphosphite ligands **L1–L5** in good yields.[15c]

With the tetraphosphite ligands **L1–L5** in hand, we began our studies by evaluating them in the linear hydroformylation of 1-octene as the model substrate with the catalyst generated *in situ* by mixing $Rh(acac)(CO)_2$ and ligands **L1–L5** in toluene. As shown in Table 1, ligands **L1–L5** displayed high reactivities and excellent regioselectivities (Table 1, entries 1–5). Almost all of the reactions finished within 2 h. To our delight, the ligand **L2** was revealed as the best ligand in terms of regioselectivity (ratio of l/b up to 31, Table 1, entry 2). Ligands screening results demonstrated that the substituents on the biphenyl ring played a key role in determining the regioselectivity.

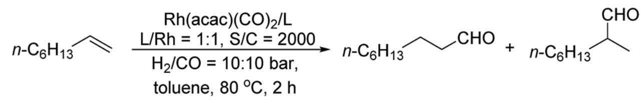
Subsequently, we investigated the effects of ligand **L2**/metal molar ratios, reaction temperature, and the pressure of CO/H_2 on the catalytic activity and regioselectivity. As expected, the ratio of ligand **L2**/$Rh(acac)(CO)_2$ has a great influence on the reaction, increasing the ratio from 1 : 1 to 3 : 1 (Table 2, entries 1–3) led to the dramatic improvement on the regioselectivity and the ratio of l/b was improved from 31 to 46. The conversion became lower when the ligand/metal ratio was increased to 4 : 1, although a little higher regioselectivity was obtained (Table 2, entry 4). The further increment of the ligand/metal ratio to 8 : 1 resulted in nearly no reactivity (Table 2, entry 5). The reaction temperature also displayed dramatic effect on the reaction. Decreasing the temperature from 80 °C to 60 °C gave lower reactivity (Table 2, entry 3 *vs.* entry 6). In addition, we found that the catalytic system is also sensitive to the pressures of CO/H_2. Excellent regioselectivity and reactivity were obtained when the pressures of CO/H_2 was maintained at 5 : 5 bar (up to 93.4% conversion and l/b ratio up to 65, Table 2, entry 7).

Solvent effects were also investigated and the results were summarized in Table 3. The reactions were performed well in



Scheme 1 Synthesis of the tetraphosphite ligands L1–L5.

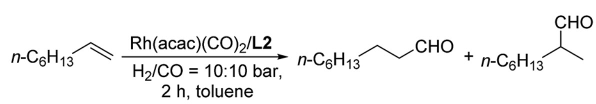
Table 1 Screening ligands for hydroformylation of 1-octene[a]



Entry	L	Conv.[b] (%)	l/b[c]	Linear[d] (%)	Iso.[e] (%)	TON[f]
1	**L1**	98.5	19	95.0	9.5	1.97×10^3
2	**L2**	88.2	31	96.9	9.1	1.76×10^3
3	**L3**	98.4	13	92.9	9.7	1.97×10^3
4	**L4**	98.9	9	90.0	5.3	1.97×10^3
5	**L5**	99.7	9	90.0	7.2	1.97×10^3

[a] S/C = 2000, [Rh] = 0.2 μM, toluene as solvent, 1-octene as the substrate, decane as internal standard, **L1–L5** as the ligand. [b] Conversion of 1-octene was determined on the basis of GC analysis. [c] Linear/branched ratio was determined on the basis of GC analysis. [d] Percentage of linear aldehyde. [e] Percentage of the isomerized alkene. [f] Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis.

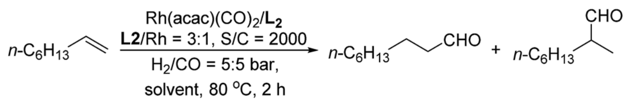
Table 2 Optimization conditions for hydroformylation of 1-octene catalyzed by $Rh(acac)(CO)_2$/**L2**[a]



Entry	L/Rh	T[b] (°C)	Conv.[c] (%)	l/b[d]	Linear[e] (%)	Iso.[f] (%)	TON[g]
1	1 : 1	80	88.2	31	96.9	9.1	1.76×10^3
2	2 : 1	80	86.9	35	97.2	8.5	1.72×10^3
3	3 : 1	80	81.8	46	97.9	5.9	1.64×10^3
4	4 : 1	80	70.7	47	97.9	5.6	1.41×10^3
5	8 : 1	80	NA	NA	NA	NA	NA
6	3 : 1	60	50.9	43	97.8	3.5	1.02×10^3
7[h]	3 : 1	80	93.4	65	98.5	6.3	1.87×10^3

[a] S/C = 2000, [Rh] = 0.2 μM, toluene as solvent, 1-octene as the substrate, decane as internal standard, **L2** as the ligand. [b] Oil bath temperature. [c] Conversion of 1-octene was determined on the basis of GC analysis. [d] Linear/branched ratio was determined on the basis of GC analysis. [e] Percentage of linear aldehyde. [f] Percentage of the isomerized alkene. [g] Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis. [h] H_2/CO = 5 : 5 bar. NA = not available.

Table 3 Screening solvents for hydroformylation of 1-octene catalyzed by $Rh(acac)(CO)_2$/**L2**[a]



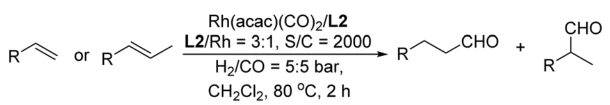
Entry	Solvent	Conv.[b] (%)	l/b[c]	Linear[d] (%)	Iso.[e] (%)	TON[f]
1	Toluene	93.4	65	98.5	6.3	1.87×10^3
2	CH_2Cl_2	96.9	86	98.8	6.8	1.94×10^3
3	EA	92.6	65	98.5	6.7	1.85×10^3
4	$CHCl_3$	88.6	84	98.8	5.8	1.77×10^3
5	iPrOH	74.9	68	98.6	5.3	1.50×10^3
6	Dioxane	97.5	67	98.6	6.6	1.95×10^3
7	CH_3CN	91.4	89	98.9	7.6	1.83×10^3
8	THF	96.9	59	98.3	7.3	1.94×10^3

[a] S/C = 2000, [Rh] = 0.2 μM, 1-octene as the substrate, decane as internal standard, **L2** as the ligand. [b] Conversion of 1-octene was determined on the basis of GC analysis. [c] Linear/branched ratio was determined on the basis of GC analysis. [d] Percentage of linear aldehyde. [e] Percentage of the isomerized alkene. [f] Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis. EA = ethyl acetate.

toluene, ethyl acetate and 1,4-dioxane with similar results (Table 3, entries 1, 3, 6). CH_2Cl_2 as the solvent afforded high l/b ratio (up to 86) and excellent conversion (96.9% conversion, Table 3, entry 2). Moderate conversion was achieved in isopropanol (74.9% conversion, Table 3, entry 5). Compared with CH_2Cl_2, chloroform and acetonitrile gave similar regioselectivies but with a little lower reactivities (Table 3, entries 4 and 7). As a result, CH_2Cl_2 was the best choice as the solvent.

Promoted by these excellent results, we turned our attention to investigate the catalytic system $Rh(acac)(CO)_2$/**L2** for the hydroformylation of representative substrates. As shown in Table 4, 1-octene and 1-hexene provided excellent results in the transformations. Conversion was up to 99.2% and the ratio of l/b was up to 90 (Table 4, entries 1–2). In addition, we also applied them into the hydroformylation of styrene, which is a well-known olefinic substrate preferring the branched aldehyde in most Rh-catalyzed hydroformylation transformations. We found that the tetraphosphite ligand **L2** displayed moderate reactivity and regioselectivity (Table 4, entry 3). To our delight, the challenging substrate internal olefin 2-octene (*trans*/*cis* molar ratio = 1 : 1) also proceeded well and obtained good regioselectivity (Table 4, entry 4).

Table 4 Scope study for the hydroformylation under optimized reaction conditions[a]



Entry	Substrate	Conv.[b] (%)	l/b[c]	Linear[d] (%)	Iso.[e] (%)	TON[f]
1	1-Octene	96.9	86	98.8	6.8	1.94×10^3
2	1-Hexene	99.2	90	98.9	6.9	1.98×10^3
3	Styrene	63.4	0.6	37.5	ND	1.28×10^3
4[g]	2-Octene	60.6	16	94.1	ND	1.20×10^3

[a] S/C = 2000, [Rh] = 0.2 μM, CH_2Cl_2 as solvent, decane as internal standard, **L2** as the ligand. [b] Conversion was determined on the basis of GC analysis. [c] Linear/branched ratio was determined on the basis of GC analysis. [d] Percentage of linear aldehyde. [e] Percentage of the isomerized alkene. [f] Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis. [g] The reaction temperature is 100 °C, and the reaction time is 10 h. ND = not determined.

Conclusions

In conclusion, new tetraphosphite ligands **L1–L5** were successfully developed and applied in the Rh-catalyzed hydroformylation of terminal and internal olefins. High catalytic reactivity and excellent regioselectivity for the linear aldehydes were obtained in the Rh-catalyzed hydroformylation of simple and unfunctionalized olefins (l/b ratio up to 90, 98.9% linear selectivity, 99.2% conversion) using the tetraphosphite ligand **L2**. In addition, the tetraphosphite ligand **L2** displayed moderate linear regioselectivity for styrene affording 3-phenylpropanal. And the challenging substrate internal olefin 2-octene also proceeded well and obtained good regioselectivity. Further application of the ligands for related catalytic reactions is underway in our laboratory.

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