This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
New Tetraphosphite Ligands for Regioselective Linear Hydroformylation of Terminal Olefins and Internal Olefin

Zongpeng Zhang†, Caiyou Chen†, Qian Wang, Zhengyu Han, Xi-Qin Dong*, and Xumu Zhang*

Abstract: We successfully developed new tetraphosphite ligands L1-L5 and applied them into 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 the 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 aldehydes products are very momentous compounds and valuable intermediates for synthesis of various chemicals, such as alcohols, amines and esters et al.[4] They were 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 (Figure 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.
COMMUNICATION

Figure 1. Tetraphosphite ligands L1-L5 and four identical coordination modes with rhodium.

Results and discussion

The new tetraphosphite ligands L1-L5 were efficiently synthesized from readily available starting materials (Scheme 1). The ligand backbone 2,6,2',6'-tetramethoxybenzene 1 was smoothly deprotected with BBr3, forming 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.

Figure 2. Synthesis of the tetraphosphite ligands L1-L5.

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/H2 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 reaction (Table 2, entry 3 vs entry 4). The further increment of the ligand/metal ratio to 8:1 also displayed dramatic effect on the reaction. Table 2. Optimization conditions for hydroformylation of 1-octene catalyzed by Rh(acac)(CO)/L2.

Table 1. Screening ligands for hydroformylation of 1-octene.

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>conv. (%)</th>
<th>l/b</th>
<th>Linear (%)</th>
<th>iso. (%)</th>
<th>TONf</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>98.5</td>
<td>19</td>
<td>95.0</td>
<td>9.5</td>
<td>1.97×10^2</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>88.2</td>
<td>31</td>
<td>96.9</td>
<td>9.1</td>
<td>1.76×10^2</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>98.4</td>
<td>13</td>
<td>92.9</td>
<td>7.9</td>
<td>1.97×10^3</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>98.9</td>
<td>9</td>
<td>90.0</td>
<td>9.3</td>
<td>1.97×10^3</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>99.7</td>
<td>9</td>
<td>90.0</td>
<td>7.2</td>
<td>1.97×10^3</td>
</tr>
</tbody>
</table>

*Comparison of linear aldehyde. 
*Conversion of 1-octene was determined based on the basis of GC analysis. 
*Linear/branched ratio was determined on the basis of GC analysis. 
*Percentage of linear aldehyde. 
*Percentage of the isomerized alkene. 
*Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis.
Table 3. Screening solvents for hydroformylation of 1-octene catalyzed by Rh(acac)(CO)/L2<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conv. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>/b&lt;sup&gt;c&lt;/sup&gt;</th>
<th>linear (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>iso. (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>TON&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>93.4</td>
<td>65</td>
<td>98.5</td>
<td>6.3</td>
<td>1.87 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96.9</td>
<td>86</td>
<td>98.8</td>
<td>6.8</td>
<td>1.94 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>EA</td>
<td>92.6</td>
<td>65</td>
<td>98.5</td>
<td>6.7</td>
<td>1.85 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>88.6</td>
<td>84</td>
<td>98.8</td>
<td>5.8</td>
<td>1.77 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>iPrOH</td>
<td>74.9</td>
<td>68</td>
<td>98.6</td>
<td>5.3</td>
<td>1.50 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>dioxane</td>
<td>97.5</td>
<td>67</td>
<td>98.6</td>
<td>6.6</td>
<td>1.95 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CN</td>
<td>91.4</td>
<td>89</td>
<td>98.9</td>
<td>7.6</td>
<td>1.83 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>96.9</td>
<td>59</td>
<td>98.3</td>
<td>7.3</td>
<td>1.94 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>S/C = 2000, [Rh] = 0.2 uM, CH2Cl2 as solvent, decane as internal standard, L2 as the ligand.<br><sup>b</sup>Conversion was determined on the basis of alkene conversion by GC analysis. EA = Ethyl Acetate. Linear/branched ratio was determined on the basis of GC analysis. Percentage of linear aldehyde. Percentage of the isomerized alkene.<br><sup>e</sup>Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis. 

Table 4. Scope study for the hydroformylation under optimized reaction conditions<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>conv. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>/b&lt;sup&gt;c&lt;/sup&gt;</th>
<th>linear (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>iso. (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>TON&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>96.9</td>
<td>86</td>
<td>98.8</td>
<td>6.8</td>
<td>1.94 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1-hexene</td>
<td>99.2</td>
<td>90</td>
<td>98.9</td>
<td>6.9</td>
<td>1.98 x 10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>styrene</td>
<td>63.4</td>
<td>0.6</td>
<td>37.5</td>
<td>ND</td>
<td>1.28 x 10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>2-octene</td>
<td>60.6</td>
<td>16</td>
<td>94.1</td>
<td>ND</td>
<td>1.20 x 10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>c</sup>S/C = 2000, [Rh] = 0.2 uM, CH2O2 as solvent, decane as internal standard, L2 as the ligand. Conversion was determined on the basis of GC analysis. Linear/branched ratio was determined on the basis of GC analysis. Percentage of linear aldehyde. Percentage of the isomerized alkene. Turn over number (TON) was determined on the basis of the alkene conversion by GC analysis. 

With CH<sub>2</sub>Cl<sub>2</sub>, chloroform and acetonitrile gave similar regioselectivities but with a little lower reactivities (Table 3, entries 4 and 7). As a result, CH<sub>2</sub>Cl<sub>2</sub> was the best choice as the solvent.

Promoted by these excellent results, we turned our attention to investigate the catalytic system Rh(acac)(CO)/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 /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).

**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 (/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.

**Acknowledgments**

We thank the grant from Wuhan University (203273463, 203410100064), and “111” Project of the Ministry of Education of China for financial support and the National Natural Science Foundation of China (Grant No. 21372179, 21432007, 21502145).

**Notes and references**


