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New Tetraphosphorus Ligands for Highly Linear Selective Hydroformylation of Allyl and Vinyl Derivatives

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Abstract: New tetraphosphorus ligands have been developed and applied in the rhodium-catalyzed regioselective hydroformylation of a variety of functionalized allyl and vinyl derivatives. Remarkably high linear selectivity was obtained by these tetraphosphorus ligands. The ligand that bears strong electron-withdrawing 2,4-difluorophenyl groups is the most effective one in affording linear aldehydes. The Rh/tetraphosphorus ligand catalyst is highly effective to produce linear aldehydes from functionalized allyl derivatives with heteroatoms or aromatic groups directly adjacent to the allyl group. For vinyl derivatives, the ligand is highly linear selective for acrylic derivatives, styrene, vinyl pyridine, and vinyl phthalimide. Linear to branch ratios of 26:1 and 10:1 were obtained for the hydroformylation of styrene and allyl cyanide, respectively.

Keywords: hydroformylation · ligand · olefin · regioselectivity · rhodium

Introduction

Hydroformylation of alkenes is one of the most important homogenous catalytic processes to produce aldehydes and alcohols. The process provides versatile intermediates and building blocks for pharmaceuticals, agrochemicals, and commodity and fine chemicals. Production of aldehydes is estimated at over 9 million tons per year.[1] Currently, highly reactive rhodium catalysts modified with monodentate or bidentate ligands are employed in most commercial hydroformylation processes. Although the process has been commercialized for many decades, it is still under constant development to address and improve reaction speed, catalyst stability, and product selectivity.[2] Over the past few decades, many ligand systems have been developed. Some elegant examples include Devon's bisbi,[3] van Leeuwen's xantphos and bisphosphoramidite,[4] Beller's naphos,[5] Union Carbide's biphephos,[6] and DuPont/DSM's bulky phosphites.[7]

Hydroformylation of vinyl and allyl derivatives is a cost-effective process to produce functionalized linear or branched aldehydes from readily available cheap starting materials. The functionalized aldehydes produced from the hydroformylation process can be further converted to dialdehydes, diols, diacids, amino aldehydes, amino alcohols, or amino acids, which can be used as versatile building blocks in organic synthesis such as indolization, alkylation, amination, and amide coupling to make polymers, macrocycles, and pharmaceutical intermediates.[8] For example, some biologically important compounds can be prepared by regioselective hydroformylation of vinyl and allyl derivatives. As shown in Figure 1, γ-aminobutyric acid (GABA) and 5-hydroxytryptamine (Serotonin) are two important naturally occurring neurotransmitters that have important regulation roles in the central nervous system of humans.[9] Cinacalcet is a calcimimetic drug developed by Amgen and used for the treatment of hyperparathyroidism.[10] The linear selective hydroformylation of styrene derivatives can be used to prepare Cinacalcet and its analogues. The development of hydroformylation technology on functionalized olefins can provide a variety of functionalized aldehydes as building blocks to explore potential chemical structure space in drug optimization.

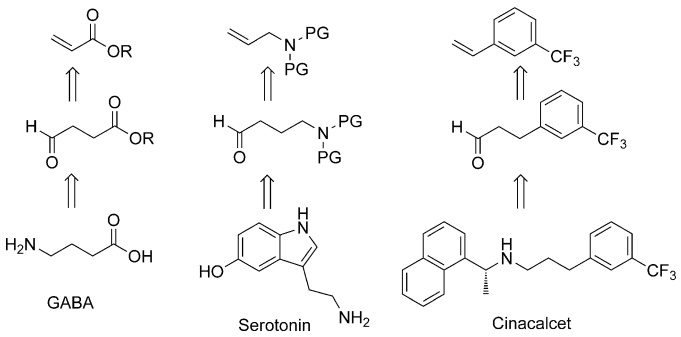

Figure 1. Biologically active compounds can be prepared by hydroformylation of functionalized vinyl and allyl derivatives. PG = protecting group.

However, many vinyl and allyl derivatives have intrinsic properties to afford branched aldehydes due to the chelating effect from the neighboring heteroatoms or arenes; there-

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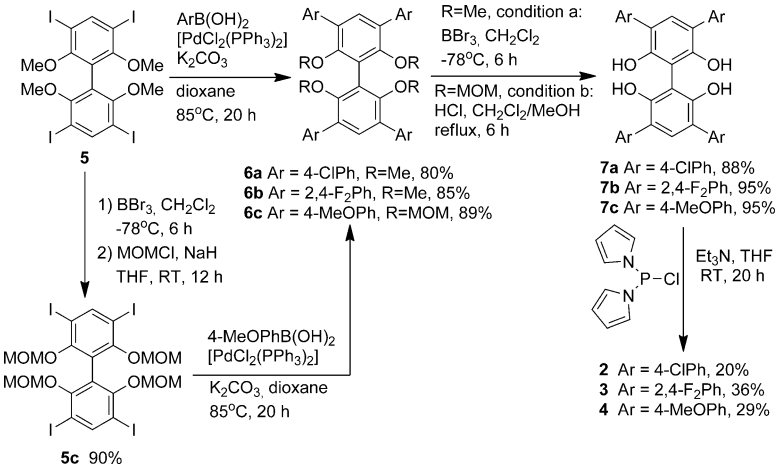
fore, commonly the hydroformylation of allyl and vinyl derivatives is limited to produce mainly branched aldehydes and is often a subject for asymmetric hydroformylation. For example, styrene, vinyl acetate, and allyl cyanide are often applied as benchmark substrates for asymmetric hydroformylation.[11] On the contrary, developing a catalyst system to control the regioselectivity to make linear aldehydes in high yields from allyl and vinyl derivatives is largely unsolved. It has been a challenging task to develop catalysts for these substrates to afford highly linear aldehydes. In the early 1990s, Botteghi et al. reported a linear-to-branch (l/b) ratio of 4.9 for the hydroformylation of allyl cyanide using a platinum complex.[12] Buchwald et al. observed typical l/b ratios from 1.8 to 18 for a few allyl derivatives using Union Carbide's biphephos ligand.[13] Recently, several ligand systems (SUPRAphos ligands by Reek,[14] 6-DPPon ligands by Breit,[15] and hemispherical phosphites by Matt[16]) have been reported to afford linear selectivities ranging from 72 to 77% for the hydroformylation of styrene. Beller et al. reported linear selectivities of 85 and 98% for styrene and *N*-vinylphthalimide, repectively, using a palladium-based catalyst modified by the 2-(dicyclohexylphosphino)-1-(2-(dicyclohexyl-phosphino)naphthalen-1-yl)-1H-pyrrole ligand.[2a] Our group have reported the development of pyrrole based tetraphosphorus ligands for highly linear selective hydroformylation of unfunctionalized simple olefins and styrenes.[17] A linear-to-branch (l/b) ratio of 22 was obtained for the hydroformylation of styrene. Herein, we would like to report our most recent development of new tetraphosphorus ligands that can afford unprecedented high linear selectivity for the hydroformylation of a variety of allyl and vinyl derivatives.



Scheme 1. Synthesis of ligands **2**–**4**.

5 was prepared by oxidative homo coupling of 1,3-dimethoxybenzene, followed by iodination.[17] Starting from compound **5**, compounds **6a** and **6b** were prepared by Suzuki coupling of the tetraiodide with the corresponding boronic acids using $[PdCl_2(PPh_3)_2]$ or $[Pd(PPh_3)_4]$ as the catalyst. Treatment of compounds **6a** and **6b** with boron tribromide removed the methyl ether protection and afforded tetraols **7a** and **7b** in 88 and 95% yields, respectively. Compound **6c** was obtained by first removing the methyl ether protection and installing the methoxymethyl ether (MOM) protection instead, followed by Suzuki coupling of compound **5c** with 4-methoxyphenyl boronic acid. The MOM protection groups can be removed under mild conditions with 4-methoxyphenyl groups untouched. Treatment of compound **6c** with concentrated HCl removed the MOM protection and afforded compound **7c** in 95% yield. Chlorodipyrrolylphosphine was prepared by reacting pyrrole with PCl_3 in a stoichiometric ratio under the presence of triethylamine,[4d] and it was freshly distilled before immediate use in the next step. Finally, the couplings of tetraols **7a**, **7b**, and **7c** with chlorodipyrrolylphosphine afforded the tetraphosphorus ligands **2–4** in yields ranging from 20 to 36%.

Results and Discussion

The structures of the pyrrole-based tetraphosphorus ligands are depicted in Figure 2. Ligand **1** was previously reported and used as a benchmark in this study.[17] The synthesis of ligands **2–4** is shown in Scheme 1. The tetraiodide compound

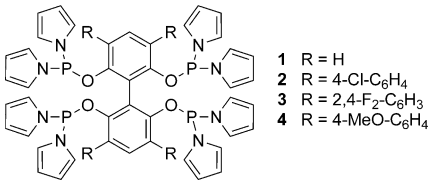
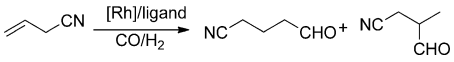


Figure 2. Tetraphosphorus ligands.

After the preparation of ligands **1–4**, the hydroformylation of functionalized allyl and vinyl derivatives was then investigated. Allyl cyanide, which usually gives branched aldehyde in hydroformylation, was selected as the model substrate to test the effectiveness of the new ligands. Ligand **1** was first applied to optimize the hydroformylation conditions of allyl cyanide with respect to CO/H_2 pressure and reaction temperature. The rhodium catalyst was prepared in situ by mixing the tetraphosphorus ligand with $[Rh(acac)(CO)_2]$ (acac = acetylacetonate) in toluene. The effect of CO/H_2 pressure was tested with pressure ranging from 5/5 to 30/30 atm (Table 1, entries 1–4). With the increase of CO/H_2 pressure, the regioselectivity decreases. The highest regioselectivity was obtained under a CO/H_2 pressure of 5/5 atm with a linear-to-branch ratio of 5.2 (Table 1, entry 1). However, a slightly higher percentage of olefin isomer was observed at this pressure, indicating that the β-H elimination

Table 1. Hydroformylation of allyl cyanide with ligands **1**–**4**.[a]



Entry	Ligand	T [°C]	CO/H_2 [atm]	t [h]	l/b[b]	Isom.[c] [%]	TON[d]
1	**1**	100	5/5	1	5.2	8	855
2	**1**	100	10/10	1	2.8	8	871
3	**1**	100	20/20	1	2.1	6	920
4	**1**	100	30/30	1	1.9	5	913
5	**1**	60	5/5	1	4.0	10	800
6	**1**	80	5/5	1	4.3	8	819
7	**1**	120	5/5	1	5.2	3	857
8	**1**	100	5/5	0.5	5.3	10	828
9	**2**	100	5/5	0.5	7.9	11	778
10	**3**	100	5/5	0.5	10.3	16	728
11	**4**	100	5/5	0.5	4.6	9	779

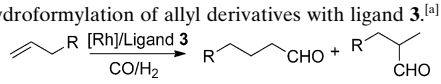
[a] S/C = 1000, $[Rh(acac)(CO)_2] = 1.0$ mM, ligand/Rh = 4:1, toluene as solvent, decane as internal standard. [b] Linear/branched ratio, determined by GC. [c] Percent of isomer. [d] Turnover number to all aldehydes, determined by GC.

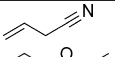
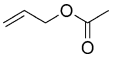
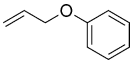
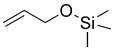
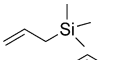
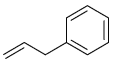
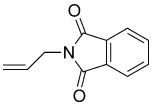
was facilitated under lower CO/H_2 pressures. The facilitation of β-H elimination made the reaction more reversible to the starting material, thus may also contribute to the improvement of regioselectivity. Under high CO/H_2 pressure, the chelating ligand in the Rh complex may be partially displaced by CO, resulting in unselective catalyst species and therefore lowering linear selectivity.[1] The effect of reaction temperature was also investigated (Table 1, entries 1 and 5–7). There was a slight increase in regioselectivity with l/b ratios improved from 4.0 to 5.2 when the temperature was raised from 60 to 100 °C. For temperatures above 100 °C, the l/b ratio did not change too much. The observed percentage of olefin isomer decreased with the increase of reaction temperature. Overall, better linear-to-branch ratios were obtained under lower CO/H_2 pressure and at higher reaction temperature.

The ligand effect on the hydroformylation regioselectivity is remarkable. Compared with ligand **1**, the substituents at the *para* position of the phenyl moiety indeed affected the regioselectivity significantly. An electron-withdrawing group has a positive effect on the linear selectivity and an increasing trend is observed when the substituent is changing from a strong electron-donating group to a strong electron-withdrawing group. The highest linear selectivity was afforded with ligand **3** (Table 1, entry 10, l/b = 10.3), which bears two strong electron-withdrawing fluoro groups on the phenyl ring; in contrast, the methoxy group, which is a strong electron-donating group, afforded the lowest linear selectivity (Table 1, entry 11, l/b = 4.6). Furthermore, compared with ligand **1**, the attachment of a 4-methoxyphenyl group at the 3,3′,5,5′-positions of the biphenyl backbone in ligand **4** did not result in a significant change in linear selectivity (Table 1, entry 8 vs. entry 11), indicating that there is little steric effect at the 3,3′,5,5′-positions on the regioselectivity for the hydroformylation of allyl cyanide. As for the catalyst activity, the electronic effect is not large, and a moderate decrease in turnover number (TON) was observed with an increased electron-withdrawing property (Table 1, entries 9–11). It is well documented in the literature that allyl cyanide is a substrate that favors branched aldehyde formation.[11] In sharp contrast, the tetraphosphorus ligands **1**–**4** afforded the terminal aldehyde with high linear selectivity. To the best of our knowledge, ligand **3** afforded the highest linear selectivity for the hydroformylation of allyl cyanide ever reported.

Next, ligand **3** was applied in the hydroformylation of functionalized allyl derivatives. The results are summarized in Table 2. We were pleased to find that ligand **3** is effective and highly regioselective to produce linear aldehydes from allyl derivatives bearing various functional groups. After 2 h at 120 °C, the hydroformylation of allyl acetate and allyl phenyl ether afforded the corresponding aldehydes in 94 and 83 % yields, respectively, with high linear selectivities (l/b ≥ 18, Table 2, entries 2 and 3). In addition, silyl and siloxy groups were tolerated under the hydroformylation conditions, and the allyl derivatives with these functional groups were converted to the corresponding aldehydes with linear to branched ratios of ≥ 43 (Table 2, entries 4 and 5). For allyl benzene, aldehydes (65 %) were obtained with a linear-to-branch ratio of 36; however, the percentage of olefin isomerization was high because its isomer, β-methylstyrene, is more stable and much less reactive than the starting material (31 % isomer, Table 2, entry 6). The hydroformylation of primary and secondary amines usually resulted in complex reaction mixtures because of the potential further reactions of the amino group with the aldehydes; however, the hydroformylation of the protected amine as phthalimide afforded aldehydes in 92 % yield with high linear selectivity (l/b = 13, Table 2, entry 7).

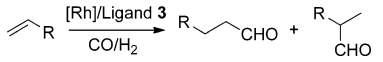
Table 2. Hydroformylation of allyl derivatives with ligand **3**.[a]

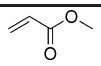
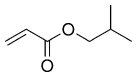
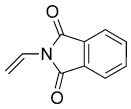


Entry	Olefin	Conv.[b] [%]	Alde.[c] [%]	l/b[d]	Isom.[e] [%]
1[f]		89	73	10	16
2		95	94	26	< 1
3		94	83	18	3
4		60	44	51	14
5		53	51	43	2
6		96	64	36	31
7		99	92	13	7

[a] S/C = 1000, $[Rh(acac)(CO)_2] = 1.0$ mM, ligand/Rh ratio = 4:1, CO/H_2 = 5/5 atm, 120 °C, reaction time 2 h, toluene as solvent, decane as internal standard, reaction results determined by GC or isolated product. [b] Conversion of starting material. [c] Percent of total aldehydes. [d] Linear/branched ratio, determined by GC or NMR spectroscopy. [e] Percent of isomerization of starting material. [f] 100 °C, 0.5 h.

Table 3. Hydroformylation of vinyl derivatives with ligand **3**.[a]



Entry	Olefin	Conv.[b] [%]	Alde.[c] [%]	l/b[d]	Hydr.[e] [%]
1		81	78	345	0
2		77	77	66	0
3		91	89	107	0
4		88	88	464	0
5		89	81	26	8
6		95	64	20	31
7		95	55	9.4	40
8		45	45	2.6	0
9		80	80	0.8	0

[a] S/C = 1000, [Rh(acac)(CO)$_2$] = 1.0 mM, ligand/Rh ratio = 4:1, CO/H$_2$ = 5/5 atm, 120 °C, reaction time 2 h, toluene as solvent, decane as internal standard, reaction results determined by GC or isolated product. [b] Conversion of starting material. [c] Percent of total aldehydes. [d] Linear/branched ratio, determined by GC or NMR spectroscopy. [e] Percent of hydrogenation of starting material.

Finally, ligand **3** was applied in the hydroformylation of functionalized vinyl derivatives. The results were summarized in Table 3. As expected, the catalyst is very effective and highly linear selective for the hydroformylation of a variety of vinyl derivatives. For vinyl acrylic substrates (Table 3, entries 1–4), remarkably high linear selectivities (l/b $\geq$ 66) were obtained. The catalyst was also found to be highly linear selective for the hydroformylation of styrene and 4-vinylpyridine, and linear-to-branched ratios of 26 and 20 were obtained, respectively (Table 3, entries 5 and 6). The hydroformylation of *N*-vinylphthalimide afforded 55% aldehyde products with a linear-to-branched ratio of 9.4 (Table 3, entry 7). Lastly, vinyl ether and ester were tested for their regioselectivities. The hydroformylation of trimethylsilyl vinyl ether afforded aldehydes with a linear-to-branched ratio of 2.6 (Table 3, entry 8). But for vinyl acetate, the linear-to-branched ratio is only 0.8 (Table 3, entry 9). It is worth noting that for most of the substrates listed in Tables 2 and 3, we usually observed only a small amount (< 2%) of hydrogenation product under the hydroformylation conditions, but for styrene, 4-vinylpyridine, and *N*-vinylphthalimide, about 8, 31, and 40% of olefin hydrogenation products were observed under the hydroformylation conditions (Table 3, entries 5–7).

Styrene is a well-studied substrate that favors the formation of the branched aldehyde in hydroformylation because the branched Rh–styrene complex linked at the α carbon is stabilized by an η^2 coordination from the phenyl ring *ortho* to the Rh-C(α) link. The high linear selectivity of ligand **3** is unique and remarkable in that it was able to override the intrinsic branch preference of styrene in the Rh–styrene complex by ligand effects. To the best of our knowledge, ligand **3** afforded the highest linear selectivity (l/b = 26, Table 3, entry 5) for the hydroformylation of styrene ever reported.

To summarize our observations on the hydroformylation regioselectivity of allyl and vinyl derivatives catalyzed by the Rh/ligand **3** catalyst listed in Tables 2 and 3, several structural features of the functionalized alkenes are worth mentioning: 1) for a terminal olefin for which the γ-atom is carbon (allyl derivatives, vinyl acrylic derivatives, styrene, 4-vinylpyridine), the heteroatom or aromatic group has little effect on directing the regioselectivity, and high linear selectivity is observed; 2) for a terminal olefin for which the γ-atom is nitrogen (*N*-vinylphthalimide), the amino group needs to be protected, and high linear selectivity is observed; and 3) for a terminal olefin for which the γ-atom is oxygen (vinyl ether and acetate), mild to poor linear selectivity is observed. For example, allyl acetate, vinyl acetate, and methyl acrylate are compounds with high structural similarity; however, the high linear selectivities of allyl acetate (l/b = 26, Table 2, entry 2) and methyl acrylate (l/b = 345, Table 3, entry 1) are in sharp contrast with the low linear selectivity of vinyl acetate (l/b = 0.8, Table 3, entry 9). This sharp contrast indicates that under the influence of ligand **3**, the oxygen bearing functional groups in methyl acrylate and allyl acetate are not able to coordinate to the Rh center effectively and hence stabilize the branched Rh–alkyl complex as the γ-ester group in vinyl acetate does; therefore, high linear selectivities were obtained for allyl acetate and methyl acrylate but not for vinyl acetate.

The reaction mechanism of the hydroformylation of simple unfunctionalized olefins catalyzed by Rh/Ph$_3$P has been well studied over decades. Wilkinson's dissociation mechanism is generally accepted,[18] and the regioselectivity has been explained to arise from the energy difference for the formations of linear and branched metal–alkyl complexes. Many functionalized allyl and vinyl derivatives have an intrinsic tendency to produce branched aldehydes due to the chelating effect from the neighboring heteroatoms or arenes; however, the Rh/tetraphosphorus catalyst system in this report is able to reverse this branch preference and to afford linear aldehydes with high regioselectivities. Further studies are required to completely elucidate the mechanism in detail.

Conclusion

New tetraphosphorus ligands have been developed and applied in the rhodium-catalyzed regioselective hydroformylation of a series of functionalized allyl and vinyl derivatives. For the hydroformylation of allyl cyanide, in contrast to the commonly observed branch selectivity reported in the litera-

ture, remarkably high linear selectivity was obtained by these tetraphosphorus ligands. The strong electron-withdrawing 2,4-difluorophenyl substituted ligand **3** is particularly effective in affording high linear selectivity. The Rh/tetraphosphorus ligand system reported herein is highly efficient in producing functionalized terminal aldehydes, which is complementary to other catalyst systems that mainly produce branched aldehydes. Ligand **3** is highly effective to produce linear aldehydes for allyl derivatives with substituents containing heteroatoms such as O, N, and Si adjacent to the allyl group. For vinyl derivatives, ligand **3** is highly linear selective for acrylic derivatives, styrene, vinyl pyridine, and vinyl phthalimide. Linear-to-branch ratios of 26 and 10 were obtained for the hydroformylation of styrene and allyl cyanide, respectively. The Rh/tetraphosphorus ligand system makes it possible to prepare functionalized terminal aldehydes from readily available vinyl and allyl derivatives through hydroformylation with high linear selectivity.

Experimental Section

General information: All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. All reagents and solvents were purchased from commercial vendors (Aldrich or TCI) unless otherwise noted. The reagents were used without further purification. Column chromatography was performed using 200–400 mesh silica gel supplied by Natland International Corporation. Thin layer chromatography (TLC) was performed on 0.25 mm silica 60-F plates. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All chemical shifts are reported in ppm. GC analysis was carried out on an Agilent 7890 gas chromatograph using capillary columns.

Typical hydroformylation procedure: Tetraphosphorus ligand (4 μmol) and [Rh(acac)(CO)$_2$] (1 μmol in 100 μL toluene, charged as stock solution) were added to an 8 mL glass vial with a magnetic stirring bar. The mixture was stirred for 5 min. Then allyl cyanide (1 mmol) was added, followed by the addition of *n*-decane (100 μL) as the internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was then transferred to an autoclave. The autoclave was sealed and purged with nitrogen at least four times and subsequently charged with CO (5 atm) and H_2 (5 atm). The autoclave was then immersed in a preheated oil bath and was well stirred. After the desired reaction time, the autoclave was taken out of the oil bath and cooled in cold water. The pressure was carefully released in a well-ventilated hood. The reaction mixture was immediately analyzed by GC and/or proton NMR spectroscopy to determine regioselectivity, conversion, and turnover number.

Synthesis of 3,3′,5,5′-tetraiodo-2,2′,6,6′-tetra(methoxymethoxy)-1,1′-biphenyl (5c): A solution of 3,3′,5,5′-tetraiodo-1,1′-biphenyl-2,2′,6,6′-tetraol (4.0 g, 5.54 mmol) in THF (10 mL) was added dropwise at 0 °C to a mixture of THF (15 mL) and NaH (640 mg, 26.6 mmol) in a 250 mL round bottom flask in an ice bath. After 1 h, the reaction mixture was allowed to warm to room temperature, and stirred for an additional 3 h. Methoxymethyl chloride (2.1 g, 26 mmol) in THF (10 mL) was added dropwise to the resulting reaction mixture. The reaction mixture was allowed to stir at room temperature for an additional 12 h. TLC indicated full conversion. The reaction mixture was poured into Et_2O (300 mL) and washed extensively with 3 N NaOH (3×75 mL). The organic layers were then combined, dried with $MgSO_4$, and concentrated to give the MOM-protected compound **5c** as an off-white solid (4.9 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.289 (s, 2H), 4.914 (s, 8H), 2.987 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 147.4, 126.3, 100.2, 87.8, 56.9 ppm.

Synthesis of 3,3′,5,5′-tetra(4-chlorophenyl)-2,2′,6,6′-tetramethoxy-1,1′-biphenyl (6a): A mixture of compound **5** (0.5 g, 0.64 mmol), 4-chlorophenyl boronic acid (0.8 g, 5.12 mmol), [Pd(PPh$_3$)$_4$] (0.148 g, 0.128 mmol), and K_2CO_3 (0.706 g, 5.12 mmol) in dioxane (10 mL) was stirred under N_2 for 24 h at 85 °C. The resulting reaction mixture was diluted by 50 mL water and extracted with EtOAc (3×75 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated to remove the solvent. The solid residue was subjected to silica gel flash chromatography (10% CH_2Cl_2 in hexane), which afforded compound **6a** as a white solid (0.44 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.555 (d, J = 8.4 Hz, 8H), 7.394 (d, J = 8.4 Hz, 8H), 7.346 (s, 2H), 3.363 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 137.0, 133.3, 132.4, 130.5, 129.6, 128.8, 124.4, 60.7 ppm.

Synthesis of 3,3′,5,5′-tetra(2,4-difluorophenyl)-2,2′,6,6′-tetramethoxy-1,1′-biphenyl (6b): A mixture of compound **5** (5 g, 6.4 mmol), 2,4-difluorophenyl boronic acid (6 g, 38 mmol), [PdCl$_2$(PPh$_3$)$_2$] (0.89 g, 1.28 mmol), and K_2CO_3 (7.06 g, 51.2 mmol) in dioxane (50 mL) was stirred under N_2 for 24 h at 85 °C. The resulting reaction mixture was diluted by 100 mL water and extracted with EtOAc (3×100 mL). The organic layers were combined, passed through a silica plug, and then dried with $MgSO_4$ and concentrated to remove the solvent. The solid residue was recrystallized from 1,2-dichloroethane (DCE) to afford compound **6b** as a white solid (4.2 g, 90% yield). ^{1}H NMR (400 MHz, DMSO): δ = 7.648 (q, J = 8.0 Hz, 4H), 7.368 (dt, J_1 = 9.8 Hz, J_2 = 2.6, 4H), 7.359 (s, 2H), 3.323 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6 (d, J_{CF} = 247.4), 160.6 (d, J_{CF} = 250.0), 157.1, 133.4, 132.4 (q, J_{CF} = 4.7), 123.9, 123.4, 122.1 (dd, J_{CF} = 16.0, 3.7), 111.2 (dd, J_{CF} = 21.0, 3.6), 104.1 (t, J_{CF} = 25.7), 60.6 ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = −109.6, −111.2 ppm.

Synthesis of 3,3′,5,5′-tetra(4-methoxyphenyl)-2,2′,6,6′-tetra(methoxymethoxy)-1,1′-biphenyl (6c): A mixture of compound **5c** (2.95 g, 3.3 mmol), 4-methoxyphenyl boronic acid (5.4 g, 36 mmol), [Pd(PPh$_3$)$_4$] (0.148 g, 0.26 mmol), and K_2CO_3 (5.1 g, 37 mmol) in dioxane (40 mL) was stirred under N_2 for 24 h at 85 °C. The resulting reaction mixture was diluted by 50 mL water, extracted with EtOAc (3×75 mL). The organic layers were combined, dried with $MgSO_4$, and passed through a silica gel plug. The solvent was then evaporated to afford compound **6c** as an off-white solid (2.4 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.536 (d, J = 8.8 Hz, 8H), 7.325 (s, 2H), 6.955 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 8H), 4.607 (s, 8H), 3.845 (s, 12H), 2.859 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 152.8, 132.3, 131.3, 131.2, 130.6, 125.1, 114.0, 98.5, 56.3, 55.5 ppm.

Synthesis of 3,3′,5,5′-tetra(4-chlorophenyl)-1,1′-biphenyl-2,2′,6,6′-tetraol (7a): Compound **6a** (1.75 g, 2.44 mmol) and CH_2Cl_2 (50 mL) were added to a 250 mL Schlenk flask. The resulting solution was cooled to −78 °C in a dry ice/acetone bath. Boron tribromide (1.05 mL, 10.8 mmol) was added dropwise to the cooled solution. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. After cooling to 0 °C, water (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization from methanol to give the title compound **7a** as a white solid (1.4 g, 88%). ^{1}H NMR (400 MHz, DMSO): δ = 8.099 (s, 4H), 7.610 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 8H), 7.438 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 8H), 7.163 ppm (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ = 153.1, 137.9, 131.4, 131.0, 130.6, 127.9, 120.0, 109.7 ppm.

Synthesis of 3,3′,5,5′-tetra(2,4-difluorophenyl)-1,1′-biphenyl-2,2′,6,6′-tetraol (7b): Compound **6b** (4.2 g, 5.8 mmol) and CH_2Cl_2 (50 mL) were added to a 250 mL Schlenk flask. The resulting solution was cooled to −78 °C in a dry ice/acetone bath. Boron tribromide (2.7 mL, 28.6 mmol) was added dropwise to the cooled solution. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. After cooling to 0 °C, water (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4, passed through a small pad of silica gel, and concentrated to remove the solvent. The crude product was purified by recrystallization from methanol to give the title compound **7b** as a white solid (3.8 g, 98%). ^{1}H NMR (400 MHz, DMSO): δ = 8.155 (s, 4H), 7.504 (q, J =

8.1 Hz, 4H), 7.232 (dt, $J_1=9.9$ Hz, $J_2=2.6$ Hz, 4H), 7.107 (dt, $J_1=8.7$ Hz, $J_2=2.7$ Hz, 4H), 6.983 ppm (s, 2H); ^{13}C NMR (100 MHz, DMSO): $\delta=$ 161.3 (dd, $J_{CF}=245.0$, 11.4), 159.7 (dd, $J_{CF}=248.1$, 12.2), 153.7, 133.6 (dd, $J_{CF}=9.4$, 5.2), 132.6, 122.7, 114.2, 111.1 (dd, $J_{CF}=20.8$, 3.2), 110.1, 103.8 ppm (t, $J_{CF}=26.3$); ^{19}F NMR (376.5 MHz, DMSO): $\delta=-109.3$, -112.7 ppm.

Synthesis of 3,3′,5,5′-tetra(4-methoxyphenyl)-1,1′-biphenyl-2,2′,6,6′-tetraol (7c): Compound **6c** (1.75 g, 5.8 mmol), CH_2Cl_2 (16 mL), and MeOH (24 mL) were added to a 250 mL flask, followed by 36% concentrated HCl (16 mL). The reaction mixture was stirred and refluxed for 6 h. After that, the reaction mixture was concentrated, diluted with 20 mL water and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, and passed through a small pad of silica gel. The solvent was then removed under reduced pressure to afford the tetraol product **7c** as a white solid (1.3 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.508$ (d, $J=8.4$ Hz, 8H), 7.346 (s, 2H), 6.989 (d, $J=8.8$ Hz, 8H), 5.428 (s, 4H), 3.848 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 159.0, 150.7, 132.9, 130.4, 129.3, 121.5, 114.3, 105.3, 55.4 ppm.

Synthesis of 3,3′,5,5′-tetra(4-chlorophenyl)-2,2′,6,6′-tetra((di-1-pyrrolylphosphino)oxy)-1,1′-biphenyl (2): A solution of triethylamine (1.4 mL) in THF (10 mL) and a solution of compound **7a** (1.321 g, 2 mmol) in THF (30 mL) at room temperature were added dropwise to a solution of chlorodipyrrolyphosphine (8.8 mmol, 1.75 g) in THF (10 mL). The Et_3N·HCl salts were formed immediately after the addition. The reaction mixture was stirred overnight ($\approx$12 h) at room temperature. The Et_3N·HCl salts were then filtered off and the solvent was removed under vacuum. The crude product was recrystallized from hexane to afford the title ligand **2** as a white solid (0.51 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.069$ (s, 2H), 7.066 (d, $J=8.5$ Hz, 8H), (s, 2H), 6.893 (d, $J=8.5$ Hz, 8H), 6.517 (s, 16H), 6.098 ppm (t, $J=2.1$ Hz, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 149.6, 134.6, 134.5, 134.0, 130.7, 130.6, 128.4, 120.8, 120.3, 112.1 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=105.7$; HRMS (ES$^+$) calcd for $C_{68}H_{51}N_8O_4P_4Cl_4$: 1307.1738 $[M]^+$; found: 1307.1609.

Synthesis of 3,3′,5,5′-tetra(2,4-difluorophenyl)-2,2′,6,6′-tetra((di-1-pyrrolylphosphino)oxy)-1,1′-biphenyl (3): A solution of triethylamine (1.4 mL) in THF (10 mL) and a solution of compound **7b** (1.333 g, 2 mmol) in THF (30 mL) at room temperature were added dropwise to a solution of chlorodipyrrolyphosphine (8.8 mmol, 1.75 g) in THF (10 mL). The Et_3N·HCl salts were formed immediately after the addition. The reaction mixture was stirred overnight ($\approx$12 h) at room temperature. The Et_3N·HCl salts were then filtered off and the solvent was removed under vacuum. The crude product was recrystallized from hexane to afford the title ligand **3** as a white solid (0.95 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.168$ (s, 2H), 6.706 (dt, $J_1=9.4$ Hz, $J_2=2.4$ Hz, 4H), 6.638 (m, 4H), 6.554 (m, 4H), 6.530 (s, 16H), 6.079 ppm (t, $J=2.1$ Hz, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.2$ (dd, $J_{CF}=250.9$, 12.6 Hz), 160.3 (dd, $J_{CF}=$ 250.0, 12.6 Hz), 151.2, 136.2, 133.1 (dd, $J_{CF}=10.1$, 4.0 Hz), 124.5, 121.0, 120.2, 119.8 (dd, $J_{CF}=15.1$, 3.0 Hz), 112.1, 111.4 (dd, $J_{CF}=21.1$, 4.0 Hz), 104.1 ppm (t, $J_{CF}=24.7$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=105.8$ ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$): $\delta=-108.7$, -109.8 ppm; HRMS (ES$^+$) calcd for $C_{68}H_{47}N_8O_4F_8P_4$: 1315.2543 $[M]^+$; found: 1315.2672.

Synthesis of 3,3′,5,5′-tetra(4-methoxyphenyl)-2,2′,6,6′-tetra((di-1-pyrrolylphosphino)oxy)-1,1′-biphenyl (4): A solution of triethylamine (1.4 mL) in THF (10 mL) and a solution of compound **7c** (1.285 g, 2 mmol) in THF (30 mL) were added dropwise to a solution of chlorodipyrrolyphosphine (8.8 mmol, 1.75 g) in THF (10 mL) at room temperature. The Et_3N·HCl salts were formed immediately after the addition. The reaction mixture was stirred overnight ($\approx$12 h) at room temperature. The Et_3N·HCl salts were then filtered off and the solvent was removed under vacuum. The crude product was recrystallized from hexane to afford the title ligand **4** as a white solid (0.75 g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.155$ (s, 2H), 7.020 (d, $J=8.4$ Hz, 8H), 6.668 (d, $J=8.8$ Hz, 8H), 6.510 (s, 16H), 6.061 (t, $J=2.0$ Hz, 16H), 3.806 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=159.0$, 134.8, 130.9, 130.7, 128.9, 121.0, 120.9, 120.8, 113.8, 111.7, 55.3 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=105.7$; HRMS (ES$^+$) calcd for $C_{72}H_{63}N_8O_8P_4$: 1291.3719 $[M]^+$; found: 1291.3721.

Synthesis of *N*-allylphthalimide (Table 2, entry 7 olefin): Potassium phthalimide (1.0 g, 5.4 mmol), tetrabutylammonium bromide (30 mg, 0.2 mmol), and DMF (25 mL) were added to a 125 mL flask. Allyl chloride (0.44 mL, 5.4 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by water (20 mL) and was stirred at 0 °C for 10 min. The resulting precipitate was filtered off, washed with water, and recrystallized from ethanol to yield the desired product (0.9 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.861$ (m, 2H), 7.725 (m, 2H), 5.894 (m,1H), 5.255 (dd, $J_1=16.8$ Hz, $J_2=1.3$ Hz, 1H), 5.199 (dd, $J_1=10.5$ Hz, $J_2=$ 1.3 Hz, 1H), 4.301 ppm (d, $J=5.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=167.9$, 134.0, 132.2, 131.6, 123.3, 117.8, 40.1 ppm.

Synthesis of 4-(1,3-dioxoisoindolin-2-yl)butanal (Table 2, entry 7): The typical hydroformylation procedure was followed. Once the reaction was complete, the solvent was removed under vacuum. The resultant crude product was subjected to flash column chromatography (silica gel, 25% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.779$ (t, $J=1.2$ Hz, 1H), 7.840 (m, 2H), 7.733 (m, 2H), 3.742 (t, $J=7.2$ Hz, 2H), 2.556 (dt, $J_1=7.3$ Hz, $J_2=1.2$ Hz, 2H), 2.030 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=200.8$, 168.3, 134.0, 132.0, 123.2, 41.0, 37.1, 21.1 ppm.

Synthesis of 3-(1,3-dioxoisoindolin-2-yl)propanal (Table 3, entry 7): The typical hydroformylation procedure was followed. Once the reaction was complete, the solvent was removed under vacuum. The resulted crude product was subjected to flash column chromatography (silica gel, 25% EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.828$ (t, $J=1.2$ Hz, 1H), 7.837 (m, 2H), 7.731 (m, 2H), 4.035 (t, $J=7.0$ Hz, 2H), 2.893 ppm (dt, $J_1=7.1$ Hz, $J_2=1.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=199.4$, 168.0, 134.1, 132.0, 123.4, 42.4, 31.7 ppm.

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Hydroformylation

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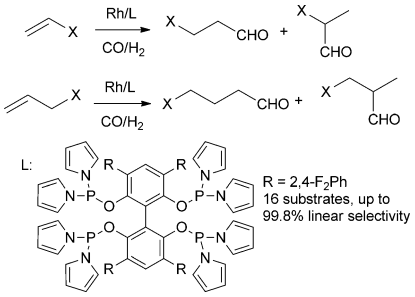
New Tetraphosphorus Ligands for Highly Linear Selective Hydroformylation of Allyl and Vinyl Derivatives



New tetraphosphorus ligands have been developed and applied in the rhodium-catalyzed regioselective hydroformylation of a variety of allyl and vinyl olefins (see scheme). Remarkably high linear selectivities were obtained by these ligands. Linear to branch ratios of 26:1 and 10:1 were obtained for the hydroformylation of styrene and allyl cyanide, respectively.

