SYNTHESIS OF NEW PHOSPHORUS LIGANDS FOR REGIOSELECTIVE HYDROFORMYLATION

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ABSTRACT OF THE THESIS

SYNTHESIS OF NEW PHOSPHORUS LIGANDS FOR REGIOSELECTIVE HYDROFORMYLATION

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Tetraphosphorous ligands with enhanced chelating ability through multiple chelating modes and increased local phosphorus concentration can provide great regioselectivity in Rh/Ligand hydroformylation system. Here we report the synthesis of a series of pyrrole-based tetraphosphorus ligands were synthesized with introducing different functional groups into 3, 3', 5, 5'-positions of the biphenyl, and their applications to the hydroformylation of internal olefins, 1, 5-hexadiene, styrene and its derivatives, and alkyl acrylates.

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. In particular, the alkyl-substituted tetraphosphorous ligands gave the best results (for 2-octene, n: i up to 207, for 2-hexene, n: i up to 362).

Double hydroformylation of 1, n-diolefins is a convenient method to produce dialdehydes. The hydroformylation of 1, 5- hexadiene can be achieved with essentially high regioselectivity (linear selectivity is up to 98%).

Styrene and its derivatives prefer the branched aldehydes under the hydro-formylation conditions. However, the linear aldehydes can also be widely used for the production of detergents and plasticizers and important intermediates. Our studies on the hydroformylation of styrene and its derivatives achieved unprecedented high linear selectivity (l/b up to 22 for styrene).

Hydroformylation of alkyl acrylate produces 1, 3- and1, 4-bifunctional compounds, which can be further converted into synthetically useful intermediates. Alkyl acrylates have been hydroformylated to the linear aldehydes with high regioselectivity (linear/branch > 99/1) and extraordinarily high average turnover frequencies (up to 5400 h^{-1}) by using a rhodium complex with a tetraphosphorus ligand. The result is in sharp contrast to the most of other processes that favor production of the branched aldehyde (typically > 95% branched for most Rh-catalyzed reaction systems).

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Chapter 1 Introduction

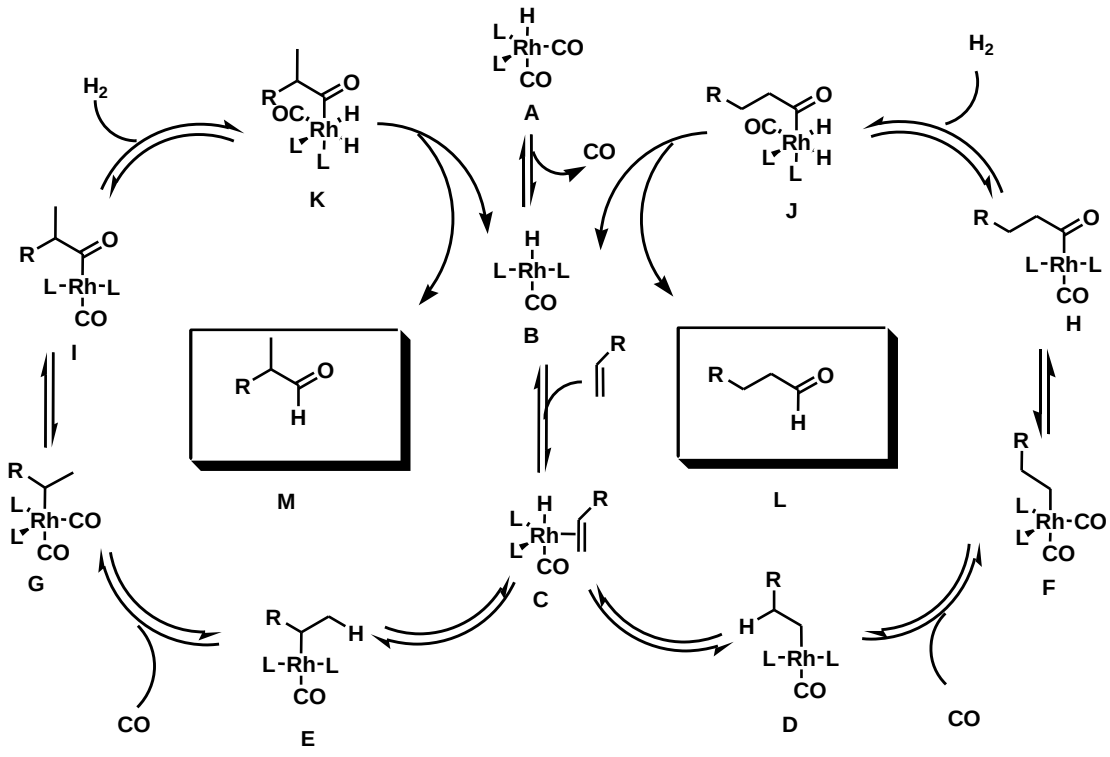
1.1 Background

Hydroformylation of olefins with carbon monoxide and hydrogen, discovered by Otto Roelen in 1938, is one of the largest industrially applied processes (eq. **1-1**).[1] Roelen's original research in hydroformylation involved the use of cobalt catalysts. Rodium complexes modified by phosphine ligands which were found by Wilkinson and coworkers are more reactive and selective than the cobalt catalysts found by Roelen.[2] About 9 million tons of oxo products were produced based on rhodium-catalyzed hydroformylation each year. The most active research area in hydroformylation is the development of highly regio- and stereoselective phosphorus ligands.

1.2 Mechanism for Rhodium-Catalyzed Hydroformylation

The mechanism of cobalt-catalyzed hydroformylation was first proposed by Breslow and Heck in the early 1960s[1b]. The so-called dissociative mechanism is applied with little modifications to the phosphine and phosphite modified rhodium-catalyzed hydroformylation (Scheme **1-1**). Thus, rhodium precursor reacts with ligand in the presence of CO and H_2 and forms an 18e trigonal bipyramidal intermediate **A**. Then a 16e coordinately unsaturated and active species **B** is formed after the dissociation of one carbon monoxide. Coordination of olefin to the rhodium center generates olefin complex **C**, which can go to either **D** (leading to linear product) or **E** (leading to branched product) based on the regio- and stereoselectivity of olefin insertion. Trigonal bipyramidal complexes **F** and **G** are formed via coordination of carbon monoxide to the rhodium

center. Migratory insertion of the alkyl group to one of the coordinated carbon monoxide gives the complex **H** and **I**. Finally, oxidative addition of hydrogen followed by reductive elimination affords the linear aldehyde **L** and the branched aldehyde **M** and regenerates the catalytically active species **B**.



Scheme **1-1** Mechanism for Rhodium-catalyzed Hydroformylation

1.3 Phosphorus Ligands for Rhodium-Catalyzed Regioselective Hydroformylation

Most of the 9 million tons of linear aldehydes produced annually by hydroformylation process are rhodium-catalyzed regioselective hydroformylation. Commercial hydroformylation processes use monophosphines as ligands. However, because bidentate ligands generally afford higher regioselectivity than monophosphines, the developments of them have attracted much more attention. In this section, we will briefly review

phosphours ligands used in regioselective hydroformylation, with the focus on bisdentate ligands and tetraphosphorous ligands.

Some representative ligands are shown in Figure **1-1**. The researchers at Eastman Kodak made a breakthrough in 1987 by introducing a bidentate phosphine ligand, Bisbi **1** (Figure **1-1**), for the rhodium catalyzed hydroformylation. Bisbi **1** achieved high regioselectivity for the hydroformylation of hex-1-ene (linear: branch =65.5:1).[3] Casey and coworkers systematically investigated the correlation between ligand bite angles and the regioselectivity in hydroformylation. They found that ligands with a natural bite angle of about 120 ^{o} such as Bisbi **1** are capable of forming equatorial-equatorial coordination at rhodium center thus leads to high regioselectivity in hydroformylation.[4] Beller and coworkers later found that NaPhos ligands **2** with strong electron-withdrawing substituents are excellent ligands for regioselective hydroformylation of internal olefins to linear aldehydes (linear branched ratio n: i of up to 9.5:1)[5]

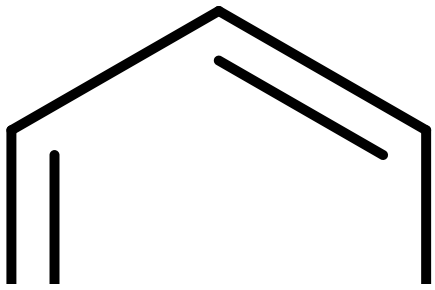


Figure **1-1** Ligands Derived from Bisbi for Regioselective Hydroformylation

Another category of highly regioselective ligands is designed based on "natural bite angle" concept. XantPhos **3** (Figure **1-2**) developed by van Leeween and coworkers

has been proved to be one of the best ligands for regioselective hydroformylation.[6] In contrast to Casey's proposal that bisequatorial coordination is a prerequisite for highly regioselective hydroformylation, van Leeuwen found that several XantPhos family ligands which prefer equatorial-axial coordination can also produce high regioselectivity. The bite angle effect on regioselectivity is now believed to be steric interactions between ligand and substrate in the steps of olefin coordination and hydride migration. Widening the bite angle leads to an increase in steric congestion around the rhodium center which results in the formation of the sterically less demanding linear alkyl rhodium species.[7] Dibenzophospholyl and phenoxaphosphanyl-substituted XantPhos type ligands **4** and **5** were later developed by van Leeuwen and coworkers.[8] These ligands showed high activity and regioselectivity in the rhodium-catalyzed hydroformylation of both terminal and internal octenes.

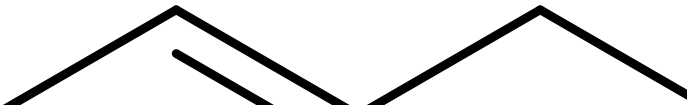


Figure **1-2** Ligands Derived from XantPhos for Regioselective Hydroformylation

Highly regioselective bulky diphosphites ligands have also been extensively developed (Figure **1-3**). With Biphephos **6**, originally developed by Billig and coworkers at Union Carbide,[9] Buchwald studied hydroformylation of a variety of functionalized olefins under mild reaction conditions with high linear selectivity.[10] High linear branched

ratios were achieved, and the catalyst can tolerate ketones, carboxylic acids, halides, acetals and thioacetals. Unsymmetrical Biphephos derivative **7** developed by van Leeuwen and coworkers also showed high regioselectivity in the hydroformylation of terminal olefins.[11]

Figure **1-3** Bulky Diphosphites for Regioselective Hydroformylation

Besides the Bisbi derivatives, XantPhos derivatives and bulky diphosphite, Figure **1-4** list some other types of phosphorus ligands used in regioselective hydroformylation. Hersh and coworkers reported electron-withdrawing *N*-sulfonylphosphoramide ligand **8**. [12] Moderate regioselectivity with linear branched ratio of up to 15.8 has been obtained with this ligand in the hydroformylation of 1-hexene. Breit and coworkers applied and synthesized a series of ligands (Figure **1-4**, **9-11**). Phosphabenzene ligand **9** in the rhodium-catalyzed hydroformylation reactions exhibits very high reactivity, even tetrasubstituted olefins were hydroformylated with noticeable rate.[13] Phosphabarrelene **10** has been synthesized and tested in hydroformylation of internal olefins. The rhodium-phosphabarrelene catalysts hydroformylate an internal double bond without olefin

isomerization. [14] Ligand **11** self-assembles through the hydrogen bonding of 6-(diphenylphosphino) pyridin-2(1H)-one with its hydroxypyridine tautomer. Highly regioselectivity has been achieved in the hydroformylation of simple terminal olefins as well as a wide range of functionalized terminal olefins by ligand **11**.[15]

Figure **1-4** Other Phosphorus Ligands for Regioselective Hydroformylation

We have reported a new ligand tetraphosphorous ligand BTPP **12** (biphenyl-2, 2', 6, 6' –tetrakis(dipyrolylphosphoramidite)[16] (Figure **1-5**) can effectively solve the issue of ligand dissociation (Scheme **1-2)**. In commercial hydroformylation 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, a large excess of ligands are employed. For known bidentate bisphosphorus ligands such as **13**[17] capable 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 five and six-membered chelations. The weak eight or nine-membered ring chelations of bisphosphorus ligands might dissociate from metal under some hydroformylation conditions.

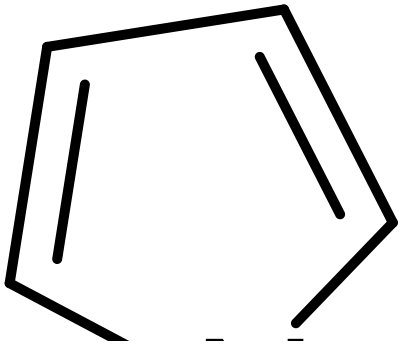
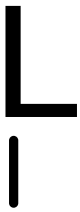
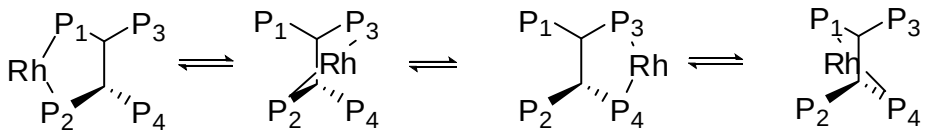


Figure **1-5** Tetraphosphoramidite Ligand and Bisphosphoramide ligand



Scheme **1-2** Ligand Dissociation in Rhodium-catalyzed Hydroformylation

This tetraphosphorous ligand BTPP **12** enhances the chelating ability of ligands. As illustrated in Scheme **1-3**, there are four identical chelating modes when a tetraphosphorus ligand complexed with metal. On the other hand, when the tetraphosphorus ligand 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. Hence, high regioselectivity for the homogeneous isomerization-hydroformylation of internal olefins (n: i values up to 80.6 for 2-hexene and up to 51.7 for 2-octene) has been achieved.



Scheme **1-3** Enhanced Chelating Ability of Tetraphosphorus Ligand **BTPP** through Multiple Chelating Modes and Increased Local Phosphorus Concentration

1.4 Objective

High regioselectivity for the homogeneous isomerization-hydroformylation of internal olefins has been achieved by using our tetraphosphorous ligand BTPP **12** (biphenyl-2, 2', 6, 6' –tetrakis(dipyrolyl phosphoramidite).[14] Meanwhile, substitution at the 3, 3' positions of the binaphthyl[18] or biphenyl[19] scaffold has a dramatic effect on the enantio- and regioselectivity of various reactions.

We would like to report the ligands design and synthesis of introducing different functional groups into 3, 3', 5, 5'-positions of the biphenyl, and their applications to the

isomerization-hydroformylation of internal olefins. In particular, the alkyl-substituted tetraphosphorous ligands gave the best results (for 2-octene, n: i up to 207, for 2-hexene, n: i up to 362).

Double hydroformylation of 1, n-diolefins is a convenient method to produce dialdehydes. Dialdehydes are valuable intermediates for the preparation of a variety of commercially products such as bicarboxylic acids and their derivatives,[20] diamines,[21] and heterocyclic compounds having different structures.[22] The hydroformylation of 1,5-hexadiene can be achieved with essentially high regioselectivity (linear selectivity is up to 98%) by using tetraphosphorus-based Rhodium catalyst.

Styrene and its derivatives prefer the branched aldehydes under the hydroformylation conditions. However, the linear aldehydes can also be widely used for the production of detergents and plasticizers and important intermediates.[23] Our studies on the hydroformylation of styrene and its derivatives achieved unprecedented high linear selectivity (l/b up to 22 for styrene) with BTPP **12**.

Alkyl acrylates are another category of substrates which prefer branched aldehydes under the hydroformylation condtions. We successfully overcome the three difficulties of alkyl acrylates: the low reactivity, preference of linear aldehydes, and suppression of the hydrogenation product.

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Chapter 2 Results and Discussion

2.1 Design and Synthesis of Tetraphosphorous Ligand

Recently, high regioselectivity for the homogeneous isomerization-hydroformylation of internal olefins (n: i values up to 80.6 for 2-hexene and up to 51.7 for 2-octene) has been achieved by using our tetraphosphorous ligand BTPP (biphenyl-2, 2', 6, 6' –tetrakis(dipyrrolyl phosphoramidite).[1] The enhanced chelating ability of BTPP and the unique properties of *N*-pyrrolylphosphorus ligand enable it serve as an effective ligand for isomerization-hydroformylation of internal olefins (Scheme **1-3**). Meanwhile, substitution at the 3, 3' positions of the binaphthyl[2] or biphenyl[3] scaffold has a dramatic effect on the enantio- and regioselectivity of various reactions.

Tuning the steric and electronic effects of ligands can achieve high regioselectivity and rate enhancement in the hydroformylation.[2] The goal of the ligands design is to introduce different functional groups into the 3, 3', 5, 5'-positions of the biphenyl, and the electronic and steric characteristics of the ligands could be systematic tuned, thereby changing the character and the environment around the metal.

We would like to report the ligands design and synthesis of introducing different functional groups into 3, 3', 5, 5'-positions of the biphenyl, and their applications to different substrates, including internal olefins, 1, 5-hexadiene, styrene and its derivatives, and alkyl acrylates.

3,3',5,5'-tetraalkyl or aryl moiety could be easily introduced to biphenyl in moderate to good yields from iodosubstituted derivative **2**[4] with arylboronic acid or trimethylsilyl acetylene by Suzuki or Sonogashira coupling (Scheme **2-1**). **3b**[5] can be

synthesized from **1** with sulfuryl chloride in chloroform at room temperature in 82% yield.

Scheme **2-1** Synthetic Route for 3, 3', 5, 5' Tetrasubstituted Biphenyl

Tetranol **4** was obtained in 87 % to 92% yield by deprotecting the aromatic methoxy moiety with boron tribromide (Scheme **2-2)**. Reaction of chloro-dipyrroylphosphine with tetraol **4** in the presence of NEt_3 afforded the desired tetraphosphoramidite ligand **5b-5g** in 21% to 34% unoptimized yield.[6] Tetranol **4b** was directly synthesized form m-xylorcinol by a two-step oxidation in the presence of ferric chloride.

Scheme **2-2** Synthetic Route for 3, 3', 5, 5' Tetraphosphorus Ligands

2.2 Isomerization-Hydroformylation of Internal Olefins

Isomerization-hydroformylation of internal olefins was then conducted under optimized reaction conditions (100 ℃, CO/H_2, 5/5 atm, ligand/metal ratio= 3)[6] with ligands **5b**-**5g** (for comparison, the data for ligand **5a** are also listed) using 2-octene and 2-hexene as standard substrates (Table **2-1** and Table **2-2**). The catalyst was prepared *in situ* by mixing $Rh(acac)_2(CO)_2$ with new ligands at 1:3 ratios. All of the ligands and particularly alkyl-substituted **5d** show among the best reported linear selectivity both for 2-octene (*n*: *i*= 136.9) and 2-hexene (*n*: *i* =289.4) (see Table **2-1**, entry 4 and Table **2-2**, entry 4). The electronic character and the size of the substituents both had impacts on selectivity. The ligands with electron-donated alkyl substituents (Table **2-1**, entry 3-4 and Table **2-2**, entry 3-4) lead to a higher ratio of linear to branch while the presence of electron-withdrawing groups (Table **2-1**, entry 2, 5-7 and Table **2-2**, entry 2, 5-7), such as

the chloro and aromatic substituents usually lead to lower selectivity but higher reactivity. As the size of the group increased from methyl to ethyl for electron-donating substituents, the *n: i* ratio increased. However, for electronwithdrawing substituents there was no clear steric effect was observed.

Table **2-1** Isomerization-Hydroformylation of 2-octene with Ligands **5**[a]

Entry	L	*n:i*[b]	linear[c] (%)	TON[d]
1	**5a**	51.7	98.1	1.5×10^3
2	**5b**	82.8	98.9	2.5×10^3
3	**5c**	106.6	99.1	1.5×10^3
4	**5d**	136.9	99.3	1.0×10^3
5	**5e**	78.1	98.7	2.3×10^3
6	**5f**	53.3	98.2	2.2×10^3
7	**5g**	65.0	98.5	1.7×10^3

[a] S/C = 10,000, [Rh] =0.57 mM, ligand/Rh ratio = 3:1, temperature = 100 ^{o}C, CO/H_2 = 5/5 atm, toluene as solvent, decane as internal standard for 1h.[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 **2-2** Isomerization-Hydroformylation of 2-hexene with Ligands **5**[a]

entry	L	*n:i*[b]	linear[c] (%)	TON[d]
1	**5a**	80.6	98.8	1.7×10^3
2	**5b**	86.1	98.9	2.4×10^3
3	**5c**	289.4	99.7	6.0×10^2
4	**5d**	167.5	99.4	9.7×10^2
5	**5e**	85.0	98.8	1.9×10^3
6	**5f**	58.0	98.3	1.9×10^3
7	**5g**	91.4	98.9	2.0×10^3

[a] S/C = 10,000, [Rh] = 0.69 mM, ligand/Rh ratio = 3:1, temperature = 100 ^{o}C, CO/H_2 = 5/5 atm, toluene as solvent, *n*-decane as internal standard.[b-d] See Table **2-1**

The effects of reaction temperature on isomerization-hydroformylation were also investigated. The isomerization-hydroformylation reactions of 2-octene and 2-hexene were carried out at various temperatures ranging from 60 ℃ to 100 ℃ under otherwise identical conditions. The results were summarized in Table **2-3**. At low temperature (below 100 $^{\circ}$C), though high regioselectivity was observed, the reaction rate was low. This low activity at low temperature can be explained by slow isomerization rate of internal olefins at low temperature. To facilitate the olefin isomerization and hydroformylation, high temperature is desired. The preferred temperature is 100 $^{\circ}$C. At this temperature, both high regioselectivity and acceptable reaction rate were achieved.

Table **2-3** Isomerization-Hydroformylation of 2-octene with **5d** at Different Temperature[a]

entry	T(^{o}C)	*n:i*[b]	linear[c] (%)	TON[d]
1	60	122.0	99.2	4.7 x 10
2	80	181.9	99.4	5.1 x 10^2
3	100	136.9	99.3	1.0 x 10^3

[a] S/C = 10,000, [Rh] = 0.57 mM, ligand/Rh ratio = 3:1,CO/H_2 = 5/5 atm, toluene as solvent, *n*-decane as internal standard for 1h. [b-d] See Table **2-1**.

The effects of total pressure of CO/H_2 were then evaluated. The isomerization-hydroformylation reactions were conducted under CO/H_2 total pressure ranging from 5/5 to 20/20 atm. As shown in Table **2-4**, the CO/H_2 total pressure significantly influences isomerization-hydroformylation reaction. At high pressure, both reaction rate and regioselectivity were low. Lowering the pressure generally resulted in higher reaction rate and regioselectivity. However, decreasing the CO/H_2 pressure from 10/10 atm to 5/5 atm did not change the reaction rate very much, while the regioselectivity could be improved to some extent.

Table **2-4** Isomerization-Hydroformylation of 2-octene with **5d** at Different Pressure[a]

entry	P (atm)	*n:i*[b]	linear[c] (%)	TON[d]
1	5/5	136.9	99.3	1.0×10^3
2	10/10	128.4	99.2	1.5×10^3
3	20/20	68.1	98.6	4.8×10^2

[a] S/C = 10,000, [Rh] = 0.57 mM, ligand/Rh ratio = 3:1,Temperature=100 ^{o}C , toluene as solvent, *n*-decane as internal standard for 1h.[b-d] See Table **2-1**

The effect of elongating reaction time was investigated, too. Ligand **5a** was reported that the linear to branch ratio would drop about 20% for a prolonged period. However, the tetrasubstituted ligands maintained high selectivity even after elongating the reaction time to 12 h which might be attributed to the stabilization of the ligands by the substituents (Table **2-5** and Table **2-6**).

Table **2-5** Isomerization-Hydroformylation of 2-octene with Ligands **5** at 12h[a]

Entry	L	*n:i*[b]	linear[c] (%)	TON[d]
1	**5a**	38.0	97.4	7.7×10^3
2	**5b**	27.2	96.5	8.6×10^3
3	**5c**	101.6	99.0	7.6×10^3

4	**5d**	106.9	99.1	5.5 x 10^3
5	**5e**	77.3	98.7	8.8 x 10^3
6	**5f**	56.7	98.3	8.7 x 10^3
7	**5g**	61.7	98.4	7.9 x 10^3

[a] S/C = 10,000, [Rh] = 1 mM, ligand/Rh ratio = 3:1, temperature = 100 ^oC, CO/H_2 = 5/5 atm, toluene as solvent, decane as internal standard for 12h. [b-d] See Table **2-1.**

Table **2-6** Isomerization-Hydroformylation of 2-hexene with Ligands **5** at 12h[a]

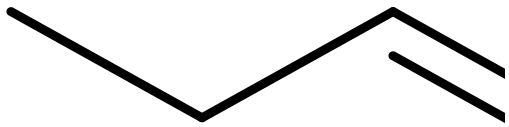
entry	L	*n*:*i*[b]	linear[c] (%)	TON[d]
1	**5a**	56.0	98.2	6.0 x 10^3
2	**5b**	30.4	96.8	7.3 x 10^3
3	**5c**	104.9	99.1	5.3 x 10^3
4	**5d**	133.5	99.2	5.7 x 10^3
5	**5e**	74.8	98.7	6.3 x 10^3
6	**5f**	43.2	97.8	6.4 x 10^3
7	**5g**	93.7	98.9	6.6 x 10^3

[a] S/C = 10,000, [Rh] = 1 mM, ligand/Rh ratio = 3:1, temperature = 100 ^oC, CO/H_2 = 5/5 atm, toluene as solvent, *n*-decane as internal standard for 12h. [b-d] See Table **2-1**.

2. 3 Isomerization-Hydroformylation of 1, 5-hexadiene

The use of the dialdehydes as cross-linking agents for polymers such as proteins,[7] polysaccharides,[8] and other functionalized macromolecular compounds[9] is very important.

Dialdehydes are also valuable intermediates for the preparation of a variety of commercially products such as bicarboxylic acids and their derivatives,[10] diamines,[11] and heterocyclic compounds having different structures.[12] Double hydroformylation of 1, *n*-diolefins is a convenient method to produce dialdehydes. However, a complex mixture of monoaldehydes and dialdehydes, arising from the consequent hydroformylation–isomerization–hydroformylation of the two double bonds made this process less practical (1, 5-hexadiene as example, Scheme **2-3**). Other methods known to transform various functionalities into the aldehyde group, which has been successfully used for the preparation of monoaldehydes, only in a few cases can be conveniently extended to the preparation of dialdehydes. The chemoselectivities are often unsatisfactory due to the formation of other products such as cyclic lactones and other side reactions.



Scheme **2-3** Hydroformylation of 1, 5-hexadiene

Morikawa reported some results concerning the oxo-reaction on 1, 4- pentadiene and 1, 5-hexadiene: the yield of linear dialdehydes did not exceed 40% and in some cases the formed aldehydes is transformed into cyclohexancarboxaldehyde through intramolecular aldol condensation. The real breakthrough was made by Marchetti who found that 1, 5-hexadiene could be converted to the corresponding linear dialdehydes selectively in over 80% yield when $RhH(CO)(PPh)_3$ formed complex with Xanphos.[13]

Here we would like to report the application of our new system to the isomerization-hydroformylation of 1, 5-hexadiene. 1, 5-hexadiene was subjected to rhodium-catalyzed hydroformylation in toluene at 100 ℃ and 10 atm (CO/H_2 = 5/5) for 2 h using ligand **5a** (Table **2-7**, entry 1). The starting material was almost completely consumed (conversion > 99%) under this reaction condition. A mixture of olefin isomers (formed via the isomerization of the carbon–carbon double bond of the original diolefins, 1,4-hexadiene was the main isomer), monoaldehydes (6-hepten-1-al **6** and 2-methyl-5-hexen-1-al **7**, and isomers **11**–**14** from the migration of the double bond of the original monoaldehydes) and dialdehyde compounds (1,8-octanedial **8**, 2-methyl-1,7-heptanedial **9**, and 2,5-dimethyl-1,6-hexanedial **10**) was obtained in 14.4%, 11.5% (1/2 = 96.3/3.7), 26.2%, and 47.9% (3/4/5 = 94.1/5.3/0.6) yields, respectively.

The influences of total pressure of CO/H_2 were also evaluated. With the total pressure increasing from 10 atm to 80 atm, the yield of dialdehydes increased steadily, along with the decreasing yield of olefin isomer and monoaldehyde. Therefore, the total pressure has a significant effect on the yield of dialdehydes.

Table **2-7** Hydroformylation of 1,5-hexadiene Using Ligand **5a** under Different Pressures[a]

Entry	Pressure H_2/CO (atm)	Olefin Isomer[b](%)	Yield (%) Monoaldehydes **6**+**7**(**6**/**7**)[c]	Monoaldehydes **11**-**14**[d]	Dialdehydes **8**+**9**+**10**(**8**/**9**/**10**)[e]
1	**5/5**	14.4	11.5(96.3/3.7)	26.2	47.9(94.1/5.3/0.6)
2	**10/10**	3.3	7.4(96.8/3.2)	17.9	71.3(95.2/4.3/0.5)
3	**20/20**	1.2	4.7(97.1/2.9)	13.5	80.6(96.7/2.9/0.4)
4	**30/30**	< 1	3.5(97.2/2.8)	8.2	87.3(97.4/2.3/0.3)
5	**40/40**	< 1	5.6(96.2/3.8)	6.3	87.6(97.4/2.3/0.3)

[a] S/C = 1,000, Rh/L = 4/1, [Rh] = 1.0 mM, *t* = 2 h, temperature=100 ℃ toluene as solvent, *n*-decane as internal standard. The oxo-products were identified by GC–mass spectroscopy. Compound 1:MS: *m*/*z* (%) 39 (47), 41 (100), 42 (32), 43 (31), 55 (45), 67 (49), 68 (78), 79 (30). 81 (16), 86 (11), 112 (1). Compound 2: MS: *m*/*z* (%) 41 (88), 55 (58), 57 (27), 58 (100), 112 (2).Compound 3: MS: *m*/*z* (%) 41 (100), 42 (27), 43 (61), 44 (65), 54 (41), 55 (67), 57 (88), 80 (26), 81 (79), 98 (13), 110 (17), 142 (5). Compound 4: MS: *m*/*z* (%) 41 (100), 43 (69), 55(35), 57 (60), 58 (83), 69 (29), 112 (15), 124 (21), 142 (2). Compound 5: MS: *m*/*z* (%) 41 (61), 43 (100), 55 (67), 57 (49), 58 (77), 71 (40), 84 (51), 96 (21), 124 (14), 142 (1). [b] The yield of 1,5-hexadiene isomerization products, determined on the basis of GC. [c] Determined on the basis of GC analysis. [d] Total yield of the monoaldehydes 6, 7, 8, and 9. [e] Determined on the basis of GC.

Effects of reaction temperature on the hydroformylation of 1, 5-hexadiene were then evaluated. The hydroformylation reactions were conducted at temperature ranging

from 60 ℃ to 100 ℃ while kept the ligand/metal ratio (4:1) and total CO/H_2 (1:1) pressure (40/40 atm) constant. The results were summarized in Table **2-8**. The decrease of temperature from 100 ℃ to 60 ℃ has little effect on the product distribution (entries 1-3).

Table **2-8** Hydroformylation of 1, 5-hexadiene Using Ligand **5a** under Different Temperature[a]

Entry	Temperature (℃)	Olefin Isomer[b](%)	Yield (%) Monoaldehydes **6**+**7**(**6**/**7**)[c]	Monoaldehydes **11**-**14**[d]	Dialdehydes[e] **8**+**9**+**10**(**8**/**9**/**10**)
1	100	< 1	5.6(96.2/3.8)	6.3	87.6(97.4/2.3/0.3)
2	80	< 1	3.6(97.4/2.6)	8.3	87.4(97.4/2.3/0.3)
3	60	< 1	6.0(97.6/2.4)	6.7	86.8(97.5/2.2/0.2)

[a-e] See Table **2-7**

Effects of the introduction of substituents at the 3, 3', 5, 5'-position of the biphenyl moiety were tested. 1,5-hexadiene was then hydroformylated using the complex formed in situ from $Rh(acac)(CO)_2$ and **5b**–**5g** under the reaction condition for ligand **5a** (100 ℃, H_2/CO = 40/40 atm, t= 2 h). The results were summarized in Table **2-9**. A high linear to branch ratio was obtained for both the monoaldehydes and the dialdehydes in all the cases. This phenomenon may imply that the steric of the biphenyl moiety is not the controlling factor of regioselectivity. However, with the introducing of electron-donating substituents such as Me, Et, and *p*-MePh, the yields of dialdehydes **11**–**14** decreased (Table **2-9**, entries 2–4 and 6).

Table **2-9** Hydroformylation of 1, 5-hexadiene Using Ligand **5b-5g** [a]

Entry	L	Olefin Isomer[b](%)	Yield (%)		
			Monoaldehydes		Dialdehydes
			6+**7**(**6**/**7**)[c]	**11-14**[d]	**8**+**9**+**10**(**8**/**9**/**10**)[e]
1	**5b**	< 1	8.0(96.2/3.6)	8.7	47.9(94.1/5.3/0.6)
2	**5c**	< 1	4.6(96.8/3.2)	17.9	71.3(95.2/4.3/0.5)
3	**5d**	< 1	8.3(95.9/4.1)	12.1	80.6(96.7/2.9/0.4)
4	**5e**	< 1	8.9(94.9/5.1)	10.5	87.3(97.4/2.3/0.3)
5	**5f**	< 1	8.0(97.4/2.6)	8.7	87.6(97.4/2.3/0.3)
6	**5g**	< 1	11.1(95.0/5.0)	16.9	67.8(96.7/3.0/0.3)

[a] S/C = 1,000, Rh/L = 4/1, [Rh] = 1.0 mM, 100 ℃, H_2/CO = 40/40 atm, *t* = 2 h, conversion >99%, toluene as solvent, *n*-decane as internal standard. [b–e] See Table **2-7**.

2.4 Highly Regioselective Hydroformylation of Styrene and Its Derivatives

The hydroformylation products of styrene, either linear or branched (eq **2-2**), are very important. The branched aldehydes constitute an important class of anti-inflammatory drugs and the linear aldehydes are widely used for the production of detergents and plasticizers and important intermediates[14] (for example, it can be used as key starting material for the synthesis of enalapril, marketed by Merck & Co. as a drug for lowering blood pressure[15]). However, the tedious and sophisticated synthesis of 3-arylpropanal inhibits the applications. For example, the reduction of *trans*-cinnamaldehyde[16] or 3-phenylpropionyl chloride[17] or the oxidation of 3-arylpropanol[18] all have limitations.

The complex formation of a stable benzylic Rh-species induced by the $\eta 2$ electron donation from the benzene ring might contribute to the regioselectivity (Scheme **2-4)**.[19] Therefore, hydroformylation of styrene will favor producing branched product. The development of chiral ligands to produce the desired branched enatioisomer in high optical purity has been focused.[20] The contrary selectivity favored linear aldehyde may also be possible through the choice of solvent,[21] biphasic system,[22] different catalytic systems (for $PtCl_2/SnCl_2$, l/b = 3.35,[23] for Co-W bimetallic catalyst l/b=1.307[24]). Recent progress on the Rh-catalyzed hydroformylation of styrene has been reported using fine-tuned ligands (xantphosphite **15** afforded l/b up to 2.3,[25] calixarenes diphosphane **16** led to l/b = 77/23[26]) So far, the bulky phosphite ligands of UCC gave the highest linear regioselectivity, a value of l/b=14.[27]

Figure **2-1** Ligands Favored Producing Linear Hydroformylated products

Scheme **2-4** The Complex of Formation of a Stable Benzylic Rh-species

Our studies on the hydroformylation of styrene and its derivatives achieved unprecedented high linear selectivity (l/b up to 22 for styrene) with BTPP (biphenyl-2, 2', 6, 6' –tetrakis(dipyrolyl phosphoramidite).

We screened the optimal conditions for our ligands system with ligand **5a** (Table **2-10**). Increasing the temperature from 40 to 80 ℃ improved activity and regioselectivity (Table **2-10**, entries 1, 2, and 7). Further increase in the temperature from 80 to 100 ℃ gave lower regioselectivity, albeit the conversion increased somewhat (Table **2-10**, entry 8). The activity and selectivity decreased sharply with the increased pressure (Table **2-10**, entries 2-4). Lower ligand/Rh was also investigated, and it was found that although there is not much effect on catalytic activity, the regioselectivity is somewhat lowered (Table **2-10**, entries 5 and 6). Thus, the optimal conditions (toluene, 80 ℃, 5/5 atm H_2/CO, substrate/L/Rh =1000/3/1) were chosen for the ligand screening.

Table **2-10** Hydroformylation of Styrene Using **5a** under Different Reaction Conditions[a]

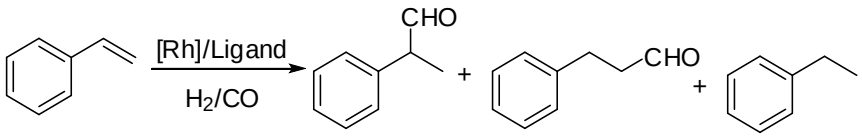
Entry	Temp (℃)	L/Rh	Pressure H_2/CO (atm)	Conv[b] (%)	Hydroformylation Ratio(%)	L%[c]	l/b[d]
1	40	3	5/5	7	>99	74.2	2.9
2	60	3	5/5	43	97.0	86.9	6.7
3	60	3	10/10	43.5	98.4	75.9	3.2
4	60	3	20/20	29	98.1	65.9	1.9
5	60	2	5/5	46.2	98.4	83.8	5.2
6	60	1	5/5	53	98.6	83.0	4.9
7	80	3	5/5	80	97.0	87.1	6.8
8	100	3	5/5	99	93.0	86.0	5.9

[a] S/C = 1,000, [Rh] = 1.0 mM, toluene as solvent, decane as internal standard time=1h. [b] Conversion, determined on the basis of GC [c] Percentage of linear aldehyde in all aldehydes. [d] Linear/branched ratio, determined on the basis of GC analysis.

Based on the best conditions for ligand **5a**, diverse substituted tetraphosphorus ligands **5b-5g** were tested in the reaction. It was found that the introducing of substitiuents on the biphenyl rings enhanced the regioselectivity greatly in the linear aldehyde as showed in Table **2-11**. The use of ligand **5b** bearing chlorine substituents gave a high regioselectivity (l/b = 12.9) (Table **2-11**, entry 1). Alkyl-substituted ligands **5c** and **5d** induced higher regioselectivities that are values of 17.2 and 15.9 respectively (Table **2-11**, entries 2 and 3). Substitution with aryl groups showed comparable

regioselectivity, of which ligand **5f** afforded the best result (Table **2-11**, entries 4-7). Comparison of these results clearly indicated that the steric property of the substituents exert a more remarkable effect on the regioselectivity of the reaction than that of electronic property of the substituents as the l/b ratio increased with large size phenyl groups.

Table **2-11** Hydroformylation of Styrene Using Lignd **5b**-**5g** [a]



Entry	ligand	conv(%)[b]	Hydroformylation		
			Ratio(%)	L%[c]	l/b[d]
1	**5b**	97.8	93.3	92.8	12.9
2	**5c**	71	93.1	94.5	17.2
3	**5d**	54.3	93.5	94.1	15.9
4	**5e**	98.9	91.7	95.1	19.3
5	**5f**	95.3	92.0	95.7	22.4
6	**5g**	99.0	97.2	95.3	20.2

[a] S/C = 1,000, [Rh] = 1.0 mM, 80°C, 5/5 atm toluene as solvent, decane as internal standard. [b-d] see Table **2-10**.

A series of styrene derivatives were hydroformylated using the Rh/**5f** catalyst under the optimized reaction conditions (Table **2-12**). The reaction of 4-fluorostyrene gave 15.1 l/b ratio for aldehyde when ligand **5c** was used, while the use of ligand **5f** gave

the product with l/b ratio 11.8. In both cases, no hydrogenation product was detected (Table **2-12**, entry 1). The reaction of 2-fluorostyren gave the linear aldehyde in 12.6 l/b ratio when ligand **5a** was used, while the use of ligand **5f** double the linear selectivity (Table **2-12**, entry 2). It should be noted that the reaction of 2-fluorostyrene and 4-fluorostyrene showed significantly different regioselectivity in the presence of ligand **5g** (Table **2-12**, entries 1 and 2). This can be explained by the greatly inhibition of the formation of the benzylic Rh-species intermediate that would produce branched aldehyde due to the presence of the ortho sustituent. This phenomenon has also been seen for 2-methylstyrene and 4-methylstyrene. As showed in Table **2-12**, up to 162.5 l/b ratio for 2-methylstyrene was observed when ligand **5g** was used while for 4-methylstyrene, this value would be 17.0. It was noted that the l/b ratio increased slightly with the electron-donating property of substistuents as the para substituents changed from fluoro, methyl to methoxy group (Table **2-12**, entry 1, 3, 5). 2, 4, 6-trimethyl styrene showed to be not a very inactive substrate due to the steric repulsion inhibited the coordination of the substrate to the rhodium center, but this steric increased the regioselectivity for linear aldehyde, no branced aldehyde and hydrogenated products were detected (Table **2-12**, entry 6).

Table **2-12** Hydroformylation of Styrene and Its Derivatives with Rh-Ligand Catalyst[a]

Entry	Substrate	Time (h)	ligand	Conv [b] (%)	Hydroformylation Ratio (%)	Hydroformylation L% [c]	Hydroformylation l/b [d]
1	4-F styrene	1	**5c**	66	100.0	93.8	15.1
		1	**5f**	51	100.0	92.2	11.8
2	2-F styrene	1	**5a**	94	93.6	92.6	12.6
		1	**5f**	91	97.5	95.9	23.5
3	4-Me styrene	1	**5c**	60.2	95.1	94.1	15.9
		1	**5f**	48.7	97.6	94.4	17.0
		3	**5f**	97.0	97.5	93.7	14.8
4	2-Me styrene	1	**5a**	82.4	90.8	98.1	51.4
		1	**5f**	59.7	96.3	99.4	162.5
		3	**5f**	99.4	95.3	99.3	144.7
5	4-MeO styrene	1	**5f**	45	95.2	95.0	18.9
		3	**5f**	95	94.2	93.9	15.3
6	2,4,6-trimethyl styrene	1	**5a**	28.9	100.0	100.0	>99
		1	**5b**	11.0	100.0	100.0	>99
		1	**5c**	5.0	100.0	100.0	>99
		1	**5d**	3.0	100.0	100.0	>99
		1	**5e**	4.0	100.0	100.0	>99

[a] S/C = 1,000, [Rh] = 1.0 mM, 80°C, 5/5 atm toluene as solvent, decane as internal standard. [b-d] see Table **2-11**.

These styrene derivatives were then hydroformylated using the Rh/**5f** catalyst. The substrate to catalyst ratio was 10000, and the catalyst concentration was 0.17 mM. The reaction was terminated after 12 h (Table **2-13**). With the results of Table **2-12** and Table **2-13**, it was found that styrene substituted with electron-withdrawing group gave a lower linear to branch ratio than that of styrene with electron-donating groups (Table **2-13**, entries 2-4). The steric hindrance of the substrates on the regioselectivity of the hydroformylation is also remarkable. When one methyl group was introduced to the ortho position of the styrene, the reactivity and the regioselectivity were improved greatly (Table **2-13**, entry 5).

Table **2-13** Hydroformylation of Styrene and Its Derivatives with Rh-**5f** Catalyst[a]

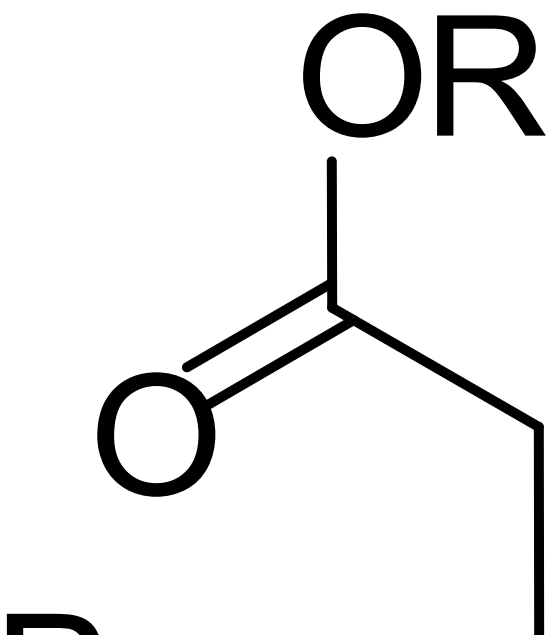
Entry	Substrate	conv(%)[b]	Hydroformylation			TOF[e]
			Ratio(%)	L%[c]	l/b[d]	
1	Styrene	98	91	95.5	21.2	1.1×10^3
2	4-F-styrene	99	89	93.4	14.2	1.3×10^3
3	4-Me-styrene	83	95	95.0	19.4	9.7×10^2
4	4-MeO-styrene	80	96	96.3	26.0	7.4×10^2
5	2-Me-styrene	99	90	99.3	144.7	1.8×10^3
6[f]	2,4,6-trimethylstyrene	16	94	99	>99	7.0×10

[a] S/C =10,000, [Rh]) 0 0.17 mM, temperature) 80 ℃, CO/H_2) 5/5 atm, *t* = 12 h, toluene as solvent, decane as internal standard. [b-d] See Table **2-7** [e] Average turnover frequency after reaction for 1 h: mole of aldehyde formed per mole of catalyst per hour, determined based on GC. [f] **5a** was used as ligand.

2. 5 Highly Regioselective and Rapid Hydroformylation of Alkyl Acrylates

Alkyl acrylates are readily available and usable feedstock.[28] Hydroformylation of alkyl acrylate produces 1, 3- and 1, 4-bifunctional compounds, which can be further converted into synthetically useful intermediates such as malonic acid, 1, 4-dicarboxylic acid derivatives and butyrolactones.[29]

There are three difficulties to overcome in hydroformylation of alkyl acrylates. Firstly, high temperature (150 ℃) and/or high pressure (100 bar) are often required to achieve high turnover.[30] The lower turnover was ascribed to be a result of the formation of thermodynamically stable five- or six-membered rings through the coordination of carbonyl group to the metal center (See Scheme **2-5** for the formation of complexes **V** and **VI**). The rate-determining step has been suggested to be the dissociation of the chelated carbonyl group to afford a coordinatively unsaturated species that is active towards the oxidative addition of H_2.[31]



Scheme **2-5** Coordination of a Carbonyl Group to the Rhodium.

Though Alkyl acrylate is less reactive to H_2/CO compared to terminal alkenes,[32] significant progresses have been made to carry out the process under mild conditions, such as using an organoaquo biphasic system[36b] or supported aqueous phase catalyst[35b] or in supercritical CO_2.[33] Secondly, the branched aldehydes are the main product in hydroformylation of alkyl acrylate with the rhodium complex (For typical results catalyzed by an Rh complex with P ligands, see Scheme **2-6**).[34] The Rh(acac)$(CO)_2$ /phosphoxophite AA is the only system that the linear aldehyde is the main product.[35] Thus, developing a highly regioselective and rapid process that gives linear aldehydes is desirable due to the wide application of 1,4-bifunctional compounds in organic synthesis.[34] Thirdly, hydrogenation byproduct in the hydroformylation of alkyl acrylate can be suppressed in some degree thorough tuning the reaction condition.

Rh complex/ligand	Production and yield	Ref.
Rh(COD)BPh_4	b:l=30:70	28e
Rh(acac)$(CO)_2/PPh_3$	l+b=94%, b:l>200	34b
[Rh(COD)Cl2]$_2$/DPPB	l+b=94%, b:l=99:1	28d
Rh(COD)(6-PhBPh_3)/P$(OPh)_3$	b:l=98:2	28d
Rh(acac)$(CO)_2$/TPPMS	l+b=83%, b:l=63:1, h=17%	32c
Rh(acac)$(CO)_2$/Phosoxophite AA	l=91%, b=1%, h=8%	35

DPPB: 1, 4-bis(diphenylphosphino)butane; TTPMS: [3-(sodium sulfonato)phenyl] diphenylphosphine.

Scheme **2-6** Typical Results for Rhodium-Catalyzed Hydroformylation of Methyl Acrylates

We would like to report that the hydroformylation of alkyl acrylates by using a rhodium complex with ligand **5a** can achieve high regioselectivity (linear/branch>99/1) and extraordinarily high average turnover frequencies (up to 5400 h^{-1}). This process prefers the production of linear aldehyde instead of the branched aldehyde which was reported in most of other processes (typically>95% branched for most Rh-catalyzed reaction systems). The high turnover number achieved by this new catalytic system is also remarkable considering the less reactive character of alkyl acrylates to the hydroformylation reaction conditions.

The hydroformylation of *n*-butyl acrylate with the tetraphosphine ligand **5a** was investigated (Table **2-14**). The reaction was conducted in toluene and *n*-decane was used as an internal standard. The rhodium catalyst was prepared *in situ* by mixing the tetraphosphine ligand **5a** with $Rh(acac)(CO)_2$. The substrate to catalyst ratio was 10,000 and the catalyst concentration was 0.17 mM. The reaction was terminated after 1 h. The effects of ligand metal ratio were first evaluated. To our surprise, the $Rh(acac)(CO)_2$-tetraphosphrus systems smoothly catalyzed the hydroformylation of *n*-butyl acrylate, and the linear aldehyde was obtained as the main product with a very high turnover. No branched aldehydes were formed under these reaction conditions. A slight increase of turnover frequency was observed when the ratio of ligand to Rh complex was increased from 1:1 to 5:1 (Table **2-14**, entries 1–5).

Table **2-14** Hydroformylation of Butyl Acrylate at Different Ligand Metal Ratios[a]

Entry	Rh/L	Temp (℃)	Pressure H_2/CO (atm)	Conv[b] (%)	h(%)[c]	Aldehyde	
						l:b[d]	TOF[e]
1	1:1	100	5/5	64	12.6	>99	4.8×10^3
2	1:2	100	5/5	57	5.3	>99	4.9×10^3
3	1:3	100	5/5	62	6.6	>99	5.1×10^3
4	1:4	100	5/5	63	5.4	>99	5.4×10^3
5	1:5	100	5/5	64	5.7	>99	5.4×10^3

[a] S/C=10,000, [Rh]=0.17 mM, time=1 h, toluene as solvent, decane as internal standard. [b] Conversion of the n-butyl acrlate, determined on the basis of GC, polymetric products account for the product balance. [c] Percentage of hydrogenated product in all products. [d] Linear/branched ratio, analyzed by proton NMR. [e] Average turnover frequency, determined based on GC, reaction time=1 h.

Then the effects of CO/H_2 pressure were tested. At high CO/H_2 pressure, the consumption of starting material greatly increased, however the formation of the linear aldehyde decreased due to the formation of polymetric products (Table **2-14**, entries 1-4).

Table **2-15** Hydroformylation of Butyl Acrylate at Different Pressure[a]

Entry	Rh/L	Temp (℃)	Pressure H_2/CO (atm)	Conv[b] (%)	h(%)[c]	Aldehyde l:b[d]	Aldehyde TOF[e]
1	1:4	100	5/5	63	5.4	>99	5.4×10^3
2	1:4	100	10/10	62	4.6	>99	4.6×10^3
3	1:4	100	20/20	68	5.2	>99	3.4×10^3
4	1:4	100	30/30	85	5.9	>99	1.3×10^3

[a-e] see Table **2-14**

Finally, the effects of reaction temperature on the hydroformylation reaction were also investigated (Table **2-16**, entries 1-3). The reaction rate was greatly improved when the reaction temperature increased from 60 ℃ to 100 ℃. The reaction can also be carried out in THF, albeit with lower activity (Table **2-16**, entry 4).

Table **2-16** Hydroformylation of Butyl Acrylate at Different Temperature[a]

Entry	Rh/L	Temp (℃)	Pressure H_2/CO (atm)	Conv[b] (%)	h(%)[c]	Aldehyde l:b[d]	Aldehyde TOF[e]
1	1:4	100	5/5	63	5.4	>99	5.4×10^3
2	1:4	80	5/5	25	1.4	>99	2.2×10^3
3	1:4	60	5/5	13	2.1	>99	9.8×10^2
4[f]	1:4	100	5/5	30	2.4	>99	2.7×10^3

[a-e] see Table **2-14** [f] THF used as solvent.

We then applied the optimized reaction conditions (100 ℃, CO/H_2=5/5 atm, ligand/metal=4, t=1h) to the hydroformylation of other alkyl acrylates in toluene. The results are summarized in Table **2-17**. In all cases, only the linear aldehydes were observed, which is in sharp contrast with the literature reports that the hydroformylation of acrylates usually affords branched aldehydes as the dominant product. Much more significantly, the turnover frequency still remains at a high level. For comparison, the bisphosphorus ligand was prepared[36] and employed in the hydroformylation of n-butyl acrylate under identical reaction conditions (Table **2-17**, entry 4). The bisphosphorus ligand was found also to show high regioselectivity for linear aldehyde and a high turnover frequency was observed.

Table **2-17** Hydroformylation of Alkyl Acrylates with ligand **5a**.[a]

Entry	Substrate (R)	Conv[b](%)	h(%)[c]	Aldehyde l:b[d]	Aldehyde TOF[e]
1	*i*-Bu	59	5.2	>99	5.1×10^3
2	t-Bu	48	5.8	>99	3.9×10^3
3	Me	56	5.2	>99	4.8×10^3
4[f]	*n*-Bu	44	6.1	>99	3.5×10^3

[a] S/C=10,000, [Rh]=0.17 mM, ligand/Rh ratio=4:1, temperature= 100 ℃, CO/H_2=5/5 atm, time=1 h, toluene as solvent, decane as internal standard. [b-e] See Table **2-14**. [f] The bisphosphorus ligand 1,1'-biphenyl-2,2'-diyl-bis(dipyrrolyl-phosphoramidite) was used.

Experimental Section

General Methods/Instrument Details

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 N2. Column chromatography was performed using 200-400 mesh silica gel supplied by Sorbent technologies. Deuterated solvents were purchased from Aldrich Chemical Company. Thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica 60-F plates. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Varian Mercury 400 MHz FT-NMR spectrometer or Varian Mercury 500 MHz FT-NMR spectrometer. All chemical shifts are reported in ppm. HRMS 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.

Chlorodipyrrolylphosphine was prepared according to the literature procedure. 1 [37]Hydroformylation reactions were repeated several times to ensure reproducibility. 3, 3', 5, 5'-Tetramethylbiphenyl-2, 2' 6, 6'-tetraol was prepared according to the literature procedures.2[38]

General Procedure for Synthesis of 3, 3', 5, 5'-tetrachloro tetraol 4b. To a 250 mL Schlenk flask was added 3, 3', 5, 5'-tetrachloro-2, 2', 6, 6'-tetramethoxybiphenyl **3b** (1.7 g, 4.1 mmol). The flask was degassed and charged with nitrogen. To the flask was added CH_2Cl_2 (20 mL). The resulting solution was cooled to -78 ℃ in a dry ice/acetone bath. To the cooled solution was added boron tribromide (1.5 mL, 18.0 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. After

cooled to 0 ℃, water (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization from hexanes to give the titled compound **4b** (1.35 g, 92%). ^{1}H NMR (500 MHz, acetone) δ 7.38 (s, 2 H); IR (film): ν 3525, 3503, 1596, 1449, 1423, 1300, 1281, 1172, 783 cm^{-1}; ^{13}C NMR (126MHz, acetone) δ 152.2, 130.20, 130.18, 112.6, 110.6; IR (film): ν 3523, 1596, 1457, 1145, 1036 cm^{-1}; HRMS (ES+) calcd for C12H5Cl4O4 [M-H]$^-$ 352.8942, found 352.8965.

General Procedure for Synthesis of Ligand 1. **3, 3', 5, 5'-Tetrachlorobiphenyl-2, 2' 6, 6'- tetrakis-(dipyrrolylphosphoramidite) (5b).** To a solution of chlorodipyrrolyl-phosphine (55 mmol, 10.9 g) in THF (50 mL) was added dropwise triethylamine (13 mL) and a solution of 3, 3', 5, 5'-tetrachloro tetraol (10 mmol, 3.6 g) in THF (100 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 recrystalization from hexanes three times to afford the pure ligand **5b** (2.2 g, 22%) as an air-sTable colorless solid: ^{1}H NMR (400 MHz, CDCl3) δ 7.26 (s, 2 H), 6.65 (brs, 16 H), 6.21 (t, *J* = 2.2 Hz, 16 H); ^{13}C NMR (100 MHz, CDCl3) δ 147.6, 131.9, 123.0, 121.40, 121,39, 121.33, 121.22, 121.15, 113.7, 113.6, 112.5, 112.4, 112.38, 112.28; ^{31}P NMR (161 MHz, CDCl3) δ 109.0; IR (film): ν 1462, 1188, 1063, 1057, 1031, 731 cm-1; HRMS (ES+) calcd for $C_{44}H_{35}C_{l4}N_8O_4P_4$ $[M+H]^+$ 1003.0486, found 1003.0463.

3, 3', 5, 5'-Tetrachloro-2, 2' 6, 6'-Tetramethoxybiphenyl (3b). A solution of 5 mL (62.5 mmol) of SO2Cl2 in 5 mL of CHCl3 was added dropwise to a solution of 2.8 g (10 mmol) of 2, 2' 6, 6'-tetramethoxybiphenyl **1** in 20 mL of CHCl3 at room temperature. The solution was sittired and monitored by TLC plate. After 30 min, saturated NaCl solution was added carefully to the reaction mixture and the organic layer was separated. The water layer was extracted three times with chloroform (20 mL) and the organic layer was combined and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated and the residue was passed through a short silica gel plug. The solvent was evaporated and 3.8 g of white solid was obtained in 91% yield. 1H NMR (500 MHz, CDCl3) δ 7.51 (s, 2 H), 3.67 (s, 12 H); 13C NMR (126 MHz,CDCl3) δ 153.4, 130.1, 125.1, 123.5, 60.9; IR (film): 1467,1419, 1284, 1102, 1017, 882 cm-1; HRMS (ES+) calcd for C16H18NCl4O4 $[M+H]^+$ 427.9990, found 427.9985.

3, 3', 5, 5'-Tetramethylbiphenyl-2, 2' 6, 6'-tetrakis-(dipyrrolylphosphoramidite) (5c).

Ligand **5c** was prepared according to the general procedure using chlorodipyrrolyl-phosphine (1.7 g, 8.3 mmol) and 3, 3', 5, 5'-tetramethylbiphenyl-2, 2', 6, 6'-tetraol **4c** (0.5 g, 1.9 mmol). Purification by recrystallization from hexanes gave **5c** as a white solid in 34% yield (0.6 g). ^{1}H NMR (400 MHz, CDCl3) δ 7.23 (brs, 16 H), 6.72 (s, 2 H), 6.20 (t, *J* = 2.2 Hz, 16 H), 1.67 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 134.1, 126.6, 121.31, 121,25, 121.21, 121.13, 113.2, 113.1, 112.0, 111.9, 111.8, 111.7, 16.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 105.6; IR (film): ν 1453, 1190, 1179, 1056, 1037, 729 cm^{-1}; HRMS (ES+) calcd for $C_{48}H_{47}N_8O_4P_4$ $[M+H]^+$ 923.2671, found 923.2651.

3, 3', 5, 5'-Tetraiodo-2, 2' 6, 6'-Tetramethoxybiphenyl (2). A 200-ml., three-necked flask is charged with 13.8 g. (50.0 mmol) of 2, 2' 6, 6'-Tetramethoxybiphenyl **1**, 9.1 g. (40.0 mmol) of periodic acid dihydrate, and 20.4 g. (80.0 mmol) of iodine. A solution of 3 mL of concentrated sulfuric acid and 20 mL of water in 100 mL of glacial acetic acid is added to this mixture. The resulting purple solution is heated at 80° with stirring for approximately 10 hours until the color of iodine disappears. The reaction mixture is diluted with approximately 250 mL of water, and the white-yellow solid that separates is collected on a Büchner funnel and washed three times with 100-mL portions of water. The product is recrystallized from boiling acetone as colorless, fine needles (31.8 g, 82%). ^{1}H NMR (500 MHz, CDCl3) δ 8.28 (s, 2 H), 3.59 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ 158.9, 147.6, 124.8, 86.7, 61.0; IR (film): ν 1641, 1450, 1397, 1250, 1154, 1059, 921 cm^{-1}; HRMS (ES+) calcd for $C_{16}H_{18}NI_4O_4$ $[M+NH_4]^+$ 795.7415, found 795.7441.

3, 3', 5, 5'-Tetraethyl-2, 2' 6, 6'-Tetramethoxybiphenyl (3d). 3, 3', 5, 5'-Tetraiodo-2, 2' 6, 6'- Tetramethoxybiphenyl **2** (7.8 g, 10 mmol) and ethynyltrimethylsilane (8.2 mL g, 58.0 mmol) in a mixture of triethylamine (100 mL) and piperidine (30 mL) was treated with $PdCl_2(PhCN)_2$, (0.4 mg, 1.0 mmol), triphenylphosphine (275 mg, 1.0 mmol), and CuI (80 mg). The originally yellow solution turned to green and then brown. After 3 h at room temperature it was heated at 80 ℃ for 24 h. The precipitate was filted and the filtration was passed through a short silica gel plug. The obtained solution was evaporated and treated with a solution of KOH (6.0 g, 108.0 mmol) in methanol (40 mL). The reaction solution was stirred at room temperature for 2 h until TLC analysis indicated that the reaction was complete. Ether-water workup and the obtained yellow liquid was dissolved in 200 mL of mixture of ethyl acetate and methanol and combined with 5 wt% Pd/C (0.5 g) in an autoclave under a 200 psi of hydrogen atmosphere. The reaction was stirred at room temperature for 2 h until no hydrogen absorption was observed. Filtration and flash chromatography afford 2.9 g of white solid in 73% yield. ^{1}H NMR (500 MHz, CDCl3) δ 7.09 (s, 2 H), 3.53 (s, 12 H), 2.69 (q, *J* = 7.5 Hz, 8 H), 1.27 (t, *J* = 7.5 Hz, 12 H); ^{13}C NMR (126 MHz, CDCl3) δ 154.6, 132.2, 128.8, 123.3, 60.4, 22.9,

15.0; IR (film): ν 1468, 1425, 1058 cm^{-1}; HRMS (ES+) calcd for $C_{24}H_{35}O_4$ $[M+H]^+$ 387.2535, found 387.2526.

3, 3', 5, 5'-Tetraethylbiphenyl-2, 2' 6, 6'-tetranol (4d). Tetranol was prepared according to the general procedure using 3, 3', 5, 5'-Tetraethyl-2, 2' 6, 6'-Tetramethoxy-biphenyl **3d** (2.9 g, 7.3 mmol) and boron tribromide (3.0 mL, 36.0 mmol). Purification by recrystallization from hexanes gave **4d** as a white solid in 92% yield (2.2 g). 1H NMR (500 MHz, acetone) δ 6.92 (s, 2 H), 6.55 (s, 4 H), 2.59 (q, *J* = 7.5 Hz, 8 H), 1.18 (t, *J* = 7.5 Hz, 12 H); 13C NMR (126 MHz, acetone) δ 152.3, 130.7, 122.8, 107.0, 23.8, 15.1; IR (film): ν 3530, 3503, 1472, 1173, 1092 cm^{-1}; HRMS (ES+) calcd for $C_{20}H_{27}O_4$ $[M+H]^+$ 331.1909, found 331.1905.

3, 3', 5, 5'-Tetraethylbiphenyl-2, 2' 6, 6'-tetrakis-(dipyrrolylphosphoramidite) (5d). Ligand **5d** was prepared according to the general procedure using 3, 3', 5, 5'-Tetraethyl-biphenyl-2, 2' 6, 6'-tetranol **4d** (2.0 g, 6.0 mmol) and chlorodipyrrolyl-phosphine (5.2 g, 25.4 mmol). Purification by recrystalization from hexanes gave **5d** as a white solid in

28% yield (1.6 g). ^{1}H NMR (400 MHz, CDCl3) δ 6.77 (brs, 18 H), 6.21 (t, *J* = 2.2 Hz, 16 H), 2.01 (q, *J* = 7.6 Hz, 8 H), 0.90 (t, *J* = 7.6 Hz, 12 H); ^{13}C NMR (100 MHz, CDCl3) δ 148.9, 132.3, 130.7, 121.1, 118.9, 111.8, 22.8, 14.3; ^{31}P NMR (161 MHz, CDCl3) δ 105.6; IR (film): ν 1453, 1174, 1083, 1044, 1025, 729 cm^{-1}; HRMS (ES+) calcd for $C_{52}H_{55}N_8O_4P_4$ $[M+H]^+$ 979.3297, found 979.3257.

3, 3', 5, 5'-Tetraphenyl-2, 2' 6, 6'-Tetramethoxybiphenyl (3e). A mixture of phenylboronic acid (14.6 g, 120.0 mmol), 3, 3', 5, 5'-Tetraiodo-2, 2' 6, 6'-Tetramethoxy-biphenyl **2** (7.8 g, 10 mmol), palladium tetrakistriphenylphosphine (1.0 g), and potassium carbonate (24 g, 160 mmol) in dry dioxane (150 mL) was stirred under nitrogen for 24 h at 85 ℃. The resulting mixture was cooled and poured into a solution of ice with concentrated hydrochloric acid (3:1) and the organic phase was extracted twice with dichloromethane, dried over magnesium sulfate. After evaporation of the solvent, the mixture was subjected to flash chromatography to give 4.5 g (78%) of 3, 3', 5, 5'-Tetraphenyl-2, 2' 6, 6'-Tetramethoxybiphenyl **3e** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 8 H), 7.44 (d, *J* = 7.5 Hz, 8 H), 7.42 (s, 2 H), 7.36 (t, *J* = 7.5 Hz, 4 H), 3.42 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 138.7, 132.6, 130.4, 129.0, 128.3, 126.9, 124.1, 60.4; IR (film): ν 1459, 1410, 1215, 1068, 929, 738 cm^{-1}; HRMS (ES+) calcd for $C_{40}H_{35}O_4$ $[M+H]^+$ 579.2535, found 579.2529.

3, 3', 5, 5'-Tetraphenylbiphenyl-2, 2' 6, 6'-tetranol(4e). Tetranol **4e** was prepared according to the general procedure using 3, 3', 5, 5'-Tetraphenyl-2, 2' 6, 6'-Tetra-methoxybiphenyl **3e** (4.5 g, 8.0 mmol) and boron tribromide (3.5 mL, 42.0 mmol). Purification by recrystalization from hexanes gave **4e** as a white solid in 89% yield (3.7 g). ^{1}H NMR (500 MHz, acetone) δ 7.69 (d, *J* = 7.5 Hz, 8 H), 7.52 (s, 4 H) , 7.40 (t, *J* = 7.5 Hz, 8 H), 7.32 (s, 2 H), 7.28 (t, *J* = 7.5 Hz, 4 H); IR (film): ν 3523, 1456, 1154, 1033 cm^{-1}; ^{13}C NMR (126 MHz, acetone) δ 154.1, 140.0, 133.7, 130.3, 129.0, 127. 2, 122.5, 108.1; HRMS (ES+) calcd for $C_{36}H_{27}O_4$ $[M+H]^+$ 523.1909, found 523.1914.

3, 3', 5, 5'-Tetraphenylbiphenyl-2, 2' 6, 6'-tetrakis-(dipyrrolylphosphoramidite) (5e). Ligand **5e** was prepared according to the general procedure using 3, 3', 5, 5'-tetraphenyl-biphenyl-2, 2' 6, 6'-tetranol **4e** (2.6 g, 5.0 mmol) and chlorodipyrrolylphosphine (4.8 g, 24.3 mmol). Purification by recrystalization from hexanes gave **5e** as a white solid in 26% yield (1.5 g). ^{1}H NMR (400 MHz, CDCl3) δ 7.26 (s, 2 H), 7.24 (m, 4 H), 7.20 (m, 8 H), 7.12 (m, 8 H), 6.49 (brs, 16 H), 6.07 (t, *J* = 2.0 Hz, 16 H); ^{13}C NMR (100 MHz, CDCl3) δ 149.42, 149.40, 136.7, 135.1, 131.2, 129.5, 128.3, 127.5, 121.0, 120.9, 118.93,

120.86, 120.79, 120.77, 120.0, 111.8; ^{31}P NMR (161 MHz, CDCl3) δ 106.5; IR (film): ν 1451, 1419, 1178, 1054, 1036, 730 cm^{-1}; HRMS (ES+) calcd for $C_{68}H_{55}N_8O_4P_4$ $[M+H]^+$ 1171.3297, found 1171.3259.

3, 3', 5, 5'-Tetratolyl-2, 2' 6, 6'-Tetramethoxybiphenyl (3f). 3, 3', 5, 5'-Tetratolyl-2, 2' 6, 6'- Tetramethoxybiphenyl **3f** was prepared according to the general procedure for synthesis of 3, 3', 5, 5'-tetraphenyl-2, 2' 6, 6'-tetramethoxybiphenyl **3e** by using tolylboronic acid (24.5 g, 180.0 mmol), 3, 3', 5, 5'-tetraiodo-2, 2' 6, 6'-tetramethoxybiphenyl **2** (11.9 g, 15.2 mmol). Purification by flash chromatography gave **3f** as a white solid in 72% yield (6.9 g). ^{1}H NMR (500 MHz, CDCl3) δ 7.57 (d, *J* = 7.5 Hz, 8 H), 7.44 (s, 2 H), 7.26 (d, *J* = 7.5 Hz, 8 H), 3.44 (s, 12 H), 2.44 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 136.5, 135.9, 132.3, 130.2, 128.97, 128.88, 124.2, 60.3, 21.2; IR (film): ν 1457, 1413, 1054 cm^{-1}; HRMS (ES+) calcd for $C_{44}H_{43}O_4$ $[M+H]^+$ 635.3161, found 635.3133.

3, 3', 5, 5'-Tetratolylbiphenyl-2, 2' 6, 6'-tetranol(4f). Tetranol **4f** was prepared according to the general procedure using 3, 3', 5, 5'-Tetratolyl-2, 2' 6, 6'-Tetramethoxybiphenyl (5.7 g, 9.0 mmol) and boron tribromide (3.9 mL, 46.8 mmol). Purification by recrystalization from hexanes gave **4f** as a white solid in 89% yield (4.6 g). ^{1}H NMR (500 MHz, acetone) δ 7.56 (d, *J* = 7.5 Hz, 8 H), 7.36 (s, 4 H), 7.28 (s, 2 H), 7.21 (d, *J* = 7.5 Hz, 8 H); ^{13}C NMR (126 MHz, acetone) δ 153.8, 137.0, 136.5, 133.4, 130.2, 129.6, 122.3, 108.1, 21.2; IR (film): ν 3520, 1593, 1455, 1155, 1024 cm^{-1}; HRMS (ES+) calcd for $C_{40}H_{35}O_4$ $[M+H]^+$ 579.2535, found 579.2532.

3, 3', 5, 5'-Tetratolylphenyl-2, 2' 6, 6'-tetrakis-(dipyrrolylphosphoramidite) (5f). Ligand **5f** was prepared according to the general procedure using 3, 3', 5, 5'-

Tetratolylbiphenyl-2, 2' 6, 6'- tetranol **4f** (2.8 g, 4.5 mmol) and chlorodipyrrolyl-phosphine (3.9 g). Purification by recrystallization from hexanes gave **5f** as a white solid in 21% yield (1.2 g). ^{1}H NMR (400 MHz, CDCl3) δ 7.20 (s, 2 H), 7.00 (d, *J* = 2.0 Hz, 8 H), 6.95 (d, *J* = 2.0 Hz, 8 H), 6.49 (brs, 16 H), 6.05 (t, *J* = 2.0 Hz, 16 H), 2.34 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 137.2, 134.8, 133.7, 131.1, 129.4, 129.0, 120.92, 120.88, 120.85, 120.78, 111.6, 21.2; IR (film): ν 1449, 1178, 1073, 1054, 1037, 730 cm^{-1}; ^{31}P NMR (161 MHz, CDCl3) δ 106.8; HRMS (ES+) calcd for $C_{72}H_{63}N_8O_4P_4$ $[M+H]^+$ 1227.3923, found 1227.3933.

3, 3', 5, 5'-Tetra(4-fluorophenyl)-2, 2' 6, 6'-Tetramethoxybiphenyl (3g). 3, 3', 5, 5'-Tetra(4-fluorophenyl)-2, 2' 6, 6'-Tetramethoxybiphenyl **3g** was prepared according to the general procedure for synthesis of 3, 3', 5, 5'-tetraphenyl-2, 2' 6, 6'-tetramethoxy-biphenyl **3e** by using 4-fluorophenylboronic acid (22.8 g, 163.0 mmol), 3, 3', 5, 5'-tetraiodo-2, 2' 6, 6'-tetramethoxybiphenyl **2** (10.6 g, 13.6 mmol). Purification by flash chromatography gave **3g** as a white solid in 80% yield (7.1 g). ^{1}H NMR (400 MHz, CDCl3) δ 7.65-7.60 (m, 8 H), 7.38 (s, 2 H), 7.17-7.11 (m, 8 H), 3.40 (s, 12 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ 115.9; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.9, 155.6, 134.40,

134.38, 132.3, 130.63, 130.54, 129.6, 124.2, 115.4, 115.1, 60.3; IR (film): ν 1586, 1461, 1420, 1055 cm^{-1}; HRMS (ES+) calcd for $C_{40}H_{31}F_4O_4$ $[M+H]^+$ 651.2158, found 651.2186.

3, 3', 5, 5'-Tetra(4-fluorophenyl)biphenyl-2, 2' 6, 6'-tetranol (4g). Tetranol **4g** was prepared according to the general procedure using 3, 3', 5, 5'-Tetra(4-fluorophenyl)-2, 2' 6, 6'-Tetramethoxybiphenyl (6.6 g, 10.2 mmol) **3g** and boron triboromide (7.7 mL, 81.0 mmol). Purification by recrystalization from hexanes gave **4g** as a white solid in 98% yield (6.0 g). ^{1}H NMR (400 MHz, acetone) δ 7.71 (td, *J1* = 7.5 Hz, *J2* = 1.2 Hz, 8 H), 7.66 (s, 4 H), 7.31 (s, 2 H),7.16 (td, *J1* = 7.5 Hz, *J2* = 1.2 Hz, 8 H); ^{19}F NMR (376 MHz, acetone) δ 113.5; ^{13}C NMR (100MHz, acetone) δ 163.0, 160.6, 153.5, 135.40, 135.37, 132.85, 132.80, 131.50, 131.43, 131.41, 120.8, 114.9, 114.7, 107.2; IR (film): ν 3526, 1593, 1458, 1157, 1018 cm^{-1}; HRMS (ES+) calcd for $C_{36}H_{23}F_4O_4$ $[M+H]^+$ 595.1532, found 595.1545.

3, 3', 5, 5'-Tetra(4-fluorophenyl)biphenyl-2, 2' 6, 6'-tetrakis-(dipyrrolylphosphor-amidite) (5g).Ligand **5g** was prepared according to the general procedure using 3, 3', 5, 5'-Tetra(4- fluorophenyl)biphenyl-2, 2' 6, 6'-tetranol **4g** (5.0 g, 8.4 mmol) and chlorodipyrrolylphosphine (7.5 g, 37.0 mmol). Purification by recrystalization from hexanes gave **5g** as a white solid in 31% yield (3.2 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2 H), 7.09-6.97 (m, 8 H), 6.87-6.76 (m, 8 H), 6.54 (brs, 16 H), 6.11 (t, *J* = 1.5 Hz, 16 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ 118.6; ^{13}C NMR(100 MHz, CDCl3) δ 163.6, 161.2, 149.59, 149.52, 134.9, 132.17, 132.14, 131.13, 131.05, 130.7, 120.76, 120.71, 120.68, 115.2, 115.0, 112.0; IR (film): ν 1453, 1152, 1011 cm^{-1}; ^{31}P NMR (162 MHz, $CDCl_3$) δ 106.6; HRMS (ES+) calcd for $C_{68}H_{51}F_4N_8O_4P_4$ $[M+H]^+$ 1243.2920, found 1243.2955.

General Procedure for the Regioselective Isomerization-Hydroformylation of Internal Olefins with Ligand 5a. A 2-mL vial with a magnetic stirring bar was charged with ligand **5a** (3 μmol, 2.6 mg) and $Rh(acac)(CO)_2$ (1 μmol, 0.1 mL of 10 mM solution in toluene). 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 atm) and H_2 (5 atm). The autoclave was then heated to 100 ℃ (the pressure was 11.3 atm). After 1 h, the autoclave was cooled in icy water, and the pressure (9.4 atm) 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 1,5-hexadiene A 2-mL vial with a magnetic stirring bar was charged with ligand **5a** (4 μmol, 3.6 mg) and Rh(acac)$(CO)_2$ (1 lmol, 0.1 mL of 10 mM solution in toluene). The mixture was stirred for 5 min, 1,5- hexadiene(1.0 mmol, 0.12 mL) was then added, followed by decane (0.1 mL) as internal standard and toluene (0.68 mL). The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen three times and subsequently charged with CO (40 atm) and H_2 (40 atm). The autoclave was then heated to 100 ℃ and the pressure was set to 80 atm. After 2 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 conversion and regioselectivity.

General Procedure for the Regioselective Hydroformylation of Styrene and Its Derivatives with Ligand 5f

A 10-mL vial with a magnetic stirring bar was charged with ligand **5f** (3 μmol, 3.6 mg) and Rh(acac)$(CO)_2$ (1 μmol, 0.1 mL of 10 mM solution in toluene). The mixture was

stirred for 5 min. Styrene (10 mmol, 0.9 mL) was then added, followed by decane (0.1 mL) as internal standard and toluene (4.9 mL). The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen three times and subsequently charged with CO (5 atm) and H_2 (5 atm). The autoclave was then heated to 80 ℃ and the pressure was set to 10 atm. After 12h, 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 conversion and regioselectivity.

Conditions for determination of linear to branch ratio:

GC, Supelco's Beta Dex 225, 90 °C for 5 min, then 160 °C for 5 min (rate: 20 ℃ /min), t_{branch} = 10.1 and 10.2 min, t_{linear} = 11.2 min

GC, Supelco's Beta Dex 225, 100 °C for 5 min, then 160 °C for 10 min (rate: 20 °C /min), t_{branch} = 15.1 and 15.2 min, t_{linear} = 16.5 min

GC, Supelco's Beta Dex 225, 120 °C for 5 min, then 160 °C for 10 min (rate: 20 °C /min), t_{branch} = 12.3 and 12.4 min, t_{linear} = 13.8 min

GC, Supelco's Beta Dex 225, 140 °C for 4 min, then 160 °C for 10 min (rate: 40 °C /min), t_{branch} = 15.4 min, t_{linear} =16.7 min

GC, Supelco's Beta Dex 225, 120 °C for 5 min, then 160 °C for 10 min (rate: 20 °C /min), t_{branch} = 12.5 min, t_{linear} =14.0 min

GC, Supelco's Beta Dex 225, 110 °C for 5 min, then 160 °C for 10 min (rate: 20 °C /min), t_{linear} = 17.3 min

General Procedure for the Regioselective Hydroformylation of n-Butyl Acrylate with Ligand 5a A 10-mL vial with a magnetic stirring bar was charged with ligand **5a** (4 mmol, 3.6 mg) and $Rh(acac)(CO)_2$ (1 mmol, 0.1 mL of 10 mM solution in toluene). The mixture was stirred for 5 min, n-butyl acrylate (10 mmol, 1.43 mL) was then added, followed by decane (0.1 mL) as internal standard and toluene (4.36 mL). The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen three times and subsequently charged with CO (5 atm) and H_2 (5 atm). The autoclave was then heated to 100 °C and the pressure was set to 10 atm. After 1 h, the autoclave was cooled in ice/water, and the pressure was carefully released in a well-ventilated hood. The

reaction mixture was immediately analyzed by GC and ^{1}H NMR to determine the conversion and regioselectivity.

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Chapter 3 Conclusion

A series of new pyrrole-based tetraphosphorus ligands **5b-5g** with multiple chelating modes were synthesized. With introducing different functional groups into 3, 3', 5, 5'-positions of the biphenyl, the steric and electronic effects of ligands can be systematically tuned to screen the effects of different substrates.

It was found that the substituents at the 3, 3', 5, 5'-positions of the biphenyl greatly affected the linear selectivity of isomerization-hydroformylation, and the alkyl-substituted tetraphosphorus ligands gave the best results (for 2-octene, n:i up to 207, for 2-hexene, n:i up to 362). These results hint that substituents' electronic character exerted more power on steric nature. The tetrasubstituted ligands maintained high selectivity even after elongating the reaction time than the parent ligand based **5a** which might be attributed to the stabilization of the ligands by the substituents.

Hydroformylation of 1, 5-hexadiene can be achieved with essentially high regioselectivity (linear selectivity is up to 98%) by using tetraphosphorus-based Rhodium catalyst. Unexpectedly, it was found that the introducing of the substituents at the ortho position of the biphenyl moiety has little effect on the regioselectivity. A high linear to branch ratio was obtained for both the monoaldehydes and the dialdehydes in all the cases. Instead of the steric of the biphenyl moiety, this phenomenon may imply that the big natural bite angle of the ligand is the controlling factor of regioselectivity.

Hydroformylation of styrene and its derivatives in our system can be achieved with high regioselectivity for linear aldehyde (l/b up to 22 for styrene) which is sharp contrast to other processes that favor producing branched aldehyde (typically >95% branched for most bidentate systems). To our best knowledge, this is the highest linear regioselectivity

reported for the hydroformylation of styrene and its derivatives. It was previously proposed for the reaction of vinylidene-type olefins catalyzed by Rh complex that the significant difference in the steric environment between the two ends of the olefin bond gave excellent regioselectivity for the linear aldehyde. The high regioselectivity can be accounted for by the steric interactions between the ligands and the substrate. It implies that the hindrance of the ligand impedes the formation of η3 Rh-complex that would favor the formation of branched aldehyde. In the present system, the dependency of the selectivity on the steric nature of the ligand was similar, as observed when higher linear to branch ratio was obtained with the more bulky ligand.

We have shown that the hydroformylation of alkyl acrylates can be achieved with essentially high regioselectivity (linear/branch ratio is up to 99:1) and extraordinarily high average turnover frequencies (up to 5400 h^{-1}). It is opposite to other processes catalyzed by rhodium complexes that produce mainly branched aldehydes. It seemed that a ligand with larger natural bite angle and electronwithdrawing moieties preferred the formation of the linear aldehyde. As for the high turnover frequency, it is highly possible that the 9-membered P-Rh-P ring and high local phosphorus concentration by using a tetraphosphorus-based Rh catalyst might inhibit the formation of another 5- or 6-membered carbonyl coordinated ring.

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Education

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Publications

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