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# Highly Regioselective Isomerization−Hydroformylation of Internal Olefins to Linear Aldehyde Using Rh Complexes with Tetraphosphorus Ligands

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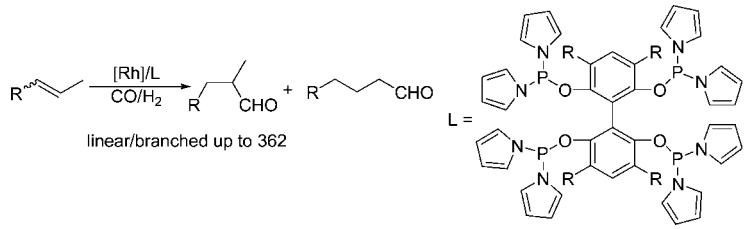
## ABSTRACT




**A series of new pyrrole-based tetraphosphorus ligands were synthesized and used for Rh-catalyzed isomerization−hydroformylation of internal olefins. It was found that the substituents at the 3,3′,5,5′-positions of the biphenyl greatly effected the linear selectivity, 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).**

Hydroformylation of olefins represents one of the most important reactions in industry. It is catalyzed by homogeneous catalysts and leads to products containing an aldehyde group that are versatile intermediates and building blocks for various pharmaceuticals, agrochemicals, and commodity and fine chemicals.[1] Most commercial hydroformylation processes use rhodium catalysts modified with monophosphorus ligands or bisphosphorus ligands to address the issue of regioselectivity and stereoselectivity. Although great progress has been achieved for regioselective hydroformylation of terminal olefins,[2] fewer examples of successful catalysts showing high regioselectivity and rate enhancement for internal olefins, which are cheaper and more readily available feedstock, have been reported to date. Those include van Leeuwen's Xantphos derivatives (linear to branched ratio (*n*:*i*) = 9.5 for 2-octene),[3] Beller's electronwithdrawing Naphos-type ligands (*n*:*i* = 10.1 for 2-octene and up to 99:1 with its sulfonated derivatives in a biphasic system),[4] Börner's acylphosphite ligands (*n*:*i* = 2.2 for mixtures of octene isomers),[5] and bulky phosphite ligands of UCC[6] (*n*:*i*

(1) (a) Pino, P.; Piacenti, F.; Bianchi, M. In *Organic Syntheses via Metal Carbonyls*; Wender, I., Pino, P., Eds.; Wiley: New York, 1977. (b) Cornils, B. In *New Syntheses with Carbon Monoxide*; Falbe, J., Ed.; Springer: Berlin, 1980; pp 1−225. (c) Kohlpaintner, C. W., Frohning, C. D. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, pp 1−39.

(2) For recent reviews, see: (a) *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer: Dordrecht, 2000. (b) Breit, B.; Seiche, W. *Synthesis* **2001**, 1–36.

(3) (a) van der Veen, L. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem.* **1999**, *111*, 349−351; *Angew. Chem., Int. Ed.* **1999**, *38*, 336−338. (b) van der Veen, L. A.; Kamer, P. C.J.; van Leeuwen, P. W. N. M. *Organometallics* **1999**, *18*, 4765–4777.

(4) (a) Klein, H.; Jackstell, R.; Wiese, K.-D.; Borgmann, C.; Beller, M. *Angew. Chem.* **2001**, *113*, 3505−3508; *Angew. Chem., Int. Ed.* **2001**, *40*, 3408−3411. (b) Klein, H.; Jackstell, R.; Beller, M. *Chem. Commun.* **2005**, 2283–2285.

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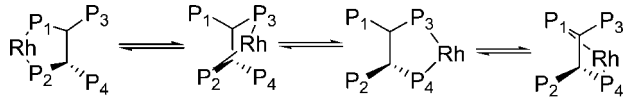
= 19 and 17 for 2-hexene and 2-octene, respectively) and DuPont/DSM ($n$:$i$ = 36 for 2-hexene).[7]

Recently, we have reported the synthesis and application of the new tetraphosphorus ligand BTPP (biphenyl-2,2′6,6′-tetrakis(dipyrrolyl phosphoramidite)),[8] which shows a 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). The high selectivity is ascribed mainly to the enhanced chelating ability (multichelating modes) and the unique electronic properties of *N*-pyrrolylphosphorus moiety (Scheme 1). Meanwhile, it

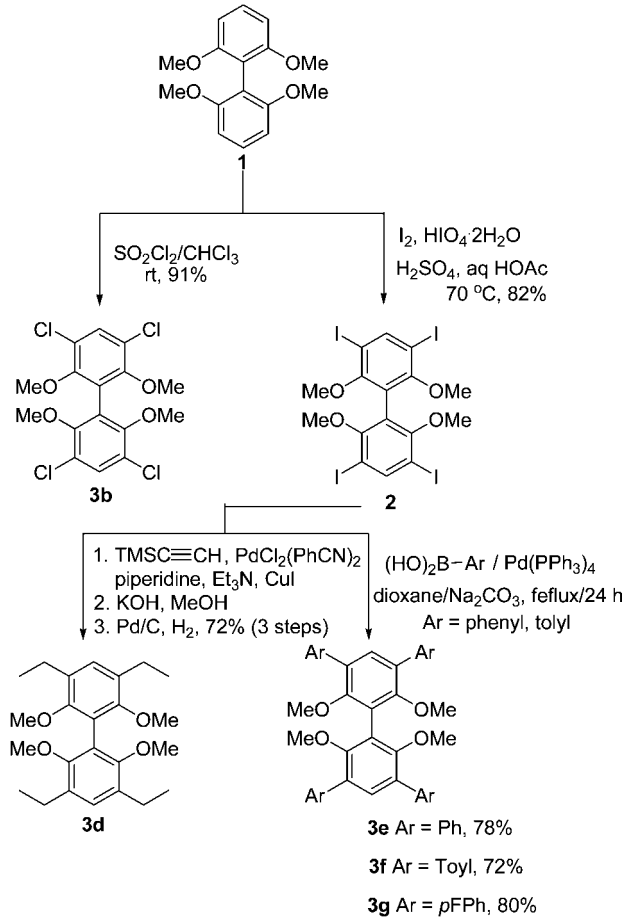
**Scheme 1.** Enhanced Chelating Ability of Tetraphosphine Ligand through Multiple Chelating Modes and Increased Local Phosphorus Concentration




has been well documented that substitution at the 3,3′-positions of the binaphthyl[9] or biphenyl[10] scaffold has a dramatic effect on the enantio- and regioselectivity of various reactions. On the basis of those results, we reasoned that on introducing different functional groups into the 3,3′,5,5′-positions of the biphenyl, the electronic and steric characteristics of the ligand could be systematic tuned, thereby changing the character and the environment around the metal center. Herein, we wish to report our prelimilary result on the synthesis of ligands and their application to the isomerization−hydroformylation of internal olefins.

Biphenyl with 3,3′,5,5′-tetraalkyl or aryl moiety could be easily prepared in moderate to good yields from iodosubstituted derivative **2**[11] with arylboronic acid or trimethylsilyl acetylene by Suzuki or Sonogashira coupling (Scheme 2). The chlorination of **1**[12] with sulfuryl chloride in chloroform at room temperature affords **3b** in 82% yield.[13] Then, the

**Scheme 2.** Synthesis of 3,3′,5,5′-Tetrasubstituted Biphenyl




new ligands were achieved in a subsequent two straightforward steps.[8] Treatment of the substituted 2,2′6,6′-tetramethoxybiphenyls with boron tribromide gave the parent tetraol, followed by reaction with freshly made chlorodipyrrolylphophine[14] in the presence of triethylamine at room temperature to furnish ligands **5b**−**5g**. The unoptimized yields for the ligands synthesis ranged from 21% to 34% (Scheme 3). Tetraol **4b** was directly synthesized from *m*-xylorcinol by a two-phase oxidation in the presence of ferric chloride.[15]

With the ligands in hand, isomerization−hydroformylation of internal olefins was then conducted under optimized reaction conditions (100 °C, $CO/H_2$ = 5/5 atm, ligand/metal ratio = 3)[8] with ligands **5b**−**5g** (for comparison, the data for ligand **5a** are also listed) using 2-octene and 2-hexene as standard substrates. No 3-formylalkane products were observed under these reaction conditions. All of the ligands and particularly alkyl-substituted **5d** show among the best reported linear selectivity both for 2-octene ($n$:$i$ = 207.6) and 2-hexene ($n$:$i$ = 362.0) (see Table 1, entry 10 and Table

(5) Selent, D.; Hess, D.; Wiese, K.-D.; Röttger, D.; Kunze, C.; Börner, A. *Angew. Chem.* **2001**, *113*, 1739−1741; *Angew. Chem., Int. Ed.* **2001**, *40*, 1696−1698.

(6) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. (UCC). European Patent EP 213639, 1987; U.S. Patent 4748261, 1988.

(7) Burke, P. M.; Garner, J. M.; Kreutzer, K. A.; Teunissen, A. J. J. M.; Snijder, C. S.; Hansen, C. B. (DSM/Du Pont). PCT Int. Patent WO 97/33854, 1997.

(8) Yan, Y.; Zhang, X.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 16058–16061.

(9) For review, see: Chen, Y.; Yekta, S.; Yudin, A. K *Chem. Rev.* **2003**, *103*, 3155–3211. For recent examples, see: (a) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731–1734. (b) Lacasse, M.-C.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440–12441. (c) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11. (d) Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822–1823.

(10) For recent examples, see: (a) Wang, Y.-G.; Maruoka, K. *Org. Process Res. Dev.* **2007**, *11*, 628–632. (b) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667. (c) Capozzi, G.; Delogu, G.; Fabbri, D.; Marini, M.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **2002**, *67*, 2019–2026.

(11) See Supporting Information for details.

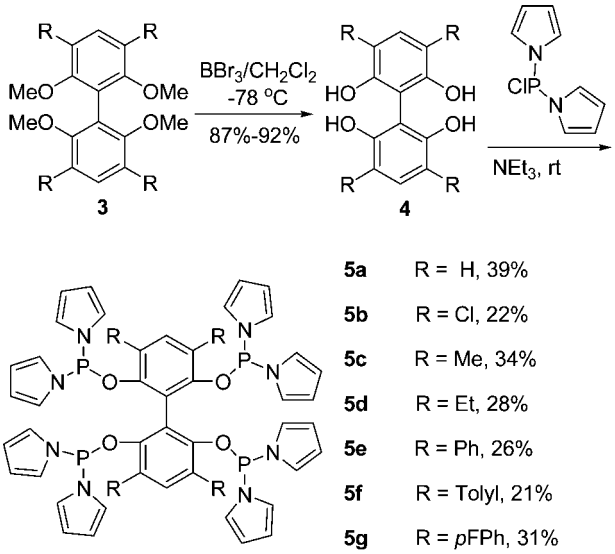
(12) Lindsten, G.; Wennerstroem, O.; Isaksson, R. *J. Org. Chem.* **1987**, *52*, 547–554.

(13) DeJongh, D. C.; Van Fossen, R. Y. *J. Org. Chem.* **1972**, *37*, 1129–1135.

(14) (a) Jackstell, R.; Klein, H.; Beller, M.; Wiese, K.-D.; Rottger, D. *Eur. J. Org. Chem.* **2001**, *20*, 3871–3877. (b) van der Slot, S. C.; Duran, J.; Luten, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2002**, *21*, 3873–3883.

(15) Davis, T. L.; Walker, J. F. *J. Am. Chem. Soc.* **1930**, *52*, 358–361.

**Scheme 3.** Synthesis of Ligands




2, entry 7). The improved selectivity and enhanced reactivity for introducing substituents are striking, and some features of those ligands are noteworthy: (1) The electronic character of substituents had an impact on regioselectivity, with the electron-donated alkyl groups leading to a higher linear to branched ratio while the electron-withdrawing groups, such as the chloro and aromatic substituents, usually led to a lower selectivity but a higher reactivity (compare ligand **5c**, **5d** in Table 1 and Table 2, to ligands **5b**, **5e**−**5g** in Tables 1 and 2). (2) It seemed that the size of the substituents also had some effects on the selectivity. As the size of the group increased from methyl to ethyl for electron-donating substituents, the *n*:*i* ratio increased. However, for electron-withdrawing substituents no clear steric effect was observed, and as chloro changed to larger phenyl groups, the *n*:*i* ratio slightly decreased. These results hint that substituents' electronic character exerted more power on steric nature (see Table 1, entries 3, 15, 17, 19 and Table 2, entries 3, 11, 13, 15). (3) The reaction temperature also plays a key role in the isomerization−hydroformylation process. For 2-octene, at low temperature, though high regioselectivity was observed, the reaction rate was rather low. To facilitate the olefin isomerization and hydroformylation, a high temperature (100 °C) is preferred to achieve a high reaction rate as well as acceptable regioselectivity (Table 1, entries 8−11). The temperature effect was especially remarkable for 2-hexene when **5d** was used as ligand; as the temperature decreased from 100 to 80 °C, the ratio of linear to branch increased from 167.5 to 362.0 (Table 2, entries 7−10). (4) The $CO/H_2$ total pressure also influences the reaction. For example, when 2-octene was subjected to the isomerization−hydroformylation under high pressure (20/20 atm), both reaction rate and regioselectivity were low. Lowering the pressure generally resulted in higher reaction rate and regioselectivity (Table 1, entries 11−13). Decreasing the $CO/H_2$ pressure from 10/10 atm to 5/5 atm did not change the reaction rate very much; however, the regioselectivity was improved to some extent. (5) As we have observed before, when ligand **5a** was subjected to the hydroformylation for a prolonged period (e.g., 12 h), the linear to branch ratio would drop about 20%, which makes the process less favorable. Interestingly, we found that our newly developed ligands with varied substituents (except ligand **5b**, which seemed to

**Table 1.** Isomerization−Hydroformylation of 2-Octene with Ligands **5**[a]

| entry | ligand | temp (°C) | $CO/H_2$ (atm) | *t* (h) | *n*:*i*[b] | linear (%)[c] | TON[d] |
|---|---|---|---|---|---|---|---|
| 1 | **5a** | 100 | 5/5 | 1 | 51.7 | 98.1 | $1.5 \times 10^3$ |
| 2 | **5a** | 100 | 5/5 | 12 | 38.0 | 97.4 | $7.7 \times 10^3$ |
| 3 | **5b** | 100 | 5/5 | 1 | 82.8 | 98.9 | $2.5 \times 10^3$ |
| 4 | **5b** | 100 | 5/5 | 4 | 70.7 | 98.6 | $5.2 \times 10^3$ |
| 5 | **5b** | 100 | 5/5 | 12 | 27.2 | 96.5 | $8.4 \times 10^3$ |
| 6 | **5c** | 100 | 5/5 | 1 | 106.6 | 99.1 | $1.5 \times 10^3$ |
| 7 | **5c** | 100 | 5/5 | 12 | 101.6 | 99.0 | $7.6 \times 10^3$ |
| 8 | **5d** | 60 | 5/5 | 1 | 122.0 | 99.2 | $4.7 \times 10$ |
| 9 | **5d** | 80 | 5/5 | 1 | 181.9 | 99.4 | $5.1 \times 10^2$ |
| 10 | **5d** | 80 | 5/5 | 12 | 207.6 | 99.5 | $3.4 \times 10^3$ |
| 11 | **5d** | 100 | 5/5 | 1 | 136.9 | 99.3 | $1.0 \times 10^3$ |
| 12 | **5d** | 100 | 10/10 | 1 | 128.4 | 99.2 | $1.5 \times 10^3$ |
| 13 | **5d** | 100 | 20/20 | 1 | 68.1 | 98.6 | $4.8 \times 10^2$ |
| 14 | **5d** | 100 | 5/5 | 12 | 106.9 | 99.1 | $6.3 \times 10^3$ |
| 15 | **5e** | 100 | 5/5 | 1 | 78.1 | 98.7 | $2.3 \times 10^3$ |
| 16 | **5e** | 100 | 5/5 | 12 | 77.3 | 98.7 | $8.8 \times 10^3$ |
| 17 | **5f** | 100 | 5/5 | 1 | 53.3 | 98.2 | $2.2 \times 10^3$ |
| 18 | **5f** | 100 | 5/5 | 12 | 56.7 | 98.3 | $8.7 \times 10^3$ |
| 19 | **5g** | 100 | 5/5 | 1 | 65.0 | 98.5 | $1.7 \times 10^3$ |
| 20 | **5g** | 100 | 5/5 | 12 | 61.7 | 98.4 | $7.9 \times 10^3$ |

[a] S/C = 10,000, [Rh] = 0.57 mM, ligand/Rh ratio = 3:1, toluene as solvent, decane as internal standard. [b] Linear to branched ratio, determined on the basis of GC analysis, the average value of 3 repeated runs and 2 injections per run. Error is estimated at <5. [c] Percentage of linear aldehyde in all aldehydes. [d] Turnover number, determined on the basis of GC, the average value of 3 repeated runs and 2 injections per run. Error is estimated at <200.

**Table 2.** Isomerization−Hydroformylation of 2-Hexene with Ligands **5**[a]

| entry | ligand | *t* (h) | *n*:*i*[b] | linear (%)[c] | TON[d] |
|---|---|---|---|---|---|
| 1 | **5a** | 1 | 80.6 | 98.8 | $1.7 \times 10^3$ |
| 2 | **5a** | 12 | 56.0 | 98.2 | $6.0 \times 10^3$ |
| 3 | **5b** | 1 | 86.1 | 98.9 | $2.4 \times 10^3$ |
| 4 | **5b** | 12 | 30.4 | 96.8 | $7.3 \times 10^3$ |
| 5 | **5c** | 1 | 289.4 | 99.7 | $6.0 \times 10^2$ |
| 6 | **5c** | 12 | 104.9 | 99.1 | $5.3 \times 10^3$ |
| 7 | **5d**[e] | 1 | 362.0 | 99.7 | $5.4 \times 10^2$ |
| 8 | **5d**[e] | 12 | 186.9 | 99.5 | $2.7 \times 10^3$ |
| 9 | **5d** | 1 | 167.5 | 99.4 | $9.7 \times 10^2$ |
| 10 | **5d** | 12 | 133.5 | 99.2 | $5.7 \times 10^3$ |
| 11 | **5e** | 1 | 85.0 | 98.8 | $1.9 \times 10^3$ |
| 12 | **5e** | 12 | 74.8 | 98.7 | $6.3 \times 10^3$ |
| 13 | **5f** | 1 | 58.0 | 98.3 | $1.9 \times 10^3$ |
| 14 | **5f** | 12 | 43.2 | 97.8 | $6.4 \times 10^3$ |
| 15 | **5g** | 1 | 91.4 | 98.9 | $2.0 \times 10^3$ |
| 16 | **5g** | 12 | 93.7 | 98.9 | $6.6 \times 10^3$ |

[a] S/C = 10,000, [Rh] = 0.69 mM, ligand/Rh ratio = 3:1, temperature = 100 °C, $CO/H_2$ = 5/5 atm, toluene as solvent, decane as internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] Temperature = 80 °C.

degrade gradually during the reaction progress as precipitate was observed after the reaction terminated (Table 1, entries 3−5)) still maintained high regioselectivity after elongated reaction time (12 h).

The exact effect of the substituents on the catalytic cycles is not clear right now. Further investigation of bite angle and electronic character of these ligands and in situ spectroscopy techniques would help us to elucidate the mechanism of the high linear selectivity.

In conclusion, we have disclosed a series of new pyrrole-based tetraphosphorus ligands with multiple chelating modes. This system shows great promise for the regioselective isomerization−hydroformylation of internal olefins. In many cases these new ligands afforded results much better than with the parent ligand based on tetraol, and our result is among the best reported in the literature. Further ligand applications and mechanism studies are now under investigation and will be reported in due course.

**Acknowledgment.** We thank the National Institutes of Health (GM58832) and Merck & Co., Inc for finacial support.

**Supporting Information Available:** Experimental procedures and full spectroscopic data for ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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