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New diphosphite ligands for enantioselective asymmetric hydroformylation

Yaping Zou, Yongjun Yan and Xumu Zhang*

104 Chemistry Building, Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA

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Abstract—A series of new diphosphite ligands have been easily prepared from BINOL derivatives; moderate enantioselectivities (up to 80% ee) and excellent regioselectivities (b/l up to 98/2) have been achieved in the Rh-catalyzed asymmetric hydroformylation of vinyl acetate.

Homogeneous catalytic hydroformylation has been extensively applied in the fine chemical and pharmaceutical industry. Asymmetric hydroformylation[1] provides a highly efficient method for the preparation of various chiral aldehydes, which can be utilized in the synthesis of important drug intermediates and pharmaceuticals. This great demand has initiated tremendous efforts in the development of effective phosphorus ligands to achieve both high enantioselectivities and regioselectivities in hydroformylation. However, to date only a few successful ligand systems have been previously reported.[2] One such example is Chiraphite, a bisphosphite ligand developed by Babin and Whiteker at Union Carbide in 1992.[2a,3] Excellent enantioselectivities (up to 90% ee) have been achieved in the hydroformylation of styrene, but only moderate enantioselectivities (up to 50% ee) were reported for vinyl acetate. The chiral centers in the (2*R*,4*R*)-pentane-2,4-diol backbone can effectively transfer the chiral information to the phosphite moieties. The presence of bulky substituents (*t*-butyl) at the *ortho*-position of the biphenyl moieties is necessary for good regio- and enantioselectivities. Kelliphite, another diphosphite ligand which is not only a good ligand for hydroformylation of allyl cyanide,[2f] but also exhibits high enantioselectivity (88% ee at 35 °C) in the hydroformylation of vinyl acetate.[4] The chiral phosphite moieties, which are connected by the bis-phenol bridge, determine the chirality of the product.

Prompted by the excellent results obtained with Chiraphite and Kelliphite, we have designed a series of new diphosphite ligands using chiral binaphthyl as the backbone. The ligand design was based on the following considerations: (i) ligand bearing binaphthyl backbone such as BINAP can provide excellent chiral induction in asymmetric reactions;[5] (ii) introduction of substitutes at 3,3′-position on binaphthyl backbone can lock the orientation of biphenyl groups of the phosphite moieties, which can facilitate highly enantioselective hydroformylation; (iii) subtle tuning of steric and electronic properties of the ligand can be achieved by varying the substitutes on 3,3′-position.

The synthetic route for ligand **L1**–**L4** is depicted in Scheme 1.[6] In the presence of catalytic amount of 1-methylpyrrolidin-2-one, reaction of PCl_3 with 3,3′-bis-*t*-butyl biphenol **1** at 95 °C for 18 h afforded phosphorochloridite **2**, which was used in the next step without further purification.[7] (*S*) BINOL derivative **3** with different 3,3′-substitutes were synthesized according to the known literature methods.[8] Deprotonation of **3** with *n*-butyl lithium followed by quenching with phosphorochloridite **2** afforded (*S*) ligands **L1**–**L4** in moderate yields.[9]

Rhodium-catalyzed asymmetric hydroformylation of vinyl acetate was conducted for preliminary examinations of the four ligands. The catalyst was prepared in situ by mixing $Rh(acac)(CO)_2$ with **L1**–**L4**. Hydroformylation reactions were performed using 1:1 CO/H_2 gas with 0.1 mol % of the catalyst loading at 40 °C for 24 h.[10] Screening of ligands **L1**–**L4** showed a strong

* Corresponding author. Tel.: +1 732 445 2674; fax: +1 732 445 6312; e-mail: xumu@chem.psu.edu

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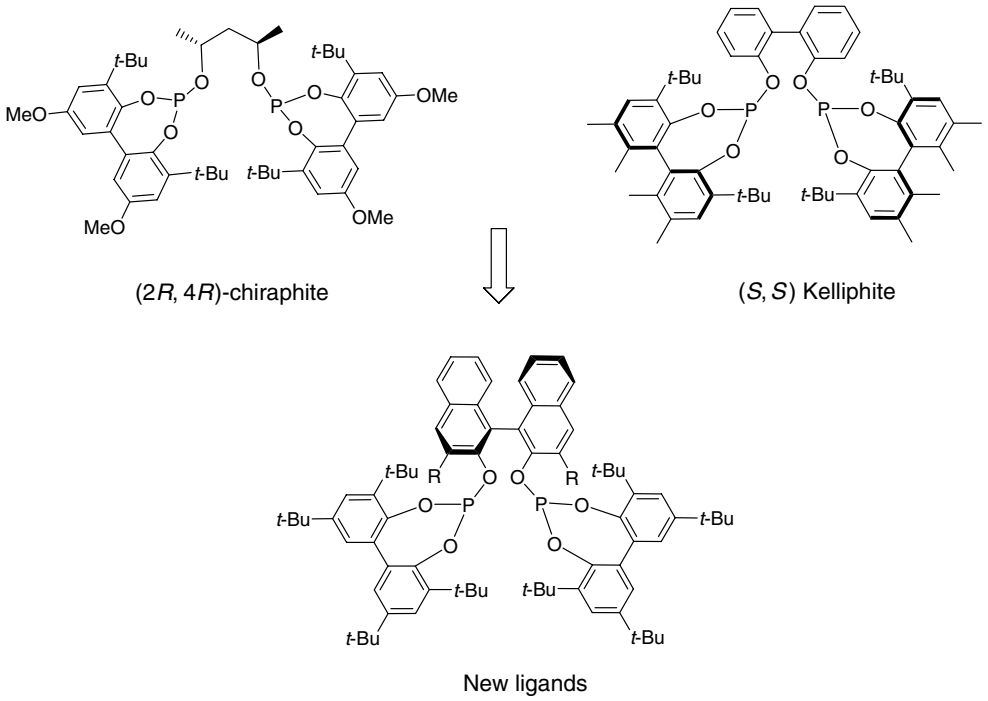
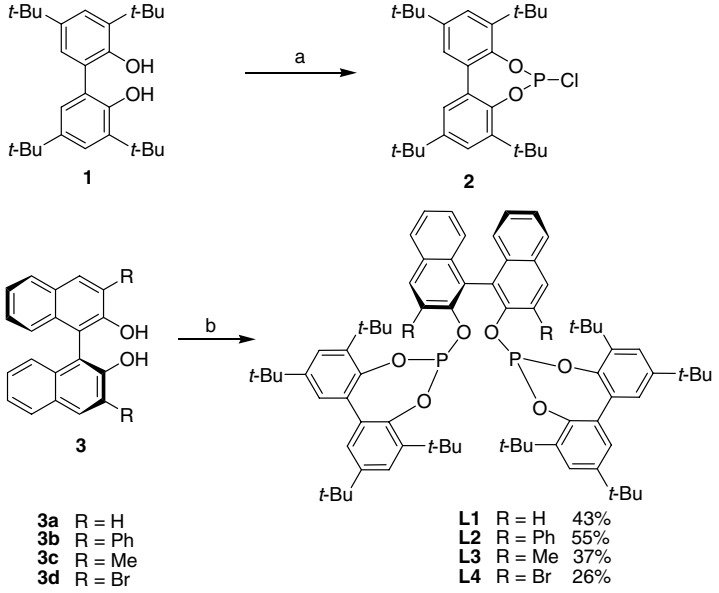


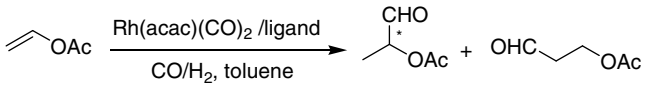
dependence of ee's on the substitutes on 3,3′-positions of the ligands. The best results were obtained by **L2** and **L3** (Table 1, entries 2 and 3), while the enantioselectivities were significantly lower using **L1** and **L4** (Table 1, entries 1 and 4). This results implies that the steric properties of 3,3′-substitutes may play an important role in the chiral induction. Good to excellent regioselectivities were also achieved using these ligands (Table 1, entries 1–4).

Reaction conditions were optimized using **L2** as the ligand and the results are shown in Table 2. The effect of ligand/metal ratio on the hydroformylation reaction was first investigated. As shown in Table 2 (entries 1 and 3), the enantioselectivity increased from 35% ee to 77% ee when ligand/metal ratios increased from 1:1 to 4:1. Higher ligand/metal ratio (6:1) did not improve the enantioselectivity (Table 2, entry 4). The reaction was also examined at higher temperature to achieve good conversions. In contrast to the moderate catalytic activity observed at 60 °C (43%, 72% ee, Table 2, entry 5), close to complete conversion was achieved at 80 °C though with diminished enantioselectivity (56% ee, Table 2, entry 6), but regioselectivities did not change significantly. The enantioselectivity in asymmetric hyd-



Scheme 1. Synthesis of diphosphite ligands **L1**–**L4**. Reagents and conditions: (a) PCl_3, 1-methylpyrrolidin-2-one, 95 °C, toluene; (b) (i) *n*-BuLi (1.5 equiv), THF; (ii) **2** (1.5 equiv), 20–60%.

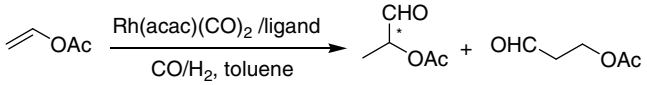
Table 1. Screening of ligands for asymmetric hydroformylation[a]



Entry	Ligand	Conv.[b] (%)	b/l[c]	ee[d] (%)
1	**L1**	29	96/4	13(*S*)
2	**L2**	23	97/3	71(*S*)
3	**L3**	45	98/2	75(*S*)
4	**L4**	23	98/2	16(*S*)

[a] Reactions were carried out under 10 atom of H_2 and CO at 40 °C for 24 h. Substrate/Rh = 1000. L/Rh = 4:1.
[b] Conversion was based on ^{1}H NMR.
[c] Branched/linear ratio. Determined based on ^{1}H NMR.
[d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-fomylethyl acetate.

Table 2. Asymmetric hydroformylation of vinyl acetate with Rh–**L2** catalyst[a]



Entry	Ligand	L/Rh	*T* (°C)	Time (h)	Conv. (%)	b/l	ee (%)
1	**L2**	1:1	40	12	6	98/2	35(*S*)
2	**L2**	2:1	40	12	16	98/2	69(*S*)
3	**L2**	4:1	40	12	23	98/2	77(*S*)
4	**L2**	6:1	40	12	3	98/2	77(*S*)
5	**L2**	4:1	60	12	43	97/3	72(*S*)
6	**L2**	4:1	80	12	>99	98/2	56(*S*)
7	**L2**	4:1	60	24	80	98/2	66(*S*)
8	**L2**	4:1	60	36	98	98/2	41(*S*)
9	**L3**	4:1	40	12	9	98/2	80(*S*)
10	**L3**	4:1	40	24	45	98/2	75(*S*)
11	**L3**	4:1	60	12	69	98/2	73(*S*)
12	**L3**	4:1	60	24	98	98/2	69(*S*)

[a] Reactions were carried out under 10 atom of H_2 and CO. Substrate/Rh = 1000.

roformylation usually decreases rapidly with prolonged reaction time due to product isomerization. This factor was examined in detail with different reaction time ranging from 12 h to 36 h. As shown in the table (Table 2, entries 5 and 8), the enantioselectivity dropped from 72% ee (12 h) to only 41% ee (36 h), with an increased conversion from 43% to 98%. Asymmetric hydroformylation with ligand **L3** was also investigated (Table 2, entries 9–12). The best enantioselectivity (80% ee) was achieved at 40 °C for 12 h, although the conversion was only 9% (Table 2, entry 9). Elevated reaction temperature and prolonged reaction time resulted in 98% conversion with lower enantioselectivity (Table 2, entry 12).

In conclusion, four structural related diphosphite ligands **L1**–**L4** have been synthesized from readily available starting materials. Their application in asymmetric hydroformylation reactions of vinyl acetate has been investigated. Moderate enantioselectivities (up to 80% ee) and excellent regioselectivities (b/l up to 98/2) have been achieved. However, low enantioselectivites (less than 30% ee) were obtained for the hydroformylation of styrene. Further ligand structure modifications are currently undergoing to increase the enantioselectivity and the reactivity.

References and notes

1. For recent reviews, see: (a) Claver, C.; Diéguez, M.; Pàmies, O.; Castillón, S. *Top. Organometall. Chem.* **2006**, *18*, 35; (b) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; (c) Agbossou, F.; Carpentier, J.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485; (d) Gladiali, S.; Bayön, J. C.; Claver, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1453; (e) Breit, B.; Seiche, W. *Synthesis* **2001**, 1; (f) Claver, C.; van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claven, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000.
2. (a) Babin, J. E.; Whiteker, G. T. Patent WO 9303839, 1992; (b) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033; (c) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413; (d) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106; (e) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem. Eur. J.* **2001**, *7*, 3086; (f) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031; (g) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040; (h) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834; (i) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. *Tetrahedron Lett.* **2005**, *46*, 7831; (j) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198.
3. Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barner, B. A. In *Catalysis of Organic Reactions*; Morrell, D. G., Ed.; Marcel Dekker: New York, 2003; p 359.
4. Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277.
5. For recent reviews, see: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857; (b) Kocovsky, P.; Vyskocyl, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213; (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.
6. Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem.* **2005**, *70*, 3363.
7. (a) Anschütz, L.; Broeker, W.; Neher, R.; Ohnheiser, A. *Chem. Ber.* **1943**, *76*, 218; (b) Anschütz, L.; Marquardt, W. *Chem. Ber.* **1956**, *89*, 1119; (c) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. US. Patents 4,668,651 (1987) and 4,769,498 (1988); (d) Pastor, S. D.; Shum, S. P.; Rodebaugh, R. K.; Debellis, A. D.; Clarke, F. H. *Helv. Chim. Acta* **1993**, *76*, 900.
8. (a) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253; (b) Simonsen, K. B.; Gothelf, K. V.; Jorgenson, K. A. *J. Org. Chem.* **1998**, *63*, 7536.
9. General procedure for synthesis of ligands **L1**–**L4**. To a solution of **3b** (438 mg, 1 mmol) in THF (15 mL) at 0 °C was added dropwise *n*-BuLi (3 mmol, 1.2 mL of 2.5 M hexane solution). The reaction mixture was allowed to warm to room temperature and stirred for 30 min to give a deep red solution. The reaction mixture was then recooled

to 0 °C, and then was added dropwise to **2** (1.43 g, 3 mmol) in THF (10 mL). After addition, the cooling bath was removed and the mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure. To the residue was added CH_2Cl_2 (10 mL), and the mixture was filtered to remove the salt. The filtration was concentrated and subjected to chromatography on silica gel (eluted with hexane/EtOAc 25:1) to afford pure ligands **L2** 722 mg (55% yield). Spectra data for ligand **L2**: ^{1}H NMR (360 MHz, CD_2Cl_2): δ 8.04 (s, 2H), 7.85 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 7.9$ Hz, 4H), 7.40–7.31 (m, 6H), 7.19–7.12 (m, 4H), 6.93 (t, $J = 7.2$ Hz, 2H), 6.84–6.77 (m, 8H), 1.31 (s, 18H), 1.16 (s, 18H), 1.14 (s, 18H), 1.00 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.34, 146.10, 145.80, 145.46, 140.10, 139.92, 137.94, 135.57, 134.39, 133.04, 132.26, 130.96, 130.26, 128.12, 127.82, 127.03, 126.98, 126.53, 126.38, 126.30, 126.24, 125.22, 123.94, 35.27, 35.09, 34.59, 34.46, 31.63, 31.50, 31.28, 31.23, 31.20. ^{31}P NMR (146 MHz, CD_2Cl_2): δ 140.18 (s). ES+HRMS calcd for $C_{88}H_{101}O_6P_2$ [MH^+] 1315.7073, found 1315.6960.

10. General procedure for asymmetric hydroformylation: To a 2 mL vial equipped with a magnetic bar were added ligand (0.004 mmol), $Rh(acac)(CO)_2$ (0.001 mmol in 0.10 mL of toluene), and vinyl acetate (1.0 mmol), and additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (120 rpm) at 40 °C (oil bath) for 24 h. The conversion and regioselectivity were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The enantiomeric excess was determined directly by GC analysis of the crude reaction mixture.