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Small Bite-Angle P–OP Ligands for Asymmetric Hydroformylation and Hydrogenation

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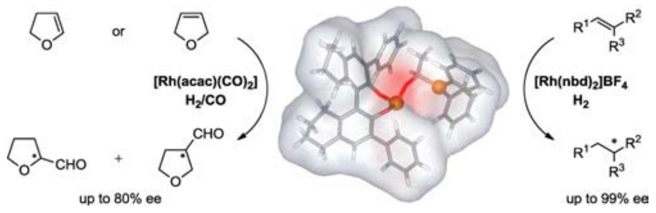
ABSTRACT



A series of small bite-angle phosphine-phosphite (P–OP) ligands have been synthesized by a two-step method. The key intermediate was prepared by an unprecedented asymmetric carbonyl reduction of a phosphamide using the CBS (Corey–Bakshi–Shibata) catalyst. The topology of these ligands (a configurationally stable stereogenic carbon with two heteroatom substituents) and their small bite-angle (created by the close proximity of the two ligating groups to the metal center) together provide a rigid asymmetric environment around this center, enabling high stereoselectivity in hydroformylations and hydrogenations of standard substrates.

Over the past few decades enantioselective transition-metal-mediated catalysis has become extremely powerful for an ever-growing number of asymmetric organic transformations.[1] Among the catalysts used, phosphine-phosphite (P–OP) ligands, which differ in the stereoelectronic properties of their ligating groups, have emerged as efficient nonsymmetric ligands. Since the seminal P–OP ligands devised by Takaya[2] and Pringle,[3] many other classes have been developed and tested, whose structures encompass diverse carbon backbones and stereogenic elements and differ in the distance between the two phosphorus groups.[4] Literature on small bite-angle P–OP ligands in asymmetric catalysis is scarce (Figure 1, **1**–**2**[5] and **3**[6]). These ligands have been applied with varying levels of success in Rh-mediated asymmetric transformations. One understudied structural feature in these ligands is the presence of a stereogenic carbon between the two P-binding groups. Following previous work in developing 1,2-P–OP ligands for numerous asymmetric transformations,[7] the authors of this paper sought to prepare and assess the geminal analogs of these ligands (Scheme 1), which contain a stereogenic carbon between the phosphine and phosphite groups. Herein are described the synthesis of these compounds as well as their catalytic performance in asymmetric hydrogenations[1] and hydroformylations.[8]

The authors envisaged that the new 1,1-P–OP ligands **6** could be synthesized in two steps (Scheme 1): formation of the borane complex of the enantiopure phosphinoalcohol **5**, followed by O-phosphorylation. Intermediate **5** was prepared by an unprecedented reduction of the phosphamide **4** using borane and the CBS (Corey–Bakshi–Shibata) catalyst.

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(1) For general references on this topic, see for example: (a) *Comprehensive Asymmetric Catalysis*, 1st ed.; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vols. I–III. (b) *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier Science: Oxford, 2012; Vols. 1–9.

(2) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.

(3) Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1993**, 314.

(4) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119 and the references cited therein.

(5) (a) Arena, C. G.; Faraone, F.; Graiff, C.; Tiripicchio, A. *Eur. J. Inorg. Chem.* **2002**, 711. (b) Farkas, G.; Balogh, S.; Madarasz, J.; Szoellosy, A.; Darvas, F.; Uerge, L.; Gouygou, M.; Bakos, J. *Dalton Trans.* **2012**, *41*, 9493.

(6) Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477.

10.1021/ol401494x

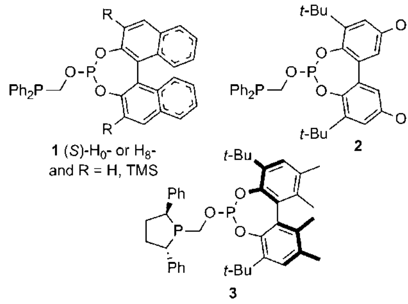
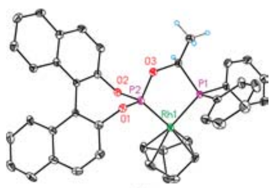


Figure 1. Reported small bite-angle P–OP ligands.

First, the reduction of the phosphamide **4**[9] was evaluated using methyloxazaborolidine (Me-CBS) as a chiral catalyst and $BH_3 \cdot DMS$ as a reducing agent. After some experimentation, the following procedure was found to provide good results: slow addition (1 h) of $BH_3 \cdot DMS$ to a solution of the (*R*)-Me-CBS catalyst (30 mol %) and **4** in THF at rt, which afforded the phosphine-alcohol **5** as the borane adduct in 87% yield and high enantiomeric ratio (er = 84:16 in favor of the *R* enantiomer,[10] Scheme 1). Optical enrichment of **5** by semipreparative HPLC on a chiral stationary phase[11] afforded the enantiomerically pure compound (*R*)-**5** in 77% yield in gram amounts.[12] This product was subsequently O-phosphorylated with several bisnaphthol phosphorochloridites under basic conditions. The resulting borane-protected 1,1-P–OP derivatives were subsequently deprotected with DABCO to afford the target ligands **6a**–**e** (Scheme 1). Interestingly, ligands **6a**–**e** were configurationally stable: the stereogenic carbon did not undergo any detectable epimerization at rt (as determined by $^{31}P\{^1H\}$ NMR).

The ability of ligands **6** to coordinate to cationic rhodium precursors suitable for catalysis was assessed by NMR spectroscopy and X-ray analysis. Rhodium complexes $[Rh(nbd)(\mathbf{6a})]BF_4$ (**7a**) and $[Rh(nbd)(\mathbf{6b})]BF_4$ (**7b**) were synthesized in almost quantitative yield by mixing stoichiometric amounts of either ligand (**6a** or **6b**) with $[Rh(nbd)_2]BF_4$. NMR and X-ray analyses established the molecular structure of **7a**–**b** (see Figure 2 for **7a** and the Supporting Information for **7b**), in which the P–OP ligands work as bidentate ligands, exhibiting small natural bite-angles of 82.25(4)° (**7a**) and 80.22(6)° (**7b**). Furthermore, the absolute configuration of the stereogenic carbon at the ligand backbone was unambiguously assigned to be (*R*). Regarding the coordination of **6** to hydroformylation rhodium precursors, [Rh(acac)(P–OP)] complexes were also efficiently formed by the reaction of stoichiometric amounts of ligands **6** and $[Rh(acac)(CO)_2]$. The NMR data are consistent with there being a bidentate coordination between the ligating groups and the metal.[11]



7a

Figure 2. Crystal structure of **7a** (ORTEP drawings showing thermal ellipsoids at 30% probability). H-atoms and the BF_4 counterion are omitted for clarity.

Having developed efficient syntheses for the P–OP ligands **6** and studied their coordination behavior with suitable rhodium precursors for catalytic studies, the authors then assessed their catalytic performance in asymmetric hydroformylations and hydrogenations.

The ligands **6a**–**e** were initially screened in asymmetric hydroformylation of vinyl acetate (**8a**), styrene (**8b**), and (allyloxy)trimethylsilane (**8c**) to the corresponding aldehydes **9a**–**c** and **10a**–**c**. This chemistry was done using preformed (*in situ*) [Rh(acac)(**6a**–**e**)] complexes under CO/H_2 (1:1, 10 bar) in toluene at 40 °C (Table 1). The results clearly indicated that catalytic performance depended on both the substrate and ligand. For instance, for substrates **8a** and **8c**, the rhodium complexes of ligands **6c**–**e** performed better than those derived from **6a**–**b** (in Table 1 compare entries 1–2 with entries 3–5); however, for substrate **8b**, full conversion was achieved with each of the P–OP ligands. These results demonstrated that greater steric bulkiness at the *ortho*-positions of the phosphite moiety leads to higher conversions and regioselectivities in the branched aldehydes. It should be also recalled here that related catalytic systems derived from 1,1-P–OP ligands **1** (with (*S*)-H_0- and R = H) failed in the hydroformylation of **8b** due to catalyst decomposition.[5a] As such, the presence of the CH-methyl group in the ligands reported here increases the stability of the resulting catalytic species (in Table 1 see entries 1–2 for substrate **8b**).

Regarding enantioselectivity, the rhodium complexes of ligands **6a**–**c** provided poor to moderate results (entries 1–3 in Table 1). However, the introduction of a more sterically hindered phosphite group in ligands **6d**–**e**

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(7) (a) Fernández-Pérez, H.; Pericàs, M. A.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2008**, *350*, 1984. (b) Donald, S. M. A.; Vidal-Ferran, A.; Maseras, F. *Can. J. Chem.* **2009**, *87*, 1273. (c) Fernández-Pérez, H.; Donald, S. M. A.; Munslow, I. J.; Benet-Buchholz, J.; Maseras, F.; Vidal-Ferran, A. *Chem.—Eur. J.* **2010**, *16*, 6495. (d) Fernández-Pérez, H.; Etayo, P.; Núñez-Rico, J. L.; Vidal-Ferran, A. *Chim. Oggi* **2010**, *28*, XXVI. (e) Núñez-Rico, J. L.; Fernández-Pérez, H.; Benet-Buchholz, J.; Vidal-Ferran, A. *Organometallics* **2010**, *29*, 6627. (f) Panossian, A.; Fernández-Pérez, H.; Popa, D.; Vidal-Ferran, A. *Tetrahedron: Asymmetry* **2010**, *21*, 2281. (g) Etayo, P.; Núñez-Rico, J. L.; Fernández-Pérez, H.; Vidal-Ferran, A. *Chem.—Eur. J.* **2011**, *17*, 13978. (h) Etayo, P.; Núñez-Rico, J. L.; Vidal-Ferran, A. *Organometallics* **2011**, *30*, 6718. (i) Nunez-Rico, J. L.; Etayo, P.; Fernandez-Perez, H.; Vidal-Ferran, A. *Adv. Synth. Catal.* **2012**, *354*, 3025. (j) Núñez-Rico, J. L.; Vidal-Ferran, A. *Org. Lett.* **2013**, *15*, 2066. (k) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728.

(8) For a general review, see: Franke, R.; Selent, D.; Boerner, A. *Chem. Rev.* **2012**, *112*, 5675 and references cited therein.

(9) Angharad, B. R.; Clarke, M. L.; Guy, O. A.; Ratcliffe, D. A. *J. Organomet. Chem.* **2003**, *667*, 112.

(10) The absolute configuration of **5** was unequivocally established by X-ray analysis of the rhodium complex of a 1,1-P–OP ligand, as shown later in the discussion.

(11) See Supporting Information for details.

(12) Although **5** was configurationally stable at −20 °C, it had racemized to the extent of 36% after 2 months at rt.

Scheme 1. Synthesis of 1,1-P−OP Ligands **6a**−**e**

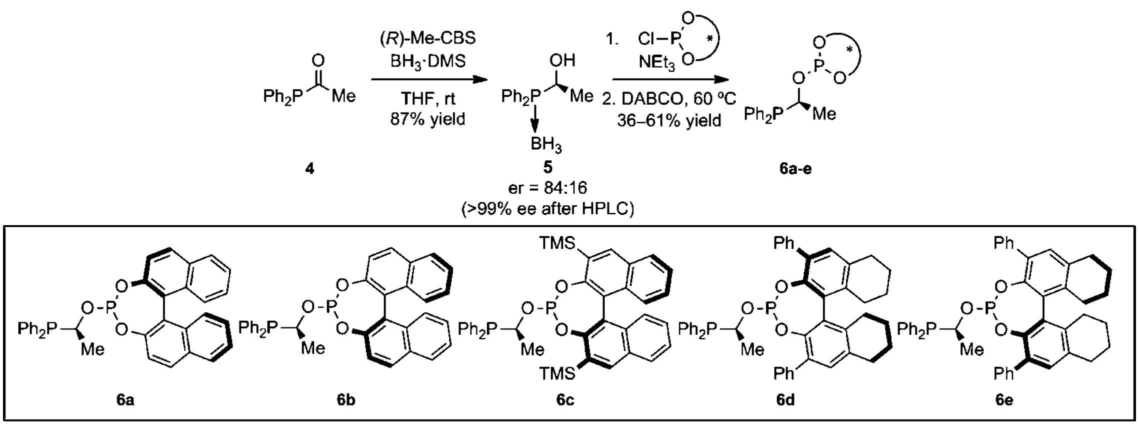
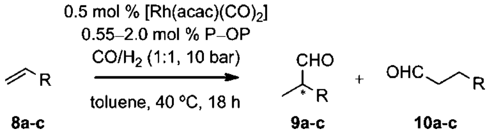


Table 1. Screening of Asymmetric Hydroformylation with the Library of P−OP Ligands[a]



			vinyl acetate **8a** (R = OAc)			styrene **8b** (R = Ph)			allyloxy-TMS **8c** (R = CH_2−OTMS)		
entry	ligand	L/M ratio	% conv[b]	b:l ratio[c]	% ee[c] (config)[d]	% conv[b]	b:l ratio[c]	% ee[c] (config)[d]	% conv[b]	b:l ratio[c]	% ee[c] (config)[d]
1	**6a**	1.1	53	92:8	29 (*S*)	>99	98:2	10 (*S*)	24	44:56	4 (*S*)
2	**6b**	1.1	51	90:10	38 (*S*)	>99	96:4	30 (*R*)	10	54:46	14 (*R*)
3	**6c**	4	92	99:1	3 (*S*)	>99	99:1	20 (*S*)	96	84:16	8 (*R*)
4	**6d**	4	>99	99:1	74 (*R*)	>99	99:1	54 (*S*)	>99	81:19	36 (*S*)
5	**6e**	4	>99	99:1	69 (*S*)	>99	98:2	30 (*R*)	>99	82:18	43 (*R*)

[a] Reactions were run in a parallel reactor. Reaction conditions are indicated in the Table 1 image. [b] Determined by ^1H NMR analysis. [c] Determined by GC analysis on chiral stationary phases. [d] Absolute configuration was assigned by comparison of the elution order in GC analysis with reported data.

significantly increased the enantioselectivity of the hydroformylation for the three substrates (in Table 1 compare entries 1−3 with entries 4−5), affording a noteworthy 74% ee for **8a** with ligand **6d**. Interestingly, the hydroformylation products obtained with ligands **6d** and **6e** had opposite configurations (in Table 1 compare entry 4 with entry 5). This indicates that the direction of stereodiscrimination was predominantly controlled by the phosphite fragment.

Encouraged by these results, the authors then considered using ligands **6a**−**e** in the hydroformylation of two challenging heterocyclic olefins for which there are few reported high-performing catalysts: 2,3-dihydrofuran (**11**) and 2,5-dihydrofuran (**14**) (Tables 2 and 3).[13] The rhodium complexes derived from **6a**−**c** gave modest conversions and regioselectivities, along with low enantioselectivities in the hydroformylation of **11** (see Table 2, entries 1−3). In contrast, ligands **6d**−**e** gave markedly better results in terms of conversion, regioselectivity, and stereoselectivity. For instance, ligand **6d** efficiently provided the 2-carbaldehyde **12** as the major isomer with high conversion and high ee's (up to 80% ee; see Table 2, entry 4). To the best of the authors' knowledge, this is one of the highest reported enantioselectivity values for **12** when obtained by hydroformylation. The minor regioisomer **13** was also obtained with good enantioselectivity (78% ee). Ligand **6e** also gave good results, although with slightly lower regio- and enantioselectivity (in Table 2 compare entry 4 with entry 5).

Hydroformylation of 2,5-dihydrofuran (**14**) (Table 3) followed basically the same trend as that observed for its related isomer, 2,3-dihydrofuran (**11**). The rhodium complex of ligand **6e** gave excellent results in terms of conversion and regioselectivity, providing a respectable ee of 72% in favor of (*R*)-**13** (Table 3, entry 5). Notably, no traces of **11** were observed under these reaction conditions. However, with ligand **6d** a slightly lower

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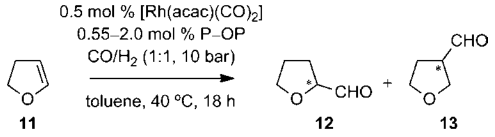
(13) (a) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van der Vlugt, J. I.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 6607. (b) Adint, T. T.; Wong, G. W.; Landis, C. R. *J. Org. Chem.* **2013**, *78*, 4231.

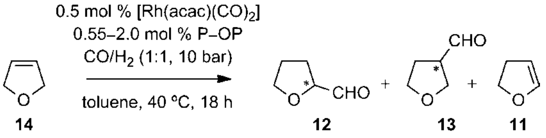
Table 2. Results for Asymmetric Hydroformylation of 2,3-Dihydrofuran (**11**) Using P−OP Ligands[a]



entry	ligand	L/M ratio	% conv[b]	regio[c] (**12**:**13**)	% ee[c] **12**[d]	% ee[c] **13**[d]
1	**6a**	1.1	26	49:51	12 (*S*)	8 (*R*)
2	**6b**	1.1	26	44:56	20 (*S*)	6 (*S*)
3	**6c**	4	46	42:58	19 (*R*)	45 (*S*)
4	**6d**	4	83	58:42	80 (*R*)	78 (*R*)
5	**6e**	4	84	55:45	78 (*S*)	76 (*S*)

[a] Reactions were run in a parallel reactor. Reaction conditions are indicated in the scheme above. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC analysis on chiral stationary phases. [d] Absolute configuration was assigned by comparison of the elution order in GC analysis with reported data.

Table 3. Results for Asymmetric Hydroformylation of 2,5-Dihydrofuran (**14**) Using P−OP Ligands[a]



entry	ligand	L/M ratio	% conv[b]	regio[c] (**12**:**13**)	% **11**[b]	% ee[c] **12**[d]	% ee[c] **13**[d]
1	**6a**	1.1	59	1:99	12	nd	5 (*S*)
2	**6b**	1.1	70	1:99	10	nd	34 (*R*)
3	**6c**	4	74	1:99	4	nd	35 (*R*)
4	**6d**	4	>99	1:99	0	nd	60 (*S*)
5	**6e**	4	>99	1:99	0	nd	72 (*R*)

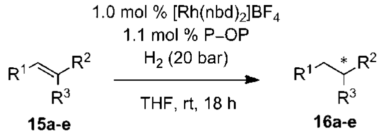
[a] Reactions were run in a parallel reactor. Reaction conditions are indicated in Table 3 image. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC analysis on chiral stationary phases. [d] Absolute configuration was assigned by comparison of the elution order in GC analysis with reported data.

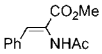
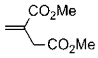
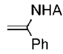
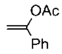
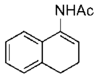
enantio-discrimination for the opposite enantiomer was observed than that for **6e** (Table 3, entry 4). This indicates that the (*R*)-methyl substituent and the (*R*)-BINOL phosphite moiety have a matched effect on the enantioselectivity for **14**, while the (*R*)-methyl and (*S*)-BINOL fragments have matching interactions in enantioselectivity for the other substrates.

Ligands **6a**−**e** were also assessed in enantioselective hydrogenations of an array of diversely substituted substrates. The reactions were performed using *in situ* prepared precatalysts [Rh(nbd)(**6a**−**e**)]BF_4 under standard hydrogenation conditions (1.0 mol %, THF, 20 bar H_2, rt, overnight) (Table 4).

The excellent results summarized in Table 4 proved the outstanding catalytic performance of the rhodium complexes derived from these 1,1-P−OP ligands. The benchmark functionalized alkenes **15a**−**d** were hydrogenated with high conversions and enantioselectivities (93−99% ee). Interestingly, the challenging, sterically hindered substrate *N*-(3,4-dihydro-1-naphthyl)acetamide **15e** was reduced with full conversion and in high enantioselectivity (up to 88% ee; Table 4, entry 5), by using [Rh(nbd)(**6a**)]BF_4 under mild conditions.

Table 4. Screening of Asymmetric Hydrogenation with the Library of P−OP Ligands[a]



entry	substrate	ligand	% conv[b]	% ee[c] (config)[d]
1	 **15a**	**6d**	> 99	99 (*R*)
2	 **15b**	**6a**	> 99	97 (*S*)
3	 **15c**	**6a**	> 99	94 (*R*)
4	 **15d**	**6a**	92	93 (*R*)
5	 **15e**	**6a**	> 99	88 (*R*)

[a] Reactions were run in a parallel reactor. Reaction conditions are indicated in the Table 4 image. Typical isolated product yields were > 90%. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC or HPLC analysis on chiral stationary phases. [d] Absolute configuration was assigned by comparison of the specific rotation with reported data.

In summary, the authors have developed an appealing two-step strategy for synthesizing new 1,1-P−OP ligands that have a stereogenic carbon center between the two P-coordinating groups. Rhodium complexes of ligands incorporating the combination of an *ortho*-diphenyl substituted octahydrobinol fragment at the phosphite moiety, and a stereogenic carbon in the backbone, were highly efficient catalysts in the asymmetric hydroformylation and hydrogenation of diverse substrates. The authors are currently optimizing these P−OP ligands, with the aim of identifying the best catalysts for challenging substrates and chirogenic transformations.

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Supporting Information Available. Text and figures covering experimental procedures, analytical and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.