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1,1-P−OP Ligands with P-Stereogenic Phosphino Groups in Asymmetric Hydrogenations and Hydroformylations

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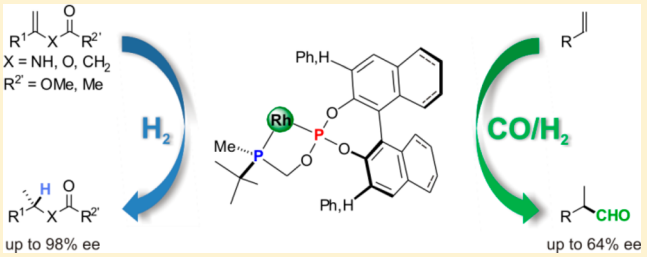
Supporting Information

ABSTRACT: A new series of narrow-bite-angle phosphine−phosphite (1,1-P−OP) ligands (**3a−d**) has been efficiently prepared from the enantiopure (S_P)-*tert*-butyl(hydroxymethyl)methylphosphino borane complex **1**, a crucial intermediate. The catalytic performance of the ligands in Rh-mediated asymmetric hydrogenations and hydroformylations is described. The corresponding rhodium complexes provided excellent efficiencies (full conversion in all cases) and high enantioselectivities (up to 98% ee) for the asymmetric hydrogenation of structurally diverse functionalized alkenes. Furthermore, rhodium catalysts derived from these 1,1-P−OP ligands were highly active and gave excellent regioselectivities (branched/linear product ratios of up to 97/3) and moderate enantioselectivities in the hydroformylation of different terminal olefins.



Hybrid bidentate enantiopure P-containing ligands have efficiently mediated a wide range of applications in transition-metal-catalyzed reactions that lead to a rich array of structurally diverse enantiopure (or enantioenriched) products.[1] Phosphine−phosphite (P−OP) ligands,[2] first developed by the groups of Takaya[3] and Pringle,[4] are an important example of nonsymmetric ligands whose coordinated functional groups differ electronically and sterically. The P−OP ligand BINAPHOS has found applications in many mechanistically unrelated enantioselective transformations,[2] thus making it one of the few "privileged ligands"[5] in asymmetric catalysis.

Several related P−OP ligands, encompassing diverse carbon backbones, different stereogenic elements, and variable distances between the coordinated functional groups, have been reported for asymmetric catalysis.[2] Among these, narrow-bite-angle[6] P−OP ligands are an attractive, understudied class. Interestingly, narrow-bite-angle ligands provide a rigid asymmetric environment around the metal, which translates into high catalytic efficiency in several asymmetric transformations.[7] The short length of the spacer between the two phosphorus functionalities (only one carbon atom) is the primary factor responsible for the low bite-angle values observed (e.g., P−Rh−PO angles of ca. 80° in rhodium complexes derived from 1,1-P−OP ligands[7b]). Interestingly, although P-stereogenic phosphines are highly efficient stereodirecting binding groups in asymmetric catalysis,[8] these groups have not been explored as molecular fragments in 1,1-P−OP ligands.

Seeking to develop new and efficient ligands for asymmetric transformations of interest,[7b,9] the authors of this article prepared the modular 1,1-P−OP ligands **3a−d** (Scheme 1). These ligands incorporate the attractive *tert*-butyl(methyl)-phosphino stereogenic group, which is well-known as a highly efficient stereodirecting moiety in asymmetric catalysis.[10] Herein are reported the synthesis of the enantiomerically pure 1,1-P−OP ligands **3a−d** and their catalytic performance in Rh-mediated asymmetric hydrogenations and hydroformylations.

The ligands **3a−d** were readily prepared in a one-pot process (Scheme 1) from borane complex **1**, based on a geminal phosphino alcohol.[10c,11] The first step involved the *O*-phosphorylation of **1** with diverse chlorophosphite derivatives using triethylamine as the auxiliary base to yield the corresponding P−OP borane complexes **2a−d**. The (relatively clean) resulting crude mixtures containing **2a−d** were immediately cleaved with DABCO in toluene at 60 °C, leading to the corresponding P−OP ligands **3a−d** in 28−44% yield after chromatography. Interestingly, the P−OP borane complexes **2c,d** were found to be highly crystalline, and their structures were confirmed by X-ray analysis.[12]

The ability of the new 1,1-P−OP ligands to form complexes with transition-metal precursors was also studied. Cationic Rh^I complexes derived from the aforementioned P−OP ligands, which are suitable for asymmetric hydrogenation (i.e., [Rh(nbd)(**3a−b**)]BF_4), were efficiently isolated upon reaction of stoichiometric amounts of the 1,1-P−OP ligand (**3a** or **3b**) with [Rh(nbd)$_2$]BF_4 in dichloromethane and subsequent precipitation. The NMR data for the resulting complexes confirm a five-membered 1/1 chelate coordination mode of the P−OP ligand to the rhodium center.[12] Interestingly, during

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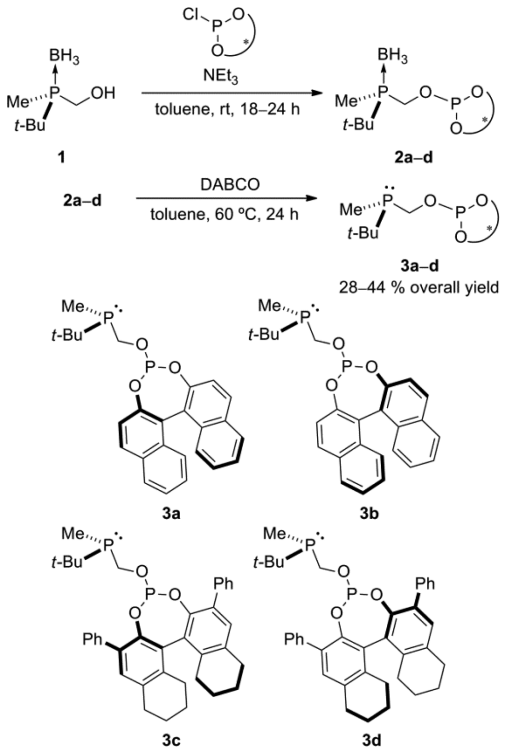
Scheme 1. Synthesis of 1,1-P−OP Ligands 3a−d



attempts to obtain single crystals of $[Rh(nbd)(\mathbf{3a})]BF_4$ for X-ray diffraction from a solvent mixture containing toluene, the product $[Rh(\eta^6\text{-}C_7H_8)(\mathbf{3a})]BF_4$ was unexpectedly isolated. X-ray analysis revealed that this product has an η^6-arene coordination mode (Figure 1). In fact, the stability of Rh^I−η^6-arene complexes with chelating diphosphines is well-known.[13] Interestingly, formation of the $[Rh(\eta^6\text{-}C_7H_8)(\mathbf{3a})]BF_4$ involved a rare displacement of the diene ligand (norbornadiene) by toluene in the absence of molecular hydrogen. In this structure, the P−OP ligand showed a bidentate coordination mode with a narrow-bite-angle of 81.32(12)°.

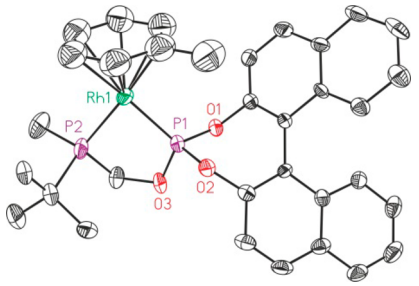
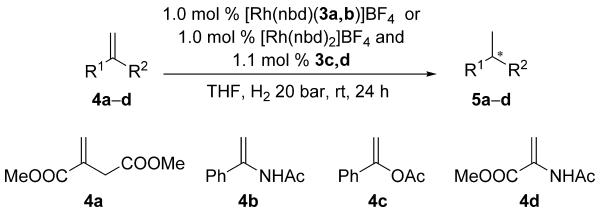


Figure 1. Crystal structure of $[Rh(\eta^6\text{-}C_7H_8)(\mathbf{3a})]BF_4$ (ORTEP drawing with thermal ellipsoids at the 50% probability level). The hydrogen atoms, solvent molecules, and BF_4 counterion have been omitted for clarity.

Coordination of the 1,1-P−OP ligands **3a−d** to the rhodium precursor $[Rh(\kappa^2O,O'\text{-acac})(CO)_2]$, which is commonly used in hydroformylations, was also studied. For example, direct reaction of stoichiometric amounts of **3a** with the precursor in toluene gave the complex $[Rh(\kappa^2O,O'\text{-acac})(\mathbf{3a})]$. The $^{31}P\{^1H\}$ NMR and MS data confirm the existence of a 1/1 chelate formed by bidentate coordination between the metal center and the two phosphorus ligand groups.[12] The ready formation of these complexes greatly facilitated subsequent studies on the corresponding hydroformylations, as the required precatalysts were cleanly generated in situ. In hydrogenation studies the Rh precatalysts derived from the 1,1-P−OP ligands **3a−d** were assessed for reactivity against a set of structurally diverse functionalized alkenes: an itaconic acid derivative (**4a**), an α-arylenamide (**4b**), an α-arylenol ester (**4c**), and an α-(acylamino)acrylate derivative (**4d**). The reaction conditions and hydrogenation results are summarized in Table 1.

Table 1. Asymmetric Hydrogenation of the Substrates 4a−d with the P−OP Ligands 3a−d[a]



entry	ligand	substrate	ee, %[b] (config)[c]
1	**3a**	**4a**	65 (*R*)
2		**4b**	89 (*S*)
3		**4c**	23 (*S*)
4		**4d**	8 (*R*)
5	**3b**	**4a**	80 (*S*)
6		**4b**	89 (*R*)
7		**4c**	83 (*R*)
8		**4d**	94 (*R*)
9	**3c**	**4a**	84 (*R*)
10		**4b**	89 (*S*)
11		**4c**	93 (*S*)
12		**4d**	98 (*S*)
13	**3d**	**4a**	75 (*S*)
14		**4b**	93 (*R*)
15		**4c**	81 (*R*)
16		**4d**	79 (*R*)

[a]Reactions were run in a parallel reactor. All hydrogenations were run under the specified conditions. Complete conversion was achieved in all cases (as determined by ^1H NMR). [b]Determined by GC or HPLC analysis on chiral stationary phases. [c]The absolute configuration was assigned by comparison of the specific rotation with reported data.

In general, regardless of the substrate, compounds **4a−d** were efficiently hydrogenated with full conversions and with variable degrees of enantioselectivity (ee values up to 98%) (Table 1). Analysis of the results indicates the existence of matched and mismatched effects for the diastereomeric ligands **3a,b**: the latter, which contains an (S_a)-configured phosphite fragment, provided higher enantioselectivities (entries 5−8, Table 1) than did the former, which contains the (R_a)-derived phosphite fragment (compare entries 1−4 in Table 1).

Interestingly, the presence of a more sterically hindered 3,3′-diphenyloctahydro-1,1′-binaphthalene-2,2′-diol-derived phosphite group (ligands **3c,d**) led to the opposite matched−mismatched effects (Table 1): in these cases, higher enantioselectivities were obtained for substrates **4a,c,d** by the combined effects of the (S_P)-phosphino and (R_a)-phosphite molecular fragments in ligand **3c**. In fact, among all of the P−OP ligands tested, **3c** gave the best performance in the asymmetric hydrogenation of **4a,c,d**.

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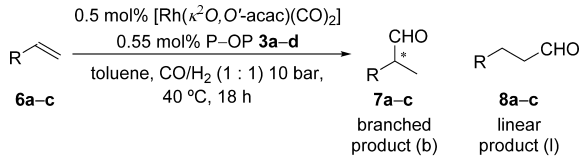
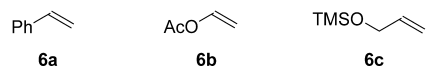
Regarding the stereochemistry of the hydrogenation products, when ligand **3c** (which contains an (R_a)-phosphite group) was used, the final products had opposite configuration to those obtained when ligand **3b** or **3d** (each of which contains an (S_a)-phosphite group) was used.[14] This observation indicates that the direction of stereodiscrimination is controlled mainly by the phosphite fragment, as has previously been reported by the present authors for asymmetric hydrogenations mediated by rhodium complexes derived from 1,2-P−OP ligands.[9c]

The P−OP ligands **3a−d** were also screened in the asymmetric hydroformylation of three structurally diverse terminal olefins: styrene (**6a**), vinyl acetate (**6b**), and (allyloxy)trimethylsilane (**6c**). For this purpose, the reactions were run under standard hydroformylation conditions, using 0.5 mol % of in situ preformed [Rh(κ^2O,O'-acac)(**3a−d**)] complexes, in toluene at 40 °C under CO/H_2 (1/1, 10 bar) overnight. The results indicate that the outcome of the catalysis experiments depended on both the substrate and the ligand. For example, in the hydroformylation of styrene (**6a**), all of the catalysts derived from the P−OP ligands **3a−d** were highly active and gave conversions higher than 90% (Table 2). In addition, excellent branched/linear product ratios (up to 97/3) were observed for the whole set of prepared ligands.

Table 2. Asymmetric Hydroformylation of the Substrates 6a−c with the P−OP Ligands 3a−d[a]





6a **6b** **6c**

entry	ligand	substrate	conversn, %[b]	b/l ratio[c]	ee[c] % (confign)[d]
1	**3a**	**6a**	90	95/5	64 (*R*)
2	**3b**		94	95/5	21 (*S*)
3	**3c**		97	97/3	49 (*R*)
4	**3d**		97	97/3	7 (*S*)
5	**3a**	**6b**	35	88/12	53 (*S*)
6	**3b**		52	93/7	38 (*S*)
7	**3c**		52	95/5	61 (*S*)
8	**3d**		67	97/3	18 (*S*)
9	**3a**	**6c**	88	49/51	6 (*R*)
10	**3b**		74	48/52	5 (*S*)
11	**3c**		>99	79/21	60 (*R*)
12	**3d**		96	73/27	9 (*S*)

[a]Reactions were run in a parallel reactor. All hydroformylations were run under the specified conditions. [b]Conversions were determined by ^{1}H NMR. [c]Branched/linear product ratios and enantiomeric excesses were determined by GC on chiral stationary phases. [d]The absolute configuration was assigned by comparison of the elution order in GC analysis with reported data.

Regarding the stereochemistry of the hydroformylation product of styrene, ligands **3a,c** (both of which have an (R_a)-phosphite group) favored the formation of the (*R*)-configured hydroformylation product, whereas ligands **3b,d** (both of which have an (S_a)-phosphite group) gave the opposite result.

The catalysts derived from ligands **3a−d** mediated the hydroformylation of (allyloxy)trimethylsilane (**6c**) in good conversion, but the branched to linear product ratios obtained with this substrate were lower than those obtained with styrene. For both substrates (**6a,c**), the phosphite group was the principal steric director: reversing its axial chirality led to switching of the configuration in the products. Interestingly, the incorporation of a bulkier phosphite moiety was an important parameter: for styrene (**6a**) higher ee values were obtained using the 3,3′-unsubstituted ligand **3a**, whereas for the allylic substrate **6c**, higher ee values were obtained with the 3,3′-diphenyloctahydro-1,1′-binaphthalene-2,2′-diol-derived ligand **3c** (Δee = 54%; compare entries 9 and 11 in Table 2).

Vinyl acetate (**6b**) was the most difficult hydroformylation substrate, as evidenced by the lower conversions obtained with the ligands **3a−d** (see Table 2). Nevertheless, regioselectivities toward the branched product remained remarkably high (branched/linear ratios up to 97/3). Interestingly, reaction of this particular substrate with each of the tested ligands gave the (*S*)-configured product exclusively; in this case, the configuration of the phosphite moiety did not influence the stereochemical outcome of the reaction. These results clearly indicate that the P-stereogenic group is the principal steric director of the hydroformylation and that it overrides the stereodirecting effects of the phosphite moiety in ligands **3b,d**.[15]

In summary, a convenient synthesis of a new series of 1,1-P−OP ligands (**3a−d**) containing the stereogenic (S_P)-*tert*-butyl(hydroxymethyl)methylphosphine fragment and a one-carbon spacer between the two phosphorus functionalities has been developed. The efficiency of these ligands has been demonstrated in asymmetric hydrogenations and hydroformylations of diverse substrates. The results indicate that, although the optimal ligand for a given combination of transformation and substrate is not easy to predict, for a given ligand the direction of stereoinduction can easily be predicted (Figure 2). Considering their simple preparation, these new, narrow-bite-angle ligands should prove valuable for asymmetric catalysis. The authors are currently performing mechanistic studies to elucidate the role of each ligand fragment in stereoinduction and catalytic studies to develop further applications.

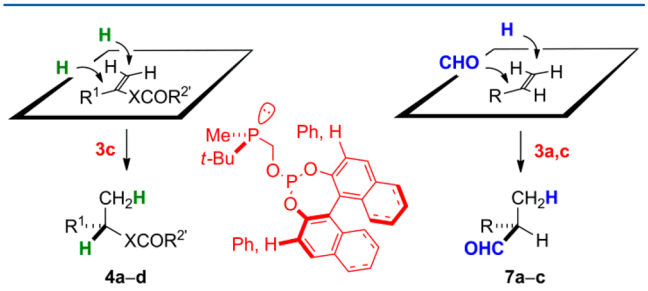


Figure 2. Stereochemical outcome for the hydrogenations and hydroformylations mediated by the 1,1-P−OP ligands **3a,c**.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, a table, and CIF files giving detailed descriptions of experimental procedures, X-ray crystallographic data, spectral data of all new compounds, and HPLC and GC data for the

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determination of the enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Interestingly, the hydrogenation product from reaction of **4d** and ligand **3a** (which contains an (R_a)-phosphite fragment; entry 4, Table 1) had the same configuration as those obtained from ligands **3b** and **3d** containing the (S_a)-phosphite fragment (entry 4, Table 1). This observation suggests a substrate- and ligand-dependent mechanistic scenario in the hydrogenations involving ligand **3a**. However, any mechanistic rationalizations about processes with low enantioselectivity (e.g., 8% ee in entry 4, Table 1) should be made judiciously.

(15) The ligands with an (R_a)-phosphite fragment (**3a,c**) led to the (*R*)-, (*S*)-, and (*R*)-configured products of **6a−c**, respectively. This stereochemistry implies incorporation of the CHO and H groups into the *Si*-alkene face (differences in the CIP *R* or *S* prefixes arise from changes in the CIP priority rules and not from attack at the other enantiotopic face of the alkene).