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New chiral phosphine–phosphites: a convenient synthesis based on the demethylation of *o*-anisyl phosphines and application in highly enantioselective catalytic hydrogenations

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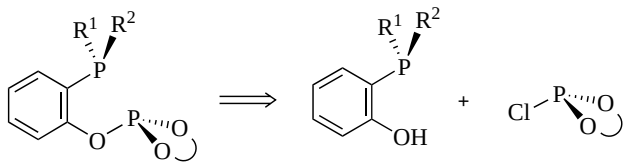
Abstract—An easy demethylation of *o*-anisyl phosphines provides a convenient access to a series of new chiral phosphine–phosphites. The screening of these derivatives as ligands in rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate has shown a profound influence of ligand structure on the enantioselectivity of the process.

The need to expand the range of efficient asymmetric-catalyzed transformations has generated an enormous interest on the synthesis and screening of new chiral ligands. An important strategy in the search for the optimum catalyst relies upon the use of bifunctional ligands that possess two chemically distinct coordinating atoms[1] and are capable of inducing different reactivity from that provided by the ubiquitous C_2 symmetric ligands.[2]

Being aware of the unsurpassed performance of phosphine–phosphite ligands in asymmetric hydroformylation,[3] as well as their utility in other enantioselective catalytic reactions,[4] we have undertaken a practical synthesis of phosphine–phosphites with general structure **A**, and have made use of these ligands in rhodium-catalyzed asymmetric hydrogenation. The possibility of locating the stereogenic elements in either the phosphine or the phosphite sites provides considerable structural flexibility for ligand optimization. Moreover, variable donating ability can be achieved by a proper selection of the phosphine substituents, whereas the rather rigid backbone of the bidentate ligand should favor an efficient transfer of chirality when coordinated to a metal center.[5]



The desired phosphine–phosphites can be conveniently prepared by condensation of a phenol–phosphine **B** with the appropriate chlorophosphite **C**, in the presence of a base.[6] Therefore, a modular approach to the synthesis of molecules **A** requires a range of reagents **B** and **C**, either achiral or chiral in both enantiomeric forms. Since a variety of chlorophosphites is readily accessible from the corresponding diols, the difficulty of the synthesis dwells in a flexible preparation of phosphines **B**.[7] An adaptation to *o*-anisyl phosphines of the well-known demethylation of aryl ethers[8] proved suitable, and accordingly the reaction of phosphine **1a** (R = Ph) with 2.3 molar equivalents of BBr_3,[9] followed by treatment with methanol, produced the phosphonium bromide **2a** (Scheme 1). The corresponding phenol–phosphine **3a** was subsequently obtained by deprotonation of the salt **2a** with NEt_3. The methyl **3b** and isopropyl **3c** derivatives were prepared following the same sequence of reactions, although on a practical basis it is easier to isolate the corresponding phosphonium salts and to effect their deprotonation in situ, before the condensation reaction. Compounds **2a** and

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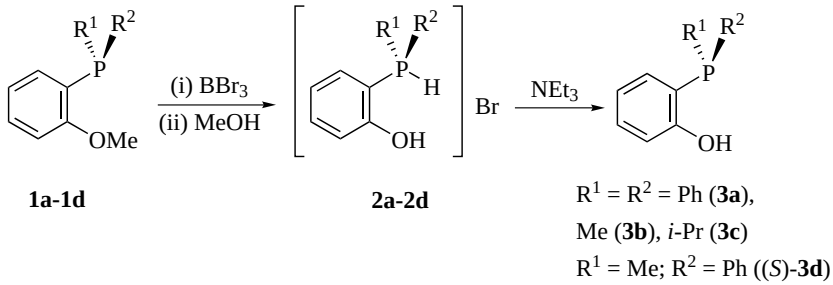


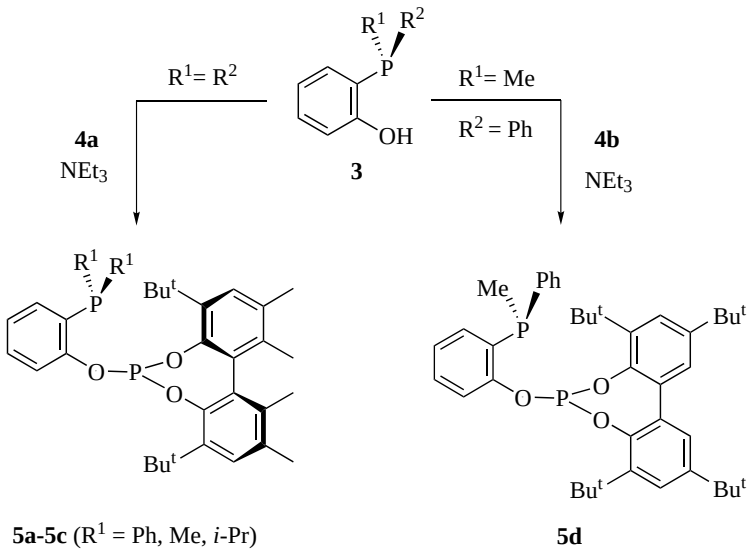
Scheme 1.

2b can be readily purified by crystallization and they are actually less air-sensitive than their phosphine counterparts.

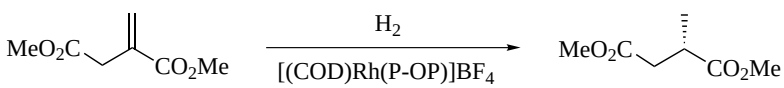
With the aim of generating a more challenging *P*-stereogenic phenol phosphine enantioselectively we next investigated the sequence of reactions in Scheme 1 on a chiral anisyl phosphine. For this purpose, *o*-anisylmethylphenylphosphine (PAMP) was chosen, as both enantiomers of this phosphine are available through various known methods.[10] Furthermore, its use would lead to a phosphine–phosphite of type **A**, with R′ groups of different bulkiness, a situation potentially useful in asymmetric catalysis. It is worth pointing out that demethylation of (*S*)-PAMP produces the corresponding phenol (*S*)-**3d** without observable racemization.[11] To the best of our knowledge, the above procedure constitutes the first synthesis of this valuable building block in a highly enantioenriched form.[12] Considering in addition the vast range of chiral *o*-anisyl phosphines described in the literature[13] this synthetic methodology should open the way to other similar phenol–phosphines.

As briefly mentioned, the preparation of the desired phosphine–phosphites can be achieved by the straightforward condensation of derivatives **3** with the appropriate chlorophosphite, in the presence of a base. For the sake of simplicity and cost effectiveness, we have prepared a series of ligands with only one stereogenic element (Scheme 2). Thus, phosphines **3a**–**c** were combined with (*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-2,2′-bisphenoxyphosphorus chloride **4a**,[14] while chiral (*S*)-**3d** was reacted with conformationally flexible 3,3′,5,5′ - tetra - *tert* - butyl - 2,2′ - bisphenoxyphosphorus chloride **4b**.[15]

To check the utility of our ligand design, we have examined the performance of ligands **5** in the rhodium-catalyzed enantioselective dimethyl itaconate hydrogenation. Previously, and to avoid an imprecise ligand to metal ratio, we have synthesized complexes of formulation $[(COD)Rh(P\text{-}OP)]BF_4$ (**6a**–**d**; P-OP = **5a**–**d**) from $[(COD)_2Rh]BF_4$ and an equimolar amount of the appropriate ligand. All compounds **6** generate active catalysts (Scheme 3) and complete the reaction under our standard



Scheme 2.



Scheme 3.

conditions (Table 1).[16] Most noteworthy, the enantioselectivity of the reaction is very sensitive to the ligand employed. For instance, for compounds **6a–c**, with chirality based on the phosphite fragment, the nature of the phosphine group has a profound effect on the enantioselectivity of the reaction. Thus, the phenyl derivative gives the product with an excellent enantioselectivity (99.3%, entry 1), whereas the isopropyl compound **6c** produces an almost racemic product (entry 3) and the methyl substituted complex **6b** gives the methyl succinate of opposite configuration, with a low enantiomeric purity (30.8% ee, entry 2).[17] Compound **6d**, which possesses a *P*-stereogenic phosphine fragment, leads only to moderate enantioselectivity (49.2% ee, entry 4). Remarkably, the best catalyst precursor **6a** shows also convenient reaction rates and it is able to complete reactions at lower catalysts loadings (S/C= 3000–10000, entries 5 and 6) with excellent enantioselectivity (ee >99.5%).

In summary, we have described a convenient preparation of a series of new chiral phosphine–phosphites based on the easy demethylation of *o*-anisyl phosphines, a methodology applied for the first time to the highly enantioselective synthesis of a *P*-stereogenic phenol phosphine. The simplicity and flexibility of this synthetic protocol allows the application of these ligands in asymmetric catalysis following a modular approach. By using this strategy, a significant catalyst optimization has been achieved in enantioselective dimethyl itaconate hydrogenation. The application of these ligands in other enantioselective metal-catalyzed processes is currently under progress.

Table 1. Results of the asymmetric hydrogenations[a]

Entry	Cat. precursor	S/C	% ee (Config.)
1	**6a**	500	99.3 (*S*)
2	**6b**	500	30.8 (*R*)
3	**6c**	500	1.8 (*R*)
4	**6d**	500	49.2 (*S*)
5[b]	**6a**	3000	99.8 (*S*)
6[b,c]	**6a**	10000	99.6 (*S*)

[a] All reactions were completed under the conditions specified. Reactions were carried out at room temperature under an initial H_2 pressure of 4 atm and 0.2 M dichloromethane solutions of substrate using the appropriate catalyst precursor for 17 h.
[b] 0.5 M substrate concentration, 5 atm initial pressure.
[c] 24 h reaction time (95% conversion after 17 h).

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11. (*S*)-**3d**. To a stirred solution of (*S*)-PAMP (0.17 g, 0.74 mmol) in CH_2Cl_2 (5 mL) cooled at −78°C was added BBr_3 (0.16 mL, 1.7 mmol) via syringe. The resulting mixture was allowed to warm to room temperature and

stirred for additional 12 h. The mixture was carefully evaporated to dryness. The residue was treated with MeOH and the mixture refluxed for 5 h. After the solvent and volatiles were removed, the resulting solid was suspended in Et_2O and NEt_3 (0.25 mL, 1.8 mmol) added. The suspension was stirred for 2 h and filtered. The resulting solution was evaporated, redissolved in CH_2Cl_2 and filtered through a short pad of silica, yielding (*S*)-**3d** as a white solid (0.13 g, 81%). $[\alpha]_D^{20} = -15.4$ (*c* 1.0, THF). ^1H NMR (C_6D_6, 300 MHz): δ 1.26 (d, $^2J(H,P) = 2.4$ Hz, 3H, Me), 6.38 (brs, 1H, OH), 6.70 (m, 1H, CH arom.), 6.85 (m, 1H, CH arom.), 6.99–7.25 (m, 7H, CH arom.). $^{31}P\{^1H\}$ NMR (C_6D_6, 121 MHz): δ −53.1. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75 MHz): δ 10.9 (d, $J(C,P) = 10$ Hz), 115.5, 121.4, 123.6 (d, $J(C,P) = 6$ Hz), 128.6, 128.9 (d, $J(C,P) = 6$ Hz), 131.5 (d, $J(C,P) = 8$ Hz), 131.7, 132.8, 139.1 (d, $J(C,P) = 7$ Hz), 159.5 (d, $J(C,P) = 20$ Hz). HRMS (EI, direct insert): m/z 216.0704 ([M^+] exact mass cald for $C_{13}H_{13}OP$: 216.0701). The lack of racemization along the demethylation reaction has been corroborated by $^{31}P\{^1H\}$ NMR analysis of the phosphine–phosphites obtained by condensation between chlorophosphite **4a** and phosphines *rac*-**3d** and (*S*)-**3d**. Configuration of the product was confirmed by its conversion to the corresponding known borane adduct.[12]

12. Very recently, Jugé and co-workers have described the first enantioselective synthesis of a *P*-stereogenic 2-hydroxyaryl phosphine ((*R*)-*o*-anisyl-2-hydroxynaphthylphenyl phosphine) using an alternative procedure. See: Moulin, D.; Bago, S.; Bauduin, C.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3939.
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16. Representative procedure for the enantioselective hydrogenations. In a glove box, a Fischer–Porter tube (80 mL) was charged with a solution of dimethyl itaconate (0.18 g, 1.1 mmol) and **6a** (0.002 g, 0.0022 mmol) in CH_2Cl_2 (5 mL). The vessel was brought outside the glove box, submitted to vacuum–hydrogen cycles and finally pressurized to 4 atm. The reaction mixture was stirred for 17 h, then the reactor was depressurized and the obtained mixture was evaporated to dryness, redissolved in ethyl acetate–hexanes (1:1) mixture and passed through a short pad of silica. The resulting residue was analyzed by ^1H NMR to determine conversion and by chiral GC for enantiomeric excess as follows: dimethyl methylsuccinate (Supelco γ-DEX 225, 70°C (5 min), then 10°C/min up to 130°C, 15.0 psi He) (*S*) $t_1 = 12.56$ min, (*R*) $t_2 = 12.74$ min.
17. The effect of the phosphine group can be due to its donating properties. Substantial electronic effects on rhodium enantioselective olefin hydrogenation with C_1 symmetric ligands have been described before. See: RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429. Studies concerning this influence are currently under way.