DOI: 10.1002/adsc.200600489

New Highly Effective Phosphite-Phosphoramidite Ligands for Palladium-Catalysed Asymmetric Allylic Alkylation Reactions

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Received: September 26, 2006; Revised: December 12, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

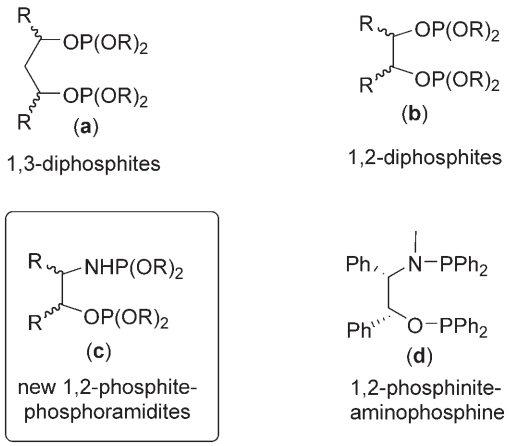
Abstract: We have designed a new family of readily available highly-modular phosphite-phosphoramidite ligands for asymmetric allylic alkylation reactions. The introduction of a phosphoramidite moiety in the ligand design is highly advantageous in the product outcome. Thus, this ligand series affords high reaction rates and enantioselectivities and, at the same time, shows a broad scope for disubstituted hindered and unhindered substrate types.

Keywords: allylic alkylation; asymmetric catalysis; P ligands; palladium

Palladium-catalysed asymmetric allylic substitution is a versatile, widely used process in organic synthesis for the enantioselective formation of C–C bonds.[1] A large number of chiral ligands, mainly P and N ligands, which possess either C_2- or C_1-symmetry, have provided high enantiomeric excesses.[1] Most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentate donor ligands (such as P-N, P-S and S-N).[1,2] The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. However, although to a lesser extent, homodonor ligands (e.g., Trost's diphosphines) have also demonstrated their potential usefulness in this process mainly based on the chiral discrimination induced by the C_2 or C_1 backbone symmetry.[1] However, one disadvantage of using these ligand systems is that they are often synthesised either from expensive chiral sources or in tedious synthetic steps. Another common disadvantage of the most successful ligands developed for this process is that they have low reaction rates and a high substrate specificity (i.e., high *ee*s are obtained in disubstituted linear hindered substrates and low *ee*s are obtained in unhindered substrates, or *vice versa*).[1]

Therefore, research into more versatile ligand systems from simple starting materials in this reaction is of great importance nowadays. In this light, a group of less electron-rich phosphorus homodonor compounds (diphosphite ligands) has demonstrated their usefulness in this process, overcoming these limitations.[3] However, a high backbone dependence has been observed. Thus, enantioselectivities were excellent with 1,3-diphosphites (*ee*s up to 99%), with the 1,2-diphosphites being less enantioselective (*ee*s up to 80%) (Scheme 1).[3a]

Because of the high enantioselectivity induced by mixed bidentate donor ligands in this process,[1] the decision was made to design a new family of ligand based on 1,2-diphosphite ligands [Scheme 1 (**b**)] in which one of the phosphite groups is replaced by a phosphoramidite moiety [Scheme 1 (**c**)]. This new ligand design therefore offers the opportunity of an electronic differentiation whilst maintaining a similar spatial disposition around the metal centre. Moreover,



Scheme 1.

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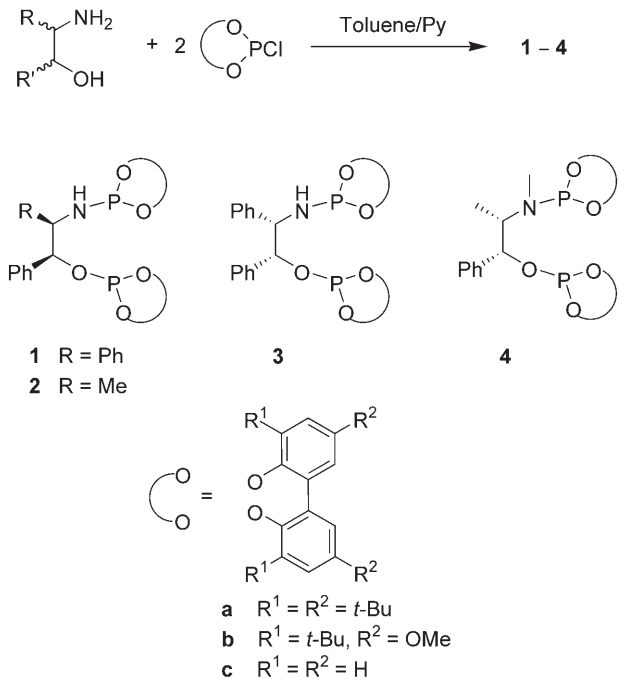


Scheme 2. Synthesis of phosphite-phosphoramidite ligands **1–4**.

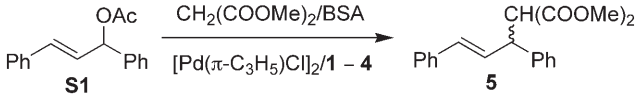
the high activities obtained with diphosphite ligands[4] are expected to be maintained because the phosphoramidite moiety is also a good π-acceptor group.[5] These new phosphite-phosphoramidite ligands **1–4** (Scheme 2) also provide a flexible ligand scaffold because they can be easily tuned in the amino alcohol backbone and in the biphenyl moieties to explore how they affect the catalytic performance. As a result, the highly enantioselective and active Pd-allylic substitution reactions of several substrates with different steric properties are reached.

The synthesis of ligands **1–4** is straightforward (Scheme 2). They are synthesised very efficiently in one step from the corresponding commercially available, cheap 1,2-amino alcohols by reaction with 2 equivs. of the desired *in situ* formed phosphorochloridite in the presence of base.

These new ligands were first investigated in the Pd-catalysed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** with dimethyl malonate as a model reaction using standard conditions (Table 1).[1] In general, activities [TOFs > 700 mol **S1** × (mol Pd × h)$^{-1}$] and enantioselectivities (*ee*s up to 99%) were high.

The effect of the biaryl substituents was investigated with ligands **1a–c** (entries 1–3). It was observed that these moieties affect both activity and enantioselectivity. Bulky substituents in the *ortho* positions of the biphenyl moieties are needed for high enantioselectivity (entries 1 and 2 *vs.* 3). Thus, ligands **1a** and **1b** with bulky *tert*-butyl groups in the *ortho* positions of the biphenyl moieties provided high enantioselectivities, while ligand **1c**, with two unsubstituted biphenyl moieties, provided almost no enantioselectivity. Moreover, the substituents in the *para* positions of the biphenyl moieties have a slight but important effect on both activity and enantioselectivity (entries 1 *vs.* 2). Activities and enantioselectitivies are therefore highest with ligand **1a**, which contains *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl moieties.

Table 1. Pd-catalysed allylic alkylation of **S1** using ligands **1–4**.[a]



Entry	Ligand	% Conv. (min)[b]	% *ee*[c]
1	**1a**	100 (15)	96 (*R*)
2	**1b**	100 (25)	92 (*R*)
3	**1c**	41 (15)	6 (*R*)
4	**2a**	100 (15)	95 (*R*)
5	**3a**	100 (15)	96 (*S*)
6	**4a**	100 (15)	95 (*S*)
7[d]	**1a**	100 (120)	99 (*R*)
8[e]	**1a**	100 (65)	96 (*R*)

[a] All reactions were run at room temperature, 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent.
[b] Reaction time in minutes shown in parentheses.
[c] Enantiomeric excesses. Absolute configuration shown in parentheses.
[d] $T = 5$ °C.
[e] **S1**/Pd = 500.

The effect of the amino alcohol backbone was studied with ligands **1–4a** (entries 1, 4–6). Ligands **1–4**, which differ in the substituents at the carbon adjacent to the amino group (ligands **1–3**) or in the amino group (ligand **4**), provided fairly similar enantioselectivities (*ee*s up to 96%) and activities. This indicates that variations in the amino alcohol backbone hardly affect the catalytic performance. Interestingly, when this new family of ligands is used both enantiomers of the product can be accessed in high enantioselectivities simply by changing the absolute configuration of the amino alcohol unit (ligands **1a** and **2a** *vs.* ligands **3a** and **4a**, entries 1 and 4 *vs.* 5 and 6).

Enantioselectivity was further improved (*ee*s up to 99%) with ligand **1a** by lowering the reaction temperature to 5 °C (entry 7). The reaction was also performed at a low catalyst concentration (**S1**/Pd = 500) using ligand **1a** (entry 8). The enantioselectivity [96% (*R*) *ee*] and activity [TOF > 700 mol **S1** × (mol Pd × h)$^{-1}$)[6] were high.

It should be pointed out that these phosphite-phosphoramidite ligands showed a much higher degree of enantioselectivity and higher reaction rates than their corresponding phosphinite-aminophosphine

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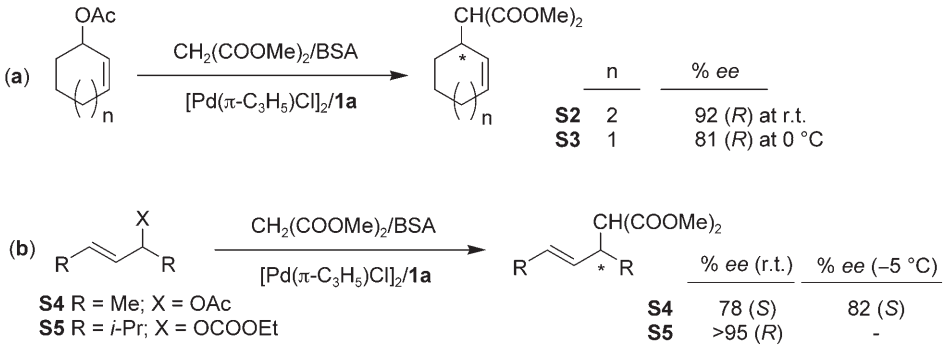


Scheme 3. Pd-catalysed allylic alkylation reaction of substrates **S2–S5**.

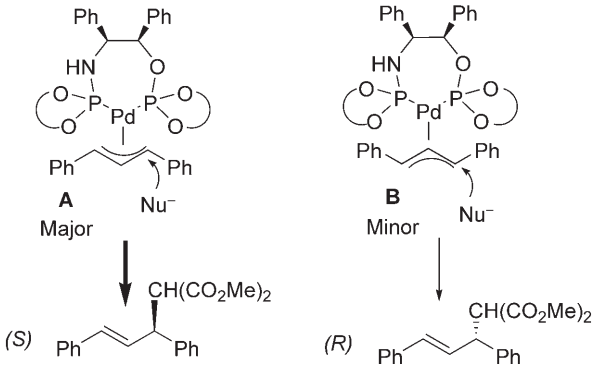
[Scheme 1 (**d**), *ee*s up to 60%][7] and 1,2-diphosphite [Scheme 1 (**b**), *ee*s up to 80%][3a] analogues under similar reaction conditions.

To further study the potential of these readily available ligands, ligand **1a** was also tested in the allylic alkylation of the cyclic substrates **S2** and **S3**, unhindered linear substrate **S4** and for the more sterically hindered linear substrate **S5**. The results are summarised in Scheme 3.

The enantioselectivity in unhindered cyclic **S2**, **S3** and linear **S4** substrates is usually more difficult to control than for the hindered substrate **S1**, mainly because of the presence of less sterically *syn* substituents.[1] Although highly enantioselective catalysts have been developed for these unhindered substrates, they generally provide low enantiocontrol in hindered substrates like **S1**. The development of enantioselective catalysts for both hindered and unhindered substrates is therefore still a challenge. Interestingly, under non-optimised conditions, for these sterically undemanding substrates, high enantioselectivities (92% *ee* for **S2**, 81% for **S3** and 82% *ee* for **S4**) were also achieved (Scheme 3). These results are among the best reported for these types of unhindered substrates.[8] Again, these results indicate that the replacement of a phosphite moiety by a phosphoramidite group in the ligand design has led to higher enantioselectivities than with related 1,2-diphosphite ligands (*ee*s up to 39%).[3a]

The allylic alkylation of substrate **S5**, which is more sterically demanding than the previously used substrate **S1**, also produced high enantioselectivity (Scheme 3). Although, as expected, the activities were lower than in the alkylation reaction of **S1**, they were much higher than those obtained with other successful ligands.[1]

The NMR study of the Pd-allyl intermediate containing ligand **3a**, [Pd(η^3-1,3-diphenylallyl)(**3a**)]BF_4, showed a mixture of two isomers in a ratio of 2:1. No changes were observed down to −80 °C. Both isomers were unambiguously assigned by NOE to the two *syn*/*syn endo* and *exo* isomers (Scheme 4). For both isomers, the carbon NMR chemical shifts indicate that the more electrophilic allyl carbon terminus is *trans* to the phosphoramidite moiety. Assuming that the nucleophilic attack takes place at the more electrophilic carbon terminus and based on the observed stereochemical outcome of the reaction, 96% (*S*) in product **5**, and the fact that the enantiomeric excess of **5** is higher than the diastereoisomeric excesses of the Pd intermediates, the **A** isomer must react faster than the **B** isomer. In addition, the reactivity of the Pd intermediates with sodium malonate at low temperature was also studied by *in situ* NMR. The study indicated that the fast reacting isomer is the major one. Therefore, it can be concluded that the nucleophilic attack takes place at the allyl terminus located *trans* to the phosphoroamidite moiety of the major **A** Pd intermediate.



Scheme 4. Diastereoisomeric Pd-allyl intermediates for **S1** with ligand **3a**.

In summary, a new series of easily accessible phosphite-phosphoramidite ligands for allylic alkylation reactions has been designed. These ligands can be prepared in one step from commercially available 1,2-amino alcohols as chiral source. The introduction of a phosphoramidite moiety in the ligand design has been advantageous, providing higher enantioselectivities (*ee*s up to 99%) than with the 1,2-diphosphite and phosphinite-aminophosphine analogues. In addition,

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the high activities were maintained. It should be noted that both enantiomers of the product can be obtained in high *ee* by using both enantiomers of the amino alcohol backbone. The preliminary study of the allyl intermediate indicates that the nucleophilic attack takes place *trans* to the phosphoramidite moiety.

The combination of high enantioselectivities (*ee*s up to 99%), high activities and high substrate versatility as well as the low cost and easy synthesis of the ligands makes these catalyst systems very attractive for further research. These results open up the allylic alkylation of a wide range of substrates to the potential effective use of readily available and highly modular 1,2-amino alcohol-based phosphite-phosphoramidite ligands. Moreover, because of the modular construction, these ligands can be easily tuned in three regions (biaryl substituents, backbone substituents at C-1 and C-2, and at the amino group) to explore their effect on catalytic performance. Studies of this kind, as well as mechanistic studies, are currently under way.

Experimental Section

General Procedure for the Preparation of Ligands 1–4a–c

The phosphorochloridite (2.2 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. The amino alcohol (1 mmol) was azeotropically dried with toluene (3×1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 mmol) was added. The phosphorochloridite solution was transferred slowly at 0 °C to the solution of the amino alcohol. The reaction mixture was warmed up to 80 °C and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene/NEt_3 = 100/1) to afford the corresponding ligand as a white powder. Yields and characterisation details of all new ligands **1**–**4a–c** are collected in the Supporting Information.

Typical Procedure for Allylic Alkylation of Substrates S1–S5

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-phosphoramidite (0.0055 mmol) in the appropriate solvent (0.5 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (0.5 mmol) in the appropriate solvent (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis-(trimethylsilyl)acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time (see Supporting Information for details), the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl solution (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^{1}H NMR and the enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL min^{-1}). For substrates **S2**–**S4**, conversion and enantiomeric excess were determined by GC using an FS-Cyclodex β-I/P 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, F.I.D. detector). For substrate **S5**, conversion was determined by ^{1}H NMR and the enantiomeric excess was determined by ^{1}H NMR using $Eu(hfc)_3$.

Preparation of $[Pd(\eta^{3}\text{-}1,3\text{-diphenylallyl})(3a)]BF_4$

Ligand **3a** (54.5 mg, 0.05 mmol) and the complex $[Pd(\mu\text{-}Cl)(\eta^{3}\text{-}1,3\text{-diphenylallyl})]_2$ (17.3 mg, 0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.5 mmol) was added after 30 min and the mixture was stirred for 30 min. The mixture was then filtered over celite under argon and the resulting solution was analysed by NMR. Characterisation details are collected in the Supporting Information.

Supporting Information

Experimental details for the preparation and characterisation of all new compounds and the allylic substitution reaction procedures are collected in the Supporting Information.

Acknowledgements

We are indebted to Prof. P. W. N. M. van Leeuwen, University of Amsterdam, for his comments and suggestions. We thank the Spanish Government (Consolider Ingenio CSD2006–0003, CTQ2004–04412/BQU and Ramon y Cajal fellowship to O.P.) and the Generalitat de Catalunya (2005SGR007777 and Distinction to M.D.) for financial support.

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