Communication

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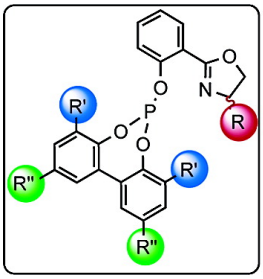

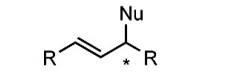

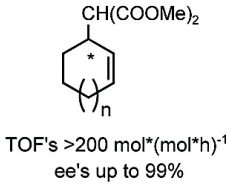

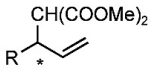

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New Phosphite−Oxazoline Ligands for Efficient Pd-Catalyzed Substitution Reactions

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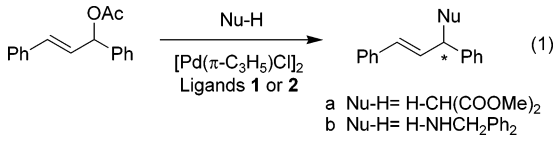
Palladium-catalyzed asymmetric allylic substitution is a versatile, widely used process in organic synthesis for the enantioselective formation of C−C and C−heteroatom bonds. The past decade has seen a huge advance in enantiocontrol in the Pd-catalyzed allylic substitution reactions.[1] However, the catalytic systems developed to date generally have two important drawbacks (Figure 1). First, they show a high substrate specificity (i.e., high ee's are obtained in disubstituted linear hindered substrates and low ee's are obtained in cyclic and unhindered linear substrates, or vice versa). Second, the reaction rates are usually low (i.e., usually TOF's ≤ 100 mol·(mol·h)$^{-1}$).

In 2001, we reported the first diphosphite ligands used for the Pd-catalyzed asymmetric alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) with dimethyl malonate. In addition to the high enantiomeric excesses, the reaction rates were extremely fast (usually 100% conversion after ≤5 min).[2]

Herein, we describe the new family of phosphite−oxazoline ligands **1** and **2** for the highly versatile Pd-allylic substitution reactions of several substrates with different steric properties (Scheme 1). These ligands maintain the basic framework of the PHOX but have a bulky biphenyl phosphite moiety instead of a phosphine moiety. This provided a larger chelate ring when coordinated to Pd. The benefits of incorporating a phosphite moiety into the ligand are: (1) the reaction rates increase because of the larger π-acceptor ability of the phosphite moiety[2a] and (2) enantioselectivity increases because the chiral pocket (the chiral cavity where the allyl is embedded) created is smaller than that for the PHOX ligands[3] yet flexible enough[4] to allow the perfect coordination of hindered and unhindered substrates (which decreases the substrate specificity).

The synthesis of ligands **1** and **2** is straightforward (Scheme 1). They are easily prepared by attaching several amino alcohols and phosphorochloridites to the 2-hydroxyphenyl cyanide scaffold. The highly modular construction of these ligands enables us to easily study the effects of both the phosphite and the oxazoline moieties on catalytic performance (activity and enantioselectivity).

We first tested the new ligands in the Pd-catalyzed asymmetric allylic substitution of **S1** with (a) dimethyl malonate and (b) benzylamine as model reactions (eq 1). In general, excellent activities (TOF's up to >2400 mol·(mol·h)$^{-1}$) and enantioselectivities (ee's up to >99%) were obtained.



(1)

The effects of the oxazoline and the phosphite moieties were first studied using dimethyl malonate as nucleophile (eq 1a, Table 1).

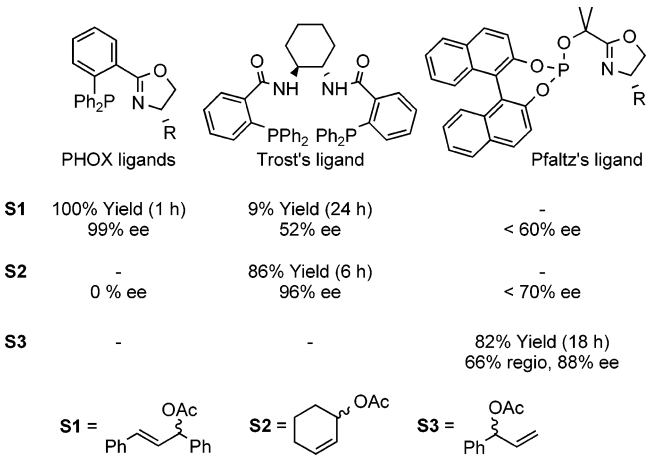
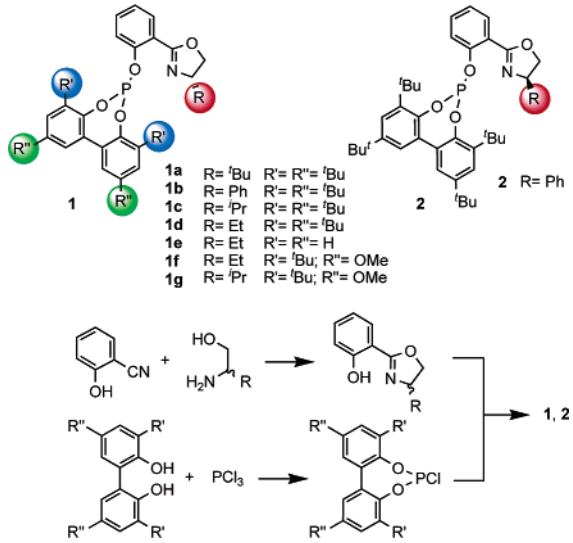


Figure 1. Summary of the best results with the model substrates **S1**−**S3** with three of the most representative ligands developed for the Pd-catalyzed allylic substitution reactions (reactions usually carried out with 2−4 mol % of Pd).

Scheme 1. Synthesis of Phosphite−Oxazoline Ligands **1** and **2**



The effect of the oxazoline substituent was studied with ligands **1a**−**d**. Enantioselectivities (>99% ee) were excellent in all cases (Table 1, entries 1−4). This indicates that varying the oxazoline substituents does not affect enantioselectivity. This behavior contrasts with the oxazoline-substituent effect observed for related PHOX ligands (ee's usually range from 85 to 99%). Our results also indicate that activity is affected by the type of oxazoline substituents: activities are higher when less sterically demanding substituents are present (i.e., Ph > Et > ^{i}Pr > ^{t}Bu).

The effect of the phosphite moieties was studied with ligands **1c**−**g**. We observed that these moieties affect enantioselectivity.

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Table 1. Pd-Catalyzed Allylic Alkylation of **S1** with Ligands **1** and **2**[a]

entry	ligand	Nu-H	% conv[b] (min)	% ee[c]
1	**1a**	$CH_2(COOMe)_2$	71 (5)	>99 (*S*)
2	**1b**	$CH_2(COOMe)_2$	100 (5)	>99 (*S*)
3	**1c**	$CH_2(COOMe)_2$	84 (5)	>99 (*S*)
4	**1d**	$CH_2(COOMe)_2$	95 (5)	>99 (*S*)
5	**1e**	$CH_2(COOMe)_2$	100 (30)	42 (*S*)
6	**1f**	$CH_2(COOMe)_2$	100 (30)	95 (*S*)
7	**1g**	$CH_2(COOMe)_2$	100 (30)	99 (*S*)
8	**2**	$CH_2(COOMe)_2$	100 (5)	99 (*R*)
9[d]	**1b**	$CH_2(COOMe)_2$	100 (25)	99 (*S*)

[a] 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in brackets. [c] Determined by HPLC. [d] **S1**/Pd = 1000.

Bulky substituents in the ortho positions of the biphenyl phosphite moiety are needed for high enantioselectivity (entries 4 and 6 versus 5). Moreover, the substituents in the *para* positions of the biphenyl phosphite moiety have a slight but important effect on both activity and enantioselectivity. Activities and enantioselectitivies are therefore highest when *tert*-butyl groups are present at both the *ortho* and *para* positions of the biphenyl phosphite moiety.

The use of ligand **2**, whose configuration of the oxazoline moiety is opposite to that of ligands **1**, produced the same high enantioselectivity, though in the *R* product (entry 8). This new family of ligands therefore offers excellent enantioselectivities in both enantiomers of the product.

We also performed the reaction at low catalyst concentration using ligand **1b** (entry 9). The excellent enantioselectivity (99% (*S*) ee) and activity (100% conversion after 25 min at room temperature, TOF > 2400 mol·(mol·h)$^{-1}$) were maintained.

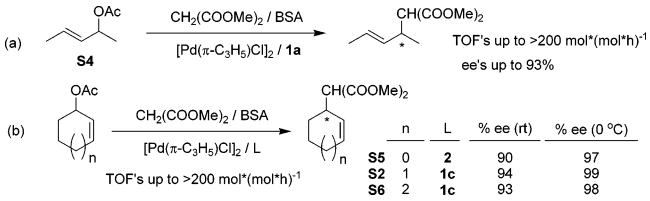
We then tested ligands **1** and **2** in the Pd-catalyzed allylic amination of **S1** with benzylamine (eq 1b). We observed that the catalytic performance follows the same trend as that for the allylic alkylation of **S1**. Both enantiomers of the product can also be obtained with high enantioselectivity (ee's up to 99%). Although, as expected, the activities are lower than that in the alkylation reaction, they are much higher than when PHOX ligands were used (reaction time usually 96 h).[5]

The enantioselectivity in unhindered linear and cyclic substrates is usually more difficult to control. For high ee's to be achieved, it is crucial that ligands create a small chiral pocket around the metal center, mainly because of the presence of less sterically syn substituents.[1] The development of enantioselective catalysts for both hindered and unhindered substrates has been a challenge because none of the existing ligands is able to tune the size of the chiral pocket adequately.[6] The presence of the bulky biphenyl in the phosphite moiety in ligands **1** and **2**, which are known to be flexible and to provide large bite angles, can therefore also provide excellent results for unhindered substrates. We therefore decided to test the new phosphite−oxazoline ligands in the Pd-catalyzed allylic alkylation of 1,3-dimethyl-3-acetoxyprop-1-ene **S4** substrate and several cyclic substrates **S2**, **S5**, and **S6**, which are less sterically demanding (Scheme 2).

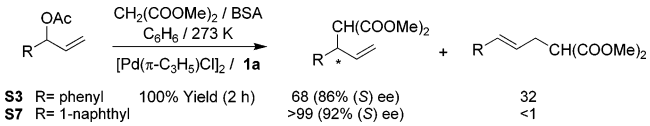
Interestingly, for these sterically undemanding substrates, high reaction rates (TOF's > 200 mol·(mol·h)$^{-1}$) and enantioselectivities (ee's up to 99%), in both enantiomers of the product, were also achieved.

Encouraged by the excellent results, we also tested ligand **1a** in the allylic alkylation of more demanding substrates: the monosubstituted linear substrates **S3** and **S7** (Scheme 3). For these substrates, the development of highly regio- and enantioselective Pd catalysts still represents a challenge. Most of the Pd catalysts

Scheme 2. Pd-Catalyzed Allylic Alkylation of Unhindered Substrates **S2** and **S4**−**S6** with Ligands **1** and **2**



Scheme 3. Pd-Catalyzed Allylic Alkylation of **S3** and **S7** Using Ligand **1a**



developed to date favor the formation of the achiral linear product rather than the desired branched isomer.[7] The catalytic system containing ligand **1a** produced under unoptimized conditions the desired branched isomers as the major products. Note the excellent regio- and enantioselectivity obtained with substrate **S7**. These results are among the best reported so far.

In short, we have designed and synthesized a new family of readily available phosphite−oxazoline ligands that shows excellent reaction rates (TOF's up to >2400 mol·(mol·h)$^{-1}$) and enantioselectivities (ee's up to >99%) and, at the same time, shows a broad scope for different substrate types. The reason for this is that the presence of π-acceptor flexible bulky biphenyl phosphite moieties allows the creation of a smaller and, at the same time, more flexible chiral pocket.

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Supporting Information Available: Experimental procedures for the preparation of ligands **1** and **2** and for the allylic substitution reactions, the catalytic alkylation results of **S2**, **S4**−**S6**, and the amination of **S1** using ligands **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1869. (c) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) (a) Diéguez, M.; Jansat, S.; Gómez, M.; Ruiz, A.; Muller, G.; Claver, C. *Chem. Commun.* **2001**, 1132. (b) Pàmies, O.; van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 8867.

(3) Bulky biphenyl phosphites are known to provide larger bite angles than phosphines. The opening of the bite angle is necessary for high chiral recognition in the Pd-catalyzed alkylation reactions. Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(4) The flexibility that offers the biphenyl moiety can be used to fine-tune the chiral pocket formed upon complexation.

(5) von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573.

(6) So far only the diphospholane developed by Osborn and co-workers have provided good ee's for substrates **S1**, **S2**, and **S4**. Dierkes, P.; Randechul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3116.

(7) For recent successful applications of Pd catalysts, see: (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.

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