ORGANIC LETTERS

2007
Vol. 9, No. 1
49−52

First Chiral Phosphoroamidite-phosphite Ligands for Highly Enantioselective and Versatile Pd-Catalyzed Asymmetric Allylic Substitution Reactions

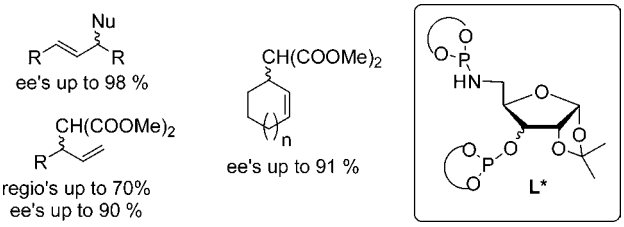
Eva Raluy, Carmen Claver, Oscar Pàmies,* and Montserrat Diéguez*

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/ Marcel·li Domingo, s/n 43007 Tarragona, Spain

montserrat.dieguez@urv.cat; oscar.pamies@urv.cat

Received October 6, 2006

ABSTRACT



A series of phosphite-phosphoroamidite ligands, derived from readily available D-xylose, has been successfully applied for the first time in the Pd-catalyzed allylic substitution of several substrates with different steric and electronic properties, with high enantioselectivities (ee's up to 98) and activities in standard conditions.

One of the main goals of modern synthetic organic chemistry is the catalytic enantioselective formation of C−C and C−heteroatom bonds.[1] In this respect, the asymmetric Pd-catalyzed allylic substitution reaction is a powerful and highly versatile procedure because it tolerates several functional groups.[1] A large number of chiral ligands, mainly P- and N-containing ligands, which have either C_2- or C_1-symmetry, have provided high enantiomeric excesses.[1,2] However, one disadvantage of using these ligands is that they are often synthesized either from expensive chiral sources or in tedious synthetic steps. Another common disadvantage for the most successful ligand families developed for this process is that they usually show 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 cyclic and unhindered linear substrates, or vice versa; Figure 1).[1] These limitations hamper their potential use in industrial scale.

Research into more versatile and efficient ligand systems based on simple starting materials in this reaction is therefore of great importance nowadays. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular constructions.[3] Although they have been

(1) For reviews, see for example: (a) Tsuji, J. *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1869. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) See for example: (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (c) Evans, D. A.; Campos, J. R.; Tedrow, J. R.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. (d) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (e) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (f) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520. (g) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. (h) 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. (i) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (j) Wiese, B.; Helmchen, G. *Tetrahedron Let.* **1998**, *39*, 5727.

(3) (a) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165. (c) Diéguez, M.; Ruiz, A.; Claver, C. *Dalton Trans.* **2003**, 2957.

10.1021/ol0624631 CCC: $37.00
Published on Web 12/13/2006

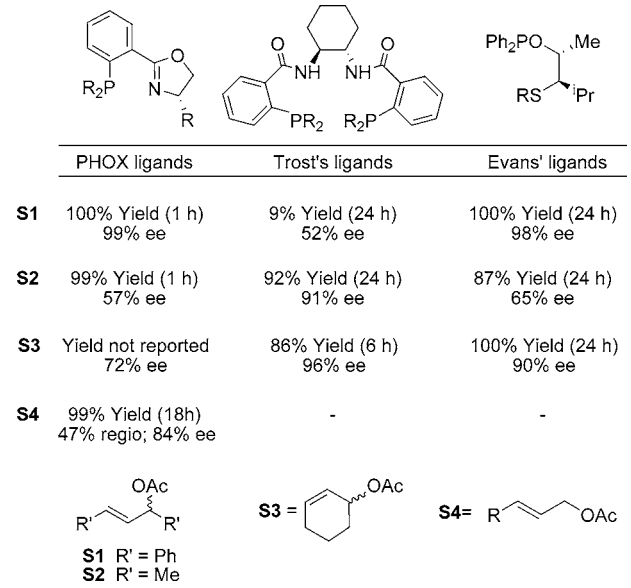


Figure 1. Summary of the best results with substrates **S1**−**S4** with three of the most representative ligand families developed for the Pd-catalyzed allylic substitution reactions (reactions usually carried out with 2−4 mol % Pd).

successfully used in other enantioselective reactions, they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process.[3,4] In this context, we have recently reported the use of xylo- and ribo-furanoside diphosphite ligands **1** and **2** (Figure 2).[5]

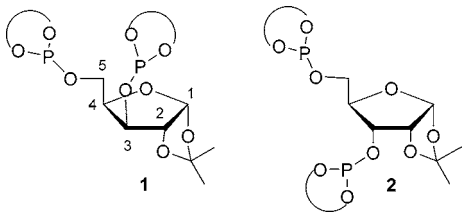


Figure 2. Xylo- and ribo-furanoside diphosphite ligands **1** and **2**.

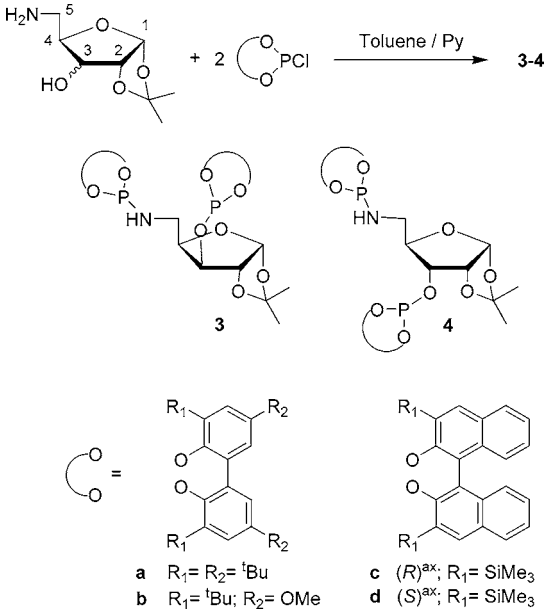
These ligands proved to be effective in the allylic substitution of hindered substrate 1,3-diphenyl-3-acetoxyprop-1-ene **S1** (ee's up to 98%), but for unhindered linear **S2** and cyclic **S3** substrates, their enantioselectivities were low (ee's up to 59% and 34%, respectively).[5]

(4) See for example: (a) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. (b) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471. (c) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419. (d) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959. (e) Yonehara, K.; Jashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374. (f) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, C. *Organometallics* **1998**, *17*, 3254. (g) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943.

(5) (a) 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. (b) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257.

Because of the high enantioselectivity induced by mixed bidentate donor ligands in the Pd-catalyzed allylic alkylation,[1] we decided to use a new family of ligands based on **1** and **2** in which the phosphite group attached at C-5 is replaced by a phosphoroamidite moiety (ligands **3** and **4**, Scheme 1).

Scheme 1. Synthesis of Phosphite-phosphoroamidite Ligands **3** and **4**



Moreover, we expected to maintain the high activities obtained with diphosphite ligands,[6] because the phosphoroamidite moiety is also a good π-acceptor group.[7] Therefore, this ligand design will overcome the drawback of low activity usually observed for other successful ligand families. The phosphite-phosphoroamidite ligands **3** and **4** also provide a flexible ligand scaffold because they can be easily tuned in different regions and their effect on catalytic performance determined. As a result, the Pd-allylic substitution reactions of several substrates with different electronic and steric properties are reached.

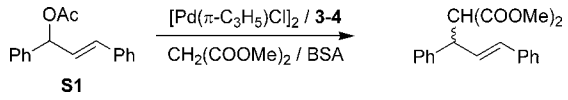
The highly modular construction of these ligands makes it easy for us to study three main effects on catalytic activity and selectivity: (a) the effect of the configuration of the stereocenter at carbon atom C-3 at the ligand bridge (ligands **3** vs **4**), (b) the effect of the substituents in the biaryl groups (ligands **3,4a** vs **3,4b**), and (c) the effect of the configuration of the biaryl moieties groups (ligands **3,4c** vs **3,4d**). By carefully selecting these elements, we achieved high enantioselectivities and improved activities for several substrates.

We first tested the series of eight phosphite-phosphoroamidite ligands in the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxy-1-ene **S1** with dimethyl malonate as a model reaction using standard conditions (Table 1).

(6) Diphosphite ligands have recently emerged as suitable ligands for this process offering high activities; see for instance: (a) Reference 5b. (b) Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem.* **2005**, *70*, 3363.

(7) van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P.W.N.M. *Eur. J. Inorg. Chem.* **1999**, 1073.

Table 1. Pd-Catalyzed Allylic Alkylation of Substrate **S1** using Ligands **3** and **4**[a]



entry	ligand	% conv (min)[b]	% ee[c]
1	**3a**	88 (15)	62 (*S*)
2	**3b**	100 (15)	59 (*S*)
3	**3c**	71 (30)	6 (*S*)
4	**3d**	96 (30)[d]	98 (*S*)
5	**4a**	64 (15)	55 (*S*)
6	**4b**	83 (15)	52 (*S*)
7	**4c**	12 (120)	80 (*S*)
8	**4d**	15 (120)	12 (*S*)

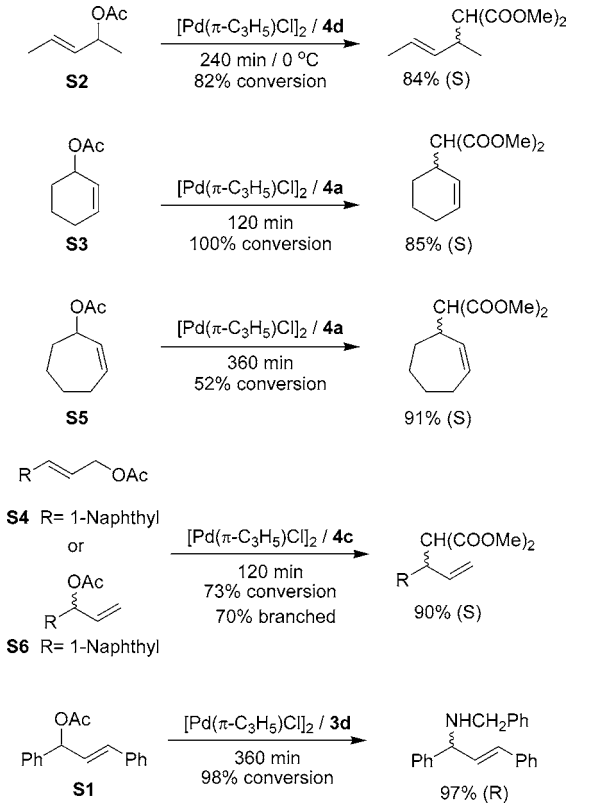
[a] 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA (*N*,*O*-bis(trimethylsilyl)acetamide)/KOAc as base, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in brackets. [c] Determined by HPLC on a Chiralcel-OD column. [d] 89% Isolated yield.

The results indicate that the catalytic performance (activity and enantioselectivity) is highly affected by the configuration of carbon atom C-3 of the tetrahydrofuran ring, the substituents of the biphenyl moieties, and the configuration of the binaphthyl groups. In general, ligands **3**, with an *S* configuration on C-3, produced better activities and enantioselectivities than ligands **4** (entries 1−4 vs 5−8). The presence of methoxy groups in the *para* position of the biphenyl moieties has a positive effect on activity but leads to lower enantioselectivities (entries 2 and 6 vs 1 and 5). We also observed a cooperative effect between the configuration of the biaryl moieties and the configuration of carbon atom C-3 (entries 3, 4, 7, and 8). The results indicated that the matched combination is achieved with ligand **3d**, which has an *S* configuration at both carbon atom C-3 and in the biaryl phosphite moieties (entry 4). In summary, the best enantioselectivity (ee's up to 98%) was obtained with ligand **3d**, with an *S* configuration at carbon C-3 of the furanoside backbone and two enantiopure binaphthyl moieties with *S* configuration and bulky trimethylsilyl groups in the *ortho* positions.

To study the potential of these readily available ligands further, we also tested them in the allylic alkylation of unhindered linear substrate **S2**, cyclic substrates **S3** and **S5**, and the monosubstituted linear substrates **S4** and **S6**, as well as the allylic amination of **S1** (Scheme 2).

The enantioselectivity in unhindered linear **S2** and cyclic **S3** and **S5** substrates is usually more difficult to control than in hindered substrate **S1**. Therefore, few catalytic systems have provided good enantioselectivities.[2e−h,j] To achieve high ee's, it is crucial that ligands create a small chiral pocket (a chiral cavity in which the allyl is embedded) around the metal center, mainly because of the presence of less sterically *syn* substituents.[1] Although highly imposing enantioselective catalyst families have been developed for these unhindered substrates, they generally provide low enantiocontrol in such hindered substrates as **S1**. The development of a enantioselective catalyst series for both hindered and unhindered

Scheme 2. Summary of Best Results Obtained in the Pd-Catalyzed Allylic Substitution of **S1**−**S6** Using Phosphite-phosphoroamidite Ligands **3** and **4**



substrates is therefore still a challenge. Interestingly, for the sterically undemanding substrates **S2**, **S3**, and **S5**, enantioselectivities were also high (84%, 85%, and 91%, respectively) (Scheme 2). These results are among the best reported for this type of unhindered substrates.[2e−h,j] It is also interesting to note that, in contrast with substrate **S1**, ligands **4** provide better ee's than ligands **3** in the alkylation of sterically undemanding substrates **S2**, **S3** and **S5**. This indicates that the size of the chiral pocket is controlled by the configuration of carbon atom C-3. Thus, ligands **4**, with *R* configuration at carbon C-3, lead to a smaller chiral pocket than ligands **3** and, therefore, to higher enantioselectivities for unhindered substrates (see Supporting Information). The results obtained with linear substrate **S2** and cyclic substrates **S3** and **S5** also show that the biaryl moiety affects enantioselectivity. Therefore, for linear substrate **S2**, ee's are best with ligand **4d**, which contains a chiral binaphthyl moiety, while for the cyclic substrates they are best with ligand **4a**, which contains atropoisomeric biphenyl groups. These remarkable results clearly show the efficiency of using highly modular scaffolds in the ligand design to increase their versatility. In addition, comparing these excellent results with the poor enantioselectivities obtained with ligands **1** and **2** (ee's up to 59%) in the alkylation of these unhindered substrates, we can conclude that the introduction of a phosphoroamidite moiety has been highly advantageous.

For substrates **S4** and **S6**, as well as controlling the enantioselectivity of the process, the regioselectivity is also

a problem, because a mixture of regioisomers can be obtained. Most Pd-catalysts developed to date favor the formation of the achiral linear product rather than the desired branched isomer.[1] Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge. Under nonoptimized conditions, the catalytic system containing ligand **4c** produced the desired branched isomer as the major product with high enantioselectivity (90% ee). This result is one of the best reported so far.[2a,g,i] Again, the replacement of a phosphite moiety by a phosphoroamidite group in the ligand design is seen to lead to higher regio- and enantioselectivities than when ligands **1** and **2** are used (% branched up to 29% and ee's up to 33%).[5b]

Finally, we evaluated this ligand library in the allylic amination process of **S1** using benzylamine as nucleophile. The results follow the same trend as in the allylic alkylation of **S1** (see Supporting Information), which is not unexpected because the reactions have a similar mechanism.[1] So enantioselectivities were also high (ee's up to 97%). Although as expected the activities were lower than in the alkylation reaction, they were again much higher than those obtained with other successful ligands.[1] The absolute stereochemistry of the amination was the same as for the alkylation reaction, though the CIP descriptor was inverted because of the change in the priority of the groups.

In summary, we have described the first application of phosphite-phosphoroamidite ligands for highly enantioselective and versatile asymmetric allylic substitution reactions. These ligands have the advantage that they are easily prepared in a few steps from commercial D-xylose, an inexpensive natural chiral feedstock. In addition, they can be easily tuned in the furanoside backbone and in the biaryl moieties so that their effect on catalytic performance can be explored. By carefully selecting the ligand components, we obtained high activities and enantioselectivities in Pd-catalyzed allylic substitution in substrates with different steric and electronic properties under unoptimized reaction conditions. Note also that these ligands afford higher activities and substrate versatility than the corresponding diphosphite analogues **1** and **2**. So this is an exceptional ligand family that competes with a few other ligand series that also provide high ee's for hindered and unhindered disubstituted and monosubstituted substrates. These results open up a new class of ligands for the highly active and enantioselective Pd-catalyzed allylic substitution reactions of a wide range of substrates. Mechanistic studies and further modifications in both the sugar backbone and the biaryl moieties are currently under way.

Acknowledgment. We are indebted to Prof. P. W. N. M. van Leeuwen, University of Amsterdam, for his comments and suggestions. We thank the Spanish Goverment (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.

Supporting Information Available: Experimental procedures for the preparation of the ligands **3** and **4** and the allylic substitution reactions, and the catalytic alkylation results of **S2**−**S6** and the amination of **S1** using ligands **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0624631