Modular Furanoside Phosphite Ligands for Asymmetric Pd-Catalyzed Allylic Substitution

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A series of diphosphite, phosphine−phosphite, and thioether−phosphite ligands **1**−**5** with a furanoside backbone have been used in the enantioselective palladium-catalyzed allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate giving low to high enantioselectivies (from close to 0% to 97% ee). The modular nature of these ligands enables systematic investigations of the effect of the ligand structure on the enantioselectivity. The enantioselectivity is mainly determined by the configuration of the stereogenic center C-3 of the furanose backbone. From this we conclude that the attack of the nucleophile takes place trans toward the donating group at the stereogenic C-5 atom. Systematic variation of the donor group attached to the carbon atom C-5 indicated that the presence of a bulky phosphite functionality has a positive effect on enantioselectivity. Thus, the highest ee's are obtained using the bulky diphosphite ligand **1b** containing a xylofuranoside backbone.

Introduction

The palladium-mediated allylic substitution reaction is known as an efficient synthetic tool for the formation of carbon−carbon and carbon−heteroatom bonds.[1] A large number of chiral ligands, mainly P- and N-containing ligands, possessing either C_2- or C_1-symmetry have been successfully applied to the asymmetric palladium-catalyzed allylic substitution.[1b,d] Among the P-ligands, diphosphines have played a dominant role in the success of allylic substitution, although recent reports have also shown the potential utility of chiral phosphite−oxazoline,[2] phosphite−thioether,[3] phosphite−phosphine,[4] and more recently diphosphite[5] ligands in asymmetric allylic alkylation. However, a systematic evaluation of the effectiveness of these phosphite ligands is hampered by the lack of a systematic design of series of ligands having a similar backbone. More research needs to be done to understand the role of the phosphite moiety in the origin of the stereochemistry of the allylic substitution reaction.

For that purpose, carbohydrates are particularly advantageous. They are readily available and highly functionalized compounds with several stereogenic centers. This allows a systematic regio- and stereoselective introduction of different functionalitites in the synthesis of series of chiral ligands that can be screened in the search for high activities and enantioselectivities.[5,6] At the same time, they can provide useful information about the origin of the stereoselectivity of the reaction.[6n]

In previous studies, several types of ligands derived from carbohydrates have been applied in asymmetric Pd-allylic substitution with varying degrees of success. Pregosin et al. reported good enantioselectivities (up to 97%) with thioglucose-based mixed ligands.[7] Widhalm et al. reported moderate (up to 79%) enantiomeric excesses at room temperature with a new diphosphine, xylophos.[8]

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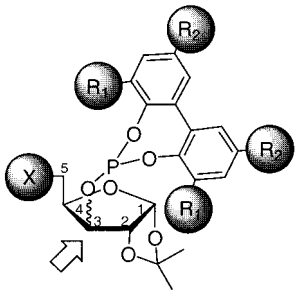
Scheme 1



Kunz et al.[9] and Uemura et al.[6b,10] reported moderate to good enantiomeric excesses (up to 96%) at low temperature (0 °C) using phosphorus−oxazoline ligands derived from D-glucosamine. RajanBabu et al. reported moderate enantioselectivities (up to 59%) using diphosphinite ligands with a glucopyranoside backbone.[11] More recently, Diéguez et al. have reported good enantioselectivities (up to 95%) with diphosphites derived from D-(+)-glucose at room temperature.[5]

Following our interest in phosphite ligands, and having in mind the modular nature of carbohydrates, we report here the use of a series of diphosphite, phosphine−phosphite, and thioether−phosphite furanoside ligands in the Pd-catalyzed allylic substitution reaction. The furanoside backbone in these ligands allows the systematic variation of the configuration at the stereogenic center C-3 and the introduction of different functionalities at the nonstereogenic center C-5 in the ligand (Scheme 1). These structural variations may provide information about the role of the phosphite moiety in the origin of the stereochemistry of the reaction.

We also investigate the effect of different substituents in the *ortho* and *para* positions of the biphenol−phosphite moiety on the catalyst performance (Scheme 1), since they have shown to have a significant effect on the product outcome in many other catalytic reactions.[6d,l,n,12]

Results and Discussion

Ligand Design. To study the role of the phosphite moiety in the determination of the stereoselectivity in the Pd-catalyzed allylic substitution reactions, we designed a series of modular furanoside ligands **1**−**5**.

Initially, we investigated the effect of stereogenic carbon atom C-3 in the sugar backbone and the effects of the different substitution in the bisphenol moiety using diphosphite ligands **1** and **2**. Thus, the influence of the configuration of the stereogenic carbon atom C-3 (see Scheme 1) on the enantioselectivity was studied using diphosphite ligands **1** and **2**, which have the opposite configuration on C-3. The different configuration on C-3 will lead to a different geometry around the palladium center.

To explore the effect of the steric bulk on the product outcome (conversion and enantioselectivity), different substituents in *ortho* positions of the biphenol moieties were investigated using ligands **1**.

We also investigated the electronic effects on the catalyst performance by varying the substituents in *para* positions of the biphenol moiety using ligands **2**.

Next, we extended the study to the influence of other ligand functionalities at carbon atom C-5 on the catalytic performance using ligands **3**, **4**, and **5**. In these mixed ligands, the phosphite moiety at C-5 has either been substituted for different thioether moieties (ligands **3**) or a phosphine moiety (ligand **4**). In the latter ligand, we also substituted the phosphite moiety with an atropisomerically pure binaphthol group to obtain ligands **5**.

Asymmetric Allylic Alkylation. In a first set of experiments, we used the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **6** with dimethyl malonate to assess the potential of ligands **1**−**5** for asymmetric catalysis. The reactions were carried out in dichloromethane at room temperature in the presence of a catalyst generated in situ from 0.5 mol % of π-allylpalladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1 mol % of the corresponding ligand, and a catalytic amount of KOAc. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA). The results are summarized in Table 1.

The reaction using xylofuranoside diphosphite ligand **1a**, containing two unsubstituted biphenol moieties, provided (*S*)-**7** in good yield but with low ee (entry 1). The introduction of bulky *tert*-butyl substituents in the *ortho* and *para* positions of both biphenol moieties (ligand **1b**) had an extremely positive effect on enantioselectivity (entry 2). Thus, the selectivity improved from 20% ee to 90% ee. Furthermore, the presence of *tert*-butyl groups also had a positive effect in activity (entry 1 vs entry 2).

Using ribofuranoside diphosphite ligands **2**, in which the configuration of the carbon atom C-3 is opposite to the configuration of this atom in ligands **1**, resulted in very low enantioselectivities, even though these ligands possess bulky *tert*-butyl groups in *ortho* position (entries 3 and 4). In line with the results of Diéguez et al.,[5] comparison of ligands **2a** and **2b** showed that the activity and enantioselectivity of the reaction was also affected by the *para* substituents on the biphenol moieties (entries 3 and 4). As compared to *tert*-butyl groups (ligand **2a**), the presence of methoxy groups at the *para* positions (**2b**) slowed the reaction down dramatically, whereas the enantioselectivity was slightly higher (ligand **2b**).

Replacing the phosphite functionality at C-5 for a thioether moiety resulted in the mixed xylofuranoside thioether−phosphite ligands **3**. The resulting Pd-complexes are less enantioselective than their diphosphite counterparts **1** (entries 5 and 6 vs 1 and 2). Different substituents in the thioether moiety largely affect the activity, but they have no significant influence on the enantiodiscrimination (entries 5 and 6). From this we conclude that the enantioselectivity is controlled mainly by the phosphite moiety. This is confirmed by the use of ligand **3c** containing the smaller unsubstituted biphenol moiety, which resulted in a drop in ee from 58% (**3a**, entry 5) to 3% (**3c**, entry 7).

Substitution of the phosphite moiety attached to C-5 in ligand **1b** for a diphenylphosphine moiety (**4**) results in a much lower activity and enantioselectivity (entries 2 and 8). The influence of the phosphite moiety in this type of ligand was studied using ligands **5** possessing enantiomerically pure binaphthol groups. The use of

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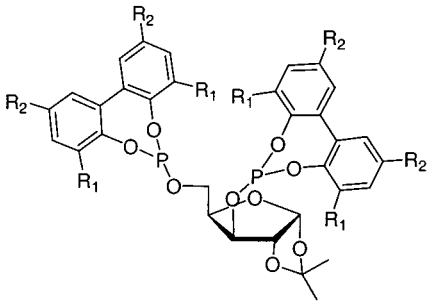
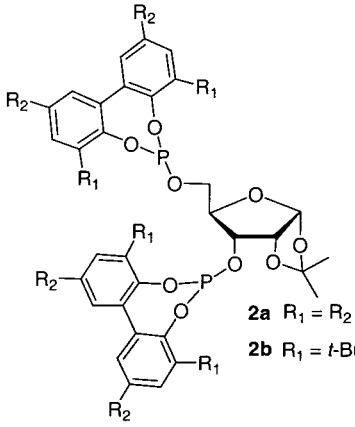
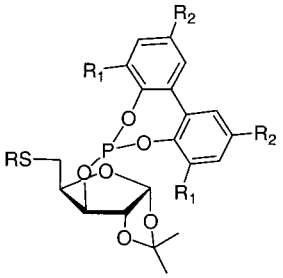
Chart 1



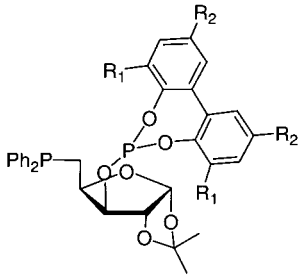
1a $R_1 = R_2 = H$
1b $R_1 = R_2 = t$-Bu



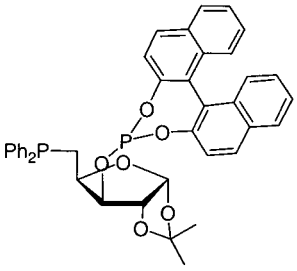
2a $R_1 = R_2 = t$-Bu
2b $R_1 = t$-Bu; R_2 = OMe



3a R = Ph; $R_1 = R_2 = t$-Bu
3b R = *i*-Pr; $R_1 = R_2 = t$-Bu
3c R = Ph; $R_1 = R_2$ = H

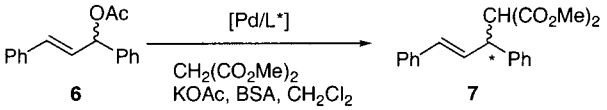


4 $R_1 = R_2 = t$-Bu



5a (S_{ax})
5b (R_{ax})

Table 1. Palladium-Catalyzed Asymmetric Allylic Alkylation with Chiral Ligands 1−5[a]



6 **7**

entry	L*	time (h)	% conv[b]	% ee[c]
1	**1a**	22	95	20 (*S*)
2	**1b**	1.5	83	90 (*S*)
3	**2a**	1.5	100	1 (*R*)
4	**2b**	22	11	5 (*R*)
5	**3a**	1.5	58	58 (*S*)
6	**3b**	1.5	23	54 (*S*)
7	**3c**	22	100	3 (*S*)
8	**4**	22	100	42 (*S*)
9	**5a**	22	100	20 (*S*)
10	**5b**	22	100	6 (*R*)

[a] All reactions were run at room temperature. Diphenylallyl acetate-to-palladium ratio is 100. Malonate-to-palladium ratio is 300. Ligand-to-palladium ratio is 1. Catalyst preparation time is 30 min. [b]Conversion percentage of acetate **7** determined by GC. [c]Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses.

ligands **5a** and **5b** in the allylic alkylation result in 20% and 6% ee, respectively. Interestingly, the sense of the asymmetric induction is reversed indicating that the absolute stereochemistry of the binaphthyl in the phosphite moiety also plays an important role in the asymmetric induction. Comparing these results with the results obtained using ligand **4**, we can assume that the atropisomeric biphenol moiety in ligand **4** probably adopts an atropoisomeric (*S*)-configuration in the allylpalladium complex responsible for the catalytic activity.

Origin of the Enantioselectivity. It has been generally accepted that the enantioselective step in the Pd-catalyzed allylation is the nucleophilic attack.[1] Usually, nucleophilic attack occurs predominantly at the allyl terminus located trans to the ligand that is the better π-acceptor.[1d,13] However, recently, Deerenberg et al. have shown that, when a phosphine−phosphite ligand is used, the attack takes place trans to the phosphine moiety.[4] Although the phosphite is a better π-acceptor, the σ-donating capacity of the phosphine has a larger influence. Thus, for phosphine−phosphite ligands **4** and **5**, we also expect the nucleophilic attack trans to the phosphine moiety. This is confirmed by our catalysis results that show that the enantioselectivity is mainly controlled by the phosphite moiety at C-3. Since the alkylated product (*S*)-**7** was obtained as the major enantiomer using ligands **4** and **5a** in the reaction of **6** with dimethyl malonate, the reaction probably proceeds through an exo-diastereoisomer **B** rather than a endo-diastereoisomer **A** intermediate in the equilibrium as shown in Figure 1.

In the case of phosphite−thioether ligands **3**, the two functionalities have similar donor properties[3] and it is difficult to predict where the nucleophilic attack will take place. Our results in catalysis (entries 5−7) clearly indicate that the thioether moiety hardly affects the enantioselectivity. The enantioselectivity is mainly controlled by the phosphite moiety. Therefore, we assume that the attack of the nucleophile takes place trans toward the thioether moiety. Similarly to phosphine−

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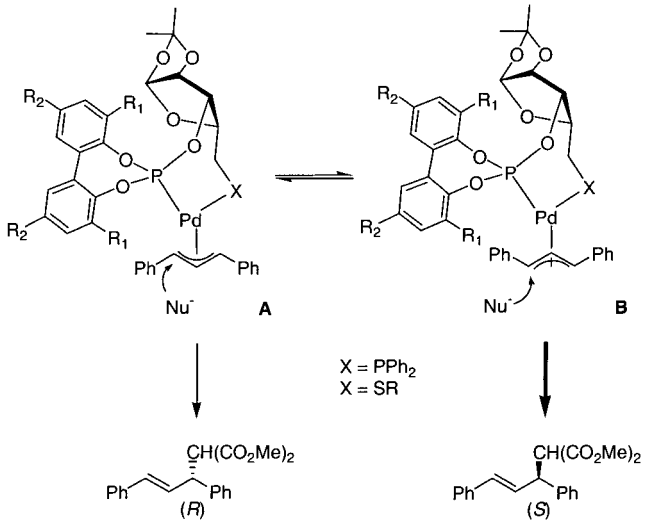


Figure 1.

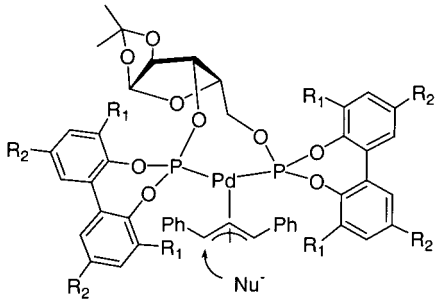


Figure 2.

phosphite ligands **4** and **5a**, the reaction may proceed through a diasteriomer **B** (Figure 1).

For the homo-donor diphosphite ligands **1** and **2**, we assume that the nucleophilic attack predominantly occurs trans to the phosphite moiety attached to C-5. This hypothesis is based on the following:

(i) The configuration of the stereocenter C-3 strongly influences the enantioselectivity. Thus, using ligands with xylofuranoside backbone, with (*R*)-configuration at C-3, give ee's up to 90%, while with ribofuranoside ligands, with opposite configuration at C-3, very low enantioselectivity is obtained.

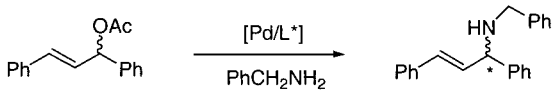
(ii) The sense of the asymmetric induction obtained with ligands **1** is the same as that obtained with hetero-donor ligands **3** and **4**, having the same configuration at C-3, for which the nucleophilic attack occurs cis to the phosphite moiety at C-3.

Further proof for this hypothesis can be found in the recent work of Diéguez et al. using related gluco-, allo-, and talo-furanoside diphosphites which showed that the configuration of carbon atom C-5 had little influence on the outcome of the reaction.[5]

In addition, ligands **1** have a strong preference for the nucleophilic attack on the exo-diastereoisomer **B** of allyl-palladium intermediate as the predominant formation of (*S*)-**7** suggests (Figure 2), while for ligands **2** the attack of the malonate is not selective.

The higher enantiodiscrimination obtained for the bulky xylofuranoside diphosphite **1b** compared with those obtained with thioether−phosphite and phosphine−phosphite ligands, containing the same phosphite moiety at stereogenic carbon atom C-3, cannot be explained by the reactivity of the nucleophile versus the different π-allyl intermediates, since the results indicate that in all cases the nucleophile predominantly attacks on the exo-diastereoisomer **B** of allyl-palladium intermediate. A plausible explanation can be found either in the enhancement of the steric interaction upon attack of the nucleophile as the result of the formation of a more bulky chiral pocket or a late transition state. Nucleophilic substitution of the (η^3-allyl)Pd cationic complex to form the Pd olefin complex must be accompanied by rotation.[14] A late transition state therefore results in larger ligand−allyl interaction.

Table 2. Palladium-Catalyzed Asymmetric Allylic Amination with Chiral Ligands 1−5[a]



6 **8**

entry	L*	% conv[b]	% ee[c]
1	**1b**	60	97 (*R*)
2	**2a**	14	32 (*S*)
3	**2b**	3	nd[d]
4	**3a**	7	67 (*R*)
5	**4**	100	66 (*R*)

[a] All reactions were run at room temperature during 22 h. Acetate-to-palladium ratio is 100. Benzylamine-to-palladium ratio is 120. Ligand-to-palladium is 1. Catalyst preparation time is 30 min. [b]Conversion percentage of acetate **7** determined by GC. [c]Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses. [d]Not determined.

Asymmetric Allylic Amination. As a model reaction of the allylic amination, we investigated the palladium-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate **6** with benzylamine as the nucleophile. The amination reaction was performed in dichloromethane at room temperature in the presence of a catalyst generated in situ as described for the alkylation experiments. The results are shown in Table 2.

In general, the results follow the same trend as that observed for the allylic alkylation, which is not unexpected because the reactions have a similar mechanism.[1c] However, the enantiomeric excesses obtained are higher, and the reaction rates are much lower. The higher ee's in the allylic amination can be explained by a later transition state, which results in larger ligand−allyl interaction.[14] The catalyst precursor containing diphosphite ligand **1b** gave an excellent compromise between activity and enantioselectivity (entry 1). The steroselectivity of the amination is the same as for the alkylation reaction, though the CIP descriptor is inverted due to the change of priority of the groups. These results support a mechanism via a exo-allyl-palladium intermediate **B** for the allylic substitution reactions described in this paper (see Figure 2).

Conclusions

A series of diphosphite, thioether−phosphite and phosphine−phosphite ligands **1-5** with furanoside backbone has been successfully applied to the Pd-catalyzed allylic

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substitution reactions. Low to good enantioselectivities (up to 97%) were obtained in the reaction of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate and benzylamine. The modular nature of these ligands enables systematic investigations of the effect of the ligand structure on enantioselectivity. From the results in catalysis we can conclude that the nucleophilic attack takes place trans toward the carbon atom C-5. Thus, the configuration of stereogenic carbon atom C-3 strongly effects the enantioselectivity. However, comparing the experiments with ligands having different functionalities at C-5, we can conclude that the presence of bulky phosphite moiety improves the enantioselectivity, due either to the formation of a more effective chiral pocket or a late transition state. Thus, the best enantioselectivities have been obtained using bulky diphosphite ligand **1b**.

Experimental Section

General Considerations. All reactions were carried out in flame-dried glasswork using standard Schlenk techniques under an atmosphere of argon. Solvents were purified by standard procedures. Diphosphites **1**[15] and **2**,[16] thioether−phosphites **3**,[6e] and phosphine−phosphite ligands **4**[6l] and **5**[6l] were prepared by previously described methods. Racemic (*E*)-1,3-diphenyl-2-propenyl acetate was prepared as previously reported.[17] ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Gas chromatographic analyses were conducted with a DB-1 J&W 30 m column (split/splitless injector, film thickness 3.0 μm, carrier gas 70 kPa He, FID detector). Enantiomeric excesses were determined by HPLC using a Daicel OD column.

Allylic Alkylation Experiments. A degassed solution of 0.005 mmol of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in dichloromethane (1.5 mL), 0.01 mmol of ligand, and 0.5 mmol of decane was stirred for 30 min. Subsequently, a solution of 1 mmol of *rac*-1,3-diphenyl-2-propenyl acetate in dichloromethane (0.736 mL, 1.31 M), 3 mmol of dimethyl malonate, 3 mmol of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. To determine the conversion by GC, a sample was quenched with a dibenzylideneacetone (DBA) solution. To determine the ee by HPLC (Daicel OD, 0.5% 2-propanol/hexane, flow = 0.5 mL/min, t_R = 35.4 min (*R*), t_R = 38.7 min (*S*), λ = 254 nm), a sample was filtered over basic alumina using dichloromethane as the eluent.

Allylic Amination Experiments. A degassed solution of 0.005 mmol of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ in dichloromethane (1.5 mL), 0.01 mmol of ligand, and 0.5 mmol of decane was stirred for 30 min. Subsequently, a solution of 1 mmol of *rac*-1,3-diphenyl-2-propenyl acetate in dichloromethane (0.736 mL, 1.31 M) and benzylamine (1.2 mmol) were added. The reaction mixture was stirred at room temperature. To determine the conversion by GC, a sample was quenched with a dibenzylideneacetone (DBA) solution. To determine the ee by HPLC (Daicel OJ, 13% 2-propanol/hexane, flow = 0.5 mL/min, t_R = 14.2 min (*S*), t_R = 17.5 min (*R*), λ = 254 nm), a sample was filtered over silica gel eluted with 10% Et_2O/hexane.

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