3. Pd-catalyzed asymmetric allylic substitution

3.1. Background

As we discussed in the introduction, most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentated donor ligands (such as P-N, P-S and S-N). The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. Among those, catalysts containing phosphine-oxazoline ligands have played a key role in the success of this process. Recently, a group of less electron-rich phosphorus compounds–biaryl phosphite ligands–have also demonstrated their potential utility in this process. In this context, our group have successfully reported the use of a phosphite-oxazoline ligand family **1** that overcomes the most common limitations of this process, such as low reaction rates and high substrate specificity (Figure 1).[1] Despite this success, reports on their use are rare.[1,2] This encourages further research into phosphite-oxazoline ligands.

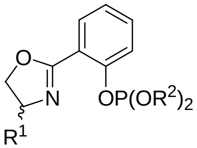
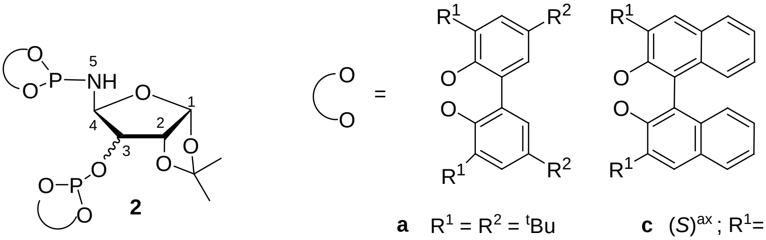


Figure 1. Phosphite-oxazoline ligands **1**.

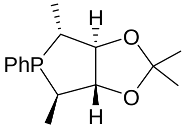
Other heterodonor ligands, such as phosphite-phosphoroamidite, have recently demonstrated their potential utility in asymmetric catalysis. To our knowledge, only our group have recently reported the successful use of this type of ligands for asymmetric allylic substition (Figure 2).[3] More research is therefore needed to study the scope for phosphite-phosphoroamidite as a new class of ligands for this process.

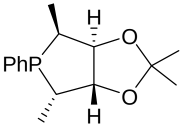


a $R^1 = R^2 = {}^tBu$ **c** $(S)^{ax}$; R^1= $SiMe_3$
b $R^1 = {}^tBu$ R^2 = OMe **d** $(R)^{ax}$; R^1= $SiMe_3$

Figure 2. Phosphite-phosphoroamidite ligands **2** derived from D-xylose.

Less attention has been paid to catalysts containing monodentated ligands in asymmetric allylic substitution reactions. However, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalysts precursors containing monophospholane ligands **3-5** (Figure 3).[4] This encourages further research into monophosphorous ligands.


3 (94% (*R*))


4 (93% (*S*))

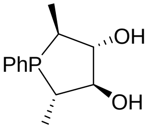

5 (94% (*S*))

Figure 3. Monophospholane ligands developed by the groups of RajanBabu and Zhang.

In this chapter, we therefore report the synthesis of three carbohydrate-based ligand libraries: phosphite-oxazoline (**L1-L5a-i**), phosphite-phosphoroamidite (**L6a-c**) and monophosphite (**L7-L11a-f**). We also report their use as catalysts precursors in asymmetric allylic substitution reactions. More specifically, in section 3.2 we report the synthesis and application of a glucopyranoside phosphite-oxazoline ligand library (**L1-L5a-i**) in the Pd-catalyzed allylic substitution of several substrate types. This ligand library has four main advantages: (1) they can be prepared in a few steps from readily available D-glucosamine; (2) the π-acceptor character of the phosphite moiety increases reaction rates; (3) the flexibility and larger bite angle created by the biaryl phosphite moiety increases versatility and (4) their modular nature enables the substituents in the oxazoline moiety and the substituents/configurations in the biaryl phosphite moiety to be easily and systematically varied. Thus, by carefully selecting the ligand components, high enantioselectivities (ee's up to 99%) and good activities have been achieved in a wide range of substrates with different steric and electronic properties. The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy makes it possible to understand the catalytic behaviour observed. This study also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety. On the basis of the previous ligand library, in next section 3.3, we designed a new glucopyranoside ligand family (phosphite-phosphoroamite; **L6a-c**) in which the oxazoline moiety is replaced by a phosphoroamidite group. These ligands were applied to the Pd-catalyzed allylic alkylation of several substrates types. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para* positions of the biphenyl moieties. However, these effects are different depending on the substrate in study. Enantiomeric excesses of up to 89% with high activities were obtained for *rac*-1,3-diphenyl-3-acetoxyprop-1-ene, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate and *rac*-3-acetoxycycloheptene. For the monosubstituted linear substrate 1-(1-naphthyl)allyl acetate, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivity by carefully selecting the substituents on the *para* position of the biphenyl moieties (ee's up to 72%). Finally, in section 3.4, we report the synthesis of a modular sugar-based monophosphite ligand library (**L7-L11a-f**) for the Pd-catalyzed allylic substitution reactions of several substrates. These ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones, and contain several substituents/configuration in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. Unfortunately, low-to-moderate enantioselectivities were obtained (ee's up to 46%).

3.1.1. References

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[2] a) Prétôt, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 323. b) Gavrilov, K. N.; Tsarev, V. N.; Zheglov, S. V.; Lyubimov, S. E.; Shyryaev, A. A.; , Petrovskii, P. V.; Davankov, V. A. *Mendeleev Commun.* **2004**, 260.

[3] Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49.

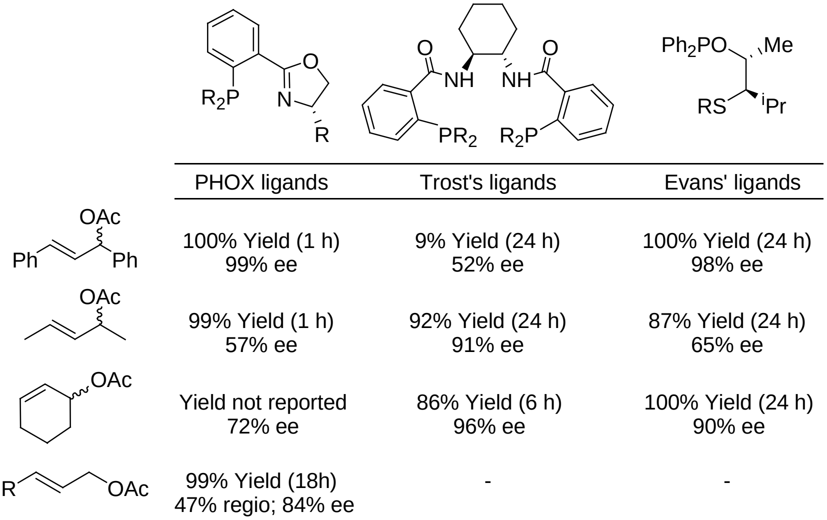
[4] a) Yan, Y. Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. b) Zhang, X. WO Patent 03/040149 A2, 2003.

3.2. A carbohydrate-based phosphite-oxazoline ligand library for Pd-catalyzed allylic substitution reactions

Abstract. We have synthesized and screened a library of modular phosphite-oxazoline ligands for asymmetric allylic substitution reactions. The library is easily prepared from commercially available cheap D-glucosamine. The introduction of a phosphite moiety to the ligand design is highly advantageous for the product outcome. Therefore, this ligand library affords good-to-excellent reaction rates (TOF's up to 600 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 99%) and, at the same time, shows a broad scope for mono- and disubstituted linear hindered and unhindered substrates and cyclic substrates. The NMR studies on the Pd-π-allyl intermediates provide a deeper understanding about the effect of the ligand parameters on the origin of enantioselectivity.

3.2.1. Introduction

Palladium-catalyzed allylic substitution reactions are an efficient synthetic tool for constructing carbon-carbon and carbon-heteroatom bonds.[1] The chiral ligands used for highly enantioselective allylic substitution have mainly been mixed bidentate donor ligands.[1,2] Mixed phosphorus-nitrogen ligands have played a dominant role among heterodonor ligands. However, one disadvantage of these ligands is that they are often synthesized from expensive chiral sources or in tedious synthetic steps. Another common disadvantages of the most successful ligand families developed for this process is that they usually have low reaction rates and high substrate specificity (i.e ee's are high in disubstituted linear hindered substrates and low in cyclic and unhindered linear substrates, or vice versa) (Scheme 1).[1]



	PHOX ligands	Trost's ligands	Evans' ligands
	100% Yield (1 h) 99% ee	9% Yield (24 h) 52% ee	100% Yield (24 h) 98% ee
	99% Yield (1 h) 57% ee	92% Yield (24 h) 91% ee	87% Yield (24 h) 65% ee
	Yield not reported 72% ee	86% Yield (6 h) 96% ee	100% Yield (24 h) 90% ee
	99% Yield (18h) 47% regio; 84% ee	-	-

Scheme 1. Summary of the best results with several linear and cyclic substrates for three of the most representative ligand families developed for Pd-catalyzed allylic substitution reactions (reactions usually carried out with 2-4 mol% of Pd).

It is therefore of great importance nowadays to conduct research into more versatile and faster mixed P-N ligand systems that can be synthetized in few steps from simple starting materials. For this purpose, carbohydrates are particularly advantageous because of their low price and easy modular constructions.[3] Although they have been 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] Notable examples include two types of phosphorous-oxazoline ligands.[4e,5] In this context, Uemura and coworkers synthesized the phosphinite-oxazoline ligands **1** (Figure 1)[4e,5b] which proved to be effective in the allylic substitution of hindered substrate 1,3-diphenyl-3-acetoxyprop-1-ene but which had low enantioselectivity for unhindered cyclic and linear substrates.[4e] On the basis of this structure, in this paper we have designed a new ligand library in which the phosphinite group is replaced by a phosphite group (Figure 2). The advantage of incorporating a phosphite moiety into the ligand is that: (i) the substrate specificity decreases because the chiral pocket created (the chiral cavity where the allyl is embedded) is smaller than for ligands **1**[1c,6] yet flexible enough[6] to allow the perfect coordination of hindered and unhindered substrates;[7] (ii) reaction rates increases because of the high π-acceptor capacity of the phosphite moiety;[8] and (iii) the regioselectivity towards the desired branched isomer in monosubstituted linear substrates increased because of the π-acceptor capacity of the phosphite moiety enhance the S_N-1 character of the nucleophilic attack.[9]

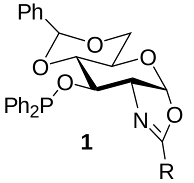


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Figure 1. Phosphinite-oxazoline ligands developed by Uemura and coworkers.

We therefore report here the design of a library of 45 potential chiral phosphite-oxazoline ligands **L1**-**L5a**-**i** (Figure 2) for Pd-catalyzed allylic substitution reactions of several substrate types.[10] We also discuss the synthesis and characterization of the Pd-π-allyl intermediates to provide greater insight into the origin of the enantioselectivity. The library was synthesized and screened using a series of parallel reactors, each of which was equipped with 12 different positions. These new phosphite-oxazoline ligands **L1**-**L5a**-**i** also have the advantage of a more flexible ligand scaffold than ligands **1** because they can be easily tuned in two different regions (oxazoline and phosphite substituents) so that their effect on catalytic performance can be determined. Therefore, with this library we fully investigated the effects of different electronic and steric properties of the oxazoline moiety (**L1**-**L5**) and different substituents/configurations in the biaryl phosphite moieties (**a**-**i**). As a result, the highly enantioselective and active Pd-allylic substitution reactions are carried out for several substrates.

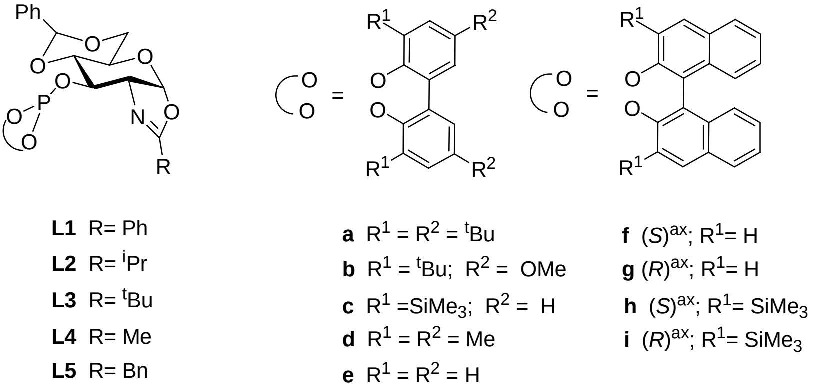
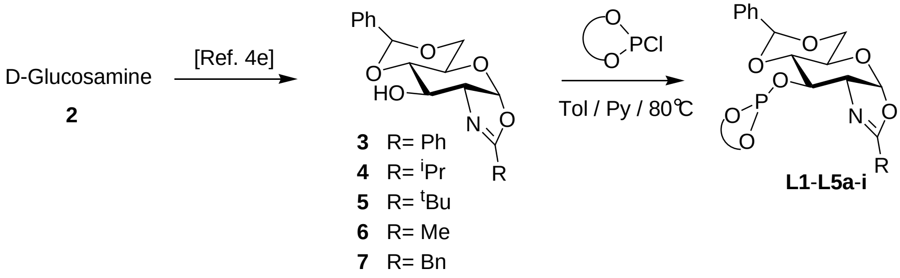


Figure 2. Phosphite-oxazoline ligand library **L1**-**L5a**-**i**.

3.2.2. Results and Discussion

3.2.2.1. Ligand synthesis.

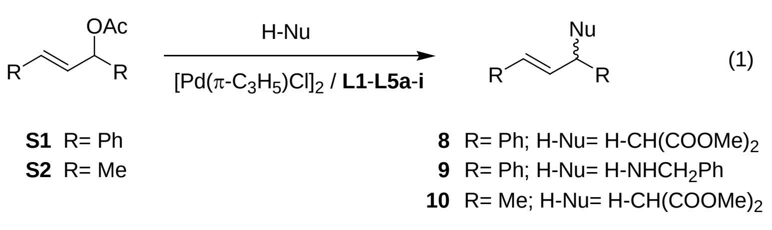
The synthesis of the phosphite-oxazoline ligand library **L1**-**L5a**-**i** is straightforward (Scheme 2). They were efficiently synthesized in one step by reacting the corresponding sugar oxazoline-alcohols (**3**-**7**) with 1 equiv of the corresponding biaryl phosphorochloridite (**a**-**i**) in the presence of pyridine (Scheme 2). Oxazoline-alcohols **3**-**7** are easily prepared from inexpensive D-glucosamine **2** on a large scale.[4e] All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in moderate-to-good yields as white solids. They were stable at room temperature and very stable to hydrolysis. The elemental analysis were in agreement with the assigned structure. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. One singlet was observed in the ^{31}P NMR spectrum. Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[11]



Scheme 2. Synthesis of phosphite-oxazoline ligand library **L1-L5a-i**.

3.2.2.2. Allylic substitution of disubstituted linear substrates

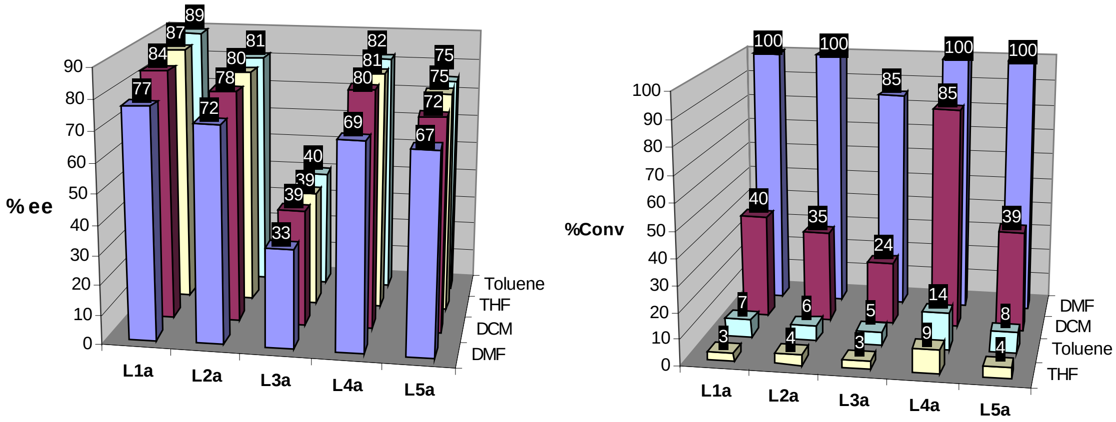
In this section, we report the use of the chiral phosphite-oxazoline ligand library (**L1-L5a-i**) in the Pd-catalyzed allylic substitution (equation 1) of two disubstituted linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S2**. In all the cases, the catalysts were generated *in situ* from the π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and a catalytic amount of the corresponding base. Two nucleophiles were used. For the allylic alkylation, the nucleophile was generated from dimethyl malonate in the presence of *N,O*-bis(trimethylsilyl)-acetamide (BSA), while for the allylic amination, benzylamine was used as the nucleophile.



3.2.2.2.1. Allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 using dimethyl malonate and benzylamine as nucleophiles (equation 1)

For an initial evaluation of this new type of ligand in the palladium-catalysed asymmetric substitution reactions, we chose the allylic substitution of **S1** (equation 1, R= Ph) and used dimethyl malonate and benzylamine as nucleophiles. As these reactions were carried out with a variety of ligands carrying different donor groups, the efficacy of different ligand systems can be directly compared.[1]

We determined the optimal reaction conditions by conducting a first set of experiments in which the solvent, the ligand-to-palladium ratio and the base were varied. We first studied the effect of four solvents (tetrahydrofurane (THF), toluene, dimethylformamide (DMF) and dichloromethane (DCM), with five ligands (**L1a-L5a**). Figure 3 shows the results when dimethyl malonate was used as the nucleophile (trends were similar in the allylic amination of **S1**). The results show that the efficiency of the process strongly depended on the nature of the solvent. The enantioselectivity was highest with toluene, THF and dichloromethane. However, although toluene provided slightly higher enantioselectivity than dichloromethane, its activity was lower. On the other hand, dimethylformamide yielded the highest relative conversions, but its ee's were the lowest of the four solvents. So, the optimum trade-off between activities and enantioselectivities was obtained by using dichloromethane as the solvent (Figure 3).



(a) (b)

Figure 3. Results of the catalytic allylic alkylation of **S1** using ligands **L1a**-**L5a** in four solvents at room temperature and a ligand-to-palladium ratio of 1.1. (a) Enantioselectivities of product **8**. The positive numbers refer to the formation of the *S*-isomer in excess. (b) Conversions after 10 minutes.

We then studied the effect of varying the ligand-to-palladium ratio. Figure 4 shows the conversion and enantioselectivity when dichloromethane and ligands **L1a-L5a** were used (similar trends were observed for the other solvents). The results show that an excess of ligand is not needed for activities and enantioselectivities to be high. Interestingly, enantioselectivities were best with a ligand-to-palladium of 0.9. At a higher ligand-to-palladium ratio (1.1 or 2), enantioselectivies were lower. This is due to the fact that at a higher ligand-to-palladium ratio of 0.9 the phosphite-oxazoline ligand acts as a monodentate ligand (see section 3.2.2.5, Origin of enantioselectivity. Study of the Pd-π-allyl intermediates).

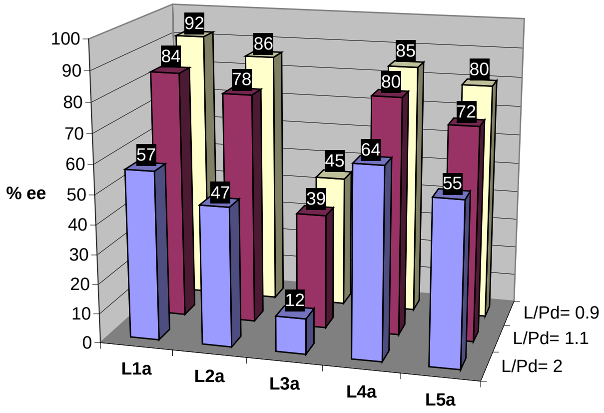


Figure 4. Enantioselectivities of product **8** using ligands **L1a-L5a** at different ligand-to-palladium ratio in dichloromethane at room temperature. The positive numbers refer to the formation of the *S*-isomer in excess. In all cases full conversion were obtained after 1 hour.

We then studied the effect of several bases. Table 1 shows the conversion and selectivity when dichloromethane was used as a solvent with ligands **L1a** and **L4a** (similar trends were observed for the other solvents and ligands). The best activities and enantioselectivities were obtained with KOAc and NaOAc (entries 1, 2, 5 and 6 vs 3, 4, 7 and 8).

For comparative purposes, the rest of the ligands were tested under conditions that provided optimum trade-off between enantioselectivities and reaction rates (i.e. a ligand-to-palladium ratio of 0.9, dichloromethane as the solvent and potassium acetate as the base). Table 2 shows the results when dimethyl malonate was used as the nucleophile. They indicate that catalytic performance (activities and enantioselectivities) is highly affected by the oxazoline substituents and the axial chirality and the substituents of the biaryl moieties. In general, activities (TOF's up to 600 mol **S1** x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 99%) were high.

Table 1. Pd-catalyzed allylic substitution of **S1** using ligands **L1a** and **L4a**. Effect of the base.[a]

Entry	Ligand	Base	% Conv (min)[b]	% ee[c]
1	**L1a**	KOAc	100 (30)	92 (*S*)
2	**L1a**	NaOAc	100 (30)	92 (*S*)
3	**L1a**	K_2CO_3	100 (60)	85 (*S*)
4	**L1a**	Li_2CO_3	100 (60)	89 (*S*)
5	**L4a**	KOAc	100 (15)	85 (*S*)
6	**L4a**	NaOAc	100 (15)	85 (*S*)
7	**L4a**	K_2CO_3	90 (30)	78 (*S*)
8	**L4a**	Li_2CO_3	100 (30)	77 (*S*)

[a] All reactions were run at 23 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 0.9 mol% ligand. [b] Reaction time shown in parentheses. [c] Enantiomeric excesses. The absolute configuration appears in parentheses.

The effect of the oxazoline substituent was studied with ligands **L1a-L5a** (Table 2, entries 1, 10-12 and 14). We found that these substituents affected both activities and enantioselectivities. The results showed that enantioselectivity is dependent on both the electronic and steric properties of the substituents in the oxazoline moiety. Therefore, enantioselectivities were best with ligand **L1a**, which contains a phenyl-oxazoline group (Table 2, entry 1). This behavior contrasts with the effect of the oxazoline-substituent observed for related phosphinite-oxazoline ligands **1**, for which enantioselectivities were higher when a methyl substituent was present.[4e] However, activities were controlled by the steric properties of the substituents in the oxazoline groups. They were higher when less sterically demanding substituents were present (i.e. Me>Ph≈Bn>^{i}Pr>^{t}Bu).

The effects of phosphite moieties were studied using ligands **L1a-i** (Table 2, entries 1-9). It was observed that these moieties affected both activity and enantioselectivity. The results indicated that the substituents at the *ortho* positions of the biphenyl moiety mainly affected activities, while the substituents at the *para* positions mainly affected enantioselectivities. Activities and enantioselectitivies were therefore highest when *tert*-butyl groups were present at both the *ortho* and *para* positions of the biphenyl phosphite moiety (ligand **L1a**, Table 2, entry 1). To further investigate how enantioselectivity was influenced by the axial chirality of the biaryl moiety, ligands **L1f-L1i** containing different enantiomerically pure binapthyl moieties were also tested (Table 2, entries 6-9). The results indicate that there is a cooperative effect between the configuration of the biaryl moiety and the configurations of the ligand backbone on enantioselectivity. This leads to a matched combination for ligands **L1f** and **L1h**, which contains an *S*-binaphthyl moiety (Table 2, entries 6 and 8 vs 7 and 9). In addition, comparing the results obtained using ligands **L1c** with binaphthyl ligands **L1h** and **L1i** (Table 2, entry 3 vs 8 and 9), we can also conclude that the atropoisomeric biphenyl moiety in ligands **L1a-d** adopts an *S*-configuration when coordinated in the Pd-π-allyl intermediate species.

To sum up, the best result was obtained with ligand **L1a**, which contains the optimal combination of substituents in the oxazoline and in the biaryl phosphite moieties. These results clearly show the efficiency of using highly modular scaffolds in ligand design.

In addition to the effect of structural parameters on enantioselectivity, the reaction parameters can also be controlled to further improved selectivity. In this case, enantioselectivity was further improved (ee's up to 95%) with ligand **L1a** by lowering the reaction temperature to 0 ºC (Table 2, entry 15). As expected, changing the solvent from dichloromethane to toluene increased enantioselectivity even further (ee's up to 99%, Table 2, entry 16). Interestingly, when this result is compared with the enantioselectivities obtained with their corresponding Pd-phosphinite-oxazoline **1** system (ee's up to 96% at 0 °C), we can concluded that adding a phosphite moiety to ligands **L1-L5a-i** has been advantageous. These results are among the best that have been reported.[1]

Table 2. Selected results for the Pd-catalyzed allylic alkylation of **S1** using phosphite-oxazoline ligand library **L1-L5a-i**[a]

Entry	Ligand	% Conv (min)[b]	% ee[c]
1	**L1a**	100 (30)	92 (*S*)
2	**L1b**	89 (30)	84 (*S*)
3	**L1c**	95 (30)	86 (*S*)
4	**L1d**	85 (30)	89 (*S*)
5	**L1e**	57 (30)	86 (*S*)
6	**L1f**	82 (30)	81 (*S*)
7	**L1g**	80 (30)	9 (*S*)
8	**L1h**	100 (30)	84 (*S*)
9	**L1i**	99 (30)	62 (*S*)
10	**L2a**	92 (30)	86 (*S*)
11	**L3a**	67 (30)	45 (*S*)
12	**L4a**	100 (15)	85 (*S*)
13	**L4c**	88 (15)	83 (*S*)
14	**L5a**	99 (30)	80 (*S*)
15[d]	**L1a**	54 (300)	95 (*S*)
16[d,e]	**L1a**	100 (360)	99 (*S*)

[a] All reactions were run at 23 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 0.9 mol% ligand. [b] Reaction time shown in parentheses. [c] Enantiomeric excesses. The absolute configuration appears in parentheses. [d] T= 0 ºC. [e] 2 mol% Pd, toluene as solvent.

We then tested ligands **L1-L5a-i** in the Pd-catalyzed allylic amination of **S1** with benzylamine (equation 1). The catalytic results are summarized in Table 3. We observed that the catalytic performance follows the same trend as for the allylic alkylation of **S1**. Therefore, the enantioselectivities were highest (even higher than in the alkylation of this substrate) with ligand **L1a** (ee's up to 94% at room temperature and dichloromethane as the solvent). As expected, the activity was lower than in the alkylation reaction of **S1**. The stereoselectivity of the amination was the same as for the alkylation reaction, though the CIP descriptor was inverted due to the change in priority of the groups.

Table 3. Selected results for the Pd-catalyzed allylic amination of **S1** using phosphite-oxazoline ligand library **L1-L5a-i**[a]

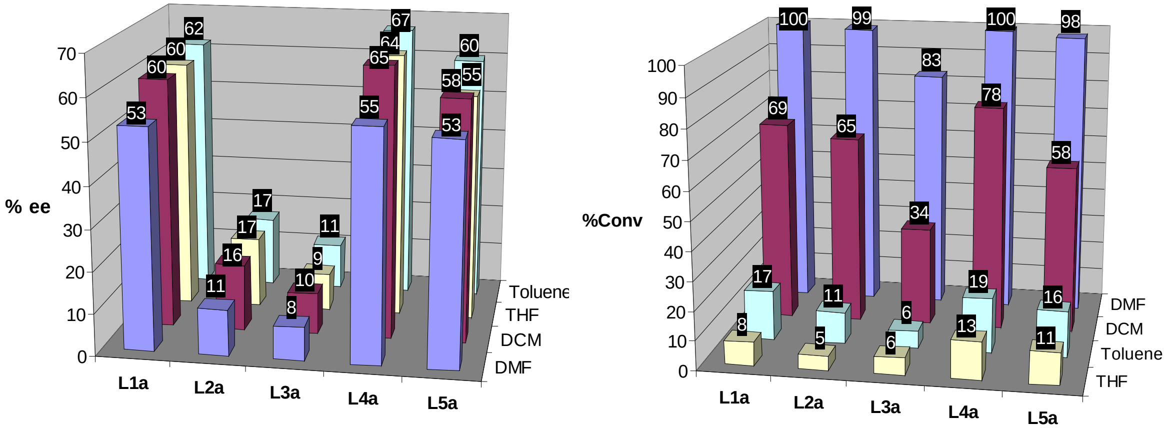
Entry	Ligand	% Conv [b]	% ee[c]
1	**L1a**	60	94 (*R*)
2	**L1b**	53	87 (*R*)
3	**L1c**	58	90 (*R*)
4	**L1d**	54	92 (*R*)
5	**L1e**	34	87 (*R*)
10	**L2a**	59	89 (*R*)
11	**L3a**	35	34 (*R*)
12	**L4a**	79	89 (*R*)
14	**L5a**	61	85 (*R*)

[a] All reactions were run at 23 ºC. 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 1.8 mol% ligand. [b] Conversion after 24 hours. [c] Enantiomeric excesses. The absolute configuration appears in parentheses.

3.2.2.2.2. Allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene S2 using dimethyl malonate as the nucleophile (equation 1)

We also evaluated the phosphite-oxazoline ligand library **L1-L5a-i** in the allylic alkylation of the linear substrate **S2** (equation 1, R= Me). This substrate is less sterically demanding than substrate **S1,** which we had used before. The enantioselectivity for **S2** is therefore more difficult to control than with hindered substrates such as **S1**. If ee's are to be high, the ligand must create a small chiral pocket (the chiral cavity where the allyl is embedded) around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.[1] Therefore, few catalytic systems have provided high enantioselectivities.[8b,12] Due to the presence of bulky biaryl phosphite moiety in ligands **L1-L5a-i**, which are know to be flexible and to provide large bite angles, we expected to be able to tune the size of the chiral pocket adequately and therefore to obtain also high enantioselectivity for this substrate.

The preliminary investigations into the solvent (Figure 5) and ligand-to-palladium ratio (Figure 6) revealed a trend that was similar to that of the previously tested substrate **S1**. The trade-off between selectivities and activities was therefore best when dichloromethane was used and the ligand-to-palladium ratio was 0.9. However, it should be noted that the negative effect of adding excess ligand is less pronounced for this unhindered substrate than for the previously tested hindered substrate **S1** (Figure 4 vs 6). This maybe because substrate **S2** is less sterically hindered than substrate **S1** (see section 3.2.2.5, Origin of enantioselectivity. Study of the Pd-π-allyl intermediates).



(a) (b)

Figure 5. Results of the catalytic allylic alkylation of **S2** using ligands **L1a**-**L5a** in four solvents at room temperature and a ligand-to-palladium ratio of 0.9. (a) Enantioselectivities of product **10**. The positive numbers refer to the formation of the *R*-isomer in excess. (b) Conversions after 30 minutes.

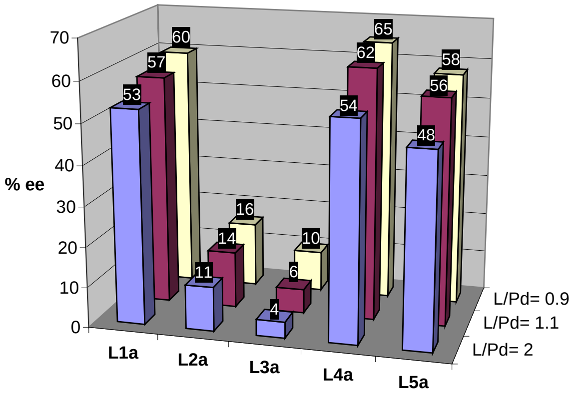


Figure 6. Enantioselectivities of product **10** using ligands **L1a**-**L5a** at different ligand-to-palladium ratio in dichloromethane at room temperature. The positive numbers refer to the formation of the *R*-isomer in excess. In all cases full conversions were obtained after 2 hours.

Table 4 summarizes the results of using the phosphite-oxazoline ligand library **L1-L5a-i** under the optimized conditions. In general, activities and enantioselectivities were also high (ee's up to 89%) in the alkylation of **S2**. Again, activities and enantioselectivities were affected by the substituents in both the oxazoline and phosphite moiety and the cooperative effect between stereocenters. However, the effect of these parameters on enantioselectivity was different from their effect on the alkylation of hindered substrate **S1**. Thus, enantioselectivity was best with ligand **L4h** (ee's up to 89%). These results again clearly shows the importance of using modular scaffolds in the ligand design.

Regarding the effect of the oxazoline substituents, the presence of bulky substituents in this position considerably decreased activities and enantioselectivities (Table 4, entries 1, 10-12 and 15). Therefore, in contrast to the alkylation of **S1**, both the activities and enantioselectivities were only dependent on the steric properties of the substituents in the oxazoline moiety and their were higher when a methyl substituent was present (ligand **L4a**, Table 4, entry 12).

Table 4. Pd-catalyzed allylic substitution of **S2** using phosphite-oxazoline ligand library **L1-L5a-i**[a]

Entry	Ligand	% Conv (min)[b]	% ee[c]
1	**L1a**	69 (30)	60 (*R*)
2	**L1b**	63 (30)	60 (*R*)
3	**L1c**	68 (30)	32 (*R*)
4	**L1d**	61 (30)	40 (*R*)
5	**L1e**	42 (30)	22 (*R*)
6	**L1f**	50 (30)	68 (*R*)
7	**L1g**	12 (30)	9 (*S*)
8	**L1h**	28 (30)	77 (*R*)
9	**L1i**	49 (30)	9 (*R*)
10	**L2a**	65 (30)	16 (*R*)
11	**L3a**	34 (30)	10 (*R*)
12	**L4a**	78 (30)	65 (*R*)
13	**L4c**	77 (30)	48 (*R*)
14	**L4h**	31 (30)	80 (*R*)
15	**L5a**	58 (30)	58 (*R*)
16[d]	**L1f**	100 (360)	81 (*R*)
17[d]	**L1h**	83 (600)	87 (*R*)
18[d]	**L4h**	88 (600)	89 (*R*)

[a] All reactions were run at 23 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 0.9 mol% ligand. [b] Reaction time shown in parentheses. [c] Enantiomeric excesses. The absolute configuration appears in parentheses. [d] T= 0 ºC.

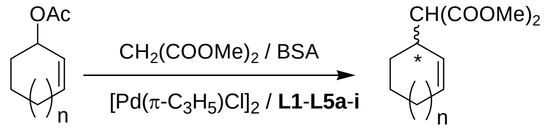
As far as the effect of the phosphite moiety on catalytic performance is concerned, bulky substituents need to be in the *ortho* position of the biphenyl moieties and substituents of any group except hydrogen need to be in the *para* positions if enantioselectivity is to be high (Table 4, entries 1 and 2 *vs* 3-5). Therefore, ligands **L1a** and **L1b** containing bulky substituents in the *ortho* positions and either *tert*-butyl or methoxy groups in the *para* positions of the biphenyl moieties provided higher enantioselectivities than ligands **L1c** (without substituents in the *para* positions), **L1d** (with small methyl substituents in *ortho* positions) and **L1e** (with an unsubstituted biphenyl moiety). The effect of the configuration of the biaryl naphthyl moiety (ligands **L1f-i**) is similar to the effect in the previous alkylation of **S1** (Table 4, entries 6-9). Therefore, ligands **L1f** and **L1h** with an *S*-binaphthyl moiety provided higher enantioselectivities than ligands **L1g** and **L1i** with a *R*-binaphthyl group. Interestingly, and in contrast to the substitution of **S1**, this cooperative effect is highly advantageous. Enantioselectivities increased from 60% to 77% ee at room temperature (Table 4, entry 1 vs 8).

In summary, results were best with ligand **L4h**, which contains the optimal combination of subsitutents in the oxazoline and in the biaryl phosphite moieties (ee's up to 89%). If this result is compared with the low-to-moderate enantioselectivities obtained with their related Pd-phosphinite-oxazoline **1** ligand systems (ee's up to 57% at 0 °C) in the alkylation of substrate **S2**, we can conclude again that the addition of a phosphite moiety has been highly advantageous in terms of activity and enantioselectivity. These results are among the best that have been reported.[8b,12]

3.2.2.3. Allylic alkylation of cyclic substrates (equation 2)

As for the unhindered substrate **S2**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *syn* substituents. These *syn* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediate.[1]

This section shows that the chiral phosphite-oxazoline ligand library **L1-L5a-i** applied above to the Pd-catalyzed allylic substitution of linear substrates (**S1** and **S2**) can also be used for cyclic substrates (ee's up to 94%). In this case, two cyclic substrates were tested (equation 2): *rac*-3-acetoxycyclohexene **S3** (which is widely used as a model substrate) and *rac*-3-acetoxycycloheptene **S4**.



(2)

S3 n=1
S4 n=2

11 n=1
12 n=2

We initially studied the allylic alkylation of *rac*-3-acetoxycyclohexene **S3** using ligands **L1-L5a-i**. Preliminary investigations into the solvent effect and ligand-to-palladium ratio showed the same trends as in the unhindered linear substrate **S2** tested previously. The trade-off between enantioselectivities and reaction rates was therefore optimum with dichloromethane and a ligand-to-palladium ratio of 0.9.

Table 5 summarizes the results of using the phosphite-oxazoline ligand library **L1-L5a-i** under the optimized conditions. In general, activities and enantioselectivities were also high (ee's up to 85%) in the alkylation of **S3**. Again, activities and enantioselectivities were affected by the substituents in the oxazoline moiety and the substituents/configuration of the phosphite moiety. However, the effect of these parameters was different from the effect observed in the substitution of linear substrates **S1** and **S2**. Therefore, results were best with ligand **L1i**.

While the effect of the oxazoline substituents on activities is similar to the effect in the alkylation of **S1** and **S2**, the effect of the phosphite moiety is different. Therefore, activities were better when less sterically demanding oxazoline substituents were present (Table 5, entries 1 and 12 *vs* 10, 11 and 14) and when bulky substituents were present at both *ortho* and *para* positions of the biphenyl moieties (Table 5, entries 1-5).

If enantioselectivity was to be high, we found that a phenyl substituent in the oxazoline moiety (Table 5, entries 1 vs 10-12 and 14) and either *ortho* trimethylsilyl disubstituted binaphthyl moiety (Table 5, entries 8 and 9) or *ortho* and *para* tetrasubstituted *tert*-butyl biphenyl moiety (Table 5, entry 1) were needed. Interestingly, in contrast to the alkylation of **S1** and **S2**, the cooperative effect resulted in a matched combination for ligand **L1i**, which contains an *R*-binapthyl phosphite group (Table 5, entries 9 and 16).

This phosphite-oxazoline ligand library **L1-L5a-i** was also effective (ee's up to 94%) in the allylic alkylation of the seven-membered ring substrate **S4** (Table 5, entries 17-19).

Table 5. Selected results for the Pd-catalyzed allylic alkylation of **S3** and **S4** using phosphite-oxazoline ligand library **L1-L5a-i**[a]

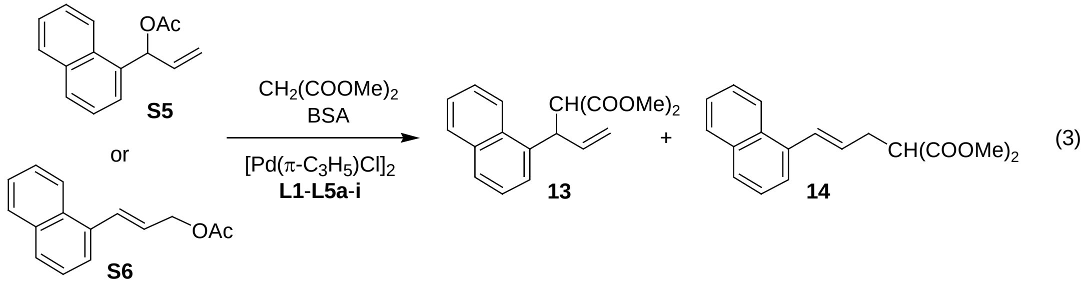
Entry	Ligand	Substrate	% Conv (h)[b]	% ee[c]
1	**L1a**	**S3**	100 (24)	75 (*R*)
2	**L1b**	**S3**	68 (24)	22 (*R*)
3	**L1c**	**S3**	72 (24)	54 (*R*)
4	**L1d**	**S3**	62 (24)	32 (*R*)
5	**L1e**	**S3**	21 (24)	5 (*R*)
6	**L1f**	**S3**	23 (24)	28 (*R*)
7	**L1g**	**S3**	28 (24)	38 (*S*)
8	**L1h**	**S3**	42 (24)	73 (*R*)
9	**L1i**	**S3**	23 (24)	83 (*R*)
10	**L2a**	**S3**	79 (24)	43 (*R*)
11	**L3a**	**S3**	51 (24)	49 (*R*)
12	**L4a**	**S3**	100 (24)	34 (*R*)
13	**L4c**	**S3**	89 (24)	28 (*R*)
14	**L5a**	**S3**	98 (24)	13 (*R*)
15[d]	**L1a**	**S3**	69 (36)	81 (*R*)
16[d]	**L1i**	**S3**	37 (36)	85 (*R*)
17	**L1a**	**S4**	100 (24)	78 (*R*)
18[d]	**L1a**	**S4**	43 (36)	92 (*R*)
19[d]	**L1i**	**S4**	19 (36)	94 (*R*)

[a] All reactions were run at 23 ºC. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Dichloromethane as solvent. 0.9 mol% ligand. [b] Reaction time in hours shown in parentheses. [c] Enantiomeric excesses. The absolute configuration appears in parentheses. [d] T= -5 ºC.

In summary, results were best with ligand **L1i**, which contains the optimal combination of configuration/substituents in the biaryl moiety and in the oxazoline group. Again the replacement of a phosphinite moiety by a phosphite group in the ligand design is seen to lead to higher enantioselectivities than when related ligands **1** are used (ee's up to 74% at 0 °C). These results are among the best that have been reported.[1d,4h,8b,12a,13]

3.2.2.4. Allylic substitution of monosubstituted linear substrates (equation 3)

Encouraged by the excellent results obtained for several disubstituted linear substrates and cyclic substrates, we examined the regio- and stereoselective allylic alkylation 1-(1-naphthyl)allyl acetate **S5** and 1-(1-naphthyl)-3-acetoxyprop-1-ene **S6** with dimethyl malonate (equation 3). It is not only the enantioselectivity of the process that needs to be controlled for these substrates; the regioselectivity is also a problem, because a mixture of regioisomers may be obtained. Most Pd-catalysts developed to date favor the formation of achiral linear product **14** rather than the desired branched isomer **13**. Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[8b,9,14] Because the π-acceptor capacity of the biaryl phosphite moiety in ligands **L1-L5a-i** is high, we expected to enhance the S_N-1 character of the nucleophilic attack, which would favor the formation of the branched isomer **13**.[9]



(3)

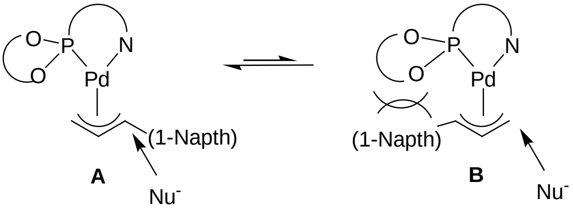
Table 6 summarizes the results obtained with the phosphite-oxazoline ligand library **L1**-**L5a**-**i**. In general, enantioselectivities were high (ee's up to 96 %) and regioselectivities good (up to 85%) for the branched product **13** under standard reaction conditions. The results indicated that the trade-off between regio- and enantioselectivities was best for ligands that contain a phenyl substituent in the oxazoline moiety and trimethylsilyl substituents at the *ortho* positions of the biaryl group. Therefore, ligands **L1c** and **L1i** produced the desired branched isomer **13** as the major product with high enantioselectivity (Table 6, entries 3 and 7). These results are among the best reported for this type of substrates.[8b,9,14]

Table 6. Selected results for the Pd-catalyzed allylic alkylation of monosubstituted substrate **S5** and **S6** using the ligand library **L1**-**L5a**-**i** under standard conditions[a]

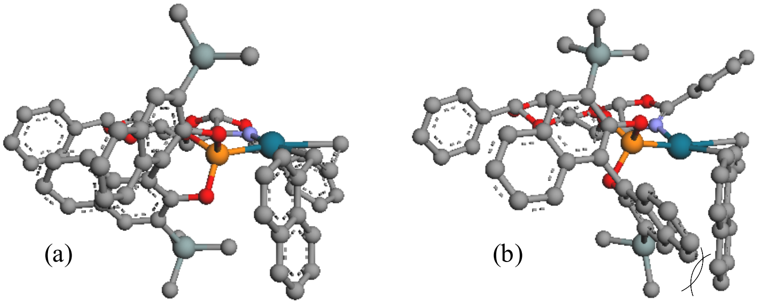
Entry	Ligand	Substrate	% Conv[b] (min)	**13**/**14**[c]	% ee[d]
1	**L1a**	**S5**	100 (60)	65/35	83 (*S*)
2	**L1b**	**S5**	100 (60)	55/45	90 (*S*)
3	**L1c**	**S5**	100 (60)	80/20	90 (*S*)
4	**L1d**	**S5**	100 (60)	65/35	63(*S*)
5	**L1e**	**S5**	100 (60)	55/45	42 (*S*)
6	**L1h**	**S5**	100 (60)	50/50	96 (*S*)
7	**L1i**	**S5**	100 (60)	85/15	88 (*S*)
8	**L2a**	**S5**	100 (60)	55/45	32 (*S*)
9	**L3a**	**S5**	100 (60)	55/45	32 (*S*)
10	**L4a**	**S5**	100 (60)	50/50	78 (*S*)
11	**L4c**	**S5**	100 (60)	75/25	80 (*S*)
12	**L5a**	**S5**	100 (60)	60/40	72 (*S*)
13	**L1c**	**S6**	100 (60)	80/20	91 (*S*)

[a] All reactions were run at 23 ºC. 1 mol% $[PdCl(\eta^3-C_3H_5)]_2$. Dichloromethane as solvent. 1.8 mol% ligand. [b] Reaction time in minutes shown in parentheses. [c] Percentage of branched (**13**) and linear (**14**) isomers [d] Enantiomeric excesses. The absolute configuration appears in parentheses.

It should be noted that the enantioselectivity was best (up to 96%) with ligand **L1h**, but selectivity towards the formation of the desired branched isomer was only moderate (Table 6, entry 6). Interestingly, the **L1i** with the opposite configuration of the binaphthyl phosphite moiety affords product **13** in 85% yield and 88% ee (Table 6, entry 7). Assuming that the nucleophilic attack takes place *trans* to the phosphite moiety (the best π-acceptor moiety) (vide infra) and taking into account that the nucleophilic attack by an S_N-2 type process should take place preferentially at the less substituted allyl terminus (Scheme 3, species **B**),[9] the study of the models (Scheme 4) indicates that the Pd-π-allyl isomer containing ligand **L1i**, with an *R*-binaphthyl, produced a steric repulsion between the phosphite moiety and the naphthyl of the substrate (Scheme 4(b)) that shifts the equilibrium to species **A** and favored the formation of regioisomer **13** (Scheme 3). In contrast, ligand **L1h** has an *S*-binaphthyl moiety and a different spatial orientation of the biaryl phosphite moiety, which reduces the steric repulsion between the phosphite and the substrate **S5** (Scheme 4(a)), thus favoring the formation of the **B** isomer.



Scheme 3. Nucleophilic attack in the Pd-catalyzed allylic alkylation of substrate **S5** with ligand **L1i**.



Scheme 4. Draws of the Pd-π-allyl intermediates containing ligand (a) **L1h** and (b) **L1i**.
H atoms are omitted for clarity.

3.2.2.5. Origin of enantioselectivity. Study of the Pd-π-allyl intermediates

In order to provide further insight into how ligand parameters affect catalytic performance, we studied the Pd-π-allyl compounds **15-24**, $[Pd(\eta^3\text{-allyl})(L)]BF_4$ (L= phosphite-oxazoline ligands), since they are key intermediates in the allylic substitution reactions studied.[1] These ionic palladium complexes, which contain 1,3-diphenyl, 1,3-dimethyl or cyclohexenyl allyl groups, were prepared using the methodology previously described from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 5).[15] The complexes were characterized by elemental analysis and by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments (see Experimental Section) were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments. Unfortunately, it was not possible to obtain any crystal of sufficient quality to perform X ray diffraction measurements.

$$[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2 \quad + \quad L \quad \xrightarrow{AgBF_4} \quad 2\ [Pd(\eta^3\text{-allyl})(L)]BF_4$$

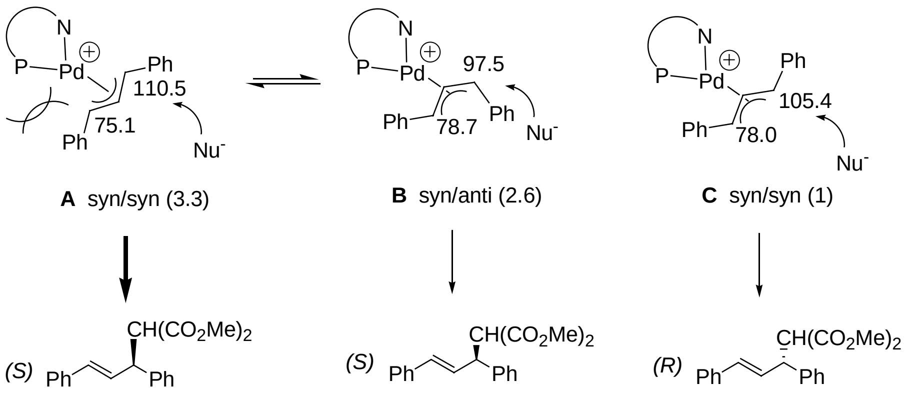
15 allyl = 1,3-Ph_2-C_3H_3; L= **L1a**
16 allyl = 1,3-Ph_2-C_3H_3; L= **L1f**
17 allyl = 1,3-Ph_2-C_3H_3; L= **L1b**
18 allyl = 1,3-Ph_2-C_3H_3; L= **L3a**
19 allyl = 1,3-Me_2-C_3H_3; L= **L1a**
20 allyl = 1,3-Me_2-C_3H_3; L= **L3a**
21 allyl = 1,3-Me_2-C_3H_3; L= **L1c**
22 allyl = *cyclo*-C_6H_9; L= **L1a**
23 allyl = *cyclo*-C_6H_9; L= **L1b**
24 allyl = *cyclo*-C_6H_9; L= **L4a**

Scheme 5. Preparation of $[Pd(\eta^3\text{-allyl})(L)]BF_4$ complexes **15-24**.

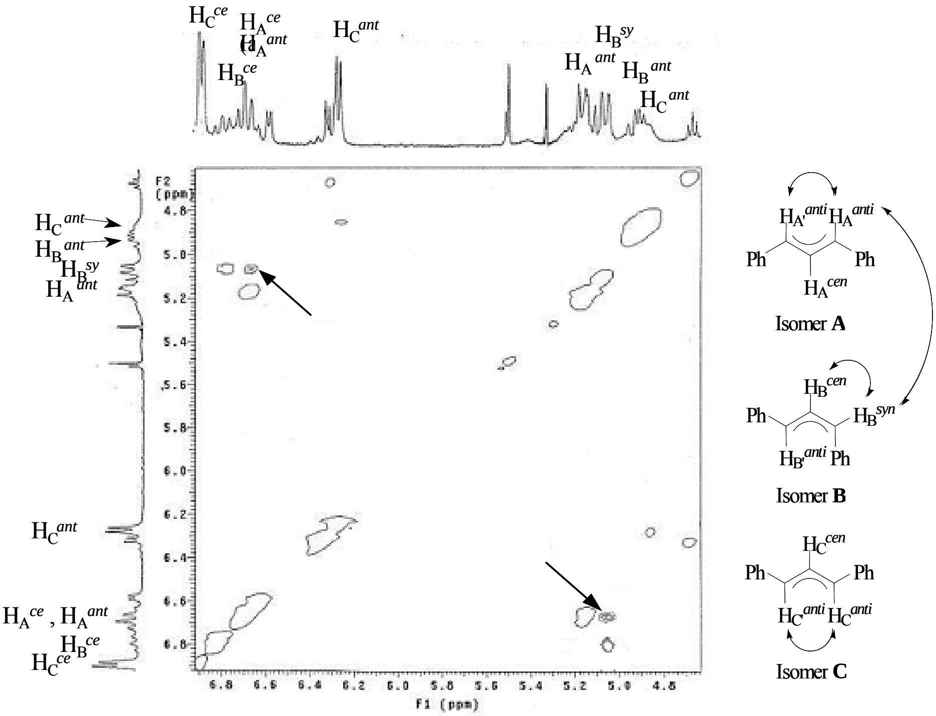
3.2.2.5.1. Palladium 1,3-diphenyl-allyl complexes

When the phosphite-oxazoline ligand library **L1-L5a-i** was used in the allylic substitution of disubstituted hindered substrate **S1**, the catalytic results indicated that for enantioselectivity to be high the combination of the substituent/configuration of the biaryl moieties and oxazoline substituent had to be correct. Therefore, a phenyl substituent in the oxazoline group and an *ortho* and *para* bulky substituted biphenyl phosphite moiety are required if enantioselectivity is to be high. In addition, the ligand-to-palladium ratio was found to have an important effect on enantioselectivity. To understand this catalytic behavior, we decided to study the Pd-π-allyl complexes **15-18** which contain ligands **L1a, L1f**, **L1b** and **L3a**, respectively, at a ligand-to-palladium ratio of 0.9 and 2. While ligand **L1a** containing a phenyl substituent in the oxazoline moiety and a tetrasubstituted *tert*-butyl biphenyl phosphite moiety provided high enantioselectivity (ee's up to 92% at room temperature), ligand **L1b**, with methoxy substituents at the *para* position of the biphenyl phosphite moiety, and ligand **L3a**, with a bulky *tert*-butyl group in the oxazoline group, were less enantioselective (ee's up to 84% and 45%, respectively, at room temperature).

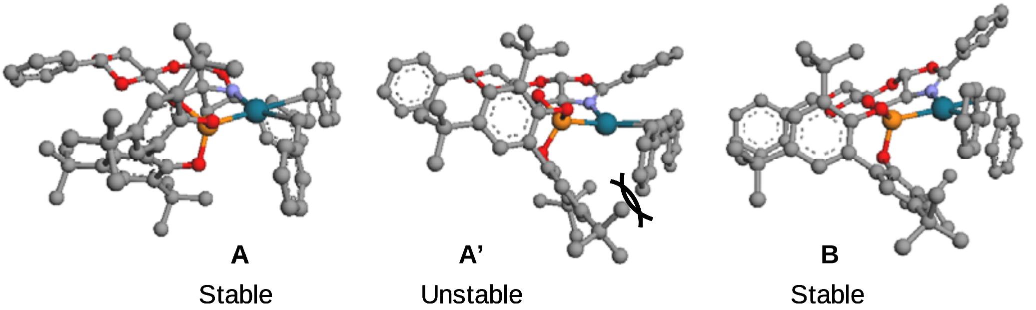
The NMR study of Pd-allyl intermediate **15,** which contains ligand **L1a**, performed at a ligand-to-palladium ratio of 0.9 had a mixture of three isomers in a ratio of 3.3:2.6:1 (see Experimental Section). The major **A** and the minor **C** isomers were assigned by NOE to the two *syn*/*syn endo* and *exo* isomers, while the isomer **B** was assigned to the *syn*/*anti* isomer (Scheme 6). In addition, the NMR spectra showed an equilibrium between isomers **A** and **B** (Scheme 7). Therefore, exchange signals between *syn*/*syn* isomer **A** and *syn*/*anti* isomer **B** were observed in the NOESY spectra. Exchange between H_A^{anti} at 6.69 ppm of the **A** isomer and H_B^{syn} at 5.15 ppm of the **B** isomer confirm η^3- η^1- η^3 movement for the exchange between isomers **A** and **B**.[16] In addition, the fact that no other H^{anty}-H^{syn} exchange is observed indicates that the exchange mechanism takes place by opening selectively one of the terminal Pd-C bond. Accordingly, the study of the models indicated that the change in configuration of the biphenyl phosphite moiety (atropoisomerism) in the major **A** intermediate increases the steric repulsion between the biaryl phosphite group and one of the phenyl substituents in **S1** (Scheme 8, species **A'**). The formation of the *syn*/*anti* isomer **B** minimizes this new steric interaction. Therefore, the open Pd-C bond belongs to the less electrophilic carbon atom containing the substituent that undergoes the biggest steric hindrance with the biaryl phosphite fragment. The study of the models also indicates that in isomer **A** there is a stabilizing π-stacking interaction between the phenyl oxazoline group and one of the phenyl substituents in **S1**. This explains the preferentially formation of *syn*/*syn* isomer **A** respect to *syn*/*syn* isomer **C**. For all isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic carbon atom, the attack at the *syn*/*syn* isomer **A** and *syn*/*anti* isomer **B** will lead to the formation of (*S*)-**8** while the attack at the *syn*/*syn* isomer **C** will lead to the formation of the opposite enantiomer of the alkylation product **8**. The fact that the enantiomeric excess of alkylation product **8** (ee's up to 92% (*S*) at room temperature) is higher than the diastereoisomeric excesses of the Pd-intermediates (de= 72%) indicated that isomer **A** must react faster than isomers **B** and **C**. This is also consistent with the fact that for all isomers, the most electrophilic allylic terminal carbon atom is the one *trans* to the phosphite in the major **A** isomer. Therefore, it can be concluded that the nucleophilic attack takes place preferentially at the allyl terminus *trans* to the phosphite moiety of the major **A** Pd-intermediate.



Scheme 6. Diastereoisomer Pd-allyl intermediates **15** for **S1** with ligand **L1a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.



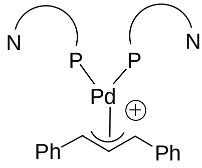
Scheme 7. Part of the NOESY spectrum (6.9-4.7 ppm) of **15**. Arrows indicate NOE exchange signals.



Scheme 8. Draws of the Pd-allyl intermediates **15A**, **15A’** and **15B** for **S1** with ligand **L1a**. H atoms are omitted for clarity.

We next performed the NMR study of Pd-allyl intermediate **15** at a ligand-to-palladium ratio of 2. The ^{31}P NMR indicated that a new species at 137.4 ppm was the major one (40%) (Scheme 9). This species was attributed to Pd-allyl complex **25**

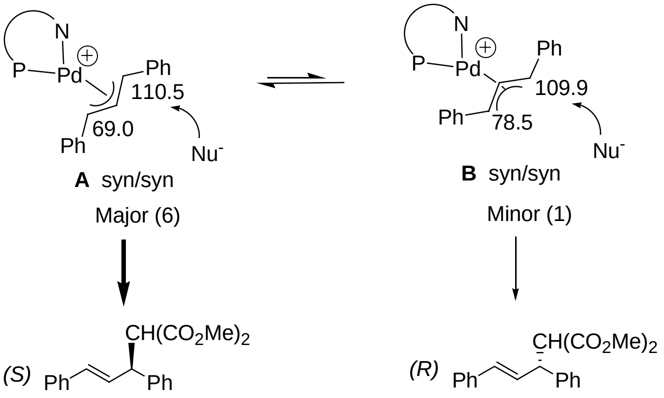
([Pd(η^3-allyl)(**L1a**)$_2$]BF$_4$) in which two phosphite-oxazoline **L1a** ligands are coordinated in a monodentate fashion through the phosphite moiety. This intermediate reacts with less enantiodiscrimination than Pd-bidentate species because it has more degrees of freedom.[17] This explains the drop in enantioselectivity observed at higher ligand-to-palladium ratios than 0.9 when the Pd/**L1a** catalyst system was used (see Figure 4).



25

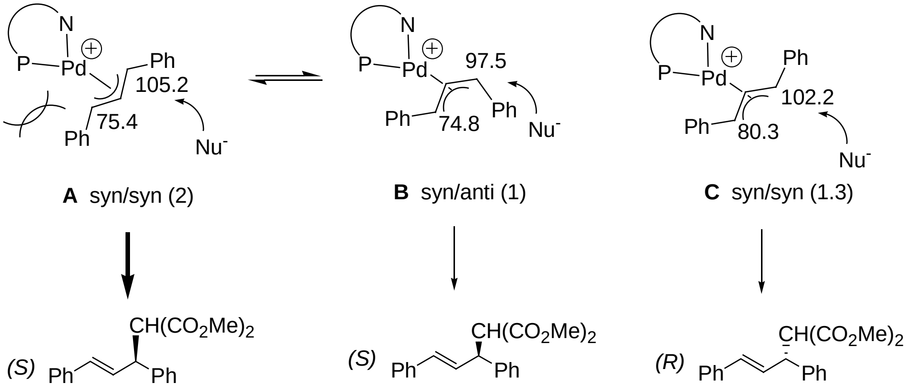
Scheme 9. Pd-intermediate with two phosphite-oxazoline **L1a** ligands coordinated as monodentated ones through the phosphite moiety.

To provide further evidence that the *syn-anti* isomerism observed in complex **15** is caused by the atropoisomerism of the biphenyl moieties, we studied the palladium allyl intermediate [Pd(η^3-1,3-diphenylallyl)(**L1f**)]BF$_4$ (**16**), which contains enantiopure *S*-binaphthyl ligand **L1f**. As expected, and in contrast to complex **15**, the VT-NMR study performed at a ligand-to-palladium ratio of 0.9 showed a mixture of two isomers in a ratio of 6:1 (see Experimental Section). No changes were observed down to –80 °C. Both isomers (**A** and **B**) were unambiguously assigned by NOE to the two *syn*/*syn* endo and exo isomers (Scheme 10). For both isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic carbon terminus and on the basis of the observed stereochemical outcome of the reaction, 81% (*S*) in product **8,** and the fact that the enantiomeric excess of alkylation product **8** is higher than the diastereoisomeric excesses of the Pd-intermediates, the **A** isomer must react faster than the **B** isomer.



Scheme 10. Diastereoisomer Pd-allyl intermediates **16** for **S1** with ligand **L1f**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

We next studied the Pd-allyl intermediate **17** (at a ligand-to-palladium ratio of 0.9) containing ligand **L1b**. This complex has the same substituent in the oxazoline moiety but differs from ligand **L1a** in the *para*-substituents in the biaryl phosphite moiety. The NMR study showed a mixture of three isomers in a ratio of 2:1:1.3 (see Experimental Section). The major **A** and the minor **C** isomers were assigned by NOE to the two *syn*/*syn endo* and *exo* isomers, while the isomer **B** was assigned to the *syn*/*anti* isomer (Scheme 11). As for complex **15**, the NMR spectra showed and equilibrium between isomers **A** and **B**. Again, this *syn*/*syn* – *syn*/*anti* equilibrium is due to the atropoisomerism of the biphenyl phosphite moiety (vide supra). As for complex **15**, it should be noted that, for all isomers, the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety and the isomer **A** reacts faster than the other isomers. Assuming that the nucleophilic attack takes place at the most electrophilic carbon atom, the attack at the *syn*/*syn* isomer **A** and at the *syn*/*anti* isomer **B** will lead to the formation of (*S*)-**8,** while the attack at the *syn*/*syn* isomer **C** will lead to the formation of the opposite enantiomer of alkylation product **8**. Therefore, the fact that the enantioselectivity was lower when the Pd/**L1b** catalyst was used (ee's up to 84%) than when the Pd/**L1a** catalyst was used (ee's up to 92%) may be due to the decrease in the relative amount of species that provides the *S*-enantiomer (**A** and **B**) respect the ones that provides *R*-**8** (**C**) compared to the population of isomers (**A** and **B** respect to **C**) for complex **15**.



Scheme 11. Diastereoisomer Pd-allyl intermediates **17** for **S1** with ligand **L1b**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

Finally, we studied the Pd-allyl intermediate **18** (at a ligand-to-palladium ratio of 0.9) containing ligand **L3a**, which has a different substituent in the oxazoline moiety and provides much lower enantioselectivity (ee's up to 45%) than the previously studied Pd/**L1a** catalyst. In contrast to complexes **15-17** studied above, the NMR spectra showed that species with two phosphite-oxazoline ligands coordinated in a monodentate fashion are the major ones (70%). We believe that this is due to the increase in the steric bulk of the oxazoline moiety because a phenyl (ligands **L1a-b** and **L1f**) was replaced with a *tert*-butyl group (**L3a**). The presence of this species fully accounts for the low enantioselectivity observed for this catalyst.

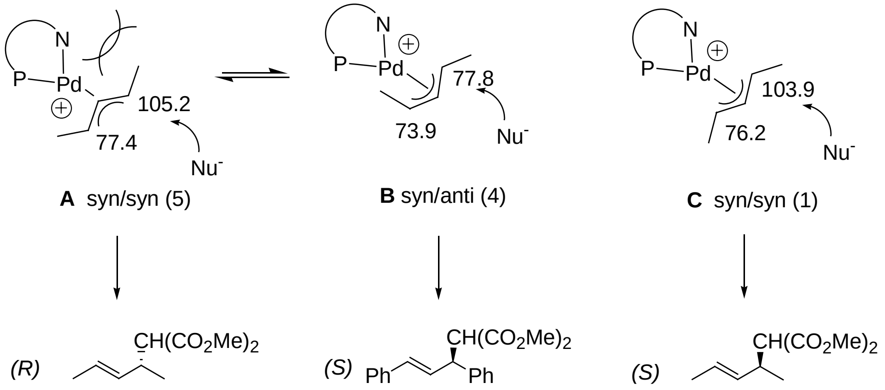
In summary, the study of the allyl intermediates indicates that: (a) changes in the substituents at the biaryl phosphite moieties mean that there are changes in the ratio of the species that provides both enantiomers of alkylation product **8**, while changes in the oxazoline substituents mean that there are changes in the amount of species with ligands coordinated in monodentate fashion and (b) the formation of species with monodentate ligands increases when the ligand-to-palladium ratio is higher than 0.9 and when there is a bulky substituent in the oxazoline moiety. Therefore, if enantioselectivity is to be high, the ligand-to-palladium ratio must be 0.9, and there must be an *ortho* and *para* bulky substituted biphenyl phosphite moiety and a phenyl substituent in the oxazoline group.

3.2.2.5.2. Palladium 1,3-dimethyl-allyl complexes

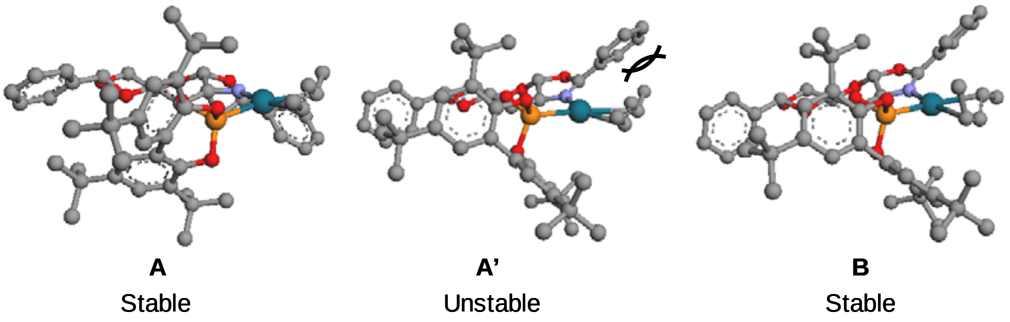
When the phosphite-oxazoline ligand library **L1-5a-i** was used in the allylic substitution of unhindered linear **S2** substrate, the catalytic results revealed that bulky substituents in the oxazoline group decreased enantioselectivities. On the other hand, enantioselectivities were high when bulky substituents were in the *ortho* position of the biphenyl moieties and the *para* positions of the biphenyl moieties were substituted with a group other than hydrogen. The ligand-to-palladium ratio was also found to have an effect on enantioselectivity. To understand this catalytic behavior, we studied the $[Pd(\eta^3\text{-allyl})(L)]BF_4$ complexes **19-21** which contain ligands **L1a**, **L3a** and **L1c**, at a ligand-to-palladium ratio of 0.9 and 2. Thus, while ligand **L1a**, which contains bulky *tert*-butyl groups at the *ortho* and *para* positions of the biaryl moiety, provided good enantioselectivities, ligand **L1c**, without substituents in the *para* positions of the biphenyl moiety, and ligand **L3a**, with a bulky *tert*-butyl group in the oxazoline group, were less enantioselective.

The NMR study of Pd-1,3-dimethyl allyl intermediate **19** at a ligand-to-palladium ratio of 0.9, which contains ligand **L1a**, indicated the presence of a mixture of three isomers at a ratio of 5:4:1 (see Experimental Section). The major **A** and the minor **C** isomers were assigned by NOE to the two *syn*/*syn endo* and *exo* isomers, while the isomer **B** was assigned to the *syn*/*anti* isomer (Scheme 12). In contrast to complex **15**, the major *syn*/*syn* isomer **19A** adopts a W spatial arrangement. This is due to the absence of the favorable π-stacking interaction observed in related complex **15**. The

NMR spectra showed a *syn-anti* equilibrium between isomers **A** and **B**, which was attributed to the atropoisomerism of the biphenyl phosphite in isomer **A** as it was in the related Pd-1,3-diphenylallyl complexes **15** and **17**. However, the study of the models indicates that the change in configuration of the biphenyl phosphite moiety results in a new steric interaction between the oxazoline phenyl group and one of the methyl substituents in **S2** (isomer **A'**, Scheme 13). The formation of the *syn*/*anti* isomer **B** minimizes this steric interaction (Scheme 13). Therefore, the open Pd-C bond belongs to the more electrophilic carbon atom containing the substituent that undergoes the biggest steric hindrance with the phenyl oxazoline fragment. Again, the most electrophilic allyl carbons are *trans* to the phosphite moiety in *syn*/*syn* isomer **A** and *syn*/*syn* isomer **C**, and the carbon in isomer **B** is far less electrophilic ($\Delta(\delta^{13}C) \approx 30$ ppm). Assuming that the nucleophilic attack takes place at the most electrophilic carbon terminus and on the basis of the relative abundance of isomers **A** and **C**, the calculated diastereomeric excess matches the enantiomeric excess obtained experimentally for product **10** (ee = 60% (*R*)).



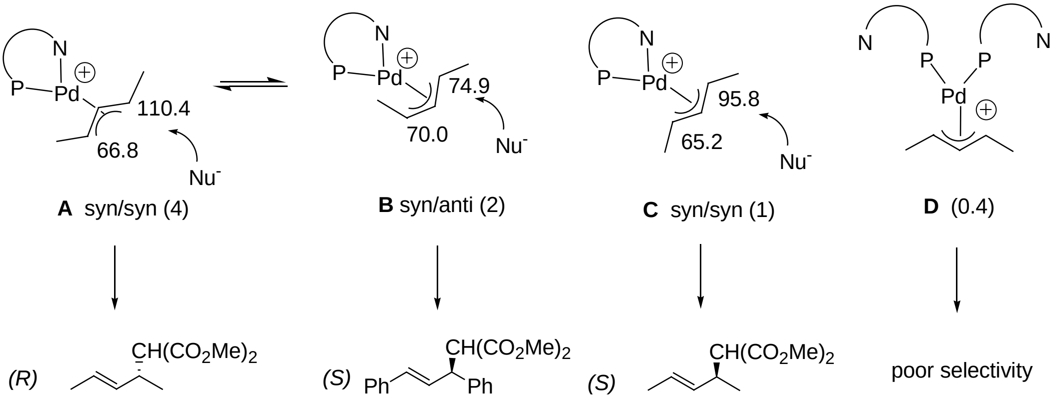
Scheme 12. Diastereoisomer Pd-allyl intermediates **19** for **S2** with ligand **L1a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.



Scheme 13. Draws of the Pd-allyl intermediates **19A**, **19A'** and **19B** for **S2** with ligand **L1a**. H atoms are omitted for clarity.

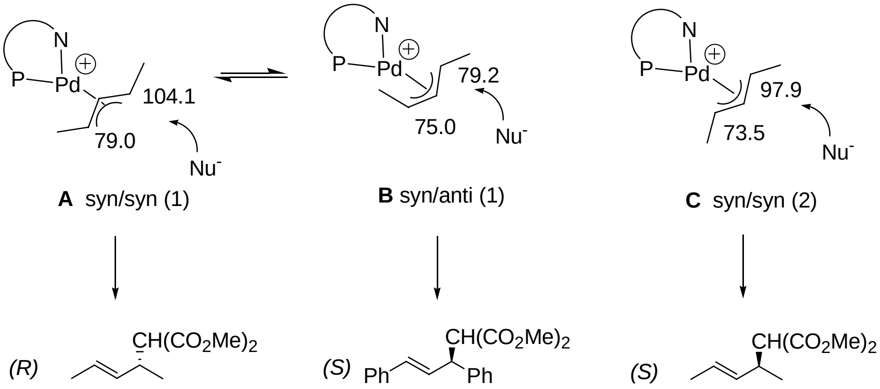
We also performed the NMR study of Pd-allyl intermediate **19** at a ligand-to-palladium ratio of 2. The ^{31}P NMR indicated the presence of a new species (10 %, δ= 136.9 ppm) which was attributed to the Pd-allyl complex in which two phosphite-oxazoline **L1a** ligands are coordinated in a monodentate fashion through the phosphite moiety ([Pd(1,3-dimethyl-allyl)(**L1a**)$_2$]BF$_4$). Interestingly, in contrast to the Pd-1,3-diphenyl allyl intermediate **15**, the amount of this ([Pd(1,3-dimethyl-allyl)(**L1a**)$_2$]BF$_4$) species is lower. This is probably due to the presence of less sterically hindered 1,3-dimethyl allyl and explains why the enantioselectivity observed at higher than 0.9 ligand-to-palladium ratios in the alkylation of **S2** decreased less than in the alkylation of **S1**.

The NMR study of Pd-1,3-dimethyl allyl intermediate **20**, which contains ligand **L3a** with a bulky *tert*-butyl group at the oxazoline, indicated the presence of a mixture of four isomers in a ratio of 4:2:1:0.4 at a ligand-to-palladium ratio of 0.9 (see Experimental Section). Isomers **A**, **B** and **C** were assigned by NOE to the *syn*/*syn endo, syn/anti and syn/syn exo* isomers, respectively, while isomer **D** was attributed to the isomer that contains two ligands coordinated in a monodentate fashion (Scheme 14). As for complex **19**, isomers **A** and **B** were in equilibrium and the most electrophilic allyl carbons were *trans* to the phosphite moiety in *syn*/*syn* isomer **A** and *syn*/*syn* isomer **C**, being the carbon in isomer **B** less electrophilic ($\Delta(\delta^{13}C) \approx 30$ ppm). Therefore, the fact that the enantioselectivity with the Pd/**L3a** catalyst system is lower than with the Pd/**L1a** catalyst system may be due to the presence of less enantioselective isomer **D** and the decrease in the relative amount of isomers **A** and **C** (5:1 ratio for complex **19** and 4:1 ratio for complex **20**).



Scheme 14. Diastereoisomer Pd-allyl intermediates **20** for **S2** with ligand **L3a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

We next studied Pd-allyl intermediate **21** (at a ligand-to-palladium ratio of 0.9) containing ligand **L1c**. This complex has the same substituent in the oxazoline moiety as complex **19** but differs from ligand **L1a** in the substituents of the biphenyl phosphite moiety. The NMR study showed a mixture of three isomers at a ratio of 1:1:2 (see Experimental Section) (Scheme 15). As for complex **19**, these were assigned to the two *syn*/*syn endo* (**A**) and *exo* (**C**) isomers and to the *syn*/*anti* isomer (**B**). Again, isomers **A** and **B** are in equilibrium and the most electrophilic allyl carbon atoms are found in species **A** and **C**. However, in contrast to complex **19**, the allylic carbon atoms *trans* to the phosphite moiety in isomer **A** is much more electrophilic than the one in isomer **C** ($\Delta(\delta^{13}C) \approx 7$ ppm). Therefore, isomer **A** should react faster than isomer **C**. Despite this, the fact that isomer **C** is the major one may explain why the enantioselectivity with this catalytic system is lower than with Pd/**L1a**.



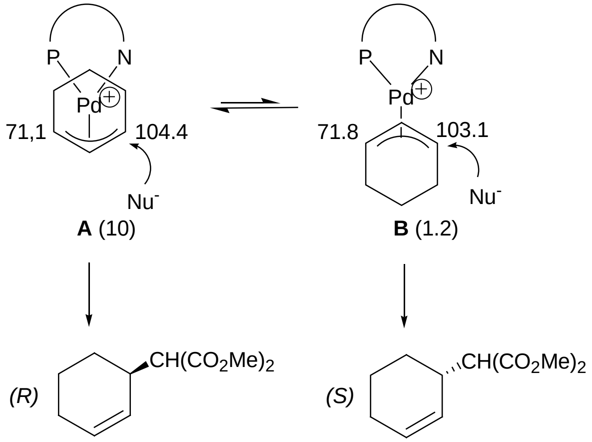
Scheme 15. Diastereoisomer Pd-allyl intermediates **21** for **S2** with ligand **L1c**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

In summary, the study of the allyl intermediate indicates that: (a) changes in the substituents in the biaryl phosphite moieties mean that there are also changes in the ratio of the species that provide both enantiomers of alkylation product **10**, while changes in the oxazoline substituents mean that there are changes in both the ratio of species and the amount of species with ligands coordinated in monodentate fashion and (b) the formation of species with monodentate ligands increases when the ligand-to-palladium ratio is higher than 0.9.

3.2.2.5.3. Palladium 1,3-cyclohexenyl-allyl complexes

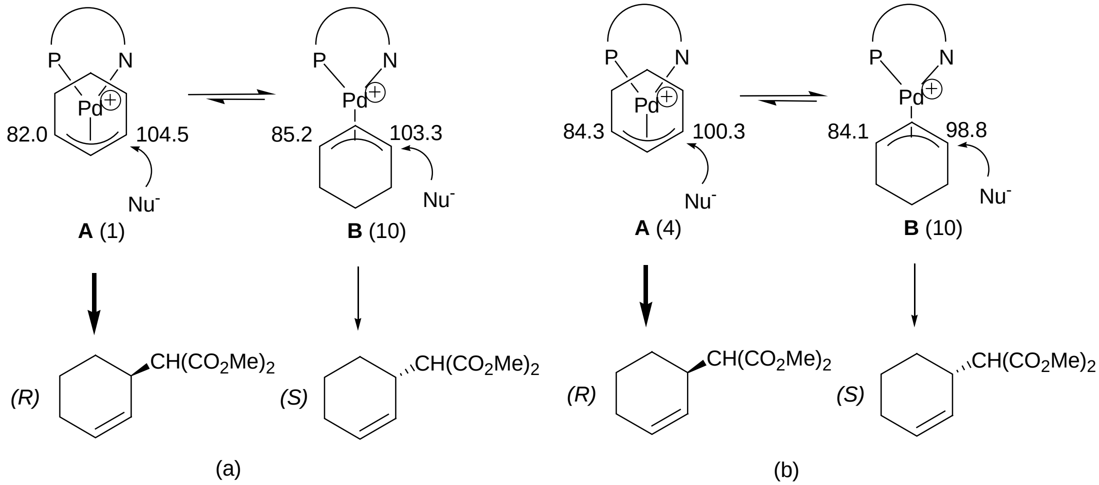
When the phosphite-oxazoline ligand library **L1-5a-i** was used in the allylic substitution of cyclic substrate **S3**, the catalytic results revealed that bulky *tert*-butyl substituents in *ortho* and *para* positions of the biphenyl phosphite moiety and a phenyl substituent in the oxazoline group are needed if enantioselectivity is to be high. To understand this catalytic behavior we studied the Pd-π-allyl complexes **22-24** which contain ligands **L1a**, **L4a** and **L1b**. Thus, while ligand **L1a**, which contains bulky *tert*-butyl groups at the *ortho* and *para* positions of the biaryl moiety, provided good enantioselectivities, ligand **L1b**, with methoxy substituent in the *para* positions of the biphenyl moiety, and ligand **L4a**, with a methyl substituent in the oxazoline group, were less enantioselective.

The NMR study of Pd-1,3-cyclohexenyl allyl intermediate **22**, which contains ligand **L1a**, showed a mixture of two isomers at a ratio of 10:1.2 at a ligand-to-palladium ratio of 0.9 (see Experimental Section). Both isomers were assigned by NOE to the two *syn*/*syn* isomers (Scheme 16). For both isomers, the carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic carbon terminus and on the basis of the relative abundance of isomers **A** and **B**, the calculated diastereomeric excess matched the enantiomeric excess obtained experimentally for product **11** (ee = 75% (*R*)).



Scheme 16. Diastereoisomer Pd-allyl intermediates **22** for **S3** with ligand **L1a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

The NMR study of Pd-1,3-cyclohexenyl allyl intermediates **23** and **24**, which contain ligands **L1b** and **L4a**, showed a mixture of two isomers in a ratio of 1:10 and 4:10, respectively (at a ligand-to-palladium ratio of 0.9, see Experimental Section). All the species were assigned by NOE to the two *syn*/*syn* isomers possible for each Pd-allyl complex (Scheme 17). For all isomers, the carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. However, in contrast to complex **22**, the nucleophilic attack at the major isomers **B** will lead to the formation of (*S*)-**11** product. Therefore, the difference between the diastereoisomeric ratio and enantioselectivity observed in the alkylation of **S3** (d.e= 80% (*S*) vs ee= 22% (*R*) for Pd/**L1b**; d.e= 40% (*S*) vs ee= 34% (*R*) for Pd/**L4a**) indicates that the nucleophile reacts faster with the minor isomer **A**.



Scheme 17. Diastereoisomer Pd-allyl intermediates (a) **23** for **S3** with ligand **L1b** and (b) **24** for **S3** with ligand **L4a**. The relative amounts of each isomer are drawn in parenthesis. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

In summary, the NMR data indicates that the fact that the enantioselectivity obtained for Pd/**L1b** and Pd/**L4a** was lower than for Pd/**L1a** may be due to the decrease in the relative amount of species that provide the *R*-enantiomer (**A**) with respect to the ones that provide *S*-**11** (**B**) compared to the population observed for Pd/**L1a** complex.

3.2.3. Conclusions

A library of phosphite-oxazoline ligands **L1-L5a-i** has been synthesized for the Pd-catalyzed allylic substitution reactions of several substrates with different electronic and steric properties. These series of ligands have four main advantages: (1) they can be prepared in a few steps from readily available D-glucosamine; (2) the π-acceptor character of the phosphite moiety increases reaction rates; (3) the flexibility and larger bite angle created by the biaryl phosphite moiety increases versatility and (4) their modular nature enables the substituents in the oxazoline moiety and the substituents/configurations in the biaryl phosphite moiety to be easily and systematically varied. Thus, by carefully selecting the ligand components, high enantioselectivities (ee’s up to 99%) and good activities have been achieved in a wide range of substrates with different steric and electronic properties. In general, activities and enantioselectivies are mainly affected by the substituents in both the oxazoline and the phosphite moieties and the cooperative effect between stereocenters. However, the effect of these parameters depends on each substrate class.

The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy makes it possible to understand the catalytic behaviour observed. This study also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety.

To sum up, the combination of high enantioselectivities (ee's up to 99%), high activities, high substrate versatility and the low cost of the ligands opens up the allylic alkylation of a wide range of substrates to the potential effective use of readily available and highly modular sugar-based phosphite-oxazoline ligands. The efficiency of this ligand design is also corroborated by the fact that these Pd-phosphite-oxazoline catalysts provided higher enantioselectivity than their phosphinite-oxazoline analogues in several substrates types.

3.2.4. Experimental section

3.2.4.1. General comments

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[18] Racemic substrates **S1-S6** were prepared as previously reported.[19-22] $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$,[23] $[Pd(\eta^3\text{-}1,3\text{-}Me_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[24] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{-}Cl)]_2$[25] were prepared as previously described. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were done based on ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

3.2.4.2. General procedure for the preparation of ligands L1-L5a-i

The corresponding phosphorochloridite (3.0 mmol) produced *in situ* was dissolved in toluene (12.5 mL) and pyridine (1.14 mL, 14 mmol) was added. The corresponding hydroxyl-oxazoline compound (2.8 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (12.5 mL) to which pyridine (1.14 mL, 14 mmol) was added. The oxazoline solution was transferred slowly at 0 ºC to the solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 ºC, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt_3= 100/1) to produce the corresponding ligand as a white solid.

L1a: Yield: 0.98 g, 44 %.^{31}P ($CDCl_3$), δ: 149.9 (s). ^{1}H ($CDCl_3$), δ: 1.29 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.64 (m, 2H, H-5, H-6’), 3.80 (m, 1H, H-4), 4.34 (m, 1H, H-6), 4.41 (dd, 1H, H-2, $^3J_{1\text{-}2}$= 7.6 Hz, $^3J_{2\text{-}3}$= 3.8 Hz), 4.73 (m, 1H, H-3), 5.47 (s, 1H, H-7), 6.05 (d, 1H, H-1, $^3J_{1\text{-}2}$= 7.6 Hz), 7.09-7.47 (m, 12H, CH=), 7.96 (m, 2H, CH=).^{13}C ($CDCl_3$), δ: 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 63.2 (C-5), 68.9 (C-6), 69.3 (C-2), 77.2 (C-3), 79.6 (C-4), 101.7 (C-7), 102.1 (C-1), 124.4 (CH=), 125.5 (CH=), 126.4 (CH=), 126,7 (CH=), 126.9 (CH=), 127.2 (CH=), 128.3 (CH=), 128.5 (CH=), 128,6 (CH=), 129.2 (CH=), 129.3 (CH=), 132.1 (C), 132.6 (C), 133.4 (C), 137.1 (C), 138.1 (C), 140.1 (C), 140.7 (C), 145.4 (C), 146.4 (C), 146.8 (C), 163.7 (C). Anal. calcd (%) for $C_{48}H_{58}NO_7P$: C 72.80, H 7.38, N 1.77; found: C 72.61, H 7.39, N 1.72.

L1b: Yield: 0.40 g, 20 %.^{31}P ($CDCl_3$), δ: 148.9 (s). ^{1}H ($CDCl_3$), δ= 1.35 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 3.70 (m, 2H, H-6’, H-5), 3.81 (s, 3H, OMe), 3.81 (s, 3H, Ome), 3. 83 (m, 1H, H-4), 4.39 (m, 1H, H-6), 4.46 (dd, 1H, H-2, $^3J_{2,1}$= 7.6 Hz, $^3J_{2,3}$= 3.2 Hz), 4.77 (m, 1H, H-3), 5.52 (s, 1H, H-7), 6.10 (d, 1H, H-1, $^3J_{1,2}$= 7.6 Hz), 6.71 (m, 2H, CH=), 6.98 (m, 2H, CH=), 7.1-7.6 (m, 8H, CH=), 7.99 (m, 2H, CH=). ^{13}C ($CDCl_3$), δ: 31.1 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 55.8 (OCH_3), 63.1 (C-5), 68.9 (C-6), 69.3(C-2), 77.4 (C-3), 79.5 (C-4), 101.7 (C-7), 102.1 (C-1), 112.8 (CH=), 113.0 (CH=), 114.5 (CH=), 125.5 (CH=), 126.4 (CH=), 127.2 (CH=), 128.3 (CH=), 128.5 (CH=), 128.6 (CH=), 128.7 (CH=), 129.3 (CH=), 132.1 (C), 134.2 (C), 137.1 (C), 138.1 (C), 140.1 (C), 140.8 (C), 145.4 (C), 146.3 (C), 146.8 (C), 156.4 (C), 157.1 (C), 173.9 (C). Anal. calcd (%) for $C_{42}H_{46}NO_7P$: C 68.19, H 6.27, N 1.89; found: C 68.09, H 6.31, N 1.81.

L1c: Yield: 0.50 g, 25 %.^{31}P ($CDCl_3$), δ: 150.3 (s). ^{1}H ($CDCl_3$), δ: 0.36 (s, 9H, $Si(CH_3)_3$), 0.43 (s, 9H, $Si(CH_3)_3$), 3.68 (m, 2H, H-6’, H-5), 3.92 (m, 1H, H-4), 4.41 (dd, 1H, H-6, $^3J_{6\text{-}6'}$=9.6 Hz, $^3J_{6\text{-}5}$= 4.2 Hz), 4.46 (dd, 1H, H-2, $^3J_{2\text{-}1}$= 7.6 Hz, $^3J_{2\text{-}3}$= 2.4), 4.87 (m, 1H, H-3), 5.52 (s, 1H, H-7), 6.12 (d, 1H, H-1, $^3J_{1\text{-}2}$= 7.6 Hz), 7.2-7.5 (m, 14H, CH=), 8.01 (m, 2H, CH=). ^{13}C ($CDCl_3$), δ: 0.3 ($Si(CH_3)_3$), 0.4 ($Si(CH_3)_3$), 62.9 (C-5), 69 (C-6), 69.8 (C-2), 75.9 (d, C-3, $J_{C\text{-}P}$= 13.6 Hz), 80.2 (d, C-4, $J_{C\text{-}P}$= 3.2 Hz), 101.2 (C-7), 101.5 (C-1), 124.8 (CH=), 125.0 (CH=), 125.5 (CH=), 126.5 (CH=), 127.0 (C), 128.3 (CH=), 128.4 (CH=), 128.6 (CH=), 129.2 (CH=), 129.3 (CH=), 132.0 (C), 133.9 (C), 132.1 (CH=), 132.5 (CH=), 132.6 (CH=), 135.3 (CH=), 137.1 (C), 138.4 (C), 163.9 (C). Anal. calcd (%) for $C_{38}H_{42}NO_7PSi_2$: C 64.11, H 5.95, N 1.97; found: C 64.19, H 5.91, N 1.89.

L1d: Yield: 0.17 g, 28 %. ^{31}P NMR (C_6D_6) δ= 150.3 (s). ^{1}H NMR (C_6D_6) δ= 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.50 (m, 1H, H-6'), 3.67 (m, 2H, H-4, H-5), 4.20 (m, 1H, H-6), 4.31 (m, 1H, H-2), 4.81 (m, 1H, H-3), 5.47 (s, 1H, H-7), 5.70 (d, 1H, H-1, $^2J_{1\text{-}2}$= 7.5 Hz), 7.0-8.3 (m, 14H, CH=). ^{13}C NMR (C_6D_6) δ= 17.2 (CH_3), 17.4 (CH_3), 21.1 (CH_3), 63.9 (C-5), 68.9 (C-6), 69.5 (C-2), 78.6 (d, C-3, $^2J_{c\text{-}p}$= 20 Hz), 79.0 (C-4), 102.2 (C-7), 103.5 (C-1), 126.0 (CH=), 127.2 (CH=), 129.0 (CH=), 129.3 (CH=), 129.4 (CH=), 129.6 (CH=), 131.0 (C), 131.6 (CH=), 131.7 (CH=), 132.3 (CH=), 134.3 (CH=), 138.2 (C), 138.31 (C), 139.3 (C), 146.9 (C), 164.1 (C). Anal. calcd (%) for $C_{36}H_{34}NO_7P$: C 69.33, H 5.50, N 2.25; found: C 69.39, H 5.52, N 2.23.

L1e: Yield: 0.14 g, 12 %.^{31}P ($CDCl_3$), δ: 152.9 (s). ^{1}H ($CDCl_3$), δ: 3.78 (m, 2H, H-5, H-6'), 3.84 (m, 1H, H-4), 4.44 (m, 2H, H-6, H-2), 4.65 (m, 1H, H-3), 5.68 (s, 1H, H-7), 6.19 (d, 1H, H-1, $^3J_{1,2}$= 7.2 Hz), 7.15-7.59 (m, 12H, CH=), 8.03 (m, 2H, CH=). ^{13}C ($CDCl_3$), δ: 63.4 (C-5), 68.8 (C-6), 69.1 (C-2), 77.4 (C-3), 79.0 (C-4), 101.7 (C-7), 102.8 (C-1), 122.3 (CH=), 122.6 (CH=), 125.4 (CH=), 125.5 (CH=), 126.3 (CH=), 128.4 (CH=), 128.5 (CH=), 128.6 (CH=), 128.7 (CH=), 129.2 (CH=), 129.3 (CH=), 129.4 (CH=), 130.0 (CH=), 132.3 (C), 137.1 (C), 138.1 (C), 163.9 (C). Anal. calcd (%) for $C_{32}H_{26}NO_7P$: C 67.72, H 4.62, N 2.47; found: C 67.84, H 4.66, N 2.39.

L1f: Yield: 0.1 g, 16 %. ^{31}P NMR (C_6D_6) δ= 154.7 (s). ^{1}H NMR (C_6D_6) δ= 3.40 (m, 1H, H-6'), 3.53 (m, 2H, H-4, H-5), 4.06 (m, 2H, H-2, H-6), 4.66 (m, 1H, H-3), 5.44 (d, 1H, H-1, ${}^{2}J_{1\text{-}2}$= 7.8 Hz), 5.51 (s, 1H, H-7), 6.90-8.15 (m, 22H, CH=). ^{13}C NMR (C_6D_6) δ= 63.7 (C-5), 68.8 (C-6), 69.3 (C-2), 78.7 (d, C-3, ${}^{2}J_{c\text{-}p}$= 13.7 Hz), 78.8 (C-4), 101.9 (C-7), 103.5 (C-1), 122.6 (CH=), 123.0 (CH=), 125.5 (CH=), 126.9 (CH=), 127.0 (CH=), 127.8 (CH=), 127.9 (CH=), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.6 (CH=), 130.2 (CH=), 131.1 (CH=), 132.0 (C), 132.3 (CH=), 132.4 (C), 133.7 (C), 133.9 (C), 138.3 (C), 148.7 (C), 148.8 (C), 164.1 (C). Anal. calcd (%) for $C_{40}H_{30}NO_7P$: C 71.96, H 4.53, N 2.10; found: C 71.59, H 4.59, N 2.07.

L1g: Yield: 0.08 g, 12 %. ^{31}P NMR (C_6D_6) δ= 154.2 (s). ^{1}H NMR (C_6D_6) δ= 3.27 (m, 1H, H-6'), 3.45 (m, 2H, H-4, H-5), 4.02 (m, 1H, H-6), 4.14 (dd, 1H, H-2, ${}^{2}J_{2\text{-}1}$= 7.6 Hz, ${}^{2}J_{2\text{-}3}$= 5.2 Hz), 4.62 (m, 1H, H-3), 5.29 (s, 1H, H-7), 5.55 (d, 1H, H-1, ${}^{2}J_{1\text{-}2}$= 7.6 Hz), 6.90-8.15 (m, 22H, CH=). ^{13}C NMR (C_6D_6) δ= 63.1 (C-5), 68.7 (C-6), 69.2 (C-2), 78.3 (d, C-3, ${}^{2}J_{c\text{-}p}$= 19.0 Hz), 78.7 (C-4), 101.7 (C-7), 103.5 (C-1), 122.5 (CH=), 123.5 (CH=), 125.5 (CH=), 125.6 (CH=), 126.9 (CH=), 127.0 (CH=), 127.1 (CH=), 127.8 (CH=), 127.9 (CH=), 128.8 (C), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.5 (CH=), 129.8 (C), 130.4 (CH=), 131.1 (CH=), 132.1 (C), 132.4 (CH=), 133.6 (C), 133.8 (CH=), 138.5 (CH=), 147.8 (C), 147.9 (C), 164.2 (C). Anal. calcd (%) for $C_{40}H_{30}NO_7P$: C 71.96, H 4.53, N 2.10; found: C 71.74, H 4.56, N 2.12.

L1h: Yield: 0.40 g, 17 %. ^{31}P NMR (C_6D_6) δ: 151.7 (s, 1P). ^{1}H NMR (C_6D_6) δ: 0.57 (s, 9H, $Si(CH_3)_3$), 0.65 (s, 9H, $Si(CH_3)_3$), 3.37 (m, 1H, H-6'), 3.52 (m, 1H, H-5), 3.91 (m, 1H, H-4), 4.02 (m, 1H, H-6), 4.23 (m, 1H, H-2), 5.12 (m, H-3), 5.40 (d, 1H, H-1, ${}^{3}J_{1\text{-}2}$= 8.0 Hz), 5.47 (s, 1H, H-7), 6.86-8.19 (m, 22H, CH=). ^{13}C NMR (C_6D_6) δ: 0.6 ($Si(CH_3)_3$), 0.9 ($Si(CH_3)_3$), 63.1 (C-5), 69.1 (C-6), 70.1 (C-2), 77.0 (d, C-3, ${}^{2}J_{c\text{-}p}$= 13.6 Hz), 80.5 (d, C-4, ${}^{2}J_{c\text{-}p}$= 4.1 Hz), 101.8 (C-7), 102.2 (C-1), 110.4 (C), 124.4 (CH=), 124.7 (CH=), 125.5 (CH=), 126.0 (CH=), 127.1 (CH=), 127.3 (CH=), 127.4 (CH=), 127.6 (CH=), 127.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.4 (CH=), 128.6 (CH=), 128.8 (CH=), 129.1 (CH=), 129.1 (CH=), 129.3 (CH=), 129.3 (CH=), 129.7 (CH=), 130.2 (C), 131.7 (C), 132.0 (C), 132.8 (C), 135.0 (C), 135.1 (C), 135.4 (C), 137.4 (CH=), 138.0 (CH=), 138.2 (CH=), 138.6 (CH=), 152.5 (C), 152.9 (C), 163.6 (C). Anal. calcd (%) for $C_{46}H_{46}NO_7PSi_2$: C 68.04, H 5.71, N 1.72; found: C 68.12, H 5.78, N 1.69.

L1i: Yield: 0.40 g, 17 %. ^{31}P NMR (C_6D_6) δ: 150.5 (s). ^{1}H NMR (C_6D_6) δ: 0.41 (s, 9H, $Si(CH_3)_3$), 0.55 (s, 9H, $Si(CH_3)_3$), 3.18 (m, 1H, H-6'), 3.49 (m, 1H, H-5), 3.66 (m, 1H, H-4), 3.90 (m, 1H, H-6), 4.41 (dd, 1H, H-2, $^{3}J_{2\text{-}1}$= 8.0 Hz, $^{3}J_{2\text{-}3}$= 2.4 Hz) 5.00 (s, 1H, H-7), 5.04 (m, 1H, H-3), 5.64 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 8.0 Hz), 6.80-8.01 (m, 22H, CH=). ^{13}C NMR (C_6D_6) δ= 0.5 ($Si(CH_3)_3$), 0.9 ($Si(CH_3)_3$), 63.4 (C-5), 69.0 (C-6), 70.9 (C-2), 77.1 (d, C-3, $^{2}J_{c\text{-}p}$= 9.1 Hz), 81.0 (C-4), 101.7 (C-1), 102.0 (C-7), 124.4 (C), 124.7 (C), 125.4 (CH=), 126.0 (CH=), 127.2 (CH=), 127.3 (CH=), 127.6 (CH=), 127.7 (CH=), 127.8 (CH=), 128.1 (CH=), 128.4 (CH=), 128.6 (CH=), 128.7 (CH=), 128.8 (CH=), 128.9 (CH=), 129.0 (CH=), 129.1 (CH=), 129.2 (CH=), 129.6 (C), 131.6 (CH=), 131.9 (CH=), 132.3 (CH=), 133.1 (CH=), 134.9 (C), 135.1 (C), 137.3 (CH=), 137.8 (CH=), 138.0 (C), 152.8 (C), 153.0 (C), 164.3 (C). Anal. calcd (%) for $C_{46}H_{46}NO_7PSi_2$: C 68.04, H 5.71, N 1.72; found: C 68.23, H 5.84, N 1.63.

L2a: Yield: 0.94 g, 35 %.^{31}P ($CDCl_3$), δ: 148.3 (s). ^{1}H ($CDCl_3$), 1.22 (m, 6H, CH_3, ^{i}Pr), 1.29 (s, 18H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 2.60 (sp, 1H, CH, ^{i}Pr, $^{3}J_{H\text{-}H}$= 7.2 Hz), 3.56 (m, 1H, H-5), 3.67 (m, 1H, H-6'), 3.80 (m, 1H, H-4), 4.21 (m, 1H, H-2), 4.38 (dd, 1H, H-6, $^{2}J_{6\text{-}6'}$= 10 Hz, $^{3}J_{6\text{-}5}$= 4.4Hz), 4.66 (m, 1H, H-3), 5.51 (s, 1H, H-7), 5.89 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 7.6 Hz), 7.1-7.6 (m, 9H, CH=). ^{13}C ($CDCl_3$), δ: 19.5 (CH_3, ^{i}Pr), 19.6 (CH_3, ^{i}Pr), 28.6 (CH, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 63.0 (C-5), 68.8 (C-2), 68.9 (C-6), 77.4 (C-3), 79.7 (C-4), 101.5 (C-1 and C-7), 124.4 (CH=), 125.5 (CH=), 126.3 (CH=), 126.6 (CH=), 126.9 (CH=), 128.4 (CH=), 128.5 (CH=), 129.2 (CH=), 129.3 (CH=), 132.2 (C), 133.1 (C), 137.1 (C), 138.1 (C), 140.1

(C), 140.7 (C), 146.3 (C), 146.7 (C), 172.0 (C). Anal. calcd (%) for $C_{45}H_{60}NO_7P$: C 71.31, H 7.98, N 1.85; found: C 71.44, H 7.89, N 1.88.

L3a: Yield: 1.13 g, 48 %.^{31}P ($CDCl_3$), δ: 148.5 (s). ^{1}H ($CDCl_3$), δ: 1.27 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 18H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 3.58 (m, 1H, H-5), 3.70 (m, 1H, H-6'), 3.79 (dd, 1H, H-4, ${}^{3}J_{4,5}$= 9.6 Hz, ${}^{3}J_{4,3}$= 7.6 Hz), 4.24 (dd, 1H, H-2, ${}^{3}J_{2,1}$= 8.0 Hz, ${}^{3}J_{2,3}$= 3.6 Hz), 4.41 (dd, 1H, H-6, ${}^{3}J_{6,6'}$= 10.8 Hz, ${}^{3}J_{6,5}$= 5.2 Hz), 4.65 (m, 1H, H-3), 5.54 (s, 1H, H-7), 5.91 (d, 1H, H-1, ${}^{3}J_{1,2}$= 8.0 Hz), 7.1-7.6 (m, 9H, CH=). ^{13}C ($CDCl_3$), δ: 27.7 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 63.0 (C-5), 68.9 (C-2 and C-6), 77.5 (d, C-3, $J_{C,P}$= 6.9 Hz), 79.6 (C-4), 101.5 (C-7), 101.9 (C-1), 124.4 (CH=), 125.5 (CH=), 126.3 (CH=), 126.6 (CH=), 126.9 (CH=), 128.4 (CH=), 128.5 (CH=), 129.2 (CH=), 129.3 (CH=), 132.7 (C), 133.5 (C), 137.1 (C), 138.1 (C), 140.1 (C), 140.8 (C), 145.4 (C), 146.3 (C), 146.8 (C), 173.9 (C). Anal. calcd (%) for $C_{46}H_{62}NO_7P$: C 71.57, H 8.10, N 1.81; found: C 71.64, H 8.05, N 1.78.

L4a: Yield: 0.28 g, 15 %.^{31}P ($CDCl_3$), δ: 148.0 (s). ^{1}H ($CDCl_3$), δ: 1.33 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 2.05 (d, CH_3, $J_{H\text{-}P}$= 1.6 Hz), 3.62 (m, 2H, H-5, H-6'), 3.82 (dd, 1H, H-4, ${}^{3}J_{4\text{-}3}$= 9.6 Hz, ${}^{3}J_{4\text{-}5}$= 6.8 Hz), 4.20 (bd, 1H, H-2, ${}^{3}J_{1\text{-}2}$= 7.6 Hz), 4.36 (dd, 1H, H-6, ${}^{3}J_{6\text{-}6'}$= 10 Hz, ${}^{3}J_{6\text{-}5}$= 4.4 Hz), 4.74 (m, 1H, H-3), 5.50 (s, 1H, H-7), 5.89 (d, 1H, H-1, ${}^{3}J_{1\text{-}2}$= 7.6 Hz), 7.1-7.5 (m, 9H, CH=). ^{13}C ($CDCl_3$), δ: 14.5 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.7 (C, ^{t}Bu), 63.0 (C-5), 69.0 (C-6), 69.2 (C-2), 76.4 (d, C-3, $J_{C\text{-}P}$= 19.7 Hz), 80.2 (b, C-4), 101.4 (C-1), 101.8 (C-7), 124.4 (CH=), 125.5 (CH=), 126.4 (CH=), 126,7 (CH=), 126.9 (CH=), 128.4 (CH=), 128.5 (CH=), 129.3 (CH=), 137.1 (C), 138.1 (C), 140.2 (C), 140.5 (C), 146.4 (C), 146.7 (C), 165.2 (C).

L4c: Yield: 0.22g, 30 %. ^{31}P NMR (C_6D_6) δ= 150.2 (s). ^{1}H NMR (C_6D_6) δ= 0.42 (s, 9H, CH_3-Si), 0.50 (s, 9H, CH_3-Si), 1.55 (d, 3H, CH_3, J_{H-P}= 1.6 Hz), 3.37 (m, 1H, H-6'), 3.52 (m, 1H, H-5), 3.84 (dd, 1H, H-4, $^{3}J_{4-3}$= 10 Hz, $^{3}J_{4-5}$= 7.6 Hz), 4.05 (m, 1H, H-2), 4.10 (m, 1H, H-6, $^{3}J_{6-6'}$= 10 Hz, $^{3}J_{6-5}$= 5.2 Hz), 4.91 (m, 1H, H-3), 5.37 (d, 1H, H-1, $^{2}J_{1-2}$= 7.6 Hz), 5.40 (s, 1H, H-7), 7.0-7.6 (m, 11H, CH=). ^{13}C NMR (C_6D_6) δ= 0.8 (CH_3-Si), 14.2 (CH_3), 63.4 (C-5), 69.4 (C-6), 70.2 (C-2), 72.2 (d, C-3, $^{2}J_{c-p}$= 13.7 Hz), 80.9 (C-4), 101.9 (C-1), 102.4 (C-7), 125.6 (CH=), 125.8 (CH=), 127.4 (CH=), 128.9 (CH=), 129.6 (CH=), 129.9 (C), 132.3 (C), 132.4 (C), 133.3 (CH=), 134.4 (C), 136.0 (CH=), 136.1 (CH=), 137.9 (C), 138.2 (C), 153.8 (C), 155.1 (C), 164.0 (C). Anal. calcd (%) for $C_{43}H_{56}NO_7P$: C 70.76, H 7.73, N 1.92; found: C 70.79, H 7.74, N 1.95.

L4h: Yield: 0.59 g, 35 %. ^{31}P NMR (C_7D_8), δ: 152.2 (b). ^{1}H NMR (C_6D_6) δ: 0.50 (s, 9H, $Si(CH_3)_3$), 0.59 (s, 9H, $Si(CH_3)_3$), 1.45 (s, 3N, CH_3-N), 3.34 (m, 1H, H-6'), 3.46 (m, 1H, H-5), 3.82 (m, 1H, H-4), 3.86 (m, 1H, H-2), 4.06 (m, 1H, H-6), 4.87 (m, H-3), 5.18 (d, 1H, H-1, $^{3}J_{1-2}$= 7.6 Hz), 5.45 (s, 1H, H-7), 6.80-8.13 (m, 15H, CH=). ^{13}C NMR (C_6D_6) δ: 0.6 ($Si(CH_3)_3$), 0.8 ($Si(CH_3)_3$), 13.9 (N-CH_3), 63.1 (C-5), 69.2 (C-6), 69.6 (C-2), 77.2 (d, C-3, $^{2}J_{c-p}$= 15.1 Hz), 80.2 (C-4), 101.7 (C-1), 102.2 (C-7), 125.3 (CH=), 125.4 (CH=), 126.0 (C), 127.2 (CH=), 127.3 (CH=), 128.7 (CH=), 128.9 (CH=), 129.0 (CH=), 129.5 (CH=), 129.7 (CH=), 131.6 (C), 131.9 (C), 132.8 (C), 135.1 (C), 137.3 (CH=), 138.0 (CH=), 153.0 (C), 164.4 (C). Anal. calcd (%) for $C_{41}H_{44}NO_7PSi_2$: C 65.66, H 5.91, N 1.87; found: C 65.77, H 5.98, N 1.91.

L5a: Yield: 0.90 g, 40 %. ^{31}P ($CDCl_3$), δ: 150.1 (s, 1P). ^{1}H ($CDCl_3$), δ: 1.41 (s, 9H, CH_3, ^{t}Bu), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 2H, CH_2), 1.85 (s, 9H, CH_3, ^{t}Bu), 3.50 (m, 1H, H-6'), 3.65 (m, 1H, H-5), 3.81 (m, 1H, H-4), 4.13 (m, 1H, H-2), 4.24 (dd, 1H, H-6, $^{2}J_{6-6'}$= 10.0 Hz, $^{3}J_{6-5}$= 4.8 Hz), 4.92 (m, 1H, H-3), 5.49 (d, 1H, H-1, $^{3}J_{1-2}$= 7.6 Hz), 5.53 (s, 1H, H-7), 7.14-7.83 (m, 14H, CH=). ^{13}C ($CDCl_3$), δ: 15.2 (CH_2), 32.9 (CH_3, ^{t}Bu), 33.1 (CH_3, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 37.1 (C, ^{t}Bu), 37.2 (C, ^{t}Bu), 64.4 (C-5), 70.1 (C-6), 70.4 (C-2), 79.0 (d, C-3, $^{2}J_{C-P}$= 20.5 Hz), 81.0 (C-4), 103.0 (C-7), 103.2 (C-1), 125.7 (CH=), 125.8 (CH=), 127.0 (CH=), 128,1 (CH=), 128.4 (CH=), 128.6 (CH=), 129.1 (CH=), 129.4 (CH=), 129,6 (CH=), 129.7 (CH=), 129.9 (CH=), 130.4 (CH=), 130.7 (CH=), 135.1 (C), 135.7 (C), 139.2 (C), 139.2 (C), 141.9 (C), 142.5 (C), 147.6 (C), 147.9 (C), 148.3(C), 146.8 (C), 165.7 (C). Anal. calcd (%) for $C_{49}H_{60}NO_7P$: C 73.02, H 7.50, N 1.74; found: C 73.14, H 7.54, N 1.73.

3.2.4.3. General procedure for the preparation of [Pd(η^3-allyl)(L)]BF_4 complexes 15-25

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (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 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated adding hexane as pale yellow solids.

[Pd(η^3-1,3-diphenylallyl)(L1a)]BF_4 (15). Isomer **A** (48%): ^{31}P NMR (CD_2Cl_2), δ: 134.3 (s). ^1H NMR (CD_2Cl_2), δ: 1.3-1.9 (36H, CH_3, *t*-Bu), 4.01 (m, 2H, H-5, H-6'), 4.24 (m, 1H, H-3), 4.34 (m, 1H, H-6), 4.41 (m, 1H, H-4), 4.54 (m, 1H, H-2), 5.18 (m, 1H, CH terminal), 5.49 (s, 1H, H-7), 6.27 (m, 1H, H-1), 6.69 (m, 2H, CH terminal, CH central), 7.0-7.9 (m, 24 H, CH=). ^{13}C NMR(CD_2Cl_2), δ: 31.2-33.0 (CH_3, *t*-Bu), 34.8-36.3 (C, *t*-Bu), 65.2 (C-5), 67.0 (C-2), 67.9 (C-6), 74.7 (m, C-3), 75.1 (m, CH terminal), 83.4 (C-4), 101.6 (C-7), 104.9 (C-1), 110.5 (m, CH terminal), 111.8 (m, CH central), 123-150 (aromatic carbons), 170.4 (C=N). Isomer **B** (38%): ^{31}P NMR (CD_2Cl_2), δ: 134.8 (s). ^1H NMR (CD_2Cl_2), δ: 1.3-1.9 (27H, CH_3, *t*-Bu), 3.84 (m, 1H, H-6'), 4.01 (m, 2H, H-5, H-6), 4.24 (m, 1H, H-3), 4.41 (m, 1H, H-4), 4.64 (m, 1H, H-2), 4.93 (m, 1H, CH terminal), 5.15 (m, 1H, CH terminal), 5.53 (s, 1H, H-7), 6.31 (m, 1H, H-1), 6.87 (m, 1H, CH central), 7.0-7.9 (m, 24 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 31.2-33.0 (CH_3, *t*-Bu), 34.8-36.3 (C, *t*-Bu), 61.5 (C-6), 65.2 (C-5), 67.0 (C-2), 74.7 (m, C-3), 78.7 (CH terminal), 83.4 (C-4), 97.5 (d, CH terminal, $J_{C\text{-}P}$= 33.4 Hz), 101.3 (C-7), 104.9 (C-1), 112.7 (m, CH central), 123-150 (aromatic carbons), 169.4 (C=N). Isomer **C** (14%): ^{31}P NMR (CD_2Cl_2), δ: 133.1 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.3-1.9 (27H, CH_3, *t*-Bu), 3.84 (m, 1H, H-6'), 4.01 (m, 2H, H-5, H-6), 4.24 (m, 1H, H-3), 4.41 (m, 1H, H-4), 4.54 (m, 1H, H-2), 4.92 (m, 1H, CH terminal), 5.49 (s, 1H, H-7), 6.28 (m, 1H, CH terminal), 6.34 (m, 1H, H-1), 6.79 (m, 1H, CH central), 7.0-7.9 (m, 24 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 31.2-33.0 (CH_3, *t*-Bu), 34.8-36.3 (C, *t*-Bu), 61.5 (C-6), 65.7 (C-5), 67.0 (C-2), 74.7 (m, C-3), 78.0 (m, CH terminal), 83.4 (C-4), 101.6 (C-7), 104.9 (C-1), 105.4 (m, CH terminal), 111.6 (m, CH central), 123-150 (aromatic carbons), 170.4 (C=N). Anal. calcd (%) for $C_{63}H_{71}BF_4NO_7PPd$: C 64.21, H 6.07, N 1.19; found: C 64.33, H 6.15, N 1.23.

[Pd(η^3-1,3-diphenylallyl)(L1a)$_2$]BF$_4$ (25). ^{31}P NMR (CD_2Cl_2), δ: 137.4 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.3-1.9 (36H, CH_3, *t*-Bu), 3.82 (m, 2H, H-6'), 4.01 (m, 8H, H-3, H-4, H-5, H-6), 4.87 (m, 2H, H-2), 5.11 (m, 1H, CH terminal), 5.15 (m, 1H, CH terminal), 5.62 (s, 2H, H-7), 6.20 (m, 2H, H-1), 6.72 (m, 1H, CH central), 6.8-7.9 (m, 38 H, CH=).

[Pd(η^3-1,3-diphenylallyl)(L1f)]BF$_4$ (16). Isomer **A** (86%): ^{31}P NMR (CD_2Cl_2), δ: 143.4 (s). ^{1}H NMR (CD_2Cl_2), δ: 3.21 (m, 1H, H-6'), 3.74 (m, 2H, H-5, H-3), 3.99 (m, 1H, H-6), 4.41 (m, 1H, H-4), 4.95 (m, 1H, CH terminal), 5.02 (m, 1H, H-2), 5.15 (s, 1H, H-7), 6.05 (m, 1H, CH central), 6.35 (m, 2H, H-1, CH=), 6.55 (m, 1H, CH=), 6.75 (m, 1H, CH terminal), 7.0-8.5 (m, 20 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 65.6 (C-5), 66.6 (C-2), 67.7 (C-6), 69.0 (m, CH terminal), 74.4 (m, C-3), 81.2 (C-4), 101.6 (C-7), 105.6 (C-1), 110.5 (d, CH terminal, $J_{C\text{-}P}$= 25.8 Hz), 112.8 (m, CH central), 132-147 (aromatic carbons), 170.4 (C=N). Isomer **B** (14%): ^{31}P NMR (CD_2Cl_2), δ: 142.9 (s). ^{1}H NMR (CD_2Cl_2), δ: 3.21 (m, 1H, H-6'), 3.42 (m, 1H, H-6), 3.59 (m, 1H, H-5), 3.64 (m, 1H, H-3), 4.38 (m, 1H, CH terminal), 4.59 (m, 1H, H-4), 4.68 (m, 1H, H-2), 5.32 (s, 1H, H-7), 6.05 (m, 1H, CH central), 6.20 (m, 1H, H-1), 6.35 (m, 1H, CH=), 6.52 (m, 2H, CH terminal, CH=), 6.9-8.5 (m, 20 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 62.6 (C-6), 66.0 (C-5), 66.6 (C-2), 74.1 (m, C-3), 78.5 (CH terminal), 84.0 (C-4), 101.6 (C-7), 105.6 (C-1), 109.9 (d, CH terminal, $J_{C\text{-}P}$= 25.8 Hz), 112.7 (m, CH central), 132-147 (aromatic carbons), 170.9 (C=N). Anal. calcd (%) for $C_{55}H_{43}BF_4NO_7PPd$: C 62.67, H 4.11, N 1.33; found: C 62.71, H 4.09, N 1.32.

[Pd(η^3-1,3-diphenylallyl)(L1b)]BF_4 (17). Isomer **A** (46%): ^{31}P NMR (CD_2Cl_2), δ: 134.1 (s). ^1H NMR (CD_2Cl_2), δ: 1.36 (s, 9H, CH_3, *t*-Bu), 1.68 (s, 9H, CH_3, *t*-Bu), 3.71 (m, 1H, H-6'), 3.79 (m, 3H, CH_3O), 3.82 (m, 3H, CH_3O), 3.95 (m, 1H, H-5), 4.14 (m, 1H, H-3), 4.25 (m, 1H, H-4), 4.36 (m, 1H, H-6), 4.51 (m, 1H, H-2), 5.10 (m, 1H, CH terminal), 5.56 (s, 1H, H-7), 6.21 (m, 1H, H-1), 6.59 (m, 1H, CH central), 6.93 (m, 1H, CH terminal), 6.8-7.9 (m, 24 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 31.7-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 55.9-56.3 (CH_3O), 65.4 (C-5), 67.2 (C-2), 68.3 (C-6), 74.8 (m, C-3), 75.4 (CH terminal), 81.8 (C-4), 101.3 (C-7), 105.2 (d, CH terminal, $J_{C\text{-}P}$= 28.6 Hz), 105.5 (C-1), 114.2 (m, CH central), 124-158 (aromatic carbons), 169.2 (C=N). Isomer **B** (23%): ^{31}P NMR (CD_2Cl_2), δ: 133.5 (s). ^1H NMR (CD_2Cl_2), δ: 1.36 (s, 9H, CH_3, *t*-Bu), 1.78 (s, 9H, CH_3, *t*-Bu), 3.71 (m, 1H, H-6'), 3.80 (m, 3H, CH_3O), 3.83 (m, 3H, CH_3O), 3.91 (m, 1H, H-6), 3.95 (m, 1H, H-5), 4.14 (m, 1H, H-3), 4.25 (m, 1H, H-4), 4.58 (m, 1H, H-2), 4.95 (m, 1H, CH terminal), 5.53 (s, 1H, H-7), 6.26 (m, 1H, H-1), 6.39 (m, 1H, CH terminal), 6.92 (m, 1H, CH terminal), 6.8-7.9 (m, 24 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 31.7-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 55.9-56.3 (CH_3O), 61.8 (C-6), 64.9 (C-5), 67.2 (C-2), 74.8 (m, 2C, C-3, CH terminal), 81.8 (C-4), 97.5 (d, CH terminal, $J_{C\text{-}P}$= 32 Hz), 101.3 (C-7), 105.5 (C-1), 113.9 (m, CH central), 124-158 (aromatic carbons), 170.6 (C=N). Isomer **C** (31%): ^{31}P NMR (CD_2Cl_2), δ: 132.5 (s). ^1H NMR (CD_2Cl_2), δ: 1.39 (s, 9H, CH_3, *t*-Bu), 1.42 (s, 9H, CH_3, *t*-Bu), 3.71 (m, 1H, H-6'), 3.82 (m, 3H, CH_3O), 3.92 (m, 1H, H-6), 3.94 (m, 3H, CH_3O), 3.95 (m, 1H, H-5), 4.14 (m, 1H, H-3), 4.25 (m, 1H, H-4), 4.36 (m, 1H, H-6), 4.51 (m, 1H, H-2), 4.91 (m, 1H, CH terminal), 5.17 (m, 1H, CH terminal), 5.56 (s, 1H, H-7), 6.21 (m, 1H, H-1), 6.57 (m, 1H, CH central), 6.8-7.9 (m, 24 H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 31.7-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 55.9-56.3 (CH_3O), 61.8 (C-6), 64.3 (C-5), 67.2 (C-2), 74.8 (m, C-3), 80.3 (m, CH terminal), 81.8 (C-4), 101.3 (C-7), 102.2 (m, CH terminal), 105.5 (C-1), 114.7 (m, CH central), 124-158 (aromatic carbons), 170.4 (C=N). Anal. calcd (%) for $C_{57}H_{59}BF_4NO_9PPd$: C 60.79, H 5.28, N 1.24; found: C 60.82, H 5.29, N 1.31.

[Pd(η^3-1,3-diphenylallyl)(L3a)$_2$]BF$_4$ (18). ^{31}P NMR (CD_2Cl_2), δ: 135.8 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.88 (s, 18H, CH_3, N-*t*-Bu), 1.33 (s, 18H, CH_3, *t*-Bu), 1.39 (s, 18H, CH_3, *t*-Bu), 1.42 (s, 18H, CH_3, *t*-Bu), 1.72 (s, 18H, CH_3, *t*-Bu), 3.77 (m, 2H, H-6’), 3.99 (m, 6H, H-3, H-4, H-5), 4.07 (m, 2H, H-6), 4.93 (m, 2H, H-2), 5.07 (m, 1H, CH terminal), 5.16 (m, 1H, CH terminal), 5.56 (s, 2H, H-7), 6.24 (m, 2H, H-1), 6.67 (m, 1H, CH central), 6.8-7.9 (m, 28 H, CH=).

[Pd(η^3-1,3-dimethylallyl)(L1a)]BF$_4$ (19). Isomer **A** (50%): ^{31}P NMR (CD_2Cl_2), δ: 134.2 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.85-0.95 (m, 6H, CH_3), 1.2-1.7 (36H, CH_3, *t*-Bu), 3.56 (m, 1H, CH terminal), 4.03 (m, 2H, H-6, H-6’), 4.09 (m, 2H, H-5, H-4), 4.51 (m, 1H, H-3), 4.69 (m, 1H, H-2), 4.98 (m, 1H, CH terminal), 5.37 (m, 1H, CH central), 5.62 (s, 1H, H-7), 6.69 (m, 1H, H-1), 7.1-8.1 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 18.5 (CH_3), 18.7 (CH_3), 31.6-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 62.3 (C-6), 65.2 (C-5), 67.5 (C-2), 75.3 (C-4), 77.4 (m, CH terminal), 81.3 (C-3), 101.8 (C-7), 105.2 (m, C-1, CH terminal), 122.9 (m, CH central), 125-152 (aromatic carbons), 170.1 (C=N). Isomer **B** (40%): ^{31}P NMR (CD_2Cl_2), δ: 133.9 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.85-0.95 (m, 6H, CH_3), 1.2-1.7 (36H, CH_3, *t*-Bu), 3.64 (m, 1H, CH terminal), 4.00 (m, 1H, CH terminal), 4.03 (m, 1H, H-6’), 4.09 (m, 2H, H-5, H-4), 4.42 (m, 1H, H-6), 4.63 (m, 2H, H-2, H-3), 5.42 (m, 1H, CH central), 5.62 (s, 1H, H-7), 6.62 (m, 1H, H-1), 7.1-8.1 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 18.2 (CH_3), 18.7 (CH_3), 31.6-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 65.2 (C-5), 67.5 (C-2), 68.1 (C-6), 73.9 (m, CH terminal), 75.3 (C-4), 77.8 (m, CH terminal), 81.3 (C-3), 101.8 (C-7), 105.2 (C-1), 123.6 (m, CH central), 125-152 (aromatic carbons), 170.1 (C=N). Isomer **C** (10%): ^{31}P NMR (CD_2Cl_2), δ: 132.8 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.85-0.95 (m, 6H, CH_3), 1.2-1.7 (36H, CH_3, *t*-Bu), 3.80 (m, 1H, CH terminal), 4.03 (m, 2H, H-6, H-6’), 4.09 (m, 2H, H-5, H-4), 4.51 (m, 1H, H-3), 4.67 (m, 1H, H-2), 4.84 (m, 1H, CH terminal), 5.37 (m, 1H, CH central), 5.62 (s, 1H, H-7), 6.62 (m, 1H, H-1), 7.1-8.1 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 18.3 (CH_3), 18.7 (CH_3), 31.6-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 62.3 (C-6), 65.2 (C-5), 67.5 (C-2), 75.3 (C-4), 76.2 (m, CH terminal), 81.3 (C-3), 101.8 (C-7), 103.9 (m, CH terminal), 105.2 (C-1), 123.2 (m, CH central), 125-152 (aromatic carbons), 170.1 (C=N). Anal. calcd (%) for $C_{53}H_{67}BF_4NO_7PPd$: C 60.38, H 6.41, N 1.33; found: C 60.45, H 6.52, N 1.36.

[Pd(η^3-1,3-dimethylallyl)(L3a)]BF_4 (20). Isomer **A** (54%): ^{31}P NMR (CD_2Cl_2), δ: 134.3 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.00 (m, 3H, CH_3), 1.2-1.7 (36H, CH_3, *t*-Bu), 1.72 (m, 3H, CH_3), 3.65 (m, 1H, CH terminal), 3.82 (m, 2H, H-4, H-6’), 4.00 (m, 1H, H-5), 4.12 (m, 1H, H-3), 4.42 (m, 1H, H-6), 4.44 (m, 1H, H-2), 5.30 (m, 1H, CH central), 5.45 (m, 1H, CH terminal), 5.60 (m, 1H, H-7), 6.34 (m, 1H, H-1), 7.1-8.0 (m, 9H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.0 (CH_3), 19.7 (CH_3), 31.0-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 65.2 (C-5), 66.8 (m, CH terminal), 67.1 (C-2), 68.5 (C-6), 75.1 (C-4), 81.5 (C-3), 101.6 (C-7), 104.7 (C-1), 110.4 (m, CH terminal), 122.1 (m, CH central), 122-151 (aromatic carbons), 181.7 (C=N). Isomer **B** (27%): ^{31}P NMR (CD_2Cl_2), δ: 134.0 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.80 (m, 3H, CH_3), 1.2-1.7 (36H, CH_3, *t*-Bu), 1.8 (m, 3H, CH_3), 3.70 (m, 1H, CH terminal), 3.82 (m, 2H, H-4, H-6’), 4.00 (m, 2H, H-5, H-6), 4.19 (m, 1H, CH terminal), 4.12 (m, 1H, H-3), 4.62 (m, 1H, H-2), 5.60 (m, 2H, H-7, CH central), 6.40 (m, 1H, H-1), 7.1-8.0 (m, 9H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 17.9 (CH_3), 19.4 (CH_3), 31.0-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 62.0 (C-6), 65.2 (C-5), 67.1 (C-2), 70.0 (m, CH terminal), 74.9 (m, CH terminal), 75.1 (C-4), 81.5 (C-3), 101.6 (C-7), 104.7 (C-1), 122.8 (m, CH central), 122-151 (aromatic carbons), 182.5 (C=N). Isomer **C** (14%): ^{31}P NMR (CD_2Cl_2), δ: 133.9 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.62 (m, 3H, CH_3), 1.2-1.7 (39H, CH_3, *t*-Bu, CH_3), 3.65 (m, 1H, CH terminal), 3.82 (m, 2H, H-4, H-6’), 4.00 (m, 2H, H-5, H-6), 4.18 (m, 1H, CH terminal), 4.54 (m, 1H, H-2), 5.30 (m, 1H, CH central), 5.60 (m, 1H, H-7), 6.37 (m, 1H, H-1), 7.1-8.0 (m, 9H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 17.4 (CH_3), 19.1 (CH_3), 31.0-33.0 (CH_3, *t*-Bu), 35.0-36.5 (C, *t*-Bu), 61.6 (C-6), 65.1 (C-5), 65.2 (m, CH terminal), 67.1 (C-2), 75.1 (C-4), 81.5 (C-3), 95.8 (m, CH terminal), 101.6

(C-7), 104.7 (C-1), 122.0 (m, CH central), 122-151 (aromatic carbons), 181.7 (C=N). Isomer **D** (5%): ^{31}P NMR (CD_2Cl_2), δ: 135.0 (s). Anal. calcd (%) for $C_{51}H_{71}BF_4NO_7PPd \cdot 0.05C_{97}H_{133}BF_4N_2O_{14}P_2Pd$: C 59.48, H 6.94, N 1.36; found: C 59.52, H 7.01, N 1.41.

[Pd(η^3-1,3-dimethylallyl)(L1c)]BF$_4$ (21). Isomer **A** (25%): ^{31}P NMR (CD_2Cl_2), δ: 137.3 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.40-0.65 (18H, CH_3-Si), 0.89 (m, 3H, CH_3), 1.31 (m, 3H, CH_3), 3.96 (m, 3H, CH terminal, H-6, H-6'), 4.07 (m, 1H, H-5), 4.29 (m, 1H, H-4), 4.56 (m, 1H, H-3), 4.83 (m, 1H, H-2), 4.95 (m, 1H, CH terminal), 5.53 (m, 1H, CH central), 5.60 (s, 1H, H-7), 6.83 (m, 1H, H-1), 7.4-8.2 (m, 16H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 0.2-0.6 (CH_3-Si), 17.3-18.9 (CH_3), 61.4 (C-6), 66.1 (C-5), 67.5 (C-2), 74.8 (C-4), 79.0 (m, CH terminal), 83.2 (C-3), 101.8 (C-7), 104.1 (m, CH terminal), 106.1 (C-1), 122.5 (m, CH central), 123-138 (aromatic carbons), 164.6 (C=N). Isomer **B** (25%): ^{31}P NMR (CD_2Cl_2), δ: 137.1 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.40-0.65 (18H, CH_3-Si), 1.01 (m, 3H, CH_3), 1.45 (m, 3H, CH_3), 3.82 (m, 1H, CH terminal), 3.90 (m, 1H, CH terminal), 3.95 (m, 1H, H-6'), 4.07 (m, 1H, H-5), 4.29 (m, 1H, H-4), 4.44 (m, 2H, H-6, H-3), 4.63 (m, 1H, H-2), 5.43 (m, 1H, CH central), 5.60 (s, 1H, H-7), 6.62 (m, 1H, H-1), 7.4-8.2 (m, 16H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 0.2-0.6 (CH_3-Si), 17.3-18.9 (CH_3), 66.1 (C-5), 67.5 (C-2), 67.9 (C-6), 74.8 (C-4), 75.0 (m, CH terminal), 79.2 (m, CH terminal), 83.2 (C-3), 101.8 (C-7), 106.1 (C-1), 122.5 (m, CH central), 123-138 (aromatic carbons), 164.8 (C=N). Isomer **C** (50%): ^{31}P NMR (CD_2Cl_2), δ: 136.7 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.40-0.65 (18H, CH_3-Si), 1.02 (m, 3H, CH_3), 1.45 (m, 3H, CH_3), 3.96 (m, 3H, CH terminal, H-6, H-6'), 4.07 (m, 1H, H-5), 4.22 (m, 1H, CH terminal), 4.29 (m, 1H, H-4), 4.43 (m, 1H, H-3), 4.72 (m, 1H, H-2), 5.53 (m, 1H, CH central), 5.60 (s, 1H, H-7), 6.67 (m, 1H, H-1), 7.4-8.2 (m, 16H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 0.2-0.6 (CH_3-Si), 17.3-18.9 (CH_3), 61.4 (C-6), 66.1 (C-5), 67.5 (C-2), 73.5 (m, CH terminal), 74.8 (C-4), 83.2 (C-3), 97.9 (m, CH terminal), 101.8 (C-7), 106.1 (C-1), 122.5 (m, CH central), 123-138 (aromatic carbons), 164.9 (C=N). Anal. calcd (%) for $C_{43}H_{51}BF_4NO_7PPdSi_2$: C 53.01, H 5.28, N 1.44; found: C 53.09, H 5.31, N 1.48.

[Pd(η^3-1,3-cyclohexenylallyl)(L1a)]BF_4 (22). Isomer **A** (89%): ^{31}P NMR (CD_2Cl_2), δ: 136.2 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.06 (m, 2H, CH_2), 1.34 (s, 9H, CH_3, *t*-Bu), 1.42 (s, 9H, CH_3, *t*-Bu), 1.55 (s, 9H, CH_3, *t*-Bu), 1.57 (s, 9H, CH_3, *t*-Bu), 1.70 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 3.95 (m, 1H, H-6’), 4.02 (m, 1H, CH terminal), 4.14 (m, 1H, H-5), 4.46 (m, 2H, H-4, H-6), 4.64 (m, 1H, H-3), 4.79 (m, 1H, H-2), 5.26 (m, 1H, CH central), 5.36 (m, 1H, CH terminal), 5.66 (s, 1H, H-7), 6.77 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.1-7.9 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.8 (m, CH_2), 27.9 (m, CH_2), 29.0 (m, CH_2), 31.5-32.1 (CH_3, *t*-Bu), 35.1-36.3 (C, *t*-Bu), 65.8 (C-5), 68.0 (C-2), 68.6 (C-6), 71.1 (d, CH terminal, $J_{C\text{-}P}$= 8.2 Hz), 81.8 (m, C-3), 84.5 (C-4), 101.6 (C-7), 104.4 (d, CH terminal, $J_{C\text{-}P}$= 36.4 Hz), 105.5 (C-1), 111.5 (m, CH central), 125-150 (aromatic carbons), 171.4 (C=N). Isomer **B** (11%): ^{31}P NMR (CD_2Cl_2), δ: 137.0 (s). ^{1}H NMR (CD_2Cl_2), δ: 0.94 (m, 2H, CH_2), 1.35 (s, 9H, CH_3, *t*-Bu), 1.40 (s, 9H, CH_3, *t*-Bu), 1.49 (s, 9H, CH_3, *t*-Bu), 1.53 (s, 9H, CH_3, *t*-Bu), 1.70 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 3.95 (m, 1H, H-6’), 4.14 (m, 2H, H-5, H-6), 4.36 (m, 1H, CH terminal), 4.46 (m, 1H, H-4), 4.55 (m, 1H, H-2), 4.64 (m, 1H, H-3), 5.26 (m, 1H, CH central), 5.36 (m, 1H, CH terminal), 5.64 (s, 1H, H-7), 6.71 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.1-7.9 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.8 (m, CH_2), 27.9 (m, CH_2), 29.0 (m, CH_2), 31.5-32.1 (CH_3, *t*-Bu), 35.1-36.3 (C, *t*-Bu), 62.0 (C-6), 65.8 (C-5), 68.0 (C-2), 71.8 (d, CH terminal, $J_{C\text{-}P}$= 6 Hz), 81.8 (m, C-3), 84.5 (C-4), 101.6 (C-7), 103.1 (d, CH terminal, $J_{C\text{-}P}$= 37.5 Hz), 105.5 (C-1), 111.5 (m, CH central), 125-150 (aromatic carbons), 171.7 (C=N). Anal. calcd (%) for $C_{54}H_{67}BF_4NO_7PPd$: C 60.82, H 6.33, N 1.31; found: C 60.96, H 6.37, N 1.30.

[Pd(η^3-1,3-cyclohexenylallyl)(L1b)]BF_4 (23). Isomer **A** (10%): ^{31}P NMR (CD_2Cl_2), δ: 136.7 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.11 (m, 2H, CH_2), 1.52 (s, 9H, CH_3, *t*-Bu), 1.56 (s, 9H, CH_3, *t*-Bu), 1.68 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 3.81 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 3.92 (m, 1H, H-6’), 4.02 (m, 2H, H-4, H-5), 4.35 (m, 1H, H-3), 4.46 (m, 2H, H-6, CH terminal), 4.85 (m, 1H, H-2), 5.33 (m, 1H, CH central), 5.45 (m, 1H, CH terminal), 5.60 (s, 1H, H-7), 6.72 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 6.8-8.0 (m, 14H, CH=).

^{13}C NMR (CD_2Cl_2), δ: 19.9 (m, CH_2), 27.8 (m, CH_2), 29.0 (m, CH_2), 31.5-32.0 (CH_3, *t*-Bu), 35.9-36.4 (C, *t*-Bu), 56.2 (CH_3O), 56.3 (CH_3O), 65.6 (C-5), 68.2 (C-6), 68.5 (m, C-2), 71.5 (m, C-3), 74.9 (C-4), 82.0 (m, CH terminal), 102.1 (C-7), 104.5 (d, CH terminal, $J_{C\text{-}P}$= 36.4 Hz), 105.6 (C-1), 111.4 (m, CH central), 114-157 (aromatic carbons), 171.4 (C=N). Isomer **B** (90%): ^{31}P NMR (CD_2Cl_2), δ: 137.3 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.11 (m, 2H, CH_2), 1.47 (s, 9H, CH_3, *t*-Bu), 1.53 (s, 9H, CH_3, *t*-Bu), 1.68 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 3.85 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 3.92 (m, 1H, H-6'), 4.02 (m, 3H, H-4, H-5, H-6), 4.35 (m, 2H, H-3, CH terminal), 4.69 (m, 1H, H-2), 5.33 (m, 1H, CH central), 5.45 (m, 1H, CH terminal), 5.56 (s, 1H, H-7), 6.68 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 6.8-8.0 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.9 (m, CH_2), 27.8 (m, CH_2), 29.0 (m, CH_2), 31.5-32.0 (CH_3, *t*-Bu), 35.9-36.4 (C, *t*-Bu), 56.2 (CH_3O), 56.3 (CH_3O), 61.6 (C-6), 65.5 (C-5), 68.5 (m, C-2), 71.5 (m, C-3), 75.6 (C-4), 85.2 (m, CH terminal), 102.1 (C-7), 103.3 (d, CH terminal, $J_{C\text{-}P}$= 35.2 Hz), 105.9 (C-1), 111.4 (m, CH central), 114-157 (aromatic carbons), 171.2 (C=N). Anal. calcd (%) for $C_{48}H_{55}BF_4NO_9PPd$: C 56.85, H 5.47, N 1.38; found: C 56.79, H 5.40, N 1.29.

[Pd(η^3-1,3-cyclohexenylallyl)(L4a)]BF_4 (24). Isomer **A** (28%): ^{31}P NMR (CD_2Cl_2), δ: 135.3 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.11 (m, 2H, CH_2), 1.35 (s, 9H, CH_3, *t*-Bu), 1.43 (s, 9H, CH_3, *t*-Bu), 1.45 (s, 9H, CH_3, *t*-Bu), 1.53 (s, 9H, CH_3, *t*-Bu), 1.62 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.25 (CH_3-N), 3.95 (m, 3H, H-6', H-5, CH terminal), 4.14 (m, 2H, H-3, H-6), 4.46 (m, 1H, H-2), 4.79 (m, 1H, H-4), 5.33 (m, 1H, CH central), 5.62 (s, 1H, H-7), 6.22 (m, 1H, CH terminal), 6.40 (d, 1H, H-1, $^{3}J_{1\text{-}2}$= 3.6 Hz), 7.2-7.9 (m, 9H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.7 (m, CH_2), 28.4 (m, CH_2), 29.0 (m, CH_2), 31.5-32.0 (CH_3, *t*-Bu), 35.9-36.4 (C, *t*-Bu), 62.6 (C-6), 65.2 (C-5), 73.6 (m, C-3), 81.1 (C-4), 84.1 (C-2), 84.3 (m, CH terminal), 100.3 (d, CH terminal, $J_{C\text{-}P}$= 38.7 Hz), 102.1 (C-7), 104.6 (C-1), 112.1 (m, CH central), 125-1507 (aromatic carbons), 171.5 (C=N). Isomer **B** (72%): ^{31}P NMR (CD_2Cl_2), δ: 136.9 (s). ^{1}H NMR (CD_2Cl_2), δ: 1.11 (m, 2H, CH_2), 1.33 (s, 9H, CH_3, *t*-Bu), 1.41 (s, 9H, CH_3, *t*-Bu), 1.45 (s, 9H, CH_3, *t*-Bu), 1.49 (s, 9H, CH_3, *t*-Bu), 1.62 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.27 (CH_3-N), 3.85 (m, 2H, H-6', CH terminal), 4.14 (m, 3H, H-3, H-5, H-6), 4.46 (m, 1H, H-2), 4.79 (m, 1H, H-4), 5.33 (m, 1H, CH central), 5.62 (s, 1H, H-7), 6.26 (m, 1H, CH terminal), 6.44 (d, 1H, H-1, $^3J_{1\text{-}2}$= 3.6 Hz), 7.2-7.9 (m, 9H, CH=). ^{13}C NMR (CD_2Cl_2), δ: 19.7 (m, CH_2), 28.4 (m, CH_2), 29.0 (m, CH_2), 31.5-32.0 (CH_3, *t*-Bu), 35.9-36.4 (C, *t*-Bu), 65.2 (C-5), 68.3 (C-6), 73.6 (m, C-3), 81.1 (C-4), 81.9 (C-2), 84.1 (m, CH terminal), 98.8 (d, CH terminal, $J_{C\text{-}P}$= 41 Hz), 102.1 (C-7), 104.6 (C-1), 111.2 (m, CH central), 125-1507 (aromatic carbons), 171.0 (C=N). Anal. calcd (%) for $C_{49}H_{65}BF_4NO_7PPd$: C 58.60, H 6.52, N 1.39; found: C 58.82, H 6.61, N 1.42.

3.2.4.4. Typical procedure of allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-oxazoline (0.0045 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 µL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 µL, 1.5 mmol) and a pinch of the corresponding base were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[26]

3.2.4.5. Typical procedure of allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene S2

A degassed solution of $[PdCl(\eta^3-C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-oxazoline (0.0045 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S2** (64 mg, 0.5 mmol) in dichloromethane (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 30 min the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversion and enantiomeric excess was determined by GC.[16]

3.2.4.6. Typical procedure of allylic alkylation of *rac*-3-acetoxycyclohexene S3 and *rac*-3-acetoxycycloheptene S4

A degassed solution of $[PdCl(\eta^3-C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-oxazoline (0.009 mmol) in dichloromethane (0.5 mL) was stirred. After 30 minutes the solution was kept to the desired temperature and subsequently, a solution of racemic substrate (0.5 mmol) in dichloromethane (1.5 mL) at the desired temperature, 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 the desired temperature. After 24 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversion and enantiomeric excess was determined by GC.[16]

3.2.4.7. Typical procedure of allylic alkylation of 1-(1-naphthyl)allyl acetate S5 and 1-(1-naphthyl)-3-acetoxyprop-1-ene S6

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-oxazoline (0.009 mmol) in dichloromethane (0.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (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. After 2 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^1H-NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[27]

3.2.4.8.Typical procedure of allylic amination of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-oxazoline (0.009 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After 24 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^1H-NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica using 10% Et_2O/hexane mixture as the eluent.[26]

3.2.5. Acknowledgements

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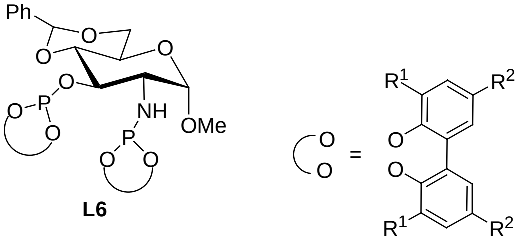
3.3. Pd-catalyzed asymmetric allylic substitution using pyranoside phosphite-phosphoroamidite ligands

Abstract. We have designed and synthesized a new family of readily available phosphite-phosphoroamidite ligands for Pd-catalyzed allylic substitution reactions of several substrates with different steric and electronic properties. These ligands are derived from D-glucosamine and contain several substituents in the biphenyl moieties, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para* positions of the biphenyl moieties. Enantiomeric excesses of up to 89% with high activities were obtained for *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-3-acetoxycycloheptene **S5**.

3.3.1. Introduction

Palladium-catalyzed asymmetric allylic alkylation is a versatile, widely used process in organic synthesis for the enantioselective formation of C-C bonds.[1] Many chiral ligands, bidentate nitrogen and phosphorus donors (both homo- and heterodonors), have been successfully applied.[1] In the last few years, a group of less electron-rich phosphorus compounds—phosphite[2] and phosphoroamidite[3] ligands—have also demonstrated their potential utility in this process. The π-acceptor ability of these type of ligands have overcoming the common limitation of low reaction rates observed for this process.

Following our interest in modular ligands and encouraged by the success of π-acceptor ligands[2-4] we here report the development of a new class of chiral phosphite–phosphoroamidite ligands **L6a-c** (Figure 1), which have the advantages of both types of ligands, for the enantioselective Pd-catalyzed allylic alkylation reactions of several substrates with different electronic and steric proprieties. These ligands are derived from natural D-glucosamine and differ in the introduction of several substitutents in the biphenyl moieties, with different steric and electronic properties, whose effect on the catalytic performance can be studied. As far as carbohydrate ligands are concerned, despite their advantages they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process.[2a,b,4b,5,6]



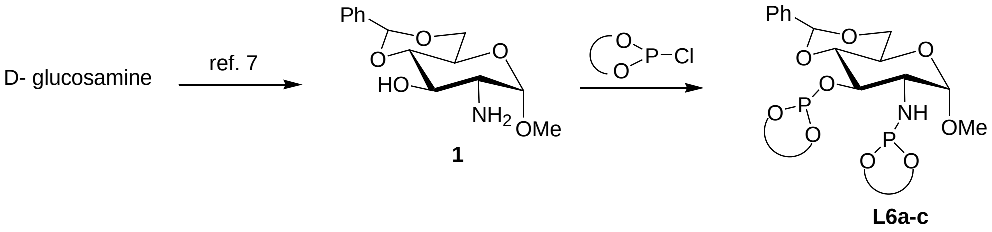
a $R^1 = R^2 = {}^tBu$
b $R^1 = {}^tBu$; $R^2 =$ OMe
c $R^1 = SiMe_3$; $R^2 =$ H

Figure 1. Phosphite-phosphoroamidite ligands **L6a-c**.

3.3.2. Results and discussion

3.3.2.1. Synthesis of the chiral phosphite-phosphoroamidite ligands

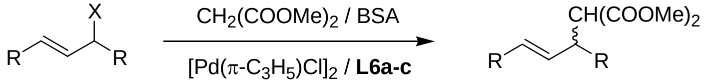
The new ligands **L6a-c** were synthesized very efficiently in one step from the corresponding aminoalcohol **1**, which are easily prepared on a large scale from D-glucosamine using a standard procedure (Scheme 1).[7] Reaction of **1** with two equivalent of the corresponding phosphorochloridite in dry toluene, under nitrogen and in the presence of pyridine, then provided the desired ligands **L6a-c** as a white solids. All ligands were stable during purification on neutral alumina under an atmosphere of argon. The elemental analysis were in agreement with the assigned structure. The ^1H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands.



Scheme 1. Synthesis of ligands **L6a-c**.

3.3.2.2. Allylic alkylation of disubstituted linear substrates

In this section, we report the use of the chiral phosphite-phosphoroamidite ligands **L6a-c** in the Pd-catalyzed allylic alkylation (equation 1) of three linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were generated *in situ* from π-allyl-palladium chloride dimer [Pd(π-C_3H_5)Cl]$_2$ and the corresponding ligand. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA).



(1)

S1 R= Ph; X= OAc
S2 R = ^{i}Pr; X= OCOOEt
S3 R= Me; X= OAc

2 R= Ph
3 R= ^{i}Pr
4 R= Me

3.3.2.2.1. Allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 (equation 1)

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** with dimethyl malonate using the chiral phosphite-phosphoroamidite ligands **L6a-c** (eq. 1).

The effect of the solvent and the ligand-to-palladium ratio were investigated using the catalyst precursor containing ligand **L6a** (Table 1).

Our results indicate that the solvent affected catalytic performance. Tetrahydrofurane (THF) as solvent provided the best combination of activity and enantioselectivity (Table 1, entries 1-4). The enantiomeric excess obtained with toluene was comparable to that with THF, but activity was lower. On the other hand, dichloromethane (CH_2Cl_2) and dimethylformamide (DMF) yielded the same activities that THF, but their ee's were the lowest of the four solvents. In summary, good activity (TOF > 200 mol **S1** x (mol Pd x h)$^{-1}$) and enantioselectivity (84% (*R*) ee) were obtained.

Table 1. Pd-catalyzed allylic alkylation of **S1** using ligand **L6a**-**c**.[a]

Entry	Ligand	Solvent	Ratio **L**/Pd	% Conv[b] (min)	% ee[c]
1	**L6a**	CH_2Cl_2	1.1	100 (30)	74 (*R*)
2	**L6a**	DMF	1.1	100 (30)	73 (*R*)
3	**L6a**	Toluene	1.1	89 (30)	84 (*R*)
4	**L6a**	THF	1.1	100 (30)	84 (*R*)
5	**L6a**	THF	0.75	100 (30)	85 (*R*)
6	**L6a**	THF	2	100 (30)	84 (*R*)
7	**L6b**	THF	1.1	100 (30)	76 (*R*)
8	**L6c**	THF	1.1	100 (30)	81 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the KOAc, room temperature. [b] Measured by ^{1}H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD). Absolute configuration drawn in parentheses.

Varying the ligand-to-palladium ratio showed that excess ligand was not needed to obtain good enantioselectivities and activities (Table 1, entries 4 - 6).

Under the optimized conditions, we studied how the biphenyl substituents at the phosphite moieties affect the catalytic performance with ligands **L6b** and **L6c** (Table 1, entries 7 and 8).

The use of ligand **L6b** with methoxy substituents at the *para* position of the biphenyl moieties showed the same activity but lower asymmetric induction than those obtained with the catalytic system Pd/**L6a** (Table 1, entry 7). The use of ligand **L6c** with trimethylsilyl substituents at the *ortho* positions of the biphenyl moiety and no substituents at the *para* positions showed slightly lower asymmetric induction than the catalytic system containing ligand **L6a** (Table 1, entry 8).

3.3.2.2.2. Allylic alkylation of *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate S2 (equation 1)

We also evaluated the phosphite-phosphoroamidite ligands **L6a-c** in the allylic substitution process of **S2** using dimethyl malonate as nucleophile (equation 1). This substrate is more sterically demanding than the previously used substrate **S1**.[1] The most remarkable results are shown in Table 2. In general, they follow the same trends as for the allylic alkylation of **S1**. However, the enantiomeric excesses were slightly higher (ee's up to 89 %).

As expected, the activities were lower than in the alkylation reaction of **S1**.[1] Again, the catalyst precursor containing the phosphite-phosphoroamidite ligand **L6a** provided the best enantioselectivity (Table 2, entries 3 and 4). The stereoselectivity of the alkylation of **S2** was the same as for the alkylation reaction of **S1**, though the CIP descriptor was inverted due to the change in priority of the groups.

Table 2. Pd-catalyzed allylic alkylation of **S2** with ligands **L6a-c**.[a]

Entry	Ligand	Solvent	% Conv (h)[b]	% ee[c]
1	**L6a**	CH_2Cl_2	100 (18)	82 (*S*)
2	**L6a**	DMF	100 (18)	77 (*S*)
3	**L6a**	Toluene	54 (18)	87 (*S*)
4	**L6a**	THF	100 (18)	89 (*S*)
5	**L6b**	THF	100 (18)	81 (*S*)
6	**L6c**	THF	100 (18)	87 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time in hours shown in parentheses.[c] Enantiomeric excesses determined by ^1H NMR using $Eu(hfc)_3$. Absolute configuration drawn in parentheses.

3.3.2.2.3. Allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene S3 (equation 1)

We also screened ligands **L6a-c** in the allylic alkylation of the linear substrate **S3** (equation 1). This substrate is less sterically demanding than the previously used substrates **S1** and **S2**. Enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1** and **S2**.[1] The results of using the phosphite-phosphoroamidite ligands are summarized in Table 3. Good activities (TOF > 200 mol **S3** x (mol Pd x h)$^{-1}$) and moderate enantioselectivities (ee's up to 61%) were obtained. The general trends that controlled enantioselectivity were different from those that controlled **S1** and **S2**. Therefore, the best enantioselectivity was obtained with ligand **L6c**, which contain bulky trimethylsilyl groups at the *ortho* positions and a small hydrogen at the *para* positions of the biphenyl moiety. These results shows the importance of using modular scaffolds in the ligand design.

Table 3. Pd-catalyzed allylic alkylation of **S3** with ligands **L6a-c**.[a]

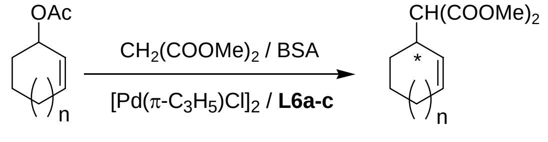
Entry	Ligand	Solvent	% Conv (min)[b]	% ee[c]
1	**L6a**	CH_2Cl_2	98 (30)	40 (*R*)
2	**L6a**	DMF	100 (30)	29 (*R*)
3	**L6a**	Toluene	43 (30)	42 (*R*)
4	**L6a**	THF	100 (30)	43 (*R*)
5	**L6b**	THF	100 (30)	45 (*R*)
6	**L6c**	THF	100 (30)	61 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N,O* bis(trimethylsilyl)acetamide (BSA), a pinch of the KOAc, room temperature. [b] Measured by GC. Reaction time in minutes shown in parentheses. [c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

3.3.2.3. Allylic alkylation of cyclic substrates S4-S5

As for the unhindered substrate **S3**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *syn* substituents. These *syn* substituents are thought to play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd-allyl intermediate.[1] To obtain high ee's, the ligand must create a small chiral pocket (the chiral cavity where the allyl is embedded) around the metal center.[1]

In this section, we report the use of the chiral phosphite-phosphoroamidite ligands **L6a-c** in the Pd-catalyzed allylic alkylation of two cyclic substrates (equation 2): *rac*-3-acetoxycyclohexene **S4** (which is widely used as a model substrate) and *rac*-3-acetoxycycloheptene **S5**.



(2)

S4 n=1
S5 n=2

5 n=1
6 n=2

We initially studied the allylic alkylation of *rac*-3-acetoxycyclohexene **S4** using ligands **L6a-c**. Preliminary investigations into the solvent effect and ligand-to-palladium ratio provided the same trends as those with the previously tested linear substrate **S1** (Table 4). The trade-off between enantioselectivities and reaction rates was therefore optimum with THF and a ligand-to-palladium ratio of 1.1. The results of using the rest of phospite-phosphoroamidite ligands under the optimized conditions are showed in Table 4 and indicated that substituents in the *para* positions of the biphenyl moieties are needed for better enantioselectivities (Table 4, entries 5 and 7 vs 8). Thus, ligands **L6a** and **L6b** with *tert*-butyl and methoxy substituents at the *para* positions of the biphenyl moieties, respectively, provided higher asymmetric induction than ligands **L6c** with small hydrogen substituents in these positions.

Table 4. Pd-catalyzed allylic alkylation of **S4** and **S5** using ligand1 **L6a-c**.[a]

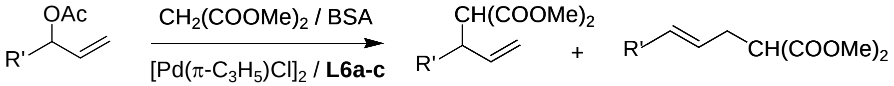
Entry	Ligand	Substrate	Solvent	Ratio **L**/Pd	% Conv[b] (h)	% ee[c]
1	**L6a**	**S4**	CH_2Cl_2	1.1	100 (2)	37 (*S*)
2	**L6a**	**S4**	DMF	1.1	100 (2)	26 (*S*)
3	**L6a**	**S4**	Toluene	1.1	32 (2)	35 (*S*)
4	**L6a**	**S4**	THF	1.1	100 (2)	48 (*S*)
5	**L6a**	**S4**	THF	0.75	100 (2)	47 (*S*)
6	**L6a**	**S4**	THF	2	100 (2)	48 (*S*)
7	**L6b**	**S4**	THF	1.1	100 (2)	46 (*S*)
8	**L6c**	**S4**	THF	1.1	100 (2)	22 (*S*)
9	**L6a**	**S5**	THF	1.1	17 (2)	82 (*S*)
10	**L6b**	**S5**	THF	1.1	16 (2)	81 (*S*)
11	**L6c**	**S5**	THF	1.1	12 (2)	42 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the KOAc, room temperature and CH_2Cl_2 as solvent. [b] Measured by GC. Reaction time in hours shown in parentheses. [c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

With these ligands, we also studied the Pd-catalyzed allylic alkylation of the seven-membered ring substrate **S5** (Table 4, entries 9-11). Interestingly, high enantioselectivity (ee's up to 82%) was obtained using ligands **L6a** and **L6b** (Table 4, entries 9 and 10).

3.3.2.4. Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S6** with dimethyl malonate (equation 3).



(3)

S6 R'= 1-Naphthyl **7** **8**

For this substrate, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[8] The results obtained with the phosphite-phosphoroamidite ligands **L6a-c** are summarized in Table 5. Unfortunately, the regioselectivity for the branched product **7** was not high. However, good enantioselectivities can be obtained (ee's up to 72 %). The results also indicate that regio- and enantioselectivities are highly affected by the substituents in the *para* position of the biphenyl moieties (Table 5, entries 1, 5 and 6). Thus, whereas the best enantioselectivities are obtained when bulky substitutents in the *para* positions of the biphenyl moieties are present (ligand **L6a**, entry 1), regioselectivities are better when unhindered hidrogens are present at these positions (ligand **L6c**, entry 6).

Table 5. Selected results for the Pd-catalyzed allylic alkylation of **S6**.[a]

Entry	Ligand	Solvent	% Conv. (t/h)[b]	**7/8**[b]	% ee[c]
1	**L6a**	CH_2Cl_2	100 (2)	20/80	72 (*S*)
2	**L6a**	DMF	100 (2)	21/79	54 (*S*)
3	**L6a**	Toluene	34 (2)	15/75	68 (*S*)
4	**L6a**	THF	100 (2)	12/88	38 (*S*)
5	**L6b**	CH_2Cl_2	100 (2)	25/75	28 (*S*)
6	**L6c**	CH_2Cl_2	100 (2)	40/60	41 (*S*)

[a] 1 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the KOAc, room temperature. [b] Conversion percentage and linear-to-branched ratio determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

3.3.3. Conclusions

We have designed and synthesized a new family of readily available phosphite-phosphoroamidite ligands for Pd-catalyzed allylic substitution reactions of several substrates with different steric and electronic properties. These ligands are derived from D-glucosamine and contain several substituents in the biphenyl moieties, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that enantioselectivities are mainly affected by the substituents at the *para* positions of the biphenyl moieties. However, these effects are different depending on the substrate in study. Therefore, for the hindered disubstituted linear substrates **S1** and **S2** and cyclic substrates **S4** and **S5** we found best enantioselectivities (ee's up to 89%) with ligand **L6a**, that contains bulky *tert*-butyl group at the *para* positions of the biaryl groups while for the unhindered disubstituted linear substrate **S3** the best selectivity (ee's up to 61%) was obtained with ligand **L6c**, that have a small hydrogen at these *para* positions. For the monosubstituted linear substrate **S6**, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivity by carefully selecting the substituents on the *para* position of the biphenyl moieties (ee's up to 72%).

It should be noted that high activities were obtained in all cases, due to the π-acceptor capacity of these phosphite-phosphoroamidite ligands.

In addition by comparing with the results obtained in the previous section 3.2 containing the phosphite-oxazoline ligand library **L1-L5a-i**, we observed that the replacement of the oxazoline moiety by a phosphoroamidite group decreases enantioselectivities and versatility.

3.3.4. Experimental section

3.3.4.1. General comments

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Compound **1**[7] and phosphorochloridites[9] were prepared by previously described methods. All other reagents were used as commercially available. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. All assignments in NMR spectra were determined by ^1H-^1H and ^{13}C-^1H spectra. Racemic substrates **S1-S6** were prepared as previously reported.[10-13]

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3.3.4.2. General procedure for the preparation of ligands L6a-c

The corresponding phosphorochloridite (2.25 mmol) produced *in situ* was dissolved in toluene (10.0 mL) and pyridine (0.60 mL, 7.4 mmol) was added. Amino-alcohol **1** (0.28 g, 1.0 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (10.0 mL) to which pyridine (0.60 mL, 7.4 mmol) was added. The solution was transferred slowly at 0 ºC to the solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 ºC, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash column chromatography (eluent: toluene/hexane/Et_3N = 50:75:2) to produce the desired ligand as a white powder.

L6a. Yield: 0.38 g (32%). ^{31}P NMR (C_6D_6) δ= 146.6 (s, 1P), 152.7 (s, 1P). ^{1}H NMR (C_6D_6) δ= 1.24 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 18H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 3.00 (s, 3H, OMe), 3.23 (m, 1H, NH), 3.61 (m, 3H, H-1, H-4, H-6'), 3.76 (m, 1H, H-5), 4.04 (b, 1H, H-2), 4.13 (m, 1H, H-6), 4.73 (m, 1H, H-3), 5.53 (s, 1H, H-7), 7.00-7.8 (m, 13H, CH=). ^{13}C NMR (C_6D_6) δ= 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 54.1 (CH_3-O, C-2), 62.8 (C-5), 68.9 (C-6), 75.3 (d, C-3, $^2J_{c\text{-}p}$= 21.3 Hz), 80.7 (C-4), 100.5 (C-1), 101.4 (C-7), 123.8 (CH=), 123.9 (CH=), 124.1 (CH=), 124.3 (CH=), 126.2 (CH=), 126.6 (CH=), 126.8 (CH=), 126.9 (CH=), 127.0 (CH=), 128.0 (CH=), 128.4 (CH=), 128.8 (CH=), 129.2 (CH=), 132.5 (C), 133.4 (C), 134.1 (C), 134.6 (C), 137.7 (C), 140.1 (C), 140.5 (C), 141.0 (C), 141.5 (C), 145.3 (C), 145.6 (C), 146.2 (C), 146.3 (C), 146.9 (C). Anal. calcd (%) for $C_{70}H_{97}NO_9P_2$: C 72.57, H 8.44, N 1.21; found: C 72.63, H 8.50, N 1.22. Melting point: 181 °C. $[\alpha]_D^{20}$= - 78.4 (c 0.5, $CHCl_3$)

L6b. Yield: 0.22 g (21%). ^{31}P NMR (C_6D_6) δ= 147.0 (s, 1P) 151.2 (s, 1P). ^{1}H NMR (C_6D_6) δ= 1.43 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 18H, CH_3, ^{t}Bu), 2.99 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.52 (m, 3H, 1NH, H-4, H-6'), 3.77 (m, 1H, H-5), 3.98 (m, 1H, H-1), 4.11 (m, 2H, H-2, H-6), 4.76 (m, 1H, H-3), 5.44 (s, 1H, H-7), 6.60-7.75 (m, 13H, CH=). ^{13}C NMR (C_6D_6) δ= 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.7 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 54.7 (C-2), 55.3 (OCH_3), 55.4 (OCH_3), 55.5 (OCH_3), 55.6 (OCH_3), 63.5 (C-5), 69.3 (C-6), 75.9 (m, C-3), 81.1 (C-4), 101.2 (C-1), 101.8 (C-7), 112.8 (CH=), 113.5 (CH=), 113.7 (CH=), 113.8 (CH=), 114.7 (CH=), 115.0 (CH=), 115.2 (CH=), 126.0 (CH=), 127.0 (CH=), 128.6 (CH=), 128.9 (CH=), 129.3 (CH=), 129.7 (CH=), 134.8 (C), 135.0 (C) 138.2 (C), 142.8 (C), 143.1 (C), 143.5 (C) 144.0 (C), 156.3 (C), 156.5 (C), 156.6 (C), 156.8 (C). Anal. calcd (%) for $C_{58}H_{73}NO_{13}P_2$: C 65.08, H 6.98, N 1.33; found: C 66.14, H 7.01, N 1.36. Melting point: 150 °C. $[\alpha]_D^{20}$= - 119.9 (c 0.5, $CHCl_3$)

L6c. Yield: 0.30 g (30%). ^{31}P NMR (C_6D_6) δ= 149.6 (s, 1P) 151.9 (s, 1P). ^{1}H NMR (C_6D_6) δ= 0.28 (s, 9H, CH_3-Si), 0.39 (s, 9H, CH_3-Si), 0.40 (s, 9H, CH_3-Si), 0.42 (s, 9H, CH_3-Si), 2.94 (s, 3H, OMe), 3.36 (m, 1H, NH), 3.47 (m, 1H, H-6'), 3.67 (m, 1H, H-4), 3.83 (m, 1H, H-5), 3.90 (m, 1H, H-2), 4.04 (m, 1H, H-6), 4.07 (m, 1H, H-1), 4.82 (m, 1H, H-3), 5.42 (s, 1H, H-7), 6.99-7.70 (m, 17H, CH=). ^{13}C NMR (C_6D_6) δ= 0.4 (CH_3-Si), 0.5 (CH_3-Si), 0.6 (CH_3-Si), 55.8 (OCH_3), 55.8 (C-2), 63.6 (C-5), 69.3 (C-6), 74.8 (m, C-3), 81.5 (C-4), 100.7 (C-1), 102.1 (C-7), 124.9 (CH=), 125.1 (CH=), 125.4 (CH=), 127.1 (CH=), 129.3 (CH=), 132.6 (CH=), 132.7 (CH=), 133.0 (CH=), 133.2 (CH=), 135.5 (CH=), 133.7 (CH=), 135.8 (CH=). Anal. calcd (%) for $C_{50}H_{65}NO_9P_2Si_4$: C 60.15, H 6.56, N 1.40; found: C 60.12, H 6.59, N 1.41. Melting point: 117 °C. $[\alpha]_D^{20}$= - 69.9 (c 0.5, $CHCl_3$)

3.3.4.3. Typical procedure of 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-phosphoroamidite (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (0.5 mmol) in THF (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, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min).[14] For substrate **S2**, conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by ^{1}H-

NMR using Eu(hfc)$_3$ as resolving agent. For substrates **S3**, **S4** and **S5**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column.[15]

3.3.4.4. Typical procedure of allylic alkylation of monosubstituted linear substrates S6

A degassed solution of [Pd(π-C_3H_5)Cl]$_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-phosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (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, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[16]

3.3.5. Acknowledgements

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3.4. Pd-catalyzed asymmetric allylic substitution using a sugar-based monophosphite ligand library

Abstract. We have synthesized a modular sugar-based phosphite ligand library for the Pd-catalyzed allylic substitution reactions of several substrates. These ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones, and contain several substituents/configurations in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety.

3.4.1. Introduction

Palladium-catalyzed asymmetric allylic alkylation is a useful synthetic method for the enantioselective formation of C-C bonds.[1] The selection of chiral ligands for highly enantioselective allylic substitution has focussed on the use of bidentate nitrogen and phosphorus donors (both homo- and heterodonors).[1] Less attention has been paid to catalysts containing monodentated ligands in this process. However, in 2000, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalysts precursors containing monophospholane ligands in the Pd-catalyzed allylic alkylation to *rac*-1,3-diphenyl-3acetoxyprop-1-ene.[2] Despite this success, few monophosphorus ligands have been applied in the Pd-catalyzed asymmetric allylic substitution.[3] This encourages further research into monophosphorous ligands to study their possibilities as a new class of ligands for this process. Recently, a group of less electron-rich phosphorus compounds–biaryl diphosphite ligands–have also demonstrated their potential utility by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[4] Therefore, these ligand systems have provided excellent enantioselectivities and activities in different substrate types.[4]

Following our interest in modular π-acceptor ligands[4] and encouraged by the success of monophosphorous ligands, we report here the design of a library of 30 potential chiral monophosphite ligands **L7-L11a-f** (Figure 1) and screen their use in the palladium allylic substitution reaction of several substrate types. These ligands are derived from natural D-glucose, D-galactose and D-fructose and have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols and facile modular constructions.[5] In addition they are less sensitive to air than typical phosphines, widely used as ligands in asymmetric catalysis. All these favourable features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity. Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions (mainly hydrogenation and allylic alkylation),[5] few good monodentate chiral ligands have been reported based on carbohydrates.[2,6]

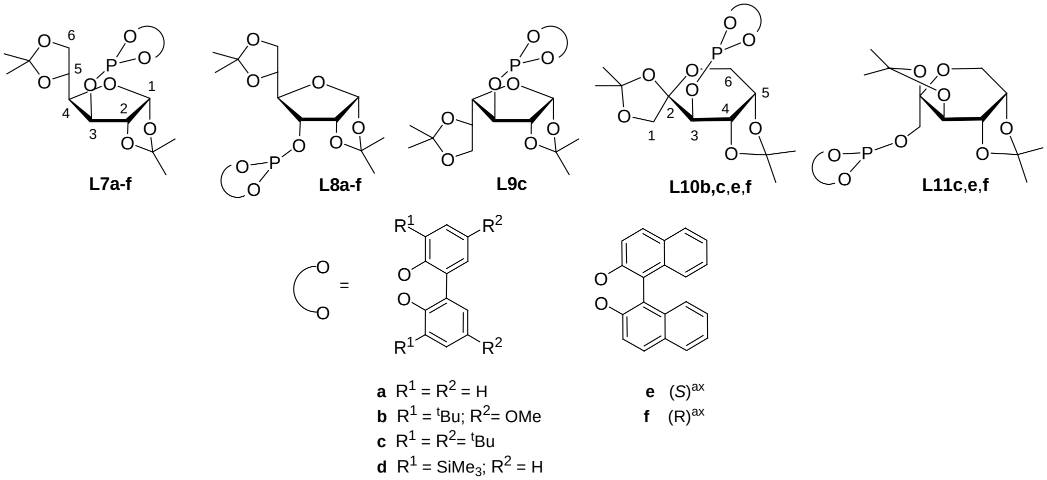


Figure 1. Carbohydrate-based phosphite ligands **L7-L11a-f**.

3.4.2. Results and Discussion

3.4.2.1. Ligand design

The sugar-based monophosphite ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones (**L7-L11**), and contain several substituents/configurations in the biaryl moiety (**a-f**), with different steric and electronic properties, whose effect on the catalytic perfomance will be studied. Therefore, ligands **L7-L11a-f** consist of chiral di-*O*-protected either furanoside (ligands **L7-L9**) or pyranoside (ligands **L10** and **L11**) backbones, which determine their underlying structure, and one hydroxyl group. Several phosphoric acid biaryl esters (**a-f**) were attached to these basic frameworks (Figure 1).

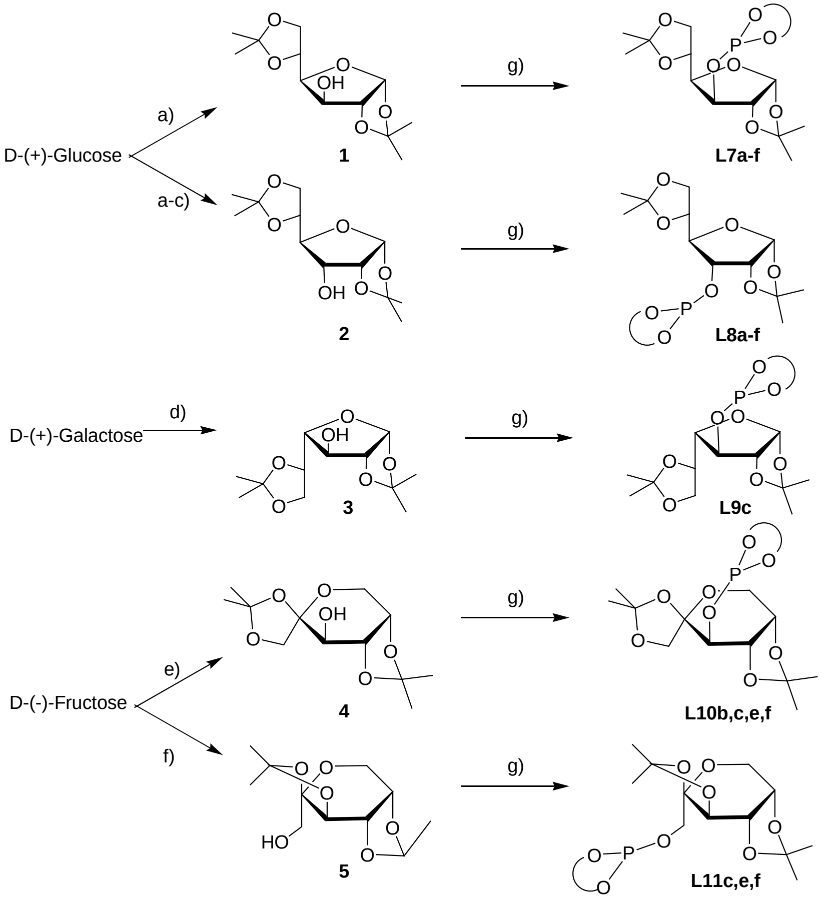
The influence of the different groups attached to the *ortho*- and *para*-positions of the biphenyl moieties on enantioselectivity was investigated using ligands **L7a-d**, which have the same configuration on the carbon atom C-3. To determine whether there is a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties, we prepared a series of enantiomerically pure binaphthol-based ligands **L7e-f** and **L8e-f**.

We studied the effects of the stereogenic carbon atom C-3 on enantioselectivity by comparing diastereomeric ligands **L7** and **L8** which have opposite configuration at C-3. The influence of the configuration of carbon atom C-4 in the catalytic performance was studied using ligands **L7** and **L9** which only differ in the configuration at C-4.

The influence of the carbohydrate ring size in the catalytic performance of the Pd-catalysts was studied with ligands **L10**, which have a pyranoside backbone and the same configuration at C-3 than ligand **L7**. Finally, with ligands **L11** we studied how the flexibility of the ligand backbone may affect the catalytic performance. These ligands have a pyranoside backbone as ligands **L10**, but differs from the rest of ligands in a phosphite moiety attached to a primary alcohol, providing a more flexible ligand.

3.4.2.2. Ligand synthesis

Ligands **L7-11a-f**[7] were efficiently synthesized in one step by reaction of the corresponding sugar alcohols (**1-5**) with 1 equiv of PCl_3 and subsequent addition of the biaryl alcohols (**a-f**) in the presence of triethylamine using a series of parallel reactors each equipped with 12 positions (Scheme 1).[6c] Sugar alcohols **1-5** were easily prepared on a large scale from inexpensive D-(+)-glucose, D-(+)-galactose and D-(-)-fructose, (Scheme 1).

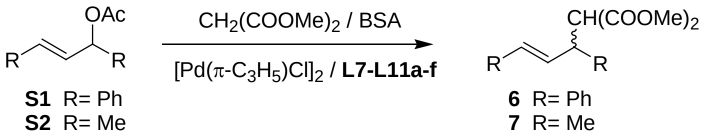


Scheme 1. Synthesis of phosphite ligands **L7-L11a-f**. a) Acetone, I_2, 6 h.[8] b) PCC, CH_2Cl_2, NaOAc, 16 h.[9] c) $NaBH_4$, EtOH, -20 °C to rt overnight.[9] d) DMF, acetone, Dowex H^+, reflux 48 h.[10] e) $HClO_4$, dimethoxypropane, 0 °C, 6 h.[11] f) $HClO_4$, dimethoxypropane, rt, 16 h.[12] g) PCl_3, NEt_3, THF, biaryl alcohol (**a-f**), rt.[6c]

All the ligands were stable during purification on neutral silica under an atmosphere of argon and isolated in moderate yields as white solids. The elemental analysis were in agreement with the assigned structure. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands.

3.4.2.3. Allylic alkylation of disubstituted linear substrates

In this section, we report the use of the chiral phosphite ligand library (**L7-L11a-f**) in the Pd-catalyzed allylic alkylation (equation 1) of two disubstituted linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S2**. In all the cases, the catalysts were generated *in situ* from 0.5 mol % of π-allyl-palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand and a catalytic amount of potassium acetate.



(1)

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, which is widely used as a model substrate. The effect of the solvent and the ligand-to-palladium ratio were investigated using the catalyst precursor containing ligand **L8b** (Table 1). The results indicated that solvent affected catalytic performance. The optimum trade-off between enantioselectivities and activities was obtained when dichloromethane was used as a solvent (Table 1, entry 4). We next studied the effect of the ligand-to-palladium ratio. Interestingly, we found that activities were best with a ligand-to-palladium ratio of 1, while enanioselectivities were similar (Table 1, entries 4 vs 5).[13]

Table 1. Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene **S1** using ligands **L8b**.[a]

Entry	Solvent	Ratio **L**/Pd	% Conv (h)[b]	% ee[c]
1	DMF	1	43 (4)	11 (*R*)
2	Toluene	1	9 (8)	19 (*R*)
3	THF	1	24 (4)	17 (*R*)
4	CH_2Cl_2	1	31 (4)	23 (*R*)
5	CH_2Cl_2	2	14 (4)	20 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD).

Under the optimized conditions, we evaluated the phosphite ligands in the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**. The results, which are summarized in Table 2, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the substituents of the biaryl moieties, the configuration of carbon atoms C-3 and C-4 and the size of the ring of the sugar backbone. In general, activities (TOF's up to 30 mol **6** x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 41%) were low.

The results using ligands **L7a-f** and **L8a-f** allow us to study the influence of the substituents/configuration of the biaryl moiety on the product outcome (Table 2, entries 1-12). We found that activities were best when binaphthyl phosphite moieties were present, while enantioselectivities were best using ligands **L7d** and **L8d**, which have trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety (Table 2, entries 4 and 10).

Table 2. Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene **S1** in CH_2Cl_2 using ligands **L7-L11a-f**.[a]

Entry	Ligand	% Conv (h)[b]	% ee[c]
1	**L7a**	4 (4)	0
2	**L7b**	35 (4)	31 (*S*)
3	**L7c**	84 (4)	22 (*S*)
4	**L7d**	42 (4)	40 (*S*)
5	**L7e**	100 (4)	19 (*R*)
6	**L7f**	100 (4)	18 (*R*)
7	**L8a**	5 (4)	0
8	**L8b**	31 (4)	23 (*R*)
9	**L8c**	81 (4)	20 (*R*)
10	**L8d**	53 (4)	41 (*R*)
11	**L8e**	99 (4)	28 (*R*)
12	**L8f**	87 (4)	4 (*S*)
13	**L9c**	100 (4)	15 (*S*)
14	**L10b**	10 (4)	15 (*S*)
15	**L10c**	8 (4)	14 (*S*)
16	**L11c**	82 (4)	11 (*R*)
17[d]	**L8d**	32 (8)	46 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD).[d] T= 0 °C.

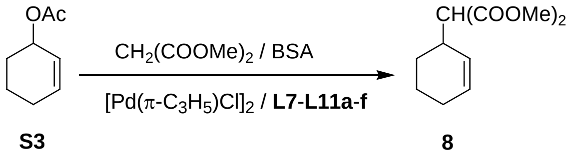
Comparing the results using ligands **L7** with **L8**, that only differ in the configuration at C-3, we observed that this configuration controls the sense of enantioselectivity. Accordingly, ligands **L7a-d** with an *S* configuration at the C-3 of the ligand backbone, gave the S-**6** product, while ligands **L8a-d** with an *R* configuration at C-3 gave *R*-**6** product (Table 2, entries 1-4 *vs* 7-10). Furthermore, comparing ligands **L7e-f** and **L8e-f**, we found a cooperative effect between the configuration of the binaphthyl phosphite moiety and the configuration at C-3, that results in a matched combination for ligand **L8e** (Table 2, entries 5, 6, 11 and 12).The results also showed that ligands **L9** with an *S* configuration at C-4 gave lower enantioselectivities than ligands **L7** with an opposite configuration at this position (Table 2, entries 3 *vs* 13). In addition, ligands **L10** which have a pyranoside backbone provided lower yields and enantioselectivities than their relative furanoside ligands **L7** (Table 2, entries 2 and 3 *vs* 14 and 15). Finally, the most flexible ligand **L11**, which has the phosphite moiety attached to a primary carbon provided the lowest enantioselectivities (Table 2, entry 16).

In addition to the effect of structural parameters on enantioselectivity, the reaction parameters can also be controlled to further improved selectivity. In this case, enantioselectivity was further improved (ee's up to 46%) with ligand **L8d** by lowering the reaction temperature to 0 ºC (Table 2, entry 17).

We then tested ligands **L7d** and **L8d** (the ones that provided the best results in the alkylation of **S1**) in the allylic alkylation of unhindered linear substrate **S2** (equation 1, R = Me). Unfortunately, activities (up to 43% in 24 hours) and enantioselectivities (32% (*R*) for **L7d** and 34% (*S*) for **L8d**) were low.

3.4.2.4. Allylic alkylation of cyclic substrates

To further study the potential of ligands **L7-L11a-f**, we also tested the best ligands **L7d** and **L8d** in the allylic alkylation of substrate **S3**. As for unhindered substrate **S2**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *syn* substituents (equation 2).[1] The results are shown in Table 3. Enantioselectivities up to 38% were obtained (Table 3, entry 2). As observed for substrates **S1** and **S2**, changing the solvent from dichloromethane to other solvents did not increase enantioselectivity (Table 3, entries 2-5).



(2)

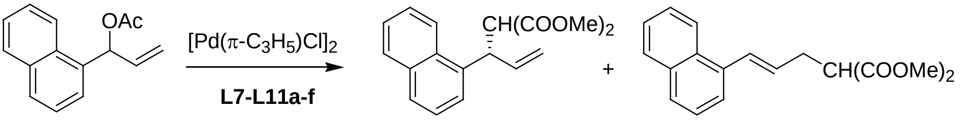
Table 3. Pd-catalyzed allylic alkylation of *rac*-3-acetoxy-cyclohexene **S3** using ligands **L7d** and **L8d**.[a]

Entry	Ligand	Solvent	% Conv (h)[b]	% ee[c]
1	**L7d**	CH_2Cl_2	10 (24)	28 (*R*)
2	**L8d**	CH_2Cl_2	12 (24)	38 (*S*)
3	**L8d**	DMF	52 (24)	21 (*S*)
4	**L8d**	Toluene	10 (24)	33 (*S*)
5	**L8d**	THF	32 (24)	17 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by GC. Reaction time in minutes shown in parentheses. [c] Determined by GC.

3.4.2.5. Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S4** with dimethyl malonate (equation 3). As we previously mentioned, for this substrate, the development of highly regio- and enantioselective Pd-catalysts is still a challenge.[4d,14]



S4 **9** **10**

(3)

The results obtained with the phosphite ligands are summarized in Table 4. Unfortunately, the enantioselectivity (ee's up to 40%) was not high. However, good regioselectivities (regio's up to 80%) has been obtained.[15] The results indicated that if regioselectivity is to be high, bulky substituents at the *ortho* positions of the biaryl phosphite moiety and a furanoside backbone with an *S* and *R* configuration at C-3 and C-4, respectively, are necessary. However, enantioselectivities were best for furanoside ligand **L9c** with *S* configurations at both C-3 and C-4.

Table 4. Pd-catalyzed allylic alkylation of **S4** in CH_2Cl_2 using ligands **L7-L11a-f**.[a]

Entry	Ligand	% Conv (h)[b]	**9**/**10**[b]	% ee[c]
1	**L7a**	100 (6)	15/85	0
2	**L7b**	100 (6)	80/20	7 (*R*)
3	**L7c**	100 (6)	75/25	9(*R*)
4	**L7d**	100 (6)	80/20	18 (*R*)
5	**L7e**	100 (6)	20/80	0
6	**L7f**	100 (6)	35/65	17 (*S*)
7	**L8a**	100 (6)	15/85	0
8	**L8b**	100 (6)	75/25	10 (*R*)
9	**L8c**	100 (6)	70/30	21 (*R*)
10	**L8d**	100 (6)	60/40	<5 (*R*)
11	**L8e**	100 (6)	25/75	3 (*S*)
12	**L8f**	100 (6)	20/80	18 (*R*)
13	**L9c**	100 (6)	45/55	40 (*R*)
14	**L10b**	100 (6)	35/65	<5 (*S*)
15	**L10c**	100 (6)	30/70	<5 (*R*)
16	**L11c**	100 (6)	70/30	25 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OJ).

3.4.3. Conclusions

A library of readily available monophosphite ligands has been synthesized and applied in the asymmetric Pd-catalyzed allylic alkylation of several substrates with different electronic and steric properties. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. In general, the catalytic performance (activities and enantioselectivities) is highly affected by these ligand parameters. Therefore for substrates **S1**-**S3** enantioselectivies were best with ligands **L7d** and **L8d**, while for substrate **S4** ligand **L9c** provided the best ee's.

3.4.4. Experimental section

3.4.4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Compounds **1-5** were prepared by previously described methods.[8-12] Ligands **L7a**, **L7c**, **L7e-f**, **L8e-f** and **L10e-f** have been previously synthesized.[7] Racemic substrates **S1-S4** were prepared as previously reported.[16-18] All other reagents were used as commercially available. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^{1}H and ^{13}C NMR spectral assignments were determined by ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra.

3.4.4.2. Synthesis of the chiral monophosphite ligands

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite)-α-D-glucofuranose (**L7b**)

To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** (390 mg, 1.5 mmol) in THF (5 mL) was slowly added PCl_3 (132 μl, 1.5 mmol) as a solution in THF (4 mL) and the resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled to -10 ºC and NEt_3 (1.07 mL, 4.5 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature, maintained under these conditions for 0.25 h, and then cooled to 0 ºC. Solid 3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diol (0.54 g, 1.5 mmol) was added and the resulting mixture was allowed to warm to room temperature and stirred overnight. Diethyl ether was added and then the solid was removed by filtration through a pad of celite, the solvent was removed in *vacuo* and the residue was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.32) to produce 100 mg (11%) of a white solid. ^{31}P NMR (C_6D_6) δ=145.2 (s). ^1H NMR (C_6D_6) δ= 1.03 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.34 (s, 3H, CH_3,), 1.39 (s, 3H, CH_3), 1.49 (s, 18H, CH_3, ^{t}Bu), 3.31 (s, 6H, OMe), 4.01 (dd, 1H, H-6', $^2J_{6'-6}$=8.4 Hz, $^2J_{6'-5}$=6.0 Hz), 4.10 (dd, 1H, H-6, $^2J_{6-6'}$=8.4 Hz, $^3J_{6-5}$=5.2 Hz), 4.27 (m, 1H, H-2), 4.44 (dd, 1H, H-4, $^3J_{4-3}$=2.4 Hz, $^3J_{4-5}$=8.0 Hz), 4.57 (m, 1H, H-5), 5.20 (dd, 1H, H-3, $^3J_{3-4}$=2.8 Hz, $^2J_{3-P}$=8.0 Hz), 5.83 (d, 1H, H-1, $^3J_{1-2}$=3.6 Hz), 6.66 (m, 1H, CH=), 6.72 (m, 1H, CH=), 7.14 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= 25.8 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 27.5 (CH_3), 31.4 (CH_3,^{t}Bu), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 36.2 (C ^{t}Bu), 36.3 (C ^{t}Bu), 55.4 (d, OCH_3, J_{c-p}=3.7 Hz), 68.0 (C-6), 73.4 (C-5), 77.6 (C-3), 81.9 (d, C-4, J_{c-p}=4.6 Hz), 85.0 (C-2), 106.1 (C-1), 112.2 (C), 113.7 (CH=), 114.0 (CH=), 115.2 (CH=), 143.1 (C), 154.1 (C), 155.6 (C), 157.0 (C). Anal. calcd (%) for $C_{34}H_{47}O_{10}P$: C 63.15, H 7.33; found: C 63.30, H 7.42.

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-di-trimethylsilyl-1,1'-biphenyl-2,2'-diyl) phosphite)-α-D-glucofuranose (**L7d**)

Treatment of 3,3'-di-trimethylsilyl-1,1'-biphenyl-2,2'-diol (0.49 g, 1.5 mmol) and **1** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L7d**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.61) to produce 210 mg (22%) of a white solid. ^{31}P NMR (C_6D_6) δ= 146.0 (s). ^1H NMR (C_6D_6) δ= 0.39 (s, 9H, CH_3-Si), 0.40 (s, 9H, CH_3-Si), 0.98 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 4.00 (dd, 1H, H-6', $^2J_{6'-6}$= 8.4 Hz, $^3J_{6'-5}$= 6.0 Hz), 4.10 (m, 2H, H-6, H-2), 4.44 (m, 1H, H-4), 4.56 (m, 1H, H-5), 5.13 (m, 1H, H-3), 5.85 (d, 1H, H-1,

$^3J_{1\text{-}2}$=4.0 Hz), 7.02 (m, 2H, CH=), 7.16 (m, 2H, CH=), 7.38 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= 0.4 (CH_3-Si), 25.8 (CH_3), 26.4 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 67.9 (C-6), 73.4 (C-5), 77.4 (C-3), 81.8 (d, C-4, $J_{c\text{-}p}$=4.6 Hz), 84.9 (C-2), 106.0 (C-1), 109.8 (C), 112.2 (C), 125.5 (CH=), 125.6 (CH=), 130.8 (C), 132.1 (C), 133.1 (CH=), 133.2 (CH=), 135.7 (CH=), 135.8 (CH=). Anal. calcd (%) for $C_{30}H_{43}O_8PSi_2$: C 58.23, H 7.00; found: C 58.43, H 6.98.

1,2:5,6-di-O-isopropylidene-3-O-((1,1'-biphenyl-2,2'-diyl)phosphite)-α-D-allofuranose (**L8a**)

Treatment of 1,1'-biphenyl-2,2'-diol (0.28 g, 1.5 mmol) and **2** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L8a**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.45) to produce 150 mg (22%) of a white solid. ^{31}P NMR (C_6D_6) δ=139.5 (s). ^{1}H NMR (C_6D_6) δ= 1.16 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.78 (m, 1H, H-6'), 3.93 (m, 1H, H-6), 4.11 (dd, 1H, H-2, $^3J_{2\text{-}3}$=4.2 Hz, $^3J_{2\text{-}1}$=3.6 Hz), 4.17 (m, 1H, H-5), 4.34 (m, 1H, H-4), 4.48 (m, 1H, H-3), 5.33 (d, 1H, H-1, $^3J_{1\text{-}2}$=3.6 Hz), 6.94-7.07 (m, 4H, CH=), 7.20 (m, 2H, CH=), 7.37 (m, 2H, CH=).^{13}C NMR (C_6D_6) δ= 25.9 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 66.5 (C-6), 75.1 (C-3), 76.5 (C-5), 79.4 (C-4), 80.0 (C-2), 104.7 (C-1), 110.6 (CMe_2) 117.4 (CH=), 122.0 (C), 122.6 (C), 123.0 (CH=), 123.1 (CH=), 125.7 (CH=), 127.8 (CH=), 129.7 (CH=), 130.0 (CH=), 130.3 (C), 130.5 (CH=), 132.3 (CH=), 132.7 (C). Anal. calcd (%) for $C_{24}H_{27}O_8P$: C 60.76, H 5.74; found: C 60.82, H 5.89.

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite)-α-D-allofuranose (**L8b**)

Treatment of 3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diol (0.54 g, 1.5 mmol) and **2** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L8b**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.30) to produce 180 mg (19%) of a white solid. ^{31}P NMR (C_6D_6) δ=144.1 (s). ^{1}H NMR (C_6D_6) δ= 1.14 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3,), 1.49 (s, 3H, CH_3), 1.54 (s, 9H, CH_3,

^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 3.33 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.76 (m, 1H, H-6'), 3.82 (m, 1H, H-6) , 4.03 (m, 1H, H-2), 4.17 (m, 1H, H-5), 4.41 (m, 1H, H-4), 4.46 (m, 1H, H-3), 5.42 (d, 1H, H-1, ${}^3J_{1\text{-}2}$=3.6 Hz), 6.71 (m, 2H, CH=), 7.15 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= 26.1 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 27.4 (CH_3), 31.6 (CH_3,^{t}Bu), 35.9 (C), 36.0 (C), 55.4 (OCH_3), 55.5 (OCH_3), 66.0 (C-6), 75.3 (C-3), 76.7 (C-5), 79.4 (d, C-4, $J_{c\text{-}p}$=3.1 Hz), 79.6 (C-2), 104.8 (C-1), 110.1 (C), 113.4 (CH=), 113.6 (C), 114.0 (CH=), 115.0 (CH=), 142.8 (C), 143.7 (C), 143.8 (C), 156.9 (C). Anal. calcd (%) for $C_{34}H_{47}O_{10}P$: C 63.15, H 7.33; found: C 63.08, H 7.42.

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl) phosphite)-α-D-allofuranose (**L8c**)

Treatment of 3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (0.62 g, 1.5 mmol) and **2** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L8c**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.41) to produce 110 mg (12%) of a white solid. ^{31}P NMR ($CDCl_3$) δ=143.2 (s). ^{1}H NMR ($CDCl_3$) δ= 1.29 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 3H, CH_3), 3.62 (m, 1H, H-6'), 3.77 (m, 1H, H-6), 3.95 (m, 1H, H-2), 4.09 (m, 1H, H-4), 4.14 (m, 1H, H-5), 4.33 (m, 1H, H-3), 5.54 (d, 1H, H-1, ${}^3J_{1\text{-}2}$=3.2 Hz), 7.12 (m, 1H, CH=), 7.18 (m, 1H, CH=), 7.43 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$) δ= 25.6 (CH_3), 26.4 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 31.1 (CH_3,^{t}Bu), 31.2 (CH_3,^{t}Bu), 31.4 (CH_3,^{t}Bu), 31.5 (CH_3,^{t}Bu), 34.6 (C), 34.7 (C), 35.4 (C), 65.1 (C-6), 73.5 (C-3), 75.3 (C-5), 77.7 (d, C-4, $J_{c\text{-}p}$=3.9 Hz), 78.5 (C-2), 103.6 (C-1), 109.6 (C), 113.1 (C), 124.0 (CH=), 124.2 (CH=), 125.3 (CH=), 126.2 (CH=), 126.8 (CH=), 128.2 (CH=), 129.0 (CH=), 140.2 (C), 140.4 (C), 133.5 (C), 133.7 (C), 146.6 (C), 146.7 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.89, H 8.63.

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-di-trimethylsilyl-1,1'-biphenyl-2,2'-diyl) phosphite)-α-D-allofuranose (**L8d**)

Treatment of 3,3'-di-trimethylsilyl-1,1'-biphenyl-2,2'-diol (0.49 g, 1.5 mmol) and **2** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L8d**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.68) to produce 180 mg (20%) of a white solid. ^{31}P NMR (C_6D_6) δ=143.4 (s). ^{1}H NMR (C_6D_6) δ= 0.43 (s, 9H, CH_3-Si), 0.45 (s, 9H, CH_3-Si), 1.11 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.66 (m, 2H, H-6', H-2), 3.76 (m, 1H, H-6), 4.12 (m, 1H, H-5), 4.37 (m, 2H, H-3, H-4), 5.33 (d, 1H, H-1, $^3J_{1-2}$=3.6 Hz), 7.02 (m, 2H, CH=), 7.18 (m, 2H, CH=), 7.40 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= -0.1 (CH_3-Si), 25.7 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 65.4 (C-6), 74.6 (d, C-4, J_{c-p}=8.4 Hz), 76.4 (C-5), 78.5 (d, C-3, J_{c-p}=3.0 Hz), 78.9 (C-2), 104.2 (C-1), 113.2 (C), 124.9 (CH=), 125.0 (CH=), 130.3 (C), 130.5 (C), 132.2 (CH=),132.8 (CH=),135.1 (CH=),135.3 (CH=). Anal. calcd (%) for $C_{30}H_{43}O_8PSi_2$: C 58.23, H 7.00; found: C 58.84, H 7.17.

1,2:5,6-di-O-isopropylidene-3-O-((3,3'-5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl) phosphite)-α-D-galactofuranose (**L9c**)

Treatment of 3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (0.62 g, 0.5 mmol) and **3** (390 mg, 0.5 mmol), as described for compound **L7b**, afforded phosphite **L9c**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.55) to produce 80 mg (23%) of a white solid. ^{31}P NMR ($CDCl_3$) δ=137.6 (s). ^{1}H NMR ($CDCl_3$) δ= 1.28 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.34 (s, 18H, CH_3, ^{t}Bu), 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 18H, CH_3, ^{t}Bu), 3.47 (m, 1H, H-6'), 3.91 (m, 2H, H-5, H-6), 4.19 (d, 1H, H-4, $^3J_{4-3}$=8 Hz), 4.27 (dd, 1H, H-2, $^3J_{2-1}$=5.2 Hz, J_{2-P}=4.8 Hz), 4.55 (dd, 1H, H-3, $^3J_{3-4}$=8 Hz, J_{3-P}=5.2 Hz), 5.47 (d, 1H, H-2, $^2J_{2-1}$=5.2 Hz), 7.14 (m, 2H, CH=), 7.41 (m, 2H, CH=), ^{13}C NMR ($CDCl_3$) δ= 24.6 (CH_3), 25.1 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 31.2 (CH_3,^{t}Bu), 31.3 (CH_3,^{t}Bu), 31.7 (CH_3,^{t}Bu), 31.8 (CH_3,^{t}Bu), 34.8 (C), 35.5 (C), 35.6 (C), 62.9 (d, C-6, J_{c-p}=2.2 Hz), 67.2 (d, C-5, J_{c-p}=2.3 Hz), 70.6 (C-4), 70.7 (C-2), 70.8 (C-3), 96.4 (C-1), 108.8 (C), 109.6 (C), 124.4 (CH=), 124.4 (CH=), 125.5 (CH=), 126.7 (CH=), 128.5 (C), 129.2 (C), 129.3 (C), 133.3 (C), 138.3 (C), 140.0 (C), 140.1 (C), 146.5 (C), 146.6 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.98, H 8.62.

2,3:5,6-di-O-isopropylidene-4-O-((3,3'-di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite)-β-D-fructopyranose (**L10b**)

Treatment of 3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diol (0.54 g, 1.5 mmol) and **4** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L10b**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.55) to produce 270 mg (29%) of a white solid. ^{31}P NMR (C_6D_6) δ=149.8 (s). ^{1}H NMR (C_6D_6) δ= 1.13 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 3H, CH_3), 1.60 (s, 12H, , CH_3, CH_3 ^{t}Bu), 3.32 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.80 (m, 1H, H-2), 3.94 (m, 2H, H-1, H-1'), 4.15 (d, 1H, H-6',$^{2}J_{6'-6}$=11.2 Hz), 4.48 (m, 1H, H-3), 4.56 (m, 1H, H-4), 4.65 (d, 1H, H-6, $^{2}J_{6-6'}$=11.6 Hz), 6.68 (m, 2H, CH=), 7.14 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= 26.1 (CH_3), 26.8 (CH_3), 27.8 (CH_3), 28.9 (CH_3), 31.3 (CH_3,^{t}Bu), 31.4 (CH_3,^{t}Bu), 31.9 (CH_3,^{t}Bu), 35.8 (C), 36.1 (C), 55.4 (OCH_3), 55.5 (OCH_3), 60.7 (C-1), 71.8 (C-6), 72.9 (d, C-4, J_{c-p}=9.2 Hz), 74.8 (C-2), 77.2 (C-3), 104.9 (C-5), 109.9 (CMe_2), 112.9 (CMe_2), 113.5 (CH=), 113.7 (CH=), 115.1 (CH=), 115.3 (CH=), 126.0 (C), 129.6 (C), 134.2 (C), 135.6 (C), 140.0 (C), 143.1 (C), 156.6 (C), 157.0 (C). Anal. calcd (%) for $C_{34}H_{47}O_{10}P$: C 63.15, H 7.33; found: C 63.44, H 7.51.

2,3:5,6-di-O-isopropylidene-4-O-((3,3'-5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl) phosphite)-β-D-fructopyranose (**L10c**)

Treatment of 3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (0.62 g, 1.5 mmol) and **4** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L10c**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.43) to produce 290 mg (28%) of a white solid. ^{31}P NMR (C_6D_6) δ=151.7 (s). ^{1}H NMR (C_6D_6) δ= 1.05 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 3H, CH_3), 1.64 (s, 12H, CH_3, CH_3 ^{t}Bu), 3.80 (m, 1H, H-2), 3.94 (m, 2H, H-1, H-1'), 4.12 (d, 1H, H-6',$^{2}J_{6'-6}$=9.6 Hz), 4.50 (m, 1H, H-3), 4.54 (m, 1H, H-4), 5.58 (d, 1H, H-6, $^{2}J_{6\text{-}6'}$=9.6 Hz), 7.28 (m, 1H, CH=), 7.33 (m, 1H, CH=), 7.55 (m, 2H, CH=). ^{13}C NMR (C_6D_6) δ= 26.2 (CH_3), 26.8 (CH_3), 28.0 (CH_3), 29.0 (CH_3), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 31.9 (CH_3,^{t}Bu), 32.0 (CH_3,^{t}Bu), 32.1 (CH_3,^{t}Bu), 34.9 (C), 35.0 (C), 35.9 (C), 36.1 (C), 60.6 (C-1), 71.8 (C-6), 72.8 (d, C-4, $J_{c\text{-}p}$=8.3 Hz), 74.8 (C-2), 77.2 (C-3), 104.9 (C-5), 109.9 (CMe_2), 112.9 (CMe_2), 124.5 (CH=), 124.9 (CH=), 126.0 (C), 127.3 (CH=), 127.6 (CH=), 133.7 (C), 134.9 (C), 138.2 (C), 140.9 (C), 141.0 (C), 146.8 (C), 147.3 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.69, H 8.62.

2,3:4,5-di-O-isopropylidene-6-O-((3,3'-5,5'-tetra-tert-butyl-1,1'-biphenyl-2,2'-diyl) phosphite)-β-D-fructopyranose (**L11c**)

Treatment of 3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (0.62 g, 1.5 mmol) and **5** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L11c**, which was purified by flash chromatography (eluent Toluene/NEt_3 (100:1), Rf: 0.55) to produce 140 mg (15%) of a white solid. ^{31}P NMR (C_6D_6) δ=135.9 (s). ^{1}H NMR (C_6D_6) δ= 0.70 (s, 3H, CH_3), 0.83 (s, 9H, CH_3, ^{t}Bu), 0.86 (s, 9H, CH_3, ^{t}Bu), 0.95 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.20 (s, 9H, CH_3, ^{t}Bu), 1.21 (s, 9H, CH_3, ^{t}Bu), 3.14 (d, 1H, H-6',$^{1}J_{6'\text{-}6}$=16.8 Hz), 3.31 (m, 2H, H-6, H-4), 3.60 (m, 1H, H-1'), 3.94 (m, 1H, H-1), 4.00 (dd, 1H, H-3, $^{3}J_{3\text{-}2}$=14.0 Hz, $^{3}J_{3\text{-}4}$=3.6 Hz), 4.18 (d, 1H, H-2, $^{2}J_{2\text{-}1}$=3.6 Hz), 6.80 (d, 1H, CH=), 6.90 (d, 2H, CH=), 7.16 (m, 1H, CH=). ^{13}C NMR (C_6D_6) δ= 24.7 (CH_3), 26.1 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 31.9 (CH_3,^{t}Bu), 32.0 (CH_3,^{t}Bu), 34.9 (C), 35.0 (C), 36.0 (C), 61.8 (C-6), 64.9 (C-1), 70.4 (C-2), 71.0 (C-3), 71.8 (C-4), 102.9 (C-5), 109.0 (CMe_2), 109.3 (CMe_2), 124.7 (CH=), 124.8 (CH=), 126.0 (C), 127.3 (CH=), 128.6 (CH=), 128.9 (C), 129.6 (C),133.9 (C), 140.6 (C), 140.8 (C), 147.1 (C), 147.3 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.99, H 8.71.

3.4.4.3. Typical procedure of allylic alkylation of substrates S1-S3

A degassed solution of $[Pd(\pi-C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-phosphoroamidite (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (0.5 mmol) in THF (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, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min).[19] For substrates **S2** and **S3**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column.[20]

3.4.4.4. Typical procedure of allylic alkylation of monosubstituted linear substrates S4

A degassed solution of $[Pd(\pi-C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-phosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (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, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7

mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.[21]

3.4.5. Acknowledgements

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Chapter 4

Pd-catalyzed asymmetric Heck reactions

4. Pd-catalyzed asymmetric Heck reaction

4.1. Background

In the last few years, the phosphine-oxazoline ligands have emerged as suitable ligands for the intermolecular Heck reaction. Two of the most representative examples of this type of ligands are the PHOX ligands developed by Pfaltz and coworkers[1] and the phosphine-oxazoline based on ketopinic acid developed by Gilberston and coworkers[2] (Figure 1). Despite these successes, ligands that provide good regio- and enantioselectivities usually have two considerable drawbacks: (1) reaction times are usually long and (2) they are prepared from expensive chiral synthons or in tedious synthetic steps. Therefore, it is very important to develop ligands that induce higher rates and selectivities (regio- and enantioselectivities) based on simple starting materials in this reaction. More research is therefore needed to study the possibilities offered by other classes of ligands in this process. As we discussed in the introduction (Chapter 1), in the last few decades carbohydrate ligands have been widely used in asymmetric catalysis. However, their full potential in providing chiral ligands has hardly been studied in Heck reactions. Only two reports on the highly enantioselective palladium-catalysed asymmetric Heck reaction have been reported using these systems.[3] To our knowledge, phosphite-oxazoline, phosphite-phosphoroamidite and monophosphite ligands have not been applied before in this process.

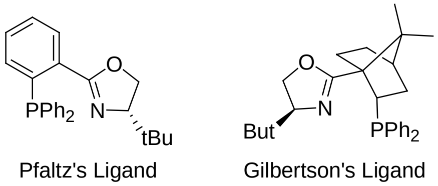

Figure 1. Representative phosphine-oxazoline ligands for asymmetric Pd-catalyzed Heck reactions

In chapter 4.2, we report the application of the phosphite-oxazoline ligand library **L1-L4a-g** previously synthesised in chapter 3 in the asymmetric Pd-catalyzed Heck reaction. We found that the degree of isomerization and the effectiveness in transferring the chiral information in the product and the activity can be tuned by correctly choosing ligand components (phosphite and oxazoline substituents). Excellent activities (up to 100% conversion in 10 minutes), regio- (up to >99%) and enantioselectivities (ee's up to 99%) were obtained in a wide range of substrates and triflate sources. Unfortunately, the preliminary studies using the phosphite-phosphoroamidite **L6a-c** and monophosphite **L7-L11a-f** ligand libraries in several reaction conditions showed low activities and selectivities. Therefore, the former library resulted to be inactive while the later showed low activities (< 20% yield after 4 days) and low regio- and enantioselectivities (< 10%).

4.1.1. References

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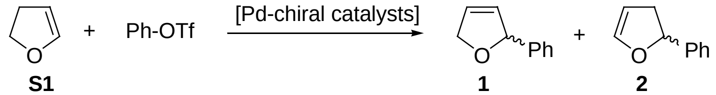
4.2. Screening of a modular sugar-based phosphite-oxazoline ligand library in asymmetric Pd-catalyzed Heck reactions

Abstract. We have also tested the previously described phosphite-oxazoline ligand library **L1-L4a-g** in the palladium-catalyzed Heck reactions. Excellent regio- (up to 99%) and enantioselectivities (ee's up to 99%) and improved activities have been achieved for several substrates in standard thermal conditions. The results indicate that the catalytic performance is highly affected by the oxazoline and biaryl-phosphite substituents and the axial chirality of the biaryl moiety of the ligand. The Heck reactions were also performed under microwave irradiation conditions, allowing a considerably shorter reaction time (full conversion in minutes) maintaining the excellent regio- and enantioselectivities.

4.2.1. Introduction

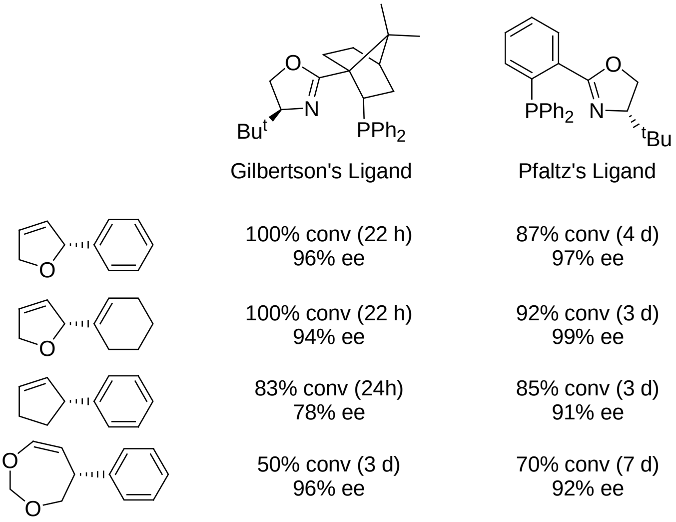
Catalytic asymmetric carbon-carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this respect, the asymmetric Pd-catalyzed Heck reaction coupling of an aryl or alkenyl halide or triflate to an alkene is a powerful and highly versatile procedure because it tolerates several functional groups.[1] Chiral bidentate phosphine ligands have played a key role in the success of this process.[1] However, in the intermolecular Heck reaction, regioselectivity is often a problem. So, for example, in the Heck reaction of 2,3-dihydrofuran **S1** with phenyl triflate, a mixture of two products is obtained - the expected product 2-phenyl-2,5-dihydrofuran (**1**) and 2-phenyl-2,3-dihydrofuran (**2**; Scheme 1). The latter is formed due to an isomerization process.[1]



S1 **1** **2**

Scheme 1. Model Pd-catalyzed Heck reaction of 2,3-dihydrofurane **S1**.

In the last few years, a class of heterodonor ligands - the phosphine-oxazoline - have emerged as suitable ligands for the intermolecular Heck reaction.[2] Two of the most representative examples of this type of ligands are the PHOX ligands developed by Pfaltz[2a,b] and coworkers and the phosphine-oxazoline based on ketopinic acid developed by Gilberston and coworkers[2e]. Despite these successes, ligands that provide good regio- and enantioselectivities usually have two considerable drawbacks: (1) reaction times are usually long and (2) they are prepared from expensive chiral synthons or in tedious synthetic steps (Scheme 2). Therefore, it is very important to develop ligands that induce higher rates and selectivities (regio- and enantioselectivities) based on simple starting materials in this reaction. Carbohydrates are particularly advantageous for this purpose due to their low price and easy modular constructions.



Scheme 2. Summary of the best results using the most representative ligand families developed for the Pd-catalyzed Heck reactions (reactions usually carried out with 3-5 mol% of Pd).

In this context, to further expand the range of ligands and to improve the performance of these asymmetric Pd-catalyzed Heck reactions, we tested the library of chiral phosphite-oxazoline ligands **L1-L4a-g** (Figure 1), previously synthesized in section 3.2. As previously mentioned in Chapter 3, these ligands are derived from natural D-glucosamine and have the advantages of carbohydrate and phosphite ligands, such as availability at a low price from readily available alcohols and facile modular constructions.[3] Furthermore, they are less sensitive to air than typical phosphines, which are widely used as ligands in asymmetric catalysis. In addition, the introduction of a phosphite moiety in the ligand design is proved to be highly advantageous in terms of activity because of its greater π-acceptor ability.[4] All these favourable features enable a series of chiral ligands to be synthesized and screened in the search for high activity and selectivity. Although carbohydrate-based ligands have been successfully used in other enantioselective reactions,[3] there are only two reports on the highly enantioselective palladium-catalysed asymmetric Heck reaction using this type of ligand.[5]

Herein, we screen the potential use of the phosphite-oxazoline ligand library **L1-L4a-g** in the Pd-catalyzed asymmetric Heck reaction of several substrates and triflate sources. The screening of the library were performed using a series of parallel reactors each equipped with 12 different positions. With this library we fully investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituents (**L1-L4**) and different substituents/configurations in the biaryl phosphite moiety (**a-g**). By carefully selecting these elements, we achieved high selectivities (regio- and enantioselectivities) and activities in different substrate types and aryl sources.

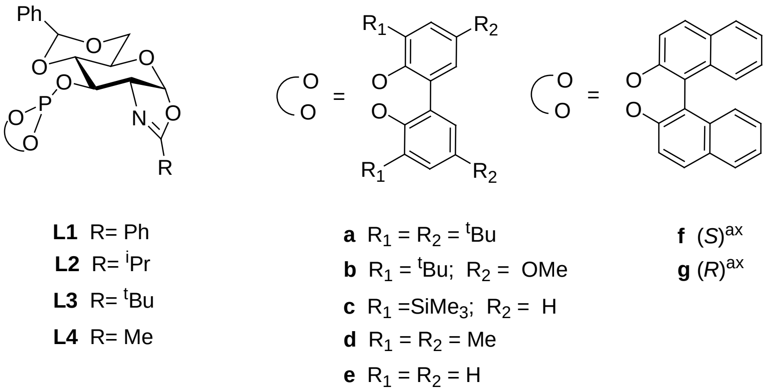


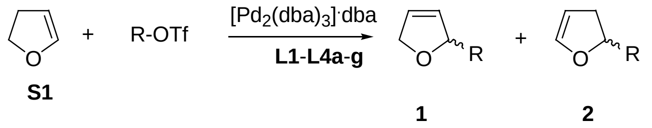
Figure 1. Carbohydrate-based phosphite-oxazoline ligands **L1**-**L4a**-**g**

4.2.2. Results and Discussion

4.2.2.1. Asymmetric Heck Reactions under thermal conditions

4.2.2.1.1. Heck reaction of 2,3-dihydrofuran S1 (equation 1)

In this section, we report the use of the chiral phosphite-oxazoline ligand library **L1-L4a-g** (Figure 1) in the Pd-catalyzed asymmetric Heck reaction of 2,3-dihydrofuran **S1** (equation 1) using several triflates with different electronic and steric properties: phenyl triflate, 1-naphthyl triflate, toluyl tryflate, *para*-nitrophenyltriflate and cyclohexenyl triflate. In all cases, the catalysts were generated *in situ* by mixing $[Pd_2(dba)_3]\cdot$dba with the corresponding chiral ligand.



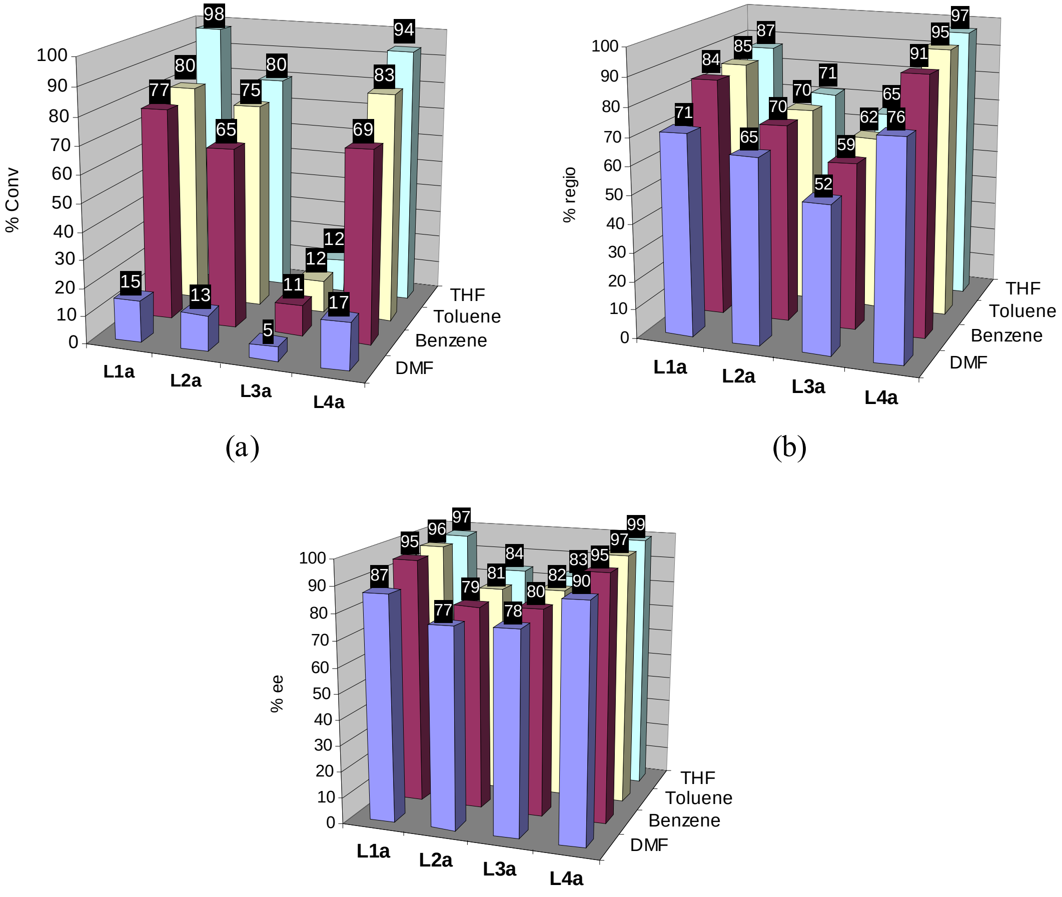
(1)

R= C_6H_5, 1-Naphthyl, p-CH_3-C_6H_4, p-NO_2-C_6H_4, C_6H_9

For an initial evaluation of this new type of ligand in the palladium-catalysed asymmetric Heck reaction, we chose the phenylation of **S1** (eq 1, R= C_6H_5). As this reaction has been carried out with a variety of ligands carrying different donor groups, it is possible to directly compare the efficacy of different ligand systems.

In a first set of experiments, we determined the optimal reaction conditions by conducting a series of experiments in which we varied the solvent, temperature and base. In all cases, the formation of the desired product 2-phenyl-2,5-dihydrofuran **1** was favored over the formation of 2-phenyl-2,3-dihydrofuran **2**.

We first studied the effect of the solvent. Four solvents (tetrahydrofurane (THF), benzene, toluene and dimethylformamide (DMF)) and four ligands (**L1a**, **L2a**, **L3a** and **L4a**) were tested. The results show that the efficiency of the process strongly depended on the nature of the solvent (Figure 1). The best activity and selectivity (regio- and enantioselectivity) was achieved with tetrahydrofurane as the solvent.



(a) (b)

(c)

Figure 1. Catalytic results of the phenylation of **S1** using ligands **L1a**, **L2a**, **L3a** and **L4a** in four solvents at 50 ºC and using $^{i}Pr_2NEt$ as base. (a) Conversions after 24h. (b) Regioselectivities in product **1**. (c) Enantioselectivities of product **1**. Positive numbers refer to the formation of the *R*-isomer in excess.

We next studied the effect of varying the temperature. The conversion and selectivity when THF was used as a solvent and ligands **L1a** and **L4a** are shown in Table 1 (similar tendencies were observed with other solvents and ligands). We observed that this parameter affected both activity and selectivity. Increasing the temperature from 50 ºC to 75 ºC had a negative effect on regio- and enantioselectivity (Table 1, entries 1 and 4 vs 2 and 5). Lowering the temperature to 25 ºC hardly affected regio- and enantioselectivity, but activities dropped considerably (Table 1, entry 1 and 3 vs 4 and 6). The best trade-off between activity and selectivity was therefore achieved at 50 ºC.

Table 1. Selected results for the Pd-catalysed enantioselective phenylation of **S1** using ligands **L1a** and **L4a**. Effect of temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	75	100 (80:20)	93 (*R*)	87 (*R*)
3	**L1a**	25	28 (88:12)	98 (*R*)	88 (*R*)
4	**L4a**	50	94 (97:3)	99 (*R*)	nd[d]
5	**L4a**	75	100 (91:9)	94 (*R*)	91 (*R*)
6	**L4a**	25	29 (97:3)	99 (*R*)	nd[d]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

We then studied the effect of several bases. The conversion and selectivity when THF was used as a solvent with ligands **L1a** and **L4a** are shown in Table 2 (similar trends were observed for the other solvents and ligands). Although the activities and regioselectivities obtained with proton sponge (PS) and diisopropylethylamine are comparable, the use of the latter base provides slightly better enantioselectivities (Table 2, entries 1 and 9 vs 2 and 10). On the other hand, sodium acetate yielded the highest regioselectivity, but its activities and enantioselectivities are lower than those of diisopropylethylamine (Table 2, entries 1 and 9 vs 3 and 11). The remainder of the bases tested provided lower activities and selectivities than those obtained with diisopropylamine (Table 2, entries 1 and 9 vs 4-8, 12 and 13). In conclusion we chose diisopropylethylamine as our base.

Table 2. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L4a**. Effect of the base.[a]

Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	PS	99 (87:13)	95 (*R*)	87 (*R*)
3	**L1a**	NaOAc	91 (91:9)	91 (*R*)	56 (*R*)
4	**L1a**	NEt_3	97 (82:18)	87 (*R*)	84 (*R*)
5	**L1a**	KOAc	53 (82:18)	43 (*R*)	47 (*R*)
6	**L1a**	K_2CO_3	89 (86:14)	88 (*R*)	27 (*R*)
7	**L1a**	Li_2CO_3	92 (68:32)	95 (*R*)	92 (*R*)
8	**L1a**	DBU	6 (72:28)	65 (*R*)	43 (*R*)
9	**L4a**	$^{i}Pr_2NEt$	94 (97:3)	99 (*R*)	nd[d]
10	**L4a**	PS	94 (96:4)	98 (*R*)	nd[d]
11	**L4a**	NaOAc	89 (98:2)	92 (*R*)	nd[d]
12	**L4a**	NEt_3	93 (88:12)	95 (*R*)	89 (*R*)
13	**L4a**	KOAc	62 (84:16)	57 (*R*)	38 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

In the end we found that, the optimum trade-off between selectivities and reaction rates was achieved with tetrahydrofurane, a temperature of 50 ºC and diisopropylethylamine as a base. These optimal conditions were then used to test the catalytic performance of the complete series of ligands. The results, which are summarized in Table 3, indicate that the catalytic performance (activity and selectivity) is highly affected by the substituents at both oxazoline and phosphite moiety and by the axial chirality of the biaryl phosphite moiety. In general, high activities, regio- (up to 98%) and enantioselectivities (ee's up to 99%) were obtained in the phenylation of **S1**.

The effect of the oxazoline substituent was studied with ligands **L1a, L2a, L3a, L4a** (Table 3, entries 1, 8-10). We found that these substituents affected both activities and selectivities. Therefore, we observed that when the size of the group on the oxazoline decreased, the regio- and enantioselectivity of the catalyst increased (i.e. Me > Ph > ^{i}Pr > ^{t}Bu). This contrasts with the oxazoline-substituent effect observed for phosphine-oxazoline PHOX ligands, whose enantioselectivities are higher when bulky *tert*-butyl groups are present.[2a,b] In terms of activity, this is mainly affected by the bulkiness of the oxazoline group. Therefore, activity decreases when bulky substituents are present (Table 3, entries 1 and 9 vs 8 and 9). However, the electronic properties of the oxazoline substituent have a slight but important effect on activity. Activities are therefore highest when a phenyl oxazoline moiety is present (Table 3, entries 1 vs 10).

The effects of phosphite moieties were studied using ligands **L1a-g** (Table 3, entries 1-7, 10, 11). We found that this moiety affected both activity and selectivity. Bulky substituents in the *ortho* positions of the biphenyl moiety are needed for high activities, regio- and enantioselectivities. Thus, ligands **L1a**, **L1b** and **L1c** with bulky substituents at the *ortho* positions of the biphenyl moiety provided higher activities and selectivities than ligands **L1d** and **L1e** with small substituents in these positions (Table 3, entries 1, 2, 3 vs 4, 5). However, substituents in the *para* positions also play a small but crucial role. Therefore, the best activities and selectivities were obtained using ligands **L1c**, which contain bulky trimethylsilyl groups at the *ortho* positions and a small hydrogen at the *para* positions of the biphenyl moiety. To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moiety, ligands **L1f** and **L1g** containing different enantiomerically pure binapthyl moieties were also tested (Table 3, entries 6 and 7). The results indicate that there is a cooperative effect between the configuration of the biaryl moiety and the configurations of the ligand backbone on enantioselectivity that results in a matched combination for ligand **L1g**, which contains an *R*-binaphtyl moiety.

To sum up, the best result was obtained with ligand **L4c**, which contains the optimal combination of substituents in the oxazoline and in the biaryl phosphite moieties (Table 3, entry 11). These results clearly show the efficiency of using highly modular scaffolds in the ligand design. In addition, the introduction of a phosphite moiety in the ligand design have been very advantageous in terms of activity (total conversion in 15 hours). These results are among the best reported so far.[2a,b,e]

Table 3. Selected results for the Pd-catalysed enantioselective phenylation of 2,3-dihydrofuran **S1** using phosphite-oxazoline ligand library **L1-L4a-g**.[a]

Entry	Ligand	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1b**	86 (85:15)	97 (*R*)	89 (*R*)
3[d]	**L1c**	100 (97:3)	99 (*R*)	nd[e]
4	**L1d**	42 (72:28)	25 (*R*)	16 (*R*)
5	**L1e**	45 (60:40)	80 (*R*)	69 (*R*)
6	**L1f**	32 (58:42)	6 (*R*)	19 (*R*)
7	**L1g**	28 (55:45)	73 (*R*)	48 (*R*)
8	**L2a**	80 (71:29)	84 (*R*)	90 (*R*)
9	**L3a**	12 (65:35)	83 (*R*)	23 (*R*)
10	**L4a**	94 (97:3)	99 (*R*)	nd[e]
11	**L4c**	100 (98:2)	99 (*R*)	nd[e]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [d] t = 15 h. [e] not determined.

To further study the effects of electronic and steric properties of the aryl triflate source on the product outcome, we tested these new ligands in the Pd-catalyzed Heck reaction of **S1** with several aryl triflates, in which these properties were systematically varied (eq 1, R= 1-naphthyl, *p*-CH_3-C_6H_4, *p*-NO_2-C_6H_4). The most noteworthy results are shown in Table 4. They followed the same trend in terms of the effect of the oxazoline and phosphite moieties as the phenylation of **S1** (see section 4.2.7. Supporting information, Table 9). In general, high activities, regio- (up to 99%) and enantioselectivities (ee's up to 99%) were also obtained in the arylation of **S1**. The results indicates that both steric and electronic parameters on the triflate affected catalytic performance. Thus, enantioselectivities are best for 1-naphthyl- and phenyltriflate (Table 4, entries 1, 2, 5, 6, 9 and 10). On the other hand regioselectivities are better when electron-withdrawing aryl triflates are used (Table 4, entries 4, 8, 12).

Table 4. Selected results for Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1** using ligands **L1a**, **L1c** and **L4a**.[a]

Entry	Ligand	R	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	C_6H_5	98 (87:13)	97 (*R*)	88 (*R*)
2	**L1a**	1-Naphthyl	88 (86:14)	97 (*R*)	89 (*R*)
3	**L1a**	*p*-CH_3-C_6H_4	99 (82:18)	94 (*R*)	91 (*R*)
4	**L1a**	*p*-NO_2-C_6H_4	94 (95:5)	88 (*R*)	nd[f]
5[e]	**L1c**	C_6H_5	100 (97:3)	99 (R)	nd[f]
6[e]	**L1c**	1-Naphthyl	89 (95:5)	99 (*R*)[d]	93 (*R*)
7[e]	**L1c**	*p*-CH_3-C_6H_4	94 (85:15)	96 (*R*)	93 (*R*)
8[e]	**L1c**	*p*-NO_2-C_6H_4	89 (>99:1)	90 (*R*)	nd[f]
9	**L4a**	C_6H_5	94 (97:3)	99 (*R*)	nd[f]
10	**L4a**	1-Naphthyl	85 (95:5)	99 (*R*)	nd[f]
11	**L4a**	*p*-CH_3-C_6H_4	95 (87:13)	96 (*R*)	89 (*R*)
12	**L4a**	*p*-NO_2-C_6H_4	87 (>99:1)	91 (*R*)	nd[f]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), aryl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Enantiomeric excesses measured by HPLC. [e] t = 15 h. [f] not determined.

We also evaluated the ligand library in the Heck reaction of **S1** using cyclohexenyl triflate. The preliminary investigations performed into the solvent and base effect revealed a different trend regarding the base effect than those with the previously tested aryl triflates. Therefore, the best selectivities (regio- and enantioselectivities) and reaction rates were obtained when THF and proton sponge are used as a solvent and base, respectively (see section 4.2.7. Supporting information, Tables 10-12).

The results of using ligands **L1-L4a-g** under the optimised conditions are shown in Table 5. In general, high activities, regio- (up to 98%) and enantioselectivities (ee's up to

98%) were also obtained in this case. Again enantioselectivity was affected by the substituents at both oxazoline and phosphite moiety and the cooperative effect between stereocenters. However, the effect of these parameters was different from those observed in the arylation of **S1**. Thus, regio- and enantioselectivities were best with ligand **L1a** (regio's up to 98%, ee's up to 98%). These results clearly show the importance of using modular scaffolds in the ligand design.

Regarding the effect of the oxazoline substituents, again the presence of bulky substituents in this position considerably decreased activities and selectivities (Table 5, entries 1, 8-10). However, in contrast to the arylation of **S1**, the electronic effect was more important. Therefore, selectivities are higher when a phenyl substituent is present (Table 5, entry 1 vs 10).

Concerning the effect of the phosphite moiety on catalytic performance, again the presence of bulky substituents in the *ortho* positions of the biphenyl moiety were necessary for high selectivities. However, the effect of the type of substituents at the *para* positions in selectivity is more pronounced than for the arylation of **S1**. Thus, whereas good selectivities are obtained with ligands **L1a** and **L1c**, regioselectivity dropped considerably for ligand **L1b**, which contains methoxy groups at the *para* positions (Table 5, entries 1 and 3 vs 2).

Finally, the effect of the configuration of the biaryl phosphite moiety follows a similar trend as those with the previous arylation of **S1** (Table 5, entries 6 and 7).

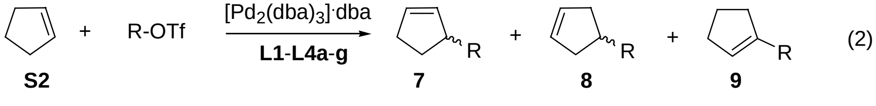
Table 5. Selected results for the Pd-catalysed enantioselective cyclohexenylation of 2,3-dihydrofuran **S1** using ligands **L1-L4a-g**.[a]

Entry	Ligand	% Conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	100 (98:2)	98 (*R*)	nd[d]
2	**L1b**	88 (80:20)	96 (*R*)	36 (*R*)
3	**L1c**	100 (92:8)	97 (*R*)	52 (*R*)
4	**L1d**	99 (74:26)	82 (*R*)	76 (*R*)
5	**L1e**	57 (58:42)	45 (*R*)	32 (*R*)
6	**L1f**	42 (55:45)	12 (*R*)	9 (*R*)
7	**L1g**	38 (53:47)	38 (*R*)	9 (*R*)
8	**L2a**	94 (84:16)	98 (*R*)	45 (*R*)
9	**L3a**	44 (51:49)	77 (*R*)	5 (*R*)
10	**L4a**	100 (88:12)	95 (*R*)	56 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), proton sponge (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not measured.

4.2.2.1.2. Heck reaction of cyclopentene S2 (equation 2)

We also screened the phosphite-oxazoline ligand library in the phenylation and alkenylation of cyclopentene **S2** (equation 2). Selectivity for **S2** is more difficult to control than for functionalized alkenes such as **S1** due to extensive double bond migration.[1] Moreover, in addition to the desired product **7**, regioisomer **8** and the achiral product **9** can also be obtained. Therefore, to date only high regio- (regio's up to 96% in product **7**) and enantioselectivities (ee's up to 91%) have been obtained with the phosphine-oxazoline PHOX ligands developed by Pfaltz and coworkers.[2a,b]



(2)

R= C_6H_5, C_6H_9

In this section, we report that the chiral phosphite-oxazoline ligands **L1-L4a-g** applied in the previous section to the Pd-catalyzed arylation and alkenylation of substrate **S1**, can also be used for unfunctionalised alkene substrate **S2**. In this case, two triflate sources were used (eq 2): phenyl triflate and cyclohexenyl triflate. In general, high activities and selectivities (regio's up to 94% and ee's up to 96%) were obtained in the phenylation and cyclohexenylation of **S2**. Interestingly, the formation of achiral product **9** did not take place. These results compete favourably with the best reported in the literature.[2a,b]

Preliminary investigations into the solvent and base effects revealed the same trends as those with the previously tested substrate **S1** with aryltriflate. The trade-off between selectivities and reaction rates was optimum with THF as solvent and diisopropylethylamine as base (see section 4.2.7. Supporting information, Tables 13-15).

The results of using the phosphite-oxazoline ligand library under the optimized conditions are shown in Table 6. In general, they follow the same trends as for the alkenylation of **S1**. Although, as expected, the activities were lower than in the alkenylation of **S1**, they were much higher than those obtained with the most successful ligand system.[2a,b] Again, the presence of a phosphite moiety in the ligand design has been highly advantageous in terms of activity and enantioselectivity.

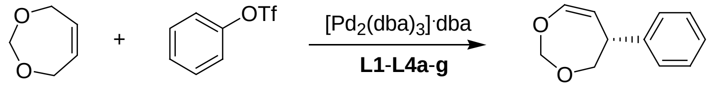
Table 6. Selected results for Pd-catalyzed enantioselective phenylation and cycloalkenylation of cyclopentene **S2** using ligands **L1-L4a-g**.[a]

Entry	Ligand	R	% Conv (**7**:**8**)[b]	% ee **7**[c]	% ee **8**[c]
1	**L1a**	C_6H_5	100 (94:6)	95 (*R*)	nd[d]
2	**L1b**	C_6H_5	98 (85:15)	94 (*R*)	66 (*R*)
3	**L1c**	C_6H_5	100 (92:8)	95 (*R*)	82 (*R*)
4	**L1d**	C_6H_5	93 (79:21)	75 (*R*)	57 (*R*)
5	**L1e**	C_6H_5	47 (51:49)	44 (*R*)	34 (*R*)
6	**L1f**	C_6H_5	42 (45:55)	12 (*R*)	9 (*R*)
7	**L1g**	C_6H_5	44 (52:48)	45 (*R*)	42 (*R*)
8	**L2a**	C_6H_5	94 (86:14)	87 (*R*)	68 (*R*)
9	**L3a**	C_6H_5	34 (49:51)	59 (*R*)	11 (*R*)
10	**L4a**	C_6H_5	100 (93:7)	94 (*R*)	86 (*R*)
11	**L1a**	C_6H_9	100 (95:5)	96 (*R*)	nd[d]
12	**L1b**	C_6H_9	94 (83:17)	95 (*R*)	67 (*R*)
13	**L1c**	C_6H_9	100 (93:7)	96 (*R*)	78 (*R*)
14	**L1d**	C_6H_9	100 (78:22)	82 (*R*)	79 (*R*)
15	**L1e**	C_6H_9	45 (54:46)	51 (*R*)	60 (*R*)
16	**L1f**	C_6H_9	41 (52:48)	11 (*R*)	5 (*R*)
17	**L1g**	C_6H_9	47 (53:47)	49 (*R*)	16 (*R*)
18	**L2a**	C_6H_9	98 (85:15)	93 (*R*)	89 (*R*)
19	**L3a**	C_6H_9	56 (63:37)	61 (*R*)	18 (*R*)
20	**L4a**	C_6H_9	100 (92:8)	94 (*R*)	89 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S2** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), T = 70 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

4.2.2.1.3. Heck reaction of 4,7-dihydro-1,3-dioxepin S3 (equation 3)

Encouraged by the excellent results obtained for the arylation and alkenylation of 2,3-dihydrofuran **S1** and cyclopentene **S2**, we also examined the phenylation of 4,7-dihydro-1,3-dioxepin **S3** (eq. 3). This substrate is of great importance since the resulting enolethers **10** are easily converted to chiral β-aryl-γ-butyrolactones, which are useful synthetic intermediates.[6] Despite this interesting characteristic, there are only few reports that study this substrate.[2a,b,e,h] An important drawback for this substrate is that the catalysts developed to date proceed at low reaction rates (i.e. the reaction takes typically 5 to 7 days for full conversion).[2a,b,e,h]



S3 **10** (3)

Interestingly, under non optimized conditions, our new ligands also proved to be highly efficient in terms of activity and enantioselectivity in the phenylation of **S3** (Table 7). The results indicated that enantioselectivities and activities are mainly affected by the steric properties of the oxazoline substituents. We found that when the size of the group on the oxazoline increased, activity and enantioselectivity of the catalyst decreased (entries 1 vs 4 and 5). The highest enantioselectivities (ee's up to 92%) and activities were obtained using ligands **L1a** and **L1c**. In addition, comparing these excellent results with the activities obtained with Pfaltz's and Gilbertson's ligand Pd-systems (Scheme 2) in the phenylation of **S3** we can conclude that the presence of a phosphite moiety has been highly advantageous. These results are among the best reported so far.[2a,b,e]

Table 7. Selected results for the Pd-catalysed enantioselective phenylation of **S3** using ligands **L1-L4a-g**.[a]

Entry	Ligand	% Conv[b]	% ee **10**[c]
1	**L1a**	100	92 (*R*)
2	**L1b**	98	88 (*R*)
3[d]	**L1c**	100	92 (*R*)
4	**L2a**	95	75 (*R*)
5	**L3a**	54	61 (*R*)
6	**L4a**	100	90 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S3** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), T = 70 ºC, t = 2.5 days. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] t = 2 days

4.2.2.2. Microwave-assisted asymmetric Heck Reactions

The benefits of microwave irradiation, including reduction of reaction rates and electricity costs, have already been reported in several C-C coupling reactions.[7] Therefore, we decided to use the advantages of microwave irradiation in the asymmetric Pd-catalyzed Heck reactions using the ligand library **L1-L4a-g**. To the best of our knowledge there is only one report on the use of microwave irradiation for the enantioselective Heck reactions using PHOX Pfaltz's and BINAP ligands. Under optimal reaction conditions they considerably shortened reaction times (from 4 days to 1 hour) but enantioselectivities were lower compared to those obtained under thermal conditions.[8]

As an initial evaluation we studied the Pd-catalyzed asymmetric Heck reaction of substrate **S1** using two different triflate sources (phenyl triflate and cyclohexenyl triflate) with ligands **L1a** and **L1c** (Table 8). After studying three different temperatures, we found that the optimal temperature was 70 ºC. At lower temperatures, activities and selectivities decreased (Table 8, entries 3 and 6 vs 1, 2, 4 and 5).

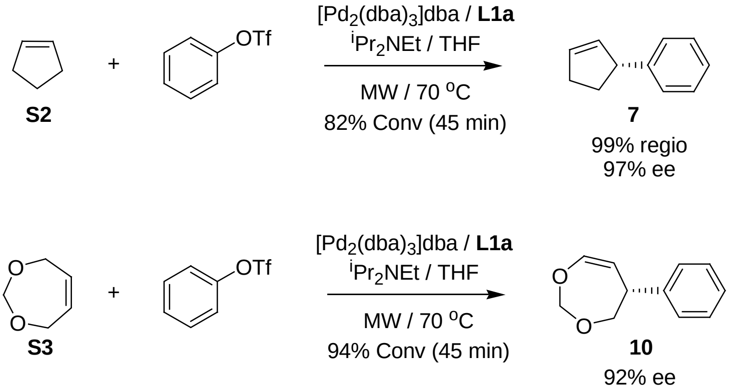
It is interesting to note that under microwave irradiation, reaction times have been dramatically improved (from 15 hours to 10 minutes) while maintaining the excellent regio- (up to 98%) and enantioselectivities (ee's up to 99%) obtained under thermal conditions.

Table 8. Microwave-assisted Pd-catalysed enantioselective arylation and alkenylation of 2,3-dihydrofuran **S1** using ligands **L1a** and **L1c**.[a]

Entry	Ligand	R	T (ºC)	t (min)	% Conv (**1**:**2**)[b]	% ee **1**[c]
1	**L1a**	C_6H_5	50	15	81 (96:4)	93 (*R*)
2	**L1a**	C_6H_5	40	15	12 (94:6)	91 (*R*)
3	**L1a**	C_6H_5	70	10	99 (96:4)	96 (*R*)
4	**L1c**	C_6H_5	70	10	100 (98:2)	99 (*R*)
5	**L1a**	C_6H_9	50	15	82 (93:7)	89 (*R*)
6	**L1a**	C_6H_9	70	10	100 (95:5)	93 (*R*)
7	**L1c**	C_6H_9	70	10	100 (93:7)	97 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol). [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC.

Encouraged by these excellent results, we also studied the phenylation of cyclopentene **S2** and 4,7-dihydro-1,3-dioxepin **S3** which required longer reaction times under thermal conditions than substrate **S1** (Scheme 4). Again, the use of microwaves was highly advantageous, providing excellent regio- and enantioselectivities with much lower reaction times (from 2 days to 45 minutes). It should be noted that for substrate **S2**, the use of microwave irradiation also improved regio- and enantioselectivity. Therefore, the reaction of cyclopentene **S2** and phenyltriflate at 70 ºC gave the coupling product **7** with 97 % ee in 99% regioselectivity.



Scheme 4. Pd-catalyzed Heck reactions of **S2** and **S3** using ligand **L1a** under microwave irradiation.

4.2.3. Conclusions

A library of readily available phosphite-oxazoline ligands has been applied in Pd-catalyzed asymmetric Heck reactions of several substrates and triflates under thermal and microwave conditions. These ligands have the advantage that they are easily prepared in a few steps from commercial D-glucosamine as an inexpensive natural chiral source. In addition, they can be easily tuned in the oxazoline and biaryl phosphite moieties, so that their effect on catalytic performance can be explored. We found that the degree of isomerization and the effectiveness in transferring the chiral information in the product and the activity can be tuned by correctly choosing ligand components (phosphite and oxazoline substituents). Excellent activities (up to 100% conversion in 10 minutes), regio- (up to >99%) and enantioselectivities (ee's up to 99%) were obtained in a wide range of substrates and triflate sources. These results compete favourably with the most successful ligands developed for this reaction.[1]Note also that these ligands provided higher activities than those for other successful ligands. The use of microwave irradiation conditions allowed a considerably shorter reaction times (full conversion in few minutes) maintaining excellent regio- and enantioselectivities. These results open up a new class of ligands for the highly active and enantioselective Pd-catalysed Heck reaction, which will be of great practical interest.

4.2.4. Experimental Section

4.2.4.1. General Considerations

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L1-L4a-f** have been previously described in Chapter 3.2. All other reagents were used as commercially available. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. The chemical shifts are referenced to tetramethylsilane (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. The ^1H and ^{13}C NMR spectral assignments were determined by ^1H-^1H and ^1H-^{13}C correlation spectra. Microwave experiments were carried out using a CEM Explorer, in which the temperature is controlled by a non-contact infrared sensor that is located beneath the cavity floor and "looks" up at the bottom of the vessel.

4.2.4.2. General procedure for the Pd-catalyzed enantioselective Heck reactions

A mixture of $[Pd_2(dba)_3]$dba (12 mg, 1.25 x 10-2 mmol) and the corresponding chiral ligand (2.8 x 10-2 mmol) in dry degassed solvent (3.0 mL) was stirred under argon at room temperature for 15 min. The corresponding olefin (2.0 mmol), triflate (0.50 mmol) and base (1.0 mmol) were added to the catalyst solution. The solution was stirred at the desired temperature under argon. After the desired reaction time, the mixture was diluted with additional diethyl ether and washed with water, dried over $MgSO_4$ and evaporated. For compounds 2-(1-naphthyl)-2,5-dihydrofuran and 2-(4-nitrophenyl)-2,5-dihydrofuran conversion was measured by ^1H-NMR and selectivity was measured by HPLC.[2b] For the rest of compounds, conversion and selectivity were determined by GC.[2e]

4.2.5. Acknowledgements

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4.2.7. Supporting information

1.- Table 9. Pd-catalyzed arylation of **S1**.

2.- Table 10. Pd-catalyzed cyclohexenylation of **S1**. Effect of the solvent.

3.- Table 11. Pd-catalyzed cyclohexenylation of **S1**. Effect of the temperature.

4.- Table 12. Pd-catalyzed cyclohexenylation of **S1**. Effect of the base.

5.- Table 13. Pd-catalyzed phenylation of **S2**. Effect of the solvent.

6.- Table 14. Pd-catalyzed phenylation of **S2**. Effect of the temperature.

7.- Table 15. Pd-catalyzed phenylation of **S2**. Effect of the base.

8.- Temperature, power and pressure vs time profiles for the microwaves experiments.

Table 9. Selected results for the Pd-catalysed enantioselective arylation of 2,3-dihydrofuran **S1**.[a]

Entry	Ligand	R	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1b**	C_6H_5	86 (85:15)	97 (*R*)	89 (*R*)
2	**L1b**	1-Naphthyl	81(86:14)	97 (*R*)[d]	90 (*R*)[d]
3	**L1b**	*p*-CH_3-C_6H_4	93 (81:19)	94 (*R*)	89 (*R*)
4	**L1b**	*p*-NO_2-C_6H_4	95 (92:8)	91 (*R*)[d]	nd[e]
5	**L1d**	C_6H_5	42 (72:28)	25 (*R*)	16 (*R*)
6	**L1d**	1-Naphthyl	42 (73:27)	26 (*R*)[d]	21 (*R*)[d]
7	**L1d**	*p*-CH_3-C_6H_4	43 (75:25)	27 (*R*)	22 (*R*)
8	**L1d**	*p*-NO_2-C_6H_4	40 (76:24)	27 (*R*)[d]	nd[e]
9	**L1e**	C_6H_5	45 (60:40)	80 (*R*)	69 (*R*)
10	**L1e**	1-Naphthyl	38 (63:37)	82 (*R*)[d]	76 (*R*)[d]
11	**L1e**	*p*-CH_3-C_6H_4	45 (65:35)	78 (*R*)	67 (*R*)
12	**L1e**	*p*-NO_2-C_6H_4	55 (70:30)	77 (*R*)[d]	nd[e]
13	**L1f**	C_6H_5	32 (58:42)	6 (*R*)	19 (*R*)
14	**L1f**	1-Naphthyl	22 (57:43)	9 (*R*)[d]	21 (*R*)[d]
15	**L1f**	*p*-CH_3-C_6H_4	34 (55:45)	11 (*R*)	19 (*R*)
16	**L1f**	*p*-NO_2-C_6H_4	44 (65:35)	7 (*R*)[d]	nd[e]
17	**L1g**	C_6H_5	28 (55:45)	73 (*R*)	48 (*R*)
18	**L1g**	1-Naphthyl	21 (52:48)	67 (*R*)[d]	43 (*R*)[d]
19	**L1g**	*p*-CH_3-C_6H_4	34 (53:47)	63 (*R*)	39 (*R*)
20	**L1g**	*p*-NO_2-C_6H_4	34 (56:44)	75 (*R*)[d]	nd[e]
21	**L2a**	C_6H_5	80 (71:29)	84 (*R*)	90 (*R*)
22	**L2a**	1-Naphthyl	75 (72:38)	84 (*R*)[d]	81 (*R*)[d]
23	**L2a**	*p*-CH_3-C_6H_4	82 (72:38)	85 (*R*)	86 (*R*)
24	**L2a**	*p*-NO_2-C_6H_4	89 (81:19)	81 (*R*)[d]	nd[e]
25	**L3a**	C_6H_5	12 (65:35)	83 (*R*)	23 (*R*)
26	**L3a**	1-Naphthyl	9 (63:37)	81 (*R*)[d]	45 (*R*)[d]
27	**L3a**	*p*-CH_3-C_6H_4	18 (65:35)	79 (*R*)	25 (*R*)
28	**L3a**	*p*-NO_2-C_6H_4	24 (71:29)	75 (*R*)	nd[e]

[a] $[Pd_2(dba)_3]$·dba (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), aryl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^{i}Pr_2NEt$ (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] Enantiomeric excesses measured by HPLC. [e] not determined.

Table 10. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a** - **L4a**. Effect of the solvent.[a]

Entry	Ligand	Solvent	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	DMF	21 (71:29)	89 (*R*)	67 (*R*)
2	**L1a**	THF	100 (98:2)	98 (*R*)	nd[d]
3	**L1a**	Benzene	83 (96:4)	96 (*R*)	nd[d]
4	**L1a**	Toluene	85 (95:5)	96 (*R*)	nd[d]
5	**L2a**	DMF	24 (69:31)	91 (*R*)	75 (*R*)
6	**L2a**	THF	94 (84:16)	98 (*R*)	45 (*R*)
7	**L2a**	Benzene	92 (83:17)	97 (*R*)	56 (*R*)
8	**L2a**	Toluene	93 (81:19)	97 (*R*)	54 (*R*)
9	**L3a**	DMF	9 (52:48)	43 (*R*)	8 (*R*)
10	**L3a**	THF	44 (51:49)	77 (*R*)	5 (*R*)
11	**L3a**	Benzene	39 (52:48)	69 (*R*)	6 (*R*)
12	**L3a**	Toluene	38 (48:52)	73 (*R*)	9 (*R*)
13	**L4a**	DMF	38 (71:294)	83 (*R*)	42 (*R*)
14	**L4a**	THF	100 (88:12)	95 (*R*)	56 (*R*)
15	**L4a**	Benzene	92 (86:14)	94 (*R*)	63 (*R*)
16	**L4a**	Toluene	91 (85:15)	95 (*R*)	61 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), solvent (3 mL), proton sponge (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 11. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a** - **L4a**. Effect of the temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	100 (98:2)	98 (*R*)	nd[d]
2	**L1a**	75	100 (94:6)	94 (*R*)	nd[d]
3	**L1a**	25	21 (98:2)	98 (*R*)	nd[d]
4	**L2a**	50	94 (84:16)	91 (*R*)	75 (*R*)
5	**L2a**	75	100 (82:18)	88 (*R*)	69 (*R*)
6	**L2a**	25	19 (86:14)	92 (*R*)	81 (*R*)
4	**L3a**	50	44 (51:49)	77 (*R*)	5 (*R*)
5	**L3a**	75	69 (49:51)	72 (*R*)	4 (*R*)
6	**L3a**	25	8 (52:48)	79 (*R*)	7 (*R*)
4	**L4a**	50	100 (88:12)	95 (*R*)	56 (*R*)
5	**L4a**	75	100 (81:19)	92 (*R*)	51 (*R*)
6	**L4a**	25	28 (89:11)	96 (*R*)	64 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25×10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8×10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 12. Selected results for the Pd-catalysed enantioselective cyclohexenylation of **S1** using ligands **L1a** - **L4a**. Effect of the base.[a]

Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	98 (97:3)	97 (*R*)	nd[d]
2	**L1a**	PS	100 (98:2)	98 (*R*)	nd[d]
3	**L1a**	NaOAc	97 (95:5)	96 (*R*)	nd[d]
4	**L1a**	NEt_3	95 (92:8)	93 (*R*)	89 (*R*)
5	**L1a**	KOAc	67 (90:10)	78 (*R*)	65 (*R*)
6	**L1a**	K_2CO_3	88 (96:4)	92 (*R*)	90 (*R*)
7	**L1a**	Li_2CO_3	91 (79:21)	93 (*R*)	90 (*R*)
8	**L2a**	$^{i}Pr_2NEt$	92 (85:15)	90 (*R*)	71 (*R*)
9	**L2a**	PS	94 (84:16)	91 (*R*)	75 (*R*)
10	**L2a**	NaOAc	93 (80:20)	88 (*R*)	65 (*R*)
11	**L3a**	$^{i}Pr_2NEt$	42 (51:49)	77 (*R*)	8 (*R*)
12	**L3a**	PS	44 (51:49)	77 (*R*)	5 (*R*)
13	**L3a**	NaOAc	39 (50:50)	75 (*R*)	9 (*R*)
14	**L4a**	$^{i}Pr_2NEt$	97 (87:13)	95 (*R*)	62 (*R*)
15	**L4a**	PS	100 (88:12)	95 (*R*)	56 (*R*)
16	**L4a**	NaOAc	93 (78:22)	93 (*R*)	78 (*R*)
17	**L4a**	NEt_3	92 (85:15)	92 (*R*)	81 (*R*)
18	**L4a**	KOAc	57 (76:24)	68 (*R*)	45 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S1** (2.0 mmol), cyclohexenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 24 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 13. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a** - **L4a**. Effect of the solvent.[a]

Entry	Ligand	Solvent	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	DMF	31 (81:19)	89 (*R*)	61 (*R*)
2	**L1a**	THF	100 (94:6)	95 (*R*)	nd
3	**L1a**	Benzene	88 (92:8)	94 (*R*)	81 (*R*)
4	**L1a**	Toluene	92 (93:7)	94 (*R*)	89 (*R*)
5	**L2a**	DMF	24 (77:23)	78 (*R*)	44 (*R*)
6	**L2a**	THF	94 (86:14)	87 (*R*)	68 (*R*)
7	**L2a**	Benzene	89 (84:16)	85 (*R*)	71 (*R*)
8	**L2a**	Toluene	90 (83:17)	84 (*R*)	72 (*R*)
9	**L3a**	DMF	8 (44:1856)	39 (*R*)	8 (*R*)
10	**L3a**	THF	34 (49:51)	59 (*R*)	11 (*R*)
11	**L3a**	Benzene	29 (45:55)	53 (*R*)	13 (*R*)
12	**L3a**	Toluene	30 (48:52)	58 (*R*)	14 (*R*)
13	**L4a**	DMF	42 (85:15)	86 (*R*)	59 (*R*)
14	**L4a**	THF	100 (93:7)	94 (*R*)	86 (*R*)
15	**L4a**	Benzene	94 (95:5)	91 (*R*)	nd
16	**L4a**	Toluene	98 (94:6)	92 (*R*)	88 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), solvent (3 mL), $^iPr_2NEt$ (1 mmol), T = 50 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

Table 14. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a** - **L4a**. Effect of the temperature.[a]

Entry	Ligand	T (ºC)	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	50	100 (94:6)	95 (*R*)	nd[d]
2	**L1a**	70	100 (89:11)	92 (*R*)	87 (*R*)
3	**L1a**	25	21 (95:5)	96 (*R*)	nd[d]
4	**L2a**	50	94 (86:14)	87 (*R*)	68 (*R*)
5	**L2a**	70	100 (80:20)	72 (*R*)	59 (*R*)
6	**L2a**	25	19 (88:12)	88 (*R*)	66 (*R*)
4	**L3a**	50	34 (49:51)	59 (*R*)	11 (*R*)
5	**L3a**	70	62 (50:50)	56 (*R*)	3 (*R*)
6	**L3a**	25	12 (48:52)	60 (*R*)	13 (*R*)
4	**L4a**	50	100 (93:7)	94 (*R*)	86 (*R*)
5	**L4a**	70	100 (90:10)	88 (*R*)	71 (*R*)
6	**L4a**	25	21 (94:6)	95 (*R*)	nd[d]

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), $^iPr_2NEt$ (1 mmol), t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

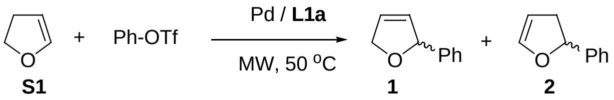
Table 15. Selected results for the Pd-catalysed enantioselective phenylation of **S2** using ligands **L1a** - **L4a**. Effect of the base.[a]

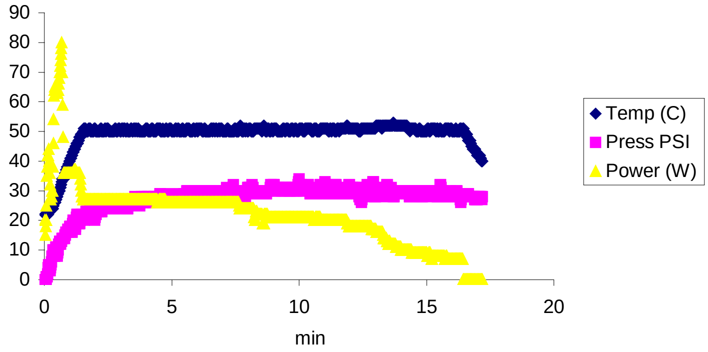
Entry	Ligand	Base	% conv (**1**:**2**)[b]	% ee **1**[c]	% ee **2**[c]
1	**L1a**	$^{i}Pr_2NEt$	100 (94:6)	95 (*R*)	nd
2	**L1a**	PS	100 (93:7)	95 (*R*)	92 (*R*)
3	**L1a**	NaOAc	98 (95:5)	92 (*R*)	nd
4	**L1a**	NEt_3	95 (89:11)	91 (*R*)	89 (*R*)
5	**L1a**	KOAc	78 (92:8)	81 (*R*)	79 (*R*)
6	**L1a**	K_2CO_3	89 (95:5)	90 (*R*)	79 (*R*)
7	**L1a**	Li_2CO_3	98 (86:14)	92 (*R*)	65 (*R*)
8	**L2a**	$^{i}Pr_2NEt$	94 (86:14)	87 (*R*)	68 (*R*)
9	**L2a**	PS	95 (85:15)	85 (*R*)	71 (*R*)
10	**L2a**	NaOAc	100 (80:20)	83 (*R*)	59 (*R*)
11	**L3a**	$^{i}Pr_2NEt$	34 (49:51)	59 (*R*)	11 (*R*)
12	**L3a**	PS	38 (50:50)	57 (*R*)	8 (*R*)
13	**L3a**	NaOAc	35 (48:52)	51 (*R*)	6 (*R*)
14	**L4a**	$^{i}Pr_2NEt$	100 (93:7)	94 (*R*)	86 (*R*)
15	**L4a**	PS	100 (91:9)	92 (*R*)	83 (*R*)
16	**L4a**	NaOAc	99 (89:11)	93 (*R*)	81 (*R*)
17	**L4a**	NEt_3	95 (90:10)	92 (*R*)	84 (*R*)
18	**L4a**	KOAc	73 (89:11)	65 (*R*)	78 (*R*)

[a] $[Pd_2(dba)_3]\cdot dba$ (1.25 x 10^{-2} mmol), **S2** (2.0 mmol), phenyl triflate (0.5 mmol), Ligand (2.8 x 10^{-2} mmol), THF (3 mL), base (1 mmol), T = 50 ºC, t = 48 h. [b] Conversion percentages determined by GC. [c] Enantiomeric excesses measured by GC. [d] not determined.

8. Temperature, power and pressure vs time profiles for the microwaves experiments

Table 8, entry 1.





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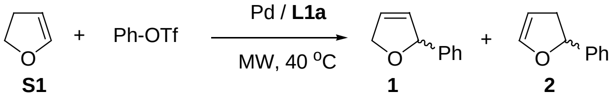

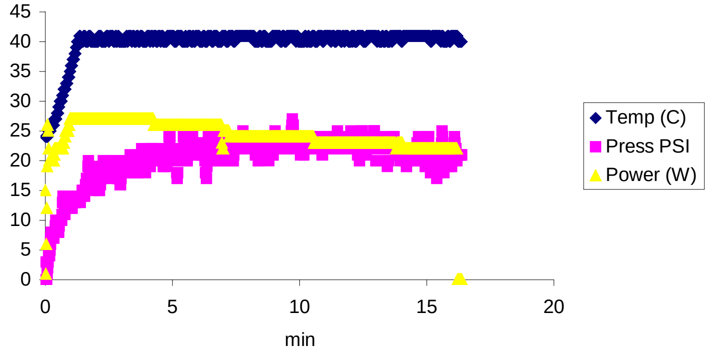

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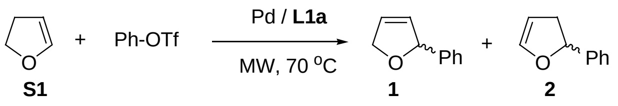

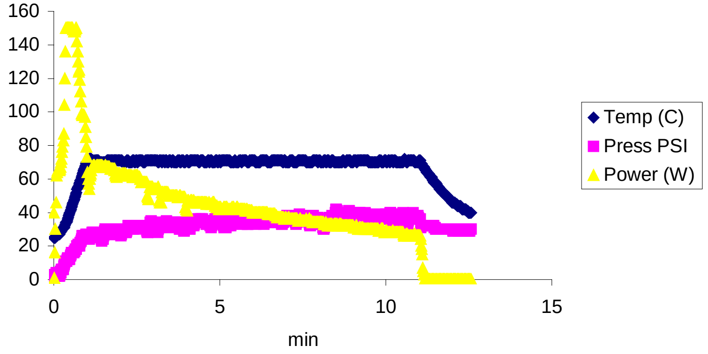

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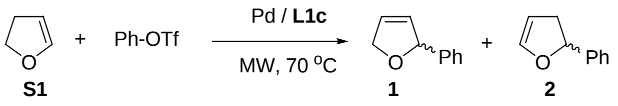

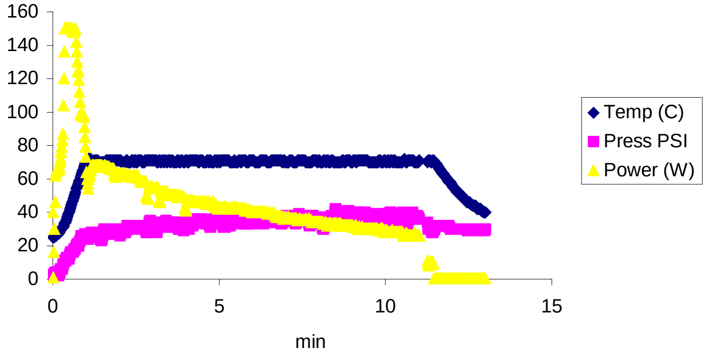

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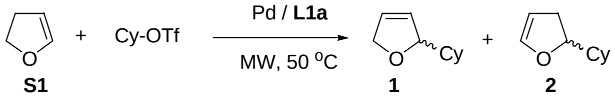

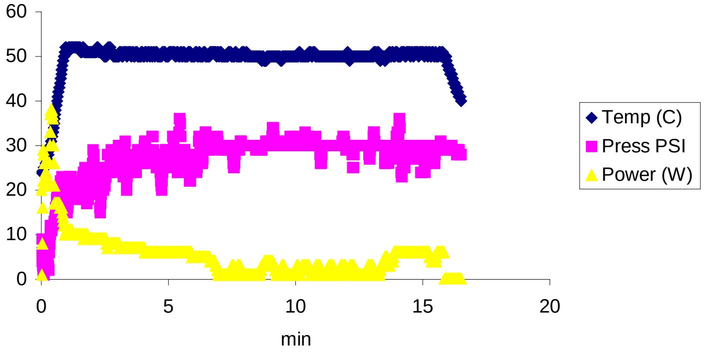

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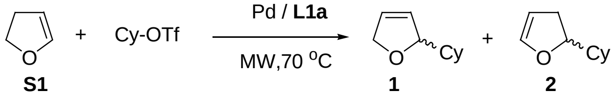

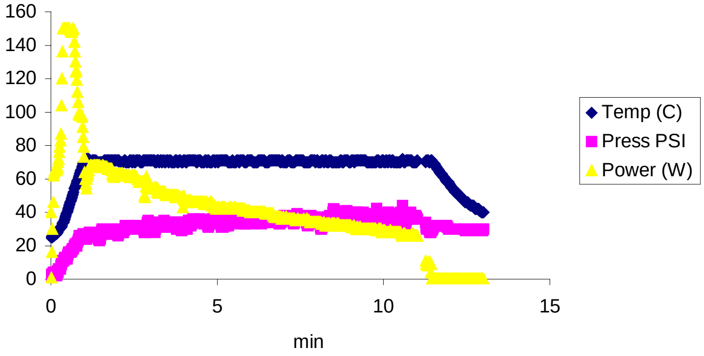

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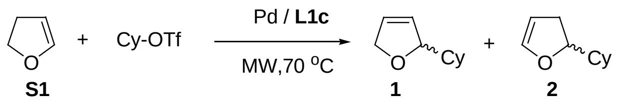
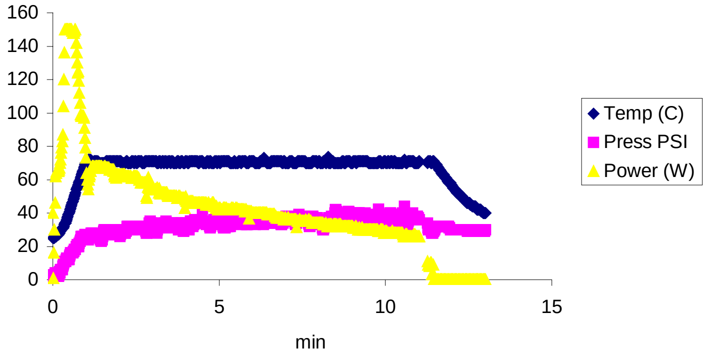
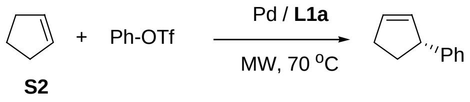
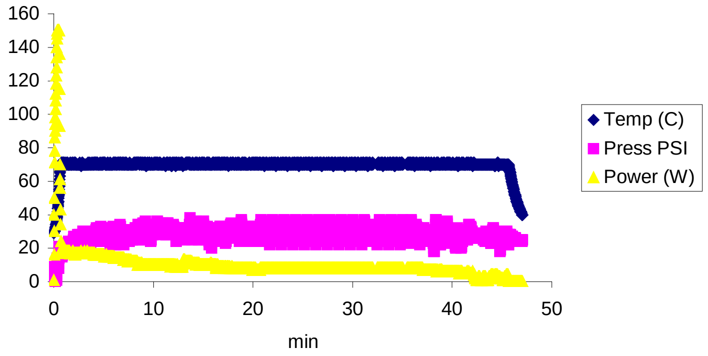
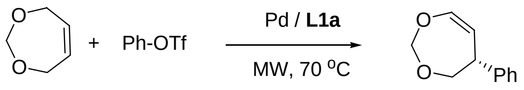




Scheme 4.



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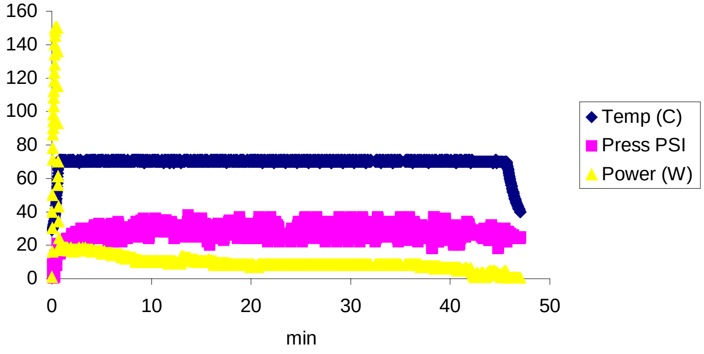
S3


160
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Chapter 5

Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes

5. Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes

5.1. Background

The catalytic addition of organoaluminium reagents to aldehydes as a route to chiral alcohols has attracted much attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. Despite the organoaluminium reagents are economically obtained in industrial scale, their use is rare. In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped in two types. The first group are the titanium complexes that usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol %) and the slow turnover rate hamper their potential utility. The second ones are the recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol %). For the latter group, only Woodward and coworkers reported the successful use of phosphoroamidite ligands as chiral source. Despite this success, the results indicate that an excess of ligand (L/Ni = 2) is necessary for high ee's to be achieved. More research is therefore needed to study the possibility offered by other ligands for this transformation.

In this chapter, we report the application of the three carbohydrate-based ligand libraries described in Chapter 3 (phosphite-oxazoline (**L1-L5a-i**), phosphite-phosphoroamidite (**L6a-c**) and monophosphite (**L7-L11a-f**) in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes. More specifically, in section 5.2 we report the application of the glucopyranoside phosphite-oxazoline (**L1-L5a-i**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries. Our results indicated that selectivity depended strongly on the type of functional group attached to the carbohydrate backbone, on the steric properties of the oxazoline substituents and on the substrate structure. The best enantioselectivities (ee’s up to 59%) were obtained using the catalysts precursor containing the phosphite-oxazoline ligand **L3a** in the 1,2-addition of several *para*-substituted aryl aldehydes. In section 5.3, we report the application of the modular sugar-based monophosphite ligand library **L7-L11a-f** for the Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes. In contrast to what we observed in section 5.2 with this monophosphite ligand library, we obtained high activities and enantioselectivities (ee's up to 94 %) in different substrate types with low catalyst loading (1 mol %) and without excess of ligand. Systematic variation of the sugar backbone, the substituents at the phosphite moieties and the flexibility of the ligand backbone, the monophosphite ligand **L7c** was found to be optimal.

5.2. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries in the asymmetric Ni-catalyzed trialkylaluminium addition to aldehydes

Abstract. The phosphite-oxazoline **L1-L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries were also tested in the asymmetric Ni-catalyzed 1,2-addition reactions to aldehydes. Systematically varying the electronic and steric properties of the oxazoline and biaryl phosphite substituents and the functional groups attached to the basic sugar-backbone, we found a strong influence of the oxazoline and the functional groups of the sugar backbone on catalytic performance. Enantioselectivity (ee's up to 59%) was best with the catalysts precursor containing the phosphite-oxazoline ligand **L3a**, that contains an sterically hindered *tert*-butyl oxazoline group.

5.2.1. Introduction

Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of chiral secondary alcohols.[1] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically available on industrial scales from aluminium hydride reagents and olefins.[2] Despite this advantage trialkylaluminium is less documented.[3,4] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped in two types. A first group are titanium complexes that although they usually afford high enantioselectivities, but have slow turnover rates hampering their potential utility and requiring high catalyst loadings (10-20 mol %).[3a-d] The second type are recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (0.05 - 1 mol %).[3e,4] For the latter nickel catalysts, only Woodward and co-workers reported the successful use of phosphoroamidite ligands as chiral source. Despite this success, the results indicate that an excess of ligand (L/Ni = 2) is necessary for high ee's to be achieved.[3e] More research is therefore needed to study the possibility offered by other ligands for this transformation.

To further expand the range of ligands in this process we report here the screening of the chiral phosphite-oxazoline **L1-L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries (Figure 1), described in the previous Chapter 3, in the asymmetric Ni-catalyzed addition of trialkylaluminium reagents to aldehydes. These ligands, derived from D-glucosamine, have the advantage of carbohydrates, such as availability at low price from readily available alcohols, facile modular constructions and high resistance to oxidation.[5] All these favourable features enable series of chiral ligands to be synthetized and screened in the search for high activity and selectivity. Therefore, with these libraries we fully investigated the effects of systematically varying the electronic and steric properties of the oxazoline substituent (**L1-L5**), the functional group attached to the basic sugar-backbone (**L5** and **L6**) and different substituents in the biaryl phosphite moiety (**a-c**).

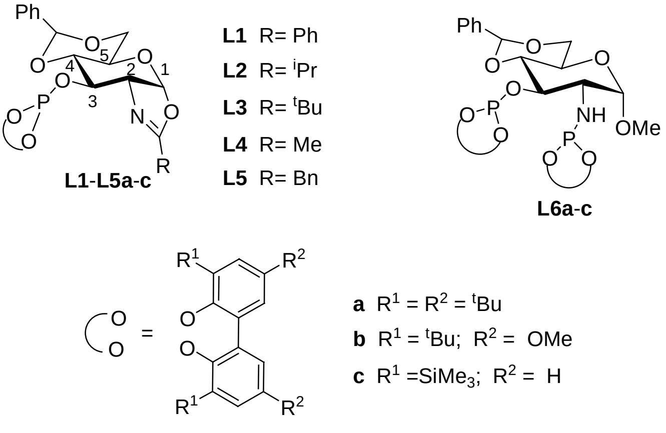
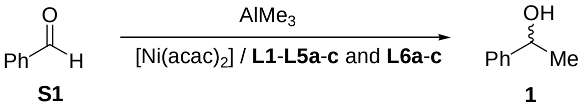


Figure 1. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries.

5.2.2. Results and Discussion

5.2.2.1. Asymmetric addition of AlR_3 to aldehydes

In a first set of experiments, we evaluated the phosphite-oxazoline (**L1-L5a-c**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries in the Ni-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde **S1**, which is used as a model substrate (eq. 1). The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of the catalyst precursor $[Ni(acac)_2]$ (acac= acetylacetonate).



(1)

The results, which are summarized in Table 1, indicate that for phosphite-oxazoline ligands the enantioselectivities are mainly affected by the steric properties of the substituent at the oxazoline moiety while the substituents at the phosphite moiety hardly affected it at all. The results were therefore best using ligand **L3a** that contains a bulky *tert*-butyl oxazoline group (Table 1, entries 1-6). Interestingly, lowering the ligand-to-nickel ratio increased activity, yield and enantioselectivity (Table 1, entry 5 *vs* 8). In addition, comparing the results obtained with ligands **L1-L5a-c** and **L6a-c**, we found that the replacement of the *tert*-butyl oxazoline function by a phosphoroamidite moiety did not improve enantioselectivities (Table 1, entries 8 *vs* 9-11).

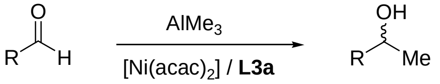
Table 1. Selected results for the Ni-catalyzed asymmetric addition of $AlMe_3$ to **S1** using **L1**-**L5a-c** and **L6a-c** ligand libraries.[a]

Entry	Ligand	L*/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L1a**	2	3	60	59	4 (*S*)
2	**L1b**	2	3	67	64	2 (*S*)
3	**L1c**	2	3	51	47	1 (*S*)
4	**L2a**	2	3	30	16	4 (*S*)
5	**L3a**	2	3	43	20	37 (*S*)
6	**L4a**	2	3	35	22	2 (*S*)
7	**L3a**	1	3	49	24	48 (*S*)
8	**L3a**	0.75	3	70	44	52 (*S*)
9	**L6a**	0.75	3	99	40	6 (*S*)
10	**L6b**	0.75	3	91	40	41 (*S*)
11	**L6c**	0.75	3	86	32	1 (*S*)

[a] Reaction conditions: T= -20 °C, $[Ni(acac)_2]$ (1 mol%), $AlMe_3$ (2 equiv.), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

We next tested the ligand that provided the best results (**L3a**) in the Ni-catalyzed addition of trimethylaluminium to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2. We found that enantioselectivity is mainly affected by the electronic properties of the groups at the phenyl moiety. Therefore, the presence of electrondonating groups at the *para* position of the phenyl group decreases enantioselectivity (Table 2, entries 1 and 4 *vs* 2, 3 and 6). As expected, we also found that the enantioselectivity was lower when a more flexible substrate **S9** was used (Table 2, entries 1 *vs* 9).

Table 2. Selected results for the nickel-catalyzed asymmetric addition of $AlMe_3$ to aldehydes using ligand **L3a**.[a]

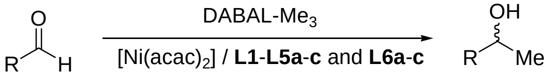


Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	70	44	52 (*S*)
2	**S2**	4-Cl-C_6H_4	64	25	35 (*S*)
3	**S3**	4-OMe-C_6H_4	29	26	32 (*S*)
4	**S4**	4-CF_3-C_6H_4	25	19	53 (*S*)
5	**S5**	4-Br-C_6H_4	55	22	40 (*S*)
6	**S6**	4-Me- C_6H_4	61	24	37 (*S*)
7	**S7**	3-Cl-C_6H_4	47	23	30 (*S*)
8	**S8**	2-Cl-C_6H_4	35	24	33 (*S*)
9[e]	**S9**	PhCH=CH	34	30	4 (*R*)

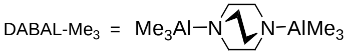
[a] Reaction conditions: T= -20 °C, $[Ni(acac)_2]$ (1 mol%), **L3a** (0.75 mol%), $AlMe_3$ (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column. [e] Reaction time 5 hours.

5.2.2.2. Asymmetric addition of DABAL-Me_3 to aldehydes

Recently, Woodward and co-workers reported for the first time the advantages of using DABAL-Me_3 as air-stable methylating reagent in the nickel-catalyzed additions to aldehydes.[3e] Therefore, we decided to also tested the phosphite-oxazoline (**L1-L5a-c**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries in the nickel-catalyzed addition of DABAL-Me_3 to aldehydes (eq. 2).



(2)



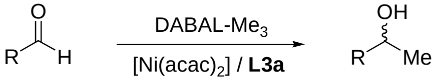
The results, which are summarized in Tables 3 and 4, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the trialkylaluminium addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminium addition and enantioselectivities were slightly better. Again the best enantioselectivities (ee's up to 59%) were obtained with ligand **L3a**, which contains the most sterically demanding oxazoline substituent.

Table 3. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to **S1** using **L1-L5a-c** and **L6a-c** ligand libraries.[a]

Entry	Ligand	L/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L1a**	1	3	32	3	31 (*S*)
2	**L1c**	1	3	52	3	25 (*S*)
3	**L2a**	1	3	42	1	25 (*S*)
4	**L3a**	1	3	24	8	59 (*S*)
5	**L4a**	1	3	42	7	19 (*S*)
6	**L5a**	1	3	52	11	24 (*S*)
7	**L6a**	1	3	53	6	14 (*S*)
8	**L6b**	1	3	53	3	27 (*S*)
9	**L6c**	1	3	49	4	7 (*S*)

[a] Reaction conditions: T= 0-5 °C, $Ni(acac)_2$ (1 mol%), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

Table 4. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to aldehydes using ligand **L3a.**[a]



Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	24	8	59 (*S*)
2	**S2**	4-Cl-C_6H_4	6	2	9 (*S*)
3	**S3**	4-OMe-C_6H_4	38	1	19 (*S*)
4	**S4**	4-CF_3-C_6H_4	22	2	4 (*S*)
5	**S5**	4-Br-C_6H_4	15	4	11 (*S*)
6	**S6**	4-Me- C_6H_4	39	3	34 (*S*)
7	**S7**	3-Cl-C_6H_4	14	3	6 (*S*)
8	**S8**	2-Cl-C_6H_4	6	4	16 (*S*)

[a] Reaction conditions: T= 0-5 °C, Ni(acac)$_2$ (1 mol%), **L3a** (1mol%), Dabal-Me_3 (1.3 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 3 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

5.2.3. Conclusions

The phosphite-oxazoline **L1-L5a-c** and phosphite-phosphoroamidite **L6a-c** ligand libraries were tested in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes. Our results indicated that selectivity depended strongly on the type of functional group attached to the carbohydrate backbone, on steric properties of the oxazoline substituents and on the substrate structure. Moderate enantioselectivities (ee's up to 59%) were obtained using the catalysts precursor containing the phosphite-oxazoline ligand **L3a** in the 1,2-addition to several *para*-substituted aryl aldehydes.

5.2.4. Experimental section

5.2.4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1-L5a-c**[6] and **L6a-c**[7] were prepared as previously described. All other reagents, including DABAL-Me_3, were used as commercially available.

5.2.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminium reagents to aldehydes

Anhydrous [Ni(acac)$_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[3e]

5.2.4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me_3 to aldehydes

Anhydrous [Ni(acac)$_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and DABAL-Me_3 (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[3e]

5.2.5. Acknowledgements

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5.2.6. References

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MONTSERRAT DIÉGUEZ FERNÁNDEZ i OSCAR PÀMIES OLLÉ, Professora Titular d'Universitat i Investigador "Ramón y Cajal" del Departament de Química Física i Inorgànica.

CERTIFIQUEN:

Que la present memòria que duu per títol: "SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS ", ha estat realitzada per YVETTE ANGELA MATA CAMPAÑA sota la nostra direcció a l'Àrea de Química Inorgànica del Departament de Química Física i Inorgànica d'aquesta Universitat.

Tarragona, maig de 2006

Dra. Montserrat Diéguez Fernández / Dr. Oscar Pàmies Ollé

5.3. Screening of a modular sugar-based phosphite ligand library in the asymmetric nickel-catalyzed trialkylaluminium addition to aldehydes

Abstract. We have synthesized a modular sugar-based phosphite ligand library for the Ni-catalyzed trialkylaluminium addition to aldehydes. This library has been designed to rapidly screen the ligands to uncover their important structure features and to determine the scope of the phosphite ligands in this catalytic reactions. After systematic variation of the sugar backbone, the substituents at the phosphite moieties and the flexibility of the ligand backbone, the monophosphite ligand 1,2:5,6-di-*O*-isopropylidene-3-*O*-((3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite)-α-D-glucofuranose **L7c** was found to be optimal, yielding high activities and enantioselectivities (ee's up to 94 %) for several aryl aldehydes.

5.3.1. Introduction

The catalytic asymmetric carbon-carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis. In this context, the catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention, since many chiral alcohols are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[1] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminium hydride and olefins.[2] Despite this advantage their use is rare.[3] In this respect, the few most successful catalysts for the enantioselective addition of trialkylaluminium to aldehydes have been titanium complexes bearing chiral diols or *N*-sulfonylated amino alcohols as ligands.[3a-d] However, the high catalyst loadings needed and the slow turnover rate[4] hamper the potential utility of these catalytic systems. Recently, Woodward and coworkers reported the first report of the asymmetric addition of a trialkylaluminium to aldehydes employing a nickel catalyst, containing a phosphoroamidite ligand. Excellent enantioselectivities with low catalyst loadings were attained.[3e]

To further expand the range of ligands and performance of this asymmetric nickel-catalyzed addition of organoaluminium reagents to aldehydes process, we designed a library of chiral monophosphite ligands **L7-L11a-f** (Figure 1) described in the previous chapter 3. These ligands are derived from natural D-glucose, D-galactose and D-fructose and have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols and facile modular constructions.[5] In addition they are less sensitive to air than typical phosphines, widely used as ligands in asymmetric catalysis. All these favourable features enable series of chiral ligands to be synthesized and screened in the search for high activity and selectivity.[5] Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions (mainly hydrogenation and allylic alkylation),[5] few good monodentate chiral ligands have been reported based on carbohydrates.[6]

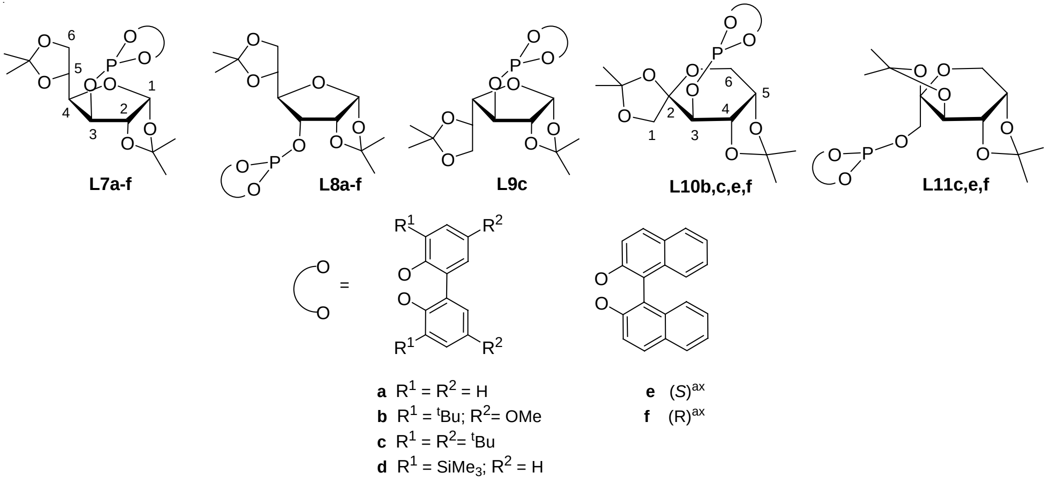


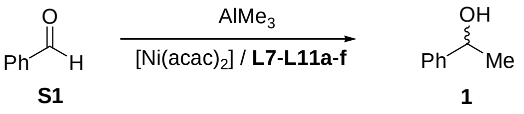
Figure 1. Carbohydrate-based phosphite ligands **L7-11a-f**.

We report here the design of a library of 30 potential sugar-based chiral phosphite ligands and screen their use in the nickel-catalyzed addition of organoaluminium reagents to aldehydes. The synthesis of this library has been discussed in Chapter 3. With this library we fully investigated the effects of systematically varying the configurations at C-3 and C-4 of the ligand backbone (**L7-L9**), different substituents/configurations in the biaryl phosphite moiety (**a-f**), the carbohydrate ring size **(L7-L10**) and the flexibility of the ligand backbone (**L10-L11**). By carefully selecting these elements, we achieved high enantioselectivities and activities in different substrate types. To the best of our knowledge this is the first example of phosphite ligands applied to this process.

5.3.2. Results and Discussion

5.3.2.1. Asymmetric addition of AlR_3 to aldehydes

In a first set of experiments, we evaluated the phosphite ligand library (Figure 1) in the nickel-catalyzed asymmetric addition of trimethylaluminium to benzaldehyde, which is used as a model substrate (eq. 1). The catalytic system was generated *in situ* by adding the corresponding phosphite ligand to a suspension of the catalyst precursor [Ni(acac)$_2$] (acac= acetylacetonate).



(1)

The results, which are summarized in Table 1, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of carbon atoms C-3 and C-4, the size of the ring of the sugar backbone and the substituents of the biaryl moieties.

Table 1. Selected results for the nickel-catalyzed asymmetric addition of $AlMe_3$ to benzaldehyde using phosphite library **L7-L11a-f**.[a]

Entry	Ligand	L/Ni	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L7a**	2	3	16	15	27 (R)
2	**L7b**	2	3	89	80	82 (S)
3	**L7c**	2	3	100	85	89 (S)
4	**L7d**	2	3	100	87	52 (S)
5	**L7e**	2	3	14	11	41 (R)
6	**L7f**	2	3	17	12	10 (R)
7	**L8a**	2	3	15	12	5 (*R*)
8	**L8b**	2	3	98	95	41 (*R*)
9	**L8c**	2	3	100	100	44 (*R*)
10	**L8d**	2	3	100	86	17(*R*)
11	**L8e**	2	3	29	22	6(*R*)
12	**L8f**	2	3	12	3	5(*S*)
13	**L9c**	2	3	100	60	70 (*R*)
14	**L10b**	2	3	99	58	9 (*S*)
15	**L10c**	2	3	100	64	52 (*S*)
16	**l11c**	2	3	83	52	36 (*R*)
17	**L7c**	2.5	3	100	68	88 (*S*)
18	**L7c**	1	3	100	100	89 (*S*)
19	**L7c**	1	1	100	100	90 (*S*)
20	**L7c**	2	1	100	87	91 (*S*)
21	**L8c**	1	1	100	95	45 (*R*)

[a] Reaction conditions: T= -20 °C, [$Ni(acac)_2$] (1 mol%), $AlMe_3$ (2 equiv.), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

With ligands **L7a-f** we studied how the biaryl phosphite moieties affects the product outcome. We found that the substitutents at the *ortho* positions of the biaryl phosphite moiety affected yield, while enantioselectivities were mainly affected by the substituents at the *para* positions of the biaryl phosphite group.

Therefore, for high yields bulky substituents in the *ortho* position of the biaryl phosphite moiety are necessary (Table 1, entries 1,5 and 6 vs 2-4). Regarding enantioselectivities, these are better when *tert*-butyl groups are present in the *para* position of the biphenyl phosphite moiety (Table 1, entries 3 vs 2 and 4). The best trade-off between yield and enantioselectivity was therefore obtained using ligand **L7c**.

With ligands **L8**, whose configuration at C-3 is opposite than those of ligands **L7**, we studied the effect of this configuration in the product outcome. The results indicated that there is an influence of this configuration on enantioselectivity (Table 1, entries 7-12). Therefore, the use of ligands **L8** with an *R* configuration at C-3 provided lower enantioselectivities than using ligands **L7**. Concerning the effect of the biaryl substituents, the results using ligands **L8a-d** confirms the previous trends observed with ligands **L7**. Therefore, yields and enantioselectivities were best using the ligand that contains *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl phosphite moiety (ligand **L8c**).

With ligands **L7e**, **L7f**, **L8e** and **L8f**, we studied the possibility of a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties (Table 1, entries 5, 6, 11 and 12). The results indicated that the matched combination is achieved with ligand **L7e**, which have *S* configuration at both carbon atom C-3 and in the biaryl phosphite moiety.

Ligands **L9**, which configuration at C-4 is opposite to those of ligands **L7**, afforded lower enantioselectivity than the catalytic system Ni/**L7** (Table 1, entry 3 vs 13) but higher than the catalytic system Ni/**L8** (Table 1, entry 9 vs 13). From these results we can conclude that the effect of the configuration of carbon C-3 is more important than the effect of C-4 on the catalytic performance.

Ligands **L10** which has a pyranoside backbone provided lower yields and enantioselectivitities (up to 52% (*S*)) than their related furanoside ligands **L7** (Table 1, entries 2 and 3 vs 14 and 15).

Finally, the most flexible ligand **L11**, which has the phosphite moiety attached to a primary carbon, provided the lowest enantioselectivities (Table 1, entries 16 vs 3, 9, 13 and 15).

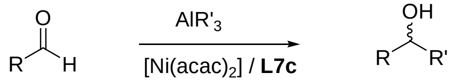
We next studied with the ligand that provided the best results (ligand **L7c**) the effect of the ligand-to-nickel ratio in the product outcome. Our results shown that no excess of ligand is needed for high yields and enantioselectivities (Table 1, entries 17 vs 3 and 16).[7] Finally, we optimized the reaction time and we found complete reaction after 1 hour (Table 1, entry 18 vs 3).

To further investigate the catalytic efficiency of these Ni/**L7**-**L11** systems, we then tested them in the nickel-catalyzed addition of trialkylaluminium (AlR'_3; R'= Me or Et) to other benchmark aldehydes with different steric and electronic properties. The results are summarized in Table 2.

We found that enantioselectivity for $AlMe_3$ addition is hardly affected by the presence of electronwithdrawing or electrondonating groups at the *para* position of the phenyl group (Table 2, entries 1, 3, 5, 6, 8 and 10). However, the best yield was achieved using benzaldehyde as substrate, while substrate 4-OMe-Ph gave the poorest (Table 2, entry 1 vs 5). Enantioselectivity of the reaction is also significantly influenced by steric factors. Therefore enantioselectivities are better when *para* substituted aryl aldehydes were used as substrates (Table 2, entries 3, 11 and 12). We have also found that enantioselectivity was more difficulty to control when a more flexible substrate is used (Table 2, entries 13 and 14).

The results of using triethylaluminium as alkylating reagent indicated that the catalytic performance follow the same trend as for the trimethylaluminium addition (Table 2, entries 1, 3, 6 and 8 vs 2, 4, 7 and 9).

Table 2. Selected results for the nickel-catalyzed asymmetric addition of AlR'$_3$ **(**R'= Me or Et) to aldehydes using ligand **L7c**.[a]

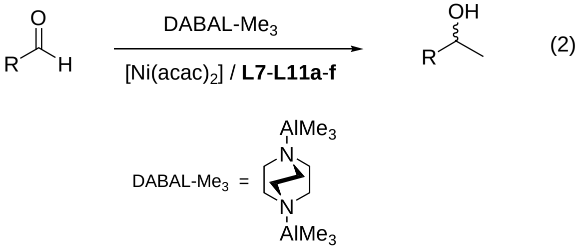


Entry	Substrate	R	R'	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	Me	100	100	90 (*S*)
2	**S1**	C_6H_5	Et	100	96	88(S)
3	**S2**	4-Cl-C_6H_4	Me	100	82	91(*S*)
4	**S2**	4-Cl-C_6H_4	Et	100	83	90 (*S*)
5	**S3**	4-OMe-C_6H_4	Me	93	53	94 (*S*)
6	**S4**	4-CF_3-C_6H_4	Me	100	95	93 (*S*)
7	**S4**	4-CF_3-C_6H_4	Et	100	96	94 (*S*)
8	**S5**	4-Me- C_6H_4	Me	94	84	91 (*S*)
9	**S5**	4-Me- C_6H_4	Et	98	85	88 (*S*)
10	**S6**	4-Br-C_6H_4	Me	98	86	92 (*S*)
11	**S7**	3-Cl-C_6H_4	Me	95	73	74 (*S*)
12	**S8**	2-Cl-C_6H_4	Me	97	85	41 (*R*)
13[e]	**S9**	$PhCH_2CH_2$	Me	100	89	25 (*S*)
14[f]	**S10**	PhCH=CH	Me	97	44	25 (*R*)

[a] Reaction conditions: T= -20 °C, [Ni(acac)$_2$] (1 mol%), **L7c** (1mol%), AlR'$_3$ (2 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1 hour. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Cyclodex-B column. [e] **L7c** (2 mol%), reaction time 6 hours. [f] **L7c** (2 mol%), reaction time 5 hours.

5.3.2.2. Asymmetric addition of DABAL-Me$_3$ to aldehydes

Recently, Woodward and coworkers reported for the first time the advantages of using DABAL-Me$_3$ as air-stable methylating reagent in the nickel-catalyzed additions to aldehydes.[3e] Encouraged by the excellent results obtained using trialkylaluminium reagents to aldehydes, we decided to also tested the phosphite library **L7-L11a-f** in the nickel-catalyzed addition of DABAL-Me$_3$ to aldehydes (eq. 2).



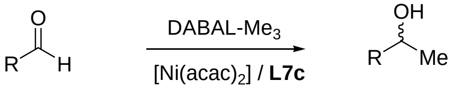
The results, which are summarized in Tables 3 and 4, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the trialkylaluminium addition to aldehydes, which is not unexpected because the reactions have a similar mechanism. However, the yields were lower than in trimethylaluminium addition. Again the catalytic precursor containing the phosphite ligand **L7c** provided the best enantioselectivity (87% ee). It is to note, that in this case the negative effect on yields of the presence of an excess of ligand is more pronounced than when trimethylaluminium was used. Therefore, yields increased almost 100% by reducing the ligand-to-nickel ratio from 2 to 1 (Table 3, entries 3 vs 14).

Table 3. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to **S1**.[a]

Entry	Ligand	L*/Ni	Dabal (eq)	t (h)	% Conv.[b]	% Yield[c]	% ee[d]
1	**L7a**	2	1.3	3	75	36	18 (*R*)
2	**L7b**	2	1.3	3	63	35	86 (*S*)
3	**L7c**	2	1.3	3	85	40	87 (*S*)
4	**L7d**	2	1.3	3	73	60	46 (*S*)
5	**L7e**	2	1.3	3	59	37	47 (*R*)
6	**L7f**	2	1.3	3	60	5	0
7	**L8a**	2	1.3	3	74	43	5 (*S*)
8	**L8b**	2	1.3	3	90	51	47 (*S*)
9	**L8c**	2	1.3	3	90	27	58 (*S*)
10	**L8d**	2	1.3	3	70	38	17 (*S*)
11	**L8e**	2	1.3	3	88	38	11 (*S*)
12	**L8f**	2	1.3	3	83	29	4 (*S*)
13	**L7c**	2	0.6	3	61	40	84(*S*)
14	**L7c**	1	1.3	1.5	97	78	88(*S*)

[a] Reaction conditions: T= 5 °C, Ni(acac)$_2$ (1 mol%), **S1** (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column.

Table 4. Selected results for the nickel-catalyzed asymmetric addition of DABAL-Me_3 to aldehydes using ligand **L7c.**[a]



Entry	Substrate	R	% Conv.[b]	Yield[c]	% ee[d]
1	**S1**	C_6H_5	85	78	88 (*S*)
2	**S2**	4-Cl-C_6H_4	99	64	91 (*S*)
3	**S3**	4-OMe-C_6H_4	92	25	78 (*S*)
4	**S4**	4-CF_3-C_6H_4	100	53	82 (*S*)
5	**S6**	4-Br-C_6H_4	93	69	90 (*S*)
6	**S5**	4-Me- C_6H_4	96	68	88 (*S*)
7	**S7**	3-Cl-C_6H_4	90	58	67 (*S*)
8	**S8**	2-Cl-C_6H_4	90	62	35 (*R*)
9[e]	**S10**	PhCH=CH	86	22	30 (*R*)

[a] Reaction conditions: T= 5 °C, Ni(acac)$_2$ (1 mol%), **L7c** (1mol%), Dabal-Me_3 (1.3 equiv.), substrate (0.25 mmol), THF (2 mL). [b] % Conversion determined by GC after 1.5 hours. [c] % Yield determined by GC using dodecane as internal standard. [d] Enantiomeric excess measured by GC using Lipodex-A column. [e] **L7c** (2mol%).

5.3.3. Conclusions

A library of readily available monophosphite ligands has been synthesized and applied for the first time in the Ni-catalyzed trialkylaluminium addition to several aldehydes. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the configurations at carbon C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. By judicious choice of the ligand components we obtained high enantioselectivities (ee values up to 94%) and high activities, in several aryl aldehydes, with low catalyst loading (1 mol %) and without excess of ligand.

To sum up, the combination of high activities and enantioselectivities with low catalyst loading and the low cost of these phosphite ligands open up a new class of ligands for the enantioselective Ni-catalyzed addition of trialkylaluminium reagents to aldehydes that competes favorably with the best ligands designed for this process.[3]

5.3.4. Experimental section

5.3.4.1. General comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. The synthesis of ligands **L7-L11a-f** is described in Chapter 3. DABAL-Me_3 was prepared as previously described.[3e] All other reagents were used as commercially available.

5.3.4.2. General procedure for the Ni-catalyzed enantioselective 1,2-addition of trialkylaluminium reagents to aldehydes

[Ni(acac)$_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at -20 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (0.5 mmol) was added dropwise after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$ and analyzed by GC.[3e]

5.3.4.3. General procedure for the Ni-catalyzed enantioselective 1,2-addition of DABAL-Me$_3$ to aldehydes

[Ni(acac)$_2$] (0.6 mg, 2.33 μmol, 1 mol %) and ligand (2.33 μmol, 1 mol %) were stirred in dry THF (2 mL) under argon atmosphere at 5 °C for 10 min. Neat aldehyde (0.25 mmol) was then added and trialkylaluminium (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. After the desired reaction time, the reaction was quenched with 2M HCl (2 mL). Then dodecane (20 μL) was added and the mixture was extracted with Et$_2$O (10 mL). The organic layer was dried over MgSO$_4$ and analyzed by GC.[3e]

5.3.5. Acknowledgements

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[7] At high ligand-to-nickel ratio the diproportionation of benzaldehyde to benzoic acid and benzyl alcohol takes place.

Chapter 6

Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones

6. Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones

6.1. Background

The last decade has seen an important breakthroughs in what is possible in the area of catalytic asymmetric 1,4-addition of alkyl organometallic nucleophiles to enones. Most of the succesfull asymmetric versions of this chemistry have made use of diorganozinc reagents, specially $ZnEt_2$, a trend started by Alexakis (Cu-catalysis) and Soai (Ni-catalysis).[1] Viable ligand classes affording > 90% ee for the addition of diorganozinc to several types of cyclic and chalcone substrates are now available.[2] However, relatively few publications describing highly enantioselective addition of organometallics to linear aliphatic enones and using trialkylaluminium reagents as alternative to organozincs have appeared.[2] This justify to expand the range of ligands for the Cu-catalyzed addition of organoaluminium reagents to enones and more specifically to the linear aliphatic ones. For this purpose, carbohydrates are particularly advantageous because they are available at low price and because their modular constructions are easy.

In this chapter, we report the application of the three carbohydrate-based ligand libraries described in Chapter 3 (phosphite-oxazoline (**L1-L5a-i**), phosphite-phosphoroamidite (**L6a-c**) and monophosphite (**L7-L11a-f**) in the asymmetric Cu-catalyzed 1,4-addition of trialkylaluminium reagents to enones. More specifically, in section 6.2 we report the application of the glucopyranoside phosphite-oxazoline (**L1-L5a-i**) and phosphite-phosphoroamidite (**L6a-c**) ligand libraries. Our results indicated that activity and selectivity depended strongly on the type of functional group attached to the carbohydrate backbone, on the electronic and steric properties of the oxazoline and biaryl phosphite substituents and on the substrate structure. In general, good activities and enantioselectivities were obtained. The best enantioselectivities (ee's up to 78%) were obtained using the catalysts precursor containing the phosphite-oxazoline ligand **L1c** in the 1,4-addition to aliphatic linear substrates. In section 6.3, we report the application of the modular sugar-based monophosphite ligand library **L7-L11a-f** for the Cu-catalyzed 1,4-addition of trialkylaluminium reagents to enones. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone and the cooperative effect between configurations of C-3 and of the binaphthyl phosphite moiety. Good activities and enantioselectivities up to 57% and 51% were achieved for cyclic and aliphatic linear enones, respectively.

6.1.1. References

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6.2. Sugar-phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries for Cu-catalyzed asymmetric 1,4-addition reactions

Abstract. The phosphite-oxazoline **L1-L5a-g** and phosphite-phosphoroamidite **L6a-c** ligand libraries were also tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Systematically varying the electronic and steric properties of the oxazoline and the biaryl phosphite substituents and the functional groups attached to the basic sugar-backbone had a strong effect on catalytic performance. In general, good activities and enantioselectivities were obtained. The enantioselectivity (up to 80%) was optimized with catalyst precursors containing the phosphite-oxazoline ligand **L1c** and **L1f**, that contains encumbered biaryl phosphite moieties and a phenyl oxazoline group.

6.2.1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon-carbon bond formation.[1] Most of the chiral ligand developed for this process are P-donor and mixed P,N-donor ligands.[1f-h,2] Among those, phosphite and phosphoramidite have played a dominant role.[1f-h] A prominent position in the rapid development of this process is occupied by the copper-catalyzed, ligand-accelerated, 1,4-addition of organozinc reagents.[1] Tryalkylalumium reagents have recently appeared as an interesting alternative to organozinc reagents since they are also readily available and also offer additional hydro- and carboalumination possibilities for their preparation.[3] Most of the chiral ligands have been developed for the enantioselective conjugate addition of organozinc reagents and less work has been devoted to the design of ligands for the conjugate addition of organoaluminium reagents. Additionally, linear aliphatic enones are another class of substrate for which the development of more active and enantioselective catalysts are still needed. Expansion of the range of ligands used for Cu-catalyzed addition of organoaluminium reagents to cyclic and linear substrates is desirable. For this purpose, carbohydrates are particularly advantageous because they are available at low price and because their modular constructions are easy.[4]

Encouraged by the success of phosphite and phosphoroamidite ligands in this process, we report here the application in the copper 1,4-addition of trialkylaluminium reagents to cyclic and linear enones of two sugar ligand libraries: (a) phosphite-oxazoline **L1-L5a-g** and (b) phosphite-phosphoroamidite **L6a-c** (Figure 1). These libraries combine a priori the advantages of both types of successful ligands.

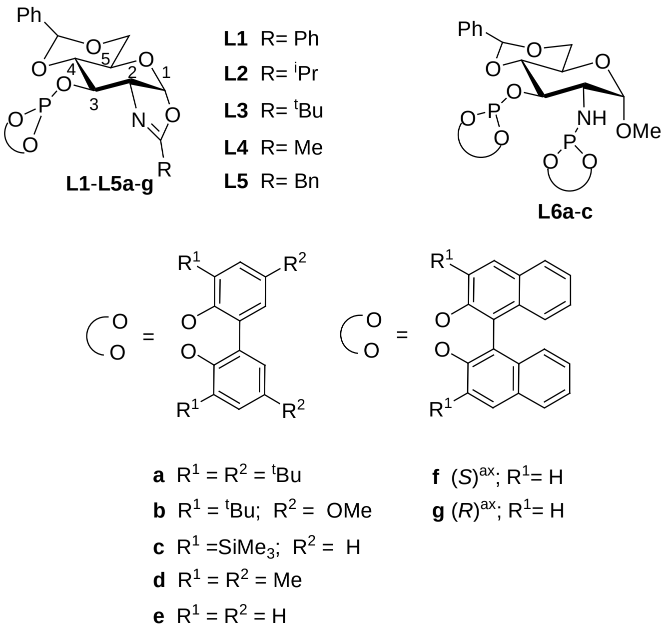


Figure 1. Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries.

6.2.2. Results and Discussion

6.2.2.1. Ligand design

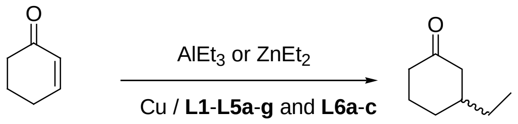
Ligand libraries **L1-L5a-g** and **L6a-c** consist of a 4,5-*O*-protected glucopyranoside backbone with a phosphite moiety at C-3 position, which determine their underlying structure, and either oxazoline (ligands **L1-L5a-g**) or phosphoroamidite (ligands **L6a-c**) groups attached to this basic backbone. The synthesis of the phosphite-oxazoline **L1-L5a-g** and the phosphite-phosphoroamidite **L6a-c** ligand libraries (Figure 1) have been previously described in Chapter 3.

We studied the influence of systematically varying the electronic and steric properties of the oxazoline substituents and different substituents/configurations in the biaryl phosphite moiety using ligands **L1-L5a-g**.

We then used both ligand libraries **L1-L5a-g** and **L6a-c** to study how a phosphoroamidite rather than an oxazoline functionality affected catalytic performance. We also studied the effect of the substituents in the phosphoroamidite moiety in catalytic performance using ligands **L6a-c**.

6.2.2.2. Asymmetric conjugated 1,4-addition of $AlEt_3$ and $ZnEt_2$ to 2-cyclohexenone S1 (equation 1)

In a first set of experiments, we tested ligands **L1-L5a-g** and **L6a-c** in the copper-catalyzed conjugated addition of triethylaluminium and diethylzinc to 2-cyclohexenone **S1** (equation 1). The latter was used as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling to direct comparison of the efficiency of various ligand systems.[1]



S1 **1** (1)

The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor under standard conditions.[1] The results are shown in Table 1.

Table 1. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligands **L1-L5a-g** and **L6a-c**.[a]

Entry	Ligand	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	-30	85	36	6 (*S*)
2	**L1b**	-30	95	20	27 (*S*)
3	**L1c**	-30	99	50	64 (*S*)
4	**L1f**	-30	88	61	64 (*S*)
5	**L1g**	-30	75	55	15 (*S*)
6	**L2a**	-30	99	70	5 (*S*)
7	**L3a**	-30	95	39	7 (*S*)
8	**L4a**	-30	91	27	3 (*S*)
9	**L5a**	-30	96	43	5 (*S*)
10[e]	**L1c**	-30	88	42	6 (*R*)
11[e]	**L1c**	0	80	18	5 (*R*)
12	**L6c**	-30	89	22	17 (*S*)

[a] Reaction conditions: Cu(OAc)$_2$ (1 mol%), ligand (4 mol%), AlEt$_3$ (0.4 mmol), **S1** (0.28 mmol), diethylether (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using Lipodex A column. [e] ZnEt$_2$ (0.4 mmol).

They indicated that enantioselectivity is mainly affected by the substituents/configuration at the biaryl phosphite moiety, while the oxazoline groups have little effect (Table 1, entries 1-9). The results were therefore best using ligands **L1c** and **L1f**, that contain trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety and an (*S*)-binaphtyl phosphite moiety, respectivelly (ee's up to 64%). In addition, the replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on yield and enantioselectivity (Table 1, entry 3 vs 12). Comparing the results using triethylaluminium with the results of using diethylzinc, we can conclude that yields and enantioselectivities were lower using diethylzinc (Table 1, entries 3 vs 10 and 11).

In addition to the effect of structural parameters on catalytic performance, the reaction parameters can also be controlled to further improve yields and selectivity. Therefore, the effect of several reaction parameters, such as catalyst precursor, solvent and ligand-to-copper ratio, were studied using ligand **L1b** (Table 2). However, yields and enantioselectivities did not improved.

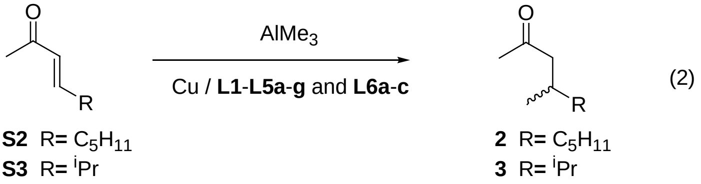
Table 2. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligand **L1b**. Effect of the catalyst precursor, solvent and ligand-to-copper ratio.[a]

Entry	Solvent	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	Et_2O	$Cu(OAc)_2$	-30	95	20	27 (*S*)
2	Et_2O	$Cu(OTf)_2$	-30	97	10	26 (*S*)
3	Et_2O	CuTC	-30	96	17	27 (*S*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	-30	94	17	25 (*S*)
5	Et_2O	CuI	-30	94	13	21 (*S*)
6	^{t}BuMeO	$Cu(OAc)_2$	-30	92	42	0
7	DCM	$Cu(OAc)_2$	-30	100	13	13 (*S*)
8	THF	$Cu(OAc)_2$	-30	95	17	20 (*S*)
9	Me_2O	$Cu(OAc)_2$	-30	90	20	17 (*S*)
10[e]	Et_2O	$Cu(OAc)_2$	-30	90	26	14 (*S*)
11[f]	Et_2O	$Cu(OAc)_2$	-30	90	26	15 (*S*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlEt_3$ (1.4 eq, 0.4 mmol), **S1** (0.28 mmol), solvent (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using Lipodex A column. [e] ligand (1 mol%). [f] ligand (2 mol%).

6.2.2.3. Asymmetric conjugated 1,4-addition of $AlMe_3$ to linear substrates S2 and S3 (equation 2)

We have also screened the use of ligands **L1-L5a-g** and **L6a-c** in the copper-catalyzed conjugated addition of trimethylaluminium (equation 2) to two linear substrates with different steric properties: *trans*-3-nonen-2-one **S2** and *trans*-5-methyl-3-hexen-2-one **S3**. These enones, possessing only aliphatic substituents, are a more demanding substrate class for asymmetric conjugated addition than **S1**. The high conformational mobility of these substrates together with the presence of only subtle substrate-catalyst steric interactions makes the design of effective enantioselective systems a real challenge.[3d,5]



We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (equation 2, R= C_5H_{11}) with trimethylaluminium under standard conditions. The results are summarized in Table 3. In contrast to **S1**, the results indicated that yields and enantioselectivities are affected by the substituents at both the biaryl phosphite and oxazoline moieties (Table 3, entries 1-10). Therefore the best yield (up to 85%) and enantioselectivities (up to 62%) were obtained again with ligands **L1c** and **L1f**, that contain sterically demanding substituents in biaryl phosphite moiety and a phenyl oxazoline group. Again, the replacement of the oxazoline by a phosphoroamidite moiety did not improve yields or enantioselectivities (Table 3, entry 2 vs 11).

We next studied by one of the best ligands (**L1c**) the effect of several reaction parameters, such as catalyst precursor (i.e. $Cu(OTf)_2$, CuTC, $Cu(OAc)_2$, CuI and $[Cu(MeCN)_4]BF_4$), solvent (i.e. diethylether, CH_2Cl_2, THF, *tert*-butylmethylether) and ligand-to-copper ratio. Interestingly, in contrast to the conjugate addition to **S1**, we found an important positive effect using $[Cu(MeCN)_4]BF_4$ as a catalyst precursor on enantioselectivity. Therefore, enantioselectivity increased from 51% to 78% (Table 3, entry 3 vs 12). The rest of reactions parameters did not improve the catalytic performance.

Table 3. Selected results for the copper-catalysed conjugate 1,4-addition of **S2** using ligands **L1-L5a-g** and **L6a-c**.

Entry	Ligand	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	$Cu(OTf)_2$	-30	92	29	31 (*R*)
2	**L1b**	$Cu(OTf)_2$	-30	60	32	32 (*R*)
3	**L1c**	$Cu(OTf)_2$	-30	97	51	51 (*R*)
4	**L1d**	$Cu(OTf)_2$	-30	76	50	45 (*R*)
5	**L1f**	$Cu(OTf)_2$	-30	92	85	62 (*R*)
6	**L1g**	$Cu(OTf)_2$	-30	90	78	52 (*R*)
7	**L2a**	$Cu(OTf)_2$	-30	93	46	40 (*R*)
8	**L3a**	$Cu(OTf)_2$	-30	97	48	33 (*R*)
9	**L4a**	$Cu(OTf)_2$	-30	76	16	49 (*R*)
10	**L5a**	$Cu(OTf)_2$	-30	68	26	34 (*R*)
11	**L6b**	$Cu(OTf)_2$	-30	80	32	26 (*S*)
12	**L1c**	$[Cu(MeCN)_4]BF_4$	-30	94	48	78 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), diethylether (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column.

Finally, we investigated the copper-catalyzed 1,4-addition of *trans*-5-methyl-3-hexen-2-one **S3** (equation 2, R= ^{i}Pr) with trimethylaluminium. The results are summarized in Table 4. As for substrate **S2**, the results indicated that yields and enantioselectivities are affected by the substituents/configurations at the biaryl phosphite and by the oxazoline groups (Table 4, entries 1-10). Again, the best yield (up to 94%) and enantioselectivity (up to 80%) was obtained with ligands **L1c** and **L1f**, that contain encumbered biaryl phosphite moieties and a phenyl oxazoline group. The replacement of the oxazoline by a phosphoroamidite moiety had a negative effect on yield and enantioselectivity (Table 3, entry 3 vs 11). The effect of several ligand parameters such as catalyst precursor (i.e. $Cu(OTf)_2$, CuTC, $Cu(OAc)_2$, CuI and $[Cu(MeCN)_4]BF_4$), solvent (i.e. diethylether, CH_2Cl_2, THF, *tert*-butylmethylether) and ligand-to-copper ratio were also studied. However, in contrast to the conjugate addition to **S2**, yields and enantioselectivities did not improve.

Table 4. Selected results for the copper-catalysed conjugate 1,4-addition of **S3** using ligands **L1**-**L5a**-**g** and **L6a**-**c**.

Entry	Ligand	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	**L1a**	$Cu(OTf)_2$	-30	60	44	32 (*R*)
2	**L1b**	$Cu(OTf)_2$	-30	39	20	44 (*R*)
3	**L1c**	$Cu(OTf)_2$	-30	94	94	68 (*R*)
4	**L1d**	$Cu(OTf)_2$	-30	75	55	52 (*R*)
5	**L1f**	$Cu(OTf)_2$	-30	96	90	80 (*R*)
6	**L1g**	$Cu(OTf)_2$	-30	92	88	55 (*R*)
7	**L2a**	$Cu(OTf)_2$	-30	43	43	69 (*R*)
8	**L3a**	$Cu(OTf)_2$	-30	53	42	40 (*R*)
9	**L4a**	$Cu(OTf)_2$	-30	57	1	50 (*R*)
10	**L5a**	$Cu(OTf)_2$	-30	51	52	53 (*R*)
11	**L6c**	$Cu(OTf)_2$	-30	93	88	8 (*S*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S3** (0.28 mmol), Et_2O (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column.

6.2.3. Conclusions

The phosphite-oxazoline **L1-L5a-g** and phosphite-phosphoroamidite **L6a-c** ligand libraries were tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that activity and selectivity depended strongly on the type of functional group attached to the carbohydrate backbone, on the electronic and steric properties of the oxazoline and biaryl phosphite substituents and on the substrate structure. Good enantioselectivities (up to 80%) were obtained using the catalyst precursors containing the phosphite-oxazoline ligands **L1c** and **L1f** in the 1,4-addition to aliphatic linear substrates.

6.2.4. Experimental Section

6.2.4.1. General Comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1-L5a-g**[6] and **L6a-c**[7] and substrate **S3**[3d] were prepared as previously described. All other reagents were used as commercially available.

6.2.4.2. General procedure for the 1,4-addition to substrates S1-S3

In a typical procedure, a solution of copper-catalyst precursor (1 mol %) and the corresponding ligand (4 mol%) in 2 mL of solvent was stirred for 30 minutes at room temperature. Then, the substrate (0.28 mmol) was added at the corresponding temperature and next the desired alkylating organometallic reagent (1.4 eq., 0.4 mmol) was added dropwise. After 2 hours, the reaction was quenched with HCl (5 mL, 2M). Then, undecane (50 μL) was added and the organic layer was filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC.[3h]

6.2.5. Acknowledgements

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6.3. Screening of a modular sugar-based phosphite ligand library in the Cu-catalyzed asymmetric 1,4-addition reactions

Abstract. The sugar-based monophosphite ligand library **L7-L11a-f** was also tested in the Cu-catalyzed asymmetric 1,4-addition to cyclic and aliphatic linear enones. These ligands are derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones, and contain several substituents/configurations in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone and the cooperative effect between configurations of C-3 and of the binaphthyl phosphite moiety. Good activities and enantioselectivities up to 57% and 51% were achieved for cyclic and aliphatic linear enones, respectively.

6.3.1. Introduction

The asymmetric copper-catalyzed conjugate addition is, nowadays, a well-developed methodology to create chiral C-C bonds.[1] Many efforts have been made in designing efficient systems and identifying new ligands to improve enantioselectivities with specific classes of substrates.[1] Among the most efficient ligands, phosphite and phosphoroamidites based on biaryl moieties have played a prominent role.[1f-h,2] Although Michael additions of organolithium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade,[1] less attention has been paid to trialkylaluminium reagents.[3] Trialkylaluminum reagents has been recently appeared as an interesting alternative to organozinc reagents since the potential exists to more easily extend their range by technically simple hydro- and carboalumination reactions. Additionally, they allow Cu-catalyzed 1,4-addition to very challenging substrates (i.e. β-trisubstituted enones) which are inert to organozinc methadologies.[3] On the other hand, linear aliphatic enones is another class of substrate for which the development of more active and enantioselective catalysts is still needed.[1]

Encouraged by the success of monophosphite ligands in this process, we report here the use of a highly modular sugar-based monophosphite ligand library (**L7-L11a-f**) in the Cu-catalyzed asymmetric 1,4-addition of trialkylaluminium to cyclic and aliphatic linear enones. These ligands have the advantage of carbohydrate and phosphite ligands, such as availability at low price from readily available alcohols, high resistance to oxidation and facile modular constructions.[4] Therefore, with this library we fully investigated the effects of systematically varying the configurations at C-3 and C-4 of the ligand backbone (**L7-L9**), different substituents/configurations in the biaryl phosphite moiety (**a-f**), the carbohydrate ring size (**L7-L10**) and the flexibility of the ligand backbone (**L10-L11**) (Figure 1).

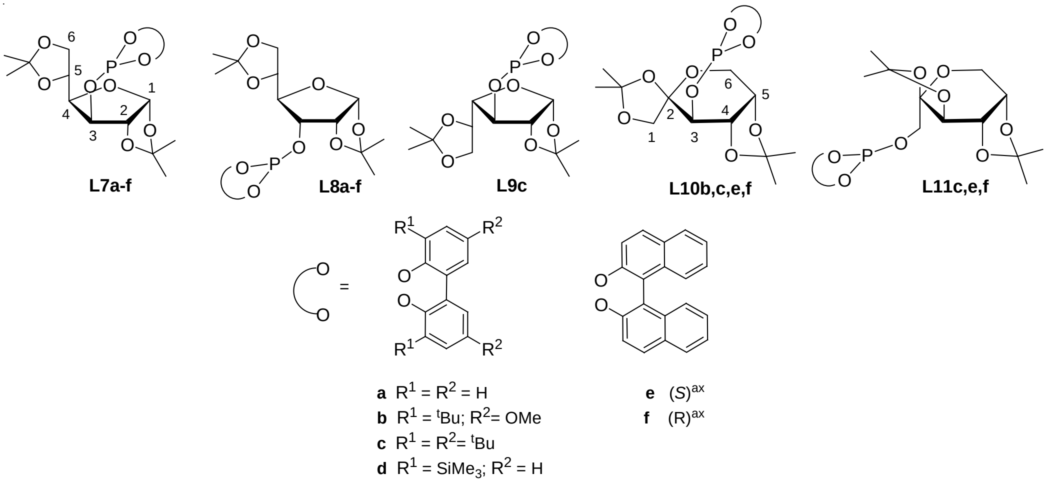
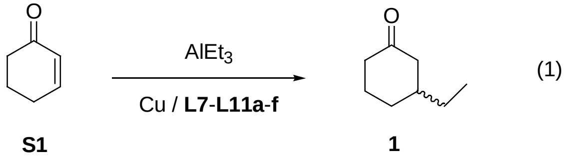


Figure 1. Carbohydrate-based phosphite ligands **L7-L11a**-**f**.

6.3.2. Results and Discussion

6.3.2.1. Asymmetric conjugated 1,4-addition of $AlEt_3$ to 2-cyclohexenone S1 (equation 1)

In a first set of experiments, we tested ligands **L7-L11a-f** in the copper-catalyzed conjugated addition of triethylaluminium to 2-cyclohexenone **S1** (eq. 1). The latter was used as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling to direct comparison of the efficiency of various ligand systems.[1] The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor.



(1)

The effect of several reaction parameters, such as catalyst precursor, solvent, ligand-to-copper ratio and temperature, were studied using ligand **L7f** (Table 1). The best result was obtained using dimethoxyethane (DME) as solvent, $Cu(OAc)_2$ as catalyst precursor and a ligand-to-copper ratio of 4 at –30 °C (Table 1, entry 9).

Table 1. Selected results for the copper-catalyzed conjugate 1,4-addition of **S1** using ligand **L7f**. Effect of the catalyst precursor, solvent, temperature and ligand-to-copper ratio.

Entry	Solvent	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	Et_2O	CuTC	-30	99	8	4 (*R*)
2	Et_2O	$Cu(OTf)_2$	-30	96	21	9 (*R*)
3	Et_2O	$Cu(OAc)_2$	-30	88	31	14 (*R*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	-30	98	18	5 (*R*)
5	Et_2O	CuI	-30	90	10	5 (*R*)
6	^tBuOMe	$Cu(OAc)_2$	-30	84	40	1 (*R*)
7	CH_2Cl_2	$Cu(OAc)_2$	-30	100	9	13 (*R*)
8	THF	$Cu(OAc)_2$	-30	83	8	35 (*R*)
9	DME	$Cu(OAc)_2$	-30	96	77	48 (*R*)
10[e]	DME	$Cu(OAc)_2$	-30	87	16	12 (*R*)
11[f]	DME	$Cu(OAc)_2$	-30	98	24	28 (*R*)
12	DME	$Cu(OAc)_2$	-20	99	10	36 (*R*)
13	DME	$Cu(OAc)_2$	-40	95	29	10 (*R*)

[a] Reaction conditions: Cu-precursor (1 mol%), **L7f** (4 mol%), $AlEt_3$ (1.4 eq, 0.4 mmol), **S1** (0.28 mmol), solvent (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using Lipodex A column. [e] ligand (1 mol%). [f] ligand (2 mol%).

Under the optimized conditions, we evaluated the rest of ligands. The results, which are summarized in Table 2, indicated that selectivities are highly affected by the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone and the cooperative effect between the configurations of C-3 and of the binaphthyl phosphite moiety.

Table 2. Selected results for the copper-catalysed conjugate 1,4-addition of **S1** using ligands **L7**-**L11a**-**f**.

Entry	Ligand	%Conv[b]	%Yield[c]	%ee[d]
1	**L7a**	99	61	21 (*R*)
2	**L7b**	99	61	37 (*R*)
3	**L7c**	98	10	8 (*R*)
4	**L7d**	99	61	21 (*R*)
5	**L7e**	98	24	20 (*S*)
6	**L7f**	96	77	48 (*R*)
7	**L8a**	92	23	6 (*S*)
8	**L8b**	98	31	15 (*S*)
9	**L8c**	99	28	23 (*S*)
10	**L8d**	91	15	14 (*S*)
11	**L8e**	99	55	57 (*R*)
12	**L8f**	93	17	7 (*S*)
13	**L9c**	99	23	4 (*R*)
14	**L10b**	98	11	8 (*S*)
15	**L10c**	94	8	4 (*S*)
16	**L10e**	99	56	12 (*S*)
17	**L10f**	100	33	2 (*S*)
18	**L11c**	99	18	8 (*S*)
19	**L11e**	99	18	23 (*S*)
20	**L11f**	100	46	33 (*R*)

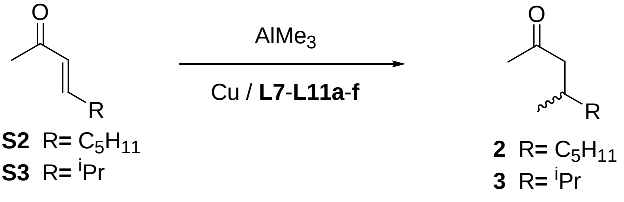
[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S1** (0.28 mmol), Me_2O (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC

The results using ligands **L7a-f** and **L8a-f** allow us to study the influence of the substituents/configurations of the biaryl moiety and the effect of the configuration at C-3 on the product outcome (Table 2, entries 1-11). We found that there is a cooperative effect between the configuration of C-3 and the configuration of the biaryl moiety. This resulted in a matched combination for ligand **L8e** (Table

2, entry 11). In addition, we also found that the biphenyl phosphite moieties in ligands **L7a-d** adopted an *R* configuration (Table 2, entries 1-4 *vs* 5 and 6), while in ligands **L8a-d** they adopted an *S* configuration (Table 2, entries 7-10 *vs* 11 and 12) when coordinated to the copper-active species. Comparing the results using ligands **L7** with **L9**, that only differ in the configuration at C-4, we found that ligands **L9** with an *S* configuration at C-4 gave lower enantioselectivities than ligands **L7** with an opposite configuration at this position (Table 2, entries 1-6 and 13). In addition, ligands **L10** and **L11** which have a pyranoside backbone provided lower yields and enantioselectivities than furanoside ligands (Table 2, entries 14-20). In summary, the best results was obtained with ligand **L8e** that contains the optimal combination of the ligand parameters (ee's up to 57%; Table 2, entry 11).

6.3.2.2. Asymmetric conjugated 1,4-addition of $AlMe_3$ to linear substrates S2 and S3 (equation 2)

In this section, we report the use of ligands **L7-L11a-f** in the copper-catalyzed conjugated addition of trimethylaluminium (equation 2) to two linear substrates with different steric properties: *trans*-3-nonen-2-one **S2** and *trans*-5-methyl-3-hexen-2-one **S3**. These enones possessing only aliphatic substituents are a more demanding substrate class for asymmetric conjugated addition than **S1**. The high conformational mobility of these substrates together with the presence of only subtle substrate-catalyst steric interactions makes the design of effective enantioselective systems a real challenge.[3d,5]



(2)

We first investigated the copper-catalyzed 1,4-addition of *trans*-3-nonen-2-one **S2** (equation 2, R= C_5H_{11}) with trimethylaluminium. Table 3 summarized the preliminary investigations into the solvent effect, the catalyst precursor and the ligand-to-copper ratio. The results indicated that the optimum trade-off between yields and enantioselectivity was obtained when diethylether was used as a solvent, the ligand-to-copper ratio was 4 and $Cu(OTf)_2$ was used as a catalyst precursor (Table 3, entry 2).

Table 3. Selected results for the copper-catalysed conjugate 1,4-addition of **S2** using ligands **L7c**.

Entry	Solvent	Precursor	T (ºC)	%Conv[b]	%Yield[c]	%ee[d]
1	Et_2O	CuTC	-30	97	21	3 (*S*)
2	Et_2O	$Cu(OTf)_2$	-30	99	79	18 (*R*)
3	Et_2O	$Cu(OAc)_2$	-30	93	31	7 (*S*)
4	Et_2O	$[Cu(MeCN)_4]BF_4$	-30	85	25	4 (*S*)
5	^tBuOMe	$Cu(OTf)_2$	-30	95	62	11 (S)
6	CH_2Cl_2	$Cu(OTf)_2$	-30	95	55	19 (*S*)
7	THF	$Cu(OTf)_2$	-30	31	7	3 (*S*)
8[e]	Et_2O	$Cu(OTf)_2$	-30	90	48	15 (*R*)
9[f]	Et_2O	$Cu(OTf)_2$	-30	91	51	15 (*R*)
10	Et_2O	$Cu(OTf)_2$	-20	88	52	15 (*R*)
11	Et_2O	$Cu(OTf)_2$	-40	93	56	18 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), **L7c** (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), solvent (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column.[3h] [e] ligand (1 mol%). [f] ligand (2 mol%).

Under optimized conditions, the results with the rest of ligands indicated that yield and enantioselectivities followed a different trend regarding the effect of the size of the ring of the sugar backbone and the cooperative effect between the configurations of C-3 and of the binaphthyl phosphite moiety to those observed for substrate **S1** (Table 4). Therefore, pyranoside ligands **L10** provided better enantioselectivities than their relative furanoside **L7** ligands and the cooperative effect between C-3 and binaphthyl moieties resulted in a matched combination for ligand **L7f**. In summary, the best result (ee's up to 52%) was obtained with ligand **L10f** that contains the optimal combination of the ligand parameters (Table 4, entry 17).

Table 4. Selected results for the copper-catalyzed conjugate 1,4-addition of **S2** using ligands **L7-L11a-f**.

Entry	Ligand	%Conv[b]	%Yield[c]	%ee[d]
1	**L7a**	32	6	8 (*R*)
2	**L7b**	66	48	18 (*R*)
3	**L7c**	99	79	18 (*R*)
4	**L7d**	93	51	4 (*R*)
5	**L7e**	95	53	42 (S)
6	**L7f**	96	51	48 (*R*)
7	**L8a**	38	9	10 (*S*)
8	**L8b**	77	83	8 (*S*)
9	**L8c**	72	65	8 (*S*)
10	**L8d**	95	52	13 (*S*)
11	**L8e**	97	40	24 (*S*)
12	**L8f**	98	50	28 (*R*)
13	**L9c**	89	63	1 (*R*)
14	**L10b**	87	49	7 (*S*)
15	**L10c**	87	49	8 (*S*)
16	**L10e**	99	61	46 (*S*)
17	**L10f**	91	66	52 (*R*)
18	**L11c**	92	64	9 (*S*)
19	**L11e**	40	11	13 (*S*)
20	**L11f**	26	4	7 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S2** (0.28 mmol), Et_2O (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column.[3h]

We finally studied the copper-catalyzed 1,4-addition of *trans*-5-methyl-3-hexen-2-one **S3** (equation 2, R= ^{i}Pr) with trimethylaluminium. The results are summarized in Table 5. Trends were similar to those observed for the previous substrate **S2**. Therefore, the best enantioselectivity (ee's up to 52%) was obtained with ligand **L10f** that contains an *R* binaphtyl phosphite moiety attached to the pyranoside backbone (Table 5, entry 16).

Table 5. Selected results for the copper-catalysed conjugate 1,4-addition of **S3** using ligands **L7**-**L11a**-**f**.

Entry	Ligand	%Conv[b]	%Yield[c]	%ee[d]
1	**L7a**	14	3	9 (*R*)
2	**L7b**	26	23	20 (*R*)
3	**L7c**	96	96	39 (*R*)
4	**L7d**	95	95	21 (*R*)
5	**L7e**	90	77	30 (*S*)
6	**L7f**	56	39	29 (*R*)
7	**L8a**	10	3	4 (*S*)
8	**L8b**	95	95	12 (*S*)
9	**L8c**	95	95	7 (*S*)
10	**L8d**	82	77	3 (*S*)
11	**L8e**	95	91	48 (*S*)
12	**L8f**	42	32	17 (*R*)
13	**L9c**	96	96	22 (*R*)
14	**L10c**	96	96	33 (*R*)
15	**L10e**	98	98	48 (*S*)
16	**L10f**	97	97	52 (*R*)
17	**L11c**	98	98	12 (*R*)
18	**L11e**	40	40	14 (*S*)
19	**L11f**	6	4	10 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (1 mol%), ligand (4 mol%), $AlMe_3$ (1.4 eq, 0.4 mmol), **S3** (0.28 mmol), Et_2O (2 mL). [b] % Conversion determined by GC using undecane as internal standard after 2 hours. [c] % Yield determined by GC using undecane as internal standard after 2 hours. [d] Enantiomeric excess measured by GC using 6-Me-2,3-pe-δ-CD column.[3h]

6.3.3. Conclusions

The sugar-based monophosphite ligand library **L7-L11a-f** was tested in the asymmetric Cu-catalyzed 1,4-conjugate addition reactions of cyclic and acyclic enones. Our results indicated that activity and selectivity depended strongly on the configuration of C-4 of the carbohydrate backbone, the size of the ring of the sugar backbone, the cooperative effect between configurations of C-3 and of the binaphtyl phosphite moiety and the substrate type. For cyclic substrate **S1**, enantioselectivities (up to 57%) were therefore best with ligand **L8e**, while for aliphatic linear substrates **S2** and **S3**, the best ligand was **L10f** (ee's up to 51%).

6.3.4. Experimental Section

6.3.4.1. General Comments

All syntheses were performed by using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L7-L11a-f**[6] and substrate **S3**[3d] were prepared as previously described. All other reagents were used as commercially available.

6.3.4.2. General procedure for the 1,4-addition to substrates S1-S3

In a typical procedure, a solution of copper-catalyst precursor (1 mol %) and the corresponding ligand (4 mol%) in 2 mL of solvent was stirred for 30 minutes at room temperature. Then, the substrate (0.28 mmol) was added at the corresponding temperature and next the desired alkylating organometallic reagent (1.4 eq., 0.4 mmol) was added dropwise. After 2 hours, the reaction was quenched with HCl (5 mL, 2M). Then, undecane (50 μL) was added and the organic layer was filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC.[3h]

6.3.5. Acknowledgements

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Chapter 7

Conclusions

7. Conclusions

1. Chapter 3. *Pd-catalyzed asymmetric allylic substitution*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Pd-catalyzed allylic substitution reactions using chiral phosphite-oxazoline ligands we observed important effects of the oxazoline substituents and the axial chirality and the substituents of the biaryl moieties. However, the effects of these parameters depended on each substrate. High enantioselectivities (up to 99%) and good activities have been achieved in a wide range of substrates with different steric and electronic properties.

The study of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy made it possible to understand the catalytic behaviour observed. This study also indicated that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety.

- Asymmetric substitution reactions with catalyst precursors containing the phosphite-phosphoroamidite ligands showed that enantiomeric excesses depend strongly on the substituents at the *para* positions of the biphenyl moieties. However, these effects were different depending on the substrate in study. Enantiomeric excesses of up to 89% with high activities were obtained for *rac*-1,3-diphenyl-3-acetoxyprop-1-ene, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate and *rac*-3-acetoxycycloheptene. For the monosubstituted linear substrate 1-(1-naphthyl)allyl acetate, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivity by carefully selecting the substituents on the *para* position of the biphenyl moieties (ee's up to 72%).

If we compare these results with those from the catalyst precursors containing the previous phosphite-oxazoline ligands, we found that the replacement of the oxazoline moiety by a phosphoroamidite group decreased enantioselectivities and versatibility.

- Asymmetric allylic alkylation with catalyst precursors containing the sugar-based monophosphite ligand library showed that the catalytic performance is highly affected by the size of the sugar backbone, the configurations at C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. Unfortunately, low-to-moderate enantioselectivities (up to 46%) were obtained.

2. Chapter 4. *Pd-catalyzed asymmetric Heck reactions*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Pd-catalyzed Heck reactions with catalysts precursors based on phosphite-oxazoline ligands, we found that the degree of isomerization and the effectiveness in transferring the chiral information in the product and the activity can be tuned by correctly choosing ligand components (phosphite and oxazoline substituents). Excellent activities (up to 100% conversion in 10 minutes), regio- (up to >99%) and enantioselectivities (up to 99%) were obtained in a wide range of substrates and triflate sources. Unfortunately, the preliminary studies using the phosphite-phosphoroamidite **L6a-c** and monophosphite **L7-L11a-f** ligand libraries in several reaction conditions showed low activities and selectivities.

3. Chapter 5. *Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes*. The conclusions of this chapter can be summarized as follows:

- In the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium to aldehydes with catalysts precursors based on phosphite-oxazoline and phosphite-phosphoroamidite ligands, we found that the selectivity depends strongly on the type of functional group attached to the carbohydrate backbone, on the steric properties of the oxazoline substituents and on the substrate structure. Enantioselectivities up to 59% were obtained using the catalyst precursor containing the phosphite-oxazoline ligand **L3a**.

- In contrast to what we observed with the previous two ligand libraries, using sugar-based monophosphite ligands in the asymmetric Ni-catalyzed 1,2-addition of trialkylaluminium to aldehydes provides high enantioselectivities (up to 94% ee) and activities in different substrate types, with low catalysts loadings and without excess of ligand.

4. Chapter 6. *Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones*. The conclusions of this chapter can be summarized as follows:

- Using phosphite-oxazoline and phosphite-phosphoroamidite ligands as chiral auxiliaries in the asymmetric Cu-catalyzed 1,4-conjugated addition of trialkylaluminium reagents to several enones provides good enantioselectivities (up to 80% ee).

- In the asymmetric Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to several enones with catalysts precursors based on sugar monophosphite ligands, we found good activites and enantioselectivities up to 57% ee.

Chapter 8

Appendix

List of papers and meeting contributions

List of papers by the author presented in this thesis (in chronological order):

1. Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C.
New Carbohydrate-Based Phosphite-Oxazoline Ligands as Highly Versatile Ligands for Palladium-Catalyzed Allylic Substitution Reactions.
Adv. Synth. Catal. **2005**, *347*, 1943.
(Chapter 3)

2. Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C.
Chiral Phosphite-oxazolines: A New Class of Ligands for Asymmetric Heck Reactions.
Org. Lett., **2005**, *7*, 5597.
(Chapter 4)

3. Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S.
Screening of a Modular Sugar-Based Phosphite Ligand Library in the Asymmetric Nickel-Catalyzed Trialkylaluminium Addition to Aldehydes.
J. Org. Chem. **2006**, *71*, 8159.
(Chapter 5)

4. Mata, Y.; Diéguez M.; Pàmies, O.; Claver, C.
Sugar-based phosphite-phosphoroamidite ligands for allylic alkylation reactions.
Tetrahedron Asymmetry **2006**, *17*, 3282.
(Chapter 3)

5. Mata, Y.; Diéguez, M.; Pàmies, O.
Screening of a modular sugar-based phosphite-oxazoline ligand library in the asymmetric Pd-catalyzed Heck reactions.
Chem. Eur. J. **2007**, *13*, 3296
(Chapter 4)

6. Mata, Y.; Diéguez, M.; Pàmies, O.
A carbohydrate-based phosphite-oxazoline ligand library for Pd-catalyzed asymmetric allylic substitution reactions.
Submitted to Chem. Eur. J.
(Chapter 3)

7. Mata, Y.; Diéguez, M.; Pàmies, O.
Pd-catalyzed asymmetric allylic substitution using a sugar-based monophosphite ligand library.
Submitted to Inorg. Chim. Acta
(Chapter 3)

8. Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S.
Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries in the asymmetric Ni-catalyzed trialkylaluminium addition to aldehydes.
In preparation
(Chapter 5)

9. Mata, Y.; Diéguez, M.; Pàmies, O.; Biswas, K.; Woodward, S.
Sugar phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries for Cu-catalyzed asymmetric 1,4-addition reactions.
Submitted to Tetrahedron: Asymmetry
(Chapter 6)

10. Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S.
Screening of a modular sugar-based phosphite ligand library in the Cu-catalyzed asymmetric 1,4-addition reactions.
In preparation
(Chapter 6)

Contributions to national and international meetings, directly related with the thesis.

1. Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C.
New Carbohydrate-Based Phosphite-Oxazoline Ligands as Highly Versatile Ligands for Palladium-Catalyzed Allylic Substitution Reactions.
XXII International Conference on Organometallic Chemistry - ICOMC.
Zaragoza. Spain. 2006. Poster communication.

2. Diéguez, M.; Mata, Y.; Pàmies, O.; Claver, C.
New carbohydrate-based phosphite-oxazoline as a highly versatile ligands for Pd-catalyzed enantioselective substitution reactions.
Stereocat 06.
Lisbon. Portugal. 2006. Poster communication.

3. Pàmies, O.; Mata, Y.; Claver, C: Diéguez, M.
Phosphite-oxazoline ligands for asymmetric Pd-catalyzed Heck reactions.
Innovation I Conference. COST D-40
Dublin. Ireland. 2007. Poster communication.

Agraïments

Va ser durant l'últim any de la llicenciatura quan l'Òscar i la Montse em van animar a fer el doctorat. Tot i acabar més tard del previst, van donar-me l'oportunitat de treballar amb ells. És admirable la seva dedicació per la feina i sense el seu esforç per les coses ben fetes, ganes d'ensenyar-me i sobretot molta paciència no tindria ara aquesta tesi entre les mans.

Vull donar les gràcies a tota la gent que forma part de l'Àrea de Química Inorgànica. Els que hi han passat, els que encara hi són, al Ramon per la seva ajuda i paciència i especialment a la Professora Carmen Claver per ser tan amable i fer-me sentir a gust dins del seu grup. També a tota una colla d'aquí i de fora... all you know who you are... pels ànims i els moments que hem passat junts durant aquest temps.

I Would also like to thank Prof Simon Woodward for welcoming me in his research group. I am grateful for his support and also to thank Miss. Dorrit, Nick and all the people I met during my 4 months in Nottingham, especially to John, Bex, Dan and Andy.

I sobretot vull agrair als meus cosins, al Manel, al Jordi i a la meva família, el seu suport. Moltes coses han passat des que vaig començar el doctorat però crec que tots hem sabut mirar endavant. Sense cap dubte aquesta tesi va dedicada a vosaltres. Us estimo.

Anyone who has never made a mistake has never tried anything new.

Albert Einstein

Table of contents

Structure of the thesis

This thesis is based on ten papers published in international journals. These papers have been reedited to provide a uniform format throughout the thesis.

The thesis is divided into eight chapters.

- Chapter 1. *Introduction*. This chapter first presents the importance of metal asymmetric catalysis in the synthesis of enantiomerically pure compounds. An important step in this synthesis is the design and synthesis of chiral ligands. Among them, new chiral ligands derived from carbohydrate are presented. These ligands are applied to four asymmetric catalytic reactions, which are reviewed in detail in this chapter. For each reaction, the antecedents, performance and main achievements are discussed, with emphasis on the application of carbohydrate ligands. The state-of-the-art and current needs in this field justify the objectives of the thesis.

- Chapter 2. *Objectives*. Based on the aspects discussed in chapter 1, this chapter presents the objectives of the thesis. These involve the synthesis and application of new sugar ligands in asymmetric catalysis.

- Chapter 3. *Pd-catalyzed asymmetric allylic substitution*. This chapter contains three sections on the development and application of new phosphite-oxazoline, phosphite-phosphoroamidite and monophosphite ligand libraries in the asymmetric Pd-catalyzed allylic substitution reactions. The first section, *A carbohydrate-based phosphite-oxazoline ligand library for Pd-catalyzed allylic substitution reactions*, describes the synthesis and application of a phosphite-oxazoline ligand library in the asymmetric Pd-catalyzed allylic substitution of several substrates with different electronic and steric properties. This paper also discusses the synthesis and characterization of the Pd-π-allyl intermediates to provide greater insight into the origin of the enantioselectivity. The second section, *Pd-catalyzed asymmetric allylic substitution using pyranoside phosphite-*

phosphoroamidite ligands, includes the development and application of new a phosphite-phosphoroamidite ligand library in asymmetric allylic substitution. The third section, *Pd-catalyzed asymmetric allylic substitution using a sugar-based monophosphite ligand library*, presents the synthesis and application of a monophosphite sugar-based ligand library in the Pd-catalyzed allylic alkylation reactions.

- Chapter 4. *Pd-catalyzed asymmetric Heck reactions.* This chapter contains one section, *Screening of a modular sugar-based phosphite-oxazoline ligand library in asymmetric Pd-catalyzed Heck reactions*, which discusses the application for the first time of phosphite-oxazoline ligands (developed in Chapter 3) in the asymmetric Pd-catalyzed Heck reactions. The effects of various triflates sources and substrates types are also studied.

- Chapter 5. *Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes.* This chapter contains two sections on the application of the phosphite-oxazoline, phosphite-phosphoroamidite and monophosphite ligand libraries (developed in Chapter 3) in the asymmetric Ni-catalyzed 1,2-addition reactions. The first one, *Phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries in the asymmetric Ni-catalyzed trialkylaluminium addition to aldehydes*, reports the investigations of the Ni-catalyzed trialkylaluminium 1,2-addition to aldehydes using the phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries. The second section, *Screening of a modular sugar-based phosphite ligand library in the asymmetric Ni-catalyzed trialkylaluminium addition to aldehydes*, includes the application of the sugar-based monophosphite ligand library in the Ni-catalyzed trialkylaluminium 1,2-addition to several aldehydes types.

- Chapter 6. *Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones.* This chapter contains two sections on the application of the phosphite-oxazoline, phosphite-phosphoroamidite and monophosphite ligand libraries (developed in Chapter 3) in the asymmetric Cu-catalyzed 1,4-addition reactions. The first one, *Sugar phosphite-oxazoline and* *phosphtie-phosphoroamidite ligand libraries for Cu-catalyzed asymmetric 1,4-addition reactions*, reports the investigations of the Cu-catalyzed 1,4-addition of organometallic reagents to enones using the phosphite-oxazoline and phosphite-phosphoroamidite ligand libraries. The second section, *Screening of a modular sugar-based phosphite ligand library in the Cu-catalyzed asymmetric 1,4-addition reactions*, includes the application of the sugar-based monophosphite ligand library in the Cu-catalyzed trialkylaluminium 1,4-addition to cyclic and linear enones.

- Chapter 7. *Conclusions*. This chapter presents the conclusions of the work presented in this thesis.
- The *Appendix* contains the list of papers and meeting presentations given by the author during the period of development of this thesis.

Chapter 1

Introduction

1. Introduction

The growing demand for enantiomerically pure compounds for the development of pharmaceuticals, agrochemicals and flavors has captured the interest of the chemist in the last few decades. Of the various methods for producing enantiopure compounds, enantioselective homogeneous metal catalysis is an attractive one, as is reflected by the many publications in this field and the award of the Nobel Prize in 2001 to W.S. Knowles, R. Noyori and K. B. Sharpless.[1] One of the main advantages of asymmetric catalysis over other methods used in asymmetric synthesis is that products can be selectively synthesized from cheap, commercially available prochiral starting materials without undesirable products being formed. Usually with this strategy, a transition-metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate to one enantiomer as major product.

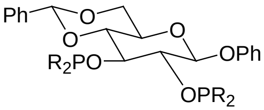
To reach the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized. Of these, the selection and design of the chiral ligand is perhaps the most crucial step. One of the simplest ways to obtain chiral ligands is to transform or derivatize natural chiral compounds, thus making tedious optical-resolution procedures unnecessary. Carbohydrates have many advantages: they are readily available, are highly functionalized and have several stereogenic centers. This enables series of chiral ligands to be synthesized and screened in the search for high activities and selectivities for each particular reaction. This tuning of the ligand structure allows for a rational design of ligands, which provides valuable information about the origin of the selectivity. One of the main limitations of using natural products as precursors for ligands is that often only one of the enantiomers (in the case of carbohydrates, the D-series) is readily available. However, this limitation can be overcome by using pseudo-enantiomer ligands or by suitable ligand tuning.[2]

In this context, this thesis focuses on the development of new chiral ligand libraries derived from carbohydrates, the synthesis of new catalyst precursors and their application in the Pd-catalyzed asymmetric allylic substitution, Pd-catalyzed asymmetric Heck reactions, Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes, and Cu-catalyzed asymmetric 1,4-conjugated addition of trialkylaluminium reagents to enones. In next section, we collect the most important carbohydrate-derivative ligand families developed for metal-catalyzed asymmetric reactions. The following sections describe the background of each of the asymmetric catalytic reactions studied in this thesis.

1.1. Carbohydrate ligands' background in asymmetric catalysis

Despite the advantages of carbohydrates, their systematic use as chiral auxiliaries in asymmetric catalysis has not been considered until recently. Nowadays, many type of carbohydrate ligands have been successfully applied in several catalytic asymmetric reactions (mainly in asymmetric hydrogenation).[2] A review of the research into carbohydrate ligands highlighted four main carbohydrate derivative ligand families:

- The first important family is the pyranoside diphosphinite ligands **1** derived from D-glucose (Figure 1) mainly developed by the groups of Selke and Rajanbabu. These ligands were the first successful application of diphosphinite ligands in asymmetric catalysis. They were applied with excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dehydroaminoacids (ee's up to 99%)[3] and in the Ni-catalyzed asymmetric hydrocyanation of vinylarenes (ee's up to 91%).[4]



1

Figure 1. Diphosphinite pyranoside ligands.

- The second family is the C_2-diphosphite ligands **2** derived from D-mannitol. These ligands, developed by Reetz and coworkers, were successfully applied in the asymmetric hydrogenation of dehydroaminoacid derivatives (ee's up to 98%).[5]

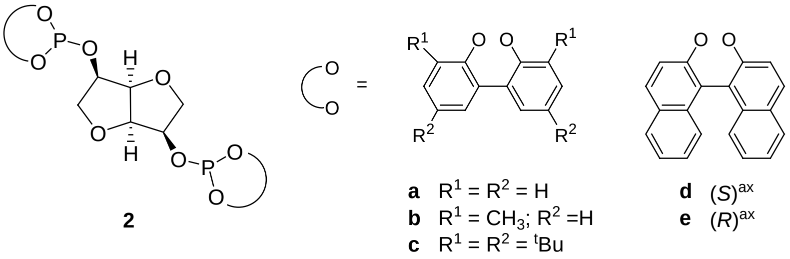
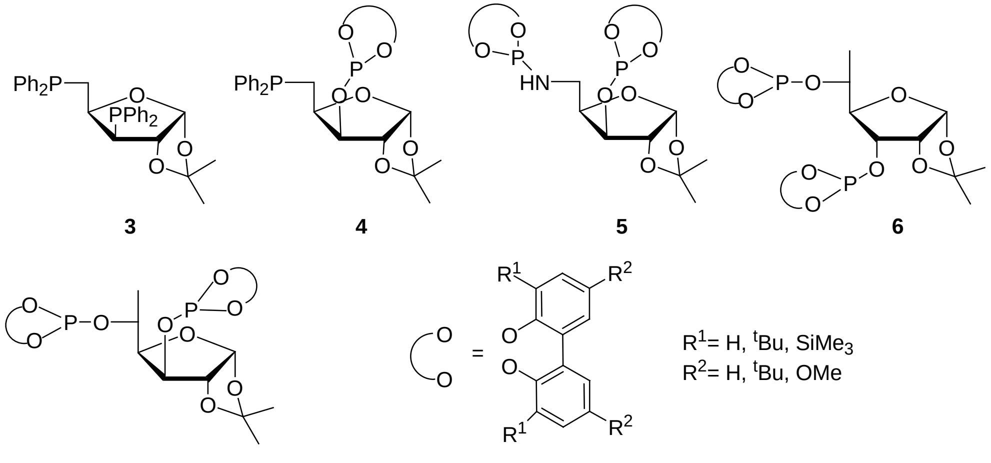


Figure 2. Diphosphite ligands derived from D-mannitol.

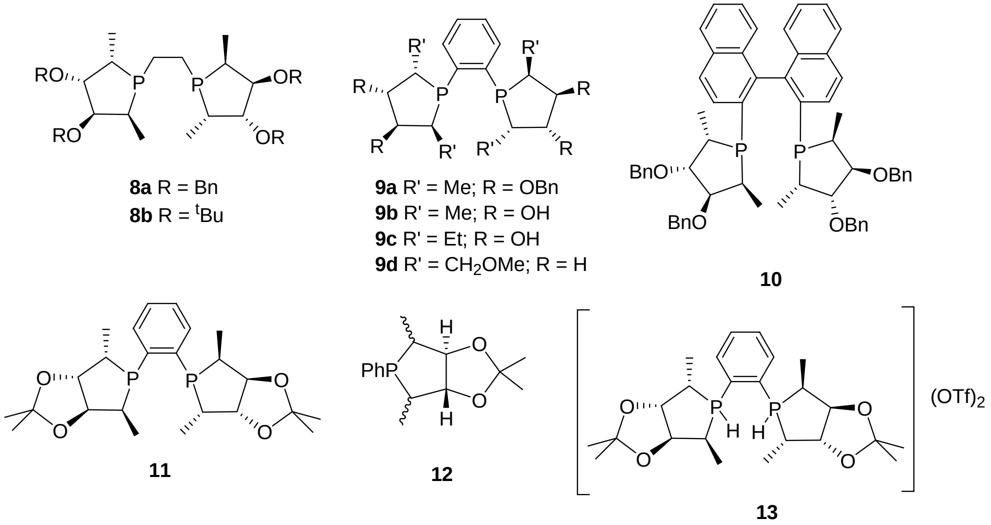
- The third important series of sugar derivative ligands in asymmetric catalysis is the 1,2-protected furanoses derived from D-(+)-xylose and D-(+)-glucose (Figure 3). These ligands were successfully applied in several asymmetric catalytic processes. It is to note the diphosphine ligand **3**[6], the phosphine-phosphite **4**[7] and phosphite-phosphoroamidite ligand **5**[8], derived from D-(+)-xylose and the diphosphite ligands **6**[9] and **7**[10] derived from D-(+)-glucose.



R^1= H, ^{t}Bu, $SiMe_3$
R^2= H, ^{t}Bu, OMe

Figure 3. Carbohydrate ligands with furanoside backbone.

- The last important family of carbohydrate ligands are the phospholane ligands derived from D-mannitol **8-13** (Figure 4). In the last few years, these ligands have emerged as a powerful new class of ligands for asymmetric hydrogenation (ee's up to 99%)[11] and for asymmetric allylic substitution (ee's up to 99%)[12] reactions.



8a R = Bn
8b R = ^{t}Bu

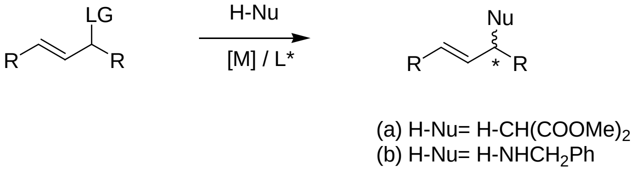
9a R' = Me; R = OBn
9b R' = Me; R = OH
9c R' = Et; R = OH
9d R' = CH_2OMe; R = H

Figure 4. Phospholane ligands derived from D-mannitol.

1.2. Asymmetric allylic substitution

Palladium-catalyzed asymmetric allylic substitution is one of the catalytic homogenous reactions that have attracted most attention in recent decades. This is mainly because this process is an efficient synthetic tool for the formation of carbon-carbon and carbon-heteroatom bonds. The mild reaction conditions, the compatibility with many functional groups and the often high enantioselectivities make this method attractive for application in the synthesis of complex natural products or pharmaceuticals.[1c,13]

In this process, an allyl acetate or carbonate is attacked by a nucleophile (typically, a carbon or nitrogen nucleophile). Therefore, a nucleophilic substitution takes place and either a new carbon-carbon bond (allylic alkylation, Scheme 1(a)) or a new carbon-nitrogen bond is generated (allylic amination, Scheme 2(b)).[1c,13]



Scheme 1. Asymmetric allylic substitution reactions: (a) Dimethyl malonate (alkylation) and (b) Benzylamine (amination). LG = leaving group.

The range of substrates (linear and cyclic) tested is quite wide. However, *rac*-(*E*)-1,3-diphenylprop-2-enyl (Figure 5, R = Ph, LG = OAc) has been the substrate of choice for testing a new ligand. With regard to the metal source, a variety of transition metal complexes derived from Pd, Ni, Ru, Rh, Ir, Mo, W and other elements are known to catalyze allylic substitutions.[1c] However, the most widely used catalysts are palladium complexes. A wide range of carbon and heteroatom *soft* nucleophiles (those derived from conjugate acids with pKa < 25) have been employed in this process. Besides dimethyl malonate, which has become the standard nucleophile for testing new catalysts, many other stabilized carbanions bearing carbonyl, sulfone, nitrile or nitro groups have also been used. There are only a few examples of enantioselective reactions with *hard* nucleophiles such as diorganozinc or Grignard reagents.[1c]

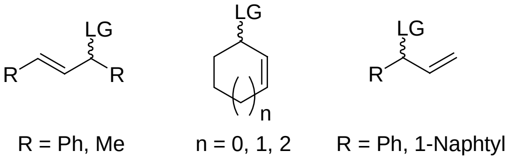


Figure 5. The most common substrates for the enantioselective allylic substitution.

1.2.1. Mechanism

The mechanism of the palladium-catalyzed asymmetric allylic substitution, with *soft* nucleophiles, is well established (Figure 6).[1c] This is partly due to the relative ease of isolating catalytic intermediates, especially the palladium allylic species **17**, although some related Pd(0) species **18** have also been characterized in solution.

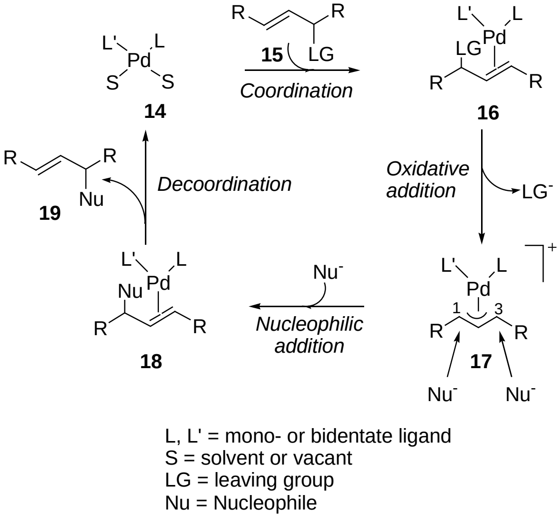


Figure 6. Catalytic cycle for the Pd-catalyzed allylic substitution with *soft* nucleophiles.

The first step in the catalytic cycle is the coordination of an allylic substrate **15** to the catalyst precursor **14**, which enters the cycle at the Pd(0) oxidation level. Both Pd(0) and Pd(II) complexes (e.g. $Pd_2(dba)_3$, $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$, dba= dibenzylideneacetone) can be used as precatalysts because Pd(II) is easily reduced *in situ* by the nucleophile to the Pd(0) form. In the next step, the cationic π-complex **16** eliminates LG^- to produce the (η^3-allyl)palladium(II) complex **17**. This is the rate-determining step of the reaction. The product of this oxidative addition has two susceptible positions for receiving nucleophilic attack (C-1 and C-3). After nucleophilic addition, an unstable Pd(0)-olefin complex **18** is produced, which readily releases the final product **19**.

It is generally accepted that the enantioselectivity of the process is controlled by the external nucleophilic attack on the more electrophilic terminal allylic carbon of **17**. Therefore, the allyl complex **17** plays a central role as a key intermediate in the catalytic cycle, which can be isolated in the absence of nucleophiles. Allyl complexes can show dynamic behavior in solution, which results in a mixture of isomers (Figure 7).

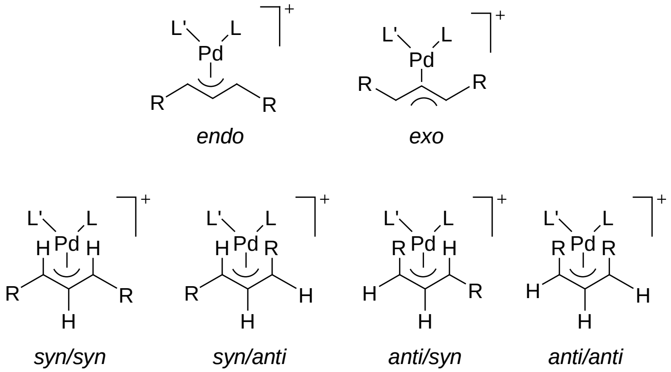


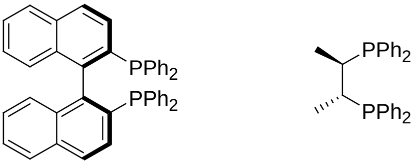
Figure 7. Possible isomers adopted by the Pd-allyl complexes.

To achieve high ee's, the formation of a single isomer is necessary if we assume that the reaction rates are similar for all possible isomers.[1c,13] Both the oxidative addition leading to **17** and the subsequent nucleophilic attack normally occur stereoselectively with inversion of configuration at the reacting allylic carbon atoms. Therefore, if the intermediate allyl complex does not undergo any isomerization that changes its configuration, the overall process **14** to **19** proceeds with the retention of configuration, i.e. the nucleophile is introduced at the same side of the allyl plane that was occupied by the leaving group LG.

1.2.2. Ligands

Since the first enantioselective catalytic process described by Trost in 1977, with moderate enantioselectivity,[14] many catalytic systems have been tested. These have provided excellent enantiomeric excesses.[1c,13]

Unlike asymmetric hydrogenation process, few diphosphines have provided good enantioselectivities in allylic substitutions. Though high ee's could be obtained in certain cases for instance, with BINAP and CHIRAPHOS (Figure 8), the scope of standard diphosphines in this process seems limited.[1c,13]



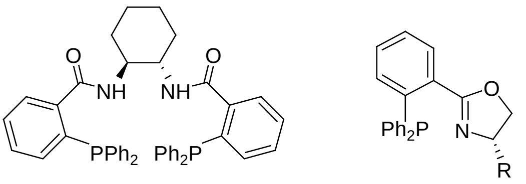
BINAP **CHIRAPHOS**

Figure 8. BINAP and CHIRAPHOS ligands.

However, one of the most versatile ligands for this process is a diphosphine **20** developed by Trost (Figure 9).[13b,15] The remarkable properties of this ligand are related to the bite angle, which is larger than in unstrained Pd-diphosphine complexes. Consequently, the P-aryl groups generated a chiral cavity, in which the allyl system is embedded, that provides high ee's for several sterically undemanding substrates. For diphosphines and other homodonor systems, the chiral discrimination is therefore induced by the C_2 or C_1 backbone of the ligand.

The selection of chiral ligands for highly enantioselective allylic substitution has mainly focused on the use of mixed bidentate donor ligands such as phosphorus-nitrogen, phosphorus-sulfur and sulfur-nitrogen.[1c,16] In this context, the phosphinooxazoline PHOX ligands represent, together with Trost's ligand, one of the most representative ligands developed for this process (Figure 9).[17] The efficiency of this type of hard-soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms that predominantly produced the nuclephilic attack at one of the allyl carbon atoms (the one located *trans* to the best π-acceptor).

Other ligands, such as bidentate nitrogen and sulfur, have also exhibited very good catalytic behavior.[1c,16]



20
Trost's ligand

PHOX ligands

Figure 9. Two of the most representative ligands developed for the Pd-catalyzed allylic substitution reactions.

Carbohydrate ligands have only recently shown their huge potential as a source of highly effective chiral ligands in this process. Several types of ligands, mainly heterodonors, have been developed for this process and some of the results are among the best ever reported.[2]

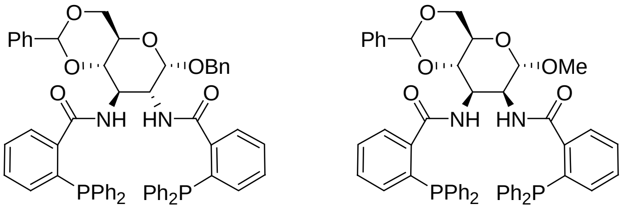
In the next section we summarize the most relevant catalytic data published for the Pd-catalyzed allylic substitution with carbohydrate ligands.

1.2.2.1. P-donor ligands

Phosphine Ligands

The most successful carbohydrate family of phosphine ligands was developed by RajanBabu and Zhang. These authors have independently reported the use of diphospholanes ligands **10** and **11** and monophospholane ligand **12**, derived from D-mannitol, in the Pd-catalyzed allylic alkylation of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate (ee's up to 99%, Figure 4).[12] In general, high enantioselectivies have been achieved. Interestingly, the sense of asymmetric induction appears to be dictated by the absolute stereochemistry of the P-carrying carbons. Both enantiomers of the product can therefore be obtained.

In 2006, Ruffo and coworkers developed a modification of the Trost-bis(phosphinoamides) ligands[15] using diamines based on glucose and mannose as chiral auxiliaries (Figure 10, ligands **21** and **22**) for the highly enantioselective Pd-catalyzed desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate (ee's up to 97%). Interestingly both enantiomers of the product can be obtained in high enantioselectivities by switching from glucose (**21**) to mannose (**22**) derivative ligands.[18]

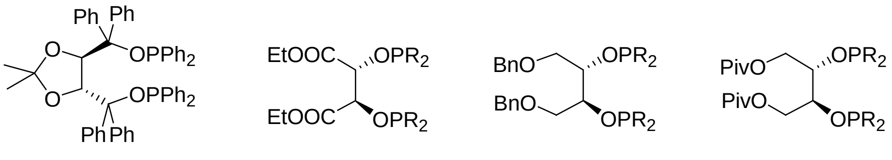


21 (97% (-)) **22** (97% (+))

Figure 10. Bis(phosphinoamides) **21** and **22** developed by Ruffo and coworkers.

Phosphinite Ligands

In 1995, Seebach and coworkers first prepared C_2-symmetric diphosphinite **23** from TADDOL, tested it in the asymmetric allylic substitution and obtained enantiomeric excesses of up to 76% (Figure 11).[19] Subsequently, RajanBabu and coworkers tested the previously mentioned ligands **1** (Figure 1) and ligands **24-26** (Figure 11), derived from tartaric acid, in the Pd-catalyzed asymmetric allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate with low-to-good enantioselectivities.[20] For ligands **1**, the best enantioselectivity (59% ee) was achieved with the ligand containing cyclohexenyl as substituent R.[20a] Interestingly, electron-withdrawing and electronic-rich diphosphinite ligands lead to products with opposite stereochemistry. Moreover, sterically bulky substituents have the same effect as electron-rich ones. For diphosphinite ligands **24-26**, the electronic effects were similar to those with ligands **1**, but enantioselectivities were up to 77% (Figure 11).[20b]



23 **24** **25** **26**

Figure 11. Diphosphinite **23-26** ligands applied in asymmetric allylic substitution.

Phosphite Ligands

In 2001, it has been reported the first diphosphite ligands family applied to Pd-catalyzed asymmetric allylic substitution reactions (Figure 12).[10d,e,21] These furanoside diphosphite ligands **27-33** (Figure 12) were successfully applied in the Pd-catalyzed allylic substitution of diethyl malonate and benzylamine to several acyclic and cyclic allylic esters (Figure 13).

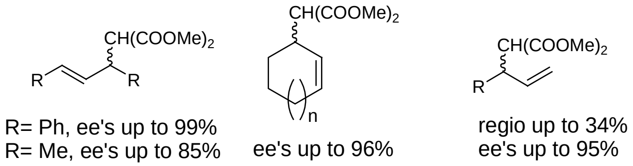
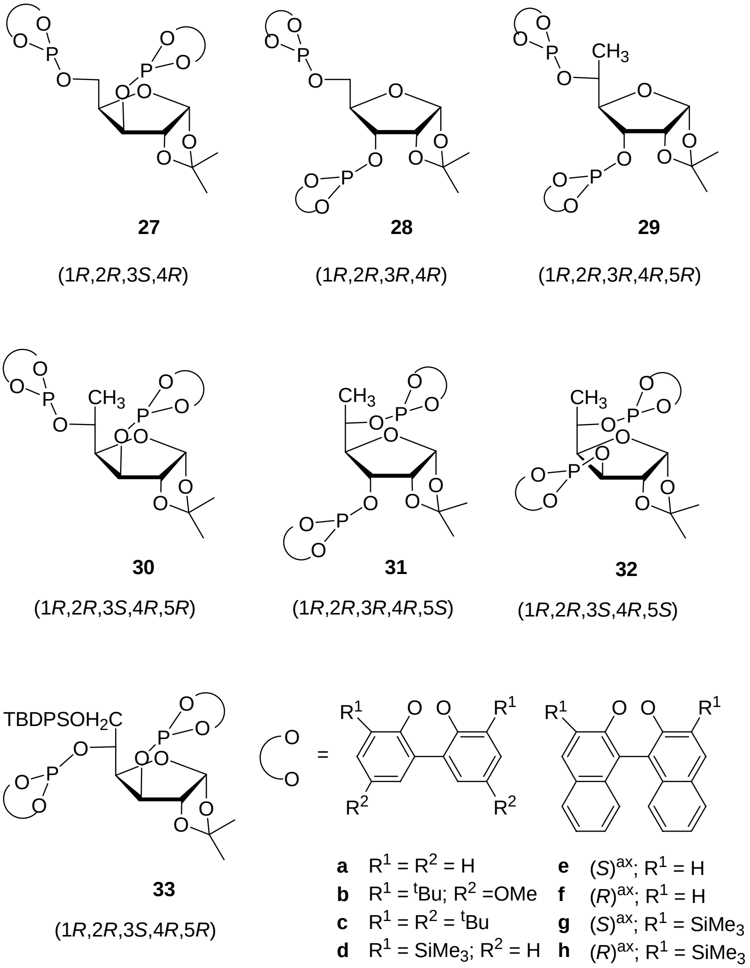


Figure 13. Acyclic and cyclic allylic esters tested with ligands **27**-**33**.

Results indicated that activities were best when the substituent at C-5 was Me and when the ligand contained bulky substituents at the *ortho* positions and electrodonating substituents at the *para* positions of the biphenyl moieties (i.e., **b**~**c**>**d**>**a**). Enantioselectivities were affected by the substituent at C-5 and the phosphite moieties and by the configuration of carbon atoms C-3 and C-5 and the configurations of the biaryl moieties. Enantioselectivities were best with ligand **30c**, which has a glucofuranoside backbone and bulky *tert*-butyl substitutents at both *ortho* and *para* positions of the biphenyl moieties. The results also indicated that the nucleophilic attack takes place *trans* to the carbon atom C-5. Ligand **27c** was also used to stabilize Pd-nanoparticles. These particles catalyzed the allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene with dimethyl malonate leading to an almost total conversion of the (*R*) enantiomer and almost no reaction with the (*S*). This gives rise to 97% ee for the alkylation product and a kinetic resolution of the substrate recovered with ca. 90% ee.[22]



27 (1*R*,2*R*,3*S*,4*R*)

28 (1*R*,2*R*,3*R*,4*R*)

29 (1*R*,2*R*,3*R*,4*R*,5*R*)

30 (1*R*,2*R*,3*S*,4*R*,5*R*)

31 (1*R*,2*R*,3*R*,4*R*,5*S*)

32 (1*R*,2*R*,3*S*,4*R*,5*S*)

33 (1*R*,2*R*,3*S*,4*R*,5*R*)

a $R^1 = R^2 = H$
b $R^1 = {}^tBu$; $R^2 = OMe$
c $R^1 = R^2 = {}^tBu$
d $R^1 = SiMe_3$; $R^2 = H$
e $(S)^{ax}$; $R^1 = H$
f $(R)^{ax}$; $R^1 = H$
g $(S)^{ax}$; $R^1 = SiMe_3$
h $(R)^{ax}$; $R^1 = SiMe_3$

Figure 12. Furanoside diphosphite ligands **27**-**33**.

Phosphoroamidite Ligands

During the last decades, there has been a huge advance in the use of phosphoroamidite ligands for several asymmetric processes.[23] However, to best our knowledge only one family of diphosphoroamidite ligands **34** based on carbohydrates has been successfully applied in asymmetric catalysis (Figure 14).[24] Good-to-excellent activities (TOF's up to 850 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 95%) have been obtained in the Pd-catalyzed allylic alkylation for several di- and monosubstituted linear and cyclic substrates. The results indicate that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. The study of the 1,3-diphenyl and cyclohexenyl Pd-π-allyl intermediates indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety attached to C-5.

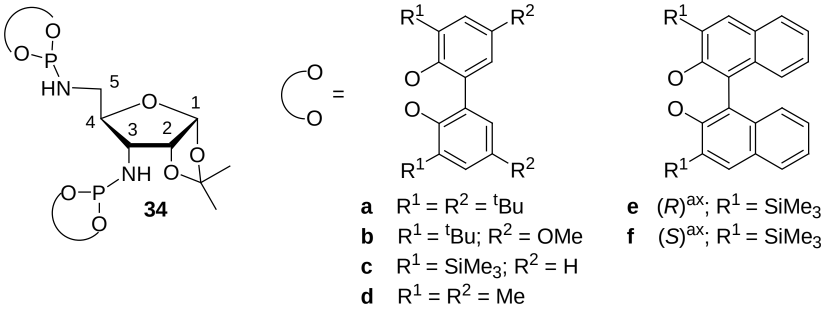
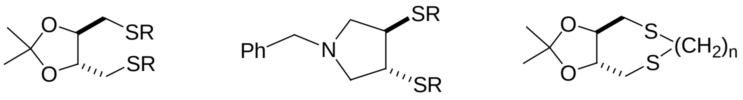


Figure 14. Diphosphophoroamidite ligands **34**.

1.2.2.2. S-donor ligands

Sulfur donor ligands have been used much less than phosphorus ligands in this process because a mixture of diastereomers can be obtained upon coordination of the thioether ligand to the metal, which can lead to a decrease in stereoselection if the relative rates of the intermediates are similar. Despite this, high enantiomeric excesses have been achieved.[16]

Among ligand backbones based on tartaric acid **35-37** (Figure 15), the five-membered ligand **36a** afforded the best enantioselectivity 81% (*S*) in the allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[25]



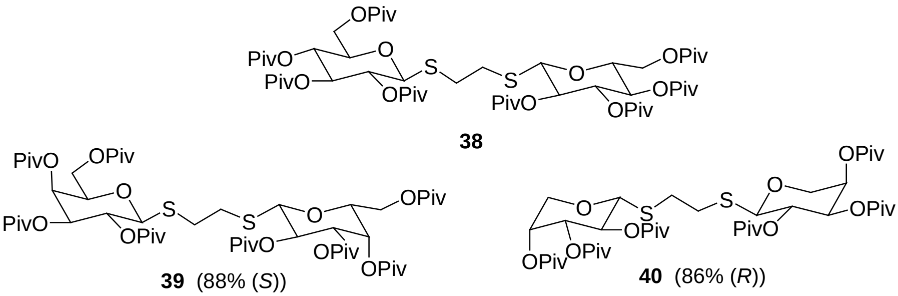
35 R = ^{i}Pr (27% (*S*))

36a R = Ph (81% (*S*))
36b R = ^{i}Pr (30% (*S*))

37a n = 2 (13% (*S*))
37b n = 3 (42% (*S*))

Figure 15. Dithioether ligands **35**-**37**.

Recently, Khiar and coworkers used a combinatorial approach to find the best dithioether ligand **38** (Figure 16) from a library of 64 potential ligands (four linkers x four sugar residues x four protective groups) for the Pd-catalyzed allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate (ee's up to 90%).[26a] In the search for both enantiomers of the alkylation product, the authors successfully prepared pseudo-enantiomers **39** and **40** derived from D-galactose and D-arabinose, respectively (Figure 16).[26b]



38

39 (88% (*S*))

40 (86% (*R*))

Figure 16. Dithioether ligands **38**-**40**.

1.2.2.3. Heterodonor Ligands

P-S ligands

Several combinations of P,S-donor ligands such as phosphine-thioether, phosphinite-thioether, phospholane-thioether, phosphine-oxathiane and phosphite-thioether have been studied. In particular, the phosphine-thioether, phosphinite-thioether and phosphine-oxathiane have proven to be effective in enantioselective Pd-catalyzed allylic substitutions.

The ferrocenylphosphine-thiosugar ligand **41** (Figure 17) with multiple stereogenic units afforded an ee of 88% in the palladium allylic substitution of diethyl malonate to 1,3-diphenylprop-2-enyl acetate.[27a] However, when the thiosugar moiety was the sole stereogenic unit on ligand **42** (Figure 17), enantioselectivities were only moderate (ee's up to 64%).[27b]

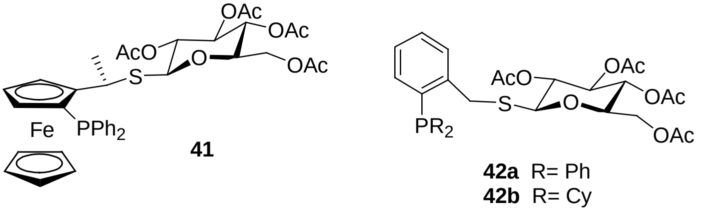
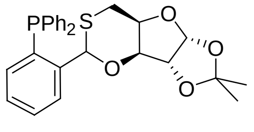


Figure 17. Thiother-phosphine ligands **41** and **42**.

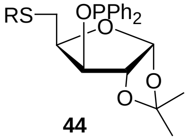
In 2003, a phosphine-oxathiane ligand **43**, derived from D-(+)-xylose, has been developed for the Pd-catalyzed allylic substitution reactions (Figure 18). Good enantioselectivities have been obtained in the addition of dimethyl malonate and benzylamine to 1,3-diphenylprop-2-enyl acetate (ee's up to 91% and 94%, respectively).[28]



43

Figure 18. Phosphine-oxathiane ligand **43**.

More recently, a series of phosphinite-thioether ligands with furanoside backbone **44a-g** (Figure 19) were applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates (ee’s up to 95%).[29] These ligands contained several thioether substituents with different electronic and steric properties. The authors found that this group had an important effect on catalytic performance. Thus, enantioselectivities were best when the bulkiest ligands **44c-d** were used.



44

a R = Ph; **b** R = Me; **c** R = ^{i}Pr; **d** R = ^{t}Bu;
e R = 4-Me-C_6H_4; **f** R = 4-CF_3-C_6H_4;
g R = 2,6-di-Me-C_6H_3

Figure 19. Phosphinite-thioether ligands **44**.

At the same time, simple phosphinite-thioether ligands **45** and **46** with pyranoside backbones (Figure 20) were successfully applied in Pd-catalyzed allylic substitution of 1,3-diphenyl-prop-2-enyl acetate (ee's up to 96%). Enantioselectivities were best when bulky *tert*-butyl substituents were present in the thioether moiety. Both enantiomers of the products were obtained by using pseudo-enantiomeric ligands **45a** and **46**.[30]

45 **46**

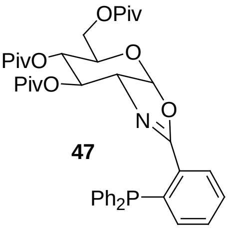
a R = ^{t}Bu; **b** R = 2-OMe-C_6H_4;
c R = 4-Me-C_6H_4

Figure 20. Phosphinite-thioether ligands **45-46**.

P-N ligands

Several types of P,N-donor carbohydrate ligands have been developed for use in Pd-asymmetric allylic substitutions.[31,32] In particular, many phosphorus-oxazoline ligands have produced excellent results.

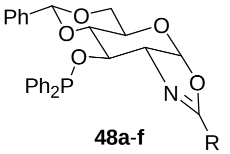
Kunz and coworkers developed a phosphine-oxazoline ligand **47** derived from D-glucosamine for the Pd-catalyzed allylic alkylation of dimethyl malonate to symmetrically and non-symmetrically substituted allyl acetates with high enantioselectivities (ee's up to 98%) (Figure 21).[32e] These results are in line with a nucleophilic attack *trans* to the phosphorus atom.



47

Figure 21. Phosphine-oxazoline ligand **47** developed by Kunz and coworkers.

Uemura and coworkers developed a series of phosphinite-oxazoline ligands **48** also derived from D-glucosamine for the Pd-catalyzed allylic substitution reactions (Figure 22).[32f,g] These ligands showed high enantioselectivity in the 1,3-diphenylprop-2-enyl acetate, but enantioselectivites were low-to-moderate for unhindered linear and cyclic substrates. The results of the allylic alkylation of diethyl malonate to 1,3-diphenylprop-2-enyl acetate indicated that the best enantioselectivity was obtained with the smallest substituent on oxazoline (R= Me, ligand **48a**). Their results also indicate that the nucleophilic attack took place *trans* to the phosphorus atom thought and *endo* π-allyl Pd-intermediate.

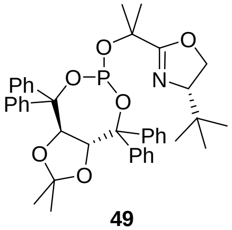


48a-f

	R	%ee
a	Me	96 (*S*)
b	^{i}Pr	90 (*S*)
c	^{i}Bu	95 (*S*)
d	^{t}Bu	83 (*S*)
e	Ph	94 (*S*)
f	Bn	78 (*S*)

Figure 22. Phosphinite-oxazoline ligands **48**. This figure shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

Pfaltz and coworkers used the phosphite-oxazoline ligand **49** (Figure 23) for the Pd-catalyzed allylic alkylation of several substrates.[31] This ligand showed good enantioselectivities in the reaction of 3-aryl-2-propenyl acetates (ee's up to 94%), whereas enantioselectivity was low in the reaction of 1,3-diphenylprop-2-enyl acetate (ee's up to 20%).



49

Figure 23. Phosphite-oxazoline ligand **49**.

In 2005 Framery and coworkers developed phosphine-amide ligands **50**-**52** (Figure 24) derived from D-glucosamine for the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The results clearly showed a cooperative effect between stereocenters that resulted in a matched combination for ligand **51** (ee's up to 86%).[33]

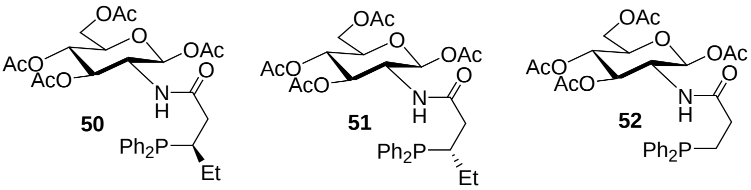


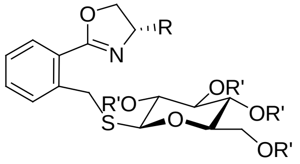
Figure 24. Phosphite-oxazoline ligand **50**-**52**.

P-P' ligands

The first successful family of P-P' carbohydrate ligands were the phosphite-phosphoroamidite ligands **5**, derived from D-xylose (Figure 3).[8b] They were successfully applied in the Pd-asymmetric allylic substitution (ee's up to 98%). Interestingly, this ligand family also provides high activity (because of the high π-acceptor capacity of the phosphoroamidite moiety) and enantioselectivities in different substrate types (mono- and disubstituted linear and cyclic substrates), which overcomes the most important limitations of the most successful catalytic systems for this process such as, low reaction rates and the high substrate specificity.

N-S ligands

Thioglucose-derived ligands **53a-d**, containing a chiral oxazoline moiety (Figure 25), used as ligands in the palladium-catalyzed allylic alkylation of diphenylprop-2-enyl acetate have provided some of the best results achieved in this reaction with mixed N,S-donor ligands.[34] The effects of the thiosugar substituents on enantioselectivity were mild. The success of this kind of system seems to lie in the combination of thiosugar function and the proximity of all stereogenic units to the palladium allylic fragment, because the Pd-N distance is shorter than the Pd-P distance in related phosphino-thiosugar palladium complexes.



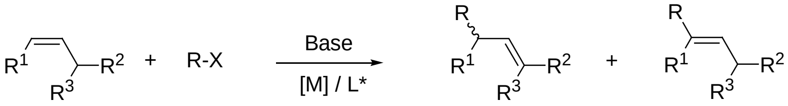
53a-d

	R	R'	% ee
a	^{i}Pr	C(O)Me	93 (*S*)
b	^{i}Pr	C(O)^{t}Bu	97 (*S*)
c	Ph	C(O)Me	90 (*S*)
d	Ph	C(O)^{t}Bu	96 (*S*)

Figure 25. Phosphinite-oxazoline ligands **53**. This figure also shows the enantioselectivities obtained in the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate to 1,3-diphenylprop-2-enyl acetate.

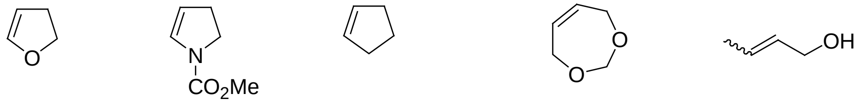
1.3. Asymmetric Heck reaction

The asymmetric Heck reaction generally referred to the palladium mediated coupling of aryl or vinyl halides or triflates with alkenes in the presence of base has become one of the most versatile methods for C-C bond formation (Scheme 2). This process has found extensive applications in asymmetric synthesis. Shibasaki and Overman have convincingly demonstrated the value of such transformation in the synthesis of complex natural molecules.[1c,35]



Scheme 2. Pd-catalyzed Heck reaction. X= Halide or triflate.

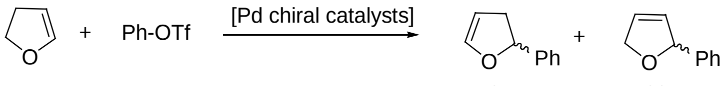
Heck reaction has been know to synthetic chemists since the late 1960's. However, reports of successful examples of the asymmetric Heck reaction were published at the end of the 1980's. The bulk of the reported examples involve intramolecular reactions, which have the advantage of allowing easy control of alkene regiochemistry and geometry in the product.[1c] In contrast, successful intermolecular reactions have until very recently been limited to quite reactive substrates, principally O-,N- heterocycles, which again simplifies the question of alkene regiochemistry.[1c,35] Nowadays several substrates have been applied in the intermolecular asymmetric Heck reactions. Most of them are cyclic substrates, such as, enol ethers, dihydropyrroles, dihydrodioxepins and alkenes (Figure 26). Traditionally, 2,3-dihydrofuran has been the substrate of choice for testing a new ligand. With regard to aryl or vinyl source, a variety of triflate compounds have been applied. However, the most widely used is phenyltriflate. The base is also an important parameter for high catalytic activity and enantioselectivity. A wide range of base have been employed in this process, being *N*,*N*-diisopropylamine and proton sponge the standard bases for testing new catalysts.[1c,35]



54 2,3-dihydrofuran **55** 2,3-dihydropirrol **56** cyclopentene **57** 4,7-dihydro-1,3-dioxepin **58** crotyl alcohol

Figure 26. The most common substrates for the intermolecular asymmetric Heck reaction.

It should be noted that in the asymmetric intermolecular Heck reaction it is not only the enantioselectivity of the process that needs to be controlled, the regioselectivity is also a problem, because a mixture of regioisomers can be obtained. So, for example, in the Heck reaction of 2,3-dihydrofuran **54** with phenyl triflate, a mixture of two products is obtained - product 2-phenyl-2,3-dihydrofuran (**59**) and the expected 2-phenyl-2,5-dihydrofuran (**60**; Scheme 3). The former is formed due to an isomerization process (see Section 1.2.1.).[1c,35]



54 **59** **60**

Scheme 3. Model Pd-catalyzed intermolecular Heck reaction.

1.3.1. Mechanism

Figure 27 illustrates a proposed catalytic cycle for the phenylation reaction of 2,3-dihydrofuran.[1c,35,36] The catalytic cycle starts with the oxidative addition of the organic triflate to a Pd(0)-complex **61** to produce compound **62**. Since the triflate ligand in **62** is a good leaving group, coordination of 2,3-dihydrofuran on **62** induces dissociation of the triflate ligand to give the cationic phenylpalladium olefin species **63**, which has a 16-electron square-planar structure convenient for the subsequent enantioselective insertion of olefin. The resulting alkyl palladium (II) complex **64** undergoes β-hydride elimination leading to a hydrido-palladium olefin complex **65**. Dissociation of this π-complex leads to the product **60** and a hydrido-palladium species **68**. Finally, the catalytic Pd(0) complex **61** is regenerated by reductive elimination of HOTf. Depending on the ligand, catalyst precursor and reaction parameters, the palladium complex **65** can also undergo re-insertion of the hydride, which leads to the alkyl palladium (II) complex **66**. β-hydride elimination of **66** followed by dissociation of the resulting π-complex **67** lead to isomer **59** and hydride **68**. Reductive elimination of HOTf in **68** regenerates active species **61**.

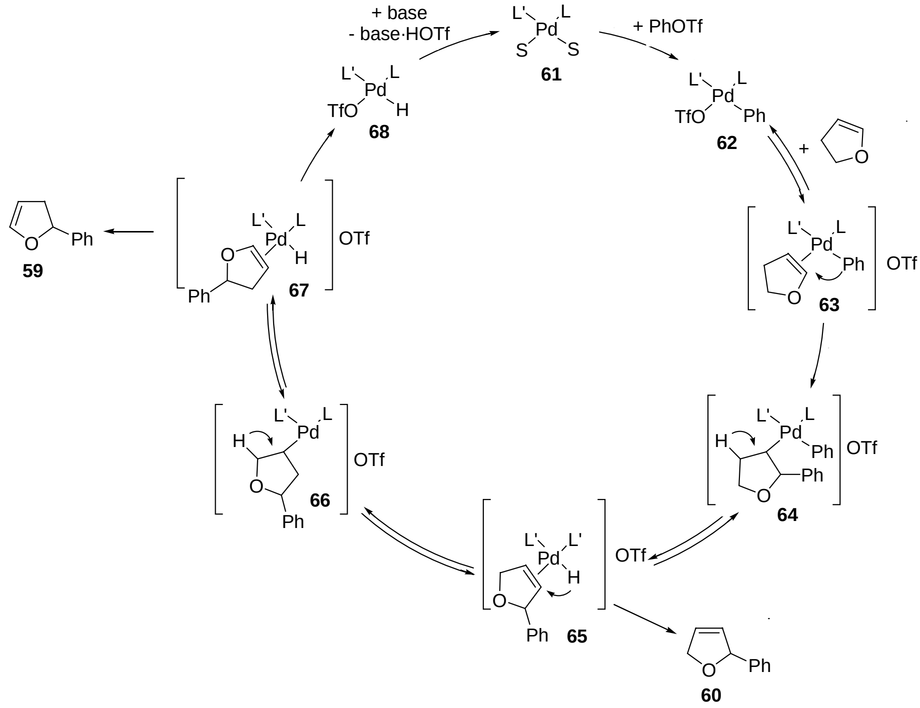
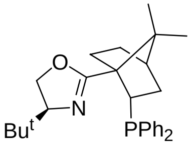


Figure 27. Proposed mechanism for the catalytic Pd-catalyzed arylation of 2,3-dihydrofuran with phenyl triflate.

1.3.2. Ligands

In 1991, Ozawa and Hayashi reported the first example of the intermolecular version of the Heck reaction using 2,3-dihydrofuran and phenyl triflate (Scheme 3).[37] Since then, this chemistry has been extensively studied using various chiral bidentate ligands. Diphosphines, which have played a key role in the success of the intramolecular version, were early applied. Among these, the Pd-BINAP were the first catalytic system that offered good regio- (in favour to product **59**) and enantiocontrol.[1c,35] In the last few years, a class of heterodonor ligands - the phosphine-oxazoline - have emerged as suitable ligands for the intermolecular Heck reaction of several substrate types and triflates sources.[38] Two of the most representative examples of this type of ligands are the PHOX ligands developed by

Pfaltz[38a,b] and coworkers (Figure 9) and the phosphine-oxazoline based on ketopinic acid developed by Gilberston and coworkers[38e] (Figure 28). In contrast to Pd-BINAP systems, they offer preferentially isomer **60** in high enantioselectivities.



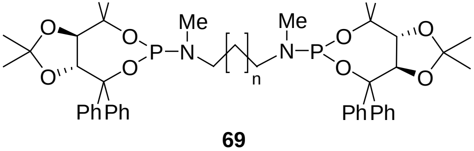
Gilbertson's Ligand

Figure 28. Phosphine-oxazoline ligand for asymmetric Pd-catalyzed Heck reactions.

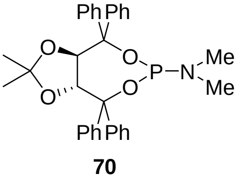
Although carbohydrate-based ligands have been successfully used in other enantioselective reactions,[2] there are only two reports on the highly enantioselective palladium-catalysed asymmetric Heck reaction using this type of ligand.[39]

The first succesfull application of carbohydrate-ligands in this process used the previously reported pyranoside phosphinite-oxazoline ligands **48** (Figure 22) in the Pd-catalyzed enantioselective arylation of 2,3-dihydrofuran (ee's up to 96%). This set of ligands were also applied in the phenylation of *trans* and *cis*-crotyl alcohols with low enantioselectivity (ee's up to 17%).[39a]

Phosphoroamidite ligands **69** and **70** (Figure 29) were applied in the Pd-catalyzed intramolecular Heck reaction of cyclohexadienone monoacetals with high enantioselectivities (ee`s up to 96%). Results indicate that the extra flexibility and rotational freedom obtained by using monodentate ligand **70** instead of bidentate ligand **69** has a beneficial effect on enantioselectivity.[39b]



69

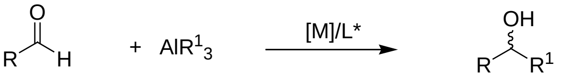


70

Figure 29. Ligands **69** and **70** derived from TADDOL.

1.4. Asymmetric 1,2-addition of organometallic reagents

Nucleophilic 1,2-addition of organometallic reagents to carbonyl compounds constitutes one of the most fundamental operations in organic synthesis for the formation of secondary alcohols, which are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products. In this context, the catalytic addition of dialkylzincs to aldehydes as a route to chiral alcohols has attracted much attention.[40] For alkylation reagents, trialkylaluminium compounds are more interesting than other organometallic reagents because they are economically obtained in industrial scale from aluminium hydride and olefins.[41] Despite this advantage their use is rare.[23f,42] In this respect, the few successful catalysts developed for the enantioselective addition of trialkylaluminium to aldehydes can be grouped in two types (Scheme 4). The first group are the titanium complexes that usually afford high enantioselectivities, but the high catalyst loadings (10-20 mol %) and the slow turnover rate hamper their potential utility.[42] The second ones are the recently studied nickel complexes that provide enantioselectivities similar to those using titanium complexes but with low catalyst loadings (1 mol %).[23f,43]



Scheme 4. Metal-catalyzed 1,2-addition of trialkylaluminium to aldehydes

Several aldehydes, such as aryl-, alkyl- and vinylaldehydes, have been tested as substrates. However, benzaldehyde has been the substrate of choice for testing a new ligand. The aluminium source is also an important parameter for high catalytic activity and enantioselectivity. Traditionally, commercially available trialkylaluminium reagents have been widely used. However, these reagents are often contamined with oxo-containing by-products formed through accidental exposure to traces of air and moisture, such impurities modify the reactivity of the reagent.[44] Recently, the group of Woodward reported the preparation of DABAL-Me_3 (Figure 30) as a new air-stable solid $AlMe_3$ adduct that is easily form from the exposure of neat $AlMe_3$ to DABCO (1,4-diazobicyclo[2,2,2]octane).[23f]

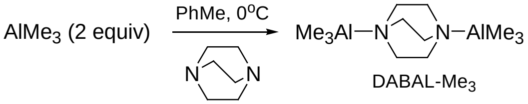


Figure 30. Formation of DABAL-Me_3.

1.4.1. Mechanism

Figure 31 shows the tentative mechanism proposed for the Ni-catalyzed 1,2-addition of trimethylaluminium reagents to aryl aldehydes.[43] The reductive generation of the active Ni(0)-catalyst **71** is followed by the formation of a π-aldehyde complex **72**, as showed possible by the seminal work of Walther who crystallized $Ni(\eta^2\text{-}O{=}CHAr)(PCy_3)_2$ (Ar= Ph, $2,4\text{-}(MeO)_2C_6H_3$).[45] Aluminium lewis acid promoted oxidative addition of the ketone complex **72** and produces Ni(II)-complex **73**. By reductive elimination, they generated product **74** and regenerate the catalytically active species **71**.

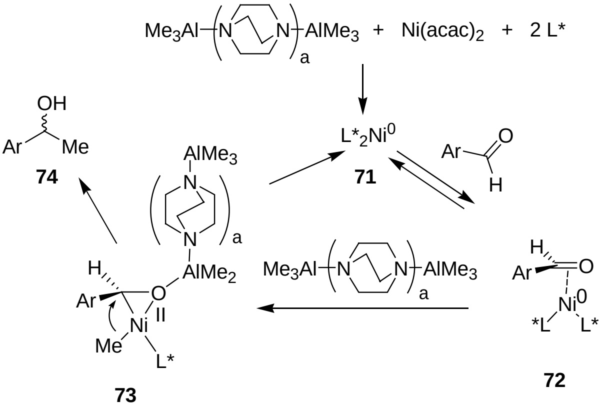
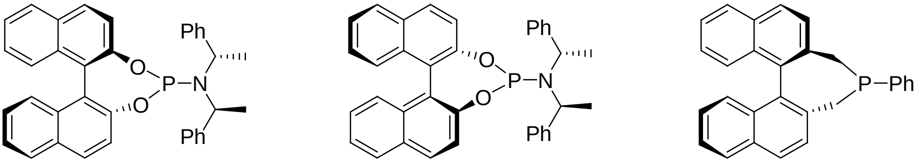


Figure 31. Proposed catalytic cycle for the 1,2-addition of DABAL-Me_3 (a = 1) or $AlMe_3$ (a = 0) to aromatic aldehydes.

1.4.2. Ligands

For the Ni-catalyzed 1,2-addition of trialkylaluminium reagents to aldehydes, only the group of Woodward have recently reported the successful use of phosphoroamidite and monophosphine ligands as chiral auxiliares (Figure 32).[23f,43] High enantioselectivities (up to 95%) were obtained using monophosphoramidite ligands **75** and **76**.

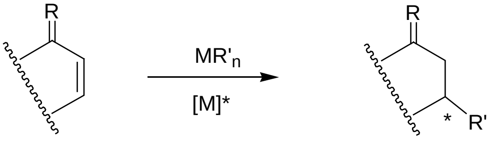


75 **76** **77**

Figure 32. Monophosphoroamidite and monophosphine ligands **75-77**.

1.5. Asymmetric 1,4-addition of organometallic reagents

The enantioselective conjugate addition (also called enantioselective Michael addition) of organometallic reagents to α,β-unsaturated compounds catalyzed by chiral transition metal complexes is a useful synthetic process for asymmetric carbon-carbon bond formation (Scheme 5).[1c,46] This process is important in the synthesis of many biologically active compounds such as steroids and terpens.

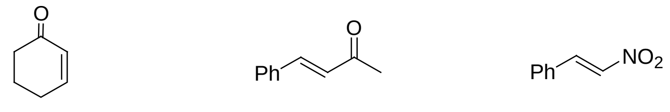


Scheme 5. Metal-catalyzed asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated compounds (R= O and NO_2).

Michael additions of organolithium, Grignard, diorganozinc and triorganoaluminium reagents to α,β-unsaturated compounds can be catalyzed by nickel, cobalt and copper-complexes.[46] The best results have been achieved with Cu(I)-catalysts, especially those in which copper is bound to a *soft* center (sulphur or phosphorus).[46] Initially, Grignard reagents were the first species to be applied in this process. However, in 1993 Alexakis and coworkers introduced the use of dialkylzinc reagents for this enantioselective reaction and found them to be more appropriate than the classical use of Grignard reagents. Trialkylaluminum reagents have been tested in only a few cases but these represented an interesting alternative since they can be easily attained by technically simple hydro- and carboalumination and because they allow to undergo Cu-catalyzed 1,4-addition of more challenging substrates (i.e. β-trisubstituted enones).[46,47] Nowadays, the copper-catalyzed asymmetric 1,4-addition of organozinc reagents has been adopted as standard procedure for testing new ligands.[46]

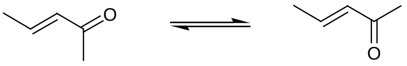
In the copper-catalyzed asymmetric 1,4-addition, the copper salt is also important for high catalytic activity and enantioselectivity. Copper (I) and copper (II) salts have been used. The true catalytic species is Cu(I), so the reduction of Cu(II) is the first step in the process. The copper (II) triflate is usually the salt of choice, though many other copper salts have demonstrated their power in this reaction.[46]

Cyclic and acyclic enones have been used as substrates in enantioselective copper-catalyzed conjugate addition (Figure 33). Traditionally, 2-cyclohexenone has been the substrate of choice for testing a new ligand. This cyclic enone avoids the *s-cis*/*s-trans* interconversion of acyclic substrates (Scheme 6).[46] For acyclic enones, the most widely studied substrate is benzylideneacetone (Figure 33). To achieve a high catalytic performance with this acyclic substrate, the class of ligands usually has to be different from those with cyclic substrates. Nitro-olefins are another class of excellent Michael acceptors for this reaction.[46] Again, the efficient ligands are different from the previous ones (Figure 33).



2-cyclohexenone benzylideneacetone nitrostyrene

Figure 33. The most common substrates in the copper-catalyzed asymmetric 1,4-addition.



s-trans *s*-cis

Scheme 6. *S-cis* and *S-trans* conformational interconversion.

1.5.1. Mechanism.

The tentative catalytic cycle proposed for the Cu-catalyzed asymmetric 1,4-addition of diorganozinc to 2-cyclohexenone is illustrated in Figure 34.[23a,46] Starting from a Cu(I), or preferably a Cu(II) species, an alkyl fragment is transferred from ZnR_2 to the copper center. Complexation of the alkylzinc fragment to the enone carbonyl and formation of the π-complex of the copper alkyl species with the enone results in complex **78**. Subsequent alkyl transfer generates zinc enolate **79**, which upon protonation may afford the β-substituted cycloalkanone **80** (E= H) or be trapped by an electrophile reagent (E).

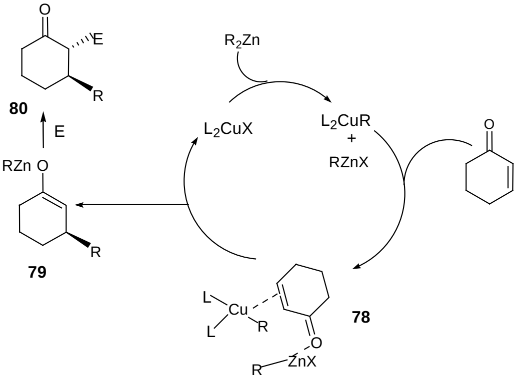
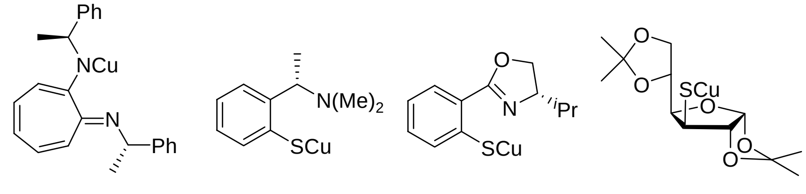


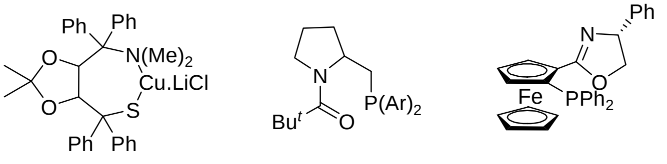
Figure 34. Proposed catalytic cycle for the Cu-catalyzed asymmetric 1,4-addition.

1.5.2. Ligands

The first enantioselective copper catalysts were reported by Lippard and coworkers in 1988.[48] The reaction of 2-cyclohexenone with Grignard reagents in the presence of the chiral aminotroponeimine copper complex as catalyst (Figure 35) gave the 1,4-adducts with low enantioselectivity (up to 14%).[48] Selectivity increased to 74% ee with the addition of hexamethylphophoric triamide (HMPA) and silyl halides.[49] Later, various copper thiolates gave moderate-to-good results on cyclic and acyclic enones (Figure 35).[50] However, the best results were obtained with external ligands developed by Tomioka and Sammakia (Figure 35).[50e,f]



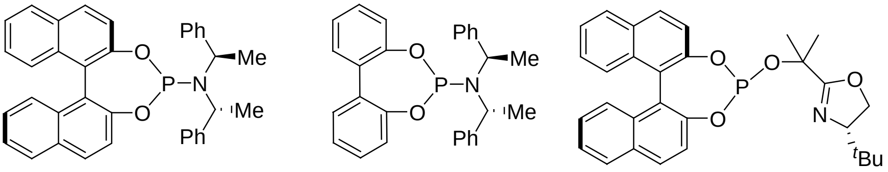
Lippard, 74 % ee van Koten, 76 % ee Pfaltz, 72 % ee Spescha, 60 % ee



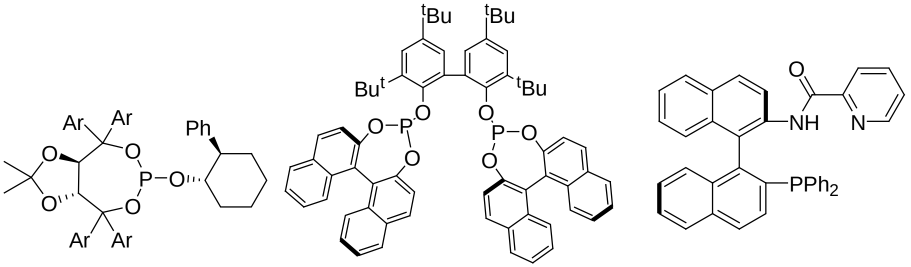
Seebach, 84 % ee Tomioka, 90 % ee Sammakia, 98 % ee

Figure 35. Heterocuprate-based ligand and chiral ligands using Grignard reagents.

Since the late 1990s all authors have focused on the dialkylzinc procedure. The selection of chiral ligands for the highly enantioselective conjugate addition of organozinc reagents to α,β-unsaturated compounds has mainly focused on P-donor and mixed P,N-donor ligands (Figure 36).[46,51] Most phosphorus ligands are of the phosphite (mainly monophosphite) and phosphoramidite type. Non-phosphorus ligands have scarcely been used with dialkylzinc reagents.[46] Some of the most representative phosphorus ligands are shown in Figure 36.



Feringa, 98 % ee   Alexakis, 98 % ee   Pfaltz, 95 % ee



Alexakis, 98 % ee   Chan, 99 % ee   Zhang, 98 % ee

Figure 36. Representative phosphorus chiral ligands for 1,4-addition of organozinc reagents to α,β-unsaturated compounds.

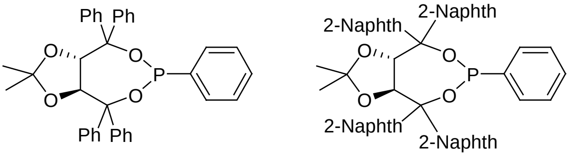
Although carbohydrate ligands have been successfully used in other enantioselective reactions,[2] there have been few reports on the highly enantioselective 1,4-addition using these systems. Notable examples, however, include monophosphonite,[52] monophosphite,[51,53] and mixed amino-thiolate.[50d,54] ligands derived from TADDOL, and furanoside diphosphite ligands.[55] Other carbohydrate ligands, such as phosphoroamidite[51d,52,53,56] and mixed S-O,[57] N-P,[58] S-P[59] and P-P'[59] heterodonor ligands, have also been tested with low-to-moderate enantioselectivities.

Here we present the most relevant catalytic data on the copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds with carbohydrate ligands.

1.5.2.1. P-ligands

Phosphonite ligands

Alexakis used phosphonite ligands **81** and **82** (Figure 37), derived from (+)-TADDOL, in the asymmetric conjugate addition of diethylzinc to nitro-olefins[52] and alkylidene malonates[60] with good-to-moderate enantioselectivities. Ligand **81** appears to be the optimal choice for the diethylzinc addition to aryl nitro-olefins (ee's up to 86%).



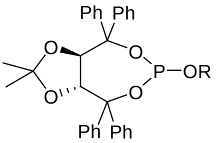
81 **82**

Figure 37. Phosphonite ligands **81** and **82** derived from (+)-TADDOL.

Phosphite ligands

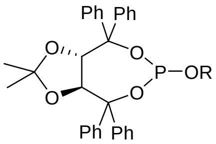
Phosphite furanoside ligands **27-33** (Figure 12) were also applied in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone.[55] Results show that enantioselectivity depends strongly on the absolute configuration of the C-3 stereogenic center and on the biaryl substituents, while the sense of enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. The best enantioselectivites were obtained with ligands **27h** and **29g** with ee's of 81% (*R*) and 84% (*S*), respectively. Interestingly, both enantiomers of the product can be obtained. Introducing a stereogenic center in C-5 had a positive effect on activity but did not affect enantioselectivity.

Alexakis and coworkers have developed a series of phosphite ligands **83** and **84**, derived from (-)-TADDOL and (+)-TADDOL (Figure 38). These ligands were applied in the Cu-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone (ee's up to 96%),[53] benzalacetone (ee's up to 35%),[51d,53] chalcone (ee's up to 50%),[51d,53] nitro-olefins (ee's up to 96%)[52] and alkylidene malonates (ee's up to 73%)[60] (Figure 38).



83

R = alkyl, cyclohexanyl,
substituted cyclohexanyl, aryl

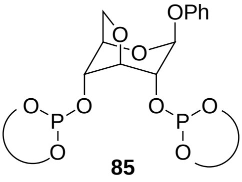


84

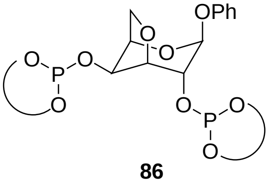
R= substituted cyclohexanyl

Figure 38. Basic structure of phosphite ligands **83** and **84**.

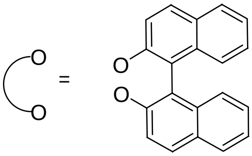
Recently, Chan and coworkers reported the synthesis of chiral pyranoside diphosphites **85** and **86**, derived from D-glucose and D-galactose, for application in the Cu-catalysed 1,4-addition of cyclic enones (Figure 39).[61] The enantioselectivity depends on the absolute configuration of the C-4 stereogenic center of the ligand backbone, while the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl moieties. Therefore, the results were best with ligand **85b** (ee's up to 88%).



85



86

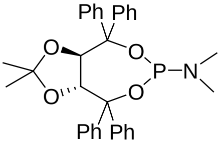


a (*S*)^{ax}
b (*R*)^{ax}

Figure 39. Pyranoside diphosphite ligands **85** and **86**.

Phosphoroamidite ligands

In the last few years several mono- and diphosphoroamidite ligands, derived from TADDOL, have been developed for the Cu-catalyzed 1,4-addition of diethylzinc to several substrates with poor-to-moderate enantioselectivity.[51d,52,53] However, Feringa and coworkers observed an unexpected improvement in enantioselectivity in the Cu-**87** (Figure 40) catalyzed addition of diethylzinc to cyclohexenone when they used powdered molecular sieves (ee's up to 71%).[56b]



87

Figure 40. Phosphoroamidite ligand **87** derived from TADDOL.

1.5.2.2. Heterodonor ligands

The groups of Seebach and Alexakis have developed a series of heterodonor O-S, N-S and N-P ligands derived from TADDOL for the Cu-catalyzed 1,4-addition of organometallic reagents to cyclic and lineal enones.[50d,51d,53,54] The best enantioselectivities were obtained with the previously mentioned N-S ligand (Figure 35) developed by Seebach and coworkers in the Cu-catalyzed addition of butylmagnesium cloride to cycloheptanone (ee's up to 84%).[50d,54]

1.6. References

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Chapter 2

Objectives

2. Objectives

The objective of this thesis is to develop new chiral ligands derived from carbohydrates for application as chiral auxiliaries in several important asymmetric catalytic reactions.

The more specific aims are:

1. To design and synthesize new highly modular phosphite-oxazoline (**L1-L5**), phosphite-phosphoroamidite (**L6**) and monophosphite (**L7-L11**) ligand libraries (Figure 1).

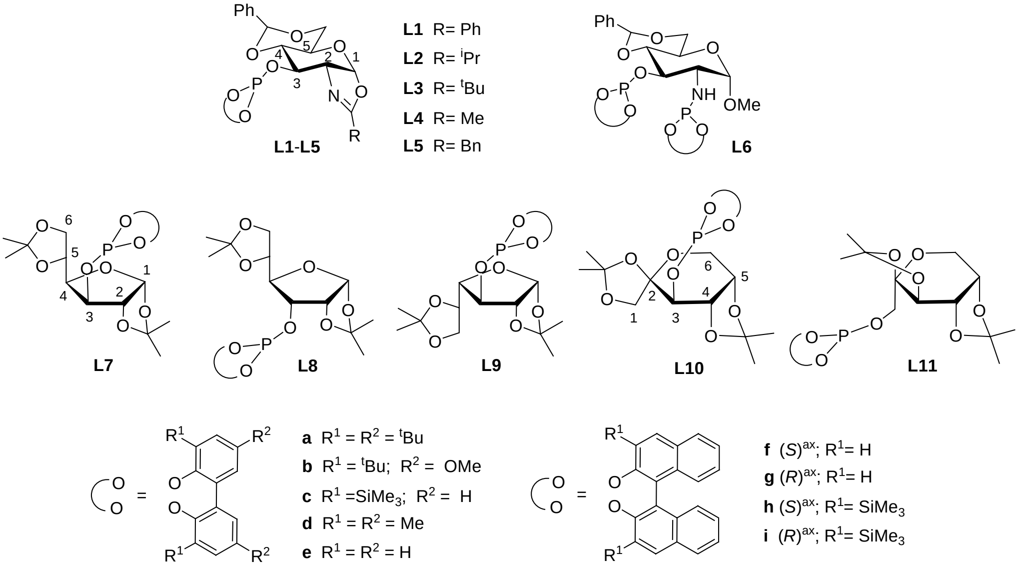

Figure 1. Phosphite-oxazoline (**L1-L5**), phosphite-phosphoroamidite (**L6**) and monophosphite (**L7-L11**) ligand libraries synthesized in this thesis.

These libraries are systematically designed to ensure a maximum diversity regarding electronic and steric properties of the ligand parameters that will ensure a wide scope in the asymmetric processes studied in this thesis. Therefore, the phosphite-oxazoline ligand library is derived from inexpensive D-glucosamine and contains substituents with different electronic and steric proprieties in the ozaxoline moiety (**L1-L5**) and several substituents/configurations in the birayl phosphite moieties (**a-i**), whose effect on the catalytic performance will be studied. The second library (**L6**) is related to the first one but has a phosphoroamidite group instead of a oxazoline moiety. This apparently simple modification produces important changes in the structural and electronic properties of the ligands, which are know to play a crucial role on the catalytic performance. Finally, the monophosphite ligand library is derived from D-glucose, D-galactose and D-fructose, which lead to a wide range of sugar backbones (**L7-L11**), and contain several substituents/configurations in the biaryl moiety (**a-i**).

2. To apply these ligand libraries in the Pd-catalyzed asymmetric allylic substitution, Pd-catalyzed asymmetric Heck reactions, Ni-catalyzed asymmetric addition of trialkylaluminium to aldehydes and Cu-catalyzed 1,4-conjugate addition of trialkylaluminium reagents to enones.

Chapter 3

Pd-catalyzed asymmetric allylic substitution