DOI: 10.1002/adsc.200900619

Pyranoside Phosphite-Oxazoline Ligand Library: Highly Efficient Modular P,N Ligands for Palladium-Catalyzed Allylic Substitution Reactions. A Study of the Key Palladium Allyl Intermediates

Yvette Mata,[a] Oscar Pàmies,[a,*] and Montserrat Diéguez[a,*]

[a] Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n, 43007 Tarragona, Spain
Fax: (+34)-97-755-9563; e-mail: montserrat.dieguez@urv.catoscar.pamies@urv.cat

Received: September 6, 2009; Revised: October 14, 2009; Published online: December 10, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900619.

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

Keywords: allylic substitution; asymmetric catalysis; carbohydrate ligands; P,N ligands; palladium

Introduction

Palladium-catalyzed asymmetric allylic substitution is a versatile process that is widely used in organic synthesis for the enantioselective formation of carbon-carbon and carbon-heteroatom bonds.[1] Many chiral ligands, bidentate nitrogen and phosphorus donors (both homo- and heterodonors) have been successfully applied. Most of the chiral ligands developed are mixed bidentate donor ligands (such as P-N, P-S, S-N and P-P′).[1,2,3] The efficiency of this type of hard-soft heterodonor ligand has been mainly attributed to the electronic effects of the donor atoms.[1] Mixed phosphorus-nitrogen ligands have played a dominant role among heterodonor ligands. Nowadays several P,N ligands have provided high enantiomeric excesses for several types of disubstituted substrates. Nevertheless, in general, there is still a problem of substrate specificity (for example, *ee*s are high in disubstituted linear hindered substrates and low in unhindered substrates, and *vice versa*) and reaction rates. On the other hand, monosubstituted substrates still require more active and more regio- and enantioselective Pd catalysts.[1] Another challenging class of substrates is that of the trisubstituted substrates. Although a few good enantioselective Pd catalytic systems have been reported, their activities are still very low.[1]

It is therefore of great importance nowadays to conduct research into more versatile and faster mixed P-N ligand systems that can be easily synthesized from simple starting materials. For this purpose, carbohydrates are particularly advantageous because of their low price and easy modular constructions.[4] Although they have been successfully used in other enantioselective reactions, they have only recently shown their huge potential as a source of highly effective chiral ligands in this process.[4,5] Notable examples include two types of phosphorous-oxazoline ligands.[5e,6] In this context, Uemura and co-workers synthesized the phosphinite-oxazoline ligands **1** (Figure 1)[5e,6b] which proved to be effective in the allylic substitution of the hindered substrate 1,3-diphenyl-3-acetoxyprop-1-ene but which had low enantioselectivity for unhindered cyclic and linear substrates.[5e] 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

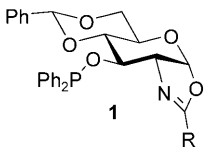


Figure 1. Phosphinite-oxazoline ligands developed by Uemura and co-workers.

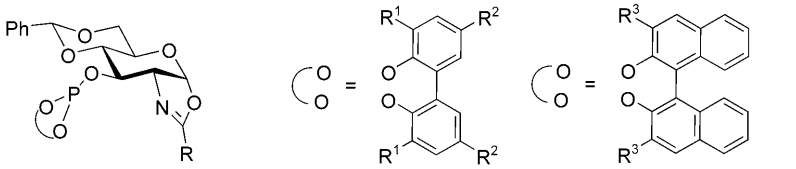
cavity where the allyl is embedded) is flexible enough to allow the perfect coordination of hindered and unhindered substrates;[7,8] (ii) reaction rates increase because of the high π-acceptor capacity of the phosphite moiety;[7] and (iii) the regioselectivity towards the desired branched isomer in monosubstituted linear substrates increase because the π-acceptor capacity of the phosphite moiety enhances the S_N1 character of the nucleophilic attack.[9] Despite these advantages, only one series of amino alcohol-based phosphite-oxazoline ligands has been extensively studied.[7b,9,10] Therefore, new series of phosphite-oxazoline ligands need to be developed and their potential studied. More research needs to be done to understand the mechanistic aspects with these ligands for an *a priori* prediction of the type of ligand needed for high selectivity.

Therefore we 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.[11] 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. As well as containing a biaryl phosphite moiety these new phosphite-oxazoline ligands **L1**–**L5a**–**i** also have the advantage of a more flexible ligand scaffold than ligands **1**. 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 several electronic and steric properties of the oxazoline moiety (**L1**–**L5**) and several 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.

Results and Discussion

Ligand Synthesis

The synthesis of the phosphite-oxazoline ligands **L1**–**L5a**–**i** is straightforward (Scheme 1). They were efficiently synthesized in one step by reacting the corresponding sugar oxazoline-alcohols (**3**–**7**) with 1 equivalent of the corresponding biaryl phosphorochloridite [$ClP(OR)_2$; $(OR)_2$ = **a**–**i**] in the presence of pyridine, in a parallel way (see Experimental Section for details). Oxazoline-alcohols **3**–**7** are easily prepared from inexpensive D-glucosamine **2** on a large scale.[5e] All the ligands were stable during purification on neutral alumina under an atmosphere of argon and were isolated in moderate-to-good yields as white solids. They were stable at room temperature and very stable to hydrolysis. The elemental analyses were in agreement with the assigned structure. The ^1H, ^{13}C and ^{31}P NMR spectra were as expected for these C_1 ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (atropoisomerization) in the biphenyl-phosphorus moieties (**a**–**e**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[12]

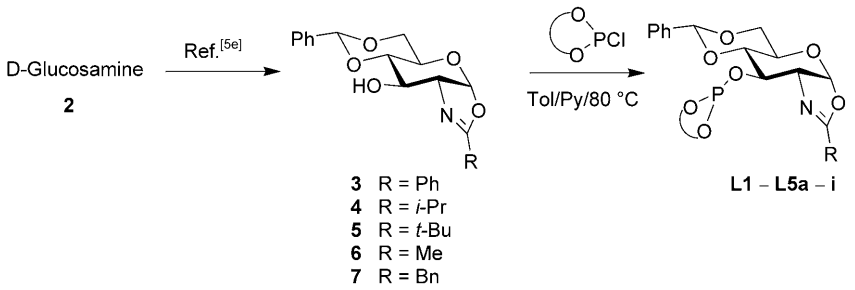


L1 R = Ph
L2 R = *i*-Pr
L3 R = *t*-Bu
L4 R = Me
L5 R = Bn

a $R^1 = R^2 = t$-Bu
b $R^1 = t$-Bu; R^2 = OMe
c $R^1 = SiMe_3$; R^2 = H
d $R^1 = R^2$ = Me
e $R^1 = R^2$ = H

f $(S)^{ax}$; R^3 = H
g $(R)^{ax}$; R^3 = H
h $(S)^{ax}$; $R^3 = SiMe_3$
i $(R)^{ax}$; $R^3 = SiMe_3$

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



Scheme 1. Synthesis of phosphite-oxazoline ligand library **L1–L5a–i**.

Allylic Substitution of Symmetrical 1,3-Disubstituted Allylic Substrates

In this section, we report the use of the chiral phosphite-oxazoline ligand library (**L1–L5a–i**) in the Pd-catalyzed allylic substitution of linear disubstituted substrates with different steric properties [Eq. (1a)]: *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**); and cyclic substrates [Eq. (1b)]: *rac*-3-acetoxycyclohexene (**S3**) (widely used as a model substrate) and *rac*-3-acetoxycycloheptene (**S4**). Two nucleophiles were used.

Allylic Substitution of *rac*-1,3-Diphenyl-3-acetoxyprop-1-ene S1 using Dimethyl Malonate and Benzylamine as Nucleophiles [Eq. (1a)]

For an initial evaluation of the phosphite-oxazoline ligand library (**L1–L5a–i**), we chose the Pd-catalyzed allylic substitution of **S1** [Eq. (1a), R = Ph], which is widely used as a model substrate. We used dimethyl malonate and benzylamine as nucleophiles.

We first determined the optimal reaction conditions (solvent, bases and ligand-to-palladium ratio). Although toluene provided slightly higher enantioselectivity than dichloromethane, its activity was lower. We found that the best combination of activities and enantioselectivities was obtained by using dichloromethane as the solvent and KOAc as base (see Supporting Information). Interestingly, enantioselectivities were best with a ligand-to-palladium of 0.9. This is due to the fact that the phosphite-oxazoline ligand acts as a monodentate ligand when excess of ligand is present (see below, Section on Origin of Enantioselectivity. Study of the Pd-π-allyl Intermediates).

Under the optimized conditions we tested the remaining ligands. Table 1 shows the results when dimethyl malonate and benzylamine were used as nucleophiles. 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. High activities [TOFs up to 600 mol **S1** × (mol Pd × h)$^{-1}$] and enantioselectivities (*ee*s up to 99%) were obtained with ligand **L1a**. Catalytic performance in the Pd-catalyzed allylic amination of **S1** followed the same trend as for the allylic alkylation of **S1** (Table 1). 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, although the CIP descriptor was inverted because the priority of the groups had changed.

The effect of the oxazoline substituent was studied with ligands **L1a–L5a** (Table 1, entries 1, 10–12 and 14). We found that these substituents affected both activities and enantioselectivities. The results showed

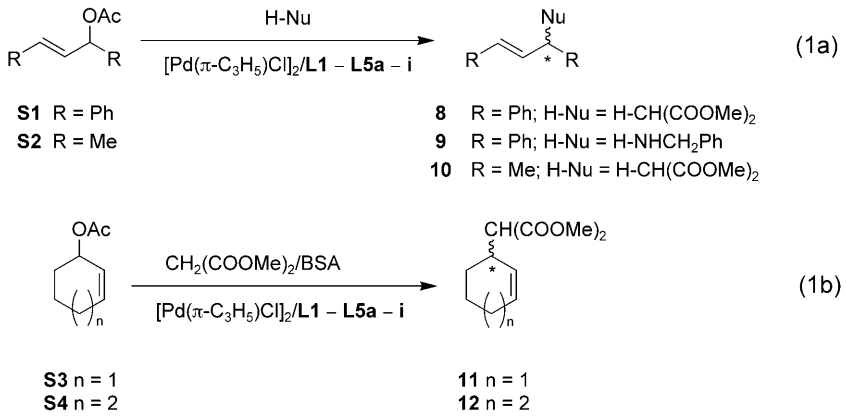


Table 1. Selected results for the Pd-catalyzed allylic substitution of **S1** using phosphite-oxazoline ligand library **L1–L5a–i**.

		H-Nu = H-CH(COOMe)$_2$[a]		H-Nu = H-NHCH$_2$Ph[b]	
Entry	Ligand	% Conv. (t [min])[c]	% ee[d]	% Conv. (t [h])[c]	% ee[d]
1[e]	**L1a**	100 (30)	92 (*S*)	60 (24)	94 (*R*)
2	**L1b**	89 (30)	84 (*S*)	53 (24)	87 (*R*)
3	**L1c**	95 (30)	86 (*S*)	58 (24)	90 (*R*)
4	**L1d**	85 (30)	89 (*S*)	54 (24)	92 (*R*)
5	**L1e**	57 (30)	86 (*S*)	34 (24)	87 (*R*)
6	**L1f**	82 (30)	81 (*S*)	49 (24)	79 (*R*)
7	**L1g**	80 (30)	9 (*S*)	53 (24)	3 (*R*)
8[e]	**L1h**	100 (30)	84 (*S*)	65 (25)	82 (*R*)
9[e]	**L1i**	99 (30)	62 (*S*)	66 (24)	65 (*R*)
10	**L2a**	92 (30)	86 (*S*)	59 (24)	89 (*R*)
11	**L2b**	67 (30)	45 (*S*)	35 (24)	34 (*R*)
12[e]	**L4a**	100 (15)	85 (*S*)	79 (24)	89 (*R*)
13	**L4c**	88 (15)	83 (*S*)	61 (24)	85 (*R*)
14	**L5a**	99 (30)	80 (*S*)	61 (24)	85 (*R*)
15[f]	**L1a**	54 (300)	95 (*S*)	–	–
16[f,g]	**L1a**	100 (360)	99 (*S*)	–	–

[a] All reactions were run at 23 °C, with 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, dichloromethane as solvent, 0.9 mol% ligand, 0.5 mmol **S1**, 1.5 mmol BSA, 1.5 mmol dimethyl malonate, and KOAc as base.
[b] All reactions were run at 23 °C with 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, dichloromethane as solvent, 1.8 mol% ligand, 0.5 mmol **S1**, and 1.5 mmol of benzylamine.
[c] Reaction time shown in parentheses.
[d] Enantiomeric excesses. The absolute configuration appears in parentheses.
[e] Isolated yields of **8** and **9** were >90% based on recovered starting material.
[f] $T = 0$ °C.
[g] 2 mol% Pd, toluene as solvent.

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 1, entry 1).[13] 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 1, entries 1–9). 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 1, entry 1). With ligands **L1f–L1i**, which contained different enantiomerically pure binapthyl moieties, we investigated how enantioselectivity was influenced by the axial chirality of the biaryl moiety (Table 1, 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 1, entries 6 and 8 *vs.* 7 and 9). Also, by comparing the results obtained using ligands **L1c** with the related binaphthyl ligands **L1h** and **L1i** (Table 1, entry 3 *vs.* 8 and 9), we can 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 ligand parameters. These results clearly show the efficiency of highly modular scaffolds in ligand design. Enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. In this case, enantioselectivity was further improved (*ee*s up to 95%) with ligand **L1a** by lowering the reaction temperature to 0 °C (Table 1, entry 15). As expected, changing the solvent from dichloromethane to toluene increased enantioselectivity even further (*ee*s up to 99%, Table 1, entry 16).[14] Interestingly, when this latter 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 conclude that introducing a phosphite moiety into ligands **L1–L5a–i** is advantageous. These results are among the best that have been reported.[1]

Allylic Alkylation of *rac*-1,3-Dimethyl-3-acetoxy-prop-1-ene S2 using Dimethyl Malonate as the Nucleophile [Eq. (1a)]

We also screened the phosphite-oxazoline ligand library **L1–L5a–i** in the allylic alkylation of the linear substrate **S2** [Eq. (1a), R = Me]. This substrate is less sterically demanding than substrate **S1**. The enantioselectivity for **S2** is therefore more difficult to control than with hindered substrates such as **S1**. If *ee* values are to be high, the ligand must create a small chiral pocket around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.[1] There are therefore fewer successful catalytic systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of hindered substrate **S1**.[7b,15] Due to the presence of a bulky biaryl phosphite moiety in ligands **L1–L5a–i**, which are known to be flexible and to provide large bite angles, we expected to be able to tune the size of the chiral pocket appropriately and therefore to obtain high enantioselectivity for this substrate, too.

Table 2 summarizes the results of using the phosphite-oxazoline ligand library **L1–L5a–i** under the optimized conditions. Again, activities and enantioselectivities were affected by the substituents in both the oxazoline and phosphite moiety and by 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%). This result, which again clearly shows the efficiency of using modular scaffolds in ligand design, is among the best that have been reported for this type of unhindered linear substrates.[7b,15]

Regarding the effect of the oxazoline substituents, the presence of bulky substituents in this position considerably decreased activities and enantioselectivities (Table 2, 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 they were higher when a methyl substituent was present (ligand **L4a**, Table 2, entry 12).

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 2, entries 1 and 2 *vs.* 3–5). Therefore, ligands **L1a** and **L1b** with 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**, **L1d** and **L1e**. The effect of the configuration of the binaphthyl moiety (ligands **L1f–i**) is similar to the effect in the previous alkylation of **S1** (Table 2, 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 2, entry 1 *vs.* 8).

In summary, results were best with ligand **L4h**, which contains the optimal combination of ligand parameters (*ee*s up to 89%, entry 18). If it is compared with the moderate enantioselectivities obtained with the related Pd-phosphinite-oxazoline **1** ligand systems (*ee*s up to 57% at 0 °C)[5e] in the alkylation of substrate **S2**, we can again conclude that the introduction of a phosphite moiety is highly advantageous in terms of activity and enantioselectivity.

Table 2. Selected results for the Pd-catalyzed allylic substitution of **S2** using phosphite-oxazoline ligand library **L1–L5a–i**.[a]

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

[a] All reactions were run at 23 °C with 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, dichloromethane as solvent, 0.9 mol% ligand, 0.5 mmol **S2**, 1.5 mmol BSA, 1.5 mmol dimethyl malonate, and KOAc as base.
[b] Reaction time shown in parentheses.
[c] Enantiomeric excesses. The absolute configuration appears in parentheses.
[d] Isolated yields of **10** were >92% based on recovered starting material.
[e] $T = 0$ °C.

Allylic Alkylation of Cyclic Substrates S3 and S4 [Eq. (1b)]

As for the unhindered substrate **S2**, the enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less steric *anti* substituents.[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 [Eq. (1b)]: *rac*-3-acetoxycyclohexene **S3** (which is widely used as a model substrate) and *rac*-3-acetoxycycloheptene **S4**.

We initially studied the allylic alkylation of *rac*-3-acetoxycyclohexene **S3** using ligands **L1–L5a–i**. Table 3 summarizes the results under the optimized conditions. Again, activities and enantioselectivities were affected by the substituents in the oxazoline moiety and the substituents/configurations 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**.

Table 3. 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[d]	**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	**L2b**	**S3**	51 (24)	49 (*R*)
12[d]	**L4a**	**S3**	100 (24)	34 (*R*)
13	**L4c**	**S3**	89 (24)	28 (*R*)
14[d]	**L5a**	**S3**	98 (24)	13 (*R*)
15[e]	**L1a**	**S3**	69 (36)	81 (*R*)
16[e]	**L1i**	**S3**	37 (36)	85 (*R*)
17[f]	**L1a**	**S4**	100 (24)	78 (*R*)
18[e]	**L1a**	**S4**	43 (36)	92 (*R*)
19[e]	**L1i**	**S4**	19 (36)	94 (*R*)

[a] All reactions were run at 23 °C, with 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, dichloromethane as solvent, 0.9 mol% ligand, 0.5 mmol substrate, 1.5 mmol BSA, 1.5 mmol dimethyl malonate, and KOAc as base.
[b] Reaction time in hours shown in parentheses.
[c] Enantiomeric excesses. The absolute configuration appears in parentheses.
[d] Isolated yields of **11** were >92%.
[e] $T = -5$ °C.
[f] Isolated yield of **12** was 95%.

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 3, 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 3, entries 1–5).

For enantioselectivities to be high, we found that a phenyl substituent in the oxazoline moiety (Table 3, entries 1 vs. 10–12 and 14) and either an *ortho* trimethylsilyl-disubstituted binaphthyl moiety (Table 3 entries 8 and 9) or an *ortho* and *para* tetrasubstituted *tert*-butyl biphenyl moiety (Table 3, entry 1) was 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 3, entries 9 and 16). These results show again the efficiency of using a modular ligand design.

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 3, entries 17–19).

In summary, results were best with ligand **L1i**. The enantioselectivities are among the best that have been reported for this type of cyclic substrates.[1d,7b,15a,16] Again the replacement of a phosphinite moiety by a phosphite group in the ligand design leads to higher enantioselectivities than when related ligands **1** are used (*ee*s up to 74% at 0 °C).[5e]

Allylic Substitution of Unsymmetrical 1,3,3-Trisubstituted and Monosubstituted Allylic Substrates

In this section, we report the use of the chiral phosphite-oxazoline ligand library (**L1–L5a–i**) in the Pd-catalyzed allylic substitution of the unsymmetrical trisubstituted substrate [Eq. (2a)] *rac*-1,1,-diphenyl-1-hepten-3-yl acetate (**S5**); and unsymmetrical monosubstituted substrates [Eq. (2b)]: *rac*-1-(1-naphthyl)allyl acetate (**S6**) and *rac*-1-(1-naphthyl)-3-acetoxyprop-1-ene (**S7**).

Allylic Substitution of Unsymmetrical *rac*-1,1,-Diphenyl-1-hepten-3-yl Acetate S5 [Eq. (2a)]

We also screened the ligands **L1–L5a–i** in the allylic substitution of *rac*-1,1-diphenyl-1-hepten-3-yl acetate (**S5**) using dimethyl malonate as nucleophile [Eq. (2a)]. This substrate is of synthetic interest because the substitution product can easily be transformed into enantiomerically enriched acid derivatives and lactones.[17] It is more sterically demanding than the

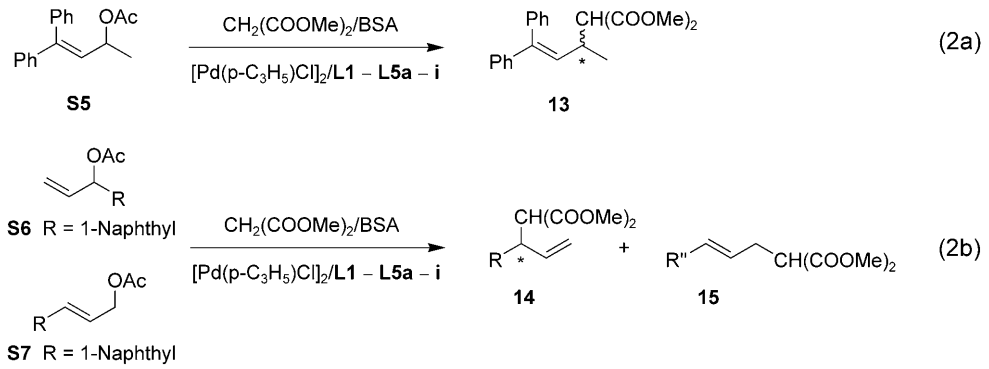


Table 4. Selected results for the Pd-catalyzed allylic alkylation of **S5** using phosphite-oxazoline ligand library **L1**–**L5a**–**i**.[a]

Entry	Ligand	% Conv. (h)[b]	% *ee*[c]
1	**L1a**	80 (24)	91 (*S*)
2	**L1b**	66 (24)	84 (*S*)
3	**L1c**	82 (24)	85 (*S*)
4	**L1d**	64 (24)	84 (*S*)
5	**L1e**	49 (24)	62 (*S*)
6	**L1f**	73 (24)	78 (*S*)
7	**L2a**	65 (24)	76 (*S*)
8	**L3a**	25 (24)	34 (*S*)
9	**L4a**	95 (24)	84 (*S*)
10	**L5a**	75 (24)	78 (*S*)

[a] All reactions were run at 23 °C, with 1 mol% [PdCl(η^3-C_3H_5)]$_2$, dichloromethane as solvent, and 1.8 mol% ligand.
[b] Conversion measured by ^{1}H NMR. Reaction time shown in parentheses.
[c] Enantiomeric excesses measured by HPLC. Absolute configuration shown in parentheses.

previously used substrate **S1**,[1] and it is therefore more difficult to achieve excellent enantioselectivities with it than with **S1**.[17,18] Interestingly, with this phosphite-oxazoline ligand library, we obtained high enantiomeric excesses (*ee*s up to 91%) under standard reaction conditions. Although, as expected, the activities were lower than in the alkylation reaction of **S1**, they were much higher than those obtained with other successful ligands under similar reaction conditions.[18] The results, summarized in Table 4, followed a trend similar to that of the more hindered substrate **S1**. Thus, ligand **L1a** provided the best enantioselectivity (*ee*s up to 91%). These results are among the best reported for this class of substrate.[18]

Allylic Substitution of Monosubstituted Linear Substrates S6 and S7 [Eq. (2b)]

To further study the potential of these ligands, we examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S6** and 1-(1-naphthyl)-3-acetoxyprop-1-ene **S7** with dimethyl malonate [Eq. (2b)]. 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 **15** rather than the desired branched isomer **14**.[19] Therefore, the development of highly regio- and enantioselective Pd catalysts is still a challenge.[7b,9,10c,20] Because the π-acceptor capacity of the biaryl phosphite moiety in ligands **L1**–**L5a**–**i** is high, we expected to enhance the S_N1 character of the nucleophilic attack, which would favor the formation of the branched isomer **14**.[9]

Table 5 summarizes the results obtained with the phosphite-oxazoline ligand library **L1**–**L5a**–**i**. High ac-

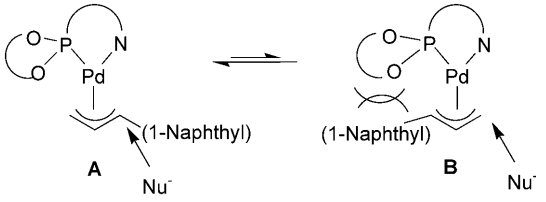
Table 5. Selected results for the Pd-catalyzed allylic alkylation of monosubstituted substrate **S6** and **S7** using the ligand library **L1**–**L5a**–**i** under standard conditions.[a]

Entry	Ligand	Substrate	% Conv.[b] (min)	**14**/**15**[c]	% *ee*[d]
1	**L1a**	S6	100 (60)	65/35	83 (*S*)
2	**L1b**	**S6**	100 (60)	55/45	90 (*S*)
3	**L1c**	**S6**	100 (60)	80/20	90 (*S*)
4	**L1d**	**S6**	100 (60)	65/35	63 (*S*)
5	**L1e**	**S6**	100 (60)	55/45	42 (*S*)
6	**L1f**	**S6**	100 (60)	50/50	96 (*S*)
7[e]	**L1i**	**S6**	100 (60)	85/15	88 (*S*)
8	**L2a**	**S6**	100 (60)	55/45	32 (*S*)
9	**L3a**	**S6**	100 (60)	55/45	32 (*S*)
10	**L4a**	**S6**	100 (60)	50/50	78 (*S*)
11	**L4c**	**S6**	100 (60)	75/25	80 (*S*)
12	**L5a**	**S6**	100 (60)	60/40	72 (*S*)
13	**L1c**	**S7**	100 (60)	80/20	91 (*S*)

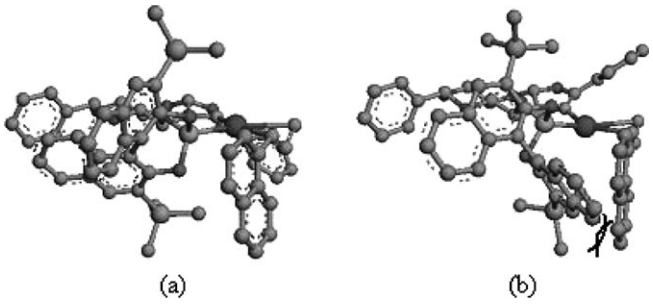
[a] All reactions were run at 23 °C, with 1 mol% [PdCl(η^3-C_3H_5)]$_2$, dichloromethane as solvent, 1.8 mol% ligand, 0.5 mmol substrate, 1.5 mmol BSA, 1.5 mmol dimethyl malonate, and KOAc as base.
[b] Reaction time in minutes shown in parentheses.
[c] Percentage of branched (**14**) and linear (**15**) isomers
[d] Enantiomeric excesses. The absolute configuration appears in parentheses.
[e] Isolated yield of **14** was 83%.

tivities and enantioselectivities (*ee*s up to 96%) combined with regioselectivities up to 85% in favor of the branched product **14** were obtained, under standard reaction conditions. The results indicated that the combination 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 **14** as the major product with high enantioselectivity (Table 5, entries 3 and 7). Again, these results are among the best reported for this type of substrates.[7b,9,10c,20]

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 **14** was only moderate (Table 5, entry 6). However, the related ligand **L1i**, with the opposite configuration of the binaphthyl phosphite moiety, affords product **14** in high amount (Table 5, entry 7). This can be explained by the different spatial arrangement of the biaryl phosphite group around the metal center, which is determined by the configuration of the binaphthyl group. Therefore, assuming that the nucleophilic attack takes place *trans* to the phosphite moiety (the best π-acceptor group) (*vide infra*) and taking into account that the nucleophilic attack by an S_N2 type process should take place preferentially at the less substituted allyl terminus (Scheme 2, species **B**),[9] the study of the models[21] (Scheme 3) 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 3 (b)] that shifted the equilibrium to species **A** and favored the formation of the desired regioisomer **14** (Scheme 2). 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 **S6** [Scheme 3 (a)], thus favoring the formation of the **B** isomer, which is responsible for the linear product.



Scheme 2. Nucleophilic attack in the Pd-catalyzed allylic alkylation of substrate **S6** with ligand **L1i**.



Scheme 3. Drawings of the Pd-π-allyl intermediates containing ligand (a) **L1h** and (b) **L1i**. H atoms are omitted for clarity.

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

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

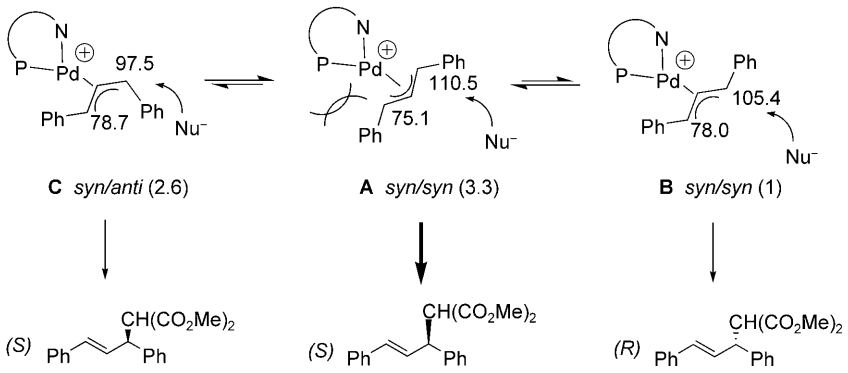
Scheme 4. Preparation of $[Pd(\eta^3\text{-allyl})(L)]BF_4$ complexes **16**–**25**.

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 **16**–**25**, $[Pd(\eta^3\text{-allyl})(L)]BF_4$ (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 4).[22] The complexes were characterized by elemental analysis and by *in situ* ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments (see Supporting Information) were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments.

Palladium 1,3-Diphenylallyl 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 enantioselectivity is highly affected by the ligand



Scheme 5. Diastereoisomer Pd-allyl intermediates **16** for **S1** with ligand **L1a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

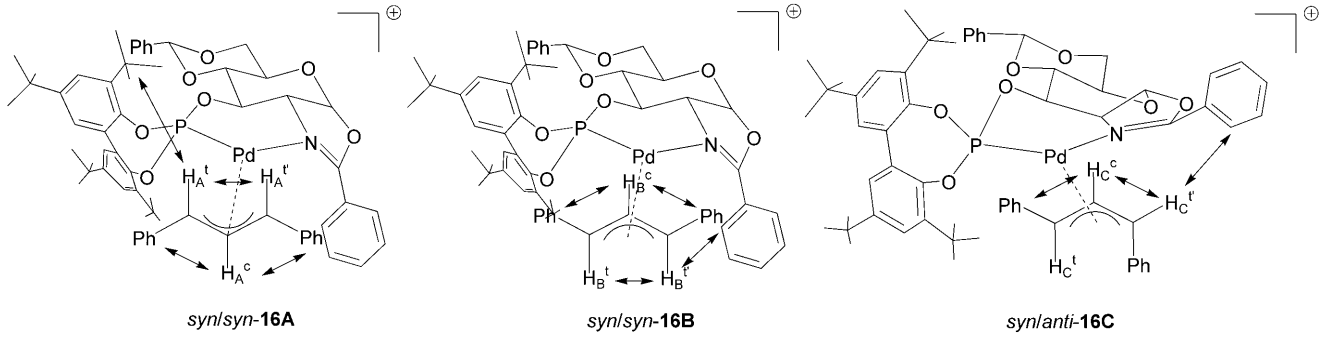
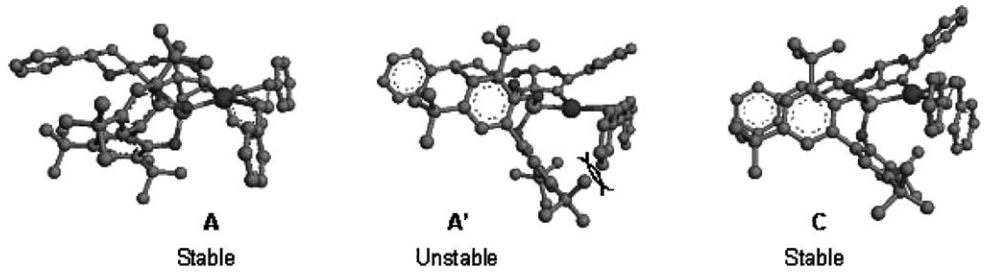


Figure 3. Relevant NOE contacts from NOESY experiment of *syn*/*syn* isomers **16A** and **16B** and *syn*/*anti* isomer **16C**.

parameters. A phenyl substituent in the oxazoline group and a biphenyl phosphite moiety with bulky substituents in *ortho* and *para* positions are therefore 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 **16**–**19** which contain ligands **L1a, L1f**, **L1b** and **L3a**, respectively, at a ligand-to-palladium ratio of 0.9 and 2. Although ligand **L1a** with 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 VT-NMR (30 °C to −85 °C) study of Pd-allyl intermediate **16**, which contains ligand **L1a**, performed at a ligand-to-palladium ratio of 0.9 had a mixture of three isomers in equilibrium in a ratio of 3.3:2.6:1 (see Supporting Information). The three isomers were unambiguously assigned by NMR to the two *syn*/*syn endo* **A** and *exo* **B** isomers, while compound **C** was assigned to the *syn*/*anti* isomer (Scheme 5). In isomers **A** and **B**, the NOE indicates interactions between both terminal protons of the allyl group and also between the central allyl proton with *ortho* hydrogens of both phenyl groups of the allyl ligand, which clearly indicates a *syn*/*syn* disposition (Figure 3). However, for compound **C** the central allyl proton shows a NOE interaction with only one of the phenyl substituents and only one of the terminal allyl protons, thus suggesting a *syn*/*anti* conformation. Moreover, the terminal allyl proton $H_B^{t'}$ of the isomer **B** shows an NOE interaction with the *ortho* hydrogen of the phenyl-oxazoline substituent, while in **A** isomer there is an interaction between the terminal allyl proton H_A^{t} and the *tert*-butyl substituents at the biaryl phosphite moiety. Such interactions can be explained by assuming a *syn*/*syn endo* arrangement for isomer **A** and a *syn*/*syn exo* arrangement for isomer **B** (Figure 3). In addition, exchange signals between *syn*/*syn* isomer **A** and *syn*/*anti* isomer **C** were observed in the NOESY spectra (see Supporting Information). This agrees with an equilibrium between isomers **A** and **C**. Exchange between $H_A^{t'}$ at 6.69 ppm of the **A** isomer and $H_C^{t'}$ at 5.15 ppm of the **C** isomer confirms η^3–η^1–η^3 movement for the exchange between isomers **A** and **C**.[23] In addition, the fact that no other H^{anti}–H^{syn} exchange is observed indicates that the exchange mechanism takes place by the se-



Scheme 6. Drawings of the Pd-allyl intermediates **16A**, **16A′** and **16C** for **S1** with ligand **L1a**. H atoms are omitted for clarity.

lective opening of one of the terminal Pd–C bond. Accordingly, the study of the models[21] 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 6, species **A′**). The formation of the *syn*/*anti* isomer **C** minimizes this new steric interaction. Therefore, the open Pd–C bond belongs to the less electrophilic carbon atom with the substituent that undergoes the biggest steric hindrance with the biaryl phosphite fragment. Together with the NOE interaction between the terminal *syn* proton and the *ortho* hydrogen of the phenyl-oxazoline substituent, this agrees with the *syn*/*anti* arrangement depicted in Figure 3 for isomer **C**. 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** (Scheme 6). This explains why *syn*/*syn* isomer **A** is preferentially formed to *syn*/*syn* isomer **B**. 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 terminal carbon atom, the attack at the *syn*/*syn* isomer **A** and *syn*/*anti* isomer **C** will lead to the formation of (*S*)-**8** while the attack at the *syn*/*syn* isomer **B** 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 compounds **B** and **C**. To prove this we used *in situ* NMR to study the reactivity of the Pd intermediates with sodium malonate at low temperature (Figure 4). Our results show that isomer **A** reacts around 10 times faster than isomer **B**, while **C** reacts much slower. If we take into account the relative reaction rates and the abundance of the reacting isomers (**A** and **B**), the calculated *ee* should be 94% (*S*), which matches the *ee* obtained experimentally. We can therefore conclude that the nucleophilic attack takes place preferentially at the allyl terminus *trans* to the phosphite

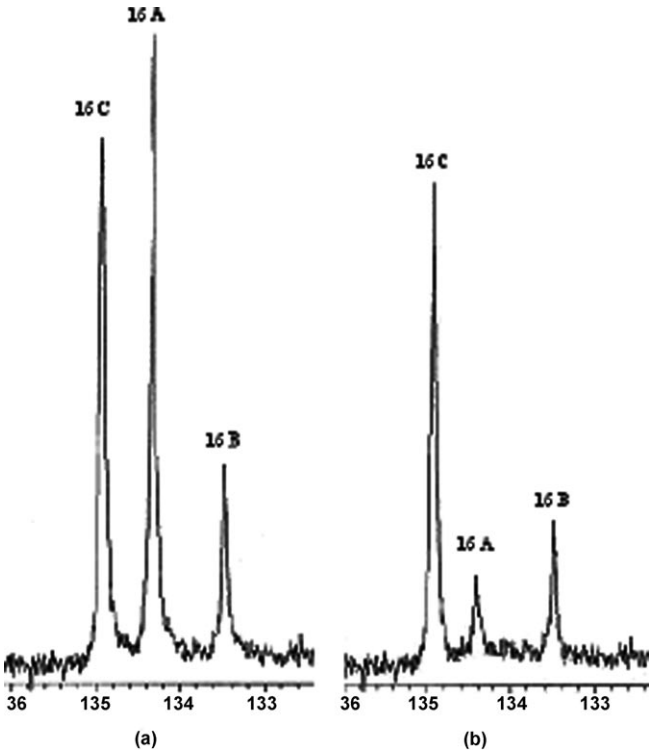
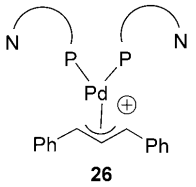


Figure 4. $^{31}P\{^{1}H\}$ NMR spectra of [Pd(η^3-1,3-diphenylallyl)-(**L1a**)]BF_4 (**16**) in CD_2Cl_2 at −70 °C (a) before the addition of sodium malonate and (b) after the addition of sodium malonate.

moiety of the major **A** Pd intermediate. 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.

We next performed an NMR study of Pd-allyl intermediate **16** at a ligand-to-palladium ratio of 2. The ^{31}P NMR indicated that the major species was a new one with a signal at 137.4 ppm (40%) (Scheme 7). This species was attributed to Pd-allyl complex **26** {[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 type of complex is known to be faster and less enantioselective than its bidentate counterpart because it has more degrees of freedom.[10a,24] This explains the drop

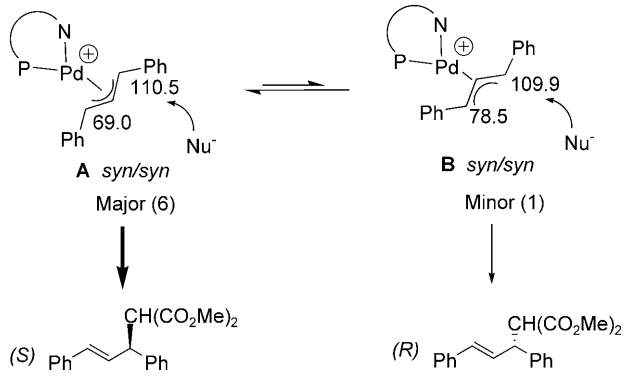


26

Scheme 7. Pd-intermediate with two phosphite-oxazoline **L1a** ligands coordinated as monodentates through the phosphite moiety.

in enantioselectivity observed at ligand-to-palladium ratios higher than 0.9 when the Pd/**L1a** catalyst system was used (see Supporting Information).

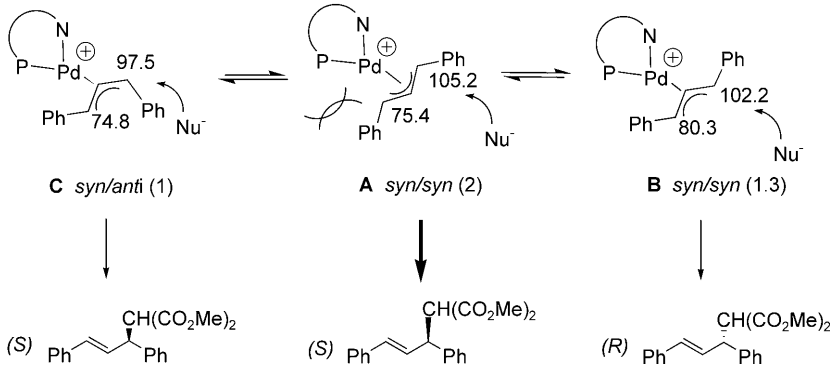
To provide further evidence that the *syn-anti* isomerism observed in complex **16** is caused by the atropoisomerism of the biphenyl moieties, we studied the palladium allyl intermediate [Pd(η^3-1,3-diphenylallyl)-(**L1f**)]BF_4 (**17**), which contains enantiopure *S*-binaphthyl ligand **L1f**. As expected, and in contrast to complex **16**, the VT-NMR study performed at a ligand-to-palladium ratio of 0.9 showed a mixture of the two *syn*/*syn endo* (**A**) and *exo* (**B**) isomers in a ratio of 6:1 but no *syn*/*anti* isomer **C** (Scheme 8). No changes were observed at temperatures as low as −85 °C. For both isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety. 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 again react faster than the **B** isomer. This was confirmed by an *in situ* NMR study of the reactivity of the Pd intermediates with sodium malonate at low temperature (the **A** isomer reacts around three times faster than the **B** isomer).



Scheme 8. Diastereoisomeric Pd-allyl intermediates **17** for **S1** with ligand **L1f**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

We next studied the Pd-allyl intermediate **18** (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 VT-NMR study showed a mixture of three isomers in equilibrium at a ratio of 2:1:1.3 (see Supporting Information). The major **A** and the minor **B** isomers were assigned to the two *syn*/*syn endo* and *exo* isomers, while isomer **C** was assigned to the *syn*/*anti* isomer (Scheme 9). As for complex **16**, the NOESY showed exchange signals between *syn*/*syn* isomer **A** and *syn*/*anti* isomer **C**. Again, this *syn*/*syn*–*syn*/*anti* equilibrium is due to the atropoisomerism of the biphenyl phosphite moiety (*vide supra*). As for complex **16**, it should be noted that, for all isomers, the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety and isomer **A** reacts faster than the other isomers. However, the lower enantioselectivity with this system than with the previous Pd/**L1a** catalytic system can mainly be attributed to the decrease in the ratio between the species that provide the *S*-enantiomer (**A** and **C**) with respect to the species that provides *R*-**8** (**B**), compared with the population of the isomers (**A–C**) for complex **16**.

Finally, we studied the Pd-allyl intermediate **19** (at a ligand-to-palladium ratio of 0.9) containing ligand



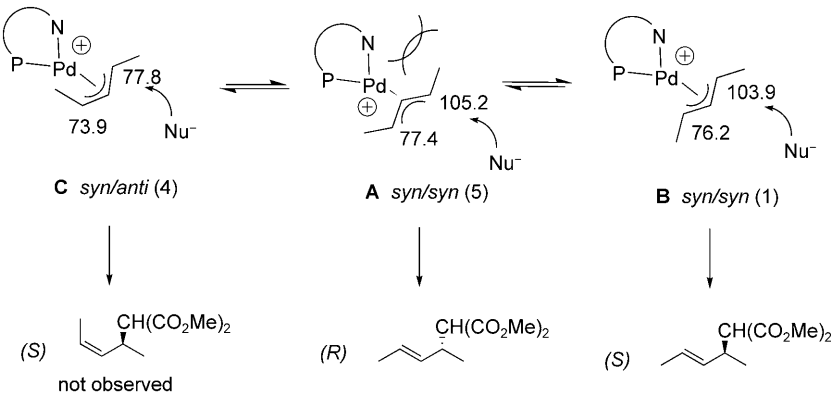
Scheme 9. Diastereoisomeric Pd-allyl intermediates **18** for **S1** with ligand **L1b**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

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 **16**–**18** studied above, the VT-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.

Palladium 1,3-Dimethylallyl Complexes

When the phosphite-oxazoline ligand library **L1**–**L5a**–**i** was used in the allylic substitution of unhindered linear **S2** substrate, the catalytic results revealed a different trend with regard to the effect of the ligand parameters than with the hindered substrate **S1**. 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 **20**–**22** 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 VT-NMR (30 °C to −85 °C) study of Pd-1,3-dimethyl allyl intermediate **20** at a ligand-to-palladium ratio of 0.9, which contains ligand **L1a**, indicated the presence of a mixture of three isomers in equilibrium at a ratio of 5:4:1 (see Supporting Information). The major **A** and the minor **B** isomers were assigned by NOE to the two *syn*/*syn exo* and *endo* isomers respectively, while isomer **C** was assigned to the *syn*/*anti* isomer (Scheme 10 and Figure 5). In contrast to complex **16**, the major *syn*/*syn* isomer **20A** adopts a W (*exo*) spatial arrangement. This is due to the absence of the favorable π-stacking interaction observed in related complex **16**. The formation of isomer **C** was at-



Scheme 10. Diastereoisomeric Pd-allyl intermediates **20** for **S2** with ligand **L1a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

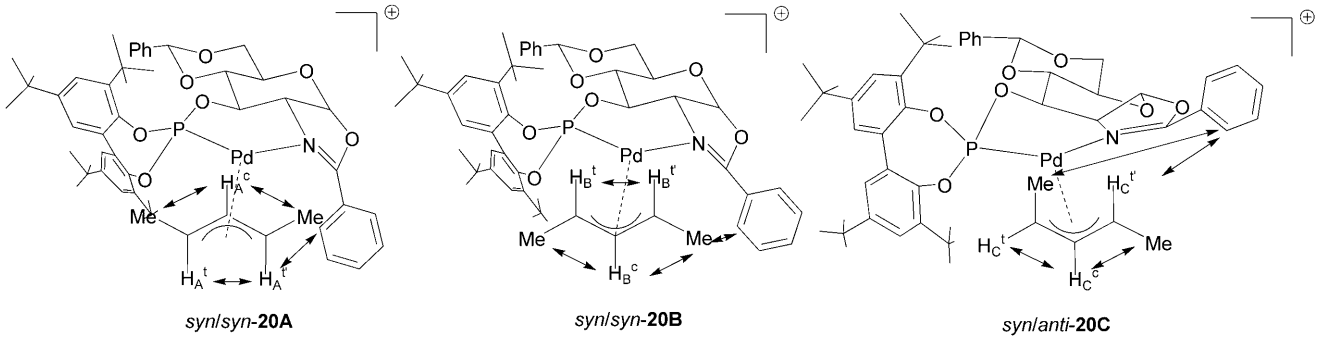
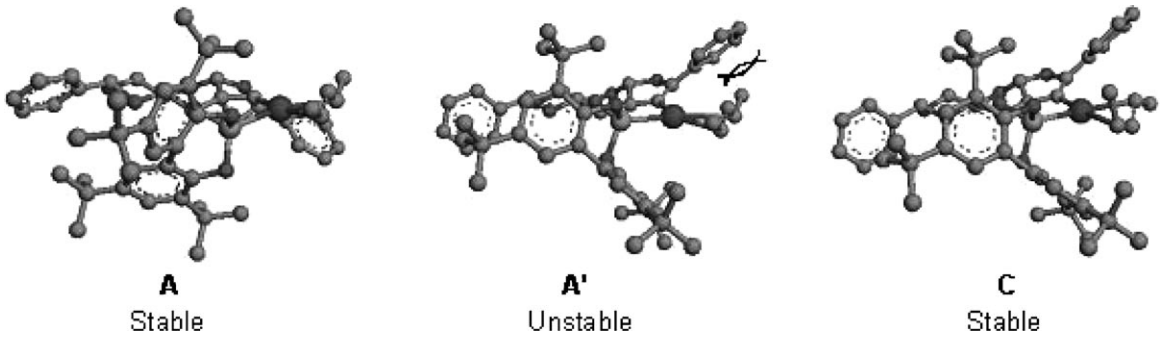


Figure 5. Relevant NOE contacts from NOESY experiment of *syn*/*syn* isomers **20A** and **20B** and *syn*/*anti* isomer **20C**

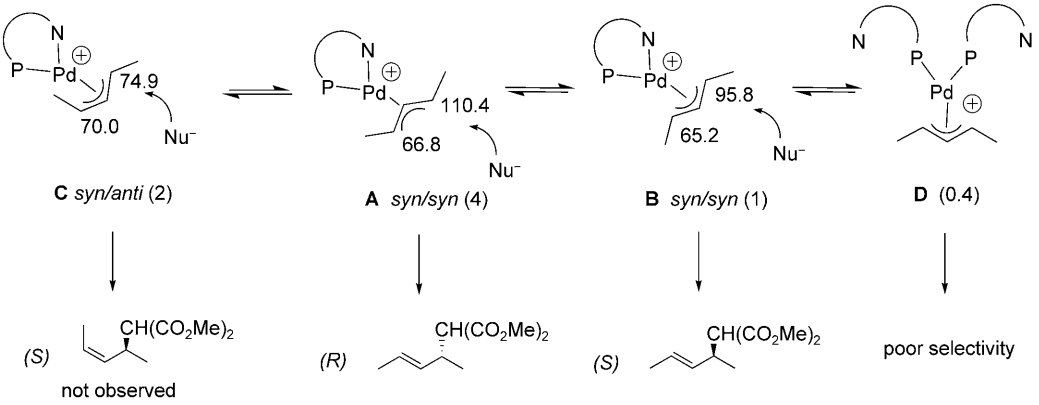


Scheme 11. Drawings of the Pd-allyl intermediates **20A**, **20A′** and **20C** for **S2** with ligand **L1a**. H atoms are omitted for clarity.

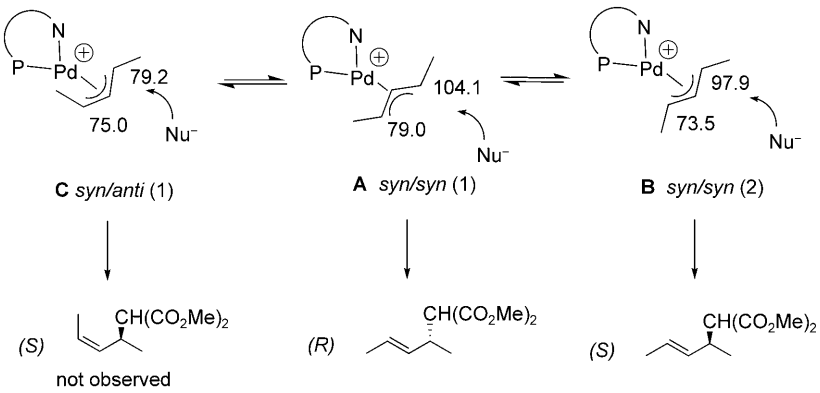
tributed to the atropoisomerism of the biphenyl phosphite in isomer **A** as it was in the related Pd-1,3-diphenylallyl complexes **16** and **18**. However, the study of the models indicates that the change in configuration of the biphenyl phosphite moiety results in a steric interaction between the oxazoline phenyl group and one of the methyl substituents in **S2** (isomer **A′**, Scheme 11). The formation of *syn*/*anti* isomer **C** minimizes this steric interaction (Scheme 11). 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 carbon terminus is *trans* to the phosphite moiety in *syn*/*syn* isomer **A** and *syn*/*syn* isomer **B**, and the allylic terminus carbon in isomer **C** is far less electrophilic [$\Delta(\delta^{13}C) \approx 30$ ppm]. On the basis of the relative abundance of isomers **A** and **B**, the calculated diastereomeric excess matches the enantiomeric excess obtained experimentally for product **10** [*ee* = 60% (*R*)].

We also performed the VT-NMR study of Pd-allyl intermediate **20** at a ligand-to-palladium ratio of 2. The ^{31}P NMR indicated the presence of a new species (10%, $\delta = 136.9$ 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-dimethylallyl)-(**L1a**)$_2$]BF_4}. Interestingly, in contrast to Pd-1,3-diphenylallyl intermediate **16**, the amount of this {[Pd(1,3-dimethylallyl)(**L1a**)$_2$]BF_4} species is lower. This is probably due to the presence of less sterically hindered 1,3-dimethylallyl and explains why the enantioselectivity observed ligand-to-palladium ratios higher than 0.9 in the alkylation of **S2** decreased less than in the alkylation of **S1**.

The VT-NMR study of Pd-1,3-dimethylallyl intermediate **21**, which contains ligand **L3a** with a bulky *tert*-butyl group at the oxazoline, indicated the presence of a mixture of four isomers in equilibrium in a ratio of 4:2:1:0.4 at a ligand-to-palladium ratio of 0.9 (see Supporting Information). Isomers **A**, **B** and **C** were assigned by NOE to the *syn*/*syn exo, syn*/*syn endo* and *syn*/*anti* isomers, respectively, while isomer **D** was attributed to the isomer that contains two ligands coordinated in a monodentate fashion (Scheme 12). As for complex **20**, the most electrophilic allyl carbon terminus was *trans* to the phosphite moiety in *syn*/*syn* isomers **A** and **B**, and the allylic carbon terminus in isomer **C** was less electrophilic [$\Delta(\delta^{13}C) \approx 30$ ppm]. Therefore, the fact that the enan-



Scheme 12. Diastereoisomeric Pd-allyl intermediates **21** for **S2** with ligand **L3a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.



Scheme 13. Diastereoisomeric Pd-allyl intermediates **22** for **S2** with ligand **L3a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

tioselectivity with the Pd/**L3a** catalyst system is lower than with the Pd/**L1a** catalyst system may be due to the presence of the less enantioselective isomer **D** and the decrease in the relative amount of isomers **A** and **B** (5:1 ratio for complex **20** and 4:1 ratio for complex **21**).

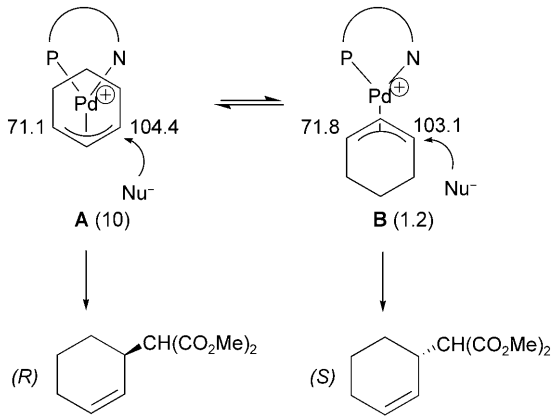
We next studied Pd-allyl intermediate **22** (at a ligand-to-palladium ratio of 0.9) containing ligand **L1c**. This complex has the same substituent in the oxazoline moiety as complex **20** but differs from ligand **L1a** in the substituents of the biphenyl phosphite moiety. The VT-NMR study showed a mixture of three isomers in equilibrium at a ratio of 1:1:2 (see Supporting Information) (Scheme 13). As for complex **20**, these were assigned to the two *syn*/*syn exo* (**A**) and *endo* (**B**) isomers and to the *syn*/*anti* isomer (**C**). Again, the most electrophilic allyl carbon terminus is found in species **A** and **B**. However, in contrast to complex **20**, the allylic carbon atoms *trans* to the phosphite moiety in isomer **A** is much more electrophilic than the one in isomer **B** [$\Delta(\delta^{13}C) \approx 7$ ppm]. Therefore, isomer **A** should react faster than isomer **B**. Despite this, the fact that **B** is the major isomer may explain why the enantioselectivity with this catalytic system is lower than with Pd/**L1a**.

Palladium 1,3-Cyclohexenylallyl 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 **23–25** 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 a 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 VT-NMR (30 °C to −85 °C) study of Pd-1,3-cyclohexenylallyl intermediate **23**, which contains ligand **L1a**, showed a mixture of two isomers in equilibrium at a ratio of 10:1.2 and at a ligand-to-palladium ratio of 0.9 (see Supporting Information). Both isomers were assigned by NOE to the two *syn*/*syn* isomers (Scheme 14 and Figure 6). For both isomers, the carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. 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*)].

The VT-NMR study of Pd-1,3-cyclohexenylallyl intermediates **24** and **25**, 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



Scheme 14. Diastereoisomeric Pd-allyl intermediates **23** for **S3** with ligand **L1a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

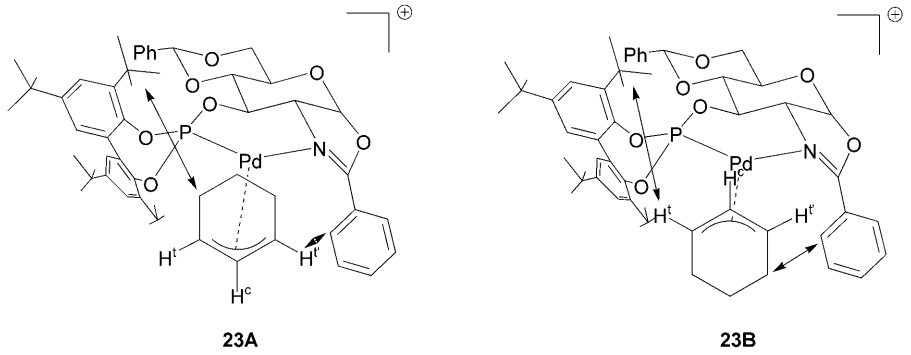
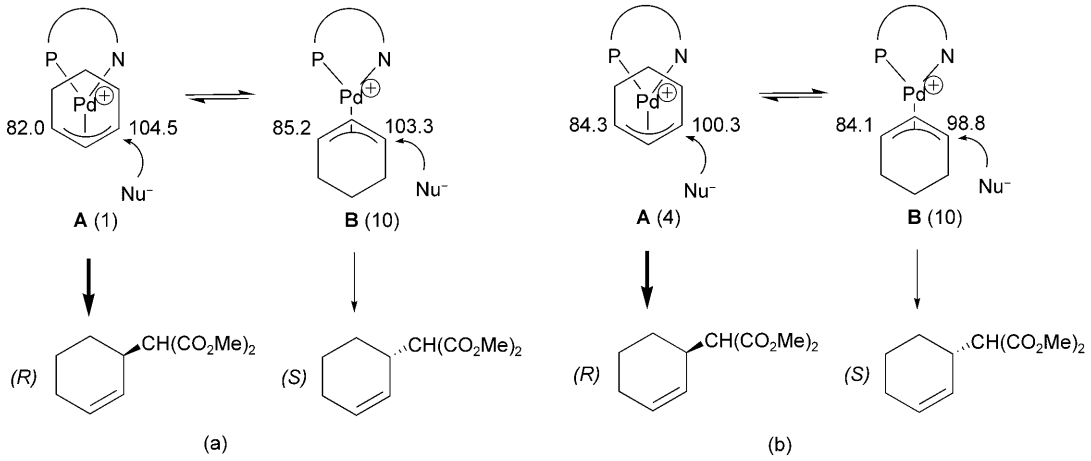


Figure 6. Relevant NOE contacts from NOESY experiment of isomers **23A** and **23B**.



Scheme 15. Diastereoisomeric Pd-allyl intermediates (a) **24** for **S3** with ligand **L1b** and (b) **25** for **S3** with ligand **L4a**. The relative amounts of each isomer are given in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are shown.

ratio of 0.9, see Supporting Information). All the species were assigned by NOE to the two *syn*/*syn* isomers possible for each Pd-allyl complex (Scheme 15). 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 **23**, the nucleophilic attack at the major **B** isomers will lead to the formation of the (*S*)-**11** product. Therefore, the difference between the diastereoisomeric ratio and enantioselectivity observed in the alkylation of **S3** [*de* = 80% (*S*) *vs.* *ee* = 22% (*R*) for Pd/**L1b**; *de* = 40% (*S*) *vs.* *ee* = 34% (*R*) for Pd/**L1b**] indicates that the nucleophile reacts faster with the minor isomer **A**. This was confirmed by an *in situ* NMR study of the reactivity of the Pd intermediates of both Pd-cyclohexenylallyl complexes **24** and **25** with sodium malonate at low temperature.[25]

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 efficiently prepared from readily available D-glucosamine; (2) the π-acceptor character of the phosphite moiety increases reaction rates; (3) the flexibility 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, so activities and enantioselectivities can be maximized for each substrate as required. The results indicate that catalytic performance is 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. By carefully selecting the ligand components, high enantioselectivities (*ee*s up to 99%) and good activities have been achieved in a broad range of mono-, di- and trisubstituted hindered and unhindered linear and cyclic substrates. These results are among the best that have been reported. Particular note should be

taken of the high enantio- and regioselectivities (up to 96% *ee* and 85%, respectively) combined with the high activities obtained for mono- and trisubstituted substrates. In addition, 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 substrate types. These results open 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 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 behavior observed. Therefore, it indicates that for enantioselectivities to be high, the substituents in the biaryl phosphite moiety and the electronic and steric properties at the oxazoline substituents need to be correctly combined in order to form predominantly the isomer that reacts faster with the nucleophile and also to avoid the formation of species with ligands coordinated in a monodentated fashion. This study also indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety.

Experimental Section

General Considerations

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.[26] Ligands **L1a–i**, **L2a**, **L3a** and **L4a,c** were prepared as previously described.[11,27,28] Racemic substrates **S1–S7** were prepared as previously reported.[29,30,31,32] $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$,[33] $[Pd(\eta^3\text{-}1,3\text{-}Me_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[34] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{-}Cl)]_2$[35] 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. All catalytic experiments were performed three times.

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 hydroxyoxazoline compound (2.8 mmol) was azeotropically dried with toluene (3×2 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 °C to the solution of the phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, 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. For yields and analytical data of the new ligands see the Supporting Information.

General Procedure for the Preparation of $[Pd(\eta^3\text{-allyl})(L)]BF_4$ Complexes 16–25

The desired amount of the corresponding ligand (0.045 mmol for a L/Pd = 0.9; 0.1 mmol for a L/Pd = 2) and the complex $[Pd(\mu\text{-}Cl)(\eta^3\text{-}1,3\text{-allyl})]_2$ (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 min and the mixture was stirred for 30 min. 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 by adding hexane. The complexes were filtered off and washed with cold hexane to afford **16–25** as pale yellow solids. For analytical data of complexes **16–25** see the Supporting Information

Study of the Reactivity of the $\{Pd[(\eta^3\text{-allyl})(L)]\}BF_4$ with Sodium Malonate by *in situ* NMR[36]

A solution of *in situ* prepared $[Pd(\eta^3\text{-allyl})(\mathbf{L})]BF_4$ (L = phosphite-oxazoline, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at −70 °C. At this temperature, a solution of cooled sodium malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR. The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

Typical Procedure for Allylic Alkylation of Substrates S1–S7

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.0025 mmol for **S1–S2**; 0.005 mmol for **S3–S4** and **S6–S7**; 0.01 mmol for **S5**) and the corresponding phosphite-nitrogen (0.0045 mmol for **S1–S2**; 0.009 mmol for **S3–S4** and **S6–S7**; 0.018 mmol for **S5**) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding 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 KOAc (1 mg) 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 aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, solvent was removed and conversion was measured by ^1H NMR. To determine the *ee* by HPLC (Chiralcel OD, 0.5% 2-propanol/hexane, flow 0.5 mL min^{-1}), a sample was filtered over basic alumina using dichloromethane as the eluent.[37] For substrates **S2–S4** conversion and enantiomeric excess was determined by GC.[23] For substrates **S5–S7**, 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^{-1}), a sample was filtered over basic alumina using dichloromethane as the eluent.[18c,38]

Typical Procedure for 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 h the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 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^{-1}), a sample was filtered over silica using 10% Et_2O/hexane mixture as the eluent.[37]

Acknowledgements

We are indebted to Prof. P. W. N. M. van Leeuwen, University of Amsterdam, for his comments and suggestions. We thank the Spanish Government (Consolider Ingenio CSD2006-0003, CTQ2007-62288/BQU, 2008PGIR/07 to O.P. and 2008PGIR/08 to M.D) and the Catalan Government (2005SGR007777 and Distinction to M.D.) for financial support.

References

[1] For recent reviews, see: a) B. M. Trost, D. L. van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) M. Johannsen, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 1689; c) A. Pfaltz, M. Lautens, in: *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, **1999**, Vol. 2, Chapter 24; d) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336; e) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; f) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

[2] a) A. M. Masdeu-Bultó, M. Diéguez, E. Martin, M. Gómez, *Coord. Chem. Rev.* **2003**, *242*, 159; b) E. Martín, M. Diéguez, *C. R. Chemie* **2007**, *10*, 188.

[3] See for instance: a) E. Raluy, C. Claver, O. Pàmies, M. Diéguez, *Org. Lett.* **2007**, *9*, 49; b) M. Diéguez, O. Pàmies, C. Claver, *Adv. Synth. Catal.* **2007**, *349*, 836; c) O. Pàmies, M. Diéguez, *Chem. Eur. J.* **2008**, *14*, 944.

[4] For recent reviews, see for example: a) M. Diéguez, O. Pàmies, C. Claver, *Chem. Rev.* **2004**, *104*, 3189; b) M. Diéguez, O. Pàmies, A. Ruiz, Y. Díaz, S. Castillón, C. Claver, *Coord. Chem. Rev.* **2004**, *248*, 2165; c) M. Diéguez, A. Ruiz, C. Claver, *Dalton Trans.* **2003**, 2957; d) M. Diéguez, C. Claver, O. Pàmies, *Eur. J. Org. Chem.* **2007**, 4621.

[5] See for example: a) Y. Y. Yan, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 199; b) D. Liu, W. Li, X. Zhang, *Org. Lett.* **2002**, *4*, 4471; c) A. Albinati, P. S. Pregosin, K. Wick, *Organometallics* **1996**, *15*, 2419; d) E. Guimet, M. Diéguez, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **2005**, *16*, 959; e) K. Yonehara, T. Jashizume, K. Mori, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 9374; f) K. Boog-Wick, P. S. Pregosin, C. Trabesinger, *Organometallics* **1998**, *17*, 3254; g) M. Diéguez, S. Jansat, M. Gomez, A. Ruiz, G. Muller, C. Claver, *Chem. Commun.* **2001**, 1132; h) E. Raluy, O. Pàmies, M. Diéguez, *J. Org. Chem.* **2007**, *72*, 2842.

[6] a) B. Gläser, H. Kunz, *Synlett* **1998**, 53; b) K. Yonehara, T. Hashizume, K. Mori, K. Ohe, S. Uemura, *Chem. Commun.* **1999**, 415.

[7] Bulky biphenyl phosphites are known to provide larger bite angles than phosphinites. The opening of the bite angle is necessary for high chiral recognition in the Pd-catalyzed alkylation reactions. See for example: a) B. M. Trost, D. L. van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741.

[8] The flexibility offered by the biphenyl moiety can be used to fine-tune the chiral pocket formed upon complexation. Phosphite ligands have therefore proven to be highly versatile and active in Pd-catalyzed asymmetric substitution reactions, See for example a) M. Diéguez, O. Pàmies, C. Claver, *J. Org. Chem.* **2005**, *70*, 3363; b) O. Pàmies, M. Diéguez, C. Claver, *J. Am. Chem. Soc.* **2005**, *127*, 3646; c) M. Diéguez, O. Pàmies, C. Claver, *Adv. Synth. Catal.* **2005**, *347*, 1257.

[9] R. Prétôt, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 337; *Angew. Chem. Int. Ed.* **1998**, *37*, 323.

[10] a) M. Diéguez, O. Pàmies, *Chem. Eur. J.* **2008**, *14*, 3653; b) K. N. Gavrilov, V. N. Tsarev, S. V. Zheglov, S. E. Lyubimov, A. A. Shyryaev, P. V. Petrovskii, V. A. Davankov, *Mendeleev Commun.* **2004**, 260; c) R. Hilgraf, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 61.

[11] The preliminary results were partly reported in the communication: Y. Mata, O. Pàmies, M. Diéguez, C. Claver, *Adv. Synth. Catal.* **2005**, *347*, 1943.

[12] O. Pàmies, M. Diéguez, G. Net, A. Ruiz, C. Claver, *Organometallics* **2000**, *19*, 1488.

[13] 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. See ref.[5e].

[14] Changing the Pd catalyst concentration from 2 mol% down to 0.5 mol% has no affect on enantioselectivity.

[15] For some successful applications, see: a) P. Dierkes, S. Randechul, L. Barloy, D. De Cian, J. Fischer, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. A. Osborn, *Angew. Chem.* **1998**, *110*, 3299; *Angew. Chem. Int. Ed.* **1998**, *37*, 3116; b) B. M. Trost, A. C. Krueger, R. C. Bunt, J. Zambrano, *J. Am. Chem. Soc.* **1996**, *118*, 6520; c) B. Wiene, G. Helmchen, *Tetrahedron Lett.* **1998**, *39*, 5727.

[16] For some successful applications, see: a) B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1994**, *116*, 4089; b) G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1997**, *69*, 513.

[17] See, for instance: a) A. Sudo, K. Saigo, *J. Org. Chem.* **1997**, *62*, 5508; b) G. J. Dawson, J. M. J. Williams, S. J. Coote, *Tetrahedron: Asymmetry* **1995**, *6*, 2535; c) C. J. Martin, D. J. Rawson, J. M. J. Williams, *Tetrahedron: Asymmetry* **1998**, *9*, 3723.

[18] For successful applications, see also: a) G. J. Dawson, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1995**, *36*, 461; b) D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagné, *J. Am. Chem. Soc.* **2000**, *122*, 7905; c) D. Popa, C. Puigjaner, M. Gomez, J. Bene *t*Buchholz, A. Vidal-Ferran, M. A. Pericas, *Adv. Synth. Catal.* **2007**, 349, 2265.

[19] In contrast to Pd-catalytic systems, Ir, Ru, W and Mo catalysts provide very high selectivity in order for the attack at the non-terminal carbon to give the chiral product. See, for instance: a) C. Bruneau, J. L. Renaud, B. Demersemen, *Chem. Eur. J.* **2006**, *12*, 5178; b) A. V. Malkov, L. Gouriou, G. C. Lloyd-Jones, I. Starý, V. Langer, P. Spoor, V. Vinader, P. Kočovský, *Chem. Eur. J.* **2006**, *12*, 6910; c) B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, *121*, 10416; d) A. Alexakis, D. Polet, *Org. Lett.* **2004**, *6*, 3529; e) B. M. Trost, M. H. Hung, *J. Am. Chem. Soc.* **1983**, *105*, 7757; f) G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem.* **1995**, *107*, 534; *Angew. Chem. Int. Ed. Engl.Angew. Chem. Int. Ed.* **1995**, *34*, 462.

[20] For recent successful applications of Pd-catalysts, see: a) S.-L. You, X.-Z. Zhu, Y.-M. Luo, X.-L. Hou, L.-X. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 7471; b) R. Hilgraf, A. Pfaltz, *Synlett* **1999**, 1814.

[21] The study of the models has been performed using molecular mechanics calculations using the universal force field (UFF).

[22] S. Deerenberg, H. S. Schrekker, G. P. F. van Strijdonck, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. Fraanje, K. Goubitz, *J. Org. Chem.* **2000**, *65*, 4810.

[23] M. A. Pericàs, C. Puigjaner, A. Riera, A. Vidal-Ferran, M. Gómez, F. Jiménez, G. Muller, M. Rocamora, *Chem. Eur. J.* **2002**, *8*, 4164.

[24] A. M. Porte, J. Reinbenspies, K. Burgess, *J. Am. Chem. Soc.* **1998**, *120*, 9180.

[25] The *in situ* NMR studies indicate that isomers **24A** and **25A** react 15 and 5 times faster than isomers **24B** and **25B**, respectively.

[26] G. J. H. Buisman, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[27] Y. Mata, O. Pàmies, M. Diéguez, *Chem. Eur. J.* **2007**, *13*, 3296.

[28] M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 7208.

[29] P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2033.

[30] C. Jia, P. Müller, H. Mimoun, *J. Mol. Cat. A: Chem.* **1995**, *101*, 127.

[31] J. Lehman, G. C. Lloyd-Jones, *Tetrahedron* **1995**, *51*, 8863.

[32] T. Hayashi, A. Yamamoto, Y. Ito, E. Nishioka, H. Miura, K. Yanagi, *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[33] P. von Matt, G. C. Lloyd-Jones, A. B. E Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Ruegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265.

[34] M. Kollmar, B. Goldfuss, M. Reggelin, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2001**, *7*, 4913.

[35] B. M. Trost, P. E. Strege, L. Weber, *J. Am. Chem. Soc.* **1978**, *100*, 3407.

[36] R. J. van Haaren, P. H. Keeven, L. A. van der Veen, K. Goubitz, G. P. F. van Strijdonck, H. Oevering, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Inorg. Chim. Acta* **2002**, *327*, 108.

[37] O. Pàmies, G. P. F. van Strijdonck, M. Diéguez, S. Deerenberg, G. Net, A. Ruiz, C. Claver, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Org. Chem.* **2001**, *66*, 8867.

[38] J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025.

