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Biaryl Phosphites: New Efficient Adaptative Ligands for Pd-Catalyzed Asymmetric Allylic Substitution Reactions

MONTSERRAT DIÉGUEZ* AND OSCAR PÀMIES

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

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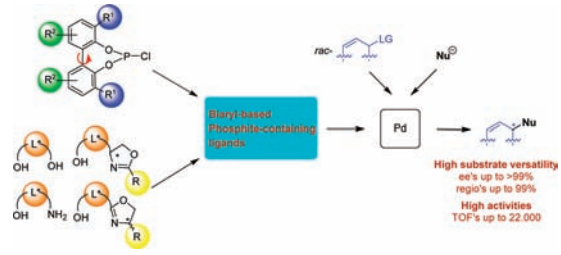

Pharmaceuticals, agrochemicals, fragrances, fine chemicals, and natural product chemistry all rely on the preparation of enantiomerically enriched compounds. The palladium-catalyzed asymmetric allylic substitution, which allows for the enantioselective formation of carbon−carbon and carbon−heteroatom bonds, is a potential synthetic tool for preparing these compounds. To date, most of the successful ligands reported for the Pd-catalyzed allylic substitution reactions have used three main design strategies. The first, developed by Hayashi and co-workers, used a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic terminal carbon atoms. The second increased the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded. To discriminate electronically between the two allylic terminal carbon atoms, the third strategy employed heterodonor ligands. Although many chiral ligands have been successfully applied in the substitution of several disubstituted substrates, problems generally remain with both substrate specificity and reaction rates using these methods. Other substrates, such as those that are monosubstituted, will require more active and more regio- and enantioselective Pd-catalysts. Overcoming these limitations requires research toward the development of new ligands.

This Account discusses the application of homo- and heterodonor biaryl-containing phosphites as new, versatile, and highly effective ligands in the Pd-catalyzed asymmetric allylic substitution of several substrate types. We and others recently demonstrated that the inclusion of biarylphosphite moieties in ligand design is highly advantageous. In these systems, the catalyst's substrate specificity decreases because the chiral pocket created (the chiral cavity with the embedded allyl ligand) is flexible enough to allow the perfect coordination of hindered and unhindered substrates. Reaction rates with these ligands increase because of the larger π-acceptor ability of these moieties. The ability of the phosphite moiety to accept π-electrons and enhance the S_N1 character of the nucleophilic attack increases the regioselectivity of the reactions toward the desired branched isomer in monosubstituted linear substrates. Finally, the easy synthesis of biaryl phosphites from readily available alcohols allows for simple ligand tuning as well as systematic modifications of several important ligand parameters.

Taking advantage of these features, we and others have designed highly adaptative biaryl-phosphite-containing ligands for asymmetric Pd-allylic substitution reactions. In this context, several diphosphites, phosphite-oxazolines, and phosphite-phosphoroamidites have recently emerged as extremely effective ligands for this process. Using a broad range of mono- and disubstituted hindered and unhindered linear and cyclic substrates, we have obtained high activities (turnover frequencies up to 22 000 mol substrate $\times$ (mol Pd $\times$ h)$^{-1}$) unprecedented in the literature along with excellent regio- (up to 99%) and enantioselectivitites (up to >99%) at low catalyst loadings (turnover numbers up to 10 000 mol substrate $\times$ (mol Pd $\times$ h)$^{-1}$). Appropriate ligand tuning allows access to both enantiomers of the substitution products.

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1. Introduction

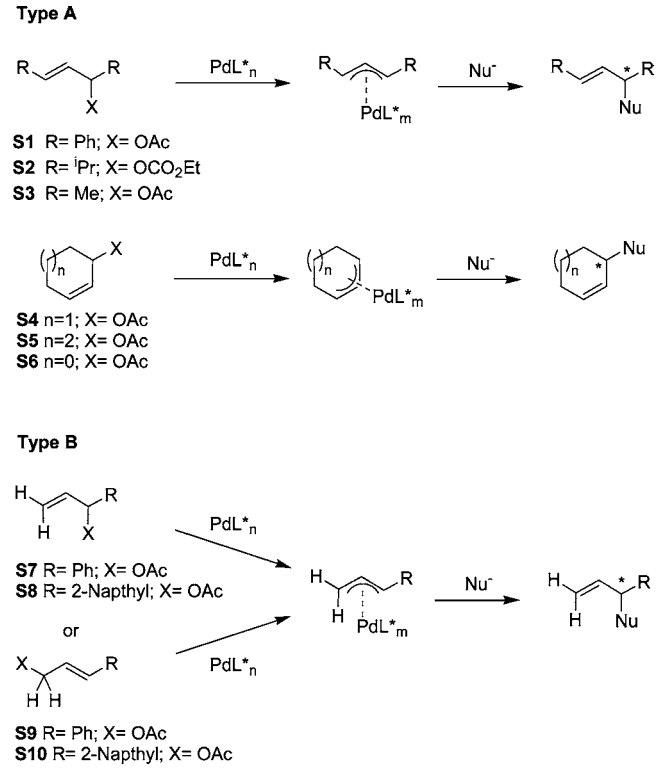
The development of methods for enantioselective formation of carbon−carbon and carbon−heteroatom bonds is one of the key issues in organic synthesis. A versatile method for achieving this is asymmetric palladium-catalyzed allylic substitution with several stabilized nucleophiles.[1] Scheme 1 shows two important classes of allylic substitutions that can be carried out enantioselectively with chiral catalysts. Type A reactions start from a racemic substrate (linear or cyclic) and proceed via symmetrical allyl systems. In this case, the enantioselectivity is determined by the regioselectivity of nucleophilic attack and therefore depends on the ability of the chiral ligand to differentiate between the two allylic termini.[1] In type B reactions, racemic or prochiral substrates possessing two identical geminal substituents at one of the allylic termini react via π-allyl intermediate which can isomerize via the well-established $\pi-\sigma-\pi$ mechanism.[1] In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition step.[1] For these latter substrates, not only does the enantioselectivity of the process need to be controlled, but the regioselectivity is also a problem because a mixture of regioisomers may be obtained. Most Pd-catalysts developed to date favor the formation of an achiral linear product rather than the desired branched isomer.[1] Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge. In contrast to Pd-catalytic systems, Ir-, Ru-, W-, and Mo-catalysts provide very high selectivity for the attack at the nonterminal carbon to give the chiral product.[1,2]

Most of the successful ligands reported to date for this process have been designed using three main strategies. The first one, developed by Hayashi and co-workers, was the use of a secondary interaction of the nucleophile with a side chain of the ligand to direct the approach of the nucleophile to one of the allylic terminal carbon atoms.[3] The second one, developed by Trost and co-workers, was to increase the ligand's bite angle in order to create a chiral cavity in which the allyl system is perfectly embedded. This idea paved the way for the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[1,4] The third strategy, developed by groups led by Helmchen, Pfaltz, and Williams, was the use of heterodonor ligands that result in an electronic discrimination of the two allylic terminal carbon atoms due to the different *trans* influences of the donor groups.[1,5] This made it possible to successfully use a wide range of heterodonor ligands (mainly P,N-ligands) in allylic substitution reactions.[1]

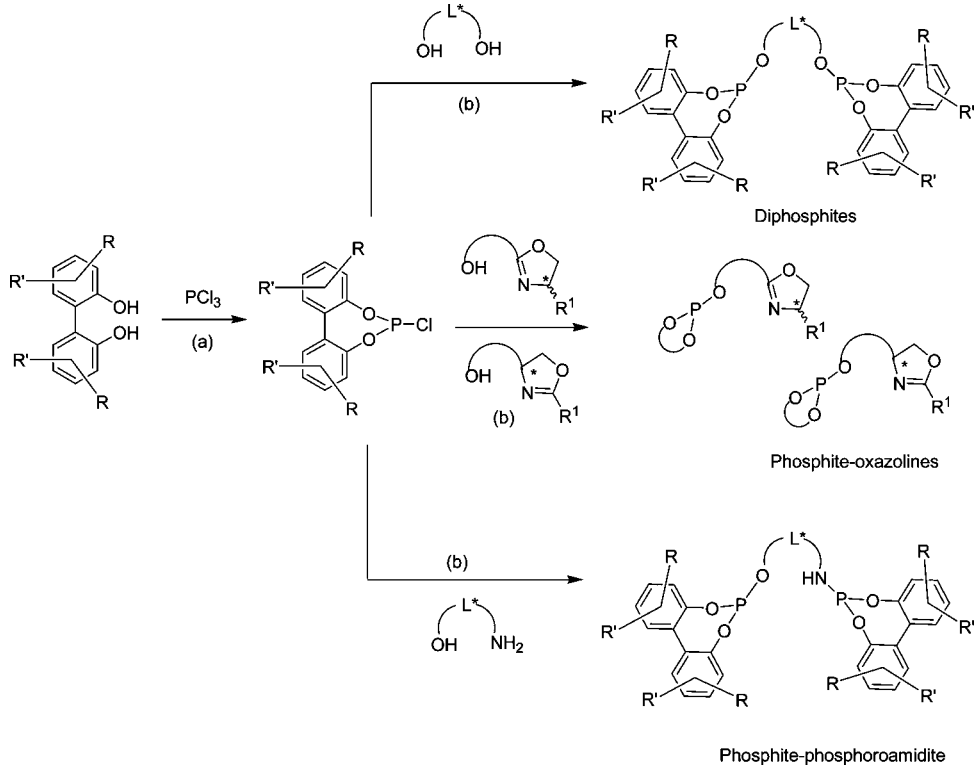
Nowadays, many chiral ligands (mainly P- and N-ligands) which possess either C_2 or C_1 symmetry have been developed, and they provide high enantiomeric excesses for several types of disubstituted substrates.[1] Nevertheless, in general, there is still a problem of reaction rates and substrate specificity (for example, ee's are high in disubstituted linear hindered substrates and low in unhindered substrates, and vice versa). Other types of substrates still require much attention. For example, for monosubstituted substrates, more active and more regio- and enantioselective Pd-catalysts are needed.[1] Therefore, more research is required on the development of new ligands that can overcome these limitations.

In this context, the authors of this study and others recently demonstrated that the presence of biaryl phosphite moieties in ligand design is highly advantageous, since (1) substrate specificity decreases because the chiral pocket created (the chiral cavity in which the allyl ligand is embedded) is flexible enough to enable the perfect coordination of hindered and unhindered substrates,[6] (2) reaction rates increase thanks to the larger π-acceptor ability of these moieties,[7] and (3) regioselectivity toward the desired branched isomer in monosubstituted linear substrates increases thanks to the π-acceptor ability of the phosphite moiety that

SCHEME 1. Two Classes of Asymmetric Allylic Substitution Reactions



SCHEME 2. General Route for the Synthesis of Diphosphite, Phosphite-Oxazoline, and Phosphite-Phosphoroamidite Ligands



enhances the S_N1 character of the nucleophilic attack.[8] In recent years, we and others have designed highly adaptative biaryl-phosphite-containing ligands for asymmetric Pd-allylic substitution reactions. In this context, several diphosphites, phosphite-oxazolines, and phosphite-phosphoroamidites have recently emerged as extremely effective ligands for this process.

This Account discusses the application of homo- and heterodonor biaryl-containing phosphites as new versatile and highly effective ligands in the Pd-catalyzed asymmetric allylic substitution of several substrate types. Diphosphite,[7b,c,9] phosphite-oxazoline,[6a,b,8,10] and phosphite-phosphoroamidite[11] are presented separately, and a summary of the steps involved in the synthesis of these ligands is given.

2. Synthesis of Homo- and Heterodonor Biaryl-Phosphite-Containing Ligands

Despite phosphites having emerged in the 1990s as successful ligands in many transition-metal-catalyzed reactions (i.e., hydroformylation,[12] hydrogenation,[13] and conjugate additions,[14] among others), their potential as highly efficient ligands in Pd-catalyzed allylic substitution reactions was not discovered until very recently. As well as the previously mentioned advantages of ligands containing biaryl phosphites for this process, phosphites are extremely attractive from a synthetic point of view: they are easy to prepare from readily available alcohols.[15] The availability of many alcohols makes simple ligand tuning possible, allowing the synthesis of many series of chiral ligands that can be screened in the search for high activity and selectivity. Another advantage of phosphite ligands is that they are less sensitive to air and other oxidizing agents than phosphines. On the other hand, phosphites are prone to decomposition reactions such as hydrolysis, alcoholysis, and the Arbuzov reaction. These side reactions can be suppressed, however, when bulky aryl phosphites are used.[15]

In general, biaryl diphosphite, phosphite-oxazoline, and phosphite-phosphororamidite ligands are synthesized very efficiently in two steps from the corresponding alcohols (Scheme 2). The first step is common for all of them. It consists of the formation of the corresponding biaryl phosphorochloridite, usually by reaction of a biaryl alcohol with PCl_3 and a base (Scheme 2, step (a)). This phosphorochloridite then reacts with the corresponding diol, hydroxyl-oxazoline or aminoalcohol in basic media to form the desired diphosphite,[7b,c,9c,16] phosphite-oxazoline[6a,b,8,10] or phosphite-phosphoroamidite[11,17] ligands, respectively (Scheme 2, step (b)). In general, biaryl-phosphite-containing ligands are stable during purification in an atmosphere of argon and isolated as white solids. They are stable at room temperature and very stable to hydrolysis.[18]

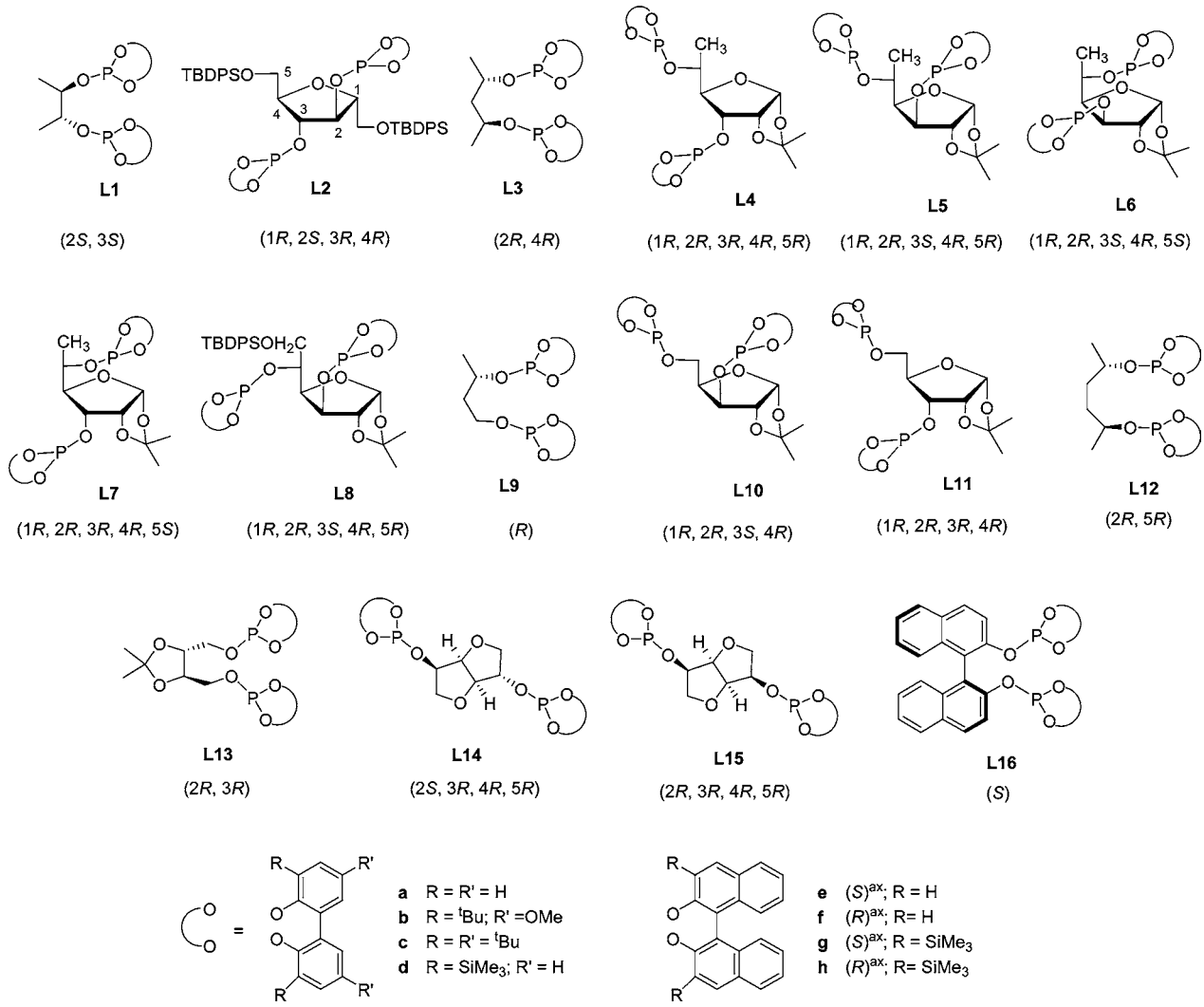


FIGURE 1. Diphosphite ligands **L1**−**L16a**−**h**.

3. Application of Diphosphite Ligands

In recent years, several biaryl diphosphite ligands have been applied in the Pd-catalyzed allylic substitution reactions of several substrates types (Scheme 1). Figure 1 shows the most representative ligands applied to this process.[7b,c,9] These ligands have been designed to ensure systematic modifications of several ligand parameters which are known to have an important effect in this process. Therefore, the effects of the ligand backbone, the length of the bridge, and the substituents/configurations of the biaryl moieties on activities and enantioselectivities have been studied.

With the purpose of fully investigating all these effects, this Account first presents the application of diphosphite ligands **L1**−**L16a**−**h** in the Pd-catalyzed allylic substitution of 1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) with dimethyl malonate and benzylamine as nucleophiles. **S1** was chosen as a standard test substrate because the reaction was performed with all the diphosphite ligands shown in Figure 1. This enabled the efficiency of the various ligand systems to be compared directly. The most representative results are shown in Table 1. Unprecedented high activities (TOFs up to 22 000 mol **S1** × (mol Pd × h)$^{-1}$) and enantioselectivities (ee's up to >99%) were obtained. The results indicated that enantioselectivities were highly affected by the length of the bridge, the ligand backbone, and the substituents/configurations of the biaryl moieties (**a**−**h**). It is worthy of note that the best results were obtained with the ligands that contain a furanoside backbone. Catalytic performance in the Pd-catalyzed allylic amination of **S1** followed the same trend as that for the allylic alkylation of **S1** (i.e., Table 1, entry 24).[19] Although, as expected, the activities were lower than those in the alkylation reaction of **S1**, they were much higher than those obtained with other homodonor ligands.[1]

TABLE 1. Selected Results for the Pd-Catalyzed Allylic Substitution of **S1** Using Diphosphite Ligands **L1**−**L16a**−**h**[a]

entry	ligand	% conv (min)[b]	% ee[c]	entry	ligand	% conv (min)[b]	% ee[c]
1	**L1c**	100 (30)	80 (*R*)	13	**L6c**	100 (5)	15 (*R*)
2[d]	**L2c**	100 (30)	98 (*S*)	14	**L7c**	100 (5)	29 (*R*)
3	**L3c**	100 (5)	94 (*R*)	15	**L8c**	100 (5)	61 (*S*)
4	**L4c**	100 (5)	45 (*R*)	16	**L9c**	93 (5)	73 (*R*)
5	**L5a**	13 (5)	31 (*S*)	17	**L10c**	21 (5)	97 (*S*)
6	**L5b**	100 (5)	96 (*S*)	18	**L11c**	18 (5)	13 (*R*)
7[d,e]	**L5c**	100 (5)	98 (*S*)	19	**L12c**	100 (30)	10 (*S*)
8	**L5d**	74 (5)	98 (*S*)	20	**L13c**	100 (30)	3 (*S*)
9	**L5e**	13 (5)	16 (*R*)	21	**L14c**	60 (30)	49 (*S*)
10	**L5f**	14 (5)	21 (*S*)	22	**L15c**	87 (30)	30 (*S*)
11	**L5g**	72 (5)	97 (*S*)	23	**L16c**	30 (30)	41 (*R*)
12	**L5h**	44 (5)	83 (*R*)	24[f]	**L5c**	100 (45)	99 (*R*)

[a] Reactions carried out at 1 mol % Pd using dimethyl malonate as nucleophile in dichloromethane at room temperature. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excess (ee) measured by chiral HPLC. [d] TON up to 10 000. [e] At 5 °C, it provides 100% conversion in 7 min and >99% ee. [f] Using benzylamine as nucleophile.

The influence of the bridge length was studied with diphosphite ligands **L1** and **L2**, which have two carbon atoms in the bridge, **L3**−**L11**, which have three carbon atoms in the bridge, and **L12**−**L16**, which have four carbon atoms in the bridge. In general, ligands which have two and three carbon atoms in the bridge provided higher enantioselectivities than ligands which have four carbon atoms in the bridge (i.e., Table 1, entries 1, 3, and 19).

The influence of the ligand backbone indicates that increasing the rigidity of the ligand is beneficial. Thus, for 1,2-diphosphite ligands, the introduction of a more rigid furanoside backbone showed higher enantioselectivity (Table 1, entries 1 vs 2). Similar behavior was observed for the 1,3-diphosphites (entries 3 and 16 vs 7 and 17, respectively) and 1,4-diphosphite ligands (entries 19 and 20 vs 21 and 22, respectively). It should be noted that for 1,3-furanoside diphosphites (**L4**−**L8** and **L10**−**L11**) it was also found that catalytic performance was affected by the substituent at C-5 and the configurations of carbon atoms C-3 and C-5 of the furanoside backbone. Therefore, the best activities and enantioselectivities were obtained using glucofuranoside ligands **L5**, which combine the presence of a methyl substituent at C-5 with an *S*-configuration at C-3 and an *R*-configuration at C-5 (entries 7 vs 4, 7, 13−15, and 17−18).

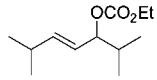
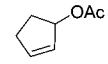
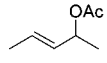
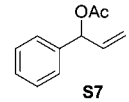
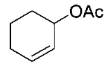
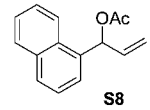
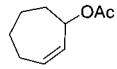
Regarding the effect of the substituents at the biaryl phosphite moiety, it was found that the presence of bulky substituents (either ^{t}Bu or $SiMe_3$ groups) at the *ortho* positions is highly beneficial in terms of enantioselectivity (Table 1, entries 6−8 vs 5). However, substituents in the *para* positions also play a small but crucial role (entries 6 and 8 vs 7). Therefore, the best activities and enantioselectivies were obtained using *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl phosphite moieties. Finally, with ligands **L5g** and **L5h**, which contain different bulky enantiomerically pure binaphthyl moieties, it was found that there is a cooperative effect between the configuration of the biaryl moiety and the configuration of the ligand backbone on enantioselectivity. This led to a matched combination for ligand **L5g**, which contains *S*-binaphthyl moieties (entries 11 and 12). In addition, by comparing the results obtained using ligand **L5d** with those of the related binaphthyl ligands **L5g** and **L5h** (entries 7 vs 11 and 12), it can also be concluded that the atropoisomeric biphenyl moieties in ligands **L5b**−**d** adopt an *S*-configuration when coordinated in the Pd-π-allyl intermediate species.

Diphosphite ligands **L1**−**L16a**−**h** were also tested in the allylic alkylation of more challenging disubstituted linear and cyclic substrates (Scheme 1, **S2**−**S6**).[7b,9c] These substrates show different steric requirements. Therefore, if enantioselectivities have to be high, the ligand has to be able to tune adequately the size of the chiral pocket to enable the perfect coordination of hindered and unhindered substrates. Thus, for the more sterically hindered linear substrate **S2**, the chiral pocket created by the Pd-catalysts needs to be bigger than that for the unhindered linear **S3** and cyclic **S4**−**S6** substrates. The vast majority of the successful Pd-catalysts reported are unable to tune the chiral pocket as required for each substrate, and therefore, they can only provide high ee's for one type of substrate: hindered or unhindered.[1] The results using diphosphites **L1**−**L16a**−**h** indicated that the ligand backbone and the flexibility of the biaryl phosphite moieties play an important role in controlling the size of the chiral pocket to achieve high versatility. Therefore, ligand **L5c**, which combines the glucofuranoside backbone with tetra-*tert*-butyl-biphenyl phosphite moieties, emerged as a privileged structure providing unprecedented high enantioselectivities for both hindered (ee's up to >99%) and unhindered substrates (ee's up to 96%) (Table 1, entry 7 and Table 2 entries 1, 2, 4, 6, and 7).[7b]

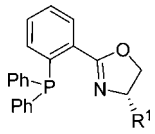
Finally, diphosphite ligands **L1**−**L16a**−**h** were also applied to the asymmetric Pd-catalyzed allylic substitution of monosubstituted substrates **S7** and **S8** (Table 2). Again, ligand **L5c** provided the best results.[7b,9c] Unfortunately, the regioselectivity for the branched products was not high. However, high enantioselectivities can be obtained by increasing the size of the substrate substituent. Ligand **L5c** provided 95% ee for substrate **S8** but only 29% ee for substrate **S7** (entries 9 vs 8). Also of note are the high activities (TOFs up to >600 mol $\times$ (mol Pd $\times$ h)$^{-1}$) observed for these substrates.[7b]

In summary, **L5c** has emerged as a privileged ligand thanks to the presence of the adaptative biaryl phosphite moieties which are able to control the size of the chiral pocket as

TABLE 2. Summary of the Best Results for the Pd-Catalyzed Allylic Substitution of **S2**−**S8** Using Diphosphite Ligands[a]

Entry	Substrate	Ligand	% ee[b]	Entry	Substrate	Ligand	% ee[b]
1	 **S2**	**L5c**	95 (*R*)	7[c]	 **S6**	**L5c**	81 (*S*)
2[c]	 **S3**	**L5c**	85 (*R*)	8[d]	 **S7**	**L5c**	29 (*S*)
3[c]	 **S4**	**L3c**	92 (*S*)	9[e]	 **S8**	**L5c**	95 (*S*)
4[c]		**L5c**	95 (*S*)				
5[c]		**L6c**	95 (*R*)				
6[c]	 **S5**	**L5c**	96 (*R*)				

[a] Reactions carried out at 1 mol % Pd at room temperature. [b] Enantiomeric excess. [c] At −20 °C. [d] Branched/linear = 24/76. [e] Branched/linear = 34/66.



PHOX ligands

FIGURE 2. Phosphine-oxazoline PHOX ligands.

required by each substrate type, and therefore, it provides high enantioselectivities.

4. Application of Phosphite-Oxazoline Ligands

Most chiral ligands developed for asymmetric Pd-catalyzed allylic substitution are mixed phosphorus−nitrogen ligands. Mixed phosphine-oxazoline ligands have played a dominant role among the P,N-ligands.[1] In this context, one of the most important series of ligands developed is the phosphine-oxazolines PHOX (Figure 2).[1e,5]

Despite the advantage of phosphite ligands in asymmetric catalysis, the application of phosphite-oxazoline ligands in this process has been scarce.[6a,b,8,10] Figure 3 shows the most representative biaryl phosphite-oxazoline ligands applied to the asymmetric Pd-catalyzed allylic substitution reactions.

The first successful application of phosphite-oxazoline ligands (**L17**−**L19a**,**e**,**f**) (Figure 3) in this process was achieved by Pfaltz and Prétôt.[8] Ligands **L17**−**L19a**,**e**,**f** were designed to overcome the problem of regioselectivity in the allylic alkylation of monosubstituted linear substrates **S7**−**S10** (Scheme 1). Pfaltz and Prétôt found that regio- and enantioselectivities were affected by substituents in the oxazoline moiety and by the substituents/configuration of the phosphite moiety. The best results were obtained with ligand **L18e**, which provides an excellent combination of regioselectivities (up to 95%) in the desired branched isomer and enantioselectivities (up to 94%). The success of these ligands is due to the combination of two ligand parameters that direct the nucleophilic attack to the most substituted allyl terminus (Scheme 3).[8] The first one is the π-acceptor capacity of the phosphite moiety, which enhances the SN1 character of the nucleophilic attack. The second one is the introduction of bulky biaryl phosphite moiety which shifts the equilibrium to the desired Pd-**A** allyl intermediate. Despite this success, these ligands produced moderate results for hindered (ee's up to 60% for **S1**) and unhindered (ee's up to 70% for **S4**) disubstituted substrates.[10b]

With the aim of finding a more versatile phosphite-oxazoline ligand, a decision was made to take one of the most successful ligand families for this process, the phosphine-oxazoline PHOX ligands, and replace the phosphine group

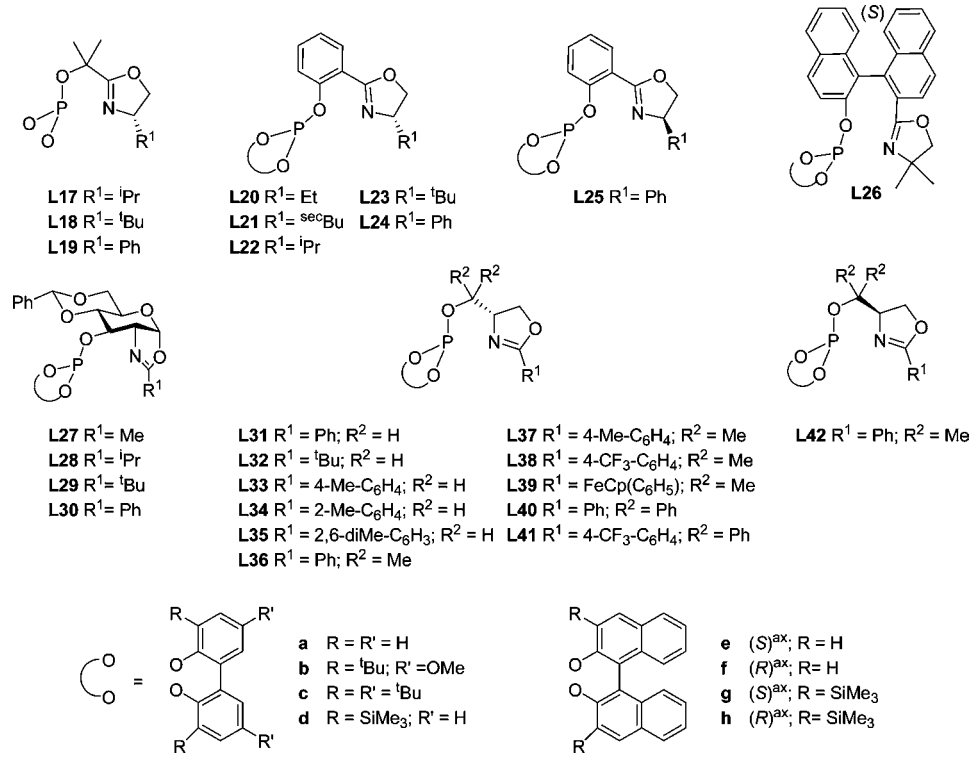
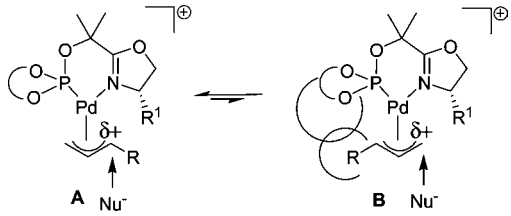


FIGURE 3. Phosphite-oxazoline ligands **L17**−**L42a**−**h**.

SCHEME 3. Key Pd-Allyl Intermediates Containing Monosubstituted Substrates



with a bulky diphenyl phosphite moiety (Figure 3, ligands **L20**−**L25a**−**d**).[6a,10d] The application of these **L20**−**L25a**−**d** ligands in the asymmetric Pd-catalyzed allylic substitution reactions was very successful. Therefore, excellent activities (TOFs > 2400 mol substrate × (mol Pd × h)$^{-1}$), regio- (up to 99%), and enantioselectivities (ee's up to >99%) were obtained for hindered and unhindered disubstituted and also monosubstituted substrates (Figure 4). It is noteworthy that these ligands show higher versatility than their phosphine-oxazoline PHOX analogues. These excellent results are in line with the presence of a π-acceptor flexible bulky biphenyl phosphite moiety that allows the creation of a more flexible chiral pocket and enhances the S_N1 character of the nucleophilic attack.

The results indicate that the enantioselectivity is affected by the substituents in the oxazoline and in the biphenyl phosphite moieties. As observed for diphosphites, the best enantioselectivities are obtained using a bulky tetra-*tert*-butylbiphenyl phosphite moiety. It should be noted that the choice of the right oxazoline substituent depends on the substrate. Thus, for hindered substrates, a phenyl substituent is required, while for unhindered substrates more sterically demanding substituents (^{t}Bu or ^{i}Pr) are needed. Also of note is the fact that both enantiomers of the substitution products can be obtained by simply changing the configuration of the oxazoline substituent (i.e., ligands **L24** and **L25**).

Following these significant contributions come the developments of three new biaryl phosphite-oxazoline ligand libraries. The first of these, developed by Gladiali and co-workers, described the application of chiral (*S*)-binaphtalene-core ligands **L26e**−**f** (Figure 3) in the Pd-catalyzed asymmetric allylic substitution of **S1**, albeit with moderate results (100% conv, ee's up to 43% in 7 h).[10c]

The second contribution reported the development of a pyranoside phosphite-oxazoline ligand library **L27**−**L30a**−**d** (Figure 3).[6b] These ligands are easily prepared from readily available D-glucosamine. 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 were maximized for each substrate. The results indicate that 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

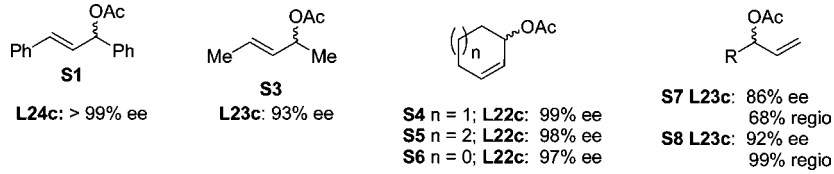


FIGURE 4. Summary of the best results obtained in the Pd-catalyzed allylic substitution of **S1**−**S8** using ligands **L20**−**L25a**−**d**.

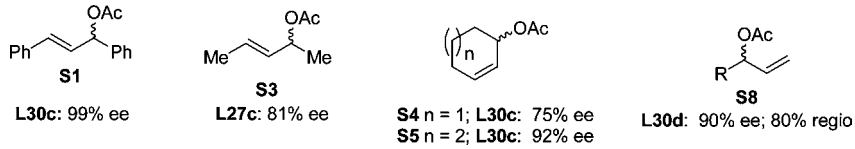


FIGURE 5. Summary of the best results obtained in the Pd-catalyzed allylic substitution of **S1**−**S8** using ligands **L27**−**L30a**−**d**.

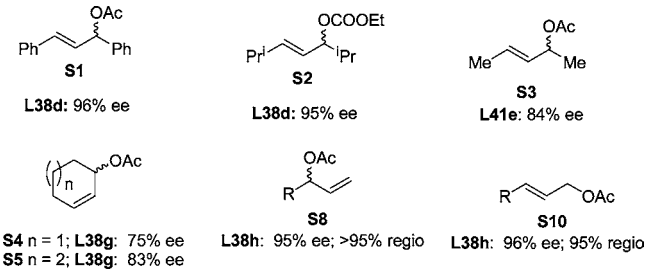


FIGURE 6. Summary of the best results obtained in the Pd-catalyzed allylic substitution of **S1**−**S10** using ligands **L31**−**L42a**−**h**.

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 (TONs up to 10 000 mol substrate × (mol Pd × h)$^{-1}$)[20] have been achieved in a broad range of mono- and disubstituted linear hindered and unhindered linear and cyclic substrates (Figure 5). In addition, the efficiency of this ligand design is corroborated by the fact that these Pd-phosphite-oxazoline catalysts provided higher enantioselectivity than their phosphinite-oxazoline analogues[21] in several substrate types.

The third contribution appeared more recently and reported the synthesis and screening of a highly modular phosphite-oxazoline ligand library **L31**−**L42a**−**h** in the Pd-catalyzed allylic substitution reactions of several substrate types (Figure 3).[10e] This series of ligands can be prepared efficiently from accessible hydroxyl amino acid derivatives. Their modular nature enables the substituents/configurations in the oxazoline moiety, alkyl backbone chain, and biaryl phosphite moiety to be systematically varied. By selecting the ligand parameters, therefore, high regio- and enantioselectivities (ee's up to 99%) have been achieved in a broad range of mono- and disubstituted linear hindered and unhindered linear and cyclic substrates (Figure 6). In addition, for substrates **S1**, **S2**, **S8**, and **S10**, both enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configuration of the alkyl backbone chain or the absolute configuration of the biaryl phosphite moiety.

Study of the Pd-allyl intermediates indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite moiety.[10e] This study makes it possible to understand the catalytic behavior observed. Therefore, the Pd-1,3-diphenylallyl and 1,3-cyclohexenylallyl intermediates indicate that, for enantioselectivities to be high, the ligand parameters 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 monodentated fashion. However, for the Pd-1,3-dimethylallyl intermediates, the difference in enantioselectivity observed cannot be explained by the reactivity of the nucleophile versus the different π-allyl intermediates. A plausible explanation can be found in the enhancement of the steric interaction upon attack of the nucleophile.

5. Application of Phosphite-Phosphoroamidite Ligands

Despite phosphite and phosphoroamidite ligands being successfully used in asymmetric catalysis,[22] the use of phosphite-phosphoroamidite ligands, which combines the advantages of both ligand types, has been scarce.[17] To the best of our knowledge, there are only two families of phosphite-phosphoroamidite ligands applied to this process (Figure 7).[11]

These two families emerged with the purpose of solving the two main problems observed using the previous diphosphite ligands **L1** and **L10**−**L11** (Figure 1): (a) the low regioselectivity obtained for monosubsituted substrates and (b) the low substrate versatility.[23] Therefore, bearing in mind the high versatility, regio-, and enantioselectivities induced by mixed bidentate P,N-donor ligands in this process,[1] it was decided that one of the phosphite moieties on diphosphites **L1** and

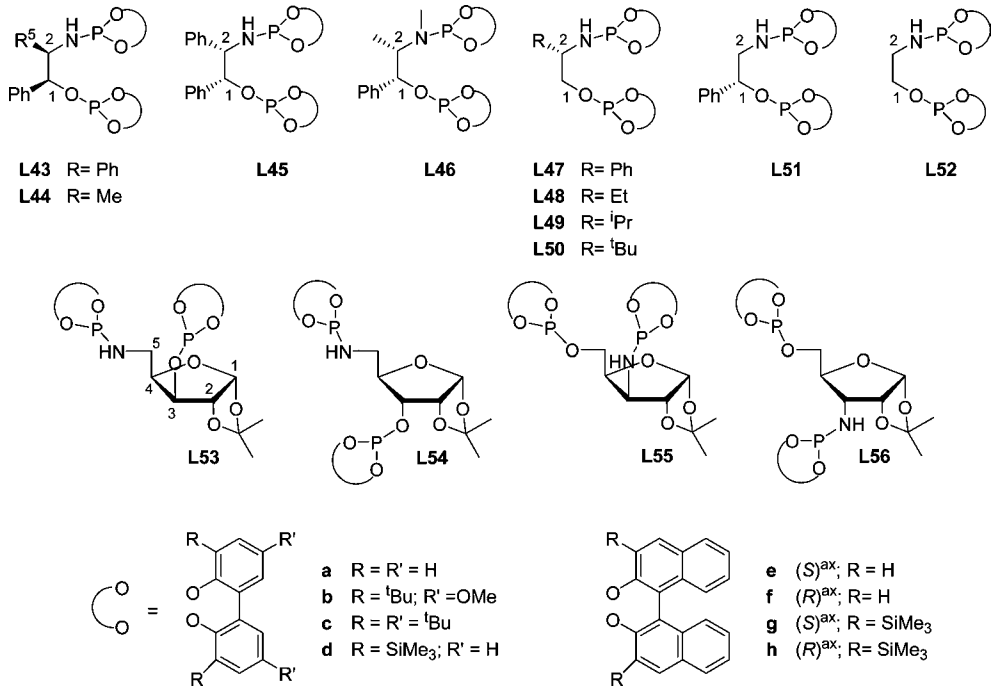


FIGURE 7. Phosphite-phosphoroamidite ligands **L43**−**L56a**−**h**.

L10−**L11** should be replaced by a biaryl phosphoroamidite group. This phosphite-phosphoroamidite ligand design therefore offers the opportunity of an electronic differentiation while maintaining a similar spatial disposition around the metal center. Moreover, the high activities obtained with diphosphite ligands[7b,c,9] are expected to be maintained in these phosphite-phosphoroamidite ligands because the phosphoroamidite moiety is also a good π-acceptor group.[7a]

For the phosphite-phosphoroamidite ligands **L43**−**L52a**−**h** (Figure 7), higher enantioselectivities (ee's up to 99%) than those for related 1,2-diphosphite **L1** and similar high activities (TOFs up to >800 mol substrate × (mol Pd × h)$^{-1}$) were achieved in a wider range of substrates by selecting the substitutents/configurations in the aminoalcohol backbone (C-1 and C-2), the amino group, and the biaryl phosphite moiety (Figure 8).[11c,d] It should be noted that both enantiomers of the product can be obtained with high ee's simply by changing either the absolute configuration of the biaryl moieties or the absolute configuration of the amino alcohol unit. Also of worthy note is that these ligands can be prepared in one step from readily available chiral 1,2-amino alcohols.

For furanoside phosphite-phosphoroamidite ligands **L53**−**L56a**−**h** (Figure 7), by correctly combining the ligand parameters (position of the phosphoroamidite group, configuration of C-3 of the furanoside backbone, and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties), high regio- and enantioselectivities (ee's up to 98%)

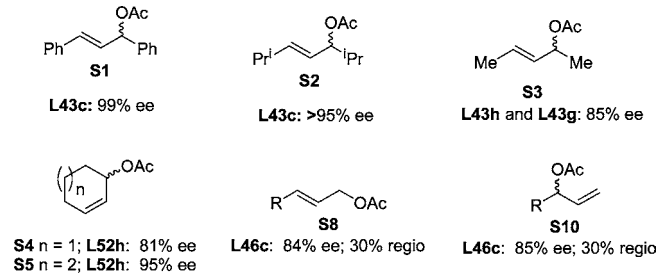


FIGURE 8. Summary of the best results obtained in the Pd-catalyzed allylic substitution of **S1**−**S10** using ligands **L43**−**L52a**−**h**.

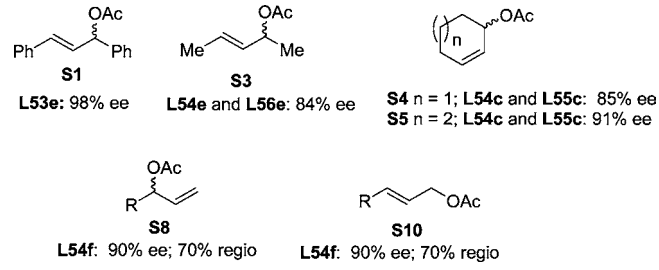


FIGURE 9. Summary of the best results obtained in the Pd-catalyzed allylic substitution of **S1**−**S10** using ligands **L53**−**L56a**−**h**.

and good activities (TOFs > 2000 mol substrate × (mol Pd × h)$^{-1}$) were achieved in a broad range of mono- and disubstituted hindered and unhindered substrates (Figure 9).[11a,b] It should be noted that, for substrates **S3**−**S5**, both enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configura-

tion of C-3 or the position of the phosphoroamidite group. In addition, the efficiency of this ligand design is also corroborated by the fact that these Pd-phosphite-phosphoroamidite catalysts provided higher enantioselectivity than their diphosphite analogues in several substrate types and overcame the drawback of low regioselectivities in Pd-allylic substitution of monosubstituted substrates **S8** and **S10** using diphosphites analogues and the previous phosphite-phosphoroamidite **L43**−**L52a**−**h** ligands.

Study of the Pd-allyl intermediates in both families indicated that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphoroamidite moiety.[11b,d] It also showed that, for enantioselectivities to be high, the ligand parameters need to be correctly combined in order to increase the electronic differentiation between the most electrophilic allylic terminus carbon atoms of the isomers formed and/or also predominantly form the isomer that reacts faster with the nucleophile.

6. Conclusions

Biaryl-phosphite-containing ligands have undoubtedly become some of the most versatile ligands for enantioselective Pd-catalyzed substitution reactions. Biaryl phosphites offer several advantages as a ligand scaffold for this process: (a) the flexibility offered by the biaryl phosphite moiety increases versatility; (b) the π-acceptor character of the phosphite moiety increases reaction rates and regioselectivity on monosubstituted substrates; and (c) their easy synthesis from readily available alcohols makes simple ligand tuning possible and enables systematic modifications of several ligand parameters which are known to have an important effect for this process. Therefore, by appropriate ligand tuning, a ligand can be selected for each substrate type and both enantiomers of the product are accessible. The excellent results obtained together with their facile synthesis are expected to lead to new designs of phosphite ligands for this process and to expand the range of substrates to be studied. This will lead to many other applications in forthcoming years.

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BIOGRAPHICAL INFORMATION

Montserrat Diéguez studied chemistry at the Rovira i Virgili University in Tarragona (Spain), where she received her Ph.D. in 1997 working in the group of Prof. C. Claver. After 1 year as a postdoctoral fellow with Prof. R. H. Crabtree at Yale University, in New Haven, CT, she returned to Tarragona in 1999. She is currently working as associate professor at the Rovira i Virgili University. Her present research is focused on organometallic chemistry, mainly the synthesis of chiral ligands and asymmetric catalysis using a combinatorial approach.

Oscar Pàmies obtained his Ph.D. in Prof. Carmen Claver's group in 1999 at the Rovira i Virgili University. After 3 years of postdoctoral work in the group of Prof. J.-E. Bäckvall at the Department of Organic Chemistry at Stockholm University, he returned to Tarragona in 2002. He is currently working as associate professor at the Rovira i Virgili University. His research interests are asymmetric catalysis, organometallic chemistry, and combinatorial synthesis.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: montserrat.dieguez@urv.cat.

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19 The stereoselectivity of the amination was the same as that for the alkylation reaction, though the CIP descriptor was inverted because the priority of the groups had changed.

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23 Diphosphite ligands **L1**, **L10**, and **L11** only provide good ee's for substrate **S1**. See refs 7b and 9c.