Asymmetric Transition-Metal Catalyzed Reactions
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Asymmetric Pd-catalyzed allylic substitution using a large sugar-based monophosphite ligand library. Scope and limitations.

Abstract: We have applied a modular sugar-based phosphite ligand library for the Pd-catalyzed allylic substitution reactions of several substrates. These ligands are derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose, which lead to a wide range of sugar backbones, and contain several substituents at the C-3 carbon of the furanoside backbone and several substituents/configurations in the biaryl moiety, with different steric and electronic properties. Systematic variation of the ligand parameters indicates that the catalytic performance (activities and enantioselectivities) is highly affected by sugar backbone, the substituents at the C-3 carbon of the furanoside backbone, the configurations at the C-3 and C-4 carbons of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety as well as the substrate type. For disubstituted substrates moderate enantioselectivities (up to 72%) were achieved using ligand **L8d**, while for monosubstituted substrates the highest enantioselectivities (up to 40%) were obtained using ligand **L9a**.

Keywords: asymmetric catalysis, palladium, allylic substitution, phosphite ligands

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1 Introduction

Palladium-catalyzed asymmetric allylic alkylation is a useful synthetic method for enantioselective formation of C-C bonds [1-12]. The selection of chiral ligands for highly enantioselective allylic substitution has focussed on the use of bidentate nitrogen and phosphorus donors (both homo- and heterodonors) [1-12]. Less attention has been paid to catalysts containing monodentated ligands in this process. However, in 2000, the groups of RajanBabu and Zhang obtained an enantioselectivity of 94% with catalyst precursors containing monophospholane ligands in the Pd-catalyzed allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene [13-14]. Despite this success, few monophosphorus ligands have been applied in Pd-catalyzed asymmetric allylic substitution [15-21]. This encourages further research into monophosphorus ligands to study their possibilities as a new class of ligands for this process. Some years ago, we and others discovered that the presence of biaryl phosphite moieties in ligand design is highly advantageous [9,10,22-32]. Introducing a biaryl phosphite into the ligand design was beneficial because its larger π-acceptor ability increased reaction rates and its flexibility allowed the catalyst chiral pocket to adapt to both hindered and unhindered substrates [9,10]. The presence of a biaryl phosphite moiety was also beneficial in the allylic substitution of more challenging monosubstituted substrates. Regioselectivity towards the desired branched isomer in this substrate class increased due to the π-acceptor ability of the phosphite moiety, which decreased the electron density of the most substituted allylic terminal carbon atom via the *trans* influence, thus favouring nucleophilic attack at this carbon atom[9,10,22-32].

Following our interest in modular π-acceptor ligands in this process [22-32] and encouraged by the success of monophosphorus ligands, we report here the application of a large library of chiral monophosphite ligands **L1**-**L11a**-**e** (Figure 1) in the palladium allylic substitution reaction of several

substrate types. These ligands are derived from natural D-(+)-glucose, D-(+)-galactose and D-(+)-fructose and share the same advantages of carbohydrate and phosphite ligands, such as low cost synthesis from commercially available alcohols and facile modular constructions [33-42]. In addition they are less sensitive to air than typical phosphines, which have been widely used as ligands in asymmetric catalysis. All these favourable features enabled us to synthesize and screen a series of chiral ligands in search of high activity and selectivity. Although carbohydrate-based bidentate ligands have been successfully used in some enantioselective reactions [33-42], only a few well performing monodentated chiral ligands derived from carbohydrates have been reported [13,15,43-48].

2 Results and discussion

2.1 Ligand design

The sugar-based monophosphite ligands are derived from D-(+)-glucose, D-(+)-galactose and D-(+)-fructose, which lead to a wide range of sugar backbones (**L1**, **L3** and **L9**-**L11**), and contain several substituents at the C-3 carbon of the furanoside backbone (**L2** and **L4**-**L8**) and substituents/configurations in the biaryl moiety (**a**-**e**), with different steric and electronic properties, whose effect on the catalytic performance will be studied. Therefore, ligands **L1**-**L11a**-**e** consist of chiral di-*O*-protected furanoside (ligands **L1**-**L9**) or pyranoside (ligands **L10** and **L11**) backbones, which determine their underlying structure, and one hydroxyl group. Several phosphoric acid biaryl esters (**a**-**e**) were attached to these basic frameworks (Figure 1).

We studied the effects of the stereogenic carbon atom C-3 on enantioselectivity by comparing diastereomeric ligands **L1** and **L3** and **L2** and **L4**, respectively, which have opposite configuration at C-3. The influence of the configuration of the C-4 carbon on the catalytic performance was studied using ligands **L1** and **L9** which only differ in the configuration at C-4.

We also studied the effect of a range of substituents having different electronic and steric properties at the C-3 carbon of the furanoside backbone using ligands **L2** and **L4**-**L8**.

The influence of the carbohydrate ring size on the catalytic performance of the Pd-catalysts was studied using ligands **L10**, which have a pyranoside backbone and the same configuration at the C-3 carbon than furanoside ligand **L1**. Finally, with ligands **L11** we studied how the flexibility of the ligand backbone may affect the catalytic performance. These ligands also have a pyranoside backbone like ligands **L10**, but differ from the rest of ligands in having a phosphite moiety attached to a primary alcohol, providing a more flexible ligand.

The influence of the different groups attached to the *ortho*- and *para*-positions of the biphenyl moieties on enantioselectivity was investigated using ligands **L1a**-**c**, which have the same configuration at the C-3 carbon. To determine whether there is a cooperative effect between the stereocenters of the ligand backbone and the configuration of the biaryl phosphite moieties, we prepared a series of enantiomerically pure binaphthol-based ligands **L1**-**L4d**-**e**.

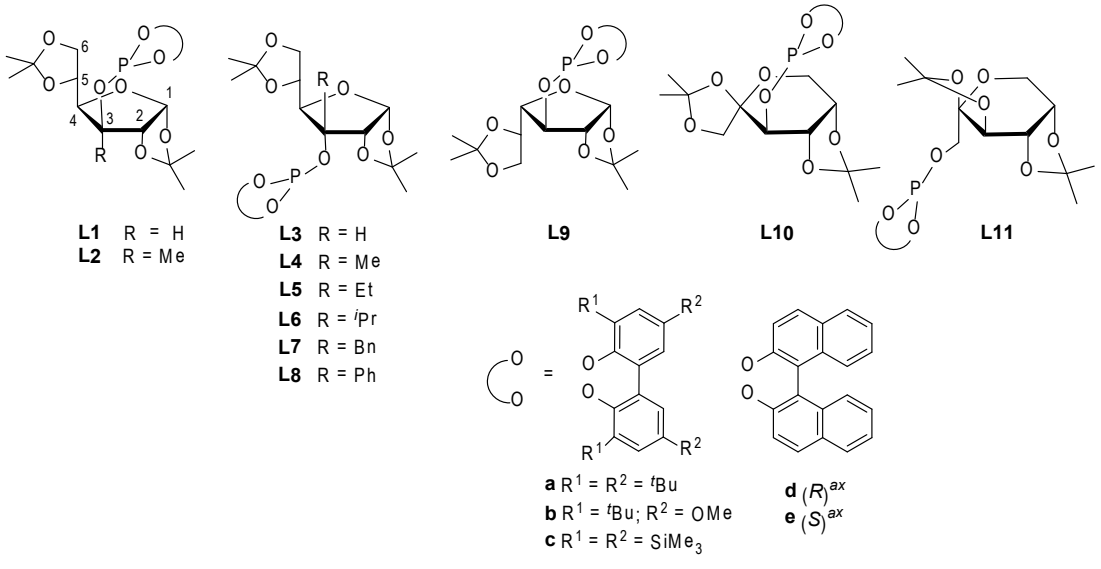


Figure 1. Sugar-based monophosphite ligand library **L1**-**L11a**-**e**.

2.2 Allylic substitution of disubstituted linear substrates

In this section, we report the use of the chiral phosphite ligand library (**L1**-**L11a**-**e**) in the Pd-catalyzed allylic alkylation (Eq. 1) of three disubstituted linear substrates with different steric properties: *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-(*E*)-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all cases, the catalysts were generated *in situ* from 0.5 mol% of π-allyl-palladium chloride dimer $[PdCl(\pi^3\text{-}C_3H_5)]_2$ and the corresponding ligand [1].

(1)

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, which is widely used as a model substrate. The effects of the solvent and the ligand-to-palladium ratio on catalytic performance were investigated using the catalyst precursor containing ligand **L1a** (Table 1). The results indicated that solvent affected catalytic performance. The optimum trade-off between enantioselectivities and activities was obtained when dichloromethane was used as a solvent (Table 1, entry 4). We next studied the effect of the ligand-to-palladium ratio. As expected the catalytic performances were best with a ligand-to-palladium ratio of 2 (Table 1, entries 4 vs 5).

Table 1: Pd-catalyzed allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene **S1** using ligand **L1a**.[a]

Entry	Solvent	L/Pd	% Conv (h)[b]	% ee[c]
1	DMF	2	100 (4)	9 (*R*)
2	Toluene	2	18 (8)	19 (*R*)
3	THF	2	45 (4)	17 (*R*)
4	CH_2Cl_2	2	84 (4)	22 (*R*)
5	CH_2Cl_2	1	79 (4)	20 (*R*)

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

Under the optimized conditions, we first evaluated the remainder of the phosphite ligands in the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**. The results, which are summarized in Table 2, indicate that the catalytic performance (activities and enantioselectivities) is highly affected by the substituents at C-3 of the furanoside backbone, the substituents/configuration of the biaryl moiety, the configuration of carbon atoms C-3 and C-4 and thering size of the sugar backbone.

The influence of the substituents/configuration of the biaryl moiety on the product outcome was investigated using ligands **L1**-**L4a**-**e** (Table 2, entries 1-16). We found that the presence of bulky substituents at the *ortho* positions of the biphenyl phosphite moiety has a negative effect on activity. The best activities were achieved when binaphthyl phosphite moieties (**d**,**e**) were present. The effect of the biaryl groups on enantioselectivity depends on the substituents attached to C-3 of the furanoside backbone. For ligands **L2** and **L4**, containing a methyl substituent at C-3, the highest enantioselectivities were achieved with an *R*-binaphthyl phosphite moiety (**d**, Table 2, entries 7 and 15). However, for ligands **L1** and **L3**, without the methyl substituent at C-3, the best enantioselectivities were achieved with ligands containing trimethylsilyl substituents at the *ortho* positions of the biphenyl phosphite moiety (**c**, Table 2, entries 3 and 11).

We next studied the effect of the substituents attached to C-3 of the furanoside backbone with ligands **L3**-**L8**. Highest enantioselectivities were obtained using ligand **L8d**, with a phenyl substituent at C-3 (Table 2, entry 20).

Comparing the results using ligands **L1** with **L3**, that only differ in the configuration at C-3, we observed that this configuration controls the sense of enantioselectivity. Accordingly, ligands **L1a**-**e** with an *S* configuration at the C-3 of the ligand backbone, gave the *R*-**1** product, while ligands **L3a**-**e** with an *R* configuration at C-3 gave *S*-**1** product (Table 2, entries 1-5 *vs* 9-13). Furthermore, comparing ligands **L1d**-**e** and **L3d**-**e**, we found a cooperative effect between the configuration of the binaphthyl phosphite moiety and the configuration at C-3, that results in a matched combination for ligand **L3d** (Table 2, entry 12).

The results also showed that ligand **L9a** with an *S* configuration at C-4 gave lower enantioselectivity than ligand **L1a** with an opposite configuration at this position (Table 2, entry 1 *vs* 21). In addition, ligands **L10** which have a pyranoside backbone gave lower yields and enantioselectivities than their analogous furanoside ligands **L1** (Table 2, entries 1-2 *vs* 22-23). Finally, the most flexible ligand **L11a**, which has the phosphite moiety attached to a primary alcohol, displayed the lowest enantioselectivity (Table 2, entry 24).

In addition to the effect of structural parameters on enantioselectivity, the reaction parameters can also be

Table 2: Pd-catalyzed allylic alkylation of linear substrates **S1**-**S3** in CH_2Cl_2 using ligands **L1**-**L11a**-**e**.[a]

Entry	Substrate	L	% Conv (h)[b]	% ee[c]	Entry	Substrate	L	% Conv (h)[b]	% ee[c]
1	**S1**	**L1a**	84 (4)	22 (*R*)	15	**S1**	**L4d**	100 (4)	37 (*S*)
2	**S1**	**L1b**	35 (4)	31 (*R*)	16	**S1**	**L4e**	40 (4)	4 (*S*)
3	**S1**	**L1c**	42 (4)	40 (*R*)	17	**S1**	**L5d**	100 (4)	36 (*S*)
4	**S1**	**L1d**	100 (4)	18 (*R*)	18	**S1**	**L6d**	42(4)	12 (*S*)
5	**S1**	**L1e**	100 (4)	19 (*R*)	19	**S1**	**L7d**	100 (4)	39 (*S*)
6	**S1**	**L2a**	48 (4)	6 (*R*)	20	**S1**	**L8d**	100 (4)	65 (*S*)
7	**S1**	**L2d**	100 (4)	12 (*R*)	21	**S1**	**L9a**	64 (4)	15 (*R*)
8	**S1**	**L2e**	100 (4)	10 (*R*)	22	**S1**	**L10a**	8 (4)	14 (*R*)
9	**S1**	**L3a**	81 (4)	20 (*S*)	23	**S1**	**L10b**	10 (4)	15 (*R*)
10	**S1**	**L3b**	31 (4)	23 (*S*)	24	**S1**	**L11a**	82 (4)	11 (*S*)
11	**S1**	**L3c**	53 (4)	41 (*S*)	25[d]	**S1**	**L8d**	29 (8)	72 (*S*)
12	**S1**	**L3d**	100 (4)	28 (*S*)	26	**S2**	**L8d**	94 (24)	66 (*R*)[e]
13	**S1**	**L3e**	100 (4)	16 (*S*)	27	**S3**	**L8d**	46 (24)	42 (*S*)[f]
14	**S1**	**L4a**	57 (4)	12 (*S*)					

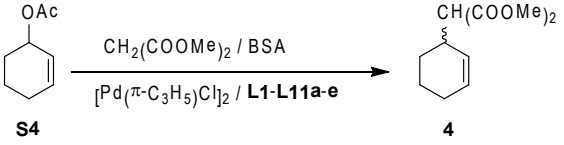
[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time shown in parentheses. [c] Determined by HPLC (Chiralcel OD).[d] T= 0°C. [e] Measured by ^1H NMR using $[Eu(hfc)_3]$. [f] Measured by GC (ChiralDex CB).

controlled to further improve selectivity. In this case, enantioselectivity was further improved (ee's up to 72%) using ligand **L8d** by lowering the reaction temperature to 0 °C (Table 2, entry 25).

We then tested ligand **L8d** (the one that provided the best result in the alkylation of **S1**) in the allylic alkylation of more hindered linear substrate **S2** and unhindered linear substrate **S3** (Eq. 1). For hindered substrate **S2**, similar enantioselectivities (66% (*R*) ee) to **S1** were achieved (Table 2, entry 26). Substrate **S3** is less sterically demanding than substrates **S1** and **S2**. The enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1** [1]. Unfortunately, the Pd-**L8d** catalytic system exhibited only moderate enantioselectivity (ee's up to 42%; Table 2, entry 27).

2.3 Allylic substitution of cyclic substrate S4

Ligands **L1**-**L11a**-**e**, were also tested in the allylic alkylation of cyclic substrate **S4** with a view to broadening the scope of their applications. Akin to unhindered linear substrate **S3**, enantioselectivity in cyclic substrates is difficult to control mainly because of the presence of less sterically demanding *anti* substituents (Eq. 2). These *anti* substituents are thought to play a crucial role in the enantioselection observed with cyclic substrates in the corresponding Pd-allyl intermediates [1].



(2)

The results are summarized in Table 3. The trend is similar to that observed for **S1**. Again, the best enantioselectivity was achieved using Pd/**L8d** catalytic system (ee's up to 44%; entry 11). As observed for linear substrates, changing the solvent from dichloromethane to other solvents did not increase enantioselectivity (Table 3, entries 11 *vs* 13-15).

2.4 Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S5** with dimethyl malonate (Eq. 3). It is not only the enantioselectivity of the process that needs to be controlled for this substrate; the regioselectivity is also a problem, since a mixture of regioisomers may be obtained.

Table 3. Selected results for the Pd-catalyzed allylic alkylation of *rac*-3-acetoxycyclohexene **S4** using ligands L1-L11a-e.[a]

Entry	Solvent	Ligand	% Conv (h)[b]	% ee[c]	Entry	Solvent	Ligand	% Conv (h)[b]	% ee[c]
1	CH_2Cl_2	**L1a**	19 (24)	11 (*R*)	9	CH_2Cl_2	**L4d**	54 (24)	29 (*S*)
2	CH_2Cl_2	**L1d**	39 (24)	9 (*R*)	10	CH_2Cl_2	**L4e**	62 (24)	7 (*S*)
3	CH_2Cl_2	**L1e**	47 (24)	6 (*R*)	11	CH_2Cl_2	**L8d**	49 (24)	44 (*S*)
4	CH_2Cl_2	**L2d**	52 (24)	7 (*R*)	12	CH_2Cl_2	**L9a**	100 (24)	2 (*R*)
5	CH_2Cl_2	**L2e**	48 (24)	9 (*R*)	13	DMF	**L8d**	84 (24)	8 (*S*)
6	CH_2Cl_2	**L3a**	11 (24)	9 (*S*)	14	THF	**L8d**	27 (24)	37 (*S*)
7	CH_2Cl_2	**L3d**	100 (24)	8 (*S*)	15	Toluene	**L8d**	12 (24)	32 (*S*)
8	CH_2Cl_2	**L3e**	100 (24)	2 (*S*)					

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2 mol% ligand, room temperature, 30 min; 3 equiv. of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of the corresponding base, room temperature. [b] Measured by GC. Reaction time shown in parentheses. [c] Determined by GC (ChiralDex

Most Pd-catalysts developed to date favor the formation of the achiral linear product **6** rather than the desired branched isomer **5**. Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge [22,25,31,49,50].

The results obtained with the phosphite ligands are summarized in Table 4. Unfortunately, the enantioselectivities (ee's up to 40%) were not high. However, good regioselectivities (up to 80%) have been obtained [51]. The results indicated that in order to have high regioselectivity, bulky substituents at the *ortho* positions of the biaryl phosphite moiety (i.e. entries 1-3 vs 4-5) and a furanoside backbone with an *R* configuration at C-4 (ligands **L1**-**L4a**-**c**) are necessary. However, enantioselectivities were best for furanoside ligand **L9a** with *S* configurations at both C-3 and C-4 of the furanoside backbone (entry 21).

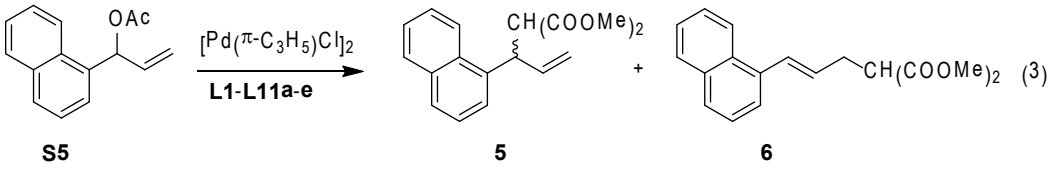


Table 4. Pd-catalyzed allylic alkylation of **S5** in CH_2Cl_2 using ligands **L1-L11a-e**.[a]

Entry	L	% Conv (h)[b]	5/6[b]	% ee[c]	Entry	L	% Conv (h)[b]	5/6[b]	% ee[c]
1	**L1a**	100 (6)	75/25	9 (*R*)	13	**L3e**	100 (6)	25/75	3 (*S*)
2	**L1b**	100 (6)	80/20	7 (*R*)	14	**L4a**	100 (6)	75/25	6 (*R*)
3	**L1c**	100 (6)	80/20	18 (*R*)	15	**L4d**	100 (6)	20/80	12 (*R*)
4	**L1d**	100 (6)	35/65	17 (*S*)	16	**L4e**	100 (6)	30/70	8 (*R*)
5	**L1e**	100 (6)	20/80	0	17	**L5d**	100 (6)	25/75	14 (*R*)
6	**L2a**	100 (6)	80/20	9 (*R*)	18	**L6d**	64 (6)	30/70	6 (*R*)
7	**L2d**	100 (6)	40/60	15 (*R*)	19	**L7d**	97 (6)	25/75	18 (*R*)
8	**L2e**	100 (6)	25/75	0	20	**L8d**	85 (6)	25/75	24 (*R*)
9	**L3a**	100 (6)	70/30	21 (*R*)	21	**L9a**	100 (6)	45/55	40 (*R*)
10	**L3b**	100 (6)	75/25	10 (*R*)	22	**L10a**	100 (6)	30/70	<5 (*R*)
11	**L3c**	100 (6)	60/40	<5 (*R*)	23	**L10b**	100 (6)	35/65	<5 (*S*)
12	**L3d**	100 (6)	20/80	18 (*R*)	24	**L11a**	100 (6)	70/30	25 (*R*)

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

3 Conclusions

A large library of readily available monophosphite ligands has been screened in the asymmetric Pd-catalyzed allylic alkylation of several substrates with different electronic and steric properties. By carefully designing this library we were able to systematically investigate the effect of varying the sugar backbone, the substituents at C-3 of the furanoside backbone, the configurations at carbons C-3 and C-4 of the ligand backbone and the type of substituents/configurations in the biaryl phosphite moiety. In general, the catalytic performance (activities and enantioselectivities) is highly affected by these ligand parameters and also by the choice of substrate. For disubstituted substrates **S1**-**S4** enantioselectivities were best with ligand **L8d** (ee's up to 72%) while for monosubstituted substrate **S5** ligand **L9a** gave the best results (ee's up to 40%).

4 Experimental Section

4.1 General Considerations

All syntheses were performed using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Ligands **L1**-**L11a**-**e** were prepared as previously described [44,45,52-54]. Racemic substrates **S1**-**S5** were prepared as previously reported [55-58]. Characterization details of alkylated compounds **1**-**6** were as previously described [59-61]. All other reagents were used as received.

4.2 General procedure for allylic alkylation of disubstituted substrates S1-S4

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding monophosphite (0.022 mmol) in dichloromethane (1 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (1 mmol) in dichloromethane (1.5 mL), dimethyl malonate (342 µL, 3 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (740 µL, 3 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated solution of NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the organic extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^{1}H-NMR and enantiomeric excess (ee) was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min) [58]. For substrate **S2**, the conversion was measured by ^{1}H-NMR and the ee was determined by ^{1}H-NMR using $[Eu(hfc)_3]$ [59]. For substrates **S3** and **S4**, conversion and enantiomeric excess were determined by GC using a ChiralDex-CB 25 m column [60].

4.3 General procedure for allylic alkylation of monosubstituted linear substrate S5

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding monophosphite ligand (0.022 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 µL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (370 µL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated solution of NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent [61].

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