UNIVERSITAT ROVIRA I VIRGILI
SCREENING OF MODULAR CARBOHYDRATE LIGAND LIBRARIES
IN ASYMMETRIC METAL-CATALYZED C-C AND C-X BOND FORMATION REACTIONS
Yvette Angela Mata Campaña
ISBN:978-84-691-0375-3/DL:T.2193-2007

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

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

3.4.1. Introduction

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

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low reaction rates and high substrate specificity.[4] Therefore, these ligand systems have provided excellent enantioselectivities and activities in different substrate types.[4]

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

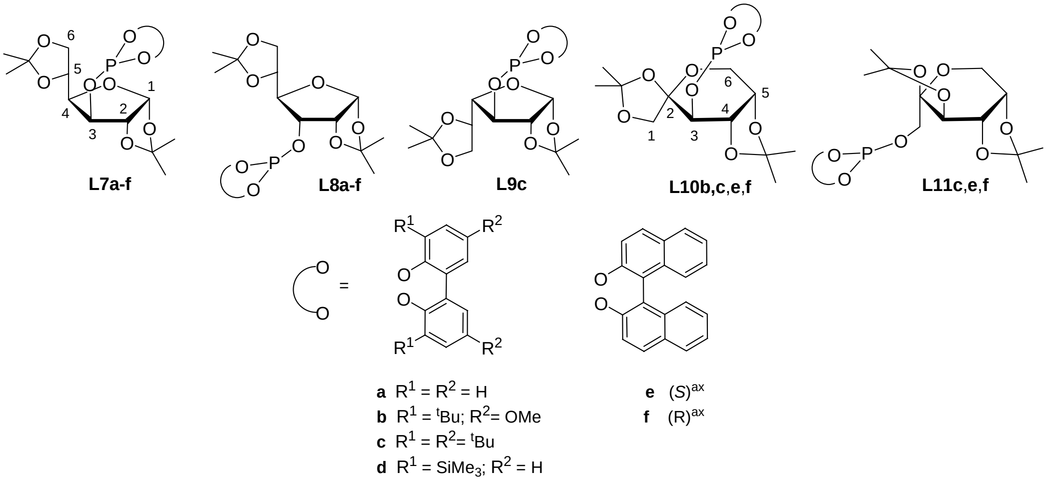

Figure 1. Carbohydrate-based phosphite ligands **L7-L11a-f**.

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3.4.2. Results and Discussion

3.4.2.1. Ligand design

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

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

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

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

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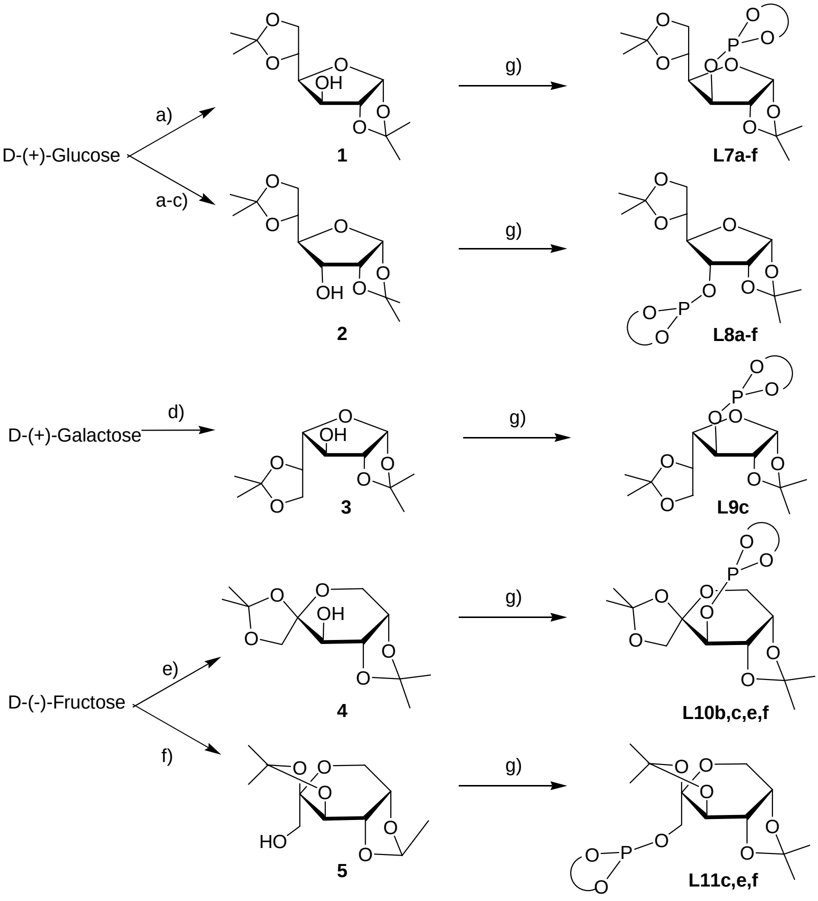
3.4.2.2. Ligand synthesis

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



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

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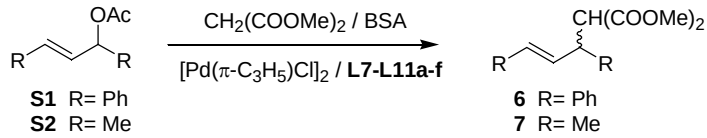
All the ligands were stable during purification on neutral silica under an atmosphere of argon and isolated in moderate yields as white solids. The elemental analysis were in agreement with the assigned structure. The ^{1}H, ^{31}P and ^{13}C NMR spectra were as expected for these C_1 ligands.

3.4.2.3. Allylic alkylation of disubstituted linear substrates

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



S1 R= Ph
S2 R= Me

6 R= Ph
7 R= Me

(1)

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

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

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

[a] 0.5 mol% $[Pd(\pi-C_3H_5)Cl]_2$, 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 ^{1}H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD).

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

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

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

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

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

Comparing the results using ligands **L7** with **L8**, that only differ in the configuration at C-3, we observed that this configuration controls the sense of enantioselectivity. Accordingly, ligands **L7a-d** with an *S* configuration at the C-3 of the ligand backbone, gave the S-**6** product, while ligands **L8a-d** with an *R* configuration at C-3 gave *R*-**6** product (Table 2, entries 1-4 *vs* 7-10). Furthermore, comparing ligands **L7e-f** and **L8e-f**, we found a cooperative effect between the configuration of the

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binaphthyl phosphite moiety and the configuration at C-3, that results in a matched combination for ligand **L8e** (Table 2, entries 5, 6, 11 and 12).The results also showed that ligands **L9** with an *S* configuration at C-4 gave lower enantioselectivities than ligands **L7** with an opposite configuration at this position (Table 2, entries 3 *vs* 13). In addition, ligands **L10** which have a pyranoside backbone provided lower yields and enantioselectivities than their relative furanoside ligands **L7** (Table 2, entries 2 and 3 *vs* 14 and 15). Finally, the most flexible ligand **L11**, which has the phosphite moiety attached to a primary carbon provided the lowest enantioselectivities (Table 2, entry 16).

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

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

3.4.2.4. Allylic alkylation of cyclic substrates

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

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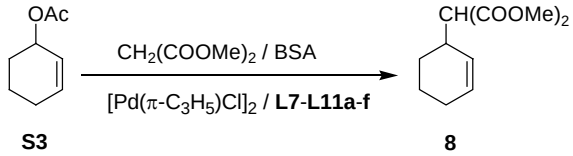


S3 8 (2)

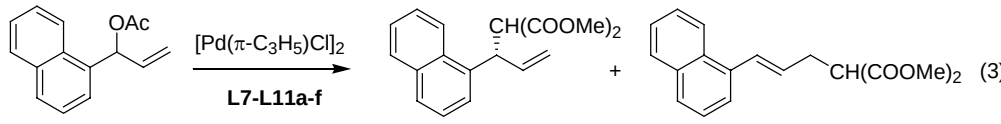
Table 3. Pd-catalyzed allylic alkylation of *rac*-3-acetoxy-cyclohexene **S3** using ligands **L7d** and **L8d**.[a]

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

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

3.4.2.5. Allylic substitution of monosubstituted linear substrates

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



S4 9 10 (3)

The results obtained with the phosphite ligands are summarized in Table 4. Unfortunately, the enantioselectivity (ee's up to 40%) was not high. However, good regioselectivities (regio's up to 80%) has been obtained.[15] The results indicated that if

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regioselectivity is to be high, bulky substituents at the *ortho* positions of the biaryl phosphite moiety and a furanoside backbone with an *S* and *R* configuration at C-3 and C-4, respectively, are necessary. However, enantioselectivities were best for furanoside ligand **L9c** with *S* configurations at both C-3 and C-4.

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

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

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

3.4.3. Conclusions

A library of readily available monophosphite ligands has been synthesized and applied in the asymmetric Pd-catalyzed allylic alkylation of several substrates with

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

3.4.4. Experimental section

3.4.4.1. General comments

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

3.4.4.2. Synthesis of the chiral monophosphite ligands

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

To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** (390 mg, 1.5 mmol) in THF (5 mL) was slowly added PCl_3 (132 µl, 1.5 mmol) as a solution in THF (4 mL) and the resulting mixture was stirred for 1 h at room temperature. The

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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146.5 (C), 146.6 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.98, H 8.62.

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

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

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

Treatment of 3,3';5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (0.62 g, 1.5 mmol) and **4** (390 mg, 1.5 mmol), as described for compound **L7b**, afforded phosphite **L10c**, which was purified by flash chromatography (eluent CH_2Cl_2, Rf: 0.43) to produce 290 mg (28%) of a white solid. ^{31}P NMR (C_6D_6) δ=151.7 (s). ^{1}H NMR (C_6D_6) δ= 1.05 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 3H, CH_3), 1.64 (s, 12H, CH_3, CH_3 ^{t}Bu), 3.80 (m, 1H, H-2), 3.94 (m, 2H, H-1, H-1'), 4.12 (d, 1H, H-6',$^2J_{6'-6}$=9.6 Hz), 4.50 (m, 1H, H-3), 4.54 (m, 1H, H-4),

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5.58 (d, 1H, H-6, $^{2}J_{6\text{-}6'}$=9.6 Hz), 7.28 (m, 1H, CH=), 7.33 (m, 1H, CH=), 7.55 (m, 2H, CH=).^{13}C NMR (C_6D_6) δ= 26.2 (CH_3), 26.8 (CH_3), 28.0 (CH_3), 29.0 (CH_3), 31.5 (CH_3,^{t}Bu), 31.6 (CH_3,^{t}Bu), 31.9 (CH_3,^{t}Bu), 32.0 (CH_3,^{t}Bu), 32.1 (CH_3,^{t}Bu), 34.9 (C), 35.0 (C), 35.9 (C), 36.1 (C), 60.6 (C-1), 71.8 (C-6), 72.8 (d, C-4, $J_{c\text{-}p}$=8.3 Hz), 74.8 (C-2), 77.2 (C-3), 104.9 (C-5), 109.9 (CMe_2), 112.9 (CMe_2), 124.5 (CH=), 124.9 (CH=), 126.0 (C), 127.3 (CH=), 127.6 (CH=), 133.7 (C), 134.9 (C), 138.2 (C), 140.9 (C), 141.0 (C), 146.8 (C), 147.3 (C). Anal. calcd (%) for $C_{40}H_{59}O_8P$: C 68.74, H 8.51; found: C 68.69, H 8.62.

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

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

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

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding phosphite-phosphoroamidite (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of corresponding substrate (0.5 mmol) in THF (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min).[19] For substrates **S2** and **S3**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column.[20]

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

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite-phosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H-NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7

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

3.4.5. Acknowledgements

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