ARTICLE

A readily accessible and modular carbohydrate-derived thioether/selenoether-phosphite ligand library for Pd-catalyzed asymmetric allylic substitutions

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A large library of thioether/selenoether-phosphite ligands have been tested in the Pd-catalyzed asymmetric allylic substitution reaction. The presented ligands are derived from cheap and available carbohydrates and they are air-stable solids and easy to handle. Their highly modular nature has made possible to achieve excellent enantioselectivities in the substitution of a range of hindered and unhindered substrates (ee's up to 99% and 91%, respectively). In addition, twelve C-, N- and O-nucleophiles can be efficiently introduced, independently of their nature. Among the whole library, ligands that contain an additional chiral centre in the alkyl backbone chain next to the phosphite group and an enantiopure biaryl phosphite group, provided the best enantioselectivities. In general, there is a cooperative effect between these two chiral elements, and therefore, a matched combination between them is necessary to reach the highest enantioselectivities. However, in the case of cyclic substrates, this cooperative effect is less pronounced and advantageously, both enantiomers of the product can be obtained by setting up the desired configuration of the biaryl phosphite group. Studies of the key Pd-π-allyl intermediates allowed us to better understand the enantioselectivities obtained experimentally.

Introduction

Asymmetric catalysis has become essential for synthesizing biologically active compounds in a sustainable way.[1] One of the most advantageous transformations is the Pd-catalyzed asymmetric allylic substitution (AAS) reaction since it allows the facile construction of a wide variety of new chiral C–C and C–heteroatom centers[2] and the products can be further derivatized due to the presence of an alkene functionality. In the last decades, hundreds of new chiral ligands have been developed. The most successful ligands contain two different heterodonor atoms that induce an electronic differentiation between both allylic carbons of the substrate and drive the nucleophilic attack to the most electrophilic carbon.[2] Several phosphine-oxazoline based catalysts that have this property have shown excellent enantioselectivities for this transformation.[2] However, they are rarely suitable for more than one substrate type and/or only few nucleophiles can be added. Consequently each type of substrate requires a particular ligand for optimal enantiopurity. In this respect, we have shown that by replacing the phosphine by a biaryl phosphite moiety can be advantageous, since its flexibility allows the creation of a chiral cavity that can accommodate substrates with different steric requirements.[2h,3] Another advantage of the phosphite functionality is that the ligands are solid and stable to air and therefore easier to handle than ligands with phosphines.[3g,h] Availability and robustness are desired features for the industrial application of those catalysts. In this context, we and others have studied the replacement of the oxazoline moiety by other donor groups with higher stability, such as thioethers[4], amines[5] and pyridines[6]. Among them, thioethers are interesting since they are easy to prepare and sulfur becomes a stereogenic center when coordinated to the metal.[7] Therefore, a new chiral center is created closer to the metal, which can enhance enantioselectivity. However, finding the optimum ligand backbone that can control the interconversion between the possible sulfur diasteroisomers formed is not a trivial task. Because of this, although some efforts have been done to develop new thioether-P ligand families for the Pd-AAS,[4] their effectiveness has not been shown until very recently.[4g,h]

On the other hand, modular ligands make it easier to identify catalysts suitable for each substrate type. Carbohydrates, which are accessible and inexpensive, are an important renewable source for modular ligands. The alcohol groups of the carbohydrates are easy to derivatize, enabling the construction of highly modular ligand families.[8] Combining the advantages of carbohydrates, phosphite and thioether groups, we have recently described a newly designed set of thioether-phosphite ligands **L1**–**L22** derived from L-tartaric acid and D-mannitol (Figure 1).[9] The exceptionally modular architecture of this ligand family allows us to systematically study different structural parameters: (a) the electronic and steric properties of the thioether functionality (ligands **L1**–**L7**); (b) several substituents in the alkyl backbone chain next to the phosphite

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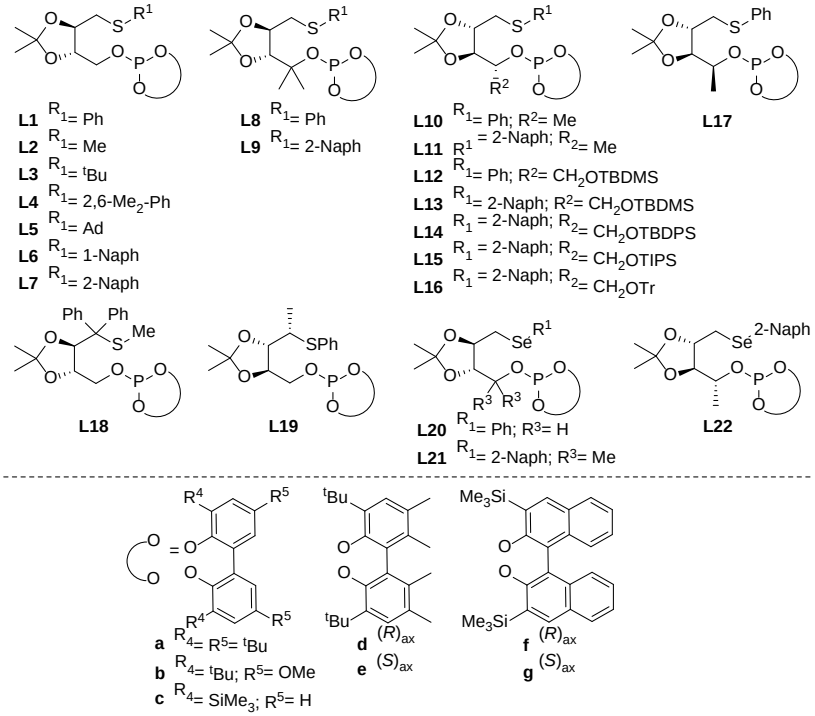
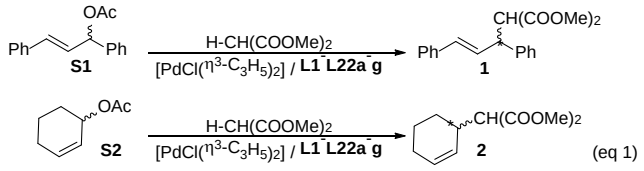


Fig. 1 Thioether/selenoether-phosphite ligand library **L1**–**L22a**–**g**.

functionality (ligands **L1** and **L7** vs L**8** and **L9**) that in some cases create a new stereogenic centre (ligands **L10**–**L17**); (c) several substituents in the alkyl backbone chain next to the thioether functionality (ligands **L2** vs **L18**) that in some cases create a new stereogenic centre (ligands **L19**); (d) the substituents and configurations in the biaryl phosphite moiety (**a**–**g**); and (e) the replacement of the thioether functionality by a selenoether functionality (**L20**–**L22**) (Figure 1). By carefully selecting these elements, we recently reported for the first time suitable catalysts in the asymmetric hydrogenation of 56 substrates with different substitution pattern and geometry.[9] In this report, we studied these ligands in the Pd-allylic substitution reaction. Again, the modular nature of these S/Se-phosphite ligands **L1**–**L22a**–**g**, was crucial to find the most efficient catalyst for the substitution of both hindered and unhindered substrates with a wide range of C-, N- and O-nucleophiles (28 products in total). We have also prepared the key Pd–allyl intermediates for a better understanding of the enantioselectivities obtained.

Results and discussion

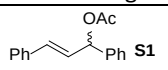
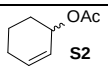
It is well known that the Pd-allylic substitution reaction is affected by the steric properties of the substrate. Usually, enantioselectivity is lower for unhindered substrates than for hindered substrates due to the existence of less bulky substituents. Therefore, we initially chose substrates **S1** and **S2**, with different steric requirements, to evaluate the thioether/selenoether-phosphite ligands **L1**–**L22a**–**g** (eq 1). In all cases, the catalysts were generated in situ from π-allyl-palladium chloride dimer ([PdCl(η^3-C_3H_5)$_2$]) and the corresponding ligand, and we used dimethyl malonate as nucleophile.



(eq 1)

Results are collected in Table 1. Full conversions were achieved after 3 h (**S1**) or 6 h (**S2**), under mild reaction conditions (0.5 mol% of catalyst loading and at room temperature). First, we used ligands **L1a**–**g** (Table 1, entries 1–7) to investigate the effect of changing the substituents and the configuration of the biaryl phosphite functionality. For both substrates, the presence of an enantiomerically pure biaryl phosphite group had a positive effect on enantioselectivity, being more pronounced for substrate **S2** (entries 4–7). In addition, the configuration of the biaryl controls the sense of the enantioselectivity (e.g., entries 4 and 6 vs 5 and 7). Modification of the substituents on the biaryl phosphite moiety had a different effect for each substrate. While for unhindered substrate **S2**, the introduction of bulky trimethylsilyl groups at the *ortho* position led to better enantioselectivities, changes were not observed for substrate **S1** (entries 4–5 vs 6–7). We initially, studied the effect of the thioether substitutent by comparing the results obtained with ligands **L1**–**L7**. The presence of a phenyl on the thioether group had always a positive effect on the enantioselectivity (e.g., 4 vs 8, 10, 13, 15, 17 and 19). We then moved to evaluate the presence of additional substituents next to the phosphite and

Table 1. Pd-AAS of **S1** and **S2** with dimethyl malonate and the ligand library **L1**–**L22a**–**g**.[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (3)	18 (*S*)	100 (6)	9 (*S*)
2	**L1b**	100 (3)	17 (*S*)	100 (6)	9 (*S*)
3	**L1c**	100 (3)	17 (*S*)	100 (6)	14 (*S*)
4	**L1d**	100 (3)	34 (*R*)	100 (6)	55 (*R*)
5	**L1e**	100 (3)	37 (*S*)	100 (6)	66 (*S*)
6	**L1f**	100 (3)	38 (*R*)	100 (6)	80 (*R*)
7	**L1g**	100 (3)	39 (*S*)	100 (6)	77 (*S*)
8	**L2a**	100 (3)	4 (*S*)	100 (6)	3 (*S*)
9	**L3a**	92 (3)	17 (*R*)	100 (6)	11 (*S*)
10	**L3d**	96 (3)	23 (*R*)	100 (6)	22 (*R*)
11	**L3e**	100 (3)	12 (*S*)	100 (6)	14 (*S*)
12	**L4a**	100 (3)	11 (*R*)	100 (6)	8 (*S*)
13	**L4d**	100 (3)	27 (*R*)	100 (6)	42 (*R*)
14	**L4e**	100 (3)	14 (*S*)	100 (6)	25 (*S*)
15	**L5d**	100 (3)	25 (*R*)	100 (6)	24 (*R*)
16	**L5e**	100 (3)	0	100 (6)	17 (*S*)
17	**L6d**	100 (3)	22 (*R*)	100 (6)	34 (*R*)
18	**L6e**	100 (3)	4 (*R*)	100 (6)	19 (*S*)
19	**L7d**	100 (3)	14 (*R*)	100 (6)	40 (*R*)
20	**L7e**	100 (3)	4 (*R*)	100 (6)	12 (*S*)
21	**L8a**	100 (3)	40 (*R*)	100 (6)	8 (*R*)
22	**L8d**	100 (3)	80 (*R*)	100 (6)	59 (*R*)
23	**L8e**	100 (3)	10 (*R*)	100 (6)	41 (*S*)
24	**L9a**	100 (3)	58 (*R*)	100 (6)	13 (*R*)
25	**L10a**	100 (3)	70 (*S*)	100 (6)	24 (*S*)
26	**L10f**	100 (3)	35 (*R*)	100 (6)	72 (*R*)
27	**L10g**	100 (3)	92 (*S*)	100 (6)	82 (*S*)
28	**L11f**	100 (3)	39 (*R*)	100 (6)	75 (*R*)
29	**L11g**	100 (3)	94 (*S*)	100 (6)	87 (*S*)
30	**L12a**	100 (3)	72 (*S*)	100 (6)	23 (*S*)
31	**L12f**	-	-	100 (6)	82 (*R*)
32	**L13a**	100 (3)	76 (*S*)	100 (6)	37 (*S*)
33	**L13g**	100 (3)	92 (*S*)	100 (6)	82 (*S*)
34	**L14g**	100 (3)	92 (*S*)	100 (6)	87 (*S*)
35	**L15g**	100 (3)	93 (*S*)	**100 (6)**	**89 (*S*)**
36	**L16g**	**100 (3)**	**97 (*S*)**	**100 (6)**	**89 (*S*)**
37	**L17a**	100 (3)	13 (*R*)	100 (6)	52 (*R*)
38	**L17f**	100 (3)	41 (*S*)	100 (6)	85 (*R*)
39	**L17g**	100 (3)	46 (*R*)	100 (6)	82 (*S*)
40	**L18f**	100 (3)	31 (*R*)	100 (6)	78 (*R*)
41	**L18g**	100 (3)	45 (*S*)	100 (6)	74 (*S*)
42	**L19a**	100 (3)	9 (*S*)	100 (6)	20 (*S*)
43	**L19f**	100 (3)	50 (*R*)	100 (6)	77 (*R*)
44	**L19g**	100 (3)	24 (S)	100 (6)	79 (*S*)
45	**L20a**	100 (3)	7 (S)	100 (6)	2 (*S*)
46	**L20f**	100 (3)	13 (*R*)	100 (6)	78 (*R*)
47	**L20g**	100 (3)	18 (*S*)	100 (6)	78 (*S*)
48	**L21f**	100 (3)	81 (*R*)	100 (6)	71 (*R*)
49	**L21g**	100 (3)	4 (*S*)	100 (6)	85 (*S*)
50	**L22f**	100 (3)	2 (*R*)	100 (6)	75 (*R*)
51	**L22g**	100 (3)	90 (*S*)	100 (6)	72 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S1** or **S2** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (3 mol%) at 23 °C. [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses determined by HPLC or GC. Absolute configuration drawn in parentheses.

the thioether moieties (**L8**–**L19**). In this case and in contrast to previous results, the presence of a 2-naphthyl thioether group provided higher enantioselectivities than the presence of a phenyl thioether moiety. It was also found that the introduction of two equal substituents next to the phosphite (**L8**–**L9**) or the thioether groups (**L18**) improved the enantioselectivity

considerably for linear substrate **S1** (e.g., ligand **L8d**, entry 22 vs. 4). However, for cyclic substrate **S2**, only the introduction of substituents next to the thioether group had a clear positive effect (ligands **L18f**,**g**, entries 40–41 vs 8). We then tested ligands **L10**–**L17** and **L19** with an extra chiral center next to both coordinating groups. For substrate **S1**, there was a remarkable cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone, which resulted in a matched combination for ligands **L10**–**L16g**, that bear an (*S*) biaryl phosphite group and an (*R*) chiral center next to the phosphite moiety (e.g. entries 26, 27 and 38, 39). This cooperative effect was less pronounced for cyclic substrate **S2**, and both enantiomers of the alkylated products were therefore easily accessible with similar enantioselectivities, by simply setting the configuration of the biaryl phosphite moiety (e.g. entries 26, 27 and 38, 39). With ligands **L10**–**L16**, we also studied the effect of different substituents on the carbon next to the phosphite functionality. By fine-tuning their steric properties we could achieve the highest enantioselectivities, up to 97% ee for substrate **S1** with ligand **L16g** (entry 36) and up to 89% ee for substrate **S2** with ligands **L15g** or **L16g** (entries 35 and 36). Finally, the replacement of the thioether functionality by a selenoether functionality had a negative effect on the enantioselectivity (e.g. 28-29 vs 50-51). This behavior contrasts with the application of these ligands in the metal-catalyzed hydrogenation of olefins, where the introduction of the selenoether group was crucial to maximize enantioselectivities for some of the olefins tested.[9b]

We next studied the Pd-AAS of **S1** and **S2** with other nucleophiles (Figures 2 and 3). We first explored the substitution reaction of **S1** with several types of C–, N–, and O–nucleophiles, with ligand **L16g**, which had provided the best enantioselectivity (Figure 2). We found that the catalytic performance was unaffected by variations of the steric properties of the ester moiety and of the substituents of the malonate nucleophiles. Hence, a broad range of malonates provided products **3**–**9** in high yields and high enanantioselectivities (up to 98 % ee), comparable to those obtained with dimethyl malonate. Of particular importance are the high enantioselectivities obtained with the nucleophiles functionalized with allyl-, butenyl, pentenyl- and propargyl-groups, whose products are key intermediates in the synthesis of more complex chiral products.[10] The use of acetylacetone also provided product **10** in high enantioselecitvity (97% ee). Enantiocontrol was also excellent when benzylamine was used as an example of N-nucleophile (product **11** with 98% ee). Finally, we wanted to test the ability of Pd/**L16g** system in the addition of aliphatic O-nucleophiles. The efficient allylic substitution with this type of nucleophiles opens up a straightforward way for the preparation of aliphatic chiral ethers, which are important building blocks.[11] Despite its importance, few successful examples exist and most of them use phenols as O-nucleophiles, being aliphatic alcohols less studied.[4f,12] Additionally, the type of aliphatic alcohol affects the enantioselectivity and simple variations in its electronic properties lead to important differences in enantioselectivity.[3e] Gratifyingly, the application of Pd/**L16g** in the etherification of **S1** using three different aliphatic O-nucleophiles that differ in their electronic properties, provided the desired substituted products **12**–**14** in high yields and enantioselectivities (up to 95%), comparable to the best ones reported in the literature.

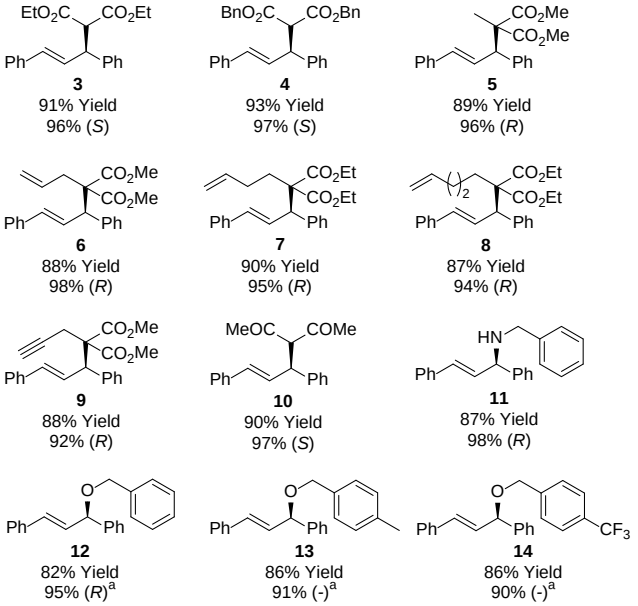


Fig. 2 Pd-AAS of **S1** with other C-, N- and O-nucleophiles using Pd/**L16g** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc (3 mol%). Full conversions were achieved after 4 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv) at 23 °C. Full conversions were achieved after 18 h.

We next studied the introduction of other C-nucleophiles in the alkylation of the more challenging cyclic substrate **S2**. As an example, Figure 3 shows the results with ligands **L15g** and **L17f** which had provided, together with ligand **L16g**, the best enantioselectivities in both enantiomers of the alkylated product **2** (see Supporting Information for full set of results). We were pleased to see that several malonates could be successfully introduced providing both enantiomers of products **15**–**17** in high yields and enantioselectivities (ee's up to 91%). Again, high enantiocontrol could be achieved with saturated malonates (products **16** and **17**), which can provide relevant intermediates for the synthesis of chiral polycyclic compounds with multiple sterocentres.[4h, 10b] The addition of acetylacetone (product **18**) also proceeded with similar high enantioselectivities (ee's up to 88%). Encouraged by the results obtained with the cyclic substrate **S2**, we explored the substitution of other cyclic substrates with different ring sizes, including the more challenging five-membered cyclic one (Figure 3). Again, both enantiomers of the alkylated products **19**–**22** were obtained in high yields and enantioselectivities (Figure 3). These results are among the best ones in the literature for these substrates, including the synthetically useful nucleophiles other than dimethyl malonate, for which only very few catalytic system have provided such high enantioselectivities.[2]

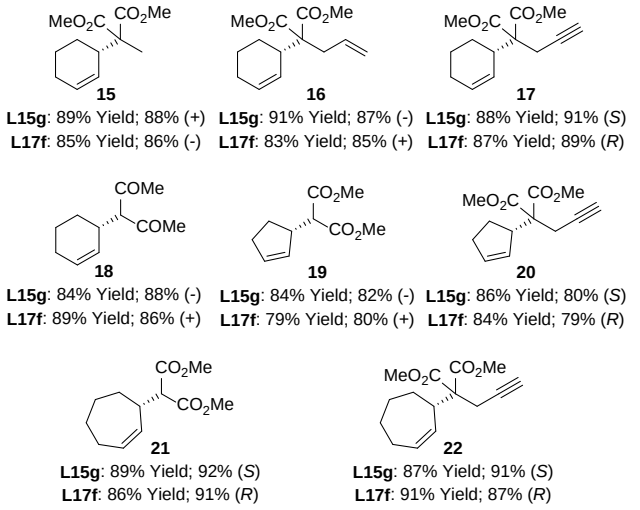


Fig. 3 Results for the Pd-allylic substitution of cyclic substrates **S2**–**S4** with several C-nucleophiles using Pd/**L15g** and Pd/**L17f** catalytic systems. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc (3 mol%). Full conversions were achieved after 6 h.

The excellent enantiocontrol achieved with cyclic substrates **S2**–**S4** (Figure 3), pushed us to test our S/Se-phosphite ligands **L1**–**L22a**–**g** in the alkylation of another challenging type of unhindered substrate, namely the less studied linear substrate *rac*-1,3-dimethyl-3-acetoxyprop-1-ene (**S5**).[13] In all cases full conversions were achieved after 6 hours. The results (Table 2) indicate that enantioselectivity is controlled by the same ligand parameters as for substrate **S1**, except for the type of substituent on the carbon next to the phosphite functionality and the existence of an opposite cooperative effect between the configurations of the biaryl phosphite moiety and the chiral substituent next to the phosphorus atom. Thus, the highest enantioselectivity (86 % ee) was achieved using ligand **L13f** (Table 2, entry 32). Again, the flexibility of our ligands allowed them to accommodate the chiral pocket to the steric demands of the substrate **S5**, providing high enantioselectivities for this challenging substrate.[2]

With the best catalytic system, Pd/**L13f**, we studied other malonates as nucleophiles (Figure 4). Once again, the high enantiocontrol achieved using dimethyl malonate was maintained. Therefore, we could prepare products **24**–**27** with enantioselectivities up to 86 % ee (Figure 4).

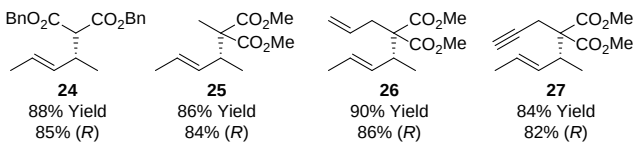
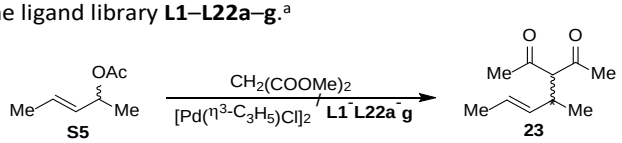


Fig. 4 Pd-allylic substitution of **S5** with several C-nucleophiles using Pd-**L13f** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc (3 mol%). Full conversions were achieved after 6 h.

Table 2. Pd-catalyzed AAS of **S5** with dimethyl malonate using the ligand library **L1**–**L22a**–**g**.[a]

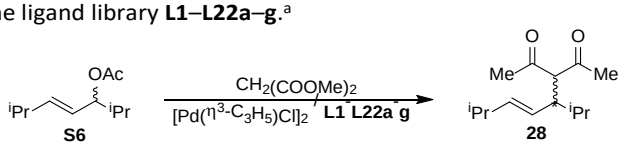


Entry	Ligand	% Conv[b]	% ee[c]	Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	11 (*S*)	27	**L10g**	100	50 (*S*)
2	**L1b**	100	9 (*S*)	28	**L11f**	100	60 (*R*)
3	**L1c**	100	10 (*S*)	29	**L11g**	100	42 (*S*)
4	**L1d**	100	59 (*R*)	30	**L12a**	100	22 (*S*)
5	**L1e**	100	12 (*S*)	31	**L12f**	100	82 (*R*)
6	**L1f**	100	62 (*R*)	32	**L13f**	**100**	**86 (*R*)**
7	**L1g**	100	12 (*S*)	33	**L13g**	100	39 (*S*)
8	**L2a**	100	3 (*S*)	34	**L14g**	100	35 (*S*)
9	**L3a**	100	15 (*R*)	35	**L15g**	100	33 (*S*)
10	**L3d**	100	21 (*R*)	36	**L16g**	100	31 (*S*)
11	**L3e**	100	19 (*S*)	37	**L17a**	100	27 (*R*)
12	**L4a**	100	8 (*R*)	38	**L17f**	100	48 (*R*)
13	**L4d**	100	22 (*R*)	39	**L17g**	100	29 (*S*)
14	**L4e**	100	15 (*S*)	40	**L18f**	100	72 (*R*)
15	**L5d**	100	20 (*R*)	41	**L18g**	100	69 (*S*)
16	**L5e**	100	10 (*S*)	42	**L19a**	100	6 (*R*)
17	**L6d**	100	24 (*R*)	43	**L19f**	100	72 (*R*)
18	**L6e**	100	7 (*R*)	44	**L19g**	100	64 (*S*)
19	**L7d**	100	40 (*R*)	45	**L20a**	100	12 (*S*)
20	**L7e**	100	8 (*R*)	46	**L20f**	100	48 (*R*)
21	**L8a**	100	8 (*R*)	47	**L20g**	100	9 (*S*)
22	**L8d**	100	64 (*R*)	48	**L21f**	100	59 (*R*)
23	**L8e**	100	29 (*R*)	49	**L21g**	100	39 (*S*)
24	**L9a**	100	13 (*R*)	50	**L22f**	100	49 (*R*)
25	**L10a**	100	21 (*S*)	51	**L22g**	100	15 (*S*)
26	**L10f**	100	71 (*R*)				

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S3** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (3mol%) at 23 °C. [b] Conversion percentage determined by ^{1}H-NMR after 6 h. [c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

Finally, in order to test the versatility of the thioether/selenoether-phosphite ligands **L1**–**L22a**–**g**, we tested them in the alkylation of the linear substrate **S6** (Table 3), which is more sterically demanding and it is usually alkylated with lower selectivity than substrate **S1**.[2] Although, as reported in the literature, longer reaction times were needed to achieve full conversions (24h), by fine-tuning the ligand parameters, we could reach a high enantioselectivity (>95% ee), comparable to the best one reported for this substrate.[2] In general, investigations into the effect of the ligand parameters on enantioselectivity showed the same trends as in the previously tested benchmark substrate **S1**, except that the bulkiness of the substituent on the carbon next to the phosphite functionality hardly affected enantioseletivity. Thus, the highest enantioselectivities were achieved with ligands **L10**–**L16g** containing an (*R*)-configured alkyl group next to the phosphite moiety, together with an (*S*)-chiral axis on the biaryl phosphite group (Table 3).

Table 3. Pd-catalyzed AAS of **S6** with dimethyl malonate using the ligand library **L1**–**L22a**–**g**.[a]

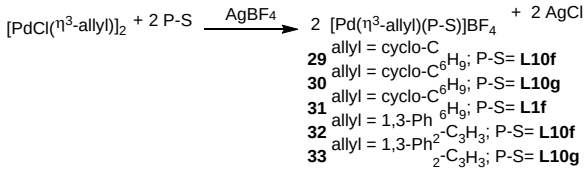


Entry	Ligand	% Conv[b]	% ee[c]
1	**L1a**	100	21 (S)
2	**L1b**	100	22 (S)
3	**L1c**	100	20 (S)
4	**L1d**	100	44 (R)
5	**L1e**	100	20 (S)
6	**L1f**	100	46 (R)
7	**L1g**	100	25 (S)
8	**L2a**	100	7 (S)
9	**L3a**	99	19 (R)
10	**L3d**	100	26 (R)
11	**L3e**	100	17 (S)
12	**L4a**	100	15 (R)
13	**L4d**	100	34 (R)
14	**L4e**	100	19 (S)
15	**L5d**	100	31 (R)
16	**L5e**	100	2 (S)
17	**L6d**	100	29 (R)
18	**L6e**	100	9 (R)
19	**L7d**	100	19 (R)
20	**L7e**	100	7 (R)
21	**L8a**	100	42 (R)
22	**L8d**	100	83 (R)
23	**L8e**	100	12 (R)
24	**L9a**	100	63 (R)
25	**L10a**	100	74 (S)
26	**L10f**	100	38 (*R*)
27	**L10g**	100	95 (*S*)
28	**L11f**	100	43 (*R*)
29	**L11g**	100	94 (*S*)
30	**L12a**	100	78 (*S*)
31	**L13a**	100	77 (*S*)
32	**L13g**	100	95 (*S*)
33	**L14g**	100	93 (*S*)
34	**L15g**	100	>95 (*S*)
35	**L16g**	100	>95 (*S*)
36	**L17a**	100	18 (*R*)
37	**L17f**	100	44 (*S*)
38	**L17g**	100	53 (*R*)
39	**L18f**	100	37 (*R*)
40	**L18g**	100	49 (*S*)
41	**L19a**	100	11 (*S*)
42	**L19f**	100	54 (*R*)
43	**L19g**	100	31 (*S*)
44	**L20a**	100	12 (*S*)
45	**L20f**	100	18 (*R*)
46	**L20g**	100	23 (*S*)
47	**L21f**	100	82 (*R*)
48	**L21g**	100	11 (*S*)
49	**L22f**	100	8 (*R*)
50	**L22g**	100	92 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), **S2** (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (3 mol%) at 23 °C. [b] Conversion percentage determined by ^{1}H-NMR after 24 h. [c] Enantiomeric excesses determined by ^{1}H using $[Eu(hfc)_3]$. Absolute configuration drawn in parentheses.

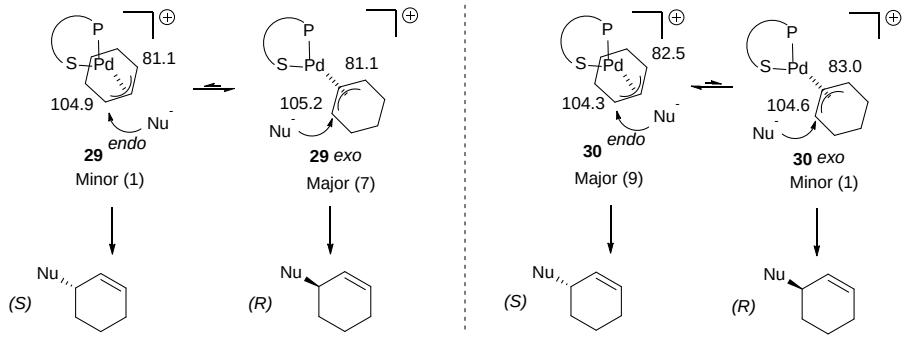
NMR mechanistic studies of the key Pd-π-allyl intermediates

Our previous DFT mechanistic studies with Pd/thioether–P catalysts pointed out that enantiocontrol takes place during the nucleophilic attack through an early transition state.[4g,h] Therefore, investigations of the Pd-π-allyl intermediates and their reactivity with the nucleophile will help to rationalize the effect of the ligand parameters on enantioselectivity with the thioether/selenoether–P Pd/catalysts reported in this paper. For this reason, we synthesized the Pd-π-cyclohexenyl/1,3-diphenyl based allyl complexes **29**–**33** (Scheme 1), following a previously reported method.[14] The chosen ligands **L1f** and **L10f**–**g** enabled us to study the effect on enantioselectivity of varying the configuration of the biaryl phosphite functionality as well as the effect of having an extra chiral center in the alkyl backbone chain next to the phosphite group. These Pd-π-allyl intermediates **29**–**33** were fully characterized by NMR spectroscopy (^{1}H, ^{13}C, ^{31}P and bidimensional ^{1}H–^{1}H, ^{13}C–^{1}H, ^{31}P–^{1}H and ^{1}H–^{1}H NOESY spectra) and by mass spectrometry. Unfortunately, we were unable to get crystals of enough quality to perform X-ray diffraction analysis. See experimental section and supporting information for characterization details.



Scheme 1 Synthesis of $[Pd(\eta^3\text{-allyl})(P\text{-}S)]BF_4$ **29**–**33** complexes.

Cyclohexenyl palladium complexes. To understand the reversal in the sense of enantioselectivity in the substitution of cyclic substrates when varying the configuration of the biaryl phosphite functionality, we initially studied the $[Pd(\eta^3\text{-cyclo-}C_6H_9)$(**L10f**)$]BF_4$ (**29**) and compare it with the analogous Pd-1,3-cyclohexenyl-allyl complex **30** containing ligand **L10g**. The variable temperature (VT) NMR study (30 to -80 °C) showed the presence of two isomers in equilibrium at a ratio of 1:7 and 9:1, respectively (Scheme 2). The major isomer of Pd-intermediate **29** was assigned by NOE to the Pd-η^3-*exo*, while the NOE indicated an *endo* disposition for major isomer of **30** (Figure 5). So, changes in the configuration of the phosphite moiety led to changes in the ratio of the species that provide both enantiomers of the alkylated product. For the major isomer of complex $[Pd(\eta^3\text{-cyclo-}C_6H_9)$(**L10f**)$]BF_4$ (**29**), one of the TMS group of the phosphite moiety showed NOE contacts with the terminal allyl proton *trans* to the S and also with the central allyl proton. In addition, the other TMS's phosphite moiety showed NOE contact with the methinic proton of the alkyl backbone chain next to the phosphite group (Figure 5a). All these NOE interactions are in agreement with an *exo* disposition for the major isomer of Pd/**L10f**. In contrast, for the major isomer of complex $[Pd(\eta^3\text{-cyclo-}C_6H_9)$(**L10g**)$]BF_4$ (**30**) the same TMS's phosphite group showed NOE interactions with the terminal allyl proton *trans* to the S and with the central allyl proton, but also with the methinic proton next to the phosphite group in agreement with an *endo* disposition (Figure 5b).



Scheme 2 Diastereoisomeric Pd-η³-allyl intermediates for **S2** with ligands **L10f–g**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown. Nu = dimethyl malonate

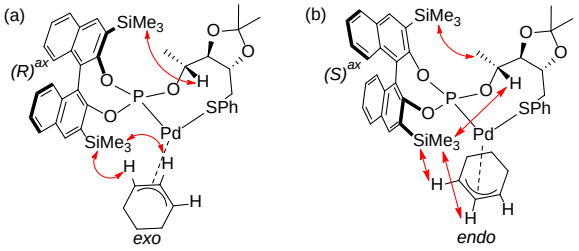
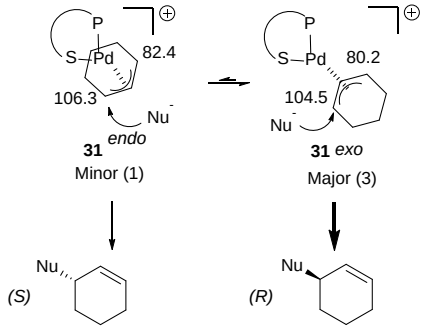


Fig. 5 Selected NOE contacts from NOESY spectra for the major isomers of Pd-η³-allyl intermediates **29** (a) and **30** (b).



Scheme 3 Diastereoisomeric Pd-η³-allyl intermediates for **S2** with ligand **L1f**. Nu = dimethyl malonate.

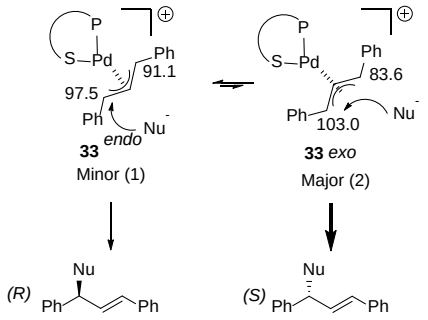
The carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic terminal carbon atom and the fact that the observed stereochemical outcome of the reactions (72% ee (*R*) for Pd/**L10f** and 82% ee (*S*) for Pd/**L10g**) is similar to the diastereoisomeric excesses of the Pd-isomers, indicates that both isomers of each Pd-intermediates react at similar rates. Consequently, the enantioselectivity is mainly controlled by the ratios of *endo* and *exo* isomers.

The VT-NMR of Pd-allyl intermediates **31**, which contains ligand **L1f** and differs from previous [Pd(η³-cyclo-C_6H_9)(**L10f–g**)]BF_4 intermediates **29** and **30** in that the substituent in the alkyl backbone chain next to the phosphite functionality has been removed, also showed a mixture of Pd-η³-*endo* and Pd-η³-*exo* isomers in equilibrium at 1:3 ratio, respectively (Scheme 3, see Supporting Information for NOE details). However, in contrast to previous Pd-allyl complexes **29** and **30** the diastereoisomeric excess of the Pd isomers (50% ee) is lower that the enantioselectivity obtained experimentally (80% ee). Therefore, the major *exo* isomer should react faster than the minor *endo* isomer and that enantioselectivity is also controlled by the different reactivity of the *endo* and *exo* isomers of **31** towards the nucleophile.[15] In agreement, the Pd/**L1f** catalyst also shows a higher electronic differentiation between the more electrophilic allylic terminal C atoms of both *endo* and *exo* isomers ($\Delta\delta(^{13}C)$= 1.8 ppm) than in Pd/**L10f–g** ($\Delta\delta(^{13}C)$= 0.3 ppm).

1,3-Diphenyl allyl palladium complexes. To understand the different impact of the configuration of the biaryl phosphite group on enantioselectivity when using hindered substrates, such as **S1**, we compared the corresponding Pd-1,3-diphenyl allyl intermediates with ligands **L10f–g**. Thus, while Pd/**L10g** catalyst system provided the (*S*)-alkylated product in 92% ee, Pd/**L10f** was less enantioselective (35% ee (*R*)).

The VT-NMR (30 to -80 °C) of Pd-allyl intermediate **33**, which contains ligand **L10g** showed a mixture of two Pd-isomers in equilibrium at 1:2 ratio. These isomers were assigned by NOE to the syn/syn *endo* and syn/syn *exo* isomers, respectively (Scheme 4). In this respect, the NOE showed interactions between the two terminal protons of the allyl group, which confirms a syn/syn disposition (Figure 6). In addition, for the major *exo* isomer one of the TMS group of the phosphite moiety showed NOE contacts with the terminal allyl protons and also with the methinic proton of the alkyl backbone chain next to the phosphite group, and the other TMS group showed NOE contact with the central allyl proton. These NOE contacts are consistent with an *exo* disposition. Again the ^{13}C NMR indicate that the most electrophilic allyl carbon terminus is *trans* to the P group. However, in contrast to the related Pd-allyl intermediate with the cyclic substrate the Pd/1,3-diphenyl allyl intermediate shows a much higher electronic differentiation between the more electrophilic allylic terminal C atoms of both *endo* and *exo* isomers ($\Delta\delta(^{13}C)$= 5.8 ppm). Therefore, the major *exo* isomer of **33** should react faster than the minor *endo* isomer and that

enantioselectivity is controlled by the different reactivities of the *endo* and *exo* isomers of **33** toward the nucleophile rather than their population, as was the case for cyclic substrate with the same ligand **L10g** (vide supra).



Scheme 4 Diastereoisomeric Pd-η³-allyl intermediates for **S1** with ligand **L10g**. Nu = dimethyl malonate.

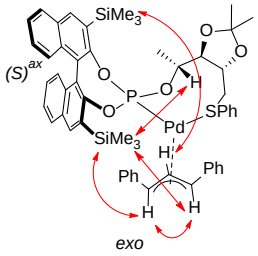
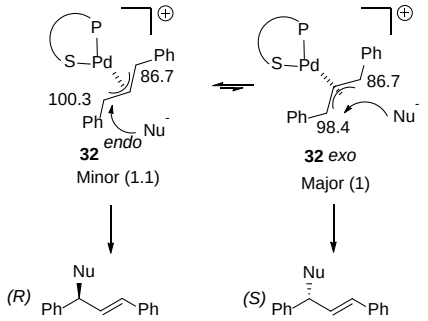


Fig. 6 Selected NOE contacts from NOESY spectra for the major isomer of Pd-η³-allyl intermediates **33**.

Finally, the VT-NMR (30 to -80 °C) spectra of Pd-allyl intermediate **32**, with a configuration of the biaryl phosphite moiety opposite to that of **33**, also shows a mixture of two *syn/syn* isomers but in a ratio of 1:1 (Scheme 5). Although the NOE contacts were not conclusive enough to assign the 3D structures of these two isomers, the ^{13}C NMR chemical shift showed for Pd/**L10f** a lower electronic difference between the more electrophilic allylic terminal C atoms of both isomers ($\Delta\delta(^{13}C)$= 1.9 ppm) than for the analogous Pd/**L10g** ($\Delta\delta(^{13}C)$= 5.8 ppm). This lower electronic difference makes both isomers of Pd/**L10f** react with more similar reaction rates than for Pd/**L10g** and fully accounts for the lower enantioselectivity achieved with Pd/**L10f** than with Pd/**L10g**.



Scheme 5. Diastereoisomeric Pd-η³-allyl intermediates for **S1** with ligand **L10f**. Nu = dimethyl malonate.

Conclusions

A large thioether/selenoether-phosphite ligand library was tested in the Pd-catalyzed allylic substitution reaction using twelve C-, N- and O-nucleophiles. The ligands are prepared from unexpensive carbohydrate derivatives, they are air-stable solids and they are easy to modulate by means of a well-established carbohydrate chemistry. That modular nature allowed many structural parameters to be tuned. Thus, after extensive screening, we could identify the best ligands for the substitution reaction of hindered (**S1** and **S6**) and unhindered (**S2**–**S5**) substrates. In all cases, to obtain the highest enantioselectivities, an (*R*)-configured bulky alkyl group next to the phosphite moiety was needed together with an enantiopure biaryl phosphite moiety. However, while an (*S*)-biaryl phosphite group was needed for hindered linear substrates **S1** and **S6**, an (*R*)-chiral biaryl phosphite group was preferred for the less sterically demanding linear substrate **S5**. In the case of cyclic substrates **S2**–**S4**, the cooperative effect between the alkyl group and the biaryl phosphite group was smaller, which made possible to obtain both enantiomers of the alkylated products by simply choosing the appropriate configuration of the biaryl phosphite group. We also found that the presence of selenium instead of sulfur did not improve the catalytic performance. In summary, we could prepare 28 valuable chiral compounds in enantioselectivities up to 99%. It is worth mentioning the high enantioselectivities obtained in the substitution of the challenging unhindered substrates **S2**–**S5**. These results pave the way for the future design of thioether-phosphite ligands, which are readily accessible and are air stable, for the Pd-AAS of substrates with different steric requirements, including the more challenging unhindered cyclic and linear ones, with a broad range of nucleophiles.

The study of the Pd-1,3-diphenyl- and 1,3-cyclohexenylallyl intermediates by NMR spectroscopy made possible to understand the catalytic behavior. It was seen that for high enantioselectivity to be obtained, the ligand parameters needed to be appropriately combined to either enhance the difference in the population of Pd-allyl isomers formed or to enhance the electronic differentiation between the most electrophilic allylic terminus carbon atoms of the isomers formed. This study also showed that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite functionality.

Experimental part

General procedures

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) or H_3PO_4 ($^{31}P\{^{1}H\}$) as internal standard. Racemic substrates **S1**–**S6** were prepared as previously described.[16]

Ligands **L1**–**L22a**–**g** were synthesized following already reported procedures. [9]

General procedure for the preparation of [Pd(η³-allyl)(P–S)]BF_4 complexes 29–33

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η³-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η³-1,3-cyclohexenyl)(L10f)]BF_4 (29). Isomer *endo* (12%): ^{31}P NMR (161 MHz, CD_2Cl_2, 218 K): δ 141.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2, 218 K): δ 0.48 (9 H, s, CH_3, $SiMe_3$), 0.51 (9 H, s, CH_3, $SiMe_3$), 0.80-1.40 (6 H, m, CH_2), 1.11 (3 H, d, $^3J_{H-H}$= 6.4 Hz, CH_3), 1.20-1.40 (3 H, m, CH_2), 1.20 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 3.72 (1 H, dd, $^2J_{C-P}$= 12.4 Hz, $^3J_{C-P}$= 6.0 Hz, CH_2-S), 3.90 (1 H, m, CH_2–S), 4.20 (1 H, m, C*H*CHOP), 4.24 (1 H, m, C*H*CH_2S), 4.50 (1 H, m, CH–OP), 4.58 (1 H, br s, CH=allyl *trans to S*), 5.56 (1 H, br s, CH=allyl *trans to P*), 5.72 (1 H, t, $^3J_{C-P}$= 7.0 Hz, CH=allyl *central*), 6.98–8.21 (15 H, m, CH=). Isomer *exo* (88%): ^{31}P NMR (161 MHz, CD_2Cl_2, 218 K): δ 140.7 (s). ^{1}H NMR (400 MHz, CD_2Cl_2, 218 K): δ 0.50 (9 H, s, CH_3, $SiMe_3$), 0.51 (9 H, s, CH_3, $SiMe_3$), 0.84 (2 H, m, CH_2), 1.09 (1 H, m, CH_2), 1.14 (3 H, d, $^3J_{H-H}$= 6.0 Hz, CH_3), 1.20-1.40 (3 H, m, CH_2), 1.35 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.83 (1 H, dd, $^2J_{C-P}$= 13.2 Hz, $^3J_{C-P}$= 5.2 Hz, CH_2-S), 4.08 (1 H, dd, $^2J_{C-P}$= 14.2 Hz, $^3J_{C-P}$= 5.4 Hz, CH_2–S), 4.13 (1 H, br s, CH=allyl *trans to S*), 4.20 (1 H, m, C*H*CHOP), 4.38 (1 H, m, C*H*CH_2S), 4.48 (1H, m, CH–OP), 4.84 (1 H, br s, CH=allyl *trans to P*), 5.24 (1 H, t, $^3J_{C-P}$= 7.0 Hz, CH=allyl *central*), 6.98–8.21 (15 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2, 218 K): δ 0.1 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 19.2 (CH_2), 19.4 (CH_3), 26.5 (CH_3), 27.5 (br, CH_2), 27.7 (CH_2), 43.2 (CH_2–S), 79.5 (*C*HCH_2S), 80.3 (*C*HCHOP), 81.1 (CH=allyl *trans to S*), 82.7 (CH–OP), 105.2 (CH=allyl *trans to P*, *exo*), 110.2 (*C*Me_2), 112.4 (CH=allyl *central*), 121.8–151.5 (aromatic carbons). MS HR-ESI [found 913.2159, $C_{46}H_{56}O_5PPdSSi_2$ $(M)^+$ requires 913.2154].

[Pd(η³-1,3-cyclohexenyl)(L10g)]BF_4 (30). Isomer *endo* (90%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 138.0 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.55 (9 H, s, CH_3, $SiMe_3$), 0.56 (9 H, s, CH_3, $SiMe_3$), 0.82 (3 H, d, $^3J_{H-H}$= 6.0 Hz, CH_3), 0.95 (2 H, m, CH_2), 1.32 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 1.53 (4 H, m, CH_2), 3.75 (1 H, dd, $^3J_{C-P}$= 4.4 Hz, CH_2–S), 3.86 (2 H, m, CH_2–S, C*H*CHOP), 4.19 (1 H, m, C*H*CH_2S), 4.50 (1 H, br, CH=allyl *trans to S*), 4.67 (1 H, m, CH–OP), 5.40 (1 H, t, $^3J_{C-P}$= 7.2 Hz, CH=allyl *central*), 5.60 (1 H, br, CH=allyl *trans to P*), 7.06–8.29 (15 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 0.36 (CH_3, $SiMe_3$), 0.66 (CH_3, $SiMe_3$), 19.6 (CH_2), 20.0 (CH_3), 26.5 (CH_3), 27.2 (d, J_{C-P}= 8.3 Hz, CH_2), 27.5 (CH_2), 42.1 (CH_2-S), 80.8 (d, J_{C-P}= 12.2 Hz, CH–OP), 81.3 (*C*HCH_2S), 82.5 (d, J_{C-P}= 5.3 Hz, CH=allyl *trans to S*), 82.8 (d, J_{C-P}= 8.3 Hz, *C*HCHOP), 104.3 (d, J_{C-P}= 38.0 Hz, CH=allyl *trans to P*), 112.1 (*C*Me_2), 112.4 (d, J_{C-P}= 9.9 Hz, CH=allyl *central*), 121.8–150.5 (aromatic carbons). Isomer *exo* (10%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 135.6 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.55 (9 H, s, CH_3, $SiMe_3$), 0.56 (9 H, s, CH_3, $SiMe_3$), 0.82 (3 H, d, $^3J_{H-H}$= 6.0 Hz, CH_3), 0.95 (2 H, m, CH_2), 1.32 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 1.53 (4 H, m, CH_2), 3.55 (1 H, dd, $^2J_{C-H}$= 12.7 Hz, $^3J_{C-H}$= 4.5 Hz, CH_2–S), 3.81 (m, 1H, C*H*CHOP), 3.86 (m, 1H, CH_2–S). 4.23 (m, 1H, C*H*CH_2S), 4.74 (1 H, m, CH–OP), 4.92 (1 H, br s, CH=allyl *trans to S*), 5.63 (1 H, br s, CH=allyl *trans to P*), 5.65 (1 H, m, CH=allyl *central*), 7.06–8.29 (15 H, m, CH=). MS HR-ESI [found 913.2158, $C_{46}H_{56}O_5PPdSSi_2$ $(M)^+$ requires 913.2154].

[Pd(η³-1,3-cyclohexenyl)(L1f)]BF_4 (31). Isomer *endo* (25%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 142.0 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.55 (9 H, s, CH_3, $SiMe_3$), 0.56 (9 H, s, CH_3, $SiMe_3$), 0.94−0.98 (2 H, m, CH_2), 1.35 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 1.48 (1 H, m, CH_2), 1.64−1.76 (3 H, m, CH_2), 3.63 (1 H, dd, $^2J_{C-H}$= 12.3, $^3J_{C-H}$= 5.1 Hz, CH_2–S), 3.76 (1 H, dd, $^2J_{C-H}$= 11.9, CH_2–S), 4.18–4.25 (2 H, m, C*H*CH_2OP, C*H*CH_2S), 4.38−4.46 (2 H, m, CH_2-OP), 4.44 (1 H, br, CH=allyl *trans to S*), 5.20 (1 H, m, CH=allyl *trans to P*), 5.36 (1 H, m, CH=allyl *central*), 7.00–8.28 (15 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 0.2 (CH_3, $SiMe_3$), 0.4 (CH_3, $SiMe_3$), 19.4 (br, CH_2), 26.4 (CH_3), 26.5 (CH_3), 27.6 (CH_2), 28.0 (d, J_{C-P}= 7.6 Hz, CH_2), 41.5 (CH_2–S), 68.6 (br, CH_2–OP), 77.9 (*C*HCH_2S), 78.8 (*C*HCH_2OP), 82.4 (br, CH=allyl *trans to S*), 106.3 (d, J_{C-P}= 36.5 Hz, CH=allyl *trans to P*), 111.4 (*C*Me_2), 112.6 (d, J_{C-P}= 9.7 Hz, CH=allyl *central*), 121.5−150.9 (aromatic carbons). Isomer *exo* (75%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 134.7 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.47 (9 H, s, CH_3, $SiMe_3$), 0.50 (9 H, s, CH_3, $SiMe_3$), 1.12 (1 H, m, CH_2), 1.14 (3 H, s, CH_3), 1.48 (1 H, m, CH_2), 1.51 (3 H, s, CH_3), 1.64−1.71 (2 H, m, CH_2), 1.82−1.87 (2 H, m, CH_2), 3.06 (1 H, m, CH_2–OP), 3.23 (1 H, m, C*H*CH_2–S), 3.44 (1 H, dd, $^2J_{C-H}$= 14.5, $^3J_{C-H}$= 10.6 Hz, CH_2-S), 4.22 (1 H, m, C*H*CH_2OP), 4.29 (1 H, d, $^2J_{C-H}$= 12.2, CH_2–S), 4.18–4.25 (1 H, m, CH_2–OP), 4.52 (1 H, br, CH=allyl *trans to S*), 4.92 (1 H, m, CH=allyl *trans to P*), 5.11 (1 H, t, $^3J_{C-H}$= 7.0, CH=allyl *central*), 7.00–8.28 (15 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2): δ -0.2 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.7 (CH_2), 27.3 (CH_2), 27.5 (CH_3), 27.9 (CH_3), 28.0 (d, J_{C-P}= 7.6 Hz, CH_2,), 43.5 (CH_2–S), 72.0 (d, $^2J_{C-P}$= 15.3 Hz, CH_2–OP), 73.0 (*C*HCH_2S), 80.2 (br, CH=allyl *trans to S*), 80.8 (d, $^2J_{C-P}$= 7.5 Hz, *C*HCH_2OP), 104.5 (d, J_{C-P}= 38.4 Hz, CH=allyl *trans to P*), 111.4 (*C*Me_2), 111.6 (d, J_{C-P}= 9.3 Hz, CH=allyl *central*), 121.5−150.9 (aromatic carbons). MS HR-ESI [found 899.2001, $C_{45}H_{57}O_5PPdSSi_2$ $(M)^+$ requires 899.1997].

[Pd(η³-1,3-diphenylallyl)(L10f)]BF_4 (32). Isomer *exo* (55%): ^{31}P NMR (161 MHz, CD_2Cl_2, 233 K): δ 135.6 (s). ^{1}H NMR (400 MHz, CD_2Cl_2, 233 K): δ 0.18 (3 H, d, ^3J= 6.6 Hz, CH_3), 0.48 (9 H, s, CH_3, $SiMe_3$), 0.68 (9 H, s, CH_3, $SiMe_3$), 1.15 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 3.14 (1 H, m, CH_2−S), 3.49 (1 H, m, CH_2−S), 3.52 (1 H, m, C*H*CHOP), 3.96−4.00 (1 H, m, C*H*CH_2S), 5.00−5.27 (2 H, m, CH= *trans to S*, *trans to P*), 6.51−6.59 (1 H, m, CH= *central*), 6.24−8.34 (25 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2, 233 K): δ 0.4 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 18.0 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 44.8 (CH_2−S), 78.9 (*C*HCHOP), 83.4 (*C*HCH_2S), 83.7−84.5 (br, CH−OP), 88.7 (CH=allyl *trans to S*), 98.4 (d, J_{C-P}= 33.9 Hz, CH=allyl *trans to P*), 109.8 (d, J_{C-P}= 10.6 Hz, CH=allyl *central*), 110.4 (*C*Me2), 121.8−151.2 (aromatic carbons). Isomer *endo* (45%): ^{31}P NMR (161 MHz, CD_2Cl_2, 233 K): δ 135.8 (s). ^{1}H NMR (400 MHz, CD_2Cl_2,

233 K): 0.24 (3 H, d, ^3J= 6.6 Hz, CH_3), 0.66, (9 H, s, CH_3, $SiMe_3$), 0.78 (9 H, s, CH_3, $SiMe_3$), 1.12, (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 3.14 (1 H, m, CH_2−S), 3.61 (1 H, m, CH_2−S), 3.52 (1 H, m, C*H*CHOP), 4.05 (1 H, m, CH−OP), 3.96−4.00 (1 H, m, C*H*CH_2S), 5.00−5.27 (2 H, m, CH= *trans to S*, *trans to P*), 6.51−6.59 (1 H, m, CH= *central*), 6.24−8.34 (25 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2, 233 K): δ 0.37 (CH_3, $SiMe_3$), 0.48 (CH_3, $SiMe_3$), 18.3 (CH_3), 26.2 (CH_3), 26.5 (CH_3), 43.8 (CH_2−S), 78.3, (*C*HCHOP), 83.6 (*C*HCH_2S), 83.7−84.5 (br, CH−OP), 86.7 (br, CH=allyl *trans to S*), 100.3 (d, J_{C-P}= 32.9 Hz, CH=allyl *trans to P*), 111.1 (*C*Me2), 111.4 (d, J_{C-P}= 11.9 Hz, CH=allyl *central*), 121.8−151.2 (aromatic carbons). MS HR-ESI [found 1025.2463, $C_{55}H_{60}O_5PPdSSi_2$ $(M)^+$ requires 1025.2467].

[Pd(η³-1,3-diphenylallyl)(L10g)]BF_4 (33). Isomer *endo* (33%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 133.6 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.12 (3 H, d, $^3J_{H-H}$= 6.2 Hz, CH_3), 0.72 (9 H, s, CH_3, $SiMe_3$), 0.73 (9 H, s, CH_3, $SiMe_3$), 1.22 (3 H, s, CH_3), 1.23 (3 H, s, CH_3), 3.25 (1 H, m, CH_2−S), 3.59−3.65 (2 H, m, CH_2−S, C*H*CHOP), 3.87 (1 H, m, C*H*CH_2S), 4.49 (1 H, m, CH−OP), 4.93 (1 H, m, CH=allyl *trans to P*), 5.52 (1 H, dd, $^3J_{H-P}$= 13.0, $^4J_{C-H}$= 2.4 Hz, CH=allyl *trans to S*), 6.53 (1 H, m, CH=allyl *central*), 6.24−8.40 (25 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 0.5 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 18.8 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 45.1 (CH_2−S), 79.4 (*C*HCH_2S), 80.8 (d, $^2J_{C-P}$= 14.9 Hz, CH−OP), 83.1 (d, $^3J_{C-P}$= 7.2 Hz, *C*HCHOP), 91.1 (d, J_{C-P}= 7.5 Hz, CH=allyl *trans to S*), 97.5 (d, J_{C-P}= 35.1 Hz, CH=allyl *trans to P*), 112.1 (d, J_{C-P}= 12.3 Hz, CH=allyl *central*), 112.4 (*C*Me2), 121.5−150.5 (aromatic carbons). Isomer *exo* (67%): ^{31}P NMR (161 MHz, CD_2Cl_2): δ 134.8 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.26 (3 H, d, ^3J= 6.2 Hz, CH_3), 0.46 (9 H, s, CH_3, $SiMe_3$), 0.77 (9 H, s, CH_3, $SiMe_3$), 1.29 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 3.31 (1 H, m, CH_2−S), 3.45 (1 H, m, CH_2−S), 3.54−3.64 (1 H, m, C*H*CHOP), 3.98 (1 H, m, C*H*CH_2S), 4.62 (1 H, m, CH−OP), 5.06 (1 H, d, $^3J_{C-H}$= 11.7 Hz, CH=allyl *trans to P*), 5.60 (1 H, t, $^3J_{H-P}$= 13.5, $^4J_{C-H}$= 2.4 Hz, CH=allyl *trans to S*), 6.40 (1 H, dd, $^3J_{H-P}$= 12.7, $^3J_{C-H}$= 13.9 Hz, CH=allyl *central*), 6.24−8.40 (25 H, m, CH=). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 0.5 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 19.3 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 44.5 (CH_2−S), 80.3 (*C*HCH_2S), 81.4 (d, $^2J_{C-P}$= 14.4 Hz, CH−OP), 82.9 (d, $^3J_{C-P}$= 7.8 Hz, *C*HCHOP), 83.6 (d, J_{C-P}= 6.7 Hz, CH=allyl *trans to S*), 103.0 (d, J_{C-P}= 29.6 Hz, CH=allyl *trans to P*), 109.3 (d, J_{C-P}= 9.8 Hz, CH=allyl *central*), 112.4 (*C*Me2), 121.5−150.5 (aromatic carbons). MS HR-ESI [found 1025.2471, $C_{55}H_{60}O_5PPdSSi_2$ $(M)^+$ requires 1025.2467].

Typical procedure for the allylic alkylation of linear (S1, S5 and S6) and cyclic (S2, S3 and S4) substrates

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-thioether/selenoether ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (3 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **1**, **3**–**10**, **15**–**16**, **22**, **24** and **27**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC. For compounds **2**, **17**–**18**, **20**–**21**, **23** and **25**–**26**, conversion and enantiomeric excesses were determined by GC. For compounds **19** and **28**, conversion was measured by ^{1}H NMR and enantiomeric excesses were determined by ^{1}H NMR using $[Eu(hfc)_3]$. See Supporting Information for characterization and enantiomeric excess determination details.

Typical procedure for the allylic amination of S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-thiother/selenoether ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL) and the corresponding amine (3 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of compound **11** (see Supporting Information for characterization and enantiomeric excess determination details).

Typical procedure for the allylic etherification of S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-thioether/selenoether ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of substrates **12**–**14** (see Supporting Information for characterization and enantiomeric excess determination details).

Conflicts of interest

There are no conflicts to declare.

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