Computationally-guided design of a readily assembled phosphite-thioether ligand for a broad range of Pd-catalyzed asymmetric allylic substitutions

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ABSTRACT: A modular approach employing indene as common starting material, has enabled the straightforward preparation in three reaction steps of P-thioether ligands for the Pd-catalyzed asymmetric allylic substitution. The analysis of a starting library of P-thioether ligands based on rational design and theoretical calculations has led to the discovery of an optimized anthracenethiol derivative with excellent behavior in the reaction of choice. Improving most approaches reported to date, this ligand presents a broad substrate and nucleophile scope. Excellent enantioselectivities have been achieved for a range of linear and cyclic allylic substrates using a large number of C-, N- and O-nucleophiles (40 compounds in total). The species responsible for the catalytic activity have been further investigated by NMR in order to clearly establish the origin of the enantioselectivity. The resulting products have been derivatized by means of ring-closing metathesis or Pauson-Khand reactions to further prove the synthetic versatility of the methodology for preparing enantiopure complex structures.

INTRODUCTION

The future of chemical production must keep up with the growing demand for fine chemicals while reducing the overall waste production and energy consumption demanded by international regulations (and common sense). Over the last decades, this need for sustainability has driven the shift from suboptimal non-catalyzed processes to high-performing catalytic processes for the production of all sorts of chemicals.[1] This has been especially noteworthy in the production of enantiopure compounds, which play a key role in many technologically and biologically relevant applications.[2] Amongst the toolkit of catalytic enantioselective transformations, asymmetric Pd-catalyzed allylic substitution stands out for its versatility (as it creates new C-C and C-heteroatom bonds starting from simple precursors), high functional group tolerance and mild reaction conditions. Moreover, the resulting products accept further derivatization thanks to the presence of an alkene functionality.[3] The key role of the ligand in the induction of chirality in this process has motivated several studies concerning the generation and evaluation of myriad candidates in terms of yield, selectivity and substrate scope. Heterodonor compounds (phosphine/phosphinite-oxazolines being the paradigmatic example) have proven especially advantageous because the different *trans* influence of the two donor groups generates an efficient electronic differentiation between the two allylic terminal carbon atoms. Indeed, the nucleophilic attack is known to take place predominantly *trans* to the donor group with stronger *trans* influence. On the basis of this premise, we have contributed with mixed ligands bearing biaryl phosphite moieties,[3j,4] which flexible nature allows the catalyst chiral pocket to adapt to the steric demands of the substrate,[4e] resulting in a broadened substrate scope.

The vast amount of Pd-catalyzed allylic substitution studies reported in the literature have led to remarkable advances in catalyst design; however, catalysts are still rarely suitable for a wide range of substrates. Instead, the most common scenario is that each allylic precursor requires independent optimization to identify the optimal catalytic system, and a similar situation takes place with the various nucleophiles. Consequently, the identification of "privileged" ligands remains a central task in this type of chemistry. In addition to giving excellent results for a broad range of allylic precursors and nucleophiles (C-, N- or O-based), such privileged ligands must be readily prepared in both enantiomeric forms from available starting materials and easy to handle (i.e. solid, robust and stable in air).[3]

To this end, we recently started a research line aimed at identifying suitable alternatives to the labile oxazoline moiety. We were especially interested in the stable and easy to prepare thioether group, which allowed the preparation of a Pd/phosphite-thioether furanoside-based catalyst that creates C-C, C-N and C-O bonds with different substrates and a variety of nucleophiles.[5] The yields and enantioselectivities obtained were comparable to the best catalytic systems reported in the literature. Although these furanoside ligands were prepared from inexpensive D-xylose, their synthesis was tedious and required a large number of steps. Other researchers have demonstrated the utility of thioether-based *P*-*S* ligands.[6] For instance, the pioneering work in Pd-catalyzed allylic substitution and other relevant asymmetric reactions of Pregosin[7] and Evans,[6a] among others, put the focus on this kind of ligands and spurred their development. Despite the many efforts devoted to develop *P*-*S* ligands, their impact has been limited for two main reasons: (a) even in the most successful cases, they were limited in substrate and nucleophile scope: enantioselectivities were mainly high for the allylic substitution of the standard (and hindered) *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile,[6] and (b) thioether-based ligands are prone to producing mixtures of diastereomeric thioether complexes, which tend to interconvert in solution.[8] However, if one could design a scaffold able to control the configuration on sulfur upon coordination of the *P*-*S* ligand, this would provide an additional chiral element in close proximity to the metal, thus giving rise to simpler ligands that can be prepared in fewer steps than their oxazoline-phosphine counterparts.

Herein, we give a new push to the study of the catalytic potential of *P,S*-ligands by screening novel, readily accessible thioether-containing compounds, including a detailed study of the species responsible for the catalytic performance. For this purpose, we designed a small but structurally diverse library of *P*-thioether ligands **L1**–**L8a**–**g** (Figure 1) that was tested in the Pd-catalyzed allylic substitution of a broad range of substrates and nucleophiles. These new *P,S*-ligands are synthesized in only three steps from inexpensive indene (ca. 20 USD/kg in bulk) and, since the corresponding enantiopure epoxide is prepared through Jacobsen epoxidation, both enantiomeric series are equally available. This modular approach[9] greatly expedites the evaluation of several thioether and phosphite/phosphinite moieties, which is deemed crucial for the iterative optimization of the most promising candidates. Consequently, the catalytic performance of the ligands depicted in Figure 1 has been studied by systematically varying: (i) the electronic and steric properties of the thioether (**L1**–**L8**) group, (ii) the configuration of the biaryl phosphite moiety (**a**–**c**), and (iii) the *P*-containing group (phosphite, **a**–**c** versus phosphinite groups, **d**–**g**).

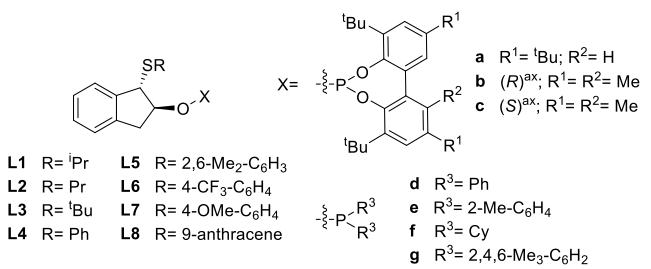
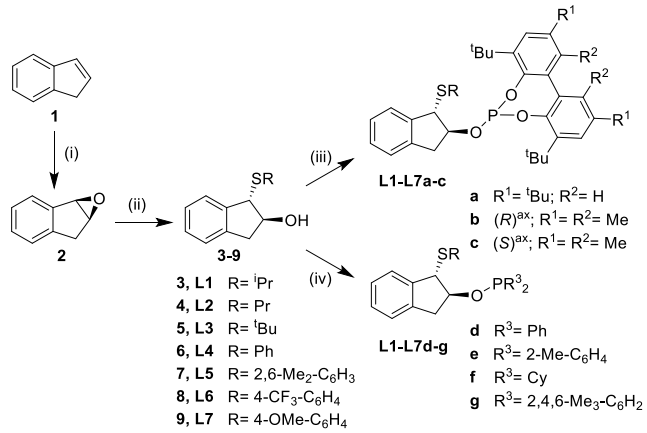


Figure 1. Phosphite/phosphinite-thioether ligand library **L1**–**L8a**–**g**.

An additional advantage of this set of ligands is the fact that their simplified backbone renders very simple NMR spectra, thus reducing signal overlap, as well as facilitating the identification of relevant intermediates and accelerating the DFT calculations performed to rationalize the behavior of the system. By combining theoretical studies and NMR spectroscopy, we have been able to rationally fine-tune the ligands, improve enantioselectivity and identify the species responsible for the catalytic performance. This optimized ligand has proven active in the Pd-catalyzed allylic substitution of both linear and cyclic substrates with a broad range of C-, N-, and O-nucleophiles (26 examples in total), even with the environmentally friendly propylene carbonate as solvent. Finally, the applicability of the new Pd/P-thioether catalysts has been further demonstrated in the practical synthesis of chiral (poly)carbo– and heterocyclic compounds using straightforward sequences of allylic substitution/ring-closing metathesis or allylic alkylation/Pauson-Khand reactions.

RESULTS AND DISCUSSION

Synthesis of the first generation ligand library L1–L7a–g. Phosphite/phosphinite-thioether ligands **L1**–**L7a**–**g** can be efficiently prepared in three steps as illustrated in Scheme 1. In the first step, epoxidation of inexpensive indene **1** with bleach using Jacobsen's catalyst, followed by low-temperature crystallization, yielded indene oxide with 99% ee.[10] Next, the regio- and stereospecific ring opening of **2** with the corresponding thiol was carried out with sodium hydroxide in a dioxane/water mixture.[11] In order to ensure chemical diversity, seven thiols with markedly different steric and electronic properties were used at this stage. Finally, we took advantage of the hydroxy group in **3**–**9** to establish a representative set of phosphite and phosphinite moieties following standard procedures.[6f,12] The resulting enantiopure ligands were isolated in good yields as white solids (phosphite-thioether ligands **L1**–**L7a**–**c**) or colorless oils (phosphinite-thioether ligands **L1**–**L7d**–**g**). Phosphite-thioether ligands were found to be stable in air and resistant to hydrolysis, whereas the phosphinite analogues proved less stable, slowly decomposing even when stored at low temperature.

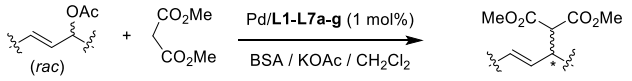


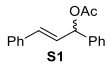
Scheme 1. Three-step synthesis of phosphite/phosphinite-thioether ligands **L1**–**L7a**–**g** from indene. (i) (*R,R*)-Mn-salen catalyst, 4-PPNO, aq. NaClO, CH_2Cl_2;[10] (ii) RSH, NaOH, dioxane/H_2O (10:1);[11] (iii) $ClP(OR^1R^2)_2$; $(OR^1R^2)_2$= **a**–**c**, Py, toluene and (iv) $ClPR^3_2$; R^3= **d**–**g**, NEt_3, toluene.

All ligands were characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and HRMS. All data were in agreement with assigned structures.[13] See experimental section for purification and characterization details.

Evaluation of the first generation ligand library in the allylic substitution of symmetrical 1,3-disubstituted allylic substrates. As already mentioned, the catalyst's ability to adjust to the steric demands of the substrate is a key factor in transferring the chiral information to the product. To assess the potential of this ligand library in the allylic substitution, we first tested **L1**–**L7a**–**g** in the Pd-catalyzed allylic substitution of two substrates with different steric requirements: the benchmark substrate **S1** and the more challenging cyclic **S2** (Table 1). Excellent yields were almost invariably obtained under mild reaction conditions (*i.e.* 1 mol% Pd, ligand-to-palladium ratio of 1.1 at room temperature) with TOF as high as 2000 mol (mol h)$^{-1}$. As for the enantioselectivities, up to 97% ee for **S1** and 88% ee for **S2** could be achieved by using ligands that combine an aryl thioether group with a chiral biaryl phosphite moiety.

Table 1. Pd-catalyzed allylic alkylation of S1–S2 with dimethyl malonate as nucleophile using ligands L1–L7a–g.[a]



		 S1		 S2	
Entry	L	% Conv (h)[b]	%ee[c]	% Conv (h)[b]	%ee[c]
1	**L1a**	100 (0.5)	17 (*R*)	100 (2)	15 (*S*)
2	**L1b**	100 (0.5)	90 (*R*)	100 (2)	66 (*R*)
3	**L1c**	100 (0.5)	75 (*S*)	100 (2)	61 (*S*)
4	**L1d**	100 (0.5)	50 (*R*)	100 (2)	28 (*S*)
5	**L1e**	100 (0.5)	25 (*R*)	100 (2)	11 (*S*)
6	**L1f**	5 (0.5)	32 (*R*)	10 (2)	28 (*S*)
7	**L1g**	100 (0.5)	4 (*R*)	100 (2)	14 (*R*)
8	**L2b**	100 (0.5)	90 (*R*)	100 (2)	62 (*R*)
9	**L3b**	100 (0.5)	84 (*R*)	100 (2)	60 (*R*)
10	**L3e**	100 (0.5)	63 (*R*)	100 (2)	77 (*S*)
11	**L4b**	100 (0.5)[d]	97 (*R*)	100 (2)	85 (*R*)
12	**L5b**	100 (0.5)	96 (*R*)	100 (2)	86 (*R*)
13	**L5c**	100 (0.5)	80 (*S*)	100 (2)	84 (*S*)
14	**L5d**	100 (0.5)	28 (*R*)	100 (2)	13 (*S*)
15	**L5e**	100 (0.5)	40 (*R*)	100 (2)	11 (*S*)
16	**L6b**	100 (0.5)	96 (*R*)	100 (2)	88 (*R*)
17	**L7b**	100 (0.5)	97 (*R*)	100 (2)	87 (*R*)
18[e]	**L5b**	100 (1)	96 (*R*)	100 (4)	85 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt. [b] Conversion measured by ^{1}H NMR. [c] Enantiomeric excesses measured by HPLC for dimethyl 2-(1,3-diphenylallyl)malonate (**10**) and by GC for dimethyl 2-(1,3-cyclohexanylallyl)malonate (**11**). [d] TOF= 2000 mol (mol h)$^{-1}$ calculated after 5 min from catalysis performed at 0.25 mol% of Pd. [e] Reactions carried out using PC as solvent at 40 °C.

In an effort to measure the contribution of the different *P*-donor groups, we analyzed the results of ligands **L1a**–**g** (entries 1–7). The trend was clearly pointing out to a superior performance of phosphite- over phosphinite-based structures (i.e. entry 2 vs. 4–7), even with very bulky ones. We wondered whether the ligand chirality might be able to control the conformation around a biphenyl moiety devoid of chiral axis. However, this possibility was ruled out by comparing entries 1-3, where the superior performance of ligands bearing a phosphite with axial chirality was evident (entries 2–3). Actually, the chiral axis seems to be the major factor in controlling the enantioselectivity. Indeed, ligands differing only in the configuration of this chiral axis (but otherwise having the same stereocenters) give rise to products with opposite absolute configuration (entries 2–3). Considering the substrates independently, with **S1** a remarkable cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone is observed, which results in a matched combination with ligand **L1b**, that bears an (*R*) chiral axis (entry 2 vs 3). This cooperative effect is less pronounced for cyclic substrate **S2**, and both enantiomers of the alkylated products are therefore easily accessible with similar levels of enantioselectivity by simply setting the configuration of the biaryl phosphite moiety (entry 2 vs 3).

Finally, by further comparing ligands **L1**–**L7b**, we found that the electronic and steric properties of the thioether substituent have a small but important effect on the enantioselectivities: ligands with aryl-thioether groups led to higher ee's (especially with cyclic substrate **S2**; *i.e.* entry 11 vs 2, 8 and 9) than their counterparts with alkyl thioether moieties, even for the bulky *tert*-butyl thiol derivative. In summary, the best enantioselectivities for **S1** (ee's up to 97%) were obtained with ligands **L4**–**L7b**, built from a combination of any aryl thioether group with an *R*-biaryl phosphite group: the above mentioned matched combination (entries 11, 12, 16 and 17). On the other hand, the best enantioselectivities recorded for substrate **S2** (ee's up to 88%), in both enantiomers of the alkylated product, were obtained with ligands **L4**–**L7b**–**c**, containing either an *R*- or *S*-biaryl phosphite group with an aryl thioether moiety (*i.e.* entries 11–13 and 16–17).

With the aim of improving the sustainability profile of the process, we studied the reactions in 1,2-propylene carbonate (PC), an environmentally friendly alternative to standard organic solvents because of its high boiling point, low toxicity, and "green" synthesis.[14] In spite of these environmental advantages, this solvent has been scarcely used in asymmetric Pd-catalyzed allylic substitution and mainly limited to the standard **S1** substrate and dimethyl malonate as nucleophile.[4d,14b,15] Thus, we repeated the allylic substitution of substrates **S1** and **S2** in PC (Table 1, entry 18; see also Table S1 in the Supporting Information for the use of PC for the allylic substitution of other substrates and nucleophiles). Gratifyingly, the enantioselectivities remained as high as those observed when dichloromethane was used.

Optimization of ligand parameters. DFT computational studies guiding to fine-tuned phosphite-thioether ligands L8. With the ultimate goal of fine-tuning the ligands to increase enantioselectivity, we carried out DFT calculations of the transition states and key Pd-olefin intermediates involved in the enantiodetermining step. Previous mechanistic studies on Pd-catalyzed allylic alkylation have established the irreversible nucleophilic attack as the enantiodetermining step, although the corresponding transition state (TS) can be either early or late, depending on the nucleophile, ligands, and reaction conditions.[16] In the latter case, if the transition states are very similar

to products the enantioselectivity of the process could also be described by the Pd-olefin complexes.

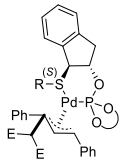
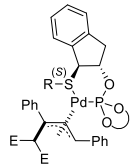
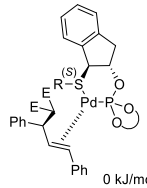
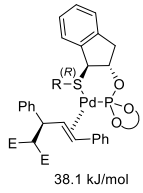
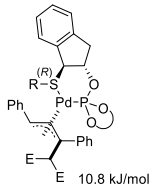
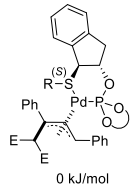
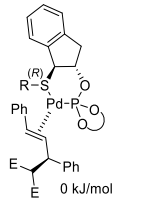
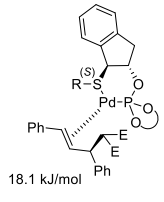
Therefore, we started by calculating the relative stability of the transition states and the Pd-olefin intermediates using the model substrate **S1** and dimethyl malonate as nucleophile with ligands **L5b**–**c**. The goal was to evaluate the effect of the chiral axis of the biaryl phosphite moiety, as these ligands differ only in the configuration of this biaryl (see Table 1, entry 12 vs 13). Only the two *syn-syn* allyl complexes were calculated, neglecting the contribution of other allylic species of higher energy (*anti-anti* and *syn-anti*).[3d] In this study, we have taken into account the configuration of the thioether and the attack of the nucleophile *trans* to P and S atoms. In contrast to *P-N* ligands, the *trans* effect exerted by the thioether and the phosphite are of a similar magnitude; indeed, previous studies have shown that small changes in the ligand can shift the *trans* preference in *P,S*-ligands.[5b,17] The results of the most stable transition states ($TS_{(R)}$ and $TS_{(S)}$) and Pd-olefin intermediates (Pd-olefin$_{(R)}$ and Pd-olefin$_{(S)}$) leading to the formation of both product enantiomers are shown in Table 2 (the full set of calculated TSs and Pd-olefin intermediates can be found in the Supporting Information). The energy differences of the calculated TSs match the results obtained in the catalytic process, the value for **L5b** ($\Delta\Delta G^{\#}$= 28 kJmol^{-1}; ee_{calc} > 99% (*R*)) being therefore higher than that of **L5c** ($\Delta\Delta G^{\#}$= 10.8 kJmol^{-1}; ee_{calc} = 96% (*S*)). This is in agreement with the higher enantioselectivities achieved using **L5b** than **L5c** (96% (*R*) ee for **L5b** vs 80% (*S*) ee for **L5c**; Table 1, entries 12 and 13). It must be mentioned here that the calculated ee values were obtained by using the eight different transition states for each ligand reported in the Supporting Information. If we had only used the two reported in Table 2, the values for **L5b** and **L5c** would have been 99% (*R*) and 98% (S), respectively.

Moreover, DFT correctly predicts the formation of the opposite product enantiomers when **L5b** and **L5c** are applied. It should be noted that, in contrast to what was observed with ligand **L5b**, both enantiomers of the substitution product obtained with ligand **L5c** arise from TSs with *exo* coordination of the substrate, with the nucleophilic attack *trans* to P (for the major enantiomer) and *trans* to S (for the minor enantiomer). Finally, the calculated energies of the Pd-olefin intermediates do not correlate well with the experimental results (Table 2). For both ligands, the most stable olefin complex corresponds to the *R*-enantiomer in more than 99% ee.

Identification of the origin of enantioselectivity from direct inspection of the structures for the two most stable transition states (TSs) with ligands **L5b** and **L5c** (shown in Figure S1 in the Supporting Information) is not trivial. We tried to apply a distortion/interaction analysis, also in the SI, but the results were inconclusive. The differences between the two systems were in the distortion part, but their analysis was difficult. A quadrant analysis (see Section SI.23) was on the contrary more indicative. The key to selectivity is in the steric repulsion between one of the phenyl substituents of the substrate and the biaryl phosphite moiety. The modifications between the **L5b** and **L5c** ligands places the steric bulk associated to the biaryl phosphite in a different quadrant, thus favoring different enantiomers. Interestingly, the steric bulk on the "sulphur side" of the catalyst is also important, as it pushes the sterically active regions of substrate and catalyst closer to each other, thus enhancing selectivity.

Based on the previous findings, we investigated whether the lower enantiomeric excesses recorded with the cyclic substrate **S2** (ee's up to 88%) could be improved by increasing the steric hindrance of the ligand. A simple way to do this is to introduce a thioether group that is bulkier than the 2,6-dimethylphenyl moiety, while maintaining the aryl group (that has been shown to perform better than its alkylic counterparts). For this purpose, we ran analogous TS calculations for **S2** with ligand **L5b** (bearing the 2,6-dimethylphenyl thioether group) and with other ligands containing instead the bulkier 2,6-diisopropylphenyl or anthryl moieties. To accelerate the DFT calcu

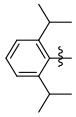
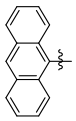
Table 2. Schematic representation and relative free energies in solution of the most stable *R*- and *S*- transition states in kJ/mol (left) and of the most stable *R*- and *S*- Pd-π-olefin complexes (right) for the substrate S1 with dimethyl malonate and L5b and L5c ligands. Computational and experimental enantiomeric excesses are also presented.

	Transition states (TSs)				Pd-olefin complexes			
Ligand	$TS_{(R)}$	$TS_{(S)}$	% ee_{calc}	% ee_{exp}	Pd-olefin$_{(R)}$	Pd-olefin$_{(S)}$	% ee_{calc}	% ee_{exp}
L5b	 0 kJ/mol *endo*	 28 kJ/mol *exo*	>99 (*R*)	96 (*R*)	 0 kJ/mol	 38.1 kJ/mol	>99 (*R*)	96 (*R*)
L5c	 10.8 kJ/mol *exo*	 0 kJ/mol *exo*	96 (*S*)	80 (*S*)	 0 kJ/mol	 18.1 kJ/mol	>99 (*R*)	80 (*S*)

E= CO_2Me

lations we used ammonia as model nucleophile.[18] The results show that the enantioselectivity is affected by the steric effects of the thioether group (Table 3), increasing from 9% (*R*) for ligand **L5b** (with a 2,6-dimethylphenyl thioether group) to 35% (*R*) with a 2,6-diisopropylphenyl thioether, and to 74% (*R*) with an anthryl thioether moiety. The results of these calculations prompted us to prepare two new ligands containing an anthryl thioether group (**L8b** and **L8c**; Figure 1)[19] and test them in the Pd-catalyzed alkylation of **S2**. To our delight, the introduction of this bulky aromatic moiety did affect positively the enantioselectivity, which increased from 86% ee to 94% ee (Table 3), as predicted by the theoretical calculations.[20] This result is comparable to the best one reported in the literature for this challenging substrate.[3] Interestingly, ligand **L8b** also provided the highest enantioselectivity in the alkylation of linear substrate **S1** (ee's up to 99% (*R*), compared to previous best value 97% with ligand **L7b**, under the same reaction conditions).

Table 3. Comparison between theoretical and experimental results in the Pd-catalyzed allylic substitution of S2.

R⁄⁄S	L	$\Delta\Delta G^{\#}_{calc}$	% ee-$_{calc}$	% ee_{exp}[a]	$\Delta\Delta G^{\#}_{exp}$[a]
	**L5b**	1.2 kJ/mol	9 (*R*)	86 (*R*)	6.3 kJ/mol
	-	2.1 kJ/mol	35 (*R*)	-	-
	**L8b**	6.8 kJ/mol	74 (*R*)	94 (*R*)[b]	8.6 kJ/mol

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 2 hours. [b] Ligand **L8c** provided the alkylated product **11** in 93% ee (*S*).

Allylic substitution of linear substrate S1 with several nucleophiles. Scope and limitations. We initially considered the allylic substitution of substrate **S1** with an extensive range of C-, N- and O-nucleophiles. Table 4 shows the results using ligand **L8b**, which had provided the best results in the allylic alkylation of **S1** with dimethyl malonate as benchmark nucleophile. A variety of malonates, including the allyl-, butenyl-, pentenyl- and propargyl-substituted ones, reacted with **S1** to provide products **13**–**19** in high yields and enantioselectivities (up to 99% ee, entries 1–7). These substituted malonates are known to be more challenging nucleophiles for Pd-catalyzed allylic substitution, but they give rise to more interesting products from a synthetic point of view (see section 2.6 below). The addition of acetylacetone also proceeded with high enantiocontrol (entry 8, ee's up to 98%). High yields and enantioselectivities were also found in the addition of malononitrile and isopropyl cyanoacetate (products **21** and **22**; ee's up to 99%, entries 9 and 10) albeit the diastereoselectivity of the latter was low, as expected for such an acidic stereocentre.[21]

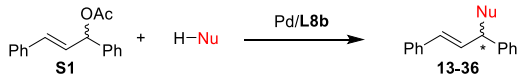
Pyrroles, which are electron-rich N-containing heterocycles interesting from a synthetic and biological point of view,[22] also performed well as nucleophiles in this reaction. Despite their importance, as far as we know only one catalytic system has been reported to be successful in the Pd-catalyzed allylic alkylation of **S1** type substrates with pyrroles, the reaction involving inconvenient low temperature (–20 ºC).[23] The difficulty of the transformation is more evident if we consider that, even two of the most successful ligands developed for this process (Trost diphosphine and phosphine-oxazoline PHOX), did not work with pyrroles.[23] Thus, we were pleased to find that using the Pd/**L8b** system we could reach ee's up to 99% and high yields working at room temperature (entries 11 and 12).

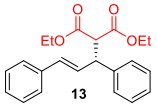
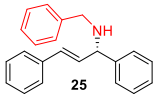
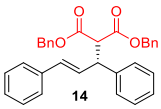
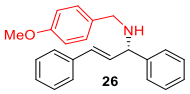
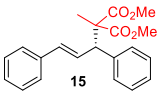
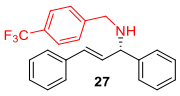
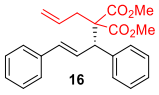
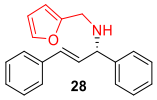
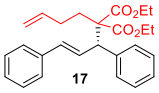
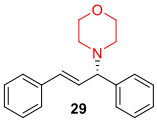
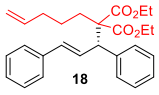
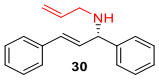
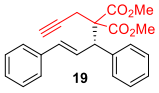
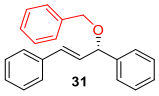
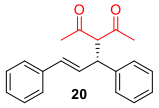
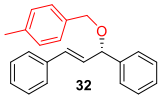
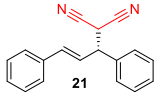
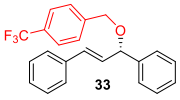
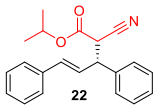
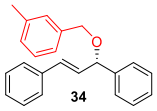
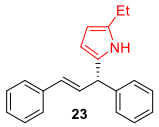
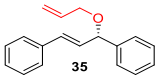
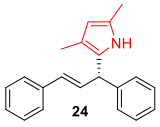
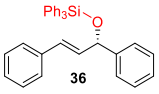
Chiral allylic amines are also ubiquitous in biologically active compounds,[3n] so we next studied the use of amine derivatives as nucleophiles. Benzylamine provided the substitution product **25** in high yield and enantioselectivity (99% ee; entry 13). To test the scope of allylic amination, the reaction of **S1** was evaluated using other N-nucleophilic compounds (entries 14–18). The combination Pd/**L8b** also proved highly efficient in the addition of *p*-methoxy- and *p*-trifluoromethylbenzylamines (compounds **26** and **27**) and the furfurylamine **28** (entries 14–16), enantiocontrol being always excellent. The addition of morpholine, a cyclic secondary amine, also gave the expected product with high enantioselectivity (product **29**; entry 17), while allylamine proceeded with comparably high enantioselectivity (97% ee; entry 18). This is especially interesting given the fact that the amination product **30** is a key intermediate in the synthesis of complex molecules. For example, the Boc protected derivative of **30** can be further applied in metathesis reactions for the construction of a dihydropyrrole derivative (see section 2.6 below).

The exquisite enantiocontrol observed for C- and N-nucleophiles can also be extended to aliphatic alcohols (compounds **31**–**35**, ee's up to 99%; entries 19–23). The effective allylic substitution with this type of O-nucleophiles opens up new synthetic avenues towards chiral ethers, which are important for the synthesis of biologically active molecules.[24] Despite the potential of the resulting products, a general catalytic solution for the Pd-catalyzed allylic etherification has remained elusive and most of the few successful examples reported to date deal with phenols,[25] while aliphatic alcohols have been less studied.[4e,6a,f,26] Moreover, the enantioselectivities reported so far largely depend on the type of aliphatic alcohol and small modifications of their electronic properties[4e,6a,f,26] can have a large impact on this parameter. Using our streamlined ligand **L8b**, we found that benzylic alcohols gave excellent results regardless of the steric and electronic properties of the aryl group (entries 19–22). Allyl alcohol also furnished the desired product in high yield and ee (entry 23). Even more outstanding are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with triphenylsilanol (entry 24), a rather unusual nucleophile that gives rise to a protected chiral alcohol.[26e] Remarkably, enantioselectivities recorded with O-nucleophiles (entries 19–24) were, at the very least, as high as those obtained with dimethyl malonate.

Allylic substitution of several linear and cyclic substrates S2–S9 using several C-nucleophiles. Scope and limitations. After the broad scope of nucleophiles displayed by the catalytic system with **S1**, we turned our attention to the use of five additional linear substrates (**S3**–**S7**) with electronic and steric requirements different from **S1** (Table 5, entries 1–6). Advantageously, we found

Table 4. Pd-catalyzed allylic substitution of linear substrate S1 with different types of C-, N- and O-nucleophiles using Pd/L8b catalytic system.[a]



Entry	Product	% Yield[b]	% ee[c]	Entry	Product	% Yield[b]	% ee[c]
1		94	99 (*R*)	13		88	99 (*S*)
2		92	98 (*R*)	14		81	99 (*S*)
3		92	97 (*S*)	15		78	99 (*S*)
4		93	98 (*S*)	16		83	97 (*S*)
5		89	98 (*S*)	17		87	98 (*S*)
6		91	95(*S*)	18		79	97 (*S*)
7		90	99 (*S*)	19[e]		92	99 (*S*)
8		88	98 (*R*)	20[e]		90	99 (*S*)
9		84	99 (*R*)	21[e]		91	98 (*S*)
10		82 (60:40 dr)	98/97[d]	22[e]		93	98 (*S*)
11[d]		87	96 (*S*)	23[e]		83	96 (*S*)
12[d]		85	>99 (*S*)	24[e]		78	99 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% ligand, CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 30 min. [b] Isolated yield. [c] Enantiomeric excesses measured by HPLC or GC. [d] 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol% ligand CH_2Cl_2 (2 mL), K_2CO_3 (2 equiv) at rt for 18 h. [e] 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol% ligand CH_2Cl_2 (2 mL), Cs_2CO_3 (3 equiv) at rt for 18 h.

that the catalytic performance was neither affected by the introduction of electron-withdrawing, electron-donating groups (entries 1–3), nor by the presence of *ortho*- and *metha*-substituents at the phenyl groups of the substrate (entries 4–5). A remarkable enantioselectivity (entry 6) was still achieved in the Pd-catalyzed allylic alkylation of **S7**, a challenging substrate that typically gives rise to the corresponding substitution products in much lower enantioselectivities than **S1** in otherwise identical conditions.

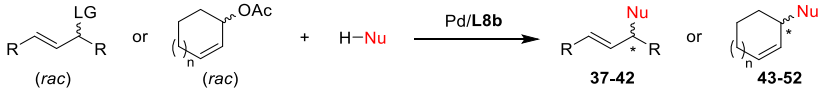
Finally, we wanted to see if the high enantioselectivities achieved in the allylic substitution of linear substrates were retained for their notoriously difficult cyclic analogues. To this end, a number of cyclic substrates with different ring sizes were tested using ligand **L8b** (Table 5, entries 7–16; for the results using the Pd/**L8c** catalytic system see Table S2 in the Supporting Information). For the cyclohexenyl derivative **S2**, a range of C-nucleophiles proved to give yields and enantioselectivities as high, if not higher, as those recorded with dimethyl malonate

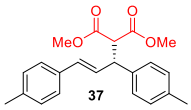
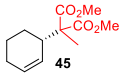
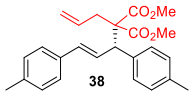
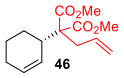
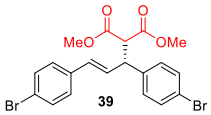
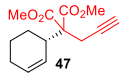
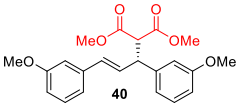
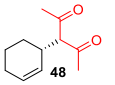
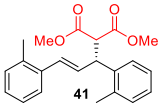
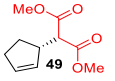
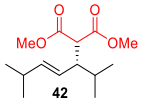
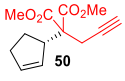
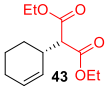
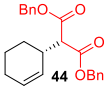
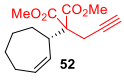
(ee's up to 97%, entries 7–11). The only exception was acetylacetone that led to somewhat lower enantioselectivity (entry 12). High enantioselectivities in both enantiomers of the substitution products were thus obtained using methyl-, allyl- and propargyl-substituted malonates (compounds **45**–**47**; Table 5; entries 9–11 and Table S2). Furthermore, the biaryl phosphite group in Pd/**L8b** and Pd/**L8c** can adapt its chiral pocket to efficiently mediate the substitution of other cyclic substrates (entries 13–16). Excellent yields and enantioselectivities, comparable to the best reported in the literature, were obtained in the allylic alkylation of a 7-membered cyclic substrate with different C-nucleophiles (products **51** and **52**; entries 15 and 16). Even more interesting is that the good performance could be also extended to the allylic alkylation of a more challenging 5-membered cyclic substrate (compounds **49** and **50**; entries 13 and 14).

Synthetic applications of the allylic substitution compounds. Preparation of chiral functionalized (poly)carbocyclic and heterocyclic compounds 53–61. To illustrate the synthetic versatility of the compounds obtained from the enantioselective Pd-catalyzed allylic substitution, we have prepared a range of chiral functionalized carbocycles (**53**–**56**), heterocycles (**57**–**58**) and polycarbocycles (**59**–**61**) from the enantioenriched allylic substitution products. These compounds have been synthesized by straightforward reaction sequences involving allylic substitution of the appropriate substrates followed by either ring-closing metathesis (Scheme 2) or Pauson-Khand enyne cyclization (Scheme 3).

According to this strategy, the alkylated compounds **16**–**18** (see Table 4 above) and **38** (see Table 5 above) undergo clean ring-closing metathesis with no loss of enantiopurity, furnishing a number of 5, 6 and 7-membered carbocyles, in high yields and enantioselectivities (ee's ranging from 95–98%; Scheme 2). In an analogous manner, the O-heterocycle (*S*)-**57** is achieved by sequential allylic etherification of **S1** with allylic alcohol and ring-closing metathesis reacti-

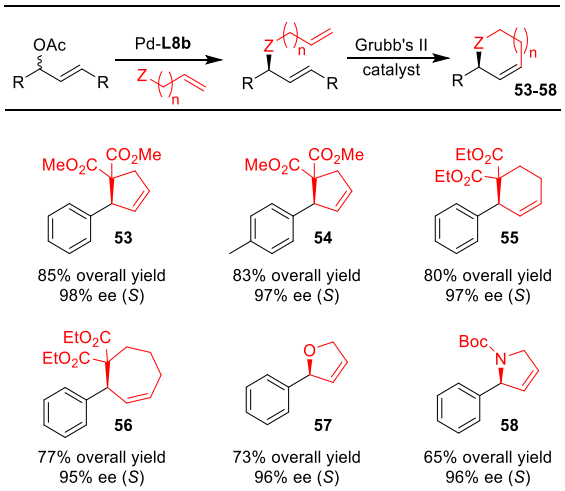
Table 5. Pd-catalyzed allylic substitution of substrates S2–S9 with several C-nucleophiles using Pd/L8b catalytic system.[a]



Entry	Substrate	Product	% Yield[b]	% ee[c]	Entry	Substrate	Product	% Yield[b]	% ee[c]
1	**S3**	 **37**	98	98 (*R*)	9	**S2**	 **45**	87	91 (*R*)
2	**S3**	 **38**	87	97 (*R*)	10	**S2**	 **46**	84	94 (*R*)
3	**S4**	 **39**	89	96 (*R*)	11	**S2**	 **47**	86	97 (*R*)
4	**S5**	 **40**	91	97 (*R*)	12	**S2**	 **48**	82	80 (-)
5	**S6**	 **41**	87	99 (*R*)	13	**S8**	 **49**	80	84 (-)
6	**S7**	 **42**	91	>95 (*R*)	14	**S8**	 **50**	83	85 (-)
7	**S2**	 **43**	87	95 (*R*)	15	**S9**	 **51**	90	96 (*R*)
8	**S2**	 **44**	84	95 (*R*)	16	**S9**	 **52**	92	96 (*R*)

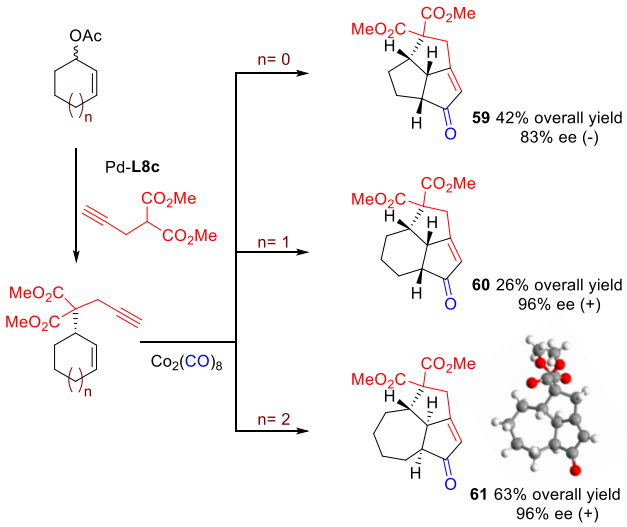
[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% ligand, CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 2 h. [b] Isolated yield. [c] Enantiomeric excesses measured by HPLC, GC or ^{1}H-NMR using $[Eu(hfc)_3]$.

tion (Scheme 2); the corresponding N-heterocycle **58** performs similarly, albeit it requires protection of the amine with Boc prior to the ring-closing metathesis reaction, presumably owing to the azophilicity of ruthenium.



Scheme 2. Preparation of chiral functionalized carbo- and heterocyclic compounds **53**–**58.**

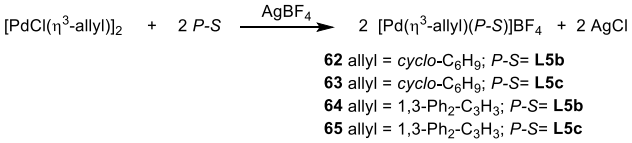
The second derivatization we tackled was the Pauson-Khand reaction of the propargylated derivatives **47**, **50** and **52** (see Table 5 above), which differ only in the size of the cycloalkene ring. Formation of the complex with $Co_2(CO)_8$, followed by thermal decomposition, gave rise to the [2+2+1] cycloadducts **59**–**61**, which feature an architecturally complex tricyclic system (Scheme 3).



Scheme 3. Preparation of chiral functionalized polycarbocyclic compounds **59**–**61**. X-ray structure of compound **61** is also included.

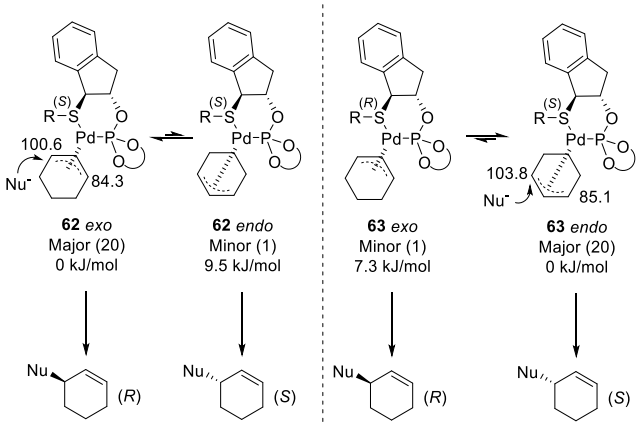
Remarkably, the chiral information on the allylic substitution products was reliably conveyed to the final products, which were isolated as single diastereomers and with ee's replicating those of the starting materials. The relative configuration of ketone **61** was assigned to be *trans–cis* on the basis of a single crystal X-ray diffraction image. In contrast, **59** and **60** are assigned as the *cis–cis* diastereomer according to literature precedents.[27]

Study of the Pd-π-allyl intermediates. Our DFT calculations have established the nucleophilic attack as the enantiodetermining step (see section 2.3, vide supra). With the aim of better understanding the catalytic process, we decided to prepare and characterize the Pd-allyl intermediates and determine their relative reactivity towards the nucleophile. Consequently, we studied the Pd-π-allyl compounds **62**–**65** [Pd(η^3-allyl)(*P-S*)]BF_4 (*P-S* = **L5b**–**c**) by NMR and DFT studies. These Pd-intermediates containing cyclohexenyl and 1,3-diphenyl allyl groups were synthesized as previously reported (Scheme 4).[28] All complexes were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy[29] and mass spectrometry. Unfortunately, we were unable to obtain crystals of sufficient quality to perform X-ray diffraction measurements. The ESI-HR-MS showed the heaviest ions at *m/z* corresponding to the cation.



Scheme 4. Preparation of [Pd(η^3-allyl)(*P-S*)]BF_4 (*P-S* = **L5b**–**c**) complexes **62**–**65**.

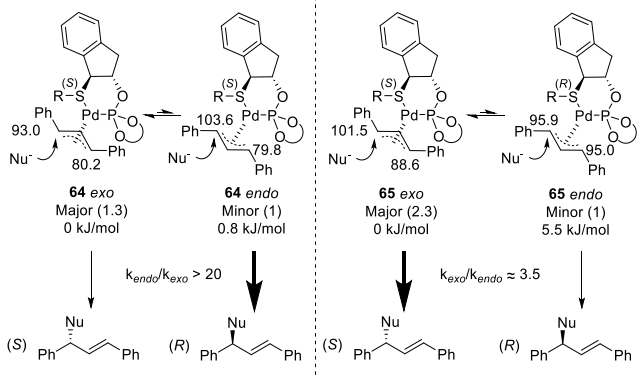
To understand why the configuration of the enantiomer of the alkylated product changes with the configuration of the biaryl phosphite group in the substitution of cyclic substrate **S2**, we compared the Pd-1,3-cyclohexenyl-allyl intermediate **62**, which contains ligand **L5b** with its counterpart Pd/**L5c** intermediate (**63**). The VT-NMR study (30 ºC to –80 ºC) showed the presence of essentially single isomers (ratio ca. 20:1; Scheme 5) for both intermediates (**62** and **63**). The major isomers were unambiguously assigned by NMR to be the *exo* isomer for **62** and the *endo* isomer for **63** (see Supporting Information for NOE details). In both cases, the thioether group had an *S*-configuration. The assignments are in agreement with the DFT calculations of the Pd-η^3-cyclohexenyl complexes (see Supporting Information for the results of the full set of calculated Pd-η^3-allyl intermediates). Thus, for Pd/**L5b** the major Pd-η^3-*exo* isomer is 9.5 kJ/mol more stable than the most stable *endo* isomer, while for Pd/**L5c** the Pd-η^3-*endo* isomer energy is 7.3 kJ/mol lower than the most stable *exo* isomer. The ^{13}C NMR chemical shifts indicate that for both major isomers the most electron-deficient allylic terminal carbon is *trans* to the phosphite group. Assuming that the nucleophilic attack takes place at the more electron-deficient allyl carbon terminus, the fact that the observed stereochemical outcome of the reaction (86% ee (*R*) for Pd/**L5b** and 84% ee (*S*) for Pd/**L5c**) is similar to the diastereoisomeric excess (de 90%) of the Pd-intermediates indicates that both major and minor species react at a similar rate. In summary, the study of Pd-allyl intermediates shows that changes in the configuration of the phosphite moiety lead to changes in the ratio of the species that provide both enantiomers of the alkylated product. The enantioselectivity is therefore mainly controlled by the population of the Pd-allyl intermediates.



Scheme 5. Diastereoisomeric Pd-η^3-allyl intermediates for **S2** with ligands **L5b** and **L5c**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons and the computed relative free energies in solution between the *endo* and *exo* Pd-allyl intermediates are also shown for compounds **62** and **63**, in kJ/mol.

Finally, to assess the impact of the phosphite chiral axis configuration on the enantioselectivity obtained for **S1**, we compared the corresponding Pd allylic intermediates with ligands **L5b** and **L5c** (**64** and **65**, respectively). In this case, **L5b** provided high enantioselectivity whereas **L5c** proved less selective, which is in contrast to the observation made for the alkylation of the cyclic substrate **S2**. The VT-NMR study (30 ºC to –80 ºC) of intermediates **64** and **65** showed a mixture of two isomers in equilibrium with ratios 1.3:1 and 2.3:1, respectively (Scheme 6). All isomers were assigned to be *syn*/*syn*, according to the NOE interaction between the two terminal protons of the allyl group. Unfortunately, the NOE contacts are not conclusive enough to unambiguously assign the 3D structure of these isomers. The final assignment of these Pd-allyl intermediates was performed by DFT studies (see Supporting Information) and further assessed by studying the reactivity of the Pd-intermediates with sodium dimethyl malonate at low temperature by *in situ* NMR studies (Figure S3 of the SI). The DFT-calculated population of the different Pd-allyl species (*i.e.* ratio of 1.4:1 for complex **64**) is in good agreement with the population obtained experimentally (*i.e.* ratio of 1.3:1 for **64**). Calculations indicate that for both systems, the most stable Pd-allyl intermediate is the *exo* isomer, the *endo* isomer being higher in energy (0.8 kJ/mol for Pd/**L5b** and 5.5 kJ/mol for Pd/**L5c**). On the other hand, the reactivity study of the Pd-intermediate **64** with sodium dimethyl malonate at low temperature reveals that the minor *endo* isomer reacts faster than the major isomer (Figure S3 of the SI; k_{endo}/k_{exo} >20). This reactivity pattern is in agreement with the previously presented TS calculations (see Section 2.2), which indicate that the most favourable (lowest in energy) transition state arises from the nucleophilic attack to the Pd-allyl *endo* intermediate, being the pathway through the *exo* TS higher in energy ($\Delta\Delta G^{\#}$= 28 kJ/mol; Table 2). All these evidences further support the DFT calculations that suggest that for intermediates **64** the major isomer has an *exo* disposition, while the minor isomer has an *endo* spatial arrangement. In contrast, the reactivity study of the Pd-allyl complex **65** indicates that the major *exo* isomer is the isomer that reacts faster with a nucleophile (Figure S3 of the SI; $k_{exo}/k_{endo} \approx 3.5$). Again, this finding is in agreement with the DFT calculations (*vide supra*, $\Delta\Delta G^{\#}$= 10.8 kJ/mol, Table 2) and corroborates the DFT isomer assignment of the Pd-allyl intermediates observed in solution, having the major isomer an *exo* arrangement.

It should be pointed out that, albeit for the Pd/**L5c** catalytic system the relative population of the faster reacting isomer is much higher than that of Pd/**L5b**, the latter provides higher enantioselectivity (96% ee for Pd/**L5b** vs 80% ee for Pd/**L5c**). Hence, in the case of **S1** the enantioselectivity seems to be controlled by the different reactivity of the allyl intermediates towards the nucleophile (rather than their population, as was the case for **S2**). These results are in line with the previous DFT calculations (see section 2.3, Table 2) and therefore further corroborate that the energy gap between the most stable TSs leading to each of the product enantiomers is higher for the Pd/**L5b** catalytic system than for Pd/**L5c**.



Scheme 6. Diastereoisomer Pd-η^3-allyl intermediates for **S1** with ligands **L5b** and **L5c**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons and the computed relative free energies in solution between the *endo* and *exo* Pd-allyl intermediates are also shown for compounds **64** and **65**, in kJ/mol.

CONCLUSIONS

A new and small library of P-thioether ligands has been tested in the Pd-catalyzed allylic substitution reaction. The modular architecture of the ligands has allowed the iterative optimization of the ligand parameters in order to fine control the chiral cavity in which the allyl system is embedded. The robustness of the thioether group adds another advantage to these ligands. Compared to previously reported larger furanoside derived P-S ligand library, the new library is easier to synthesize, in only three steps, from inexpensive indene. The simpler backbone of these new ligands gives rise to neat NMR spectra with less signal overlap, which facilitates the identification of relevant intermediates and accelerates the DFT calculations in the search for better catalysts. The combination of experimental and theoretical studies has therefore lead us to the rational design of an optimal, solid, air-stable P-S ligand for the Pd-catalyzed enantioselective allylic substitution. This ligand consistently gave excellent enantioselectivities for 40 compounds involving linear and cyclic substrates and a broad range C-, N-, and O-nucleophiles. The results were maintained using the propylene carbonate as green solvent. In comparison with previous furanoside-based P-S ligands, which have emerged as some of the most successful catalyst for this process, the new P-S ligand also provided a better activity and a wider nucleophile scope (i.e. including the addition of pyrroles and a broader range of amines). The species responsible for the catalytic performance were also identified by mechanistic studies based on NMR spectroscopy, thus ra-

tionalizing the origin of the enantioselectivity. For enantioselectivities to be high, the ligand parameters therefore need to be correctly chosen to either increase the difference in population of the possible Pd-allyl intermediates (for cyclic substrates) or to increase the relative rates of the nucleophilic attack for each of the possible Pd-allyl complexes (linear substrates). Finally, to assess the potential impact of this catalytic system in synthesis, the products have been employed in ring-closing metathesis or Pauson-Khand reactions, giving rise to a set of chiral (poly)carbo- and heterocyclic compounds with faithful transmission of the chiral information. The results presented here compete very well with a few other ligands that also provide high catalytic performance in several substrate and nucleophiles.

EXPERIMENTAL SECTION

General considerations. All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[30] Enantiopure (–)-indene oxide **2**[10] and phosphinite-thioether ligands **L1d**[12a] and **L5d**[12a] were prepared as previously described. Racemic substrates **S1**-**S9**[31] and Pd-allyl complexes $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[32] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{-}Cl)]_2$[33] were prepared as previously reported. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

General procedure for the regio- and stereospecific ring opening of 2. Preparation of thioether-alcohols 3-9 and 12. A solution of (–)-indene oxide **2** (2 mmol, 264 mg) in dioxane (4.5 mL/mmol of indene oxide) is treated with the corresponding thiol (3 mmol). Then, a solution of NaOH (3 mmol, 120 mg) in water (0.45 mL/mmol of indene oxide) is added dropwise. The reaction mixture is capped and stirred at 55 °C until the epoxide is consumed according to TLC analysis (*ca*. 45-60 min). After this, the mixture is cooled to room temperature, diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give a residue that is purified by flash chromatography on silica gel (eluent specified in each case) to give the desired thioether-alcohol (see Supporting Information for characterization details).

General procedure for the preparation of phosphite-thioether ligands L1–L8a–c. The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL), and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80 ºC for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (Hexane/Toluene/NEt_3 = 7/3/1) to produce the corresponding ligand as a white solid (see Supporting Information for characterization details).

General procedure for the preparation of phosphinite-thioether ligands L1–L8d–g. The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at rt, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at room temperature. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil (see Supporting Information for characterization details).

Typical procedure for the allylic alkylation of disubstituted linear (S1 and S3–S7) and cyclic (S2 and S8–S9) substrates. A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (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 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 ^1H NMR and enantiomeric excesses were determined either by HPLC (compounds **10**, **13**–**22**, **37**–**41** and **43**–**46**) or by GC (compounds **11**, **47**–**48** and **50**–**52**) or by ^1H NMR using $[Eu(hfc)_3]$ (compounds **42** and **49**). For characterization and ee determination details see Supporting Information.

Typical procedure for the allylic alkylation of disubstituted linear substrate S1 using pyrroles. A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite/phosphinite-thioether (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), the corresponding pyrrole (0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) were added. The reaction mixture was stirred at room temperature. After 18 h, 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 ^1H NMR and enantiomeric excesses were determined by HPLC. For characterization and ee determination details see Supporting Information.

Typical procedure for the allylic amination of disubstituted linear substrate S1. A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5 mL), the corresponding amine (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 2 hours, 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 ^1H NMR and enantiomeric excesses were determined by HPLC. For characterization and ee determination details see Supporting Information.

Typical procedure for the allylic etherification and silylation of disubstituted linear substrate S1. A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the

corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alcohol or silanol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After 18 h, 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 ^1H NMR and enantiomeric excesses were determined by HPLC. For characterization and ee determination details see Supporting Information.

Typical procedure for the preparation of chiral carbo- and heterocyclic compounds 53–58. A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was directly purified by flash chromatography (Hex/EtOAc 95:5) to obtained the desired compounds. For characterization and ee determination details see Supporting Information.

Typical procedure for the preparation of chiral tricyclic compounds 59–61. A solution of the starting enyne (0.187 mmol) in 1 mL of *tert*-butylbenzene was added to a solution of $Co_2(CO)_8$ (83 mg, 0.243 mmmol) in 0.5 mL of *tert*-butylbenzene under air. The flask was rinsed with 0.5 mL more of the same solvent. The resulting mixture was stirred at room temperature for 1 h, until full consumption of the starting material was observed by TLC. After that, the system was heated at 170 °C for a further hour. Then, it was cooled to room temperature, filtered on Celite with CH_2Cl_2 and concentrated in vacuo. The crude mixture was purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc (gradient form 90:10 to 70:30) to furnish the desired tricyclic compound as a white solid. For characterization and ee determination details see Supporting Information.

General procedure for the preparation of [Pd(η^3-allyl)(L)]BF_4 complexes 62–65. The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-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 (see Supporting Information for characterization details).

Study of the reactivity of the [Pd(η^3-allyl)(L))]BF_4 with sodium dimethyl malonate by *in situ* NMR.[34] A solution of *in situ* prepared [Pd(η^3-allyl)(**L**)]BF_4 (L= phosphite-thioether, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at –80 °C. At this temperature, a solution of cooled sodium dimethyl malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR. The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

Computational details. All calculations were performed using the Gaussian 09 program.[35] Optimizations of minima and transition states were performed employing the B3LYP[36] density functional and the 6-31G(d) basis set for all elements except for Pd for which the LANL2DZ[37] was used.[38] All energies presented correspond to single point calculations with the B3LYP-D3 functional[39] and the larger 6-311+G(d,p)[40] basis set for all elements except Pd. Solvation was taken into account along optimization and single points through the use of the PCM continuum model with the default parameters for dichloromethane.[41] No symmetry constraints were applied. The validity of the model was confirmed by a series of geometry optimizations at the B3LYP-D3 level on the four key transition states. The qualitative trends were unchanged: ligand **L5b** favored the *R* product (corrected ee of 64 *vs* uncorrected ee of 99.99) and ligand **L5c** favored the *S* product (corrected ee of 99.6 *vs* uncorrected ee of 97.5). Normal mode analysis of all transition states revealed a single imaginary mode corresponding to the expected nucleophilic attack of the nucleophile to one of the two allylic termini carbons. All energies reported are Gibbs free energies in solution at 298.15 K and calculated as $\Delta G_{reported} = \Delta G_{B3LYP/6\text{-}31G(d)} + (\Delta E_{B3LYP\text{-}D3/6\text{-}311+G(d,p)} - \Delta E_{B3LYP/6\text{-}31G(d)})$. A data set collection of the computational results is available in the ioChem-BD repository.[42]

ASSOCIATED CONTENT

Characterization details and copies of NMR spectra of the new ligands **L1**–**L8a**–**g**, ligand intermediates **3**–**9** and **12**, and Pd-allyl intermediates **62**–**65**. NOE experiments and reactivity studies of Pd-intermediates. NMR and ee determination details of substitution products and chiral functionalized (poly)carbocyclic and heterocyclic compounds.

Full sets of results for the allylic substitution of **S1**–**S9** in propylene carbonate as solvent and of cyclic substrates using Pd/**L8c** catalytic system.

Crystal data and structure refinement of compound **61**.

Calculated energies and coordinates for all computational structures.

Deformation and interaction energies for the TS containing ligands **L5b**–**c**.

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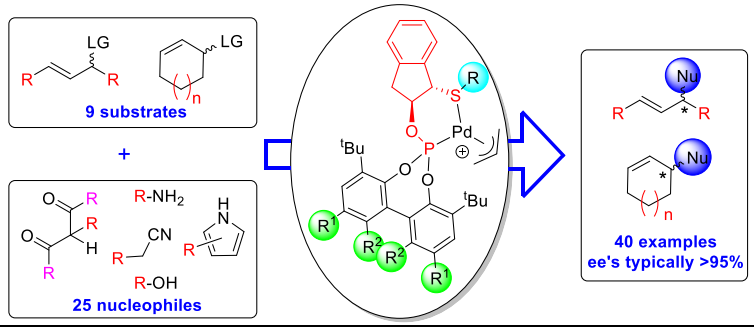
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