Conformational Preferences of a Tropos Biphenyl Phosphinooxazoline – a Ligand with Wide Substrate Scope

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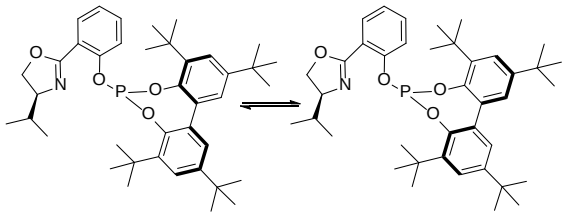
Supporting Information

Abstract: Excellent enantioselectivities are observed in palladium-catalyzed allylic substitutions of a wide range of substrate types and nucleophiles using a bidentate ligand composed of oxazoline and chirally flexible biarylphosphite elements. This unusually wide substrate scope is shown by experimental and theoretical studies of its η^3-allyl and η^2-olefin complexes not to be a result of configurational interconversion of the biaryl unit, since the ligand in all reactions adopts S_a,*S* configuration when coordinated to palladium, but rather the ability of the ligand to adapt the size of the substrate-binding pocket to the reacting substrate. This ability also serves as an explanation to its excellent performance in other types of catalytic processes.



Keywords: Palladium, allylic substitution, tropos P,N-ligands, NMR study, DFT study

INTRODUCTION

Enantioselective metal-catalyzed synthetic processes are ubiquitous for the construction of nonracemic chiral organic compounds.[1] The stereodirecting power of a catalyst usually relies on the choice of chiral ligand bound to the metal. Ligands with

broad substrate scope are desirable in order to limit time-consuming ligand design and preparation. The identification of privileged ligands[2] useful for a wide range of substrates and for different types of reactions is therefore an important issue.

Conformationally flexible ligands are viable candidates for the design of catalysts with wide substrate scope. Mikami and co-workers[3] have demonstrated that stereochemically dynamic, tropos[3d,4] ligands are capable of adapting their sense of chirality to a proximal chiral motif bound to the same metal center, and consequently to be able to replace rigid analogues with either absolute configuration. In a similar manner, adaptable ligand systems composed of a stereochemically flexible part covalently bound to a group with a rigid stereogenic element have been successfully employed in asymmetric catalysis.[5] In order to further exploit self-adaptable ligands in asymmetric catalysis, studies of their conformational preferences under different reaction conditions are desirable.

We have previously studied the conformational behavior of phosphepine and azepine ligands, such as **1** and **2** (Figure 1(a)).[6] By using palladium-catalyzed asymmetric allylic alkylation as an illustrative model process to probe the conformational issues, we found that the conformation of these flexible ligands may be influenced not only by structural units present in the catalyst, but also by the substrate undergoing reaction. In this particular catalytic process different ligands are usually required for different types of substrates in order to obtain products with high enantiopurity.[7] By using bisazepine ligands with two flexible biaryl moities, we were able to demonstrate that in palladium olefin complexes **3** and **4**, aimed to mimic the product olefin complexes from reaction of bulky linear ("broad") and small cyclic ("narrow") substrates, respectively, *R**,*R** (C_2) configuration was preferred in the complex containing the trans olefin, whereas *R**,*S** (C_s) was preferred in the complex with the cis olefin (Figure 1(b)).[8] In contrast, *R**,*S** configuration of the ligand was observed in η^3-allyl palladium complexes derived from (*E*)-1,3-diphenyl-2-propenyl acetate as well as from 3-cyclohexenyl acetate (not shown).

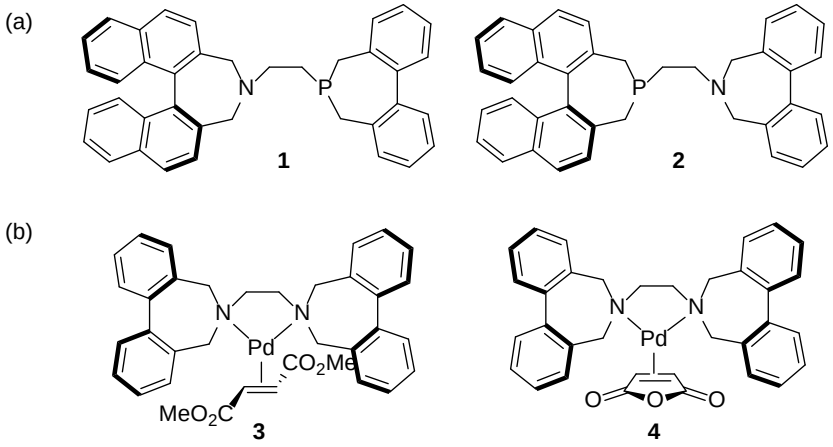


Figure 1. (a) Conformationally flexible phosphephine and azepine ligands **1** and **2**. (b) Palladium olefin complexes **3** and **4**.

Although tropoisomerization in azepine derivatives occurs while the ligand is coordinated to the metal center,[9] conformational change in ligands **1** and **2** was slow compared to nucleophilic attack, and the flexible ligands therefore behaved essentially as a mixture of the analogous rigid ligands, and thus proved to be less general than desired.

Ligands that tolerate a wide range of substrates are indeed rare. In this context, some of us were able to show that substrate versatility in Pd-catalyzed allylic substitutions can benefit from the introduction of a conformationally flexible biaryl phosphite element.[10] Thus, phosphite-oxazoline (*S*)-**5a** (Figure 2) constitutes one of the few examples of ligands that have provided high ee's in the Pd-catalyzed allylic alkylation of both the hindered model compound *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and unhindered cyclic substrate *rac*-3-cyclohexenyl acetate (**S2**).[11] This ligand has also been successfully applied in enantioselective palladium-catalyzed Heck reactions,[12] rhodium-catalyzed hydrosilylation of ketones,[13] and iridium-catalyzed hydroboration of 1,1-disubstituted olefins.[14] Since the barrier to inversion in phosphite ligands is known to be lower than that in phosphepine and azepine ligands,[15] we assumed that the broad substrate tolerance of (*S*)-**5a** may originate in its ability to adapt the conformation to the substrate undergoing reaction. In order to test if this was the case, we decided to study the conformational preferences of ligand (*S*)-**5a** in palladium complexes with relevance for asymmetric allylic alkylation. To this aim, we needed access to rigid analogues of (*S*)-**5a**. For this reason, (S_a,*S*)-**5b** and (R_a,*S*)-**5c** were prepared (Figure 2), their behavior in the catalytic reactions investigated, and the

structures of the corresponding olefin complexes studied by NMR spectroscopy and DFT calculations.

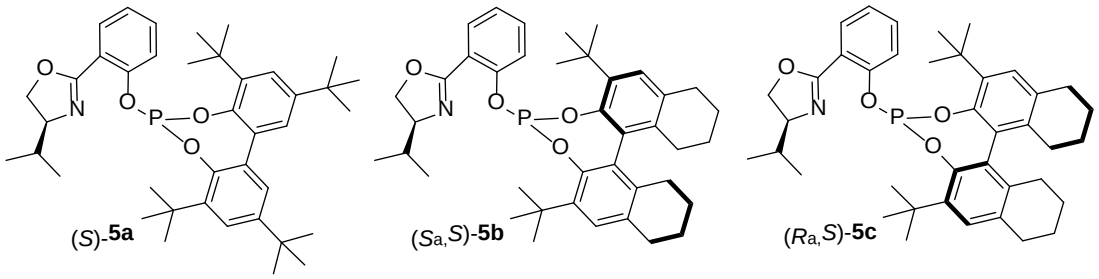
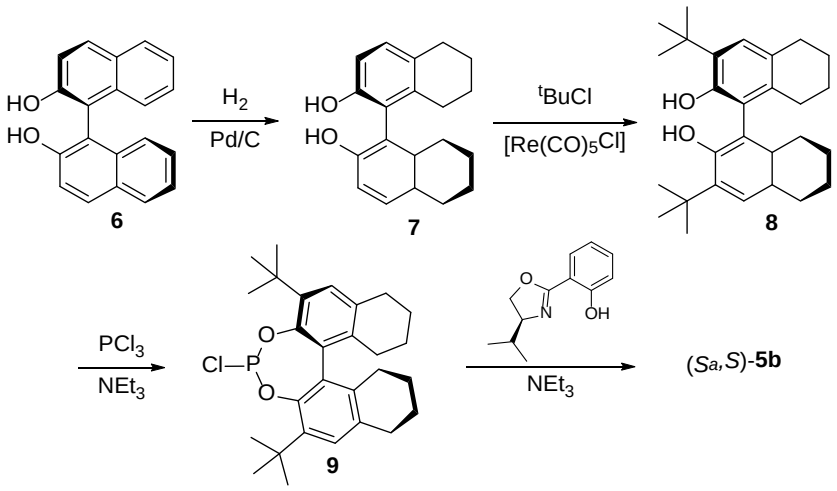


Figure 2. Phosphite-oxazoline ligands (*S*)-**5a**, (*S*$_a$,*S*)-**5b** and (*R*$_a$,*S*)-**5c**.

We have also extended the previous work on dimethyl malonate and benzylamine to other C-nucleophiles and to O-nucleophiles, among which are the rarely studied α-substituted malonates, β-diketones, alkyl alcohols, silanols, and fluorobis(phenylsulfonyl)methane, and to alkylations of other substrates, thereby further underlining the versatility of ligand **5a**.

RESULTS

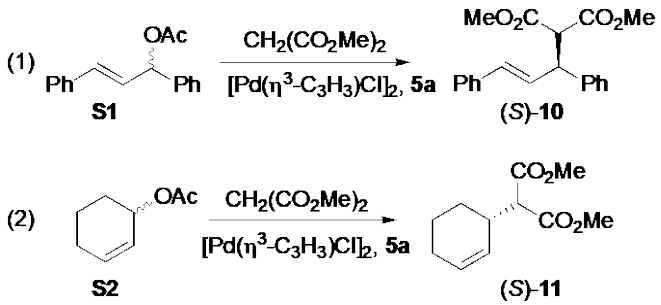
Preparation of Ligands. Ligand (*S*$_a$,*S*)-**5b** was prepared starting from (*S*)-binol (**6**), as shown in Scheme 1. Catalytic hydrogenation following a published procedure gave (*S*)-**7**,[16] which was reacted with *tert*-butyl chloride in the presence of chloropentacarbonylrhenium(I)[17] to yield (*S*)-**8**. Reaction with phosphorus trichloride gave compound (*S*)-**9**. Condensation of chlorophosphite (*S*)-**9** with (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol[18] afforded in good yield the final product (*S*$_a$,*S*)-**5b**. Ligand (*R*$_a$,*S*)-**5c** was prepared analogously starting from (*R*)-binol. The flexible ligand (*S*)-**5a** was prepared as previously described.[11]



Scheme 1. Preparation of ligand (S_a,*S*)-**5b**.

The rigid ligands gave rise to single signals in the ^{31}P NMR spectra, (S_a,*S*)-**5b** at 127.9 ppm and (R_a,*S*)-**5c** at 129.3 ppm. A single ^{31}P resonance was also observed from compound (*S*)-**5a**, at 136.6 ppm. Interestingly, upon gradual cooling this signal first broadened and at around –20 °C split into two signals originating from the S_a and R_a conformers, as a result of tropoisomerization being slow on the NMR time scale. The original spectrum, containing a single ^{31}P resonance, was restored by warming the sample to 25 °C. In the ^{1}H NMR spectrum several signals were split upon cooling (see Supporting Information).

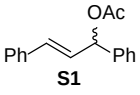
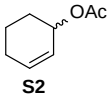
Catalytic Reactions. Palladium-catalyzed allylic alkylations of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and *rac*-3-cyclohexenyl acetate (**S2**), with dimethyl malonate as nucleophile and $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ as palladium source were studied employing the three ligands (Scheme 2, Eqs 1; Table 1). In reactions with **S1** as substrate, use of the catalyst containing flexible ligand (*S*)-**5a** resulted in full conversion to the product (**10**) with *S* absolute configuration with >99% ee within 10 minutes (Table 1, entry 1). Whereas use of (S_a,*S*)-**5b** also gave essentially enantiopure product with *S* absolute configuration (entry 2), a catalyst containing (R_a,*S*)-**5c** gave the opposite product enantiomer with merely 20% ee (entry 3). By employing a mixture of (S_a,*S*)-**5b** and (R_a,*S*)-**5c**, the (*S*)-enantiomer was obtained with 90% ee (entry 4). This demonstrates that the catalyst containing the former ligand forms a considerably more reactive catalyst. These experiments also demonstrate that the flexible ligand thus behaved essentially in the same way as ligand (S_a,*S*)-**5b**.



Scheme 2. Allylic alkylations of *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) and *rac*-3-cyclohexenyl acetate (**S2**).

Also with **S2** as substrate the flexible ligand (*S*)-**5a** gave the same product enantiomer, (*S*)-**11**, as (S_a,*S*)-**5b** (Table 1, entries 1 and 2), but with somewhat lower selectivity (94% as compared to 99% ee). Reaction in the presence of ligand (R_a,*S*)-**5c** resulted in the formation of the opposite enantiomer with lower enantioselectivity also in reactions with this substrate, although the difference was considerably smaller than for **S1** (entry 3). The higher reactivity of (S_a,*S*)-**5b** was again shown from the results of an experiment where a mixture of the two rigid ligands was used (entry 4). The absolute configurations of the products obtained demonstrate that the binaphthyl part of the ligand is mainly responsible for chirality transfer, and that the conformation of (*S*)-**5a** in the selectivity-determining complex resembles that of (S_a,*S*)-**5b**.

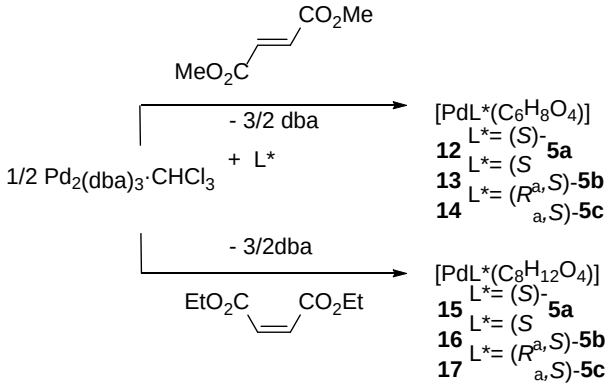
Table 1. Palladium-catalyzed allylic alkylation of **S1** and **S2** with ligands (*S*)-**5a**, (S_a,*S*)-**5b** and (R_a,*S*)-**5c**.[a]

		 S1		 S2	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	(*S*)-**5a**	100	>99 (*S*)	100	94 (*S*)
2	(S_a,*S*)-**5b**	100	>99 (*S*)	100	99 (*S*)
3	(R_a,*S*)-**5c**	100	20 (*R*)	100	92 (*R*)
4	(S_a,*S*)-**5b** + (R_a,*S*)-**5c**	100	90 (*S*)	100	68 (*S*)

[a] 0.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] Measured by ^1H NMR after 10 min. [c] Determined by HPLC. [d] Determined by GC after 30 min. [e] Determined by GC.

Preparation and NMR Studies of Palladium Olefin Complexes. Nucleophilic attack on the allyl group in palladium-catalyzed allylic alkylations has been argued to

occur via a late, i.e. product-like, transition state, and the stereochemistry accordingly governed by formation of the most stable olefin complex.[19] With the aim of gaining a deeper insight into the conformation of flexible ligand (*S*)-**5a** in the selectivity-determining step, palladium(0) olefin complexes with the three ligands were prepared in order to mimic the product olefin complexes from allylic alkylations. Dimethyl fumarate and diethyl maleate were selected as olefins in order to form complexes with sufficient stability to allow isolation and studies by NMR spectroscopy. The complexes were obtained by stirring equimolar amounts of ligand and olefin with one equivalent of $Pd_2(dba)_3CHCl_3$ in deuterated dichloromethane (Scheme 3). Complex formation with dimethyl fumarate was achieved within 30 minutes at ambient temperature, whereas 16 hours were required to obtain the desired complexes from diethyl maleate.



Scheme 3. Preparation of Pd(0)-olefin complexes **12**–**17**.

As a result of the symmetry of the olefins employed, a maximum of two olefin complexes can form with each ligand, those from dimethyl fumarate depicted as **A** and **B** in Figure 3, and those from diethyl maleate as **C** and **D**. Attempts were first made to determine the configuration of flexible ligand (*S*)-**5a** in complexes with the two types of olefins by comparison of the spectra of **12** and **15** with those of the complexes with rigid ligands, i.e. **13**–**14** and **16**–**17**, respectively.

The ^{31}P as well as ^{1}H NMR spectra of the complexes containing rigid ligands (**13**–**14** and **16**–**17**) suggested that essentially single isomers were obtained in each case. For instance, the proton coupled ^{31}P NMR spectrum of complex **13**, containing (S_a,*S*)-**5b** and dimethyl fumarate, showed a doublet of doublet at δ 152.6 (J_{PH} = 15.9 and 4.7 Hz), along with a small signal at 151.7 (ratio ca 50:1), while the fumarate complex with (R_a,*S*)-**5c** (**14**) showed a doublet of doublet at δ 154.0 (J_{PH} = 15.1 and 5.5 Hz) and

a minor signal at 145.6 ppm (ratio ca 12:1), as well as a signal at 151.1, probably originating from a complex with dba. Diethyl maleate complex **16** showed a ^{31}P NMR signal at 153.2 ppm, which slowly replaced an initially observed signal at 149.3 ppm and that of **17** a signal at 155.1 (minor signal at 147.7 ppm and a signal at 152.5 ppm originating from a complex with dba). In the ^{31}P NMR spectra of complexes **12** and **15**, with the flexible ligand (*S*)-**5a**, signals at 153.6 and 155.8 ppm, respectively, were observed together with minor signals (155.7 in **12** and at 156.6 ppm in **15**) originating from minor isomers (ratio ca 11:1 in both cases). No separation of signals in the ^{31}P or ^{1}H NMR spectra occurred upon cooling to –70 °C, thus demonstrating that the spectra observed at ambient temperature are not a result of rapid equilibration of isomers (see Supporting Information). Characteristic ^{1}H and ^{31}P signals are shown in Table 2.

Although the NMR spectra of the three complexes **12**–**14** have many features in common (Table 2 and Supporting Information), that of **12**, with flexible ligand (*S*)-**5a**, resembles more that of the complex with rigid ligand S_a,*S*-**5b** than that with R_a,*S*-**5c**, as judged by the chemical shifts and coupling constants of the oxazoline ring protons (see Supporting Information) and the olefinic protons as well as by the chemical shift difference of the *tert*-butyl protons ortho to the phosphite function (Δδ ppm ca 0.2 ppm in **12** and **13** and 0.01 ppm in **14**), which is influenced by the proximity of the coordinated olefin and thereby by the conformation of the ligand. These spectral features suggest that the ligand in complex **12** adopts S_a,*S* configuration. Complete assignment of the ^{1}H NMR spectrum of **16** was hampered due to overlapping signals, but due to the similarity of the spectra **15** and **16**, in particular the chemical shifts of the oxazoline ring protons (see Supporting Information) and the *tert*-butyl protons ortho to the phosphite moiety, it was assumed that **15** and **16** have the same absolute configuration. Although the NMR study thus suggests that the flexible ligand adopts (S_a,*S*) configuration in complexes with both types of olefins, the spectra do not allow definite conclusions about the configuration of the flexible ligand in the two complexes. For this reason DFT calculations were performed (see below).

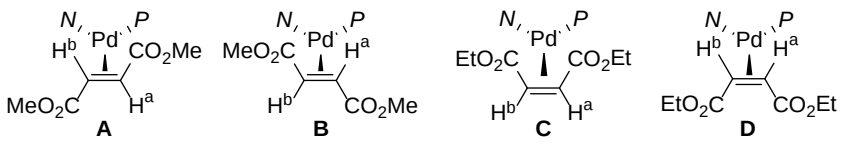


Figure 3. Possible isomers of palladium(0) olefin complexes.

Table 2. Characteristic NMR data for olefin protons H^a and H^b for complexes **12**–**17**.

Cmpd	δ H^a (ppm)	δ H^b (ppm)	δ P (ppm)	$J_{H^aH^b}$ (Hz)	J_{H^aP} (Hz)	J_{H^bP} (Hz)	δ Me_{ligand} (ppm)	δ Me_{olefin} (ppm)	δ ^tBu (ppm)
12	3.72	3.57	153.6	10.2	4.6	15	0.94, 1.01	3.42, 2.93	1.10, 1.3
13	3.72	3.55	152.6	10	4.7	16	0.88, 1.01	3.07, 3.41	1.07, 1.32
14	3.86	3.51	154.0	10	5.5	15	0.69, 0.95	2.97, 3.37	1.26, 1.29
15	3.76	3.42	155.8	10	5.1	12	0.93, 1.04	0.65, 1.04	1.10, 1.3
16[a]			153.2				0.90, 1.04	0.83, 1.03	1.08, 1.31
17	3.88	3.49	155.1	10	5.5	15	0.72, 1.00	0.78, 1.38	1.28, 1.29

[a] Assignments hampered due to overlapping signals

Knowing that the catalyst with (S_a,*S*)-**5b** leads to the *S* product enantiomer and that with (R_a,*S*)-**5c** to the opposite enantiomer, each olefin was expected to coordinate with different faces to palladium in complexes with the two ligands. Nucleophilic attack trans to phosphorus rather than trans to nitrogen is expected as a result of the stronger trans influence of phosphorus.[20] Due to the analogy of the product olefin complexes and our model complexes, those containing the (S_a,*S*)-**5b** ligand were thus expected to be **A** and **C**, and those with the diastereomeric (R_a,*S*)-**5c** ligand, **B** and **D** (Figure 3). However, NOESY experiments of the three palladium fumarate complexes **12**–**14** showed NOE interactions between the olefinic proton located trans to the phosphite moiety (H^b) and the proton of the isopropyl oxazoline substituent (Figure 4). This suggests that, in contrast to expectations, all fumarate complexes coordinate as in **A**, regardless of the configuration of the biaryl phosphite moiety.

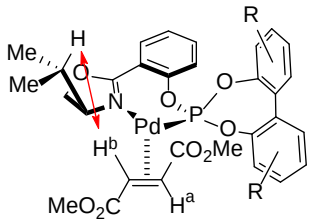


Figure 4. Relevant NOE contacts of Pd-complexes **12**–**14**.

Theoretical Studies. In order to determine the configuration of the flexible ligand in reactions with the two substrates as well as whether the olefins coordinate via the same face in complexes with the two rigid ligands although products with different

absolute configuration were obtained, DFT calculations were performed. The relative stabilities of the product olefin complexes were initially calculated, using the olefin complexes obtained from nucleophilic addition of dimethyl malonate to allyl complexes derived from the two substrates (Figures 5 and 6).

In agreement with the results of the NMR study, it was found that complexes containing product olefins with *S* absolute configuration were more stable than those with *R* configuration for both ligands and for both olefins (Figures 5 and 6); large energy differences were indeed found for the two complexes (S_a,*S*)-*S* (**A**) and (S_a,*S*)-*R* (**B**) with linear olefin **10** (Figure 5a) as well as for (R_a,*S*)-*S* (**C**) and (R_a,*S*)-*R* (**D**), containing cyclic olefin **11** (Figure 6a).

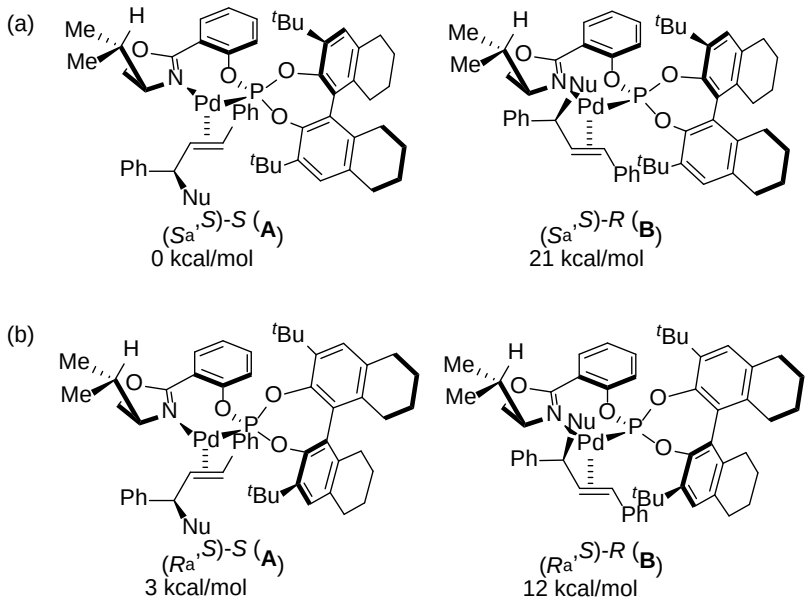


Figure 5. Calculated relative energies for palladium complexes **A** and **B** containing olefin **10** using ligands (a) (S_a,*S*)-**5b** and (b) (R_a,*S*)-**5c**. For use of A and B, compare Figure 3.

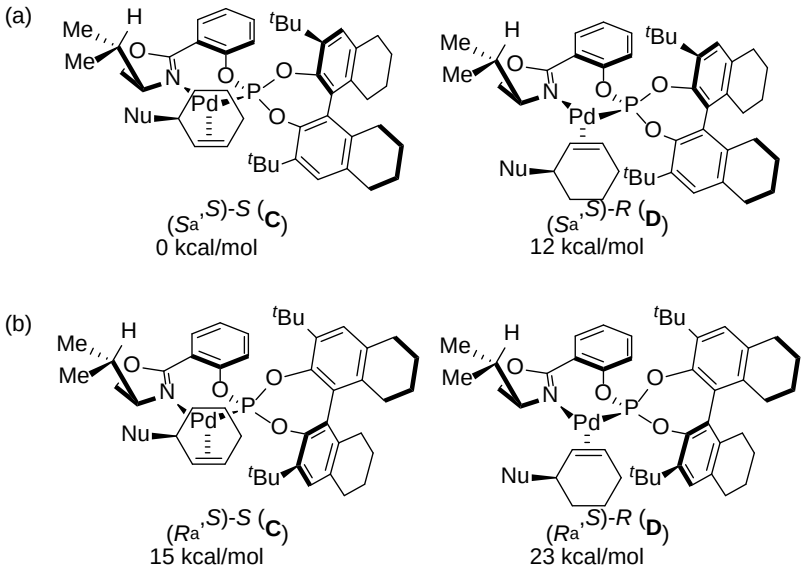


Figure 6. Calculated relative energies for palladium complexes **C** and **D** containing olefin **11** using ligands (a) (S_a,*S*)-**5b** and (b) (R_a,*S*)-**5c**. For use of C and D, compare Figure 3.

A smaller energy difference between the two olefin complexes (R_a,*S*)-*S* (**A**) and (R_a,*S*)-*R* (**B**) was observed, although the configuration of the product **10** predicted by the calculations is opposite to that observed experimentally (Figure 5b). The opposite isomer is also predicted for reaction with 3-cyclohexenyl acetate using (R_a,*S*)-**5c** (Figure 6b). The explanation for the formation of products with opposite absolute configuration from catalytic reactions using complexes containing (S_a,*S*)-**5b** and (R_a,*S*)-**5c** should therefore be sought in the relative stabilities of the transition states leading to the different products. Transition state (TS) calculations were therefore performed. In order to simplify the calculations, NH_3 was used as the nucleophile.

Neglecting anti,anti and anti,syn complexes, which constitute minor isomers, two syn,syn Pd-η^3-allyl, exo and endo, complexes derived from 1,3-diphenyl-2-propenyl acetate are possible from each ligand, as illustrated for (S_a,*S*)-**5b**, (R_a,*S*)-**5c**, and (*S*)-**5a** in Figure 7. Assuming that nucleophilic attack on the allyl complex to form the product olefin complex proceeds by a least-motion reaction path,[21] allyl complexes (S_a,*S*)-*exo* and (R_a,*S*)-*endo* are those which lead to the observed products, with *S* and *R* configuration, respectively.

The calculated energies of the transition states leading to the observed product and the enantiomers are shown in Table 3. A larger energy difference was found between the two TSs leading to opposite enantiomers in reactions with ligand (S_a,*S*)-**5b** as

compared to those with (R_a,*S*)-**5c**, which is in accordance with the experimental results (>99% (*S*) vs 20% (*R*); Table 1, entries 2 vs 3). In addition, the TSs for (R_a,*S*)-**5c** are higher in energy than the most stable TS for (S_a,*S*)-**5b**, which fully accounts for the lower reactivity observed for the Pd/(R_a,*S*)-**5c** catalytic system. The high ee's observed in reactions using (*S*)-**5a** as ligand are also reflected in the energy difference calculated for the endo and exo structures with this ligand.

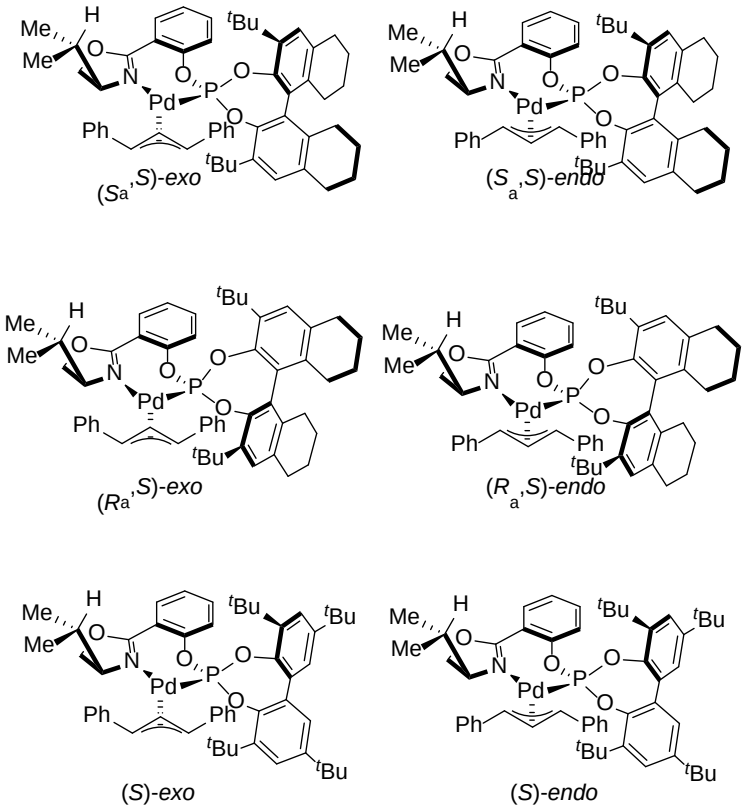


Figure 7. Pd-η^3-allyl exo and endo complexes from 1,3-diphenyl-2-propenyl acetate (**S1**).

Table 3. Calculated relative energies (in kcal/mol) for the TSs from exo and endo Pd-η^3-allyl intermediates, using **S1** and **S2** and NH_3 as nucleophile.

	S1		**S2**	
Ligand	exo	endo	exo	endo
(S_a,*S*)-**5b**	0	4	2	0
(R_a,*S*)-**5c**	2.6[a]	2.5[a]	2.2[b]	2.8[b]
(*S*)-**5a**	0	4.3	1	0

[a] Energies relative to that of *exo*-(S_a,*S*)-**5b**. [b] Energies relative to that of *endo*-(S_a,*S*)-**5b**.

Analogous calculations were performed for complexes from 3-cyclohexenyl acetate (Figure 8). The calculated TS energy differences between the exo and endo complexes (Table 3) are in agreement with the high enantiomeric excesses observed using (S_a,*S*)-**5b** as ligand, and also with the observation of opposite enantiomers of alkylated product **11** using the two diastereoisomeric ligands (S_a,*S*)-**5b** and (R_a,*S*)-**5c** (99% (*S*) using (S_a,*S*)-**5b** vs 92% (*R*) for (R_a,*S*)-**5c**; Table 1, entries 2 vs 3). Again, the energy of the TS for the reaction catalyzed by (R_a,*S*)-**5c** is higher than that of the reaction catalyzed by (S_a,*S*)-**5b**, which is in agreement with the higher reactivity observed for Pd/(S_a,*S*)-**5b** compared to Pd/(R_a,*S*)-**5c** catalyst.

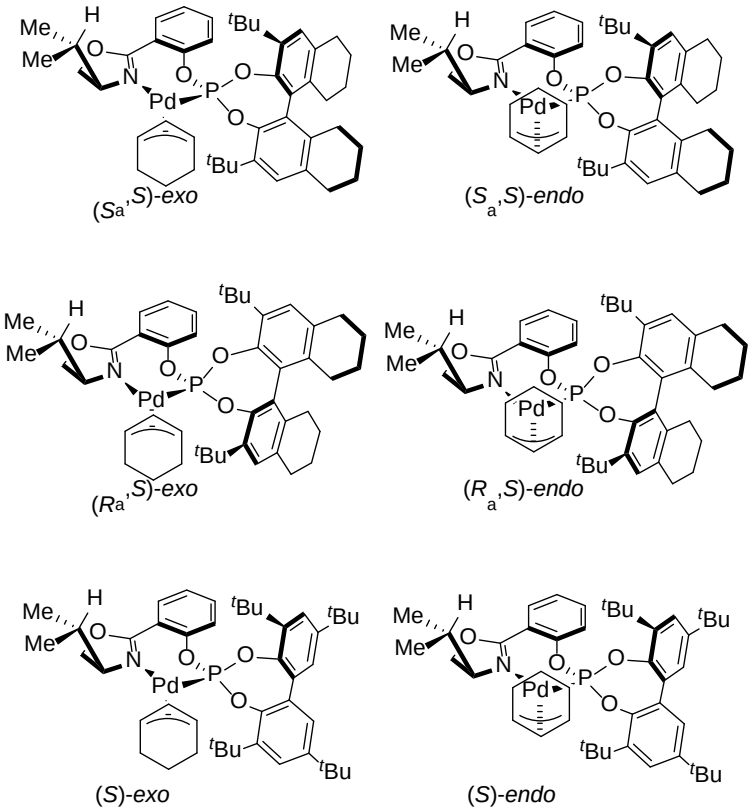


Figure 8. Pd-η^3-allyl exo and endo complexes from 3-cyclohexenyl acetate (**S2**).

The conclusion of the calculations is thus that in the reaction of (*E*)-1,3-diphenyl-2-propenyl acetate with (S_a,*S*)-**5b** the TS leading to the product with *S* configuration, which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**5c**, the TS leading to the product with *R* configuration, which is the product observed

experimentally, is lowest in energy, whereas the olefin complex of the product with *S* configuration is lowest in energy.

In the reaction of 3-cyclohexenyl acetate with (S_a,*S*,)-**5b**, the TS leading to the product with *S* configuration, which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**5c**, the TS leading to the product with *R* configuration, which is the product observed experimentally, is lowest in energy, whereas the olefin complex of the product with *S* configuration is lowest in energy. Thus, in reactions with both types of substrates where (R_a,*S*)-**5c** is used as ligand, the lowest energy transition state complexes lead to product olefin complexes which are higher in energy than those from olefins with opposite absolute configuration. The calculations thus provide an explanation why the model olefins coordinate to palladium via the same face in complexes with the two rigid ligands, although they lead to products with opposite absolute configuration in the catalytic reactions.

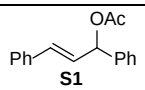
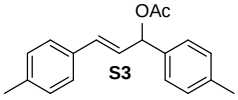
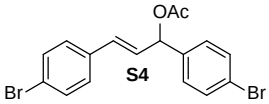
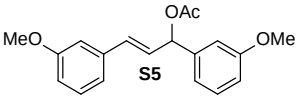
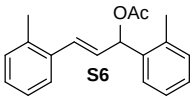
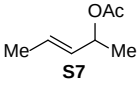
Other Substrates and Nucleophiles. Scope and Limitations. To further study the behavior of ligand (*S*)-**5a** and its rigid analogues (S_a,*S*)-**5b** and (R_a,*S*)-**5c**, and to investigate whether the similar behavior of the two best ligands (*S*)-**5a** and (S_a,*S*)-**5b** is general, we extended the previous work to O-nucleophiles and C-nucleophiles other than dimethyl malonate as well as to the alkylation of other substrates (Tables 4–7).

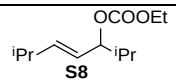
Table 4 shows the results of the use of Pd/(*S*)-**5a** in the allylic substitution of several symmetrically disubstituted linear substrates, with different steric and electronic properties using a wide range of C- and O-nucleophiles. We initially considered the allylic substitution of substrate **S1** (Table 4, entries 1–18). We were pleased to note that Pd/(*S*)-**5a** is very tolerant to variation of the steric properties of the ester moiety and the substituents of the malonate nucleophiles (entries 2–8). A broad range of malonates provided products **18**–**24** in high yields and with excellent enantioselectivities, comparable to those obtained with dimetyl malonate (ee's up to >99%). Of particular interest are the high enantioselectivities achieved with allyl-, butenyl-, pentenyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[22] The addition of acetylacetone (compound **25**) also proceeded with similar high enantioselectivities (ee's up to 98%, entry 9). Interestingly, we could also reach ee's up to 99% and high yield in the allylic fluorobis(phenylsulfonyl)methylation of **S1** using Pd/(*S*)-**5a** (compound **26**, entry 10). The efficient allylic substitution with this type of nucleophile

opens up a path for obtaining highly appealing chiral monofluoromethylated compounds, which are attracting significant attention in the field of medicinal chemistry.[23] Despite this, only one catalytic system has previously been successfully applied, although it resulted in lower enantioselectivity (ee's up to 96%) than the present system and also required lower temperature (0 ºC) than our Pd/(*S*)-**5a** catalyst.[24]

We then considered the allylic substitution of **S1** using several O-nucleophiles (entries 11–18). The asymmetric Pd-catalyzed allylic etherification has recently attracted the attention of many researchers because the resulting chiral ethers and related derivatives are important intermediates in the synthesis of biologically active compounds.[25] Despite its importance, few successful examples exist and most of them use phenols as O-nucleophiles,[26] aliphatic ethers[27] and silanols[27d] being much less studied. The application of Pd/(*S*)-**5a** to several aliphatic alcohols provided the desired products in excellent yields. For benzylic alcohols, the enantioselectivity was affected by the electronic nature of the nucleophile. The best enantioselectivity (97% ee, entry 13) was achieved with an electron-withdrawing group in the para position of the aryl group. Even more interesting are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with silanols (entries 17–18). The results surpass those of the only Pd/CycloN_2P_2-Phos catalytic type system that has provided high enantioselectivities (up to 94%)[27d] so far. Therefore Pd/(*S*)-**5a** can be used for preparing chiral silyl ethers that can be easily transformed into high-value compounds such as chiral aromatic allylic alcohols.

Table 4. Pd-catalyzed allylic substitution of disubstituted linear substrates using ligand (*S*)-**5a**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (%Yield)	% ee[c]
1	 **S1**	H-CH(CO_2Me)$_2$	**10**	100 (94)	>99 (*S*)
2	**S1**	H-CH(CO_2Et)$_2$	**18**	100 (93)	>99 (*S*)
3	**S1**	H-CH(CO_2Bn)$_2$	**19**	100 (95)	>99 (*S*)
4	**S1**	H-CMe(CO_2Me)$_2$	**20**	96 (91)	99 (*R*)
5	**S1**	H-Callyl(CO_2Me)$_2$	**21**	100 (92)	>99 (*R*)
6	**S1**	H-Cbutenyl(CO_2Et)$_2$	**22**	100 (89)	>99 (*R*)
7	**S1**	H-Cpentenyl(CO_2Et)$_2$	**23**	100 (93)	93 (*R*)
8	**S1**	H-Cpropargyl(CO_2Me)$_2$	**24**	100 (91)	>99 (*R*)
9	**S1**	H-CH($COMe$)$_2$	**25**	100 (89)	98 (*S*)
10[d]	**S1**	H-CF(SO_2Ph)	**26**	100 (76)	99 (*R*)
11[d]	**S1**	H-OCH_2Ph	**27**	76 (69)	33 (*R*)
12[d]	**S1**	H-OCH_2(*p*-Me-C_6H_4)	**28**	82 (76)	25 (-)
13[d]	**S1**	H-OCH_2(*p*-CF_3-C_6H_4)	**29**	100 (93)	97 (-)
14[d]	**S1**	H-OCH_2(*m*-Me-C_6H_4)	**30**	75 (69)	37 (-)
15[d]	**S1**	H-Oallyl	**31**	89 (81)	32 (-)
16[d]	**S1**	H-Opropargyl	**32**	75 (70)	40 (*R*)
17[d]	**S1**	H-OSi(Me)$_2$Ph	**33**	94 (79)	98 (*R*)[e]
18[d]	**S1**	H-OSiPh_3	**34**	100 (91)	99 (*R*)[e]
19	 **S3**	H-CH(CO_2Me)$_2$	**35**	100 (93)	99 (*S*)
20	**S3**	H-Callyl(CO_2Et)$_2$	**36**	100 (91)	99 (*R*)
21	**S3**	H-Cbutenyl(CO_2Et)$_2$	**37**	100 (92)	94 (*R*)[f]
22	 **S4**	H-CH(CO_2Me)$_2$	**38**	100 (89)	99 (*S*)
23	 **S5**	H-CH(CO_2Me)$_2$	**39**	100 (91)	99 (*S*)
24	 **S6**	H-CH(CO_2Me)$_2$	**40**	100 (90)	99 (*S*)
25[g]	 **S7**	H-CH(CO_2Me)$_2$	**41**	100 (89)	93 (*S*)
26[g]	**S7**	H-CH(CO_2Bn)$_2$	**42**	100 (91)	82 (*S*)
27[g]	**S7**	H-CH($COMe$)$_2$	**43**	100 (90)	85 (*S*)
28[g]	**S7**	H-CMe(CO_2Me)$_2$	**44**	100 (86)	80 (*S*)
29[g]	**S7**	H-Callyl(CO_2Me)$_2$	**45**	100 (89)	90 (*S*)
30[g]	**S7**	H-Cbutenyl(CO_2Et)$_2$	**46**	100 (90)	87 (*S*)
31[g]	**S7**	H-Cpropargyl(CO_2Me)$_2$	**47**	100 (87)	72 (*S*)

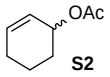
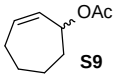
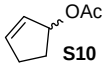
32[d]		H-CH(CO_2Me)$_2$	**48**	100 (92)	>95 (*S*)[h]

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Conversions and yields measured after 18 h. [e] Measured after desilylation to the corresponding alcohol. [f] Measured after transformation to the corresponding RCM-adduct. [g] Reactions carried out at 0 ºC for 18 h. [h] Ee measured by ^{1}H NMR using [Eu(hfc)$_3$].

The scope of Pd/(*S*)-**5a** was further investigated by using other symmetrical linear substrates with steric and electronic requirements (**S3**–**S8**) different from those of **S1**. The Pd/(*S*)-**5a** catalytic system can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, with various carbon nucleophiles with excellent enantioselectivities and yields, comparable to those of **S1** (Table 4, entries 19–24**)**. We also found that the biaryl-phosphite group in Pd/(*S*)-**5a** can adapt its chiral pocket and successfully catalyze the alkylation of **S7** (entries 25–31). This substrate is less sterically demanding and therefore enantioselectivities tend to be lower than with model substrate **S1**. The present results are among the best in the literature for this substrate,[7] even using highly appealing nucleophiles such as α-substituted with methyl, allyl and butenyl groups, for which only very few catalytic systems have provided high enantioselectivities.[22] Interestingly, Pd/(*S*)-**5a** can also successfully be used for the alkylation of **S8** (ee's up to >95%, entry 32). This substrate is more sterically demanding and it usually reacts with inferior catalytic performance than **S1** and **S3**–**S4**.

We then focused our attention on the allylic substitution of cyclic substrate **S2** with more challenging nucleophiles than dimethyl malonate and on the alkylation of other cyclic substrates with different ring sizes (**S9** and **S10**). Table 5 shows that a wide range of C-nucleophiles, including the less studied α-substituted malonates and acetylacetone, can efficiently react with **S2** to provide the corresponding compounds (**49**–**54**) with high yields and enantioselectivities (ee's up to >99%), comparable to those obtained with dimethyl malonate (**11**). The exception was propargyl-substituted malonate, which led to somewhat lower enantioselectivity (compound **53**, ee's up to 92%), but still good for this challenging C-nucleophile. Remarkably, Pd/(S_a,*S*)-**5b** also efficiently catalyzes the alkylation of cyclic substrates **S9** and **S10** (Table 5, entries 8–11, compounds **55**–**58**). Excellent-to-high enantioselectivities (ee's between 96% and >99%) were obtained in both cases, even with **S10**, which usually provides products with much lower enantioselectivities than cyclic **S2**.7

Table 5. Pd-catalyzed allylic substitution of cyclic substrates using ligand (S_a,*S*)-**5b**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (% yield)	% ee[c]
1	 **S2**	H-CH(CO_2Me)$_2$	**11**	100 (92)	99 (*S*)
2	**S2**	H-CH(CO_2Et)$_2$	**49**	100 (93)	>99 (*S*)
3	**S2**	H-CH(CO_2Bn)$_2$	**50**	100 (90)	97 (*S*)
4	**S2**	H-CMe(CO_2Me)$_2$	**51**	100 (89)	99 (+)
5	**S2**	H-Callyl(CO_2Me)$_2$	**52**	100 (91)	>99 (-)
6	**S2**	H-Cpropargyl(CO_2Me)$_2$	**53**	100 (88)	92 (*S*)
7	**S2**	H-CH(COMe)$_2$	**54**	100 (93)	99 (-)
8	 **S9**	H-CH(CO_2Me)$_2$	**55**	100 (92)	>99 (*S*)
9	**S9**	H-Cpropargyl(CO_2Me)$_2$	**56**	69 (65)	>99 (*S*)
10	 **S10**	H-CH(CO_2Me)$_2$	**57**	100 (86)	>95 (-)[d]
11	**S10**	H-Cpropargyl(CO_2Me)$_2$	**58**	100 (87)	96 (*S*)

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t. [b] % Conversion measured after 30 min. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC or GC. [d] Ee measured by ^{1}H NMR using [Eu(hfc)$_3$].

We next studied if the rigid analogues of (*S*)-**5a** (ligands (S_a,*S*)-**5b** and (R_a,*S*)-**5c**) follow the same trend in the allylic substitution of unsymmetrical monosubstituted substrates **S11** and **S12** (Eqs 2) as in reactions with disubstituted substrates. The challenge in these substrates is that both the enantioselectivity and regioselectivity need to be controlled, and most palladium catalysts favor the formation of the usually undesired achiral linear product.[7,28,29] In our previous work we found that alkylation of **S11** and **S12** catalyzed by Pd/(*S*)-**5a** proceeded with regio- and enantioselectivities comparable to those of the best ones reported.[11] As observed with the previously studied linear disubstituted substrates, Pd/(S_a*S*)-**5b** gave the best results and provided the desired branched isomers (compounds **59** and **61**), with enantioselectivities that were as high as those obtained with Pd/(*S*)-**5a**, as major products (Table 6).

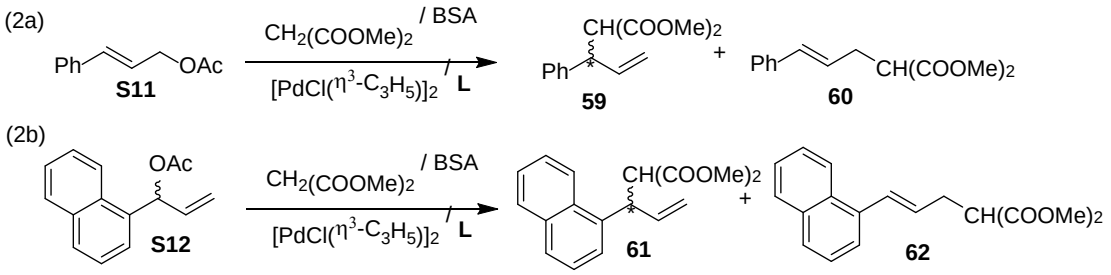


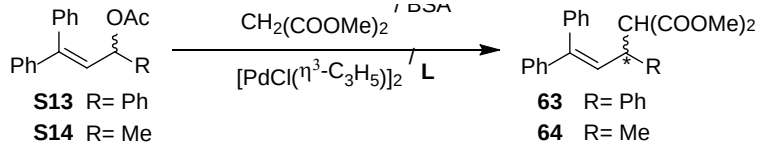
Table 6. Pd-catalyzed allylic substitution of monosubstituted substrates **S11** and **S12**.[a]

Entry	Substrate	Ligand	% Conv[b] (%yield)	% branched[c]	% ee[d]
1	**S11**	(*S*)-**5a**	100 (91)	68	86 (*S*)
2	**S11**	(S_a,*S*)-**5b**	100 (90)	65	85 (*S*)
3	**S11**	(R_a,*S*)-**5c**	100 (90)	15	42 (*R*)
4	**S11**	(S_a,*S*)-**5b**+(R_a,*S*)-**5c**	100 (91)	50	79 (*S*)
5	**S12**	(*S*)-**5a**	100 (92)	>99	92 (*S*)
6	**S12**	(S_a,*S*)-**5b**	100 (89)	95	90 (*S*)
7	**S12**	(R_a,*S*)-**5c**	100 (90)	40	41 (*R*)
8	**S12**	(S_a,*S*)-**5b**+(R_a,*S*)-**5c**	100 (91)	70	61 (*S*)

[a] 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, benzene as solvent, BSA/KOAc as base, 0 ºC. [b] % Conversion measured after 2 h. Isolated yield shown in parenthesis. [c] Regioselectivity measured by ^{1}H NMR. [d] Enantiomeric excesses determined by chiral HPLC.

Finally, the good performance of Pd/(*S*)-**5a** and Pd/(S_a,*S*)-**5b** also extended to the allylic substitution of unsymmetrical 1,3,3,-trisubstituted allylic substrates (**S13**–**S14**, Table 7). These reactions have a large interest because the substitution products can easily be transformed into chiral acid derivatives and lactones.[30] Theses substrates have been less studied and less successfully alkylated than disubstituted substrates because they are more sterically demanding than model substrate **S1**.[31] The results shown in Table 7 show the same trend as for the allylic substitution of **S1**. The Pd-catalysts containing ligands (*S*)-**5a** and (S_a,*S*)-**5b** provided the best enantioselectivities (ee's up to >99% for both substrates). Again the flexibility conferred by the biaryl phosphite moiety was enough to adequately control the size of the chiral pocket in order to achieve enantioselectivities comparable to the best one reported.[31] In line with the literature results, and as observed for **S8**, the activities were lower than in the alkylation reaction of **S1**.

Table 7. Pd-catalyzed allylic substitution of trisubstituted substrates **S13** and **S14**.[a]



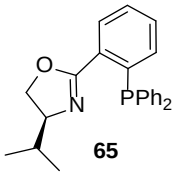
Entry	Substrate	Ligand	% Conv[b] (%yield)	% ee[c]
1	**S13**	(*S*)-**5a**	87 (84)	>99 (*R*)
2	**S13**	(S_a,*S*)-**5b**	84 (79)	99 (*R*)
3	**S13**	(R_a,*S*)-**5c**	65 (62)	41 (*S*)
4	**S14**	(*S*)-**5a**	98 (95)	>99 (*R*)
5	**S14**	(S_a,*S*)-**5b**	95 (90)	99 (*R*)
6	**S14**	(R_a,*S*)-**5c**	71 (65)	24 (*S*)

[a] 2 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4.4 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt. [b] % Conversion measured after 24 h. Isolated yield shown in parenthesis. [c] Enantiomeric excesses determined by chiral HPLC.

DISCUSSION

High enantiocontrol is achieved in a variety of processes employing metal complexes with phosphinooxazoline, PHOX, ligands (**65**) as catalysts,[32] and for this reason phosphinooxazolines are classified as privileged ligands.[2] In a variety of catalytic processes phosphite ligand (*S*)-**5** has properties similar to those of phosphine ligands **65**.[33] However, whereas (4*S*)-2-(2'-diphenylphosphino)phenyl-4-isopropyl-4,5-dihydrooxazole (**65**, R = ^{i}Pr; Figure 9) gives excellent results in asymmetric allylic alkylations with *rac*-(*E*)-1,3-diphenyl-2-propenyl as substrate (98% ee), modest to good results are obtained with 1,3-dialkyl-2-propenyl substrates, and racemic product with the 3-cyclohexenyl derivatives. In contrast, **5a** provides excellent results with all these types of substrates. The chiral PHOX ligands interact with the substrate mainly at its wings. As a consequence, allylic systems with bulky substituents show high exo:endo ratios and high enantioselectivities, whereas narrow systems give low selectivity.[33] In contrast, ligands (*S*)-**5a** and (S_a,*S*)-**5b** are more flexible and can accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for both "broad" and "narrow" substrates. In fact, by replacing the phosphine moiety by a biaryl phosphite in the PHOX ligand, we were able to identify unprecedented catalytic systems (Pd/(*S*)-**5a** and Pd/(S_a,*S*)-**5b**) that with high

enantiocontrol generate C-C, C-N, and C-O bonds for a number of hindered and unhindered mono-, di- and tri-substituted substrates using a wide range of C, N and O-nucleophiles.



65

Figure 9. Phosphinooxazoline ligand **65**.

The enantioselectivity of the catalytic reactions is reflected by the energy difference between the exo and endo like transition states, provided that nucleophilic attack occurs only trans to phosphorus. In the reaction of (*E*)-1,3-diphenyl-2-propenyl acetate (**S1**) in the presence of (S_a,*S*)-**5b** (with NH_3 as nucleophile) this difference was calculated to 4 kcal/mol, in good agreement with the selectivity observed experimentally (>99% ee). The selectivity observed experimentally in reaction with the cyclic substrate **S2** was slightly lower, 99% ee, well corresponding to the computed energy difference between the two transition states, 2 kcal/mol. For reactions of the two substrates in the presence of PHOX ligand **65** (R = ^{i}Pr; Figure 9) the corresponding values were calculated to 2.2 and 0 kcal/mol, respectively, thus reflecting the somewhat lower selectivity obtained from **S1** as compared to that obtained using (S_a,*S*)-**5b** , and the formation of racemic product from **S2**.[21]

Contrary to expectations, the absolute configuration of the products could not be entirely predicted from the structure of the most stable olefin complex, implying that at least for reactions employing (R_a,*S*)-**5c** as ligand, the transition states resemble the palladium allyl complexes rather than the olefin complexes. For (*S*)-**5a** and (S_a,*S*)-**5b** exo complexes are more stable than endo complexes, in analogy to complexes with PHOX ligands, whereas for (R_a,*S*)-**5c** the endo complex has slightly higher stability than the exo complex.

While the previously studied semiflexible ligands **1** and **2** (Figure 1) adopt different configurations in product olefin complexes obtained in reactions with the two types of substrates, (*S*)-**5a** prefers a (S_a,*S*) configuration with both “broad” and “narrow” substrates. The ability of this ligand to adapt the size of the substrate-binding pocket to

the reacting substrate is therefore a result of the high flexibility of the biaryl phosphite group.

CONCLUSIONS

Contrary to previously studied flexible ligands, (*S*)-**5a** adopts (S_a,*S*) configuration in complexes mimicking product olefin complexes obtained in palladium catalyzed allylic alkylations of both "broad" and "narrow" allylic substrates. Although the olefins coordinate with the same face to palladium in diastereomeric rigid ligands with (S_a,*S*) and (R_a,*S*) configuration, products with opposite absolute configuration are obtained. The explanation is found in the different energies of the transition state complexes.

The origin of the exceptionally broad substrate scope of the ligand as well as its ability to control the stereochemistry in a variety of catalytic processes is connected to its defined stereochemical structure combined with the high flexibility of the tropos unit. The unique ability of the ligand to modify its chiral pocket would justify its addition to the family of privileged ligands.

EXPERIMENTAL

General Procedures. Unless stated otherwise, reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. NMR spectra (^{1}H, ^{13}C, and ^{31}P) were measured on Bruker DRX 400 MHz and Bruker DRX 500 MHz instruments; $CDCl_3$ was used as a solvent, if not further specified.

Materials. With exception of the compounds given below, all reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: (*S*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*S*)-**7**,[16] (*R*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*R*)-**7**,[16] and (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol.[18] Racemic substrates **S1**–**S14**,[34] diethyl 2-(3-butenyl)malonate[35] and diethyl 2-(4-penten-1-yl)malonate[36] were prepared as previously reported.

Computational details. The geometries of all intermediates were optimized using the Gaussian 09 program,[37] employing the B3LYP[38] density functional and the LANL2DZ[39] basis set for iridium and the 6-31G* basis set for all other elements.[40] Solvation correction was applied in the course of the optimizations using the PCM

model with the default parameters for dichloromethane.[41] The complexes were treated with charge +1 and in the single state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[42] basis set was used for all elements except iridium, and by applying dispersion correction using DFT-D3[43] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + EDFT\text{-}D3$.

Synthesis compound (*S*)-8.[17] In a Schlenk were placed (*S*)-**7** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*S*)-**8** (1.34 g, yield 97%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (s, 2H), 4.78 (s, 2H), 2.66 (m, 4H), 2.11 (m, 2H), 2.02 (m, 2H), 1.65 (m, 4H), 1.59 (m, 4H), 1.33 (s, 18H); ^{13}C NMR (126 MHz): 150.1 (C), 134.5 (C), 133.8 (C), 129.1 (C), 128.3 (C), 119.5 (C), 34.5 (CH), 29.6 (CH_3), 29.5 (CH_2), 26.8 (CH_2), 23.2 (CH_2).

Synthesis of compound (*S*)-9.[44] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to -78 °C and a solution of (*S*)-**8** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left to warm to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (*S*$_a$,*S*)-5b. To a solution of compound (*S*)-**9** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1 to 3:1) and then crystallized from hexane/Et_2O 5:1 to afford (*S*$_a$,*S*)-**5b** (75 mg, 10% over two steps) as white crystals. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.64 (m, 1H), 7.12 (d, *J* = 10.1 Hz, 1H),

6.98 (m, 1H), 6.93 (s, 1H), 6.92 (s, 1H), 5.58 (m, 1H), 4.29 (dd, *J* = 17.8, 9.6 Hz, 1H), 4.02 (dd, *J* = 17.1, 7.7 Hz, 1H), 3.95 (dd, *J* = 18.1, 8.3 Hz, 1H), 2.84 – 2.74 (m, 2H), 2.67 (m, 2H), 2.25 (m, 2H), 1.94 – 1.77 (m, 2H), 1.71 (m, 4H), 1.57 (m, 4H), 1.46 (m, 1H), 1.40 (d, *J* = 10.1 Hz, 9H), 1.21 (d, *J* = 10.1 Hz, 9H), 0.97 (dd, *J* = 10.0, 6.7 Hz, 3H), 0.86 (dd, *J* = 10.0, 6.8 Hz, 3H). ^{13}C NMR (126 MHz) δ 160.9 (CH), 151.7 (C), 151.0 (C), 145.4 (C), 138.8 (C), 138.3 (CH), 135.7 (CH), 135.5 (CH), 133.6 (CH), 133.0 (CH), 131.5 (C), 130.2 (CH), 127.8 (CH), 127.6 (CH), 124.1 (CH), 123.7 (C), 73.5 (CH_2), 70.2 (CH_2), 34.9 (CH), 34.7 (CH), 33.6 (CH_2), 31.2 (CH_3), 30.7 (CH_2), 29.9 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 23.38 (CH_2), 23.35 (CH_2), 19.3 (CH_3), 18.8 (CH_3). ^{31}P NMR (202 MHz) δ 129.0. MS HR-ESI [found 662.3377, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

Synthesis compound (*R*)-8.[17] In a Schlenk were placed (*R*)-**7** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under a stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*R*)-**7** (1.0 g, yield 72 %) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (s, 2H), 4.78 (s, 2H), 2.66 (m, 4H), 2.11 (m, 2H), 2.02 (m, 2H), 1.65 (m, 4H), 1.59 (m, 4H), 1.33 (s, 18H); ^{13}C NMR (126 MHz): 150.1 (C), 134.5 (C), 133.8 (C), 129.1 (C), 128.3 (C), 119.5 (C), 34.5 (CH), 29.6 (CH_3), 29.5 (CH_2), 26.8 (CH_2), 23.2 (CH_2).

Synthesis compound (*R*)-9.[44] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to –78 °C and a solution of (*R*)-**8** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left warming to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (R_a,*S*)-5c. To a solution of compound (*R*)-**9** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of the (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was

filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1) to afford (R_a,*S*)-**5c** (69 mg, 9% over two steps) as a white foam. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.71 (m, 1H), 7.09 (m, 1H), 6.98 (m, 2H), 6.12 (m, 1H), 4.28 (m, 1H), 3.94 (m, 2H), 2.77 (m, 2H), 2.70 (m, 2H), 2.30 (m, 2H), 1.92 (m, 2H), 1.66 (m, 8H), 1.47 (s, 2H), 1.38 (m, 9H), 1.34 (m, 1H), 1.21 (m, 10H), 0.96 (d, *J* = 8.0 Hz, 3H), 0.82 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz) δ 161.7 (CH), 150.8 (C), 145.3 (C), 144.9 (C), 139.0 (C), 138.6 (CH), 135.45 (CH), 135.47 (CH), 133.9 (CH), 133.2 (CH), 131.8 (C), 130.0 (CH), 128.1 (CH), 127.8 (CH), 124.2 (CH), 121.7 (C), 73.6 (CH_2), 70.7 (CH_2), 35.07 (CH), 35.05 (CH), 33.6 (CH_2), 31.5 (CH_3), 31.3 (CH_2), 30.2 (CH_2), 27.9 (CH_2), 23.51 (CH_2), 23.48 (CH_2), 23.47 (CH_2), 23.38 (CH_2), 23.35 (CH_2), 19.6 (CH_3), 18.7 (CH_3).^{31}P NMR (162 MHz) δ 129.33. MS HR-ESI [found 662.3379, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

General procedure for the preparation of the Pd(0)-olefin complexes for NMR studies: A solution of ligand (0.015 mmol)**,** olefin (dimethyl fumarate or diethyl maleate) (0.015 mmol), and [$Pd_2(dba)_3{\cdot}CHCl_3$] (0.0075 mmol) in CD_2Cl_2 (15 mM) was stirred for 30 min when dimethyl fumarate was used, and for 16 h when diethyl maleate was used. After this time the mixture was transferred into a 5 mm NMR tube and the spectra were recorded. For NMR data, see Table 3 and Supporting Information.

Typical procedure for the allylic alkylation of linear (S1, S3–S8 and S11–S12) and cyclic (S2, S9 and S10) substrates. A degassed solution of [$PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **5** (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N,O*-bis(trimethylsilyl)-acetamide (1.5 mmol) and f 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 **10**, **18**–**26**, **35**–**40**, **42**, **45**–**47**, **49**–**52**, **56**, **59**, **61** and **63**–**64**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC. For compounds **11**, **41**, **43**–**44**, **53**–**55** and **58**, conversion and enantiomeric excesses were determined by GC. For compounds **48** and **57**, conversion were measured by ^{1}H NMR and ees were

determined by ^{1}H NMR using [Eu(hfc)$_3$]. For characterization and ee determination details see Supporting Information.

Typical procedure for the allylic etherification and silylation of substrate S1. A degassed solution of [PdCl(η^3-C$_3$H$_5$)]$_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **5** (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 or silanol (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 $MgSO_4$. Conversion was measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of substrates **27**–**34**. For characterization and ee determination details see Supporting Information.

ASSOCIATED CONTENT

Supporting Information

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of (*S*)-**8** and (*R*)-**8**, ^{1}H, ^{13}C, and ^{31}P NMR spectra of **5b** and **5c**, ^{1}H and ^{31}P NMR spectra of **12**–**17**, computed structures and energies of Pd-olefin complexes and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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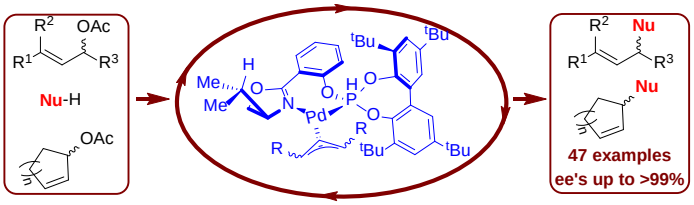

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