Indole-based phosphorus ligands in asymmetric catalysis
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IndolPhosphole and IndolPhos palladium-allyl complexes in asymmetric allylic alkylation$^\dagger$

**Abstract:** Palladium allyl complexes of novel phosphole-containing IndolPhosphole and previously reported IndolPhos hybrid bidentate ligands were studied by X-ray crystallography and multidimensional NMR spectrometry. The complexes were evaluated as catalysts in asymmetric allylic alkylation, providing enantioselectivities up to 90% ee.

7.1 Introduction

Chiral hybrid bidentate phosphine-phosphoramidite ligands have recently gained much attention by the synthetic community for their use in highly efficient asymmetric catalytic transformations.\(^1\) Along with the renaissance of chiral monodentate\(^2\) and the introduction of supramolecular bidentate ligands,\(^3\) hybrid ligands are among the most significant developments in the field of asymmetric transition-metal catalysis in the new millennium. Compared to classical chiral bidentate phosphines such as BINAP and DuPHOS, hybrid ligands offer several advantages. Firstly, the presence of two different phosphorus donor atoms, in addition to one or more chirality elements, results in desymmetrization of the coordination sphere in the transition metal complexes of hybrid ligands. This enables specific binding of prochiral substrates thus providing an additional handle for enantiodiscrimination. Secondly, the facile preparation resulting from the often modular synthetic sequence in two or three steps allows for rapid scale-up for industrial use and provides an economical advantage over conventional chiral diphosphines.

In 2000, Leitner et al. introduced the first hybrid bidentate phosphine-phosphoramidite QUINAPHOS and demonstrated its use in the asymmetric Rh-catalyzed hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate.\(^4\) Up to now several other chiral phosphate-phosphoramidites have been reported, including ferrocene-based derivatives,\(^5\) PEAPhos,\(^6\) NOBIN-based derivatives,\(^7\) Me-AnilaPhos,\(^8\) beta-aminoalcohol-based derivatives,\(^9\) THNA-Phos,\(^10\) and HY-Phos.\(^11\) The ligands have been employed in a range of asymmetric transformations including Rh- and Ru-catalyzed hydrogenation, hydroformylation, and Cu-catalyzed conjugate addition to enones. Our group contributed to this field with the development of IndolPhos 1, which is based on a rigid 3-methylindole backbone resulting in a very small bite-angle (Figure 7.1).\(^12\) Good to excellent enantioselectivities were obtained using this ligand in Rh-catalyzed hydrogenation and hydroformylation. It was observed that the steric and electronic properties of the phosphine part played a crucial role in obtaining high selectivity’s in these transformations. Changing a diphenylphosphine for a disopropylphosphine results in some cases to an increase of enantioselectivity up to 90 % ee. Encouraged by these findings we aim to introduce more variation on this position. Phospholes, unsaturated phosphorus-containing five-membered heterocycles, exhibit different steric and electronic properties compared to phosphines, making them suitable candidates to introduce more variety on the IndolPhos platform.\(^13\)

Phosphole derivatives were found to show excellent activity in the Pd-catalyzed allylic substitution, prompting us to investigate the reactivity of the phosphole containing IndolPhos derivatives in this transformation.\(^14\) To the best of our knowledge, hybrid phosphine-phosphoramidite ligands have not been used up to now in this reaction despite their potential to direct nucleophilic attack specifically to one position of the coordinated allyl.\(^15,16\) However, excellent results in the asymmetric allylic alkylation have been obtained with diphosphites and phosphite-
phosphoramidites.\textsuperscript{17} Here, we introduce IndolPhospholes as a new class of hybrid phosphole-phosphoramidite ligands and describe their synthesis, coordination properties, and reactivity in the Pd-catalyzed asymmetric allylic alkylation. Furthermore, IndolPhos palladium complexes are described along with their catalytic performance in the asymmetric allylic alkylation.

Figure 7.1 Structure of IndolPhos ligands 1a-f.

### 7.2 Ligand synthesis

IndolPhosphole ligands 3 were prepared in a 2-step procedure analogous to the synthesis of IndolPhos ligands 1.\textsuperscript{12} Instead of reacting 3-methylindole with a chlorophosphine, P-cyano-2,5-diphenyl (DPP) and 3,4-dimethyl (DMP) phospholes were used as electrophiles. The cyanophospholes were selected in favor of their chloro- and bromo- derivatives which are very reactive and difficult to handle.\textsuperscript{18} In the first step, the 3-methylindole NH is protected \textit{in situ} with carbon dioxide which also acts as a directing group for the selective deprotonation in 2-position of the indole (Scheme 7.1). Addition of the corresponding cyanophosphole gives indolylphospholes 2a and 2b as yellow and white solids, respectively, in good yields (71-84 \%), requiring no chromatographic work-up. Deprotonation of the NH of the indolylphospholes 2 at low temperature followed by condensation with (S)-Bisnaphtol phosphorochloridite results in the formation of IndolPhosphole ligands 3a and 3b (Scheme 7.2). They are obtained in moderate yield (48-63 \%) after chromatographic purification as yellow and white solids, respectively.

We reported previously that the $^{31}$P NMR signals of IndolPhos ligands 1 exhibit large coupling constants in the range of 200 Hz.\textsuperscript{12a} Their phosphole derivatives 3 on the other hand do not exhibit such large couplings, but the $^{31}$P NMR spectrum of 3a exhibits two singlets. Two doublets are obtained for 3b with a coupling constant of 43.1 Hz. The large difference in these parameters can be attributed to the difference

\[ \text{Scheme 7.1 Synthesis of indolylphospholes 2a-b.} \]
Scheme 7.2 Synthesis of IndolPhospholes 3a-b.

\[
\begin{align*}
\text{1. } & n-\text{BuLi, THF, } -70 \, ^\circ\text{C} \\
\text{2. (S)-BINOL-PCI}
\end{align*}
\]

3a R₁ = Ph, R₂ = H  
3b R₁ = H, R₂ = Me

in electronic properties of phospholes compared to phosphines.

7.3 Synthesis of palladium allyl complexes

The coordination properties of ligands 1a and 3b were investigated in their cationic palladium allyl complexes. Reaction of the ligand with 0.5 equivalent of [Pd₂(η³-C₃H₅)₂Cl₂] in dichloromethane followed by abstraction of the chloride with AgPF₆ afforded 4a and 5 as pale yellow solids in good to excellent yield (79-99 %, Scheme 7.3). Similarly, the bright yellow Pd-diphenylallyl complex 4b was obtained using [Pd₂(η³-1,3-diphenylallyl)_2Cl₂] and 1a in 60 % yield. The allyl complexes are fully characterized by NMR techniques (¹H, ³¹P, ¹³C), mass spectrometry, and X-ray crystallography. Phosphole 3a was also reacted with the Pd-allyl chloride dimer, resulting in the formation of the desired coordination compound in a complex product matrix from which isolation proved impossible.

Scheme 7.3 Synthesis of Palladium Allyl complexes 4 and 5.
7.4 NMR study of palladium allyl complexes

Complexes 4a-b and 5 were studied by one- and two-dimensional NMR spectroscopy in order to determine their structure in solution. Complex 4a displays duplicated signals for all allyl-protons and for some of the protons on the IndolPhos ligand. This effect can be attributed to isomerism of the allyl-fragment, which can adopt two orientations (Figure 7.3). The isomers are able to interconvert via a formal \( \pi \)-rotation involving a \( \eta^3 - \eta^1 - \eta^3 \) isomerization. It was found previously in Josiphos\(^{19}\) and other bidentate ligands containing different phosphorus donor atoms,\(^{20}\) that this isomerization is selective involving opening of only one Pd-C bond of the allyl fragment. In order to establish if such a selectivity is also present in complex 4a, a phase-sensitive \(^1\)H 2D NOESY experiment was carried out (Figure 7.2). The spectrum shows exchange peaks (blue) for the central proton \( H^2 \) of both isomers and their selective NOE contacts (red) with the syn-protons within each isomer. There is no exchange of syn- and anti-protons at C3, i.e. \( H^{3s} \) of isomer I becomes \( H^{3s} \) of isomer II and likewise for \( H^{3a} \). At C1 on the other hand, syn-anti exchange does occur, interconverting \( H^{1s} \) of isomer I into \( H^{1a} \) of isomer II and vice versa. The exchange pathways are summarized in Figure 7.3.

![Figure 7.2](image)

**Figure 7.2** Section of the phase-sensitive \(^1\)H 2D NOESY spectrum (CD\(_2\)Cl\(_2\), 500 MHz, 298 K) for complex 4a. The blue off-diagonal peaks arise from exchange, whereas the red peaks arise from NOE.
Figure 7.3 Exchange pathways interconverting isomers (I) and (II) of complex 4a.

The selective syn-anti exchange at C₁, cis to the phosphoramidite moiety, indicates that the η³–η¹–η³ isomerization follows a mechanism in which the Pd-C₃ bond opens, forming a η¹-transition state wherein the C₁-C₂ bond rotates 180 degrees, completed by re-formation of the η³-allyl (Scheme 7.4). Importantly, the selective opening of the η³-allyl occurs cis to the phosphine and can be rationalized by the greater steric bulk of the diphenylphosphine compared to the Bispaphthol phosphoramidite, as was observed earlier in related systems.¹⁹b The increased Pd-C₃ bond length in the crystal structure of 4a supports this observation (vide infra).

Scheme 7.4 Mechanism of η³–η¹–η³ isomerization in complex 4a.

The room temperature ¹H NMR spectrum of complex 5 exhibits broad signals for all protons except for the indole backbone protons. A variable temperature NMR study was performed to analyze the dynamic process (Figure 7.4). The broadening can be attributed to a faster η³–η¹–η³ isomerization compared to complex 4a, as individual signals are obtained for the allyl protons of both isomeric complexes (III) and (IV). The coalescence temperature could unfortunately not be established in CD₂Cl₂, the only suitable solvent with regard to stability and solubility of the complex, due to its low boiling point. Nevertheless, using line shape analysis at various temperatures, the thermodynamic parameters for the isomerization could be determined (Table 7.1). The free energy of activation is found to be 16.3 kcal mol⁻¹, which is in good agreement with previous measurements of dynamic allyl palladium complexes.²¹ The positive entropy contribution results from the additional degree of freedom gained from the intramolecular isomerization. At 20 °C, the rate of exchange is 3.6 s⁻¹. However, this rate can not be related to the catalytic experiments as substituted allyl ligands are known to isomerize much slower if at all.¹⁵a
Figure 7.4 $^1$H VT NMR spectra (CD$_2$Cl$_2$, 500 MHz) of complex 5.

Table 7.1 Thermodynamic parameters for the $\eta^3$–$\eta^1$–$\eta^3$ isomerization in complex 5.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_a^a$ (kcal mol$^{-1}$)</td>
<td>21.0</td>
</tr>
<tr>
<td>$\Delta G^\ddagger_a$ (kcal mol$^{-1}$)</td>
<td>16.3</td>
</tr>
<tr>
<td>$\Delta H^\ddagger_b$ (kcal mol$^{-1}$)</td>
<td>20.4</td>
</tr>
<tr>
<td>$\Delta S^\ddagger_b$ (kcal mol$^{-1}$ K$^{-1}$)</td>
<td>$1.4 \cdot 10^{-2}$</td>
</tr>
<tr>
<td>$k^b$ (s$^{-1}$)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

$^a$ At 298 K. $^b$ Rate of exchange at 293 K.

The $^1$H 2D NOESY spectrum of complex 5 was recorded at -10 °C (Figure 7.5). As for complex 4a, the central allyl protons are exchanged in the $\eta^3$–$\eta^1$–$\eta^3$ isomerization. All syn- and anti-allyl protons of one isomer exhibit exchange peaks with the signals for the other rotational isomer, although with low intensity. This implies that the isomerization is unselective, and Pd-C bond opening occurs at both termini of the allyl ligand. The decreased steric demand of the 3,5-dimethylphosphole in 5 compared to the diphenylphosphine in 4a, leads both donor atoms (phosphoramidite and phosphole) to be similar in size and thus no selective bond opening occurs.

The phenyl allyl complex 4b does not exhibit rotational isomerism in solution or syn-anti interconversion. The $^1$H 2D NOESY spectrum shows no off-diagonal exchange signals but only signals arising from NOE (Figure 7.6). In spite of severe overlap of signals, the signals stemming from the phenylallyl fragment could be assigned unambiguously. NOE contacts between one of the anti allyl protons (H$^{1a}$) and the adjacent phenyl ring with the downfield Bisnaphthol protons (top left of NOESY spectrum) indicate that the phenyl group of the allyl fragment points away from the...
Figure 7.5 Section of the phase-sensitive $^1$H 2D NOESY spectrum (CD$_2$Cl$_2$, 500 MHz, 263 K) for complex 5. The blue off-diagonal peaks arise from exchange, whereas the red peaks arise from NOE.

Figure 7.6 Section of the phase-sensitive $^1$H 2D NOESY spectrum (CDCl$_3$, 500 MHz, 298 K) for complex 5. The blue off-diagonal peaks arise from exchange, whereas the red peaks arise from NOE.
bulk imposed by the chiral Bisnaphthol moiety. The contacts are confirmed by the DFT calculated structure (BP86, SV(P)) shown in Figure 7.7, which lies 0.5 kcal mol\(^{-1}\) lower in energy than the other possible rotational isomer. According to the Boltzmann distribution, this other isomer is accessible and indeed the \(^{31}\)P NMR spectrum shows the presence of a second species in trace amounts (< 2%), which may be assigned to the second rotational isomer. As 4b is the key catalytic intermediate in the allylic alkylation of rac-1,3-diphenylprop-2-enyl acetate, nucleophilic attack on this species leads to the product and determines the enantioselectivity (\textit{vide infra}).

![Image of calculated lowest energy structure of 4b](image)

**Figure 7.7** Calculated lowest energy structure of 4b (DFT, BP86, SV(P), green = C, blue = N, red = O, orange = P, marine blue = Pd).

### 7.5 X-ray crystallography

Crystals of complexes 4a and 5 suitable for single crystal X-ray diffraction were obtained by slow diffusion of hexanes into a saturated dichloromethane solution. Displacement ellipsoids plots for compounds 4a and 5 are shown in Figures 7.8 and 7.9, respectively. The relevant bond distances and angles are listed in the corresponding figure captions.

In the crystal structure of 5, the four crystallographically independent Pd-complexes and two of the four independent PF\(_6^-\) counter anions of the asymmetric unit form two-dimensional (hereafter, 2-D) planes parallel to (001). Along these planes, each PF\(_6^-\) counterion is encapsulated into a tetrameric box built of the four independent cations (Figure 7.10). The formation of these tetrameric boxes can be attributed to weak C–H···F intermolecular interactions [C···F distances (C = carbon atoms of the allyl groups/phosphole rings/Bisnaphtol moieties) vary in the range of 3.23–3.54 Å, all standard uncertainties are lower than 0.01 Å] and the templating effect.
Figure 7.8 Displacement ellipsoid plot (50% probability level) of one Pd complex of 4a. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): C(1)–C(2), 1.393(9); C(2)–C(3), 1.373(11); Pd(1)–C(1), 2.167(12); Pd(1)–C(2), 2.183(4); Pd(1)–C(3), 2.218(15); Pd(1)–P(1), 2.2255(7); Pd(1)–P(2), 2.2844(7); P(1)–N(1), 1.688(2); P(2)–C(4), 1.812(3); C(2)–Pd(1)–P(1), 134.15(13); C(2)–Pd(1)–P(2), 135.80(13); P(1)–Pd(1)–P(2), 87.93(3).

Figure 7.9 Displacement ellipsoid plot (50% probability level) of one Pd complex of 5. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (°): C(1)–C(2), 1.382(6); C(2)–C(3), 1.357(6); Pd(1)–C(1), 2.170 (3); Pd(1)–C(2), 2.157(4); Pd(1)–C(3), 2.181 (4); Pd(1)–P(1), 2.2243(8); Pd(1)–P(2), 2.2870(9); P(1)–N(1), 1.680(3); P(2)–C(4), 1.794(3); C(2)–Pd(1)–P(1), 138.34(13); C(2)–Pd(1)–P(2), 134.20(13); P(1)–Pd(1)–P(2), 85.80(3).
IndolPhosphole and IndolPhos palladium-allyl complexes in asymmetric allylic alkylation

Figure 7.10 a) The packing of one 2-D plane built of the four independent Pd-complexes and two of the four independent PF$_6^-$ counter anions looking down the normal to (001) in the crystal structure of 5. The symmetry independent residues are colored differently. The black outline corresponds to one tetrameric box. The disorder of one allyl ligand and of one PF$_6^-$ counter anion, and the H-atoms were omitted for the sake of clarity. b) One tetrameric box in space filling style (grey = C, blue = N, red = O, orange = P, yellow = F, green = Pd) projected down the c* direction. The disorder of one allyl ligand was omitted for clarity.

of the two spherical PF$_6^-$ counter anions. Within each tetrameric box, the four independent Pd-complexes are always found in close contacts with each other. These contacts are found between i) one proton of the bisnapthol moiety of one complex and the $\pi$-system of the Bisnapthol moiety of the adjacent complex, ii) one indole proton of one complex and the $\pi$-system of the Bisnapthol moiety of the adjacent complex, iii) one proton of the allyl ligand of one complex and the $\pi$-system of the indole moiety of the adjacent complex. There is no evidence that the tetrameric boxes are stable in solution. The presence of the phosphole ligand might be important for the formation of the box structure, which is not found in the crystal structure of 4a.

The remaining independent PF$_6^-$ counter anions and lattice solvent molecules (i.e. dichloromethane) are found to be intercalated between the 2-D planes including the tetrameric boxes. These counter anions are in short contact with the Pd-complexes via C–H···F interactions, which are comparable with those found for other encapsulated anions. 22

Both molecular structures of 4a and 5 display a square planar geometry around the palladium atom. Differences in the structures mainly arise from the increased bulkiness of the diphenylphosphine compared to the phosphole. This is reflected in the larger bite angle and Pd(1)–C(3) distance for 4a. In addition, the phosphoramidite group in 5 is tilted out of the coordination plane, which is probably the result of packing effects that allow for the formation of the tetrameric box.
7.6 Palladium catalyzed asymmetric allylic alkylation

The catalytic activity of the Pd-complexes of ligands 1a-f and 3a-b was evaluated in the palladium-catalyzed asymmetric allylic substitution. Preliminary experiments using nitrogen nucleophiles in this reaction such as aniline and benzylamine did not yield the desired products. Therefore, dimethyl malonate was chosen as nucleophile in the alkylation of racemic allylic acetates. Catalysts were generated in situ from \([\text{Pd}_2(\eta^3-C_3H_5)_2\text{Cl}_2]\) and the corresponding ligand.

Table 7.2 Pd-catalyzed allylic alkylation of 6 with ligands 1 and 3.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Conv(^b)</th>
<th>% ee(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (R = Ph, R' = H)</td>
<td>100</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>1b (R = 'Pr, R' = H)</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>1c (R = Cy, R' = H)</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>1d (R = 'Tol, R' = H)</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1e (R = Ph, R' = SiMe(_3))</td>
<td>15</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>1f (R = i-Pr, R' = Me)</td>
<td>18</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>3a (R(^1) = Ph, R(^2) = H)</td>
<td>99</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>3b (R(^1) = H, R(^2) = Me)</td>
<td>100</td>
<td>56</td>
</tr>
</tbody>
</table>

\(^a\) 0.5 mol % of \([\text{Pd}_2(\eta^3-C_3H_5)_2\text{Cl}_2]\), 1.1 mol % of ligand, CH\(_2\)Cl\(_2\), room temperature, 3 eq. of dimethyl malonate, 3 eq. of BSA, pinch of KOAc. \(^b\) Conversion percentage of acetate after 1 h determined by GC. \(^c\) Enantiomeric excess determined by chiral HPLC (Chiralcel-ODH). The (S)-enantiomer was obtained in all cases.

All ligands provided active catalysts for the allylic alkylation of rac-1,3-diphenylprop-2-enyl acetate 6, a benchmark substrate for new ligands in the asymmetric allylic alkylation (Table 7.2). The reactivity and selectivity are highly affected by the ligand’s substituents and nature of the phosphine donor group. For IndolPhos ligands 1a-d, which vary only in the type of phosphine, similar reactivities are observed (entries 1-4). Sterically more demanding phosphines give rise to higher ee’s compared to diphenylphosphine, whereas the electronic properties seem to be less important. When introducing substituents in 3 and 3’ positions on the Bisnaphtol moiety, the reactivity decreases while the ee increases up to 90 % (entries 5-6).

IndolPhospholes 3a and 3b both give full conversion and enantioselectivities of 32 % and 56 %, respectively (entries 7-8). Surprisingly, the sterically less congested phosphole now gives higher selectivity, which opposes the trend observed for IndolPhos ligands 1a-d as discussed above.
From the screening experiments outlined above it was observed that ligand 1e gave rise to the highest enantioselectivity but showed only 15 % conversion after 1 h of reaction. However, longer reaction times allow for quantitative formation of the product. A solvent study using 1e as ligand was carried out, in an attempt to increase the activity while maintaining the high selectivity (Table 7.3). Acetonitrile proves to be the only solvent giving a significantly higher rate compared to dichloromethane (entry 3). However, the enantioselectivity drops to 76 % ee. The trade-off in selectivity is not compensated by the gain in activity and we thus carried out all further experiments using dichloromethane as solvent.

<table>
<thead>
<tr>
<th>Table 7.3 Pd-catalyzed allylic alkylation of 6 with ligand 1e.</th>
</tr>
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<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

* 0.5 mol % of [Pd₂(η³-C₅H₅)₂Cl₂], 1.1 mol % of 1e, room temperature, 3 eq. of dimethyl malonate, 3 eq. of BSA, pinch of KOAc.  
* Conversion percentage of acetate determined by GC.  
* Reaction time in hours shown in parentheses.  
* Enantiomeric excess determined by chiral HPLC (Chiralcel-ODH).

To investigate the effect of the structure of the substrate on the catalytic performance, rac-1,3-dimethylprop-2-enyl acetate 8 was subjected to the alkylation conditions (Table 7.4). It is known that changing the Ph-group for a methyl results in most cases in lower enantioselectivity and rate enhancement.15a This is also observed for the catalysts generated from ligands 1 and 3. Remarkably, the enantioselectivity obtained with arylphosphine substituted ligands is lowered to a lesser extent than in the case of alkylphosphines (entries 1-6). In addition, substituents on the Bisnaphtol moiety are not beneficial for this substrate (entries 5-6). The highest selectivity of 51 % ee is reached with o-tolyl substituted ligand 1d. When the performance of phospholes 3a and 3b are compared, the more bulky 3a gives higher selectivity, which opposes the ligand effects observed in the alkylation of 6. We speculate that the smaller Me-substituents of 8 require a catalyst containing more steric bulk compared to 6 to achieve efficient enantioselection.

Cyclic substrates are usually more difficult to alkylate in high enantioselectivity. The small syn-substituents, a proton in most cases, poorly interact with the chiral steric environment imposed by the ligand. Indeed, very low enantioselectivities are obtained for most ligands in the allylic alkylation of 3-acetoxy cyclohexene 10 (Table 7.5). Only
bulky ligands 1d-f are able to induce significant enantioselection up to 50 % ee (entries 4-6).

Table 7.4 Pd-catalyzed allylic alkylation of 8 with ligands 1 and 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Conv</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (R = Ph, R’ = H)</td>
<td>100</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>1b (R = ‘Pr, R’ = H)</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>1c (R = Cy, R’ = H)</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1d (R = o-Tol, R’ = H)</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>1e (R = Ph, R’ = SiMe3)</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>1f (R = ‘Pr, R’ = Me)</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>3a (R1 = Ph, R2 = H)</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>3b (R1 = H, R2 = Me)</td>
<td>100</td>
<td>26</td>
</tr>
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</table>

* 0.5 mol % of [Pd(η3-C3H5)Cl]2, 1.1 mol % of ligand, CH2Cl2, room temperature, 3 eq. of dimethyl malonate, 3 eq. of BSA, pinch of KOAc. b Conversion percentage of acetate after 1 h determined by GC. c Enantiomeric excess determined by chiral GC (Chiralsil DEX CB).

When the efficiency of IndolPhos(phole) ligands in the asymmetric allylic alkylation is compared to other hybrid ligand systems such as phosphite-phosphoramidites, it can be noted that our system is less active. The lower reactivity can be explained in terms of electronic effects. Phosphines are less π-acidic compared to phosphites, which leads to lower reaction rates as the rate-limiting step is a reductive elimination. Concerning the enantioselectivity, IndolPhos(phole) systems give similar ee’s compared to phosphite-phosphoramidite ligands containing a rigid pyranoside sugar backbone. On the other hand, phosphite-phosphoramidite ligands containing a more simple amino alcohol backbone are more selective than our system. These results indicate that a more flexible backbone is beneficial for the enantioselectivity in this transformation.
Table 7.5 Pd-catalyzed allylic alkylation of 10 with ligands 1 and 3.\(^a\)

\[
\begin{array}{llll}
\text{Entry} & \text{Ligand} & \% \text{Conv}\(^b\) & \% \text{ee}\(^c\) \\
1 & 1a (R = Ph, R’ = H) & 73 & < 1 \\
2 & 1b (R = ’Pr, R’ = H) & 94 & 19 \\
3 & 1c (R = Cy, R’ = H) & 82 & 26 \\
4 & 1d (R = ’Tol, R’ = H) & 100 & 44 \\
5 & 1e (R = Ph, R’ = SiMe\(_3\)) & 15 & 50 \\
6 & 1f (R = ’Pr, R’ = Me) & 12 & 38 \\
7 & 3a (R\(^1\) = Ph, R\(^2\) = H) & 6 & < 1 \\
8 & 3b (R\(^1\) = H, R\(^2\) = Me) & 34 & 7 \\
\end{array}
\]

\(^a\) 0.5 mol % of [Pd\(_2\)(η\(^3\)-C\(_3\)H\(_5\))Cl\(_2\)], 1.1 mol % of ligand, CH\(_2\)Cl\(_2\), room temperature, 3 eq. of dimethyl malonate, 3 eq. of BSA, pinch of KOAc. \(^b\) Conversion percentage of acetate after 1 h determined by GC. \(^c\) Enantiomeric excess determined by chiral GC (Supelco β-DEX 225).

Table 7.6 Pd-catalyzed allylic alkylation of 12 with ligands 1 and 3.\(^a\)

\[
\begin{array}{llll}
\text{Entry} & \text{Ligand} & \% \text{Conv}\(^b\) & \text{13/14}\(^c\) & \% \text{ee}\(^d\) \\
1 & 1a (R = Ph, R’ = H) & 100 & 9/91 & 12 \\
2 & 1b (R = ’Pr, R’ = H) & 100 & 5/95 & < 5 \\
3 & 1c (R = Cy, R’ = H) & 100 & 5/95 & < 5 \\
4 & 1d (R = ’Tol, R’ = H) & 100 & 14/86 & 81 \\
5 & 1e (R = Ph, R’ = SiMe\(_3\)) & 100 & 11/89 & < 5 \\
6 & 1f (R = ’Pr, R’ = Me) & 100 & 5/95 & 10 \\
7 & 3a (R\(^1\) = Ph, R\(^2\) = H) & 80 & 10/90 & < 5 \\
8 & 3b (R\(^1\) = H, R\(^2\) = Me) & 100 & 7/93 & < 5 \\
\end{array}
\]

\(^a\) 0.5 mol % of [Pd\(_2\)(η\(^3\)-C\(_3\)H\(_5\))Cl\(_2\)], 1.1 mol % of ligand, CH\(_2\)Cl\(_2\), room temperature, 3 eq. of dimethyl malonate, 3 eq. of BSA, pinch of KOAc. \(^b\) Conversion percentage of acetate after 1 h determined by GC. \(^c\) Branched-to-linear ratio determined by GC. \(^d\) Enantiomeric excess determined by chiral HPLC (Chiralcel-OJH).

7.7 Mechanism of enantiodiscrimination

It is known that in the case of 1,3-disubstituted substrates, enantiodiscrimination results from preferential attack on one of the enantiotopic termini of the allylpalladium complex.\(^{15b}\) In the case of ligand 1a, Pd-allyl complex 4b is the actual intermediate in
the catalytic cycle. As the structure in solution was assigned with NOESY and DFT calculations (Figure 7.6-7), and no syn-anti-interconversion was observed, attack on this complex determines which enantiomer is obtained. The other rotational isomer is observed in trace amounts by NMR spectroscopy, for which DFT calculations in the gas-phase indicate that this isomer would be 0.5 kcal mol\(^{-1}\) higher in energy. Even though present in trace amount, it can not be excluded that this second rotational isomer plays a role in the reaction as it is known that species that are present in only very low amount can carry out most of the reaction flux.

The stereochemical pathway of the reaction can be described in terms of the diagram depicted in Scheme 5.\(^{26}\) Nucleophilic attack can take place on either the major or minor Pd allyl complex. For the major isomer, rotation accompanied with formation of the \(\eta^2\)-alkene species favors pathway b towards the (S) enantiomer. The steric bulk of the Bisnaphthol hinders the substrate rotation by having unfavorable steric interactions with the newly formed tertiary substituent in the case of path a. If on the other hand nucleophillic attack occurs on the minor isomer, no preferred sense of rotation would be expected on steric grounds.

**Scheme 7.5** Enantiocontrol provided by IndolPhos(phole) Pd catalysts
Experimentally, we found that the (S)-enantiomer of the alkylation product was formed in excess with all ligands. The selective isomerization and crystal structure of 4a indicate a labilization of the Pd-C\textsubscript{3} bond (vide supra). These observations support a mechanism following path b, \textit{i.e.} attack on the C\textsubscript{3} allyl terminus of the major allyl isomer. This mechanism is in agreement with an early as well as a late transition state model. The former is supported by the labilization of the Pd-C\textsubscript{3} bond, and the latter by repulsive steric interactions during rotation of the substrate upon nucleophilic attack.\textsuperscript{27} If the main reaction flux would be carried out by the minor allyl isomer, a much lower enantiomeric excess would be expected as rotation of the substrate in both cases (path c and d) is not majorly hindered by repulsive steric interactions. Therefore we believe that formation of the alkylation product proceeds by path b.

### 7.8 Conclusions

Phosphole substituted IndolPhos derivatives 3a and 3b have been successfully synthesized and characterized. For 3b, the coordination to palladium(II) was investigated in the allyl palladium complex 5 and compared to the corresponding IndolPhos palladium species 4a. In solution these complexes exist each as two isomers in a 1:1 ratio, which interconvert through a \( \eta^3 - \eta^1 - \eta^3 \) isomerization. A selective isomerization was found for 4a where Pd-C bond opening only occurs \textit{trans} with regard to the diphenylphosphine donor group due to steric effects. For complex 5, no such selectivity has been found, which is explained by the smaller phosphole substituent. As a result, the steric demand of phosphole and phosphoramidite are similar, and Pd-C bond opening occurs at both allyl termini. The rate constant of the isomerization process for 5 is \( k = 3.6 \text{ s}^{-1} \). 4a does not display dynamic behavior at room temperature, and consequently its rate constant could not be determined.

In the solid state, complexes 4a and 5 display disorder in the coordinated allyl fragments, confirming the rotational isomerism observed in solution. Interestingly, the phosphole containing complex 5 forms a tetrameric box structure in the solid state which is templated by encapsulation of one PF\textsubscript{6} counter anion. The encapsulation is driven by eight C−H···F interactions between hydrogen atoms located on the phosphole ligand and the PF\textsubscript{6} anion.

IndolPhospholes 3a-b and IndolPhos ligands 1a-f were evaluated in the Pd-catalyzed asymmetric allylic alkylation. For 1,3-disubstituted propenyl acetates, high activity was found and good enantioselectivity up to 90 \% ee. For cyclic substrate 10, only moderate ee up to 50 \% was obtained. The alkylation of cinnamyl acetate was achieved in good enantioselectivity up to 81 \% ee but in a low b/l of 14/86. The results show that hybrid ligands are able to induce moderate to good enantioselectivities for a range of substrates in the asymmetric allylic alkylation. The introduction of phosphole-containing ligands did not lead to an increase in selectivity, which was anticipated based on earlier successful application of phospholes in the allylic substitution.
Based on the structural data for the complexes 4a and b, the formation of the (S)-enantiomer in the case of 1,3-diphenylprop-2-enyl acetate can be rationalized by a selective nucleophilic attack cis to the phosphine in the Pd-allyl intermediate. In contrast to other C_{i}-symmetrical ligands possessing two different donor atoms such as P-N ligands, the ratio of isomeric Pd-allyl intermediates observed in solution is much larger in our case (> 50:1 vs. 9:1). Analogously however, the enantioselectivity arises from the regioselective attack on the major isomeric Pd-allyl complex. Our results from X-ray crystallography and 2D NMR spectroscopy indicate that steric rather than electronic effects play the dominant role in this step.

7.9 Experimental section

General procedures. All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. 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: phosphorochloridite of (S)-(−)-2,2′-bisnaphthol, l-cyano-3,4-dimethylphosphole, l-cyano-2,5-diphenylphosphole, [Pd₂(η³-1,3-diphenylallyl)₂Cl₂], rac-1,3-diphenylprop-2-enyl acetate 6, rac-1,3-dimethylprop-2-enyl acetate 8, and rac-3-acetoxychlohexene 10. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl; CH₂Cl₂, MeCN, EtOAc i-PrOH and MeOH were distilled from CaH₂, and toluene was distilled from sodium under nitrogen. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

NMR spectra (¹H, ³¹P and ¹³C) were measured on a Varian INOVA 500 MHz or a Varian MERCURY 300 MHz. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer; for FAB-MS 3-nitrobenzyl alcohol was used as matrix. Gas chromatographic analyses were run on a Shimadzu GC-17A apparatus. Chiral GC separations were conducted on an Interscience Focus GC Ultra. Chiral HPLC separations were conducted on a Shimadzu 10A HPLC, equipped with a UV-detector.

Synthesis of indolylphosphole 2a. To a solution of 3-methylindole (126 mg, 0.96 mmol) in THF (5 mL) was added dropwise 0.40 mL of n-BuLi (2.5 M in hexanes) at -70 °C. The resulting suspension was stirred at -70 °C for 20 min. Carbon dioxide was bubbled through the suspension for 10 min to give a clear pale yellow solution which was allowed to warm to room temperature after which the solvent was removed in vacuo. The resulting white residue was dissolved in THF (5 mL) to give a clear pale yellow solution, which was cooled to -70 °C. To this solution, 0.63 mL of t-BuLi (1.6 M in pentanes) was added and the resulting orange solution was stirred at -70 °C for 30 min. To this solution, a solution of 1-cyano-2,5-diphenylphosphole (250 mg, 0.96 mmol) in THF (2 mL) was added and the reaction mixture was stirred for 1 h at -70 °C. The resulting yellow solution was allowed to warm to room temperature and stirred for 16 h after which it was washed with 5 mL degassed sat. aq. NH₄Cl. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo to yield the product as a bright yellow solid. Yield: 293 mg (84 %). Mp = 144 °C. ¹H NMR (CDCl₃, 499.8 MHz, 298 K): δ (ppm) 7.57 (m, 5H), 7.51 (br s, 1H), 7.42 (d, J₈,₉ = 11.0 Hz, 2H), 7.29 (t, J₉,₁₀ = 7.5 Hz, 4H), 7.20 (t, J₁₀,₁₁ = 7.5 Hz, 2H), 7.13 (m, 2H), 7.07 (m, 1H), 2.76 (s, 3H). ¹³C NMR (CDCl₃, 125.7 MHz, 298 K): δ (ppm) 150.3 (C₈), 138.5 (C₉), 136.2 (d, J₈,₁₀ = 16.5 Hz, C₁₀), 132.8 (d, J₉,₁₁ = 10.2
Hz), 129.0, 127.8, 126.4 (d, J_{P,C} = 9.2 Hz), 124.3 (C_q), 124.0 (C_q), 123.7, 121.6 (d, J_{P,C} = 16.5 Hz, C_q), 119.5, 119.3, 111.1, 10.5 (d, J_{P,C} = 10.6 Hz, CH_3). 31^P{^1}H NMR (CDCl_3, 202.3 MHz, 298 K): δ (ppm) -32.25 (s). HRMS (FAB) calcd for [M + H]^+ C_{25}H_{21}NP, 366.1412; found, 366.1414.

**Synthesis of IndolPhosphole 2b.** The same procedure was followed as for 2a, except for using 1-cyano-3,4-dimethylphosphole (208 mg, 1.52 mmol) instead of 1-cyano-3,4-diphenylphosphole and 200 mg of 3-methylindole (1.52 mmol) to obtain the product as an off-white solid. Yield: 262 mg (71 %). Mp = 117 °C. {^1}H NMR (CDCl_3, 499.8 MHz, 298 K): δ (ppm) 7.58 (d, J_{H,H} = 8.0 Hz, 1H), 7.41 (br s, 1H), 7.21 (2H, 7.11 (t, J_{H,H} = 7.0 Hz, 1H), 6.47 (d, J_{P,H} = 38.5 Hz, 2H), 2.58 (s, 3H), 2.21 (d, J_{P,H} = 3.5 Hz, 6H). 13{^C} NMR (CDCl_3, 125.7 MHz, 298 K): δ (ppm) 150.5 (C_q), 150.4 (C_q), 137.9 (C_q), 129.1, 123.5, 122.9 (C_q, J_{P,C} = 29.0 Hz), 122.03 (C_q, J_{P,C} = 21.1 Hz), 121.95 (J_{P,C} = 33.3 Hz), 119.3, 110.8, 18.1 (CH_3, J_{P,C} = 3.8 Hz), 10.2 (CH_3, J_{P,C} = 10.6 Hz). 31^P{^1}H NMR (CDCl_3, 202.3 MHz, 298 K): δ (ppm) -37.70 (s). HRMS (FAB) calcd for [M + H]^+ C_{23}H_{12}NP, 242.1099; found, 242.1093.

**Synthesis of IndolPhosphole 3a.** To a solution of indolylphosphole 2a (70 mg, 0.19 mmol) in THF (3 mL) was added dropwise 0.76 mL of n-BuLi (0.25 M in hexanes) at -70°C. The resulting orange solution was stirred for 10 min at -70 °C. To this solution, a solution of (S)-(−)-2,2'-Bisnaphthol phosphorochloridite (67 mg, 0.19 mmol) in THF (1 mL) was added at -70 °C. The reaction mixture was stirred for 1 h at -70 °C and then allowed to warm to room temperature. The resulting yellow solution was filtered through a plug of SiO2 and concentrated in vacuo. The crude product was further purified by SiO2 chromatography (5 % EtOAc/Hexane) to obtain a bright yellow solid. Yield: 81 mg (63 %). Mp = 147 °C. [α]_D^{20} = +36.0 (c = 0.5, CHCl_3). {^1}H NMR (CDCl_3, 499.8 MHz, 298 K): δ (ppm) 8.01-7.92 (m, 3H), 7.71 (d, J_{H,H} = 7.0 Hz, 1H), 7.60 (d, J_{H,H} = 7.5 Hz, 4H), 7.53 (d, J_{H,H} = 8.0 Hz, 1H), 7.50-7.22 (m, 15H), 6.81 (t, J_{H,H} = 7.5 Hz, 1H), 6.21 (br s, 1H), 6.11 (t, J_{H,H} = 8.0 Hz, 1H), 5.55 (br s, 1H), 2.92 (br s, 3H). 13{^C} NMR (CDCl_3, 125.7 MHz, 298 K): δ (ppm) 150.1 (C_q), 148.7 (C_q), 136.9 (C_q), J_{P,C} = 16.0 Hz), 133.1 (C_q), 132.8 (C_q), 132.0 (C_q), 131.4 (C_q), 130.8, 130.5, 129.1, 129.0, 128.6 (J_{P,C} = 22.4 Hz), 127.5, 127.4, 126.9 (J_{P,C} = 9.7 Hz), 126.8, 126.6, 126.4, 125.5, 125.0, 122.9 (C_q), 121.9, 121.2, 121.0, 119.2, 116.2, 111.0, 11.4 (CH_3). 31^P{^1}H NMR (CDCl_3, 202.3 MHz, 298 K): δ (ppm) 148.57 (s), -32.66 (s). HRMS (FAB) calcd for [M + H]^+ C_{41}H_{30}NO_2P_2, 680.1908; found, 680.1906.

**Synthesis of IndolPhosphole 3b.** The same procedure was followed as for 3a, except for using indolylphospholene 2b (70 mg, 0.29 mmol) instead of 2a, 1.16 mL of n-BuLi (0.25 M in hexanes) and 102 mg of (S)-(−)-2,2'-Bisnaphthol phosphorochloridite (0.29 mmol) to obtain the product as a white solid. Yield: 77 mg (48 %). Mp = 167 °C. [α]_D^{20} = +188.0 (c = 0.5, CHCl_3). {^1}H NMR (CDCl_3, 499.8 MHz, 298 K): δ (ppm) 8.02 (d, J_{H,H} = 8.5 Hz, 1H), 7.97 (d, J_{H,H} = 8.0 Hz, 1H), 7.81 (d, J_{H,H} = 8.0 Hz, 1H), 7.52 (dd, J_{H,H} = 9.0 Hz, J_{H,H} = 4.0 Hz, 2H), 7.50-7.43 (m, 4H), 7.37 (d, J_{H,H} = 8.0 Hz, 1H), 7.34-7.30 (m, 2H), 6.82 (m, 2H), 6.76-6.68 (m, 2H), 6.39 (d, J_{H,H} = 8.5 Hz, 1H), 6.15 (t, J_{H,H} = 8.0 Hz, 1H), 2.49 (s, 3H), 2.12 (br s, 6H). 13{^C} NMR (CDCl_3, 125.7 MHz, 298 K): δ (ppm) 150.6 (C_q, J_{P,C} = 5.5 Hz), 149.0 (C_q), 141.1 (C_q), J_{P,C} = 7.5 Hz), 133.2 (C_q), 132.9 (C_q), 131.9 (C_q), 131.5 (C_q), 130.8, 130.6, 129.9 (C_q, J_{P,C} = 27.0 Hz, J_{P,C} = 5.0 Hz), 129.2, 128.6 (J_{P,C} = 10.9 Hz), 127.4, 126.9, 126.6, 126.5, 125.1, 124.8 (C_q, J_{P,C} = 5.9 Hz), 123.8, 122.9 (C_q), 122.0, 121.8, 121.0, 118.7, 116.2, 18.1 (CH_3), 10.8 (CH_3, J_{P,C} = 14.3 Hz). 31^P{^1}H NMR (CDCl_3, 202.3 MHz, 298 K): δ (ppm) 148.33 (d, J_{P,P} = 43.1 Hz), -37.03 (d, J_{P,P} = 43.1 Hz). HRMS (FAB) calcd for [M + H]^+ C_{35}H_{30}O_2NP_2, 556.1595; found, 556.1594.
Synthesis of Complex 4a, [Pd(1a)(C₃H₅)]PF₆. To a solution of INDOLPhos 1a (100 mg, 0.16 mmol) in CH₂Cl₂ (4 mL) was added [Pd₂(η³-C₃H₅)₂Cl₂] (29 mg, 0.08 mmol) at room temperature. The solution was stirred for 5 min. Silver hexafluorophosphate salt (41 mg, 0.16 mmol) was then added and the resulting suspension was stirred for 30 min. Filtration over Celite and evaporation of the solvent afforded the product as a white solid. Colorless needles suitable for X-ray crystallographic analysis were obtained by slow diffusion of hexanes into a saturated dichloromethane solution. Yield: 117 mg (79 %). Mp = 174 °C (decomp.). [α]D²⁰ = + 263.0 (c = 1.0, CHCl₃). ¹H NMR (CDCl₃, 499.8 MHz, 298 K): δ (ppm) 8.34 (d, JₗH = 9.0 Hz, 0.5H), 8.32 (d, JₗH = 9.0 Hz, 0.5H), 8.16 (t, JₗH = 7.5 Hz, 1H), 7.98 (t, JₗH = 8.5 Hz, 1H), 7.81-7.54 (m, 15H), 7.51-7.43 (m, 4H), 7.12 (t, JₗH = 7.5 Hz, 1H), 6.86 (d, JₗH = 9.0 Hz, 0.5H), 6.75 (d, JₗH = 9.0 Hz, 0.5H), 6.48 (m, 1H), 6.40 (d, JₗH = 8.5 Hz, 0.5H), 6.37 (d, JₗH = 8.5 Hz, 0.5H), 5.75 (t, JₗH = 7.5 Hz, JₕH = 0.5 Hz), 5.47 (t, JₗH = 14.0 Hz, JₕH = 7.0 Hz, 0.5H), 4.82 (t, JₗH = 7.5 Hz, 0.5H), 4.68 (t, JₗH = 8.5 Hz, 0.5H), 4.58 (m, 0.5H), 4.36 (m, 0.5H), 3.47 (m, 0.5H), 3.33 (t, JₗH = 15.0 Hz, 0.5H), 3.22 (t, JₗH = 15.0 Hz, 0.5H), 2.96 (m, 0.5H), 2.09 (s, 3H). ¹³C NMR (CDCl₃, 125.7 MHz, 298 K): δ (ppm) 149.5 (C₁₈, Jₚ,P = 6.4 Hz), 149.4 (C₁₇, Jₚ,P = 5.9 Hz), 147.1 (C₁₄, Jₚ,P = 5.2 Hz), 147.0 (C₁₃, Jₚ,P = 5.5 Hz), 139.2 (C₁₂), 136.7 (C₁₁), 133.6, 133.5, 133.3, 133.2, 133.1, 133.01 (C₁₀), 132.96, 132.91 (C₁₀), 132.86, 132.77, 132.73 (C₉), 132.68, 132.51, 132.42, 130.7 (Jₚ,P = 12.3 Hz), 130.4 (Jₚ,P = 8.4 Hz), 130.3 (Jₚ,P = 8.4 Hz), 129.5 (Jₚ,P = 8.0 Hz), 129.2 (Jₚ,P = 2.1 Hz), 128.09, 128.05, 127.6 (Jₚ,P = 11.8 Hz), 127.4 (Jₚ,P = 4.1 Hz), 127.2 (Jₚ,P = 4.3 Hz), 127.0 (Jₚ,P = 3.0 Hz), 126.8, 125.3 (Jₚ,P = 6.3 Hz), 125.2 (Jₚ,P = 6.4 Hz), 124.3, 124.2 (C₉), 122.5 (C₈), 121.2, 121.0, 120.2 (Jₚ,P = 8.0 Hz), 115.7, 73.94 (CH₂, Jₚ,P = 44.1 Hz), 73.89 (CH₂, Jₚ,P = 45.1 Hz), 73.0 (CH₂, Jₚ,P = 8.2 Hz), 72.8 (CH₂, Jₚ,P = 8.0 Hz), 10.9 (CH₃). ³¹P [¹H] NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) 293.13 (septuplet, Jₚ,P = 710.1 Hz, PF₆), 151.45 (d, Jₚ,P = 83.5 Hz, 0.5P), 151.42 (d, Jₚ,P = 83.5 Hz, 0.5P), 16.99 (d, Jₚ,P = 83.5 Hz, 0.5P), 16.86 (d, Jₚ,P = 82.3 Hz, 0.5P). HRMS (FAB) caleld for [M – PF₆]⁺ C₄₄H₃₂OₕNPd. 776.1116; found, 776.1119.

Synthesis of Complex 4b, [Pd(1a)(1,3-diphenylallyl)]PF₆. To a solution of INDOLPhos 1a (100 mg, 0.16 mmol) in CH₂Cl₂ (5 mL) was added [Pd₂(η³-1,3-diphenylallyl)₂Cl₂] (53 mg, 0.08 mmol) at room temperature. The solution was stirred for 15 min. Silver hexafluorophosphate salt (41 mg, 0.16 mmol) was then added and the resulting suspension was stirred for 30 min. Filtration over Celite gave a bright yellow solution. Hexanes (10 mL) was added to precipitate a bright yellow solid. The solvent was removed by syringe, and the product was dried in vacuo. Yield: 103 mg (60 %). Mp = 221 °C (decomp.). [α]D²⁰ = + 420.0 (c = 1.0, CHCl₃). ¹H NMR (CDCl₃, 499.8 MHz, 298 K): δ (ppm) 8.19 (d, JₗH = 9.0 Hz, 1H), 8.13 (d, JₗH = 9.0 Hz, 1H), 8.01 (d, JₗH = 8.5 Hz, 1H), 7.85 (d, JₗH = 8.0 Hz, 1H), 7.68-7.54 (m, 6H), 7.50 (t, JₗH = 7.5 Hz, 2H), 7.37-7.22 (m, 8H), 7.05 (d, JₗH = 8.5 Hz, 1H), 7.02 (t, JₗH = 7.5 Hz, 2H), 6.94 (t, JₗH = 7.5 Hz, 1H), 6.90 (d, JₗH = 7.5 Hz, 2H), 6.81 (m, 3H), 6.65 (d, JₗH = 7.5 Hz, 1H), 6.63 (d, JₗH = 7.5 Hz, 1H), 6.26 (m, 3H), 6.19 (d, JₗH = 6.5 Hz, 1H), 6.17 (m, 1H), 5.93 (d, JₗH = 8.5 Hz, 1H), 5.77 (vt, J = 10.0 Hz, 1H), 5.60 (vt, J = 15.0 Hz, 1H), 1.84 (s, 3H). ¹³C NMR (CDCl₃, 125.7 MHz, 298 K): δ (ppm) 149.3 (C₁₈, Jₚ,P = 14.8 Hz), 147.1 (C₁₇, Jₚ,P = 5.4 Hz), 138.6 (C₁₄, Jₚ,P = 6.7 Hz), 137.3 (C₁₃, Jₚ,P = 5.0 Hz), 136.1 (C₁₂, Jₚ,P = 4.7 Hz), 135.5 (C₁₁, Jₚ,P = 12.7 Hz), 134.5, 134.3, 133.1, 132.8 (C₁₀), 132.6 (C₉), 132.5, 132.1 (C₉), 131.7 (Jₚ,P = 2.5 Hz), 131.6, 131.3 (Jₚ,P = 11.8 Hz), 129.9 (Jₚ,P = 12.2 Hz), 129.8 (C₈, Jₚ,P = 10.9 Hz), 129.2, 129.1, 128.7, 128.5, 128.3 (Jₚ,P = 10.2 Hz), 127.6, 127.5, 127.3, 127.0, 126.4 (Jₚ,P = 9.2 Hz), 126.1, 125.71 (C₁₇, Jₚ,P = 20.6 Hz), 125.70, 125.3 (C₁₄, Jₚ,P = 19.4 Hz), 123.4, 122.3 (C₁₄, Jₚ,P =
the reaction mixture was diluted with Et₂O and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 1 h, dimethyl malonate (86 µL, 0.75 mmol), was stirred for 30 min. Subsequently, a solution of C₇H₆NP₂Pd (0.46 mg, 1.25 µmol) was then added and the resulting suspension was stirred for 30 min. Filtration over Celite and evaporation of the solvent afforded the product as a white solid. Needles suitable for X-ray crystallographic analysis were obtained by slow diffusion of hexanes into a saturated dichloromethane solution. Yield: 42 mg (99 %). Mp = 166 °C (decomp.). [α]D²⁰ = +354.0 (c = 0.5, CHCl₃). ¹H NMR (CD₂Cl₂, 499.8 MHz, 263 K): δ (ppm) 8.29 (d, J = 9.0 Hz, 0.5H), 8.26, J₂,₃H = 9.0 Hz, 0.5H), 8.13 (t, J₂,₃H = 8.5 Hz, 1H), 7.99 (t, J₂,₃H = 7.5 Hz, 1H), 7.80 (d, J₂,₃H = 9.0 Hz, 0.5H), 7.76 (d, J₂,₃H = 9.0 Hz, 0.5H), 7.72 (d, J₂,₃H = 9.0 Hz, 0.5H), 7.65-7.58 (m, 2H), 7.52-7.42 (m, 5H), 7.06 (t, J₂,₃H = 8.5 Hz, 2H), 6.67-6.44 (m, 2H), 6.42 (t, J₂,₃H = 7.5 Hz, 1H), 6.18 (d, J₂,₃H = 8.5 Hz, 0.5H), 6.14 (d, J₂,₃H = 8.5 Hz, 0.5H), 5.62 (tt, J₂,₃H = 13.5 Hz, J₂,₃H = 6.5 Hz, 0.5H), 5.35 (tt, J₂,₃H = 13.5 Hz, J₂,₃H = 7.0 Hz, 0.5H), 4.34 (m, 1H), 4.26 (t, J₂,₃H = 9.0 Hz, 0.5H), 4.16 (m, 0.5H), 3.28 (m, 1H), 3.12 (t, J₂,₃H = 15.0 Hz, 0.5H), 2.89 (m, 0.5H), 2.35 (m, 1.5H), 2.34 (s, 1.5H), 2.32 (s, 3H), 2.04 (s, 3H). ¹³C NMR (CD₂Cl₂, 125.7 MHz, 298 K): δ (ppm) 156.2 (C₂), 150.0 (C₂), 147.6 (C₂), 139.1 (C₂), 136.6 (C₂), 133.3 (C₂), 133.0 (C₂), 132.9 (C₂), 132.7 (C₂), 129.5, 129.2, 128.0, 127.7, 127.5, 127.2, 127.0, 126.2, 124.8, 124.4 (C₂), 124.1, 122.4 (C₂), 121.0, 120.8, 120.5, 120.1, 119.3, 115.6, 73.9 (CH₂), 73.2 (CH₂), 18.2 (CH₃), 8.9 (CH₃). ³¹P {¹H} NMR (CD₂Cl₂, 202.3 MHz, 263 K): δ (ppm) 292.94 (septuplet, J₂P,₃P = 74.4 Hz, 0.5P), 289.84 (m, 0.5P), 276.84 (m, 0.5P), 263.84 (m, 0.5P). HRMS (FAB) calcd for [M – PF₆]⁺ C₉H₅O₂NP₃Pd, 702.0958; found, 702.0950.

**Allylic Alkylation of rac-1,3-Diphenylprop-2-enyl Acetate (6).** A solution of [Pd₂(η³-C₃H₆)Cl₂] (0.46 mg, 1.25 µmol) and INDOLPhos(phole) ligand (2.75 µmol) in CH₂Cl₂ (1 mL) was stirred for 30 min. Subsequently, a solution of rac-6 (63 mg, 0.25 mmol) in CH₂Cl₂ (1 mL), dimethyl malonate (86 µL, 0.75 mmol), N,O-bis(trimethylsilyl)acetamide (185 µL, 0.75 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 1 h the reaction mixture was diluted with Et₂O (3 mL) and sat. aq. NH₄Cl (10 mL). The aqueous phase was removed. To determine the conversion, a sample for GC-analysis was taken from the organic phase. The solvent was removed in vacuo. To determine the ee by HPLC (Chiralcel-ODH, 0.5 % 2-propanol/hexane, flow 0.5 mL/min) a sample was filtered over SiO₂, using hexanes as eluent.

**Allylic Alkylation of rac-1,3-Dimethylprop-2-enyl Acetate (8).** A solution of [Pd₂(η³-C₃H₆)Cl₂] (0.46 mg, 1.25 µmol) and IndolPhos(phole) ligand (2.75 µmol) in CH₂Cl₂ (1 mL) was stirred for 30 min. Subsequently, a solution of rac-8 (32 mg, 0.25 mmol) in CH₂Cl₂ (1 mL), dimethyl malonate (86 µL, 0.75 mmol), N,O-bis(trimethylsilyl)acetamide (185 µL, 0.75 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 1 h the reaction mixture was diluted with Et₂O (3 mL) and sat. aq. NH₄Cl (10 mL). The aqueous
phase was removed. Conversion and ee were determined by chiral GC (Chiralcel DEX CB, isothermal at 65 °C).

**Allylic Alkylation of rac-3-Acetoxycyclohexene (10).** A solution of [Pd₂(η³-C₃H₅)₂Cl₂] (0.46 mg, 1.25 µmol) and IndolPhos(phole) ligand (2.75 µmol) in CH₂Cl₂ (1 mL) was stirred for 30 min. Subsequently, a solution of rac-10 (35 mg, 0.25 mmol) in CH₂Cl₂ (1 mL), dimethyl malonate (86 µL, 0.75 mmol), N,O-bis(trimethylsilyl)acetamide (185 µL, 0.75 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 1 h the reaction mixture was diluted with Et₂O (3 mL) and sat. aq. NH₄Cl (10 mL). The aqueous phase was removed. Conversion and ee were determined by chiral GC (Supelco β-DEX 225, isothermal at 50 °C for 2 min, 3 °C/min to 190 °C).

**Allylic Alkylation of Cinnamyl Acetate (12).** A solution of [Pd₂(η³-C₃H₅)₂Cl₂] (0.46 mg, 1.25 µmol) and IndolPhos(phole) ligand (2.75 µmol) in CH₂Cl₂ (1 mL) was stirred for 30 min. Subsequently, a solution of 12 (42 µL, 0.25 mmol) in CH₂Cl₂ (1 mL), dimethyl malonate (86 µL, 0.75 mmol), N,O-bis(trimethylsilyl)acetamide (185 µL, 0.75 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 1 h the reaction mixture was diluted with Et₂O (3 mL) and sat. aq. NH₄Cl (10 mL). The aqueous phase was removed. To determine the conversion, a sample for GC-analysis was taken from the organic phase. The solvent was removed in vacuo. To determine the ee by HPLC (Chiralcel-OJH, 3.0 % 2-propanol/hexane, flow 0.7 mL/min) a sample was filtered over SiO₂, using hexanes as eluent.

**X-ray Crystallography of 4a and 5.** All reflection intensities were measured at 110(2) K using a Nonius KappaCCD diffractometer (rotating anode) with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) under the program COLLECT. The programs PEAKREF was used to refine the cell dimensions. Data reduction was done using the programs EVALCCD. The structure of 4a was solved with the program DIRDIF08, and that of 5 with the program SHELXS-97. The two structures were refined on F² with SHELXL-97. Analytical absorption corrections based on crystal face-indexing were applied to the data using SADABS (transmission ranges for 4a: 0.80-0.92, and for 5: 0.87-1.00). The temperature of the data collection was controlled using the system OXFORD CRYOSTREAM 600 (manufactured by OXFORD CRYOSYSTEMS). The H-atoms were placed at calculated positions (AFIX 23 or AFIX 43 or AFIX 93 or AFIX 137) with isotropic displacement parameters having values 1.2 or 1.5 times Ueq of the attached C atom, and were refined with a riding model. In the crystal structure of 4a, the asymmetric unit contains two crystallographically independent Pd complexes, two hexafluorophosphate counter anions and two dichloromethane solvent molecules. The allyl ligands are disordered, and their major components refine to 0.703(8) and 0.623(9). In the crystal structure of 5a, the asymmetric unit was modeled with four Pd complexes, four hexafluorophosphate counter anions and two dichloromethane solvent molecules. One allyl ligand and one counter anion PF₆⁻ were found to be disordered. The major component of the disordered allyl ligand refines to 0.718(8) and that of the disordered counter anion refines to 0.717(6). One void, which probably contains very disordered solvent molecules, was found at (-0.169, 0.748, 0.606). The contribution of these solvent molecules was taken out for the last stage of the refinement using the program SQUEEZE. For both structures, the absolute configuration was established by the structure determination of a compound containing a chiral reference molecule of known absolute configuration and confirmed by anomalous-dispersion effects in diffraction measurements on the crystals. Geometry calculations were performed with the
**PLATON** program. Graphical illustrations were made using **ORTEP-3** (2.02) and **Mercury** 1.4.2 (Build 2).

4a: C$_{45}$H$_{38}$Cl$_2$F$_2$NO$_2$P$_3$Pd, $M_w$ = 1006.96, colorless block, 0.23 x 0.12 x 0.12 mm$^3$, monoclinic, $P2_1$ (no. 4), $a$ = 9.6088(2) Å, $b$ = 41.1341(6) Å, $c$ = 10.4629(2) Å, $\beta$ = 91.581(1)°, $V$ = 4133.88(13) Å$^3$, $Z$ = 4, $D_\alpha$ = 1.618 g.cm$^{-3}$, $\mu$ = 0.76 mm$^{-1}$. 74134 Reflections were measured. 18866 Reflections were unique ($R_{int}$ = 0.038) and 16822 reflections were observed using the criterion $I > 2\sigma(I)$. 1139 Parameters were refined with 217 restraints. $R1/wR2$ [$I > 2\sigma(I)$]: 0.033/0.056. $R1/wR2$ (all refl.): 0.043/0.058. $S$ = 1.06. Residual electron density between -0.47 and 0.58 e Å$^{-3}$. Flack parameter = -0.018(10).

5a: C$_{38}$H$_{33}$Cl$_2$F$_3$NO$_2$P$_3$Pd, $M_w$ = 890.42, colorless block, 0.19 x 0.19 x 0.16 mm$^3$, triclinic $P1$ (no. 1), $a$ = 15.6617(4) Å, $b$ = 15.8329(4) Å, $c$ = 16.2065(5) Å, $\alpha$ = 98.715(1)°, $\beta$ = 92.600(1)°, $\gamma$ = 90.599(2)°, $V$ = 3967.63(19) Å$^3$, $Z$ = 4, $D_\alpha$ = 1.491 g.cm$^{-3}$, $\mu$ = 0.72 mm$^{-1}$. 90387 Reflections were measured. 36340 Reflections were unique ($R_{int}$ = 0.034) and 32022 reflections were observed using the criterion $I > 2\sigma(I)$. 1989 Parameters were refined with 421 restraints. $R1/wR2$ [$I > 2\sigma(I)$]: 0.036/0.077. $R1/wR2$ (all refl.): 0.046/0.080. $S$ = 1.06. Residual electron density between -0.68 and 0.87 e Å$^{-3}$. Flack parameter = -0.016(8). **SQUEEZE** details: void of 319 Å$^3$ per unit cell filled with 55 electrons per unit cell. * excluding the disordered solvent contribution.

**DFT calculations.** The geometry optimization of complex 4b was carried out with the Turbomole program coupled to the PQS Baker optimizer. Geometries were fully optimized as minima at the BP86 level using the SV(P) basis set on all atoms.

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### 7.11 References


