Direct activation of allylic alcohols in palladium catalyzed coupling reactions

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Chapter 3

Applications of Urea Functionalized Ligand Complexes in Allylic Substitution Reactions
3.1 Introduction

Palladium catalyzed allylic substitution reactions are well-known transformations widely applied in organic synthesis. Recent developments focus on replacing the typical activated allylic reagents (typically substituted with carboxylates, halides or phosphates) by unactivated allylic alcohols in order to prevent stoichiometric amounts of waste formation. In early attempts, additional stoichiometric amounts of Lewis acid activators, such as BEt₃, SnCl₂ or Ti(O-i-Pr)₄, were required to pre-activate the allylic alcohols, but this approach again leads to stoichiometric waste formation. Recently, the waste-free catalytic activation of unactivated allylic alcohols in Pd coupling reactions was explored by us⁶ and others⁷. The hydrogen-bond assisted palladium catalyst, 1a, that we developed afforded linear alkylated and aminated products selectively (Figure 1a). The monodentate phosphoramidite ligand, 1, based palladium complex operated best when activated by 1,3-diethylurea. The yields in the absence of 1,3-diethylurea were lower and the reactions displayed poor reproducibility. Mechanistic studies showed that the oxidative addition of the allylic alcohol was the rate determining step (based on zero order kinetics in [nucleophile], first order kinetics in [urea] and [alcohol]). Along with this, DFT calculations demonstrated a H-bonding array between the catalyst, the substrate and the urea moiety, suggesting that urea assists in the oxidative addition step (Figure 1b).

![Figure 1](image_url)

**Figure 1.** a) The phosphoramidite ligand, 1, and the corresponding Pd complex, 1a. b) Schematic representation and DFT calculated structures of the proposed intermediates.⁵

As the reactions only required one equivalent urea additive with respect to Pd complex, we wondered if the use of ligands with a covalently attached urea moiety would improve the catalytic activity. Such urea functionalized ligands might prevent the need of additional urea as the activation process could operate in an intramolecular manner, thus avoiding unfavorable entropy effects. To study this concept, selected urea functionalized ligands with different electronic properties, such as phosphine, phosphoramidite and phosphite, were explored in allylic substitution reactions and characterization studies were performed.
3.2 Results and Discussions

The supramolecular approach, which we developed previously for the activation of allylic alcohols, was based on catalysts 1a and 1,3-diethylurea as a H-bonding co-catalyst. To design a similar system with urea functionalized ligands operating in an intramolecular manner, we first investigated the ureaphosphinineligands, 2 and 3, which were developed previously in our group (Scheme 1).

Catalysis with the electronically similar but urea-free triphenylphosphine, 4, was also studied as a control experiment. The alkylation of cinnamyl alcohol with indole was the model reaction that we explored to examine this new concept (Table 1). The catalytic reactions were performed under the previously optimized conditions, in toluene at 80 °C, and all Pd complexes were prepared in situ by mixing the ligand with [(η^3-allyl)Pd(cod)]BF_4.

As reported earlier, catalysis with ligand 1 afforded the alkylation product in 62% yield in the absence of 1,3-diethylurea, whereas the yield increased to 86% yield in the presence of this co-catalyst (entries 1 and 2, Table 1). The catalysts based on ligands 2 and 3 afforded the same product in only 12% and 17% yield, respectively (entries 3 and 4). When urea-free ligand 4 was used, the product was obtained in 21% yield, while the presence of urea increased the yield to 39% (entries 5 and 6). Other studies have shown a clear relation between the electronic properties of the ligands and catalytic activity in allylic substitution reactions, showing that strong π-acceptor ligands show a higher activity in allylic substitution reactions. In agreement with this, a higher yield was...
observed with the stronger $\pi$-accepting phosphoramidite ligand 1 compared to (aryl)phosphines 2, 3 and 4. Most importantly, the comparison of ureaphosphine ligands with simple triphenylphosphine demonstrated that the urea as a part of the ligand did not lead to higher activity while having the urea moiety freely in solution did enhance the results.

Next, we explored the urea functionalized phosphoramidite and phosphite based ligands 5 and 6, which design was based on the original ligand 1 but are equipped with a covalently attached urea moiety. The same bi-phenyl backbone containing bulky $t$-Bu groups was employed. It should be noted that this type of bi-phenyl backbones, *tropos*, are dynamic around the axis that the motion can be regulated by the chiral substituents.10 As the L-phenylalanine moiety of the ligand 1 possibly leads to a chiral induction onto the *tropos* backbone, we intended to examine this feature also in the new generation urea functionalized ligands. Therefore we prepared the achiral and chiral ligands ureaphosphoramidite, 5, and ureaphosphite, 6, which were synthesized by the coupling of substituted bi-phenyl phosphochlorides with functionalized phenylurea amine and alcohol, respectively (Scheme 2).

The palladium complexes of these ligands were prepared in situ and subsequently applied in the allylic amination reaction in the presence and absence of 1,3-diethylurea. Amination of cinnamyl alcohol with $N$-methylaniline was chosen as the model reaction for analysis (Table 2). The complex based on ligand 1 resulted in 72 % product formation, which improved to 85 % in the presence of 3 mol % 1,3-diethylurea (entries 1.

![Scheme 2. Ureaphosphoramidite ligand 5 and ureaphosphite 6.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>1 + 1,3-diethylurea</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>5 + 1,3-diethylurea</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>6 + 1,3-diethylurea</td>
<td>26</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: Cinnamyl alcohol (0.5 mmol), N-methylaniline (0.75 mmol), 3 mol% [(η3-allyl)Pd(cod)]BF4, 6 mol% ligand, toluene (2.5 ml), r.t. [b] GC results, 4h, (see experimental for the reaction progress profile in time, Figure 6). [c] 3 mol% 1,3-diethylurea was added. [d] Reactions were performed at 80 °C.
Applications of the Urea Substituted Ligand Complexes in Allylic Substitution Reactions

and 2, Table 2). The Pd complex of ligand 5 was active only after the reaction was heated to 80 °C. The product was obtained in 16 % and in 34 % yield in the absence and presence of additional 1,3-diethylurea, respectively (entries 3 and 4). Compared to the catalytic system based on ligand 1 that of ligand 5 displayed a much lower reaction rate. The complex of ureaphosphite ligand 6 also afforded the product in poor yield, but already at room temperature. Addition of 1,3-diethylurea did not lead to appreciably higher yields in this case (entries 5 and 6). In short, the urea functionalized ligand complexes showed lower activity compared to ligand 1 and the addition of external 1,3-diethylurea still improved the yields (see experimental section, Figure 6). This suggested that the covalently attached urea functional group has no or little effect on the catalysis.

To establish the characteristic properties of the complex 1a and the respective Pd complexes of ligand 5 and 6, we have analyzed the ligands and complexes by 31P-NMR spectroscopy at variable temperatures. The free ligand 1 and complex 1a reveal singlet signals with chemical shifts of 146 ppm and 134 ppm, respectively (Figure 2). The sharp singlet of ligand 1 broadened upon cooling down and splits into two signals at 193 K. These two broad signals of ligand 1 at low temperatures represent the interchangeable tropos-based diastereomers \( L_1^{RS} \) and \( L_1^{SS} \), which are in fast dynamic exchange at room temperature, originated by the prevalent stereochemical configuration on the tropos backbone (Figure 3). This we could detect by CD experiments, which showed R configuration is prevalent for both ligand 1 and complex 1a (see experimental section for details, Figure 7).

![Figure 2. VT-31P-NMR spectra of (a) Ligand 1 and (b) complex 1a (293-183 K).](image)

The signal observed in the 31P-NMR spectrum of complex 1a did not change in the temperature range 293-183 K, thus indicating that the bi-phenyl backbone has an absolute R chirality (assignment of the R configuration is based on CD measurements, see experimental, Figure 7) when ligand 1 is coordinated to palladium (Figure 2b). The sharp singlet (\( \delta=134 \) ppm) was attributed to the homocomplex \( L_1^{RS}PdL_1^{RS} \), as the exchange between diastereoisomers \( L_1^{RS} \) and \( L_1^{SS} \) is slow on the NMR time scale at this temperature.
Chapter 3

Figure 3. The dynamic equilibrium between two diastereoisomers $L_1^{RS}$ and $L_1^{SS}$ that is slow on the NMR time scale at 183 K. In the description of $L_1^{ab}$, ‘a’ represents the configuration of the atropisomeric biphenyl moiety and ‘b’ is the stereogenic center of the amino-ester moiety, (S). The major isomer $L_1^{RS}$ was determined according to CD measurements (see experimental section, Figure 7).

As ligand 5 is racemic, but does contain a tropos-type biphenyl moiety, existence of two enantiomeric configurations, $L_5^R$ and $L_5^S$, which are exchangeable in solution, were expected. As these are enantiomers, they should give the same signal in the NMR. Indeed a sharp phosphorus signal of this ligand ($\delta = 146$ ppm, singlet) was observed at room temperature, which broadened at low temperature change (298K to 183K). This broadening may reflect coalescence of these enantiomers (Figure 4a). The Pd-allyl complex of ligand 5, complex 5a, gave rise to one broad signal at room temperature in the $^{31}$P-NMR spectra, which splits into four doublets and one singlet after cooling (293 K-193 K) (Figure 4b). The correlations between these signals were determined by two dimensional $^{31}$P-COSY analysis at 213 K.

Figure 4. VT-$^{31}$P-NMR spectra of (a) Ligand 5 and (b) complex 5a. Upon complexation the broad singlet of the ligand splits into two doublet of doublets ($\delta = 133$ ppm, 129 ppm, $J = 94$ Hz assigned with (♠) and $\delta = 132$ ppm, 127 ppm, $J = 94$ with (♦)) and the singlet ($\delta = 132$ ppm, ●) overlapping with one of the doublet (293-183K).

The two doublet of doublelets ($\delta = 133$ ppm, 129 ppm, $J = 94$ Hz and $\delta = 132$ ppm, 127 ppm, $J = 94$ Hz) and one singlet ($\delta = 132$ ppm) are suggesting that the complex 5a exists in three different forms (conformers and/or interchangeable tropos-based diastereomers, see experimental section, Figure 8). Heating this sample to 353 K led to
coalescence of these signals into one broad singlet, which indicates that the conformers/diastereomers are in exchange in solution (see experimental section, Figure 9). Additionally, as the racemic ligand 5 has no element of chirality, we did not observe any Cotton effects on CD measurements considering the *tropos* nature of ligand 5. Mass analysis of 5a revealed that all species in solution have the same mass (see experimental section for CD analysis, Figure 10).

VT-31P-NMR studies showed that the phosphorous signal of the ligand 6 (δ=138 ppm) broadens upon lowering the temperature, and below the coalescence temperature of ~233 K the signal splits into two new signals (Figure 5a). As in case of ligand 1, these peaks were assigned as two possible diastereoisomers of the ligand 6, L₆⁵⁵⁵ and L₆⁶⁶⁶, that are in equilibrium. In line with this, we observed a single peak in the mass spectrum. In contrast to 1, CD spectroscopy showed no Cotton effects, indicating that there is no chirality transfer from the S stereogenic center of ligand 6 to the bi-phenyl moiety (see experimental section, Figure 15). The ³¹P-NMR spectrum Pd complex, 6a (based on ligand 6) gave rise to multiple signals at room temperature, which we further investigated with 2D-³¹P-COSY spectroscopy (see experimental section, Figure 11). Two sets of signals, the singlet (δ = 126 ppm) and two doublets, which are coupling with each other (δ = 132 ppm, 105 ppm, J=118 Hz), were determined as a mixture of two different complexes. Importantly, we first observed the formation of a singlet at 126 ppm and then the slow generation of doublets (see experimental section, Figure 12). As this appeared to be an irreversible conversion, this indicates the formation of a different complex by decomposition of complex 6a. Analysis of the freshly prepared complex, which has single complex represented by the singlet, and an old sample, which mainly contained the complex showing the above described doublet of doublets confirms that new complexes are formed. The fresh sample has the molecular mass corresponding to complex 6a while the aged sample showed a peak with a much higher mass, which did not correlate with any expected complex. Importantly, the old sample, which is either the

![Figure 5. VT-³¹P-NMR spectra of (a) Ligand 6 and (b) complex 6a consisted of mixture of complexes that the one gave rising to singlet (δ = 126 ppm) and the other one to doublet of doublets, which are signed by * (δ = 132 ppm, 105 ppm, J=118 Hz) (293-183K).](image-url)
decomposed or derived complex, did not show any activity in allylic amination catalysis (see experimental section, Table 3).

Reflecting on the catalytic experiments of the complexes 1a, 5a and 6a in the light of the above characterization studies, the high activity of 1a could well be explained by the fact that this species exists as only one single (active) species in solution, as is clear from NMR spectroscopy and mass analysis. The poor activity of complex 5a (even at high temperatures) might well be caused by the fact that this species exists as a mixture of compounds (conformers/interchangeable *tropos*-based diastereomers) in dynamic exchange. These different isomers may not all have the same catalytic activity and some of them may actually be ‘dormant states’. In case of complex 6a, the thermal decomposition of the Pd-allyl homo-complex into an unknown inactive complex is hampering the catalytic activity. As a result of these observations, the effect of the covalently attached urea functionalities on the catalytic performance of the complexes remained rather inconclusive as other variables (i.e. formation of a mixture of complexes and catalyst decomposition) prevented us from making a fair comparison.

### 3.3 Conclusions

We investigated a catalytic system containing a covalently attached urea moiety to investigate the effect of intramolecular H-bonding in the direct activation of allyl alcohols. This system was inspired by our previously reported catalyst 1a using external 1,3-diethylurea to activate allyl alcohols in allylic substitution reactions. We expected that intermolecular H-bonding to a covalently attached urea moiety of the catalyst’s ligand might be beneficial for entropic reasons. To investigate this, urea functionalized ligands with different electronic properties were prepared and studied in the model coupling reaction of cinnamyl alcohol with *N*-methylaniline. Unexpectedly, the application of ureaphosphine ligands 2 and 3 showed much lower activities than the simple phosphine 4 combined with external urea. In addition to this, the presence of 1,3-diethylurea in catalysis with ureaphosphoramidite 5 and ureaphosphite 6 led to higher yields in Pd catalyzed allylic substitution reactions. Characterization of complex 5a revealed the presence of a mixture of complexes in solution, which are in dynamic equilibrium (conformers/interchangeable *tropos*-based diastereomers). Complex 6a proved thermally instable and decomposed into an unknown, catalytically inactive species over time. The thermal instability of 6a and the presence of different species (some of which may be ‘dormant’) in case of 5a may well explain the poor activity of these systems as compared to 1a. The combination of complex 1a (which exists as only one single species in solution) and 1,3-diethylurea acting as a non-covalently attached supramolecular allyl-alcohol activator remains thus far the most efficient catalyst system for allyl alkylation/amination of unactivated allyl alcohols with palladium. Having the urea moiety freely in solution rather than as a functional group covalently attached to the catalyst...
seems to give rise to higher activities, possibly due to a smaller influence of unfavorable steric interactions. However, this conclusion is somewhat hampered by other effects decreasing the activity of 5a and 6a.

3.4 Experimental Section

3.4.1 General

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried using solvent purification system (SPS). NMR spectra were measured on a Varian Inova spectrometer (500 MHz, 125.7 MHz and 202.3) and Bruker AMX 400 (400.1MHz, 100.6MHz and 162.0) for 1H, 13C and 31P respectively. High resolution ESI (electrospray ionization) mass spectra were recorded on a JEOL Accu TOF LC-plus mass spectrometer (JMS-T100LP) with EI+ method. For the reaction progress analysis an Interscience Focus Chiral GC equipped with a Varian capillary column (CP-Chirasil-Dex CB 25 m column, 0.32 mm diameter, 0.25 μm film thickness) was used.

3.4.2 Ligand Synthesis

All reagents were purchased from commercial suppliers and were used without further purification. Ligand 1, 2 and 3 were synthesized according to a published procedure.8

**Synthesis of urea-amine [1-(2-aminoethyl)-3-phenylurea]:** A solution of 5 mmol phenylisocyanate in 10 ml toluene/hexane (1/1) was added dropwise to a vigorously stirred solution of 10 mmol ethylenediamine in 20 ml toluene/hexane (1/1) at 0 °C. The mixture was then allowed to warm up to room temperature and was stirred for 1 hour. The formed precipitate was filtered off and washed twice with hexane. Remaining solvents were evaporated to obtain the product.

**Synthesis of urea-alcohol [1-(1-hydroxypropan-2-yl)-3-phenylurea]:** A solution of 5 mmol phenylisocyanate in 10 ml CH2Cl2 was added dropwise to a vigorously stirred solution of 5 mmol aminoalcohol in 20 ml CH2Cl2 at 0 °C. The mixture was then allowed to warm up to room temperature and was stirred for 1 hour. The formed precipitate was filtered off and washed twice with hexane. Remaining solvents were evaporated to obtain the product.

**Synthesis of the phosphorochloridite [4,8-di-tert-butyl-6-chloro-2,10-dimethoxydibenzo[d,f]-[1,3,2] dioxaphosphepine]:** A solution of distilled NEt3 (9.2 mmol) in THF (11 mL) was added to distilled PCl3 (4.9 mmol) under inert conditions. The prepared diol13 (4.5 mmol) was pre-dried with toluene by co-evaporation, dissolved in THF (4.5 mL) and was slowly added to a NEt3-PCl3 mixture at -78 °C. The reaction mixture was stirred for 30 min at -78 °C and then allowed to warm up to room temperature. The excess of PCl3 was removed in vacuo by co-evaporation with toluene. The product was used directly in the synthesis of ureaphosphoramidite, 5, and ureaphosphite, 6.

**Ligand 5 [1-(2-((4,8-di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)amino)ethyl)-3-phenylurea]:** A solution of 1 mmol phosphorochloridite dissolved in 10 ml THF was added to a vigorously stirred solution of 1 mmol urea-amine and excess of Et3N in 20 ml THF kept at 0 °C. The reaction mixture was subsequently warmed up to room temperature and left stirring for 12 h. Next, the excess amine and reaction solvent co-evaporated with toluene. Dissolving again in small amount of toluene and adding hexane drop wise precipitate the product, which can be obtained after decantation of the liquid as white powder. 1H NMR (CDCl3, 400 MHz): δ 7.29-7.20 (m, 5H), 7.00 (d, J = 3.1 Hz, 2H), 6.70 (d, J = 3.0 Hz, 2H), 6.24
(s, 1H), 4.83 (t, J = 5.9 Hz, 1H), 3.82 (s, 6H), 3.44 (dt, J = 29.4, 6.6 Hz, 1H), 3.19 (q, J = 5.9 Hz, 2H), 3.09 (t, J = 6.2 Hz, 2H), 1.49 (s, 18H). 13C NMR (101 MHz, CD2Cl2) δ 155.44, 144.47, 142.30, 138.86, 133.69, 128.98, 128.88, 128.15, 125.22, 123.16, 119.99, 114.88, 114.17, 112.98, 112.49, 100.00, 55.54, 53.88, 40.77, 35.23, 30.74, 30.72, 30.42, 29.27, 21.14, 10.11. 31P NMR (162 MHz, CDCl2): δ 146 (s).


Ligand 6 [(S)-1-((4,8-di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)propan-2-yl]-3 phenylurea]: A solution of 2.6 mmol phosphoro chloride dissolved in 13 ml THF was added to a vigorously stirred solution of 2.6 mmol urea-alcohol and excess of Et3N in 52 ml THF kept at 0 °C. The reaction mixture was subsequently warmed up to room temperature and left stirring for 12 h. Next, the excess amine and reaction solvent co-evaporated with toluene. Dissolving again in small amount of toluene and adding hexane drop wise precipitates the product, which can be obtained after decantation of the liquid part as white powder. 1H NMR (CD2Cl2, 400 MHz): δ 7.23-7.11 (m, 5H), 6.89 (t, J = 3.0 Hz, 2H), 6.61 (dd, J = 3.0, 1.6 Hz, 2H), 6.31 (s, 1H -N-H), 4.73 (d, J = 8.1 Hz, 1H,NH), 3.89 (dtq, J = 10.4, 6.7, 3.6 Hz, 1H, CH), 3.76 (dd, J = 6.1, 3.6 Hz, 2H, CH2), 3.71 (d, J = 1.3 Hz, 6H, OMe), 1.35 (d, J = 4.0 Hz, 18H, t-Bu), 1.07 (d, J = 6.8 Hz, 3H, Me).

13C NMR (101 MHz, CD2Cl2): δ 155.66, 154.27, 142.19, 142.01, 141.73, 138.79, 133.34, 133.24, 128.83, 128.02, 125.09, 122.95, 119.86, 114.22, 114.19, 112.64, 67.43, 67.40, 55.44, 55.42, 46.15, 46.11, 35.12, 30.50, 30.47, 30.38, 30.35, 29.95, 17.46. 31P NMR (162 MHz, CD2Cl2): δ 138.0 (s).

3.4.3 Catalysis

**General procedure for alkylation and amination reactions:** Allylic alcohol, 6a, (0.5 mmol) and the nucleophile, 8a, (0.75 mmol) were added to a mixture of 3 mol% [(η3-allyl)Pd(cod)]BF4, 3 mol% 1,3-diethylurea and 6 mol% of the respective ligand in toluene (2.5 ml). The reactions were performed at room temperature unless stated otherwise. The yields of the products were determined by NMR and GC analysis using an internal standard.

3.4.4 Characterization Studies

The mixture of 0.07 mmol [(η3-allyl)Pd(cod)]BF4 and 0.014 mmol ligand 5 in 0.7 ml CD2Cl2 were stirred for 5 minutes at room temperature and then transferred into an NMR tube for subsequent analysis.

3.4.4.1 Complex 1a

1H NMR (CD2Cl2, 400 MHz): δ 7.31-7.23 (m, 6H), 7.14-7.02 (m, 4H), 6.96-6.88 (m, 2H), 6.84-9.78 (m, 6H), 6.59-6.29 (m, 1H), 4.56-4.36 (m, 2H), 4.06-3.96 (m, 6H), 3.93-3.80 (m, 6H), 3.50-3.37 (m, 5H), 3.31-3.15 (m, 1H), 2.97-2.90 (m, 3H), 1.50-1.21 (m, 36H). 13C NMR (101 MHz, CD2Cl2): δ 159.93, 156.59, 156.20, 155.86, 155.08, 142.12, 142.11, 140.35, 134.07, 133.66, 133.41, 132.51, 129.44, 128.83, 128.45, 128.08, 128.02, 127.14, 125.27, 125.09, 121.73, 120.80, 118.52, 114.95, 114.38, 113.86, 113.70, 113.56, 113.44, 113.14, 112.60, 78.21, 72.82, 55.51, 55.48,

Figure 6. Reaction profile in time with the complexes 1a, 5a and 6a in the absence and presence of 1,3-diethylurea.
Applications of the Urea Substituted Ligand Complexes in Allylic Substitution Reactions

51.55, 44.65, 35.40, 35.28, 31.80, 31.64, 31.30, 31.22, 31.13, 31.01, 30.77, 29.95, 27.86, 21.02, 19.35, 17.96. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$): δ 134.0 (s). HR MS (ESI): calcd. for C$_{65}$H$_{85}$N$_6$O$_{10}$P$_2$Pd [M+H]$^+$: 1277.4613, found: 1277.4110.

3.4.4.1.1 CD Measurements

Chiral induction to the tropos backbones could lead to the formation of interchangeable tropos-based diastereomers. The dynamic motion of the tropos is not necessarily locked in a stable configuration, and has the possibility to exchange. This can lead to formation of mixtures of compounds, each of which may have a different catalytic activity (some of which may be ‘dormant’). Cotton effects measured can unveil the prevalent chiral configuration of the tropos-backbone, especially in combination with variable temperature (VT) NMR experiments.$^{10}$

Ligand 1 and its respective Pd complex 1a gave rise to two clear signals at ~300 and 260 nm showing that the remote stereogenic center of the amino-ester moiety (Figure 7) induces chirality at the substituted bi-phenyl moiety (Figure 7).$^{11}$ The positive signals indicate the formation of an (R) configured biphenyl backbone configuration, based on literature.$^{12}$

3.4.4.2 Complex 5a

$^1$H NMR (CD$_2$Cl$_2$, 400 MHz): δ 7.53-6.90 (m,18H), 6.84-6.69 (m, 3H), 3.96-3.65 (m, 12H), 3.28 (s, 4H), 2.70 (s, 4H), 1.96-1.59 (m, 3H),1.66-1.06 (m, 36H). $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$): δ 128.94, 128.74, 128.56, 128.13, 125.21, 118.97, 115.02, 111.91, 99.98, 76.57, 55.63, 53.90, 53.63, 53.42, 53.36, 52.88, 35.43, 31.31, 31.17, 31.09, 31.01, 30.41, 29.24, 28.00, 27.98, 21.12. $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$): δ 132.0 (bs). HR MS (ESI): calcd. For C$_{65}$H$_{85}$N$_6$O$_{10}$P$_2$Pd [M+H]$^+$:1277.4837, found: 1277.4587.
3.4.4.2.1 CD Measurements

Ligand 5 has no element of chirality and therefore the *tropos* backbone should always be in a racemic form. As a result both ligand 5 and complex 5a do not give rise to any signal in the CD spectra (Figure 10).

![Figure 10. The CD spectrum of ligand 5 and respective Pd complex 5a](image)

3.4.4.3 Complex 6a

![Figure 11. $^{31}$P-COSY-NMR spectra of Complex 6a consisted of two mixture of complexes as the singlet ($\delta = 126$ ppm) and doublet of doublets ($\delta = 132$ ppm, 105 ppm, $J=118$ Hz) at 293 K.](image)

The freshly prepared complex 6a was analyzed by NMR in broad time interval (30 min, 8 hours, 3 days, 5 months) (Figure 12). We initially observed the formation of a single singlet at 126 ppm which converted into a doublet of doublets over time. After 3 days at RT the species showing a singlet at 126 ppm no longer existed and was fully converted into (an) unidentified species.
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Figure 12. $^{31}$P-NMR spectra of complex 6a collected over a broad time interval. The singlet at $\delta = 126$ ppm disappears and a doublet of doublets appears ($\delta = 132$ ppm, $105$ ppm, $J=118$ Hz) at 293 K.

Figure 13. Mass spectra of the freshly prepared complex 6a:
3.4.4.3.1 Control Experiments

We have performed the allylic amination reaction with the months old sample in the presence and absence of urea and compared the catalytic results with the freshly prepared sample. The results are shown in Table 3.

**Table 3.** Control experiments of complex 6a in Pd-catalyzed allylicamination reactions.[a]

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Yield (%) [b]</th>
<th>Time</th>
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</thead>
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<tr>
<td>1</td>
<td>Complex 6a</td>
<td>19</td>
<td>4h</td>
</tr>
<tr>
<td>2</td>
<td>Complex 6a +1,3-diethylurea[c]</td>
<td>26</td>
<td>4h</td>
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<td>Complex 6a (OLD)</td>
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<td>4 days[d]</td>
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<tr>
<td>4</td>
<td>Complex 6a (OLD) +1,3-diethylurea[c]</td>
<td>6</td>
<td>4 days[d]</td>
</tr>
</tbody>
</table>

[a]Reaction conditions: Cinnamyl alcohol (0.5 mmol), N-methylaniline (0.75 mmol), 3 mol% [(η⁵-allyl)Pd(cod)]BF₄, 6 mol% ligand, toluene (2.5 ml), r.t. [b] GC results. [c] 3 mol% 1,3-diethylurea was added. [d] After 5 hours only trace amount of product formed.

3.4.4.3.2 CD Measurements

Ligand 6 does have a stereogenic quaternary carbon center, which directs the configuration at the *tropos* bi-phenyl backbone. The lack of a Cotton effect indicated that the free ligand (6) does
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not have a pre-organized chiral configuration of the trans backbone. Two cotton effects were observed for complex 6a, at 300 and 260 nm in the negative region (Figure 4). The coordination of ligand 6 to the Pd metal assisted to induce a prevalent chirality on the trans backbone, as small negative peaks were observed corresponding to a prevalent (S) configuration of the biphenyl moiety in complex 6a.12

Figure 15. The CD spectrum of ligand 6 and respective Pd complex 6a.

3.5 Acknowledgment

We kindly acknowledge Rosa Kromhout for the contribution to the work.

3.6 References


