Transition Metal Catalyzed Formation and Transformations of allylic N,O-acetals with a focus on olefinic α-amino acids
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CHAPTER 2

ALLYLIC N,O-ACETAL FORMATION BY A NOVEL PALLADIUM CATALYZED AMIDATION OF 1-ALKOXY 1,2-PROPADIENES

2.1 Introduction

Linear O,O- and N,O-acetals represent two important and useful compound classes (chart 2.1). The O,O-acetals (1) are in fact masked aldehydes and ketones and serve as precursors for oxycarbenium ion chemistry. The N,O-acetals (2) are synthetically especially valuable when an electron-withdrawing group is present on the nitrogen (3). These types of N,O-acetals have been frequently used over the last few decades in N-acyliminium ion chemistry. Allylic O,O-acetals (4) or N,O-acetals (6) constitute a special class of acetals, because of their potential rearrangement to the more stable enol ethers or enamides (5) and (7), respectively. Besides, the vinyl functionality renders these acetals particularly attractive reaction partners for cross- or ring-closing metathesis reactions. Among the most frequently used methods to generate linear N,O-acetals are (i) the addition of primary or secondary amides to aldehydes or ketones, (ii) the electrochemical oxidation of amides, (iii) the α-halogenation of glycine-derived amino acids, and (iv) the acylation of imines.

Chart 2.1 Linear (allylic) O,O- and N,O-acetals.

The allylic O,O-acetals of the general type 4 have been prepared and used for the synthesis of 6-membered dihydropyranos and chromenes via ring-closing metathesis. For example, alcohol 8 could be converted into a mixed acetal when treated with acetal 9 (eq. 2.1).
Subsequent ring-closing metathesis formed dihydropyran 10 and set the stage for the construction of callystatin A (11).

A new alkoxypalladation was developed in our laboratories inspired by Alper et al. who had reported the formation of the interesting side product 15 while studying the palladium catalyzed carbonylation of ortho-iodophenols such as 12 with allenes (eq. 2.2).

\[
\begin{align*}
\text{Pd(OAc)}_2, \text{dppb}, & \quad \text{DIPEA, CO (20 atm)} \quad \text{expected 14 (0\%)} \quad \text{unexpected 15 (21\%)} \\
\text{12} & \quad \text{MeO} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \\
\text{60 °C, 20 h} & \\
\end{align*}
\]

Optimization of the reaction conditions (dppp as ligand, Et3N as base, excess methyl propadienyl ether, MeCN, 80 °C, sealed tube) led to a viable method for the preparation of allylic mixed O,O-acetals. Thus, the mixed O,O-acetal 17 was efficiently constructed via the novel palladium catalyzed addition of alcohol 16 onto methyl propadienyl ether 13 (eq. 2.3). Ring-closing metathesis of diolefin 17, followed by oxycarbenium ion chemistry gave rise to functionalized dihydropyrans of type 18. A similar strategy using ortho-vinylphenols resulted in the synthesis of 2-substituted chromenes.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\text{Et3N, MeCN, 80 °C} & \quad \text{1. RCM} \quad \text{2. BF}_3\text{OEt}_2, \text{Nu} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \quad \text{OMe} \quad \text{OMe} \quad (2.3) \\
\text{16} & \quad \text{17} & \quad \text{18} \\
98\% & \\
\end{align*}
\]

In conjunction with the previously summarized research on the palladium catalyzed formation of mixed O,O-acetals, this chapter describes the research performed to extend the scope to N,O-acetals. Such an extension would provide a novel, mild and convenient synthesis of allylic, mixed N,O-acetals of type 6 (chart 2.1). These N,O-acetals would provide versatile building blocks for the synthesis of nitrogen-containing heterocycles.

### 2.2 Amidopalladations of 1-alkoxy allenes

Palladium-catalyzed inter- and intramolecular nucleophilic additions to allenes have been extensively studied, but the use of 1-alkoxy allenes in palladium-catalyzed processes received notably less attention. α-Lithiation and subsequent nucleophilic addition is the most widely used application of 1-alkoxy allenes. There are only a limited number of palladium-catalyzed nucleophilic additions onto 1-alkoxy allenes known. Therefore, extension to N,O-acetal formation would not only provide a novel, catalytic and unique
Allylic N,O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes

(under basic conditions!) way to synthesize the acetals, but also open up a whole new field of catalytic, nucleophilic additions onto 1-alkoxyallenenes.

Pioneering experiments were performed on a system equivalent to alcohol 12. The same reaction conditions were applied with the exception of the propadienyl ether. Benzyl propadienyl ether (20) was chosen as the allene of choice, because Doodeman found that coupling of this allene with phenols took place at a very fast rate at room temperature. Different protective groups on nitrogen were tested and the results are depicted in table 2.1.

**Table 2.1 Amidopalladation with protected allylglycines.**

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor</th>
<th>PG</th>
<th>R</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19a</td>
<td>Bn</td>
<td>CO₂Me</td>
<td>reflux, 24 h</td>
<td>21a</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>19b</td>
<td>Cbz</td>
<td>CO₂Me</td>
<td>reflux, 24 h</td>
<td>21b</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>19c</td>
<td>Fmoc</td>
<td>CO₂Me</td>
<td>reflux, 24 h</td>
<td>21c</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>19d</td>
<td>COCl₂</td>
<td>CO₂Me</td>
<td>reflux, 24 h</td>
<td>21d</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>19e</td>
<td>PO(OPh)₂</td>
<td>CO₂Me</td>
<td>60 °C, 6 h</td>
<td>21e</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>19f</td>
<td>4-CH₃C₆H₄SO₂</td>
<td>CO₂Me</td>
<td>rt, 2 h</td>
<td>21f</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>19g</td>
<td>4-CH₃C₆H₄SO₂</td>
<td>H</td>
<td>rt, 16 h</td>
<td>21g</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>19h</td>
<td>4-NO₂C₆H₄SO₂</td>
<td>CO₂Me</td>
<td>rt, 2 h</td>
<td>21h</td>
<td>84</td>
</tr>
</tbody>
</table>

From these results it was immediately clear that the nature of the protecting group was of vital importance. With the benzylic amine 19a no reaction occurred at all (entry 1). The same was observed for the commonly used amino acid protective groups as the Cbz (19b) and Fmoc (19c, entries 2, 3). Other carbamate protecting groups (Boc, Alloc) also lacked reactivity. A more electron-withdrawing group on the nitrogen (19d) did not lead to any product formation either (entry 4). In contrast, amidophosphate 19e was converted with complete regioselectivity into the desired N,O-acetal 21e at a reasonable rate at 60 °C (entry 5). After 16 h an isolated yield of 55% was obtained, while at rt no conversion was observed. Superior precursors for the amidopalladation turned out to be the ones with a sulfonyl-protecting group on the nitrogen (entries 6-8). The p-toluenesulfonyl protected amino acid 19f already showed fast conversion at room temperature, yielding the corresponding acetal 21f in 85% yield after column chromatography (entry 6). The coupling was also carried out with the unsubstituted precursor 19g (entry 7), which gave the corresponding N,O-acetal 21g in a good yield of 82%. The ester moiety therefore did not hinder the reaction at all; in some cases, as for 19g, the rate of the reaction even seemed lower without an α-substituent. The p-nitrobenzenesulfonyl (Ns) protecting group also showed a fast conversion, leading to the acetal 21h in 84% yield (entry 8). In all these cases, the only product was the one arising from
nucleophilic addition at the 1-position of the allene.\textsuperscript{14} Only at elevated temperatures some addition at the 3-position of the allene could be observed.\textsuperscript{12a}

Next, a comparison between different 1-alkoxy-1,2-propadienes was made (table 2.2). The allenes were tested on two straightforward test systems, the tolenesulfonamide \textsuperscript{22a} and the amidophosphate \textsuperscript{22b}. In all cases the standard conditions (5 mol\% \text{Pd(OAc)}\textsubscript{2}/dppp, 1.5 equiv Et\textsubscript{3}N, MeCN) were applied, except for the temperature. Methyl propadienyl ether \textsuperscript{13} gave a fast and clean conversion at room temperature (entry 1) and N,O-acetal \textsuperscript{27} could be isolated in 88\% after purification by column chromatography. 1-Methoxy-1-benzyl-1,2-propadiene \textsuperscript{23} did not show any reactivity at rt nor at elevated temperatures (up to reflux, entry 2). By increasing the temperature, the 1,1-disubstituted allene showed degradation, probably to the 1,3-diene by base induced isomerization of the double bond. Benzyl and phenyl propadienyl ether (\textsuperscript{20, 24}, entries 3, 4) showed both reactivity at room temperature and the N,O-acetals \textsuperscript{29} and \textsuperscript{30} were isolated in 72 and 50\% yield, respectively. In the case where allene \textsuperscript{25} was used as the coupling partner, no reaction was observed (entry 5). Whether this was caused by the change in the electronic properties of the allene or the presence of an amide moiety was unclear. The allene appeared to be stable under the reflux conditions.

Table 2.2 Scope of the 1-alkoxy-1,2-propadienes in the amidopalladation.

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor</th>
<th>1-alkoxy allene (R, R')</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textsuperscript{22a}</td>
<td>\textsuperscript{13} (Me, H)</td>
<td>rt, 30 min</td>
<td>\textsuperscript{27}</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>\textsuperscript{22a}</td>
<td>\textsuperscript{23} (Me, Bn)</td>
<td>reflux, 24 h</td>
<td>\textsuperscript{28}</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>\textsuperscript{22a}</td>
<td>\textsuperscript{20} (Bn, H)</td>
<td>rt, 6 h</td>
<td>\textsuperscript{29}</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>\textsuperscript{22a}</td>
<td>\textsuperscript{24} (Ph, H)</td>
<td>rt, 6 h</td>
<td>\textsuperscript{30}</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>\textsuperscript{22a}</td>
<td>\textsuperscript{25} (CONi-Pr\textsubscript{2}, H)</td>
<td>reflux, 24 h</td>
<td>\textsuperscript{31}</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>\textsuperscript{22b}</td>
<td>\textsuperscript{13}</td>
<td>60 °C, 16 h</td>
<td>\textsuperscript{32}</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>\textsuperscript{22b}</td>
<td>\textsuperscript{20}</td>
<td>60 °C, 3 h</td>
<td>\textsuperscript{33}</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>\textsuperscript{19e}</td>
<td>\textsuperscript{13}</td>
<td>60 °C, 16 h</td>
<td>\textsuperscript{34}</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>\textsuperscript{19h}</td>
<td>\textsuperscript{13}</td>
<td>rt, 16 h</td>
<td>\textsuperscript{35}</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>\textsuperscript{19f}</td>
<td>\textsuperscript{24}</td>
<td>rt, 16 h</td>
<td>\textsuperscript{36}</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>\textsuperscript{19h}</td>
<td>\textsuperscript{24}</td>
<td>rt, 16 h</td>
<td>\textsuperscript{37}</td>
<td>55</td>
</tr>
</tbody>
</table>

The amidophosphate precursor \textsuperscript{22b} showed good conversions for both methoxy- and benzyloxy-1,2-propadiene (entries 6, 7). The corresponding N,O-acetals \textsuperscript{32} and \textsuperscript{33} were obtained in 89 and 71\% yield. For the amino acid derived phosphate \textsuperscript{19e}, the yield dropped for methyl propadienyl ether. The isolated yield of 52\% in this case might be improved when...
Allylic N.O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes

the reaction would be performed in a sealed tube, to prevent evaporation of the allene at elevated temperatures. The nosyl and tosyl protected allylglycines were also tested with other allenes. Coupling of 19h with methyl propadieny1 ether gave a good conversion en led to 82% isolated yield (entry 9). Compared to this, the phenoxy-substituted allene showed a significant drop in yields to 69 and 55% for 19f and 19h, respectively (entries 10, 11), which might be due to the lower stability of the acetal.

Precursor 19h was used to study the effect of the palladium catalyst on the sulfonamide couplings. The use of Pd(PPh3)4 without a base gave 21h in an isolated yield of 62% (entry 1). With the sulfonamide precursors the presence of Et3N as base seemed not as crucial as for some other couplings (vide infra), but did enhance the reaction notably (entry 2). Pd2(dba)3 also served as a good catalyst for the amidopalladation and again in the presence of dppp and Et3N, a good conversion was observed (83%, entry 3).

Table 2.3 The use of different palladium catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (5 mol%)</th>
<th>base</th>
<th>conditions</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)4</td>
<td>-</td>
<td>rt, 16 h</td>
<td>62a</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>rt, 16 h</td>
<td>86b</td>
</tr>
<tr>
<td>3</td>
<td>Pd2(dba)3/dppp</td>
<td>Et3N</td>
<td>rt, 16 h</td>
<td>83b</td>
</tr>
</tbody>
</table>

a Isolated yield. b Determined by 1H NMR.

While initially for the oxygen nucleophiles a Pd(II) catalyzed mechanism was suggested,6 the results in table 2.3 indicate that the process could be mediated by a Pd(0) species as well. The alternative mechanism would then consist of a rather acidic sulfonamide that oxidatively adds to a Pd(0) species. The resulting palladium hydride would then attack the allene at the central sp carbon, leading to a Pd-π-allyl complex. The allyl complex might then be attacked by the nitrogen nucleophile via an inter- or intramolecular process, leading to the product and concomitant release of Pd(0).

The reaction was also carried out in the presence of an aryl iodide, with the aim to introduce an aryl group to the central carbon of the allene instead of a proton.15 In the course of the reaction, both the oxidative insertion of Pd(0) into the aryl iodide and in the nitrogen hydrogen bond can take place. Therefore, incorporation of an aryl during the coupling would require higher reactivity of the Pd-aryl species towards the allene, compared to the Pd hydride. Interestingly, the only product found was the N,O-acetal without incorporation of the aryl (eq. 2.4). This implies a remarkably high reactivity of the sulfonamide towards oxidative addition and a fast hydride-transfer to the allene in the amidopalladation process.
The recently reported asymmetric addition of carbon nucleophiles to benzyl propadienyl ether by the Trost group would in principle open up a route toward enantioselective $N,O$-acetal formation.\textsuperscript{12c} In analogy to this work, asymmetric addition attempts were conducted with nosyl-protected allylglycine. Pioneering experiments with the Trost ligand in the amidopalladation led to good yields of the desired product, but did not lead to any asymmetric induction. Realizing that this asymmetric $N,O$-acetal formation would require a whole different type of fine-tuning, this line of research was left for future investigations.

Puzzled by the unwillingness of carbamates to react with alkoxyallenes under the standard conditions, other approaches were pursued. Inspired by the work of Yamamoto on cyclizations of allene-containing tosylamides,\textsuperscript{16} the amidopalladation was carried out in the presence of an organic or inorganic acid\textsuperscript{17} in amounts ranging from catalytic up to equimolar. The rationale was that initially oxidative addition of the acid (being a much better proton donor than a carbamate) onto Pd(0) would take place, resulting in a Pd hydride species, followed by reaction with the allene. The resulting Pd-$\pi$-allyl complex can then be attacked by the amide to give the product and Pd(0). Unfortunately, but still in line with what Yamamoto reported (acetyl, trifluoroacetyl, Cbz and Troc protected amines did not give any cyclization), the carbamates refused to give any intermolecular addition.

The same group reported the interesting Pd/acid catalyzed hydroamination of alkynes such as 39 (eq. 2.5). The reaction takes place via \textit{in situ} formation of the allene (hydropalladation of the alkyn, $\beta$-elimination), followed by the addition of sulfonamide 21a to the Pd-$\pi$-allyl complex (formed by the hydropalladation of the allene). One example of a methoxy substituted alkyne was given, resulting in $N,O$-acetal 40.\textsuperscript{12b}

This time, the reaction not only worked for tosylamides, but also for basic amines. Initial attempts to apply these conditions to the allylglycine derived sulfonamides resulted in complex mixtures and low yields in our hands. Therefore extension to carbamates was not even tried. Besides, the \textit{in situ} allene formation was only successful for aryl substituted alkynes and would hence be of limited scope.
Being convinced of the probability of the Pd(0) catalyzed mechanism, our attention returned to the base/Pd-catalyzed process. An early attempt was made to perform a base-catalyzed one-pot reaction with the propargyl ether 41. This would mean \textit{in situ} allene formation with the base used for the regular propargyl/allene isomerization, followed by the amidopalladation. Therefore, t-BuOK was investigated as a ‘dual-action’ base for both the isomerization and amide deprotonation (eq. 2.6).

No conversion was observed, using temperatures up to 60 °C. This seems reasonable when considering that the oxidative addition a weak acid to Pd(0) is of prime importance for the reaction to start. But in our observation, the isomerization of the propargyl ether to the allene was also not taking place at a sufficient rate. Therefore, a closer comparison was made between the pK\textsubscript{a}’s of the sulfonamides and phenols (showing high reactivity), carbamates and amides (showing no reactivity) on the one hand and the pK\textsubscript{a}’s of different tertiary amine bases on the other hand (table 2.4).

Table 2.4 pK\textsubscript{a} comparison.\textsuperscript{a}

<table>
<thead>
<tr>
<th>amide</th>
<th>pK\textsubscript{a}</th>
<th>solvent\textsuperscript{ef}</th>
<th>amine bases</th>
<th>pK\textsubscript{a}</th>
<th>solvent\textsuperscript{ef}</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHR</td>
<td>9-11</td>
<td>-</td>
<td>NH\textsuperscript{+}</td>
<td>5.2</td>
<td>H\textsubscript{2}O\textsuperscript{18e}</td>
</tr>
<tr>
<td>O=S=O</td>
<td>10-11</td>
<td>-</td>
<td>Et\textsubscript{3}NH\textsuperscript{+}</td>
<td>11</td>
<td>H\textsubscript{2}O\textsuperscript{18d}</td>
</tr>
<tr>
<td>PhOH</td>
<td>~18</td>
<td>DMSO\textsuperscript{18g}</td>
<td>17-18</td>
<td>MeCN\textsuperscript{18a}</td>
<td></td>
</tr>
<tr>
<td>(EtO)\textsubscript{2}PNHPh</td>
<td>~18</td>
<td>DMSO\textsuperscript{18h}</td>
<td>24-25</td>
<td>MeCN\textsuperscript{18a}</td>
<td></td>
</tr>
<tr>
<td>RHN</td>
<td>~15-16</td>
<td>H\textsubscript{2}O</td>
<td>NH\textsubscript{3}</td>
<td>~33</td>
<td>H\textsubscript{2}O\textsuperscript{18c}</td>
</tr>
<tr>
<td>R\textsuperscript{'}</td>
<td>~20-22</td>
<td>DMSO\textsuperscript{18i}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHN</td>
<td>21-27</td>
<td>DMSO\textsuperscript{18h,j}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>~38</td>
<td>H\textsubscript{2}O\textsuperscript{18d}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) The data are meant to give an indication; note the differences between the solvents.

Following these data, tertiary amines will be able to abstract the amide proton, but will not remove it from the system. Triethylamine will be sufficiently basic to facilitate proton loss of both sulfonamides and phenols, but lacks the basicity to abstract a proton from carbamates and amides. Besides, from the experiments with sulfonamides it became clear that these
substrates also react without a base. For the unreactive amides, the use of a tertiary amine with a pKa value that is high enough to generate a sufficient concentration of deprotonated amide in the solution would probably initiate the reaction. Looking at the minimum basicity necessary for carbamates and amides to show reactivity, DMAP would be the base needed. A pioneering experiment with Cbz protected allylglycine confirmed this hypothesis: indeed, the desired reactivity was observed! Switching to DBU proved even better, which is shown in table 2.5.

Table 2.5 The use of DBU as base in the amidopalladation.

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor (PG)</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19b (Cbz)</td>
<td>60 °C, 6 h</td>
<td>21b</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>19i (Boc)</td>
<td>60 °C, 16 h</td>
<td>21i</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>19c (Fmoc)</td>
<td>60 °C, 16 h</td>
<td>21c</td>
<td>deprotection</td>
</tr>
<tr>
<td>4</td>
<td>19d (COCCH₃)</td>
<td>60 °C, 24 h</td>
<td>21d</td>
<td>0</td>
</tr>
</tbody>
</table>

The Cbz protected compound 19b showed very low conversion rates at room temperature so that the temperature was raised to 60 °C (entry 1). After 6 hours, an isolated yield of 50% was obtained. Longer reaction times or higher temperatures up to reflux (78 °C) did not lead to a significantly higher conversion, but instead gave rise to the formation of side products (i.e. addition at the 3-position of the allene and decomposition of the allene). Boc-protected allylglycine 19i could be converted to the allylic N,O-acetal 21i in an isolated yield of 67% after 16 hours at 60 °C (entry 2). With this bulky substrate, at slightly higher temperatures a more complex reaction mixture was formed. Furthermore, these carbamate derived N,O-acetals were not completely stable when they were dissolved in chloroform for longer times. Probably, isomerization to the more stable enamide (viz. 7) may take place in this solvent that contains traces of acid over time. The Fmoc protected compound 19c suffered from complete deprotection and did not show any addition to the allene (entry 3). The rather bulky trichloroacetamide 19d (entry 4) did not give any addition either, probably mainly due to sterics (vide infra).

Amides and especially lactams also showed good reactivity in the intermolecular amidopalladation using DBU as base (table 2.6). Methyl acetamide 42, a small linear amide, could be converted into the N,O-acetal 47 in 21% yield (entry 1). Longer reaction times over 64 h did not lead to any improvement. The N,O-acetal consisted of a ~1:2 mixture of rotamers as indicated by NMR. Especially the five-membered cyclic amides 43 and 44 showed good reactivity in the amidopalladation (entry 2 and 3). Both products 48 and 49...
could be isolated in 77 and 72% yield, respectively. The acetylene moiety of 44 was completely tolerated in the reaction, and this substituent caused a diastereoisomeric ratio of 3:1. A drop in yield was observed for the larger lactams 45 and 46. For δ-valerolactam an isolated yield of 41% for 50 could be reached (entry 4), while for ε-caprolactam the conversion hampered to result in a 14% isolated yield of 51 (entry 5).

Table 2.6 Amidopalladations with secondary amides.

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor</th>
<th>conditions</th>
<th>product</th>
<th>yield (%) (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>60 °C, 64 h</td>
<td>47</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>60 °C, 24 h</td>
<td>48</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>60 °C, 16 h</td>
<td>49</td>
<td>72 (3:1)</td>
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<tr>
<td>4</td>
<td>45</td>
<td>60 °C, 24 h</td>
<td>50</td>
<td>41</td>
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<tr>
<td>5</td>
<td>46</td>
<td>60 °C, 24 h</td>
<td>51</td>
<td>14</td>
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</tbody>
</table>

Elevating the temperature up to 100 °C in dioxane only led to side product formation and decomposition of both the N,O-acetals as well as the benzyl propadieny1 ether. At higher temperatures also addition at the 3-position of the allene took place, especially for the more hindered amides. Therefore, to improve the amidopalladation of these substrates, further investigations will be necessary to improve the catalytic system.

2.3 Mechanistic considerations

Taking all the foregoing experiments into account, the following Pd(0)-driven mechanistic cycle is proposed (chart 2.2). For non-acidic amides (52), a tertiary amine base (51) is necessary to effect oxidative addition to the Pd(0) species and give an intermediate palladium hydride species (54 or 55). Upon coordination to the alkoxy allene of either one of these species and delivery of the proton to the central carbon of the allene, π-allyl complex 56
or 57 is formed. The intramolecular pathway allows for attack of the amide from within the coordination sphere of palladium complex 56, to give the N,O-acetal 58 or 59 and release of Pd(0). Alternatively, an intermolecular pathway can occur. Going through complex 57 one can think of two possible routes for product formation: (i) the tertiary amine ligand might be exchanged for the amide, allowing for intramolecular attack of the amide to the allene, or (ii) direct intermolecular attack of the amide to the allene from outside of the coordination sphere. The existence of this intermolecular pathway might be the reason for the long reaction times necessary for the carbamates and amides. In contrast, in case of the sulfonamides the intramolecular pathway will predominate to give a fast reaction. Besides, for the rather acidic sulfonamides, the action of a base is not necessary to form the palladium hydride. This might be an additional reason for the high reactivity of these precursors in the amidopalladation. As was observed in some cases where bulky amides were used in combination with elevated temperatures, the Pd-n-allyl complex can also lead to addition of the amide onto the 3-position of the allene giving products of type 59. But in general, under mild conditions the addition takes selectively place at the 1-position of alkoxyallenes.

Chart 2.2 Proposed mechanistic cycle for the amidopalladation of 1-alkoxyallenes.
2.4 Conclusions

The palladium-catalyzed addition of oxygen nucleophiles onto 1-alkoxy allenes has been successfully extended to various nitrogen nucleophiles. Thus, a novel type of amidopalladation has been developed. The amidopalladation shows in all cases high regioselectivity and tolerates the presence of steric bulk. A number of alkoxy allenes were tested for their reactivity, with benzyl and methyl propadienyl ether being most widely applicable and giving the highest yields. For reasons of large scale preparation and volatility, benzyl propadienyl ether was preferred over methyl propadienyl ether, although the latter showed somewhat increased reactivity for the majority of substrates. Benzyl propadienyl ether could be successfully used up to 60 °C; above this temperature side products arose. Sulfonamides and amidophosphates could be transformed into their corresponding allylic N,O-acetals through a mild and clean reaction, leading to high isolated yields. For less acidic amide precursors, the action of a stronger tertiary amine base was necessary. Especially five-membered ring lactams could be efficiently transformed into the N,O-acetals, but for the first time, also bulky amides could be coupled in an intermolecular fashion through this new type of amidopalladation. The products thus created are highly valuable precursors for further functionalization and the newly introduced 1-benzyloxyallyl might as well serve as a (bulky) nitrogen-protective group, easily removable under mildly acidic conditions. A new mechanistic cycle is proposed for this type of amidopalladation, with a tertiary amine being of prime importance for the action of Pd(0).

2.5 Acknowledgements

Dr. W. F. J. Karstens is thanked for providing amide 44. K. C. M. F. Tjen is kindly acknowledged for her contribution to this chapter. M. Zimmerman (University of Münster, Germany) is thanked for providing allene 25.

2.6 Experimental section

General remarks

Unless otherwise noted, materials were purchased from commercial suppliers and used without purification. Toluene, dichloromethane and acetonitrile were freshly distilled from calcium hydride. Tetrahydrofuran and diethyl ether were freshly distilled from sodium with benzophenone as indicator. Triethylamine was stored over potassium hydroxide pellets and used as such. All air and moisture sensitive reactions were carried out under an inert atmosphere of dry nitrogen, except for the ring-closing metathesis reactions, which were stirred under a dry argon atmosphere. Column chromatography was performed using Aldrich silica gel (70-230 mesh, 60Å). Rf values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F254) with the indicated solvents. Infrared spectra were recorded on a Bruker IFS 28 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker ARX 400 or a Varian Inova-
Spectra are reported in units of ppm on the δ scale, relative to chloroform (7.26 ppm for 1H NMR and 77.0 ppm for 13C NMR). Only for diastereoisomerically pure phosphorus-containing compounds, the carbon-phosphorus coupling constant is listed in the 13C NMR listing. Mass spectra were measured using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Melting and boiling points are uncorrected. Melting points were determined with Büchi melting point B-545. Methyl 1,2-propadienyl ether 13,18 benzyl 1,2-propadienyl ether 20, benzyl 1-benzyl-1,2-propadienyl ether 23 and phenyl 1,2-propadienyl ether 24 were prepared following the procedure described by Brandsma et al.19,20 Caution! Upon distillation of the alkoxyallenes, small concentrated amounts of peroxides present can lead to an explosive mixture upon contact with oxygen from the air! In all cases, the residue remaining after the distillation should be cooled, carefully put under an inert atmosphere and diluted. Allene 25 was obtained from M. Zimmerman, University of Münster.

Racemic allylglycine is commercially available. Allylglycine methyl ester was prepared using SOCl2 in dry methanol at 0 °C. The protected allylglycines 19a-19f, 19h-i were prepared by treating allylglycine methyl ester with either BnBr (19a), CbzCl (19b), FmocCl (19c), CICOCCl3 (19d), CIPO(OPh)2 (19e), TsCl (19f), NsCl (19h) or Boc2O (19i) at 0 °C in the presence of Et3N (3 equiv) in CH2Cl2. Amide 22a was prepared by refluxing tosylamide and benzyl bromide in MeCN in the presence of excess K2CO3 for 24 h. Amidophosphate 22b was prepared by treating benzylamine (1 equiv) with diphenylphosphoryl chloride (1 equiv) in CH2Cl2 at 0 °C with Et3N (1 equiv) as base. The amides 42,43, 45 and 46 are commercially available. Amide 44 can be synthesized according to a literature procedure.21

General procedure A
For the amidopalladation of sulfonamides and amidophosphates with alkoxy propadienyl ethers. To a 0.1 M solution of the sulfonamide in acetonitrile (P.A. from the bottle) was added Et3N (1.5 equiv), Pd(OAc)2 (5 mol%), dppe (5 mol%) and the alkoxyallene (1.1 equiv). After stirring at room temperature (for sulfonamides) or 60 °C (for amidophosphates) for the appropriate time, the solvent was removed in vacuo and the crude residue purified by column chromatography as indicated.

General procedure B
For the amidopalladation of carbamates, linear amides and cyclic amides with alkoxy propadienyl ethers. To a 0.1 M solution of the amide in acetonitrile (P.A. from the bottle) was added DBU (1.5 equiv), Pd(OAc)2 (5 mol%), dppe (5 mol%) and the alkoxyallene (1.2 equiv). After stirring at 60 °C for the given time, the solvent was removed in vacuo and the crude residue purified by column chromatography as indicated.

2-[(1-Benzylxoyallyl)benzoyloxycarbonylamino]pent-4-enoic acid methyl ester (21b). Amide 19b (100 mg, 0.38 mmol) was treated with benzyl propadienyl ether according to the general procedure B. Column chromatography (pentane/ethyl acetate 4:1-1:1) afforded the product as a colorless oil, being ~ 1:1 mixture of diastereoisomers. Yield 78 mg (0.19 mmol, 50%). IR (CHCl3) ν 1049, 1300, 1706, 2953 cm⁻¹; 1H NMR (CDCl3, 500 MHz) both diastereoisomers with hindered rotation δ 7.37-7.22 (m, 9H), 6.96-6.90 (m, 1H), 6.08 (s, 1H), 5.85-5.67 (m, 2H), 5.49-5.42 (m, 1H), 5.35-5.12 (m, 4H), 4.89-4.66 (m, 2H), 3.78-3.71 and 3.85-3.71 ppm.
Allylic N,O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes

3.49-3.47 (m, 1H), 3.61 (s, 3H), 2.34-2.28 and 2.10-2.05 (m, 2H); \[\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{)} \] both diastereoisomers \(\delta\) 165.6, 165.5, 156.1, 155.8, 148.0, 147.0, 138.0, 138.1, 136.4, 136.3, 133.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 127.3, 118.8, 118.1, 86.2, 70.5, 67.5, 52.0, 51.9, 22.3, 21.9; HRMS (FAB) calcd. for \(\text{C}_{24}\text{H}_{28}\text{NO}_5\) (MH\(^+\)) 410.1967, found 410.1931.

2-[(1-Benzoyloxyallyl)(diphenoxyphosphoryl)amino]pent-4-enolic acid methyl ester (21e). Amide 19e (0.5 g, 1.38 mmol) was reacted with benzyl propadienyl ether according to the general procedure A. Column chromatography (pentane/diethyl ether 4:1:1) afforded the 21e as a colorless oil (~1:1 mixture of diastereoisomers). Yield 0.382 g (0.75 mmol, 55%). \(R_f\) 0.28 (pentane/diethyl ether 1:1); \(\text{IR (CHCl}_3\text{)} \) \(\nu\) 1026, 1161, 1190, 1276, 1491, 1593, 1744, 2930, 3150 cm\(^{-1}\); \(\text{\textsuperscript{1}H NMR (CDCl}_3\text{)} \) both diastereoisomers \(\delta\) 7.40-7.14 (m, 15H), 6.02-5.90 (m, 1H), 5.83-5.77 (m, 1H), 5.67 and 5.60 (s, 0.5H), 5.64 (s, 0.5H), 5.57-5.55 and 5.54-5.52 (m, 1H), 5.36 (d, \(J = 10.5\) Hz, 1H), 5.16 (d, \(J = 17.1\) Hz, 0.5H), 5.14-4.96 (m, 2H), 4.85 (d, \(J = 12.2\) Hz, 0.5H), 4.68 (d, \(J = 11.5\) Hz, 1H), 4.13-4.02 (m, 1H), 3.62 and 3.51 (s, 3H), 3.04-2.98 (m, 1H), 2.90-2.86 and 2.72-2.68 (m, 1H); \(\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{)} \) both diastereoisomers \(\delta\) 172.3, 150.8, 137.9, 137.7, 135.3, 135.0, 134.8, 129.6, 129.4, 128.4, 128.3, 127.6, 127.5, 127.3, 125.0, 124.9, 124.8, 120.4, 120.3, 120.2, 118.9, 118.7, 117.6, 117.5, 85.7, 85.6, 70.0, 69.8, 56.4, 56.0, 52.0, 36.9, 36.7; HRMS (FAB) calcd. for \(\text{C}_{28}\text{H}_{31}\text{NO}_6\) (MH\(^+\)) 508.1889, found 508.1870.

2-[(1-Benzoyloxyallyl)(toluene-4-sulfonyl)amino]pent-4-enolic acid methyl ester (21f). Amide 19f (2.85 g, 10.0 mmol) was reacted with benzyl propadienyl ether according to the general procedure A. Column chromatography (petroleum ether/diethyl ether 2:1-1:1) afforded the product as a slightly yellow colored oil (1:1 mixture of diastereoisomers). Yield 3.64 g (8.5 mmol, 85%); \(\text{IR (film)} \) \(\nu\) 1163, 1350, 1531, 1746, 2952, 3032, 3105 cm\(^{-1}\); \(\text{\textsuperscript{1}H NMR (CDCl}_3\text{)} \) \(\delta\) 7.78-7.75 (m, 2H), 7.35-7.22 (m, 7H), 5.79-5.70 and 5.59-5.55 (m, 2H), 5.51-5.46 (m, 1.5H), 5.39-5.37 (m, 0.5H), 5.26-5.22 (m, 1H), 5.11-4.96 (m, 2H), 4.88 and 4.52 (d, \(J = 12.0\) Hz, 1H), 4.59 and 4.44 (d, \(J = 12.2\) Hz, 1H), 4.14-4.05 (m, 1H), 3.71 and 3.61 (s, 3H), 3.08-3.06 (m, 1H), 2.68-2.58 (m, 0.5H), 2.42 (s, 3H), 2.37-2.28 (m, 0.5H); \(\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \) both diastereoisomers \(\delta\) 171.4, 170.8, 143.5, 137.9, 137.7, 135.7, 135.0, 134.3, 133.9, 131.3, 129.5, 129.3, 128.2, 127.8, 127.5, 127.4, 127.1, 119.6, 118.8, 118.7, 117.5, 86.0, 85.8, 70.0, 69.7, 57.3, 56.7, 55.2, 52.3, 52.0, 37.4, 36.8, 35.8, 21.4; HRMS (FAB) calcd. for \(\text{C}_{28}\text{H}_{26}\text{NO}_4\) (MH\(^+\)) 430.1688, found 430.1682.

N-(1-Benzoyloxyallyl)-N-but-3-enyl-4-methylbenzenesulfonamide (21g). \(\text{N-Tosyl-3-buteneamin e (19g, 1.0 g, 4.43 mmol)} \) was reacted with benzyl 1,2-propadienyl ether according to the general method A. Column chromatography (pentane/diethyl ether 2:1-1:1) yielded 21g as a colorless oil. Yield 1.34 g, 82%. \(\text{IR (film)} \) \(\nu\) 2930, 1708, 143.5, 137.9, 137.7, 135.7, 135.0, 134.3, 133.9, 131.3, 129.5, 129.3, 128.2, 127.8, 127.5, 127.4, 127.1, 119.6, 118.8, 118.7, 117.5, 86.0, 85.8, 70.0, 69.7, 57.3, 56.7, 55.2, 52.3, 52.0, 37.4, 36.8, 35.8, 21.4; HRMS (FAB) calcd. for \(\text{C}_{21}\text{H}_{26}\text{NO}_3\) (MH\(^+\)) 430.1688, found 430.1682.
afforded the product as a colorless oil (1:1 mixture of diastereomers). Yield 3.17 g, 84%. Rf 0.85 (petroleum ether/diethyl ether 1:2); IR (film) v 2952, 1745, 1530, 1350, 1164 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) both diastereoisomers δ 8.26 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 7.35-7.24 (m, 5H), 5.85-5.63 (m, 1H), 5.54-5.43 (m, 2H), 5.32-5.27 (m, 1H), 5.15-4.99 (m, 2H), 4.79 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.57-4.52 (m, 1H), 4.29-4.24 (m, 1H), 3.68 and 3.57 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) both diastereoisomers δ 170.5, 149.8, 146.5, 136.7, 134.3, 128.8, 128.3, 127.5, 123.8, 119.6, 117.9, 86.4, 70.0, 57.4, 52.2, 35.8; HRMS (FAB) calcd. for C₆₂H₅₃N₂O₇S (MH⁺) 461.1382, found 461.1363.

N-Benzyl-N-(1-methoxyallyl)-4-methyl-benzenesulfonamide (27). Amide 22a (100 mg, 0.38 mmol) was reacted with methyl propadienyl ether according to the general procedure A. Column chromatography (hexane/diethyl ether 4:1-2:1) afforded the product as a colorless oil. Yield 111 mg (0.335 mmol, 88%). Rf 0.50 (hexane/diethyl ether 1:1). IR (CHCl₃) v 1092, 1162, 1339 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.63 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 7.1 Hz, 2H), 7.28-7.23 (m, 5H), 5.53-5.47 (m, 2H), 5.38 (d, J = 15.9 Hz, 1H), 5.23 (d, J = 10.5 Hz, 1H), 4.41 (d, J = 15.6 Hz, 1H), 4.23 (d, J = 15.6 Hz, 1H), 3.20 (s, 3H), 2.43 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 143.2, 138.0, 137.5, 133.8, 129.5, 128.9, 128.0, 127.1, 118.9, 88.8, 55.5, 46.6, 21.5; HRMS (FAB) calcd. for C₁₈H₂₂N₂O₂S (MH⁺) 332.1320, found 332.1328; Anal. calcd. for C₁₈H₂₁N₂O₂S: C, 65.23; H, 6.39; N, 4.23; found C, 65.14; H, 6.46; N, 4.16.

N-Benzyl-N-(1-benzyloxyallyl)-4-methylbenzenesulfonamide (29). Amide 22a (100 mg, 0.38 mmol) was converted into the acetal with benzyl propadienyl ether according to the general procedure A. Column chromatography (pentane/diethyl ether 4:1) afforded the 29 as a colorless oil. Yield 111.2 mg (0.273 mmol, 72%). Rf 0.48 (pentane/diethyl ether 1:1).
Allylic N,O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes

IR (CHCl₃) v 1031, 1095, 1161, 1337, 1495, 2254, 2928, 3033 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.67 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.34-7.26 (m, 8H), 7.14 (d, J = 7.8 Hz, 2H), 5.74 (d, J = 3.9 Hz, 1H), 5.54-5.49 (m, 1H), 5.48 (d, J = 15.4 Hz, 1H), 5.28 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.45 (d, J = 4.4 Hz, 2H), 4.30 (d, J = 15.6 Hz, 1H), 2.44 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 143.2, 137.9, 137.6, 137.3, 133.8, 129.5, 128.8, 128.1, 127.6, 127.5, 127.1, 127.0, 119.1, 86.7, 69.4, 46.9, 21.4; HRMS (FAB) calcd. for C₂₄H₂₆NO₃S (MH⁺) 408.1633, found 408.1638; Anal. calcd. for C₂₄H₂₅NO₃S: C, 70.73; H, 6.18; N, 3.44; found C, 70.59; H, 6.16; N, 3.52.

N-Benzyl-4-methyl-N-(1-phenoxallyl)benzenesulfonamide (30). Amide 22a (56 mg, 0.42 mmol) was reacted with phenyl propadieny ether following the general procedure A. Column chromatography (pentane/diethyl ether 4:1) afforded the product as a colorless oil. Yield 75 mg (0.19 mmol, 50%). IR (CHCl₃) v 939, 1095, 1162, 1230, 1341, 1492, 15955 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.59 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 7.3 Hz, 2H), 7.30-7.25 (m, 5H), 7.17 (d, J = 7.8 Hz, 2H), 7.01 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 2H), 6.56 (s, 1H), 5.76-5.70 (m, 1H), 5.43 (d, J = 17.1 Hz, 1H), 5.26 (d, J = 10.5 Hz, 1H), 4.50 (d, J = 6.6 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 156.5, 143.4, 137.5, 136.7, 133.1, 129.3, 128.0, 128.1, 127.7, 120.1, 119.8, 115.9, 85.6, 47.3, 21.4; HRMS (FAB) calcd. for C₂₃H₂₄NO₃S (MH⁺) 394.1477, found 394,1467; Anal. calcd. for C₂₃H₂₃NO₃S: C, 70.20; H, 5.89; N, 3.56; found C, 70.08; H, 5.98; N, 3.48.

Benzyl-(1-methoxyallyl)phosphoramidic acid diphenyl ester (32). Amide 22b (100 mg, 0.295 mmol) was treated with methyl propadieny ether according to the general procedure A. Column chromatography (hexane/ethyl acetate 2:1-1:1) afforded the product as a slightly yellow oil. Yield 108 mg (0.264 mmol, 89%), Rf 0.56 (hexane/ethyl acetate 1:1). IR (CHCl₃) v 941, 1191, 1491, 1593, 2934 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.46 (d, J = 7.3 Hz, 2H), 7.34-7.27 (m, 7H), 7.20-7.16 (m, 6H), 5.75-5.68 (m, 1H), 5.48-5.45 (m, 2H), 5.28 (d, J = 10.7 Hz, 1H), 4.47-4.32 (m, 2H), 3.28 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 150.9 (d, J = 7.6 Hz, C), 150.7 (d, J = 7.2 Hz, C), 138.4 (d, J = 1.3 Hz, C), 135.1 (d, J = 5.1 Hz, CH), 129.6, 129.5 (d, J = 3.8 Hz, CH), 129.2, 128.0, 127.1, 124.8 (d, J = 2.1 Hz, CH), 120.1 (d, J = 5.1 Hz, CH), 120.0 (d, J = 5.1 Hz, CH), 118.3, 88.5 (d, J = 8.0 Hz, CH), 55.3, 46.1 (d, J = 3.0 Hz, CH₂); ³¹P NMR δ 0.31; HRMS (FAB) calcd. for C₂₃H₂₄NO₄P (MH⁺) 410.1521, found 410,1513; Anal. calcd. for C₂₃H₂₃NO₄P: C, 67.47; H, 5.91; N, 3.42; found C, 67.34; H, 5.85; N, 3.36.

Benzyl-(1-benzyloxallyl)phosphoramidic acid diphenyl ester (33). Amide 22b (100 mg, 0.295 mmol) was reacted with benzyl propadieny ether according to the general procedure A. Column chromatography (pentane/diethyl ether 2:1-1:1) afforded the product as a colorless oil. Yield 99 mg (0.21 mmol, 71%), Rf 0.44 (pentane/diethyl ether 1:1). ¹H NMR (CDCl₃, 500 MHz) δ 7.50 (d, J = 7.6 Hz, 2H), 7.37-7.28 (m, 10H), 7.23-7.18 (m, 8H), 5.81-5.75 (m, 1H), 5.71-5.69 (m, 1H), 5.56 (d, J = 17.3 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.58-4.39 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 150.9 (d, J = 7.6 Hz, C), 150.7 (d, J = 7.2 Hz, C), 138.5 (d, J = 1.3 Hz, C), 137.7, 135.2 (d, J = 4.6 Hz, CH), 129.5 (d, J = 2.1 Hz, CH), 129.3, 128.1 (d, J = 8.9 Hz, CH), 127.5, 127.4, 127.1, 124.9 (d, J = 2.1 Hz, CH), 120.2 (d, J = 5.1 Hz, CH), 120.0 (d, J = 5.1 Hz, CH), 118.6, 86.5 (d, J = 8.0 Hz, 2H), 51.47; H, 5.91; N, 3.42; found C, 67.34; H, 5.85; N, 3.36.
2-{(Diphenoxophosphoryl)-(1-methoxyallyl)amino}pent-4-enoi c acid methyl ester (34). The amide 19e (107 mg, 0.295 mmol) was converted into the N,O-acetal according to the general procedure A using methyl propadienyl ether. Column chromatography (pentane/ethyl acetate 2:1-1:1) afforded the product as a colorless oil (1:1 mixture of diastereoisomers). Yield 66 mg (0.153 mmol, 52%). \(^1\)H NMR (CDCl\(_3\), 500 MHz) both isomers δ 7.38-7.19 (m, 8H), 7.16 (d, J = 7.1 Hz, 2H), 5.99-5.90 (m, 1H), 5.82-5.75 (m, 1H), 5.53 (dd, J = 4.9, 17.1 Hz, 1H), 5.35-5.30 (m, 2H), 5.17 (d, J = 15.6 Hz, 0.5H), 5.08-5.06 (m, 1H), 5.03 (d, J = 16.1 Hz, 0.5H), 4.04-3.94 (m, 1H), 3.65 and 3.53 (s, 3H), 3.52 and 3.48 (s, 3H), 3.03-2.97 (m, 1H), 2.82-2.79 (m, 0.5H), 2.65-2.61 (m, 0.5H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) both isomers δ 172.2, 172.0, 151.2, 151.1, 150.9, 150.8, 135.3, 135.2, 134.9, 134.8, 134.7, 129.7, 129.6, 129.5, 129.4, 125.2, 125.0, 124.9, 124.8, 120.4, 120.3, 120.2, 120.1, 118.6, 118.4, 117.5, 117.4, 88.1, 87.9, 85.6, 56.5, 56.4, 56.3, 55.9, 52.0, 51.9, 36.9, 36.7; HRMS (FAB) calcd. for C\(_{29}\)H\(_{29}\)NO\(_4\)P (MH\(^+\)) 486.1834, found 486.1829; Anal. calcd. for C\(_{29}\)H\(_{28}\)NO\(_4\)P: C, 71.74; H, 5.81; N, 2.88; found: C, 71.64; H, 5.85; N, 2.76.

2-{(1-Methoxyallyl)-(4-nitrobenzenesulfonyl)amino}pent-4-enoi c acid methyl ester (35). Amide 19g (119 mg, 0.38 mmol) was reacted with methyl propadienyl ether following the general procedure A. Column chromatography (hexane/diethyl ether 21:1-1:1) afforded the product as a slightly yellow oil (1:1 mixture of diastereoisomers). Yield 100 mg (0.26 mmol, 82%). \(^1\)H NMR (CDCl\(_3\), 500 MHz) both diastereoisomers δ 8.38-8.36 (m, 2H), 8.13 (d, J = 9.0 Hz, 2H), 5.82-5.63 (m, 2H), 5.48-5.43 (m, 1H), 5.32-5.27 (m, 2H), 5.16 (d, J = 17.1 Hz, 0.5H), 5.10 (d, J = 10.0 Hz, 0.5H), 5.03 (d, J = 11.7 Hz, 1H), 4.19-4.14 (m, 1H), 3.71 and 3.65 (s, 3H), 3.36 and 3.35 (s, 3H), 3.04-2.95 (m, 1H), 2.68-2.64 (m, 0.5H), 2.42-2.38 (m, 0.5H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) both diastereoisomers δ 170.9, 170.6, 150.0, 149.9, 147.0, 146.8, 146.7, 134.4, 134.3, 133.5, 129.1, 129.0, 124.0, 123.9, 119.6, 119.5, 118.1, 118.0, 89.2, 88.9, 57.9, 57.4, 56.8, 56.5, 56.4, 56.3, 55.9, 52.0, 51.9, 36.9, 36.7; HRMS (FAB) calcd. for C\(_{16}\)H\(_{21}\)N\(_2\)O\(_7\)S (MH\(^+\)) 385.1069, found 385.1046; Anal. calcd. for C\(_{16}\)H\(_{20}\)N\(_2\)O\(_7\)S: C, 49.99; H, 5.24; N, 7.29, found C, 50.11; H, 5.18; N, 7.22.

2-{(1-Phenoxyallyl)(toluene-4-sulfonyl)amino}pent-4-enoi c acid methyl ester (36). 2-(Toluene-4-sulfonylamino)pent-4-enoi c acid methyl ester 19f (1.0 g, 3.53 mmol) was reacted with phenyl propadienyl ether according to the general method A. Column chromatography (pentane/diethyl ether 4:1-2:1) afforded the product as a colorless oil (1:1 mixture of diastereoisomers). Yield 0.904 g, 62%. \(^1\)H NMR (CDCl\(_3\), 500 MHz, 4:1) δ 7.68 (m, 2H), 7.18-7.30 (m, 4H), 7.01 (t, J = 7.3 Hz, 1H), 6.94-6.85 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.35-6.33 (m, 1H), 6.17-6.08 and 5.90-6.00 (m, 1H), 5.85-5.78 (m, 1H), 5.56-5.46 (m, 2H), 5.10-5.04 (m, 2H), 4.43-4.48 and 4.33-4.30 (m, 1H), 3.72 and 3.62 (s, 3H), 3.04-2.99 (m, 1H), 2.58-2.55 (m, 1H), 2.43 and 2.42 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) major diastereoisomer δ 170.9, 156.8, 143.6,
Allylic N-O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes

2-[(4-Nitrobenzenesulfonyl)-(1-phenoxyallylamino)pent-4-enoic acid methyl ester (37). Amide 19g (0.57 g, 1.81 mmol) was reacted with phenyl propadienyl ether according to the general method A. Column chromatography (pentane/ethyl acetate 8:1-2:1) afforded the product as a colorless oil as a colorless oil (1:1 mixture of diastereoisomers). Yield 0.444 g (0.994 mmol, 55%). Rf 0.66 (pentane/ethyl acetate 2:1); IR (CHCl₃) ν 1165, 1225, 1351, 1491, 1531, 1745, 2360 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) both diastereoisomers δ 8.15-8.12 (m, 2H), 7.95-7.89 (m, 2H), 7.32-7.17 (m, 2H), 7.03-6.99 (m, 1H), 6.73-6.68 (m, 2H), 6.33 and 6.25 (s, 1H), 6.11-6.04 and 6.00-5.94 (m, 1H), 5.81-5.74 (m, 1H), 5.15-5.03 (m, 2H), 4.47 and 4.34 (m, 1H), 3.71 and 3.62 (s, 3H), 2.99-2.93 (m, 1H), 2.69-2.63 and 2.56-2.51 (m, 1H); ^13C NMR (125 MHz, CDCl₃) both diastereoisomer: 170.5, 170.4, 156.9, 156.7, 149.9, 146.3, 145.9, 134.2, 133.0, 132.6, 129.7, 129.6, 129.4, 129.1, 123.8, 123.6, 122.7, 121.2, 121.0, 118.4, 118.1, 116.5, 115.9, 86.7 (2x), 58.9, 58.4, 52.6, 52.4, 36.2, 35.6; HRMS (FAB) calcld. for C₂₁H₂₃N₂O₇S (MH⁺) 447.1226, found 447.1230.

N-(1-Benzoxoallyl)-N-methylacetamide (47). According to general procedure B, methyl acetamide 42 (56 mg, 0.76 mmol) was reacted with benzyl propadienyl ether. Column chromatography (pentane/ethyl acetate 1:1) afforded the product as a colorless oil. Yield 34.4 mg (0.157 mmol, 21%). Rf 0.23 (pentane/ethyl acetate 1:1); IR (CHCl₃) ν 1005, 1060, 1398, 1646, 2866, 2932, 3031 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) 1:2 mixture of conformers: δ 7.38-7.28 (m, 5H), 6.40 (q, J = 17.0 Hz, 0.6H), 5.41 (s, 0.4H), 5.88-5.81 (m, 0.4H), 5.78-5.71 (m, 0.6H), 5.48 (d, J = 17.3 Hz, 0.6H), 5.46-5.45 (d, J = 5.6 Hz, 0.4H), 5.38 (d, J = 10.7 Hz, 0.4H), 5.31 (d, J = 10.7 Hz, 0.6H), 4.63 (d, J = 12.2 Hz, 0.4H), 4.54 (d, J = 12.0 Hz, 0.6H), 4.49 (d, J = 12.0 Hz, 0.4H), 4.40 (d, J = 12.0 Hz, 0.4H), 2.84 and 1.79 (s, 3H), 2.11 and 2.04 (s, 3H); ^13C NMR (125 MHz, CDCl₃) 1:2 mixture of conformers, major: δ 171.8, 137.8, 134.1, 128.6, 128.3, 127.6, 118.0, 81.3, 70.0, 29.2, 22.1; minor: δ 170.4, 136.9, 133.9, 128.6, 128.0, 127.6, 118.4, 85.6, 68.6, 26.8, 21.6; HRMS (FAB) calcld. for C₁₃H₁₈N₂O₂ (MH⁺) 220.1338, found 220.1318.

1-(1-Benzoxoallyl)pyrrolidin-2-one (48). 2-Pyrrolidinone (65 mg, 0.76 mmol) was reacted with benzyl propadienyl ether according to general procedure B. Column chromatography (pentane/ethyl acetate 2:1-1:1) afforded 48 as a colorless oil. Yield 134.6 mg (0.582 mmol, 77%). Rf 0.26 (pentane/ethyl acetate 1:1); IR (CHCl₃) ν 1059, 1215, 1422, 1681, 2890, 3024 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 7.39-7.29 (m, 5H), 5.89 (q, J = 1.46 Hz, 1H), 5.84-5.78 (m, 1H), 5.49 (d, J = 17.3 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 3.33 (t, J = 7.1 Hz, 2H), 2.46-2.34 (m, 2H), 2.00-1.94 (m, 1H), 1.89-1.83 (m, 1H); ^13C NMR (125 MHz, CDCl₃) δ 175.8, 137.9, 133.6, 128.3, 127.7, 127.6, 118.3, 80.3, 70.2, 41.7, 31.5, 18.0; HRMS (FAB) calcld. for C₁₄H₁₆N₂O₂ (MH⁺) 232.1338, found 232.1325.

1-(1-Benzoxoallyl)-5-prop-2-ynylpyrrolidin-2-one (49). Pyrrolidinone 44 (94 mg, 0.76 mmol) was reacted with benzyl propadienyl ether according to general procedure B. Column chromatography (pentane/ethyl acetate 2:1) afforded 49 as a colorless oil (3:1 mixture of diastereoisomers). Yield 147.4 mg (0.547 mmol, 72%). Rf 0.37
(pentane/ethyl acetate 1:1); IR (CHCl₃) ν 1056, 1124, 1672, 3032, 3306 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.23 (m, 5H), 5.95-5.91 (m, 1H), 5.90-5.72 (m, 1H), 5.60-5.53 (m, 1H), 5.35 (d, J = 10.6 Hz, 0.75H), 5.27 (d, J = 10.5 Hz, 0.25H), 4.76 (d, J = 11.8 Hz, 0.75H), 4.66 (d, J = 5.8 Hz, 0.25H), 4.57 (d, J = 11.9 Hz, 0.75H), 4.52-4.45 (m, 0.25H), 3.91-3.83 (m, 1H), 2.75-2.63 and 2.63-2.61 (m, 1H), 2.58-2.56 and 2.48-2.46 (m, 2H), 2.39-2.12 (m, 2H), 2.09-1.89 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) both diastereoisomers: δ 176.3, 176.2, 137.8, 137.3, 135.0, 133.2, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 118.8, 117.3, 80.7, 80.5, 80.0, 79.9, 70.8, 70.7, 70.6, 70.2, 54.0, 53.1, 30.1, 30.0, 25.2, 24.9, 24.1, 23.4; HRMS (FAB) calcd. for C₁₇H₂₀NO₂ (MH⁺) 270.1494, found 270.1489.

1-(1-Benzyloxyallyl)piperidin-2-one (50). δ-Valerolactam (38 mg, 0.38 mmol) was reacted with benzyl propadieny1 ether according to general procedure B. Column chromatography (pentane/ethyl acetate 2:1-1:1) afforded 50 as a colorless oil. Yield 38 mg (0.155 mmol, 41%). Rf 0.19 (pentane/ethyl acetate 1:1); IR (CHCl₃) ν 1053, 1215, 1299, 1620, 2953 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 6.50-6.48 (m, 1H), 5.79-5.73 (m, 1H), 5.50 (d, J = 17.3 Hz, 1H), 5.31 (d, J = 10.7 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 3.22-3.12 (m, 2H), 2.44-2.40 (m, 2H), 1.75-1.70 (m, 3H), 1.62-1.59 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.7, 137.9, 133.9, 128.2 (2*), 127.6, 118.0, 81.0, 70.1, 40.5, 32.3, 22.7, 20.8; HRMS (FAB) calcd. for C₁₅H₂₀NO₂ (MH⁺) 246.1494, found 246.1498.

1-(1-Benzyloxyallyl)azepan-2-one (51). ε-Caprolactam (43 mg, 0.38 mmol) was reacted with benzyl propadieny1 ether according to general procedure B. Column chromatography (pentane/ethyl acetate 2:1-1:1) afforded 51 as a colorless oil. Yield 14 mg (0.054 mmol, 14%). Rf 0.34 (pentane/ethyl acetate 1:1); IR (CHCl₃) ν 1058, 1188, 1414, 1638, 2859, 2935 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.29 (m, 5H), 6.37-6.36 (m, 1H), 5.79-5.72 (m, 1H), 5.53 (d, J = 17.1 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 4.59-4.52 (m, 2H), 3.36-3.19 (m, 2H), 2.58-2.57 (m, 2H), 1.73-1.62 (m, 4H), 1.38-1.28 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 176.9, 138.0, 134.5, 128.3, 127.6, 127.5, 118.0, 81.7, 69.9, 42.5, 37.7, 30.0, 29.3, 23.6; HRMS (FAB) calcd. for C₁₆H₂₂NO₂ (MH⁺) 260.1651, found 260.1649.

2.7 References and notes


Allylic N,O-Acetal Formation by a Novel Palladium Catalyzed Amidation of 1-Alkoxy 1,2-Propadienes


17 For the use of EtNHz as proton source for oxidative addition, see ref. 14.

