Enantioselective synthesis of lactams and lactones
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CHAPTER 8

Palladium Catalyzed Allylic Substitution of Acyloxypyrrolinones

8.1 Introduction

Enantiomerically pure alkoxypyrrolinones have been shown to be facile building blocks for a variety of stereoselective syntheses involving Diels-Alder cycloadditions, 1,3-dipolar reactions, conjugate additions, and acyliminium ion intermediates. In particular the application in the asymmetric synthesis of alkaloids based on N-acyliminium ion chemistry is of current interest. For example, (R)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one (compound (–)-8.3a \((R^2 = i\text{-Pr})\) in Scheme 8.1) has been used by Hiemstra and Speckamp as an intermediate in the synthesis of gelsemine. However, the stereoselective synthesis from (S)-malic acid is laborious and more practical routes would be desirable.

In Chapter 3 and 4, we reported a simple and efficient enzymatic methodology to obtain enantiomerically pure acyloxypyrrolinones 8.2 from hydroxypyrrolinones 8.1. In this process both enantiomers of an acyloxypyrrolinone can be obtained by the same enzyme (Candida antarctica lipase B CAL) using either an esterification (Scheme 8.1) or a transesterification. Although compounds 8.2 have been applied with success in various stereoselective transformations, they are not suitable as acyliminium ion precursors (see Chapter 7). In order to generate an acyliminium ion the acyl group on nitrogen must be removed. This is possible with an alkoxy group at the 5-position, but not with a more sensitive acyloxy group (see Chapter 7).

In the previous chapter we already mentioned the discovery of a method to convert acyloxypyrrolinones 8.2 stereospecifically to alkoxypyrrolinones 8.3 by means of a palladium catalyzed allylic substitution. This way the enzymatic method can be combined with a palladium catalyzed allylic substitution to generate optically active alkoxypyrrolinones (Scheme 8.1), which can readily be transformed to acyliminium ion precursors.

\[\text{Ac} \quad \text{O} \quad \text{R}^1 \text{C=CH}_2 \quad \text{CAL} \quad 100\% \quad \text{e.e.} > 99\% \]

\[\text{Ac} \quad \text{O} \quad \text{R}^1 \text{CO} \quad \text{R}^2 \text{OH} \quad [\text{Pd}^0] \quad \text{R}^1 \text{C=CH}_2 \quad \text{Ac} \quad \text{O} \quad \text{R}^2 \text{OH} \quad \text{acyliminium ion chemistry} \]

Scheme 8.1  Pd-catalyzed allylic substitution in a route to enantiopure N-acyliminium ion precursors
Palladium catalyzed nucleophilic substitution reactions of allylic substrates have found widespread use in organic synthesis and have often been used as key steps in natural product synthesis. Although many nucleophiles have been employed, emphasis so far has been on carbon-carbon bond formation. The use of alcohols as nucleophiles in Pd-catalyzed allylic substitution is rare, because alcohols are generally considered poor nucleophiles. The few reported examples are often intramolecular substitutions, or reactions in which use is made of derivatives of alcohols. During the course of our studies Trost et al. reported the use of phenols.

In this chapter we will discuss the synthesis of enantiopure alkoxypyrrolinones from enantiopure acyloxypyrrolinones by allylic substitutions of alcohols with the use of achiral Pd catalysts. Furthermore, we report the conversion of racemic acyloxypyrrolinones in an enantioselective palladium catalyzed allylic substitution to optically active alkoxypyrrolinones with the use of several chiral ligands.

### 8.2 Enantioselective Palladium Catalyzed Allylic Substitution by Alcohols

When a solution of (R)-(−)-8.2a (R1 = CH3) in i-propanol was stirred at room temperature for 7 h in the presence of 0.5 mol. % Pd(PPh3)4, 5-isoproxy derivative (R)-(−)-8.3a (R2 = i-Pr) was obtained in 99% yield with 95 % e.e. (Table 8.1, entry 1). The optically active acyloxypyrrolinone was thus converted into optically active alkoxypyrrolinone via Pd0 catalyzed allylic substitution with isopropanol as the nucleophile, with nearly complete retention of configuration. On the basis of cumulative data on Pd-catalyzed allylic substitutions an allyl palladium intermediate most probably is involved (Scheme 8.2).

![Scheme 8.2](image)

When the reaction was performed in the presence of Pd(OAc)2 (5 mol %) and PPh3 (20 mol %) the reaction rate was appreciably lower (90 % conversion in 3 d at 20°C, e.e. > 95% ). An important feature of this reaction is that the nucleophile i-propanol is also used as solvent. In the presence of another solvent like THF containing a small amount of i-propanol (1-5 equivalents) no product was obtained after 18 h at room temperature.
Table 8.1  *Pd*-catalyzed nucleophilic substitution of (–)-8.2 (see Scheme 8.1)\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>8.2</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>T (°C)</th>
<th>catalyst</th>
<th>t (h)</th>
<th>c(^b) (%)</th>
<th>e.e.(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>i-Pr</td>
<td>25</td>
<td>Pd(PPh(_3))(_4), 0.5%</td>
<td>7</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>2(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>i-Pr</td>
<td>25</td>
<td>Pd(PPh(_3))(_4), 0.5%</td>
<td>5.5</td>
<td>72</td>
<td>97</td>
</tr>
<tr>
<td>3(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>Et</td>
<td>18</td>
<td>Pd(PPh(_3))(_4), 5%</td>
<td>1</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>4(^e)</td>
<td>8.2b</td>
<td>CH(_3)=CH</td>
<td>i-Pr</td>
<td>20</td>
<td>Pd(OAc)(_2),+PPh(_3), 5%</td>
<td>63</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>5(^e)</td>
<td>8.2c</td>
<td>C(<em>9)H(</em>{19})</td>
<td>i-Pr</td>
<td>20</td>
<td>Pd(OAc)(_2),+PPh(_3), 10%</td>
<td>63</td>
<td>40</td>
<td>84</td>
</tr>
<tr>
<td>6(^e)</td>
<td>8.2d</td>
<td>t-Bu</td>
<td>i-Pr</td>
<td>20</td>
<td>Pd(OAc)(_2),+PPh(_3), 5%</td>
<td>48</td>
<td>29</td>
<td>95</td>
</tr>
<tr>
<td>7(^e)</td>
<td>8.2e</td>
<td>C(_6)H(_5)</td>
<td>i-Pr</td>
<td>20</td>
<td>Pd(OAc)(_2),+PPh(_3), 5%</td>
<td>18</td>
<td>33</td>
<td>93</td>
</tr>
<tr>
<td>8(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>i-Pr</td>
<td>25</td>
<td>Pd(MeCN)(_2)Cl(_2),+PPh(_3), 5%</td>
<td>21</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>9(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>i-Pr</td>
<td>25</td>
<td>Pd(MeCN)(_2)Cl(_2), 5%</td>
<td>3</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10(^d)</td>
<td>8.2a</td>
<td>CH(_3)</td>
<td>Et</td>
<td>25</td>
<td>Pd(MeCN)(_2)Cl(_2), 5%</td>
<td>3</td>
<td>94</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\)The alcohol was also used as solvent. \(^b\)The conversion was determined by G.C. \(^c\)The e.e. of 8.3 was determined by chiral G.C.; >99% indicates that the other enantiomer was not detected. \(^d\)(+)-8.2a (e.e. >99%) was used as starting material. \(^e\)The e.e. of starting material 8.2 is unknown (see Chapter 4).

When the allylic substitution of 8.2 was performed at higher temperatures (than given in Table 8.1), the reaction was very fast, but the enantioselectivity decreased in the course of the reaction (Table 8.2). This lowering of e.e. might be due either to loss of stereochemical integrity of the allyl palladium intermediate or by partial racemization of acyloxypyrrolinone 8.2 or alkoxyppyrrolinone 8.3.

Table 8.2  *Pd*-catalyzed nucleophilic substitution of (+)-8.2a (R\(^1\)=CH\(_3\)) at 70 °C.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>time (min)</th>
<th>conversion (%)(^b)</th>
<th>e.e. (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>43</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>91</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>100</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\)5% Pd(OAc)\(_2\)+4 PPh\(_3\) was used as catalyst, i-PrOH was used as solvent. \(^b\)The conversion was determined by G.C. \(^c\)The e.e. of (+)-8.3a was determined by chiral GC.

The substitution with the use of Pd(PPh\(_3\))\(_4\) can easily be performed on a gram scale with equal efficiency (99%) and selectivity (94% e.e.). A lower rate was observed in the presence of additional triphenylphosphine, probably because the equilibrium for the oxidative addition of the palladium complex is shifted to the left (Scheme 8.2).\(^{12}\) The effect on the enantioselectivity, however, is negligible.

When ethanol was used instead of isopropanol as a nucleophile the reaction was much faster, probably because of the higher solubility of the substrate in this solvent. A slight decrease in selectivity was observed. Ethoxypyrrolinone 8.3b was obtained with 93% e.e. (Table 8.1, entry 3).
The palladium catalyzed allylic substitution has also been performed successfully with acyloxypyrrolinones with other acyl groups 8.2b - 8.2e (Table 8.1, entry 4-7). The optically active starting materials were obtained via enzymatic esterifications, as was reported in Chapter 4. Because a method for direct e.e. determination of these 5-acyloxypyrrolinones has not yet been found, the palladium catalyzed allylic substitution and subsequent e.e. determination of the 5-isopropoxypyrrolinone provide a useful alternative for determination of the e.e. of the starting materials.

Other palladium catalysts were also examined since the use of Pd(PPh₃)₄ did not result in complete stereoselectivity (e.e. 95 - 97%). Pd(Bn(PPh₃)₂Cl gave, under the same conditions in i-propanol, less than 5% conversion after 23 h (71 % e.e), whereas with Pd(DIPHOS)₂ no product was obtained. Palladium(II) complexes such as Pd(OAc)₂ were also tested without triphenylphosphine. In this case the reaction did not proceed, but surprisingly when LiCl was added 22% conversion was found after 23 h (e.e. 42%). A mixture of Pd(MeCN)₂Cl₂ (5 mol %) and PPh₃ (20 mol %) was also used, but, although this reaction was faster than with Pd(OAc)₂ and PPh₃ (100% conversion in 21 h), the selectivity was not improved (Table 8.1, entry 8). A remarkable improvement was achieved when Pd(MeCN)₂Cl₂ (5 mol%) was used without PPh₃. With this catalyst the reaction is fast, quantitative and proceeds with complete stereoselectivity (Table 8.1, entry 9). This reaction is also stereoselective when ethanol is used as a nucleophile and 8.3b is formed (entry 10). On 0.5 g scale with 5mol% of Pd(II) - catalyst 96% yield of (S)-8.3a (R² = i-Pr, e.e. = 99%) was obtained.

The palladium catalyzed nucleophilic allylic substitution of acyloxypyrrolinones 8.2 with alcohols as nucleophiles was further improved. Instead of using the nucleophile as a solvent several common organic solvents in combination with 25 equivalents of nucleophile were used (Scheme 8.3). This increases the solubility of acyloxypyrrolinone and gives the reaction a wider scope for other nucleophiles. When a 0.25 mmol solution of (R)-(−)-8.2 in dry THF is stirred with 25 equivalents of benzyl alcohol or isopropanol in the presence of 5 % Pd(MeCN)₂Cl₂ complete conversion to the corresponding alkoxypyrrolinone 8.3 takes place in 45 min with retention of configuration (Scheme 8.3). We have not yet been successful in using carbon or nitrogen nucleophiles in this type of reaction. A significant problem with the use of such strong nucleophiles is that a competing conjugate addition occurs. This is not a problem with most substrates that are used in allylic substitutions reported in the literature because in those cases no enone moiety is present.

During the preparation of a new batch of racemic starting material 8.2a, this was found to crystallize as a conglomerate with a melting point of 98 °C for racemic 8.2a and of 128 °C for enantiopure 8.2a. After slow crystallization the crystals obtained have an e.e. of >99 %. However, crystal picking is not possible because the crystals are symmetric and therefore this is not a suitable way to obtain enantiopure acetoxyppyrrlinone 8.2a.
8.3 Synthesis of Diastereomers

A successful method to obtain enantiopure furanones and pyranones, which was developed several years ago in the Feringa group, involves derivatization of hydroxyfuran or hydroxypyranone with enantiopure menthol\textsuperscript{14} or pantholactone\textsuperscript{15} as a chiral auxiliary (see Chapter 1, Section 1.5). In this context we have investigated the possibility of obtaining enantiopure alkoxypyrrolinones from racemic acetoxypyrrolinone 8.2a, using the palladium catalyzed allylic substitution described above, but now with enantiopure alcohols.

With the use of chiral alcohols as a nucleophiles diastereomeric alkoxypyrrolinones 8.3 are formed in quantitative conversion in the palladium catalyzed allylic substitution (Table 8.3). \textit{d}-Menthol provides yellow crystals of \textit{d}-menthyloxypyrrolinone in 80 % isolated yield with a diastereomeric ratio of 2:1 as was determined by \textsuperscript{1}H-NMR (Table 8.3, entry 1). The diastereomers can be separated by column chromatography. With \textit{d}-pantholactone derivatives are also obtained with a diastereomeric ratio of 2:1 and with \textit{l}-borneol the diastereomeric ratio was 1:1 (entries 2 and 3). This method was not further investigated because of the modest diastereoselectivity, instead we focussed our attention on the new method of obtaining enantiopure pyrrolinones described in the next section.

<table>
<thead>
<tr>
<th>product</th>
<th>R*OH</th>
<th>conversion\textsuperscript{a}</th>
<th>yield\textsuperscript{b}</th>
<th>d.r.\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3c</td>
<td>\textit{d}-menthol</td>
<td>100</td>
<td>80</td>
<td>2:1</td>
</tr>
<tr>
<td>8.3d</td>
<td>\textit{d}-pantholactone</td>
<td>100</td>
<td>12</td>
<td>2:1</td>
</tr>
<tr>
<td>8.3e</td>
<td>\textit{l}-borneol</td>
<td>100</td>
<td>55</td>
<td>1:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The conversion was determined by G.C. \textsuperscript{b}After purification by column chromatography, without separation of the diastereomers. \textsuperscript{c}Based upon the \textsuperscript{1}H NMR of the crude product.
Chapter 8

8.4 Asymmetric Synthesis

Since we are able to obtain enantiomerically pure alkoxypyrrolinones in two steps from racemic acyloxypyrrolinones by catalytic enantioselective lipase and palladium based methodology, it was an even bigger challenge to find a one step route from racemic acyloxypyrrolinones to enantiopure alkoxypyrrolinones. The most elegant way to achieve this would involve a catalyst system that is able to convert a racemic acyloxypyrrolinone quantitatively into an enantiopure alkoxypyrrolinone and therefore make our successful enzymatic synthesis step redundant. For a quantitative conversion of racemic starting material into enantiopure product in one step an in situ racemization of the starting material or an intermediate is necessary. In Chapter 4 we already have encountered an example of a dynamic kinetic resolution in which a hydroxypyrrolinone racemizes during the reaction. We have, however, no evidence of the possibility of in situ racemization of acyloxypyrrolinones. Therefore a dynamic kinetic asymmetric transformation of acyloxypyrrolinones probably could only be accomplished by means of an inversion of the allyl palladium complex.

The first goal in developing an asymmetric synthesis of pyrrolinones by palladium catalyzed allylic substitution of alcohols was to find a chiral ligand that generated a chiral catalyst that was both active and selective in this reaction. Therefore several of chiral ligands were tested. Most of these ligands are chiral diphosphines and bisoxazolines. In all cases the effect of a variation of the ligand structure, palladium source, nucleophile, solvent and temperature was studied. The most significant part of the results is summarized here.

The first group of ligands that was tested consisted of commercially available chiral diphosphines 8.5 – 8.9 (Figure 8.1).

![Figure 8.1 Chiral ligands](image)

At first the results were disappointing. When a mixture of acetoxyprrolinone 8.2a and isopropanol was stirred at 40 °C for 5 hours with a catalytic amount of Pd(OAc)₂ and (+) DIOP 8.5 in THF isopropanoxypyrrolinone 8.3a with an e.e. of only 10 % was obtained after 74
% conversion (Table 8.4, entry 1). This means that, although the reaction was fast, the selectivity with which the product was formed is low. This reaction is probably a kinetic resolution with a selectivity value of $s = 1.5$. As for E-values in enzymatic resolutions $s$-values above 20 are preferred (see Chapter 1, Equation 1.2, Figure 1.4). When (+) BINAP 8.6 was used as a ligand the selectivity is similar but the reaction is much slower (entry 2). We also used benzyl alcohol as a nucleophile because it might give favorable π stacking with the (+) BINAP and therefore higher e.e.’s. However, only the rate improved but the selectivity remained low (entry 3).

On changing the leaving group from an ester to a carbonate (8.2f, entry 4) the rate was lower and the selectivity was the same. With the use of CHIRAPHOS 8.7 no e.e. in the product 8.3a was observed. The use of two other commercially available ligands, (−)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine 8.8 and BPPF0Ac 8.9 resulted in almost no conversions and e.e.’s.

We also tested ligands developed in our laboratories such as the pyridinethiol 8.10 and dithiol ligands 8.11 that were used in Pd-catalyzed allylic substitution and the binaphthol derived phosphoramidite ligand 8.12 that was used in conjugate additions. These ligands were not reactive in our allylic substitutions (< 5% conversion after 14 h).

![Scheme 8.5](image)

**Table 8.4**  
*Pd-catalyzed allylic substitution according to Scheme 8.5, using several chiral ligands***

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv.* (%)</th>
<th>e.e.* (%) of 8.2</th>
<th>e.e.* (%) of 8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.5</td>
<td>Me</td>
<td>i-Pr</td>
<td>40</td>
<td>5</td>
<td>74</td>
<td>nd</td>
<td>10</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.6</td>
<td>Me</td>
<td>i-Pr</td>
<td>40</td>
<td>23</td>
<td>21</td>
<td>nd</td>
<td>18</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.6</td>
<td>Me</td>
<td>Bn</td>
<td>40</td>
<td>5</td>
<td>28</td>
<td>nd</td>
<td>11</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.6</td>
<td>PhO</td>
<td>Bn</td>
<td>40</td>
<td>70</td>
<td>20</td>
<td>nd</td>
<td>11</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.7</td>
<td>Me</td>
<td>i-Pr</td>
<td>25</td>
<td>12</td>
<td>55</td>
<td>nd</td>
<td>0</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.13</td>
<td>Me</td>
<td>Bn</td>
<td>40</td>
<td>8</td>
<td>62</td>
<td>78</td>
<td>50</td>
</tr>
<tr>
<td>7&lt;sup&gt;g&lt;/sup&gt;</td>
<td>8.14</td>
<td>Me</td>
<td>Bn</td>
<td>40</td>
<td>23</td>
<td>99</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>8&lt;sup&gt;f&lt;/sup&gt;</td>
<td>8.21</td>
<td>Me</td>
<td>Bn</td>
<td>RT</td>
<td>21</td>
<td>61</td>
<td>&gt;99</td>
<td>71</td>
</tr>
<tr>
<td>9&lt;sup&gt;fg&lt;/sup&gt;</td>
<td>8.21</td>
<td>Me</td>
<td>Bn</td>
<td>40</td>
<td>0.7</td>
<td>20</td>
<td>6</td>
<td>89</td>
</tr>
</tbody>
</table>

*The conversion was determined by GC using tridecane as an internal standard. <sup>a</sup>The e.e. was determined by chiral GC. <sup>b</sup>25 equivalents of alcohol in THF were used. <sup>c</sup>50 equivalents of alcohol in THF were used. <sup>d</sup>25 equivalents of alcohol in acetonitrile were used. <sup>e</sup>1.25 mol % Pd<sub>2</sub>dba<sub>3</sub>, 2.5% of ligand, and 25 equivalents of alcohol in CH<sub>2</sub>Cl<sub>2</sub> were used. <sup>f</sup>30 mol % of n-Bu<sub>4</sub>NCl was added.
The second group of ligands that we have tested consisted of 7 commercially available C₂-symmetric bisoxazolines 8.13–8.19 developed by Helmchen and Pfaltz¹⁹ (see Figure 8.2).

![Chemical structures](image)

**Figure 8.2  Chiral (bis)oxazoline ligands**

When a solution of acetoxypyrrolinone 8.2a with benzyl alcohol, 5 mol % Pd(OAc)₂ and 10 mol % of bisoxazoline ligand 8.13 in acetonitrile was stirred under argon for 9 hours, a kinetic resolution was found which reached 100 % with an s-factor¹⁶ of 7 (Table 8.4, entry 6, Figure 8.3a). The catalyst had a preference for (R)-(–) 8.2a and an excess of (R)-(–) benzyloxypryrolinone was obtained, meaning that the reaction proceeded with retention of configuration. Bisoxazoline 8.14, however, gave completely different results. Under the same conditions in THF an asymmetric transformation takes place which reached 100 % conversion whereas the benzyloxypryrolinone 8.3f was obtained with a constant e.e. of 24 % during the conversion and the starting material 8.2 stayed racemic (Table 8.4, entry 7, Figure 8.3b). Also the stereochemistry was different from the reaction with ligand 8.13 described above. Although the stereochemistry of the ligand was the same, (S)-(+) benzyloxypryrolinone was the major enantiomer of the product in the reaction using ligand 8.14.

The other bisoxazoline ligands gave inferior results. Ligand 8.15 caused the reaction to proceed similar to the reaction using 8.13, only in this case the stereoselectivity and reactivity were lower. With 8.16 and 8.19 the other enantiomer of the benzyloxypryrolinone (S) was obtained, like with 8.14, although the conversion was lower with 8.16 and the e.e. of the product was lower with 8.19. The same reaction using ligands 8.17 and 8.18 did not yield the desired product.

We also used mixed diphenylphosphate/oxazoline ligand 8.20, synthesized according to the procedure reported by Helmchen and coworkers,¹⁹a but no conversion of 8.2a was observed.
Palladium Catalyzed Allylic Substitution of Acyloxypyrrolinones

Figure 8.3  (a) E.e. of the starting material 8.2a (continuous) and the product 8.3f (dashed) against the conversion during the reaction catalyzed by Pd(OAc)$_2$ and ligand 8.13
(b) The same as (a), with ligand 8.14

Another diphosphine ligand 8.21 (Figure 8.4), based on (R),(R)-1,2-diaminocyclohexane, we have also tested in the palladium catalyzed allylic substitution of Scheme 8.5, was the ligand, developed by Trost and coworkers. This ligand has been successfully used in several reported palladium catalyzed asymmetric reactions.

Figure 8.4

With this diphosphine ligand we observed a kinetic resolution in the Pd-catalyzed allylic substitution. The reaction of 8.2a with benzylalcohol, 1.25 mol % Pd$_3$dba$_3$ (dba = dibenzylideneacetone) and 5 mol % ligand 8.21 in CH$_2$Cl$_2$ at room temperature, according to Scheme 8.5, stopped after 21 h at 61 % conversion. The e.e. of the starting material 8.2a is >99% and the e.e. of benzylloxypyrrolinone 8.3f was 71 %, corresponding with an s-factor of 20. The catalyst had a preference for (R)-(−) 8.2 and gave retention of configuration. The e.e.’s of acetoxypyrrolinone 8.2a and benzylloxypyrrolinone 8.3f are plotted against the conversion in Figure 8.5a.
At this point were able to perform a kinetic resolution with a reasonable high selectivity from which the remaining enantiomer of the acyloxy pyrrolinone 8.3a was obtained enantiomerically pure after 61% conversion (max. 39% yield) and the alkoxypyrrolinone product 8.3f was obtained with 71% e.e. (8.3a and 8.3f can be separated by column chromatography). It was, however, our goal to obtain enantiopure product in high yield. Therefore we were looking for a method to turn this reaction into a dynamic kinetic asymmetric transformation. To achieve this goal we had to find a way to promote the in situ racemization of the allyl palladium intermediate.

According to Trost et al. chloride salts like n-Bu$_4$NCl are able to speed up the racemization of an allyl palladium intermediate.$^{11b,c}$ We performed the above described reaction at 40 °C with 30 mol % of n-Bu$_4$NCl. The addition of n-Bu$_4$NCl had a tremendous influence on the course of the reaction. After 0.7 h alkoxypyrrolinone 8.3f was obtained with 89% e.e., whereas the e.e. of the starting material 8.2a was only 6% (Table 8.4, entry 9). However, at this point the reaction stopped, the conversion being only 20%, probably because the large amount of chloride salt had deactivated the catalyst. However, to distinguish unequivocally a normal kinetic resolution from an asymmetric transformation, conversions exceeding 50% in the latter case are essential. That no normal kinetic resolution occurs on addition of n-Bu$_4$NCl can be better illustrated from the same reaction performed with 3 mol % of n-Bu$_4$NCl. In this reaction the e.e. of the product is somewhat lower (78%) and the e.e. of the starting material is 76%. Furthermore the reaction stops at 65% conversion and both the e.e. for 8.2a and for 8.3f stay the same during the course of the reaction. These findings suggest that there is neither a normal kinetic resolution nor a perfect asymmetric
transformation. Further optimization of this reaction by varying the amount of chloride, the temperature and the solvent is in progress.

The mechanism of the allylic substitution of pyrrolinones with in situ racemization is not fully understood and it remains possible that more than one mechanism occurs at the same time (kinetic resolution and asymmetric transformation). We can, however, imagine the racemization step to proceed analogously to the mechanism proposed by Trost for the corresponding furanones (Scheme 8.6). After formation of an allyl-Pd intermediate the chloride ion is thought to increase the rate of interconversion of 8.22 and 8.24 through coordination to palladium which would favor the aromatic complex 8.23. Since one of the diastereomeric complexes (here 8.24, path b) reacts faster with the alcohol in the presence of the chiral ligand a dynamic kinetic asymmetric transformation seems possible.

Scheme 8.6 Possible course of a dynamic kinetic asymmetric transformation.

8.5 Conclusions

Enantiopure acyloxy.pyrrolinones have been quantitatively converted into alkoxy.pyrrolinones with retention of configuration by a palladium catalyzed allylic substitution using achiral ligands. This provides a key step in a short chemo-enzymatic route to acyliminium ion precursors.
We have found that starting from racemic acetoxy- or alkoxy-pyrrolinone both starting material and alkoxy-pyrrolinone product can be obtained with high e.e. in an asymmetric palladium catalyzed nucleophilic substitution, depending upon the chiral ligand and the conditions that are used. These reactions probably proceed through a kinetic resolution or an asymmetric transformation.

Although the conversions still need to be improved, this procedure provides a highly efficient catalytic one-step synthesis of enantiomerically pure acetoxy- or alkoxy-pyrrolinones from racemic starting material.

8.6 Experimental Section

**General information** The conversions were measured on a Hewlett Packard 5890 GC, equipped with a 50m x 0.53mm HP-1 crosslinked methyl silicon gum column, using tridecane as an internal standard. E.e.’s were determined with chiral GC according to Table 8.5 (vide infra).

For further general remarks see Chapter 2.

**General procedure for the palladium catalyzed allylic substitution of acyloxypyrrolinones (8.3).** (Method I) To a stirred solution of 0.5 mmol acyloxypyrrolinone 8.2 and 0.03 g of tridecane in 8 mL of alcohol under an argon atmosphere an amount of achiral catalyst (given in Tables 8.1, 8.2, and 8.3) was added. The reaction mixture was stirred for the time given at the indicated temperature. Aliquots of 0.2 mL were taken at regular intervals and filtered over silica with 0.4 mL of CH$_2$Cl$_2$. Conversions and e.e.’s were determined by GC.

(Method II) To a stirred solution of 0.25 mmol acyloxypyrrolinone 8.2, 0.01 g of tridecane, and an amount of alcohol (given in Table 8.4) in 3 mL of dry solvent under an argon atmosphere, an amount of chiral catalyst (given in Table 8.4) was added. The reaction mixture was stirred during the time given at the indicated temperature. Aliquots of 0.1 mL were taken at intervals and filtered over silica with 0.5 mL of CH$_2$Cl$_2$. Conversions and e.e.’s were determined by GC.

**1-Acetyl-5-isopropoxy-1,5-dihydro-pyrrol-2-one** (–)-(8.3a). To a solution of 1.00 g (5.46 mmol) of acetoxypyrrolinone (–)-8.2a in 80 mL of isopropanol under an argon atmosphere 0.071 g Pd(MeCN)$_2$Cl$_2$ (5%, 0.273 mmol) was added. The reaction mixture was stirred at room temperature. Aliquots of 0.2 mL were take at intervals and filtered over silica with 0.4 mL of CH$_2$Cl$_2$. After 2 h the starting material was almost completely converted according to GC. The mixture was filtered over silica, washed with CH$_2$Cl$_2$ and concentrated in vacuo. Purification by flash chromatography (n-hexane/ ethyl acetate 1:1) afforded (–)-8.3a (0.962 g, 5.26 mmol, 96 %) as a colorless oil which solidifies on standing, R$_f$ 0.57, e.e. 99%. [α]$_D$ -149 (c=0.5, CHCl$_3$), e.e. > 99% as estimated by chiral GC. ^1$H$ NMR (CDCl$_3$): $\delta$ 1.15 (d, $J = 8.8$ Hz, 3H), 1.18 (d, $J =$
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8.8 Hz, 3H), 2.49 (s, 3H), 4.23 (sept, J = 6.1 Hz, 1H), 5.92 (d, J = 2.0 Hz, 1H), 6.06 (d, J = 6.1 Hz, 1H), 6.97 (dd, J = 2.0, 6.1 Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): d 22.87 (q), 22.96 (q), 24.86 (q), 73.03 (d), 86.34 (d), 126.85 (d), 147.73 (d), 168.74 (s), 169.98 (s).

**1-Acetyl-5-ethoxy-1,5-dihydro-pyrrol-2-one (8.3b).** \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 1.15 (t, J = 7.1 Hz, 3H), 2.51 (s, 3H), 3.68-3.81 (m, 2H), 5.97 (d, J = 1.5 Hz, 1H), 6.11 (dd, J = 0.5, 6.1 Hz, 1H), 7.05 (dd, J = 2.0, 6.1 Hz, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 15.41 (q), 24.86 (q), 64.73 (t), 86.98 (d), 128.10 (d), 147.18 (d), 176.18 (s).

**1-Acetyl-5-(2-isopropyl-5-methyl-cyclohexyloxy)-1,5-dihydro-pyrrol-2-one (8.3c).** The product was obtained as a mixture of diastereomers. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.42-1.15 (m, 12H), 1.21-1.40 (m, 1H), 1.48-1.58 (m, 3H), 1.84-1.99 (m, 2H), 2.42 (s, 3H), 3.47 and 3.75 (dt, J = 4.4, 10.6 Hz, 1H), 5.96-5.99 (m, 2H), 6.89 and 7.04 (dd, J = 1.8, 5.9 Hz, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 22.25 (t), 24.73 (q), 24.93 (q), 34.16 (t), 42.33 (t), 48.72 (q), 79.25 (d), 86.42 (d), 126.87 (d), 148.09 (d), 168.82 (s), 167.77 (s). HRMS calcd for C\textsubscript{16}H\textsubscript{25}NO\textsubscript{3}: m/z 279.182. Found: 279.183. Anal. calcd for C\textsubscript{16}H\textsubscript{25}NO\textsubscript{3}: C 68.77 H 9.02 N 5.02. Found: C 69.17 H 9.61 N 4.89.

**1-Acetyl-5-(4,4-dimethyl-2-oxo-tetrahydro-furan-3-yloxy)-1,5-dihydro-pyrrol-2-one (8.3d).** \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 1.08 (s, 3H), 1.10 (s, 3H), 2.56 (s, 3H), 3.89-4.11 (m, 2H), 6.10 and 6.19 (d, J = 5.8 Hz, 1H), 6.16 and 6.33 (s, 1H), 7.02-7.18 (m, 1H), 7.34 and 7.40 (dd, J = 2.2, 5.8 Hz, 1H)

**1-Acetyl-5-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yloxy)-1,5-dihydro-pyrrol-2-one (8.3e).** \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.69-1.15 (m, 12H), 1.50-1.63 (m, 4H), 1.75-1.83 (m, 1H), 2.02-2.10 (m, 1H), 2.43 (s, 3H), 3.91-3.99 (m, 1H), 5.88-5.92 (dd, J = 1.8, 10.8 Hz, 1H), 6.01-6.04 (t, J = 5.49 Hz, 1H), 6.91-6.93 and 6.99-7.02 (dd, J = 1.8, 5.9 Hz, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 13.10 (q), 13.50 (q), 18.63 (q), 19.58 (q), 26.14 (s), 26, 27 (s), 27.74, 36.76 (d), 37.20 (d), 44.86 (t), 82.94 (d), 85.38 (d), 127 (d), 147.39 (d), 168 (s), 169 (s).

**1-Acetyl-5-benzyloxy-1,5-dihydro-pyrrol-2-one (8.3f).** \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 2.45 (s, 3H), 4.71 (dd, J = 11.7, 32.6 Hz, 2H), 6.02 (m, 2H), 6.89 (dd, J = 2.2, 6.0 Hz, 1H), 7.28 (m, 5H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 24.58 (q), 71.43 (t), 86.68 (d), 127.23 (d), 127.94 (d), 128.01 (d), 128.44 (d), 137.39 (s), 146.99 (d), 168 (s), 170 (s). HRMS calcd for C\textsubscript{13}H\textsubscript{13}NO\textsubscript{3}: m/z 231.090. Found: 231.088.
Carbonic acid (1-acetyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl) phenyl ester (8.2f). $^1$H NMR (CDCl$_3$): $\delta$ 2.52 (s, 3H) 6.25 (d, J = 5.8 Hz, 1H) 7.04 (d, J = 1.8 Hz, 1H) 7.16-7.36 (m, 6H).

| Table 8.5 Resolution of alkoxypyrrolinones 8.3 by chiral GC$^a$ |
|-----------------|-----------------|------|--------|--------|
| compound       | column          | oven temp. ($^\circ$C) | R$_1$ (min) | R$_2$ (min) |
| 8.3a            | GTA$^b$         | 150  | 12.4   | 13.1   |
| 8.3a            | CP$^d$          | 110  | 52     | 53     |
| 8.3b            | BTA$^d$         | 100  | 33     | 36     |
| 8.3f            | GTA             | 150  | 120    | 124    |

$^a$Base-line separation on HP 5890 Series II; column pressure 100 kPa, inj. & det. temp 200 $^\circ$C. $^b$GTA = Chiraldex G-TA capillary column (73035 Astec, $\alpha$-cyclodextrine trifluoroacetylated phase, 50 m x 0.25 mm x 0.125 m). $^c$CP = CP cycloextrin-$\beta$-2,3,6-M-19 capillary column (Chrompack, diluted $\beta$-cyclodextrine phase, 50 m x 0.25 mm x 0.25 m). $^d$BTA = Chiraldex B-TA capillary column (Astec, G9409-15, $\beta$-cyclodextrine trifluoroacetylated phase, 30 m x 0.25 mm x 0.125 m).

8.7 References


16 (a) The s-factor, a measure of the enantioselectivity can be calculated from $s = \ln\left(\frac{1-c(1+e_e.P)}{1-c(1-e_e.P)}\right)$ or from $s = \ln\left(\frac{1-c(1-e_e.S)}{1-c(1+e_e.S)}\right)$. (b) Eliel, E.L.; Wilen, S.H. in Topics in Stereochemistry, Vol. 18, John Wiley & Sons, Inc., 1988.