Synthesis and application of new chiral amines in Dutch resolution

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Chapter 3

Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

The synthesis of enantio-enriched 1-aryl-1-butylamines via a highly diastereoselective addition of allylzinc bromide to imines derived from (R)-phenylglycine amide is described. A three-step procedure is applied, which involves: (a) formation of the chiral imines; (b) asymmetric addition of the allylzinc reagent; (c) removal of the chiral auxiliary under reductive conditions. This overall protocol leads to a broad range of 1-aryl-1-butylamines with high enantiomeric purity, which can be used in Dutch Resolution experiments. The scope and limitations of the reductive removal step will also be discussed.

Chapter 3

3.1 Introduction

Enantiomerically pure amines with a stereogenic centre at the α-position are valuable synths in the synthesis of biologically active natural products and compounds of pharmaceutical interest.\(^1\) One of the strategies used to obtain enantiomerically pure amines is an asymmetric 1,2-addition of nucleophiles to the electrophilic C=N imino group of chiral aldines\(^2\) or hydrazones\(^3\) (Scheme 3.1). Other methods include e.g. catalytic asymmetric addition of dialkylzinc to imines,\(^4\) diastereoselective reduction of chiral imines,\(^5\) asymmetric reduction of prochiral imines and enamides\(^6\) and oximes\(^7\) or use of a transaminase.\(^8\) The most frequently employed methodology for the synthesis of homoallylamines is the allylation of imines or hydrazones by allyl Si, Sn, Sm, Li, Mg, Zn, Ce, Cr, B, Ba or Cr reagents.\(^{3c, 9,10}\)

\[
\begin{align*}
\text{N} & \quad \text{R}^2 \quad \text{H} \quad + \quad \text{R}^3 \text{M} \\
\text{R}^1 & \quad \text{NH}_2 \\
\text{M} & = \text{Metal}
\end{align*}
\]

Scheme 3.1 Synthesis of enantiomerically enriched primary amines by asymmetric 1,2-addition.

Enantiopure imines can be generated, in most cases fairly easily, by condensation of an enantiopure amine R²-NH₂ used as a (readily available) chiral auxiliary, with the corresponding carbonyl compound. High asymmetric induction during the addition has been reported by using imines derived from chiral auxiliaries such as α-arylethylamines,\(^11\) β-amino alcohols, β-alkoxy amines, and β-amino acid esters.\(^12\) A common feature of the latter three auxiliaries is the presence of a second heteroatom, which is capable of rigidifying the transition state of the 1,2-addition through chelation.\(^11\) This effect is also referred to as “chelation control”.\(^13\) Possible drawbacks in the use of chiral auxiliaries are the availability, in some cases, of only one enantiomer, high costs, low regioselectivity in the cleavage of the auxiliary, immolative removal and/or the need of removal of these auxiliaries by procedures unsuitable for large-scale preparations (i.e. oxidation with Pb(OAc)₄,\(^14\) or treatment with HIO₄/MeNH₂).\(^{10c,11,12b}\) Often the obtained enantiomeric excesses (ee’s) are not satisfactory.\(^{5c,6,7,15}\)

In the next two chapters the preparation of easily accessible substituted 1-aryl-1-butylamines and 1-aryl-3-butenylamines is described, which we intend to use as new families of resolving agents in “Dutch Resolution experiments”.\(^16\) A metal-mediated Cope reaction (Figure 3.1) is a key element of the synthesis. There is extensive precedent for such reactions.\(^{9b,9g,17a}\)
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

In preliminary publications, (R)-phenylglycine amide, (R)-PGA (3.1), was shown to be a highly efficient chiral auxiliary for this process. Enantiomerically pure (R)-PGA (3.1) is a key intermediate in the industrial (enzymatic) route for the preparation of cephalexin, a semi-synthetic antibiotic, in which (R)-PGA is incorporated.

In this chapter we expand upon the scope of the metal-mediated aza-Cope reaction. The imines derived from (R)-PGA, are capable of forming rigid chelated intermediates, and have been subjected to addition of allylzinc reagents. Both reductive and non-reductive methods for the removal of the chiral auxiliary have been used to obtain the desired substituted enantiomerically pure primary amines. In this chapter, the reductive removal of the (R)-PGA chiral auxiliary will be discussed. Finally, the selectivity of cleavage of the chiral auxiliary in the reductive removal has been investigated.
3.2 Formation of (R)-PGA Aldimines

Aldimines (R)-3.2–3.29 are easily obtained in excellent yields and > 99 % ee by stirring a mixture of (R)-PGA (3.1) and the corresponding substituted benzaldehyde (ArCHO) in CH₂Cl₂ overnight at room temperature (Table 3.1). In practically all cases no catalyst is required, although the formation of aldime (R)-3.27 required elevated temperatures and acid catalysis. In all cases, after removal of the water and the CH₂Cl₂, chemically pure and stereochemically homogeneous products were obtained. This conclusion is based on the fact that clean singlets for both the proton adjacent to the carboxamide group as well as the imine proton are observed in the ¹H-NMR spectra. Imines 3.2–3.29 are crystalline and have sharp melting points. On the basis of thermodynamic considerations the products should all have the E-configuration. This was confirmed by COSY- and NOESY-2D NMR spectroscopy. After work-up, the CH₂Cl₂ can be easily re-used without further purification.

Table 3.1 Formation of (R)-PGA imines 3.2–3.29 by condensation with substituted benzaldehydes and the formation of (R,R)-PGA homoallylamines 3.33–3.60 by addition of allylzinc bromide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Ar</th>
<th>Yield (%)⁴</th>
<th>Allylamine</th>
<th>Yield (%)⁴</th>
<th>dr (R,R):(R,S)³⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.2</td>
<td>C₆H₅</td>
<td>99</td>
<td>3.33</td>
<td>&gt;99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
<td>o-Me C₆H₄</td>
<td>&gt;99</td>
<td>3.34</td>
<td>93</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>m-Me C₆H₄</td>
<td>97</td>
<td>3.35</td>
<td>&gt;99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>p-Me C₆H₄</td>
<td>&gt;99</td>
<td>3.36</td>
<td>97</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>3.6</td>
<td>o-OMe C₆H₄</td>
<td>93</td>
<td>3.37</td>
<td>98</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>3.7</td>
<td>m-OMe C₆H₄</td>
<td>81</td>
<td>3.38</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>7</td>
<td>3.8</td>
<td>p-OMe C₆H₄</td>
<td>98</td>
<td>3.39</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>8</td>
<td>3.9</td>
<td>o-F C₆H₄</td>
<td>97</td>
<td>3.40</td>
<td>&gt;99</td>
<td>98:2</td>
</tr>
</tbody>
</table>

1H-NMR spectra.
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Ar</th>
<th>Yield (%)(^{[a]})</th>
<th>Allylamine</th>
<th>Yield (%)(^{[a]})</th>
<th>(dr (R,R):(R,S))(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3.10</td>
<td>(m)-F (C_6H_4)</td>
<td>96</td>
<td>3.41</td>
<td>97</td>
<td>98:2</td>
</tr>
<tr>
<td>10</td>
<td>3.11</td>
<td>(p)-F (C_6H_4)</td>
<td>95</td>
<td>3.42</td>
<td>94</td>
<td>99:1</td>
</tr>
<tr>
<td>11</td>
<td>3.12</td>
<td>(o)-Cl (C_6H_4)</td>
<td>97</td>
<td>3.43</td>
<td>98</td>
<td>97:3</td>
</tr>
<tr>
<td>12</td>
<td>3.13</td>
<td>(m)-Cl (C_6H_4)</td>
<td>98</td>
<td>3.44</td>
<td>83</td>
<td>98:2</td>
</tr>
<tr>
<td>13</td>
<td>3.14</td>
<td>(p)-Cl (C_6H_4)</td>
<td>95</td>
<td>3.45</td>
<td>98</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>14</td>
<td>3.15</td>
<td>(o)-Br (C_6H_4)</td>
<td>99</td>
<td>3.46</td>
<td>98</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>15</td>
<td>3.16</td>
<td>(m)-Br (C_6H_4)</td>
<td>98</td>
<td>3.47</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>16</td>
<td>3.17</td>
<td>(p)-Br (C_6H_4)</td>
<td>99</td>
<td>3.48</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>17</td>
<td>3.18</td>
<td>(o)-Ph (C_6H_4)</td>
<td>85</td>
<td>3.49</td>
<td>89</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>18</td>
<td>3.19</td>
<td>(m)-Ph (C_6H_4)</td>
<td>89</td>
<td>3.50</td>
<td>85</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>19</td>
<td>3.20</td>
<td>(p)-Ph (C_6H_4)</td>
<td>95</td>
<td>3.51</td>
<td>99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>20</td>
<td>3.21</td>
<td>(o)-NO(_2) (C_6H_4)</td>
<td>97</td>
<td>3.52</td>
<td>&gt;99</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>21</td>
<td>3.22</td>
<td>(m)-NO(_2) (C_6H_4)</td>
<td>98</td>
<td>3.53</td>
<td>96</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>22</td>
<td>3.23</td>
<td>(p)-NO(_2) (C_6H_4)</td>
<td>92</td>
<td>3.54</td>
<td>93</td>
<td>99:1</td>
</tr>
<tr>
<td>23</td>
<td>3.24</td>
<td>(o)-OH (C_6H_4)</td>
<td>97</td>
<td>3.55</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>24</td>
<td>3.25</td>
<td>(m)-OH (C_6H_4)</td>
<td>98</td>
<td>3.56</td>
<td>97</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>25</td>
<td>3.26</td>
<td>(p)-OH (C_6H_4)</td>
<td>92</td>
<td>3.57</td>
<td>95</td>
<td>99:1</td>
</tr>
<tr>
<td>26</td>
<td>3.27(^{[c]})</td>
<td>3-Piperonyl</td>
<td>85</td>
<td>3.58</td>
<td>81</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>27</td>
<td>3.28</td>
<td>1-Naphthyl</td>
<td>83</td>
<td>3.59</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>28</td>
<td>3.29</td>
<td>2-Naphthyl</td>
<td>91</td>
<td>3.60</td>
<td>73</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Isolated yield. \(^{[b]}\) Diastereomeric ratios were determined with \(^3\)H-NMR spectroscopy. 
\(^{[c]}\) In CHCl\(_3\) with catalytic \(p\)-TolSO\(_2\)H for 2h at reflux.
The phenyl-substituted benzaldehydes for the formation of imines 3.18–3.20 were prepared from the corresponding bromobenzaldehydes by a Suzuki coupling using 10% palladium on carbon as a heterogeneous catalyst (Table 3.2).

**Table 3.2 Preparation of phenyl-substituted benzaldehydes 3.30–3.32 via a Pd-C catalyzed Suzuki coupling. Reagents and conditions: i-propanol/H$_2$O/Na$_2$CO$_3$, Pd-C (10%), PhB(OH)$_2$, 65 °C.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Arylaldehyde</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-Br C$_6$H$_4$</td>
<td>3.30</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>m-Br C$_6$H$_4$</td>
<td>3.31</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>p-Br C$_6$H$_4$</td>
<td>3.32</td>
<td>95</td>
</tr>
</tbody>
</table>

This palladium source is relatively inexpensive and can easily be removed. The palladium on carbon catalyzed Suzuki reaction has been used recently for the preparation of a range of resolving agents based on 4-arylmandelic acid derivatives. Attempts to perform a Suzuki coupling reaction in a later stage of the synthetic route failed.

### 3.3 Diastereoselective Allylation of (R)-PGA Aldimines

The addition of aldimines (R)-3.2–3.29 to preformed allylzinc bromide (1.5 equiv.) in THF at 0 °C afforded the (R,R)-PGA allylamines 3.33–3.60 in yields up to 99% and dr’s of at least 97:3 (Table 3.1). In all cases, the dr could be increased to more than 99:1 by recrystallization from acetone/hexane (1:20). The configurations of the stereogenic centers were determined by X-ray analysis and will be discussed later in this paragraph.

Allylzinc bromide proved to be the organometallic reagent of choice since it is easily prepared and compatible with most organic functional groups. Note that the phenylglycine amide chiral auxiliary in imines 3.2–3.29 contains a chiral center that could
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

potentially racemize under basic conditions. Removal of the proton at the \( \alpha \)-position of the phenylglycine moiety would give a 2-aza allyl anion (Scheme 3.2).\[23\] The resulting carbanion could be stabilized by both the adjacent carbon-nitrogen double bond as well as the carboxamide group.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{CONH}_2 \\
\text{Ar} & \quad \text{H}
\end{align*}
\]

Scheme 3.2 2-Aza allyl anion resonance structures.

Despite these potential problems, it has been demonstrated previously by chiral HPLC that the addition reaction proceeds without any racemization of the chiral auxiliary for the cases 3.33 and 3.58.\[17a\] However, although this has not been explicitly checked, the ee’s of the end products indicate that this is also the case for the other addition products 3.34–3.60 (vide supra).

The addition reaction has also been performed under Barbier-type conditions with imines 3.2–3.11, 3.18–3.20 and 3.28–3.29 giving similar results. “Barbier conditions” are referred to as reactions wherein the organometallic reagent is formed \( \text{in situ} \). In this procedure the imines are stirred with zinc and allyl bromide in THF at 0 °C and the reaction mixture is allowed to warm to room temperature. This procedure in our experience is considerably easier from an experimental point of view.

The compatibility of allylzinc bromide with relatively acidic functionalities such as an amide or hydroxyl group is remarkable. In view of the approximate relative \( pKa \) of 17 for amides,\[24\] the basic allylzinc reagent could well be protonated by the amide group. The lack of reaction with an even more acidic functionality such as a phenolic hydroxyl group (\( pKa 8–11 \)) is even more striking (entries 23–25). The addition of 1.5 equiv. of allylzinc bromide to \((R)-3.24–3.26\) furnished homoallylamines \((R,R)-3.55–3.57\) as the only products in up to 97 % isolated yields.

For determination of the diastereoselectivity with \(^1\text{H}-\text{NMR}\), analogous reactions were performed with magnesium turnings.\[25\] This process furnishes the adducts with lower \( dr \) values. The ratio of \((R,R)\) and \((R,S)\) can be determined from the integrals of the vinyllic proton (v), which is typically in the region of 5.3–5.9 ppm in the \(^1\text{H}-\text{NMR}\) spectra, as
shown below in the case of PGA allylamine 3.39 obtained by reaction with the more reactive allylic Grignard reagent (Figure 3.2).

![Diagram of reaction](image)

**Figure 3.2** Analogous reactions with more basic allylmagnesium bromide lead to lower dr values.

The high diastereoselectivity of the Zn-mediated allylation of the (R)-PGA imines can be rationalized by chelation control, as shown in Figure 3.3.[9] The two heteroatoms of the amide-imine moiety chelate the zinc atom of the allylzinc reagent to form a five-membered ring.[11,13] Simultaneously, a six-membered chair-like transition state can be formed with the allylic system and the C=N double bond of the imine. The re-face 1,2-addition proceeds in a concerted fashion via an allylic aza-Cope-like rearrangement.

![Diagram of proposed chelation controlled addition](image)

**Figure 3.3** Proposed chelation controlled addition of allylzinc bromide to (R)-PGA imines.

The allylic rearrangement was confirmed by addition of crotylzinc bromide[26] to benzaldimine (R)-3.2 (Scheme 3.3). Product 3.61 was isolated in 98 % yield (dr > 99:1) as a mixture of two isomers in a ratio of 1:1.3. As a demonstration of this scope, the addition of methallylzinc bromide to 3.2 furnished (R,R)-3.62 in 98 % isolated yield (dr > 99:1).[17a]
In accord with the model proposed in Figure 3.3, the absolute configuration of the adducts 3.33–3.60 should be (R,R). This was unambiguously established by X-ray crystallographic analysis of 3.57 (Figure 3.4).[^17a][27] The absolute configuration of adducts 3.33–3.60 is assigned by analogy.

[^17a]: Reference for X-ray crystallographic analysis
[^27]: Reference for analogy assignment
Chapter 3

3.4 Reductive Removal of the Chiral Auxiliary

The chiral auxiliary can easily be removed by selective catalytic debenzylation using H₂ and 10 % palladium on carbon in i-propanol and aqueous acetic acid.\[28,29\] The amines were hydrogenolysed in an acidic medium to eliminate the poisoning effect of the basic nitrogen on the catalyst. However, since PGA allylamines 3.33–3.60 are ‘di-N-benzyl’, reductive removal of the auxiliary by catalytic hydrogenation may proceed via route a or route b (Scheme 3.4). In addition, this reductive removal of the chiral auxiliary leads to reduction of the allylic double bond.

\[
\text{(R)-3.64-3.74} \quad \text{a} \quad (R, R)-3.33-3.60 \quad \text{b} \quad 3.63
\]

\textbf{Scheme 3.4} Selectivity of cleavage in the catalytic hydrogenation process. Reagents and conditions: i-propanol/H₂O/AcOH, H₂, Pd-C (10 %).

Hydrogenolytic cleavage via route b leads to the undesired substituted 1-butylbenzene 3.63, whereas cleavage via route a provides the desired saturated 1-arylbutylamines (R)-3.64–3.74.

There is not much literature precedent to allow prediction whether path a or path b will dominate, although steric and electronic effects are expected to influence the outcome of the hydrogenolysis in a predictable fashion. With this in mind we began a systematic investigation. Initially 2-(benzylamino)-2-phenylacetamide 3.75 \[30\] was examined as a model compound (Scheme 3.5) and we were very much encouraged to observe only benzylamine and phenylacetamide 3.76 (route a). The formation of toluene and (R)-PGA 3.1 were not observed (route b).

\[
\text{3.75} \quad \text{route a} \quad \text{3.76}
\]

\textbf{Scheme 3.5} Regioselectivity in the debenzylation process of 3.75. Reagents and conditions: Et₂O, H₂, Pd-C (10%).
The electron-withdrawing carboxamide group, by means of inductive interactions, withdraws some electron density from the sigma bond involved in path \( a \). One could therefore well expect this sigma bond to be a better hydrogen acceptor.

The selectivities \((a:b)\) for products 3.64–3.74 were determined by \(^1\)H-NMR spectroscopy. Analysis of \(^1\)H-NMR spectra of the reaction mixtures revealed that cleavage according to route \( a \) gave rise to a characteristic triplet of the benzylic CH-group between \( \delta = 3.9–4.2 \) ppm, and competitive cleavage according to route \( b \) gave rise to a triplet of the benzylic CH\(_2\)-group at approx. \( \delta = 2.5–2.8 \) ppm. By comparing the ratio of the integrals for both signals, the selectivity for each case could be determined (Table 3.3). For instance, in the case of the unsubstituted PGA allylamine 3.33 the selectivity of the cleavage process is 91:9 in favour of path \( a \) (Figure 3.5).

![Figure 3.5 Selectivity of cleavage of homoallylamine 3.33 after hydrogenation.](image)
### Table 3.3 Regioselective cleavage of the chiral auxiliary and generation of primary 1-aryl-1-butylamines 3.64–3.74 and 3.82 by catalytic hydrogenation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylamine</th>
<th>Ar</th>
<th>Butylamine</th>
<th>Yield [%] [a]</th>
<th>Selectivity (a:b) [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.33</td>
<td>C₆H₅</td>
<td>3.64</td>
<td>70</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>3.34</td>
<td>o-Me C₆H₄</td>
<td>3.65</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>3.35</td>
<td>m-Me C₆H₄</td>
<td>3.66</td>
<td>92</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>3.36</td>
<td>p-Me C₆H₄</td>
<td>3.67</td>
<td>91</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>3.37</td>
<td>o-OMe C₆H₄</td>
<td>3.68</td>
<td>91</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>3.38</td>
<td>m-OMe C₆H₄</td>
<td>3.69</td>
<td>89</td>
<td>98:2</td>
</tr>
<tr>
<td>7</td>
<td>3.39</td>
<td>p-OMe C₆H₄</td>
<td>3.70</td>
<td>89</td>
<td>97:3</td>
</tr>
<tr>
<td>8</td>
<td>3.40</td>
<td>o-F C₆H₄</td>
<td>3.71</td>
<td>88</td>
<td>98:2</td>
</tr>
<tr>
<td>9</td>
<td>3.41</td>
<td>m-F C₆H₄</td>
<td>3.72</td>
<td>58</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>10</td>
<td>3.42</td>
<td>p-F C₆H₄</td>
<td>3.73</td>
<td>79</td>
<td>&gt;99:1</td>
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<td>3.77</td>
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<td>3.78</td>
<td>nd</td>
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<td>3.55</td>
<td>o-OH C₆H₄</td>
<td>3.79</td>
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<td>3.81</td>
<td>nd</td>
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<td>3.58</td>
<td>3-Piperonyl</td>
<td>3.82</td>
<td>80</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

\[a\] Isolated yield. \[b\] Regioselectivity values were determined with \(^1\)H-NMR spectroscopy. 
\[c\] Confirmed by mass analysis, \(^1\)H- and \(^13\)C-NMR. nd: Not determined.
The PGA allylamines 3.33–3.42, 3.49 and 3.58 showed pleasingly high selectivities in cleavage of the C-N bond of the chiral auxiliary via route a. The free primary 1-arylbutylamines (R)-3.64–3.74 and (R)-3.82 were obtained in yields up to 95%. The regioselectivities of cleavage range from 91:9 up to more than 99:1, depending on the substituent. The earlier work of Baltzly and Russel [28c] showed that the electronic nature of the substituent rather than its position is critical in its effect on the regioselectivity of debenzylation. Most substituents studied here are electron-donating and increase the electron density and stability towards cleavage of the N-benzyl linkage, promoting cleavage according to route a. A third factor that plays a role is steric hindrance, as can be seen in the debenzylation of the phenyl-substituted aryl groups (entries 11-13).

The desired cleavage according to route a takes place with phenyl at the ortho-position (entry 11) whereas cleavage is almost exclusively via route b for phenyl as meta- or para-substituents (entries 12 and 13). Obviously, the aromatic rings of the biphenyl moiety bind more efficient to the Pd-surface (Eley-Rideal mechanism).[31] A steric effect is doubtlessly present for the case that phenyl is an ortho-substituent, yielding the desired arylbutylamine 3.74 as the major product.

Attempts to convert the chloro- and bromo-substituted PGA allylamines 3.43–3.48 into the corresponding substituted amines were frustrated by dehalogenation, which occurred prior to debenzylation,[28b,28e] as was established by NMR spectroscopy and mass analysis. In all cases the only product isolated was 1-phenyl-1-butylamine 3.64.

To our surprise, catalytic hydrogenolysis of the ortho-bromo substituted PGA allylamine 3.46 yielded the ortho-hydroxy substituted phenylbutylamine 3.79 (Scheme 3.6).

A possible explanation for this phenomenon could be that the phenylglycine amide acts “pincer-like” as shown in Figure 3.6, in analogy to work described by van Koten et al.[32]
Chapter 3

Probably an attack of a water molecule or an acetate (followed by hydrolysis) present in the reaction mixture occurs.

![Proposed Pincer-Pd-complex](image)

**Figure 3.6 Proposed Pincer-Pd-complex.**

This idea is supported by the fact that this result could not be repeated for the *meta* - and *para*-bromo substituted PGA allylamine under the same conditions. In these cases the only product obtained was the dehalogenated product, *(R)*-1-phenyl-1-butylamine 3.62. We have not had the opportunity to further investigate this phenomenon in our laboratory.

In the case of the catalytic hydrogenation of the nitro-substituted PGA allylamines *(R,R)-3.52–3.54*, the only products obtained were the aniline-derivatives 3.84–3.86 (Scheme 3.7). The NO₂-moiety is reduced prior to debenzylation. Apparently, the electron-withdrawing effect of the cationic NH₃⁺ group of intermediate 3.83 [33] weakens the nearby N-benzylic bond, resulting in the observed regioselectivity towards 3.84–3.86.

![Regioselectivity of the nitro-substituted PGA allylamines](image)

**Scheme 3.7 Regioselectivity of the nitro-substituted PGA allylamines 3.52–3.54 under reductive conditions.** Reagents and conditions: i-propanol/H₂O/AcOH, H₂, Pd-C (10%).
A demonstration of the synthetic value of this methodology is the preparation of (R)-α-3-piperonylbutylamine ((R)-3.82). This chiral butylamine is an important building block of the human leukocyte elastase inhibitor L-694,458, which was prepared earlier with an enantiomeric excess of 94 % via a three-step reaction sequence.

When 1-naphthyl PGA allylamine 3.59 and 2-naphthyl PGA allylamine 3.60 were subjected to analogous hydrogenation conditions, we found reduction of either of the rings of the naphthyl moieties before debenzylation occurred (Scheme 3.8). No further attempts to separate half-products 3.87–3.88 or 3.89–3.90, respectively, or further debenzylation have been performed.

Scheme 3.8 Reduction of the naphthyl moiety of PGA allyl amines 3.59 and 3.60. Reagents and conditions: i-propanol/H$_2$O/AcOH, H$_2$, Pd-C (10 %).
In the catalytic hydrogenation of the hydroxy-substituted PGA allylamines 3.55–3.57 to remove the benzylic fragment of the chiral PGA auxiliary, the regioselectivity of cleavage towards the desired hydroxy-substituted butylamines 3.78–3.59 was poor in all cases ($a:b > 99:1$).

### 3.5 Conclusions

The results presented here illustrate the versatility of ($R$)-phenylglycine amide 3.1 as a readily available chiral auxiliary for the preparation of enantiomerically pure arylbutylamines starting from substituted benzaldehydes. Aldimines derived from ($R$)-PGA are obtained in excellent yield and in high purity. Allylation is readily accomplished in excellent diastereoselectivities with allylzinc bromide, prepared in situ from relatively inexpensive allyl bromide. In most cases, the chiral auxiliary is conveniently removed under reductive conditions, with high selectivities of cleavage. In the reduction of the bromo- and chloro-substituted PGA allylamines, dehalogenation is a competing reaction. The sensitivity of the nitro-group prevented the synthesis of the desired nitro-substituted phenylbutylamines using the reductive removal of the chiral auxiliary. Alternative routes to synthesize these compounds, also including the naphthylbutylamines and the hydroxy-substituted phenylbutylamines, will be described in Chapter 4.

Since ($S$)-phenylglycine amide is also available, the opposite configuration of the described products can be generated at will.

### 3.6 Experimental Section

**General information:** Reagents were purchased from Aldrich Chemical Company and were used without further purification. ($R$)-Phenylglycine amide 3.1 was provided by DSM (Geleen, The Netherlands). THF was freshly distilled from benzenephene/sodium. Zinc-wool was cut prior to use or zinc-granules (–30 + 100 mesh) were used. Optical rotations were measured at ambient temperatures using a Perkin-Elmer 241 polarimeter. Melting points were measured on a Büchi B-545 or a Mettler FP1 equipped with a Mettler FP-21 microscope, and are uncorrected. $^1$H-NMR spectra were recorded on either a Varian AS-400 spectrometer (400MHz), Varian VXR-300 spectrometer (300 MHz) or a Varian Gemini spectrometer (200 MHz). $^{13}$C-NMR spectra were recorded on a Varian Gemini 200 (50MHz). Chemical shifts are denoted in parts per million ($\delta$) and are referenced to the residual solvent. Coupling constants $J$, are denoted in Hz and splitting patterns are designated as follows: s (singlet); d (doublet); dd (double doublet); t (triplet); dt (double triplet); q (quartet); m (multiplet) and brs (broad singlet). High resolution mass spectra were recorded on a AEI-MS-902 mass spectrometer by A. Kievit.
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

Typical procedure for the synthesis of (R)-PGA-aldimines 3.2–3.23. To a suspension of (R)-phenylglycine amide 3.1 (30.0 gram, 200 mmol) in CH2Cl2 (200 mL) at ambient temperature was added 200 mmol of the substituted benzaldehyde. The reaction mixture was stirred overnight at room temperature. After removal of the CH2Cl2 and the water in vaco, the residual solid was washed with acetone/hexane (1:20) and recrystallized once from acetone/hexane (1:20). In all cases exclusively the more stable E-isomer was obtained, as judged from the appearance of only one vinyl proton in the 1H-NMR spectrum.

(2R)-2-phenyl-2-[(E)-phenylmethylidene]amino acetamide (3.2): (colorless crystals, 99% yield). m.p. 143.0–144.4 °C. 1H-NMR (200MHz, CDCl3): δ = 4.99 (s, 1H), 6.01 (brs, 1H), 7.03 (brs, 1H), 7.26–7.51 (m, 8H), 7.78–7.83 (m, 2H), 8.31 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 75.45 (d), 125.72 (d), 126.47 (d), 127.00 (d), 127.23 (d), 130.06 (d), 133.89 (s), 137.74 (s), 161.81 (d), 172.67 (s) ppm. Anal. calcd for C15H14N2O: C, 75.61 %; H, 5.92 %; N, 11.76 %. Found: C, 75.61 %; H, 6.02 %; N, 11.65 %. MS (Cl): m/z = 239 [M + H⁺].

(2R)-2-[(E)-(2-methylphenyl)methylidene]amino-2-phenyl acetamide (3.3): (colorless needles, >99 % yield). m.p. 168.0–168.4 °C. 1H-NMR (200MHz, CDCl3/[D₆]DMSO): δ = 2.53 (s, 3H), 4.99 (s, 1H), 5.91 (brs, 1H), 7.01 (brs, 1H), 7.19-7.53 (m, 8H), 7.95 (dd, J = 7.95, J = 1.71 Hz, 1H), 8.61 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D₆]DMSO): δ = 17.94 (q), 76.36 (d), 124.95 (d), 126.26 (d), 126.73 (d), 127.23 (d), 129.67 (d), 129.80 (d), 132.44 (s), 137.00 (s), 139.42 (s), 160.26 (d), 171.61 (s) ppm. Anal. calcd for C16H16N2O: C, 76.16 %; H, 6.39 %; N, 11.10 %. Found: C, 75.78 %; H, 6.37 %; N, 11.09 %. MS (Cl): m/z = 253 [M + H⁺].

(2R)-2-[(E)-(3-methylphenyl)methylidene]amino-2-phenyl acetamide (3.4): (pale yellow needles, 97 % yield). m.p. 118.0–118.9 °C. 1H-NMR (200MHz, CDCl3): δ = 2.41 (s, 3H), 4.98 (s, 1H), 5.67 (brs, 1H), 7.05 (brs, 1H), 7.26–7.64 (m, 9H), 8.21 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 18.88 (q), 74.47 (s), 123.46 (s), 124.70 (d), 125.45 (d), 126.14 (d), 126.22 (d), 126.30 (d), 129.88 (d), 132.87 (s), 136.01 (s), 136.74 (s), 161.03 (d), 171.54 (s) ppm. Anal. calcd for C16H16N2O: C, 75.16 %; H, 6.39 %; N, 11.10 %. Found: C, 75.09 %; H, 6.30 %; N, 11.11 %. MS (Cl): m/z = 253 [M + H⁺].
Chapter 3

(2R)-2-[(E)-(4-methylphenyl)methylidene]amino]-2-phenyl acetamide (3.5): (colorless prisms, >99 % yield). m.p. 153.8–154.0 °C. 1H-NMR (200MHz, CDCl3): δ = 2.40 (s, 3H), 4.96 (s, 1H), 5.68 (bs, 1H), 7.05 (bs, 1H), 7.22–7.51 (m, 8H), 7.69 (d, J = 7.57 Hz, 2H), 8.27 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 20.10 (q), 75.42 (d), 125.77 (d), 126.40 (d), 126.99 (d), 127.19 (d), 127.95 (d), 131.37 (s), 137.93 (s), 140.50 (s), 161.64 (d), 173.04 (d) ppm. Anal. calcd. for C16H16N2O: C, 75.16 %; H, 6.39 %; N, 11.10 %. Found: C, 76.06 %; H, 6.41 %; N, 11.09 %. MS (CI): m/z = 253 (M + H+).

(2R)-2-[(E)-(2-methoxyphenyl)methylidene]amino]-2-phenyl acetamide (3.6): (colorless plates, 93 % yield). m.p. 174.3–175.2 °C. 1H-NMR (200MHz, CDCl3): δ = 3.85 (s, 3H), 4.98 (s, 1H), 5.93 (bs, 1H), 6.89–7.04 (m, 3H), 7.26–7.52 (m, 6H), 8.07 (dd, J = 7.57, J = 1.71 Hz, 1H), 8.77 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 54.00 (q), 75.91 (d), 109.66 (d), 119.17 (d), 122.36 (s), 125.67 (d), 125.76 (d), 126.29 (d), 127.14 (d), 131.32 (d), 138.13 (s), 172.94 (s) ppm. Anal. calcd. for C16H16N2O2: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.54 %; H, 5.97 %; N, 10.47 %. MS (CI): m/z = 269 [M + H+].

(2R)-2-[(E)-(3-methoxyphenyl)methylidene]amino]-2-phenyl acetamide (3.7): (colorless needles, 81 % yield). m.p. 131.9–132.4 °C. 1H-NMR (200MHz, CDCl3/[D6]DMSO): δ = 3.64 (s, 3H), 4.74 (s, 1H), 6.07 (bs, 1H), 6.78–6.82 (m, 2H), 6.88 (bs, 1H), 7.04–7.27 (m, 6H), 8.07 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 55.37 (q), 76.87 (d), 112.55 (d), 117.61 (d), 126.98 (d), 127.20 (d), 127.95 (d), 128.71 (d), 129.75 (d), 136.76 (s), 139.15 (s), 159.87 (s), 163.18 (d), 174.07 (s) ppm. Anal. calcd. for C16H16N2O2: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.62 %; H, 6.09 %; N, 10.41 %. MS (CI): m/z = 269 [M + H+].

(2R)-2-[(E)-(4-methoxyphenyl)methylidene] amino]-2-phenyl acetamide (3.8): (yellow solid, 98 % yield). m.p. 92.5–93.3 °C. 1H-NMR (200MHz, CDCl3): δ = 3.85 (s, 3H), 4.94 (s, 1H), 5.81 (bs, 1H), 6.95 (d, J = 8.79 Hz, 2H), 7.06 (bs, 1H), 7.26–7.50 (m, 5H), 7.75 (d, J = 8.79 Hz, 2H), 8.23 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 53.92 (q), 75.37 (d), 112.60 (d), 125.75 (d), 126.35 (d), 126.91 (s), 127.17 (d), 128.66 (d), 138.05 (s), 160.77 (s), 160.99 (d), 173.13 (s) ppm. Anal.
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

calc. for C_{16}H_{16}N_{2}O_{2}: C, 71.62 %; H, 6.01 %; N, 10.44 %. Found: C, 71.30 %; H, 5.95 %; N, 10.44 %. MS (CI): m/z = 269 [M + H⁺].

(2R)-2-{{[(E)-(2-fluorophenyl)methylidene]amino}}-2-phenyl acetamide (3.9): (pale yellow needles, 97 % yield). m.p. 153.7–154.2 °C. ¹H-NMR (300MHz, CDCl₃/[D₆]DMSO): δ = 4.80 (s, 1H), 6.28 (brs, 1H), 6.80 (brs, 1H), 6.91 (t, J = 9.34 Hz, 1H), 7.04 (t, J = 7.33 Hz, 1H), 7.10–7.30 (m, 6H), 7.90 (t, J = 7.33 Hz, 1H), 8.43 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃/[D₆]DMSO): δ = 74.95 (d), 113.39 (d, J_C-F = 21.98 Hz), 120.52 (s, J_C-F = 9.76 Hz), 121.83 (d, J_C-F = 3.67Hz), 124.65 (d), 125.24 (d, J_C-F = 2.44 Hz), 125.35 (d), 126.11 (d), 130.66 (d, J_C-F = 9.77 Hz), 136.69 (s), 154.00 (d, J_C-F = 4.88 Hz), 159.82 (s, J_C-F = 253.92 Hz), 171.12 (s) ppm. Anal. calcd. for C_{15}H_{13}N_{2}OF: C, 70.30 %; H, 5.10 %; N, 10.90 %. Found: C, 70.40 %; H, 5.04 %; N, 10.87 %. MS (CI): m/z = 257 [M + H⁺].

(2R)-2-{{[(E)-(3-fluorophenyl)methylidene]amino}}-2-phenyl acetamide (3.10): (yellow plates, 96 % yield). m.p. 121.6–121.9 °C. ¹H-NMR (300MHz, CDCl₃/[D₆]DMSO): δ = 4.71 (s, 1H), 6.39 (brs, 1H), 6.74 (brs, 1H), 6.91 (dd, J = 8.24 Hz, 1H), 7.02–7.28 (m, 7H), 7.34 (d, J = 9.16 Hz, 1H), 8.04 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃/[D₆]DMSO): δ = 74.42 (d), 111.55 (d, J_C-F = 23.20 Hz), 115.73 (d, J_C-F = 20.76 Hz), 122.32 (d, J_C-F = 2.44 Hz), 124.64 (d), 125.27 (d), 126.05 (d), 127.73 (d, J_C-F = 7.32 Hz), 135.09 (s, J_C-F = 7.32 Hz), 136.65 (s), 159.14 (d, J_C-F = 2.44 Hz), 160.26 (s, J_C-F = 246.60 Hz), 170.92 (s) ppm. Anal. calcd. for C_{15}H_{13}N_{2}OF: C, 70.30 %; H, 5.11 %; N, 10.93 %. Found: C, 70.00 %; H, 5.23 %; N, 10.87 %. MS (CI): m/z = 257 [M + H⁺].

(2R)-2-{{[(E)-(4-fluorophenyl)methylidene]amino}}-2-phenyl acetamide (3.11): (colorless plates, 95 % yield). m.p. 119.4–120.5 °C. ¹H-NMR (200MHz, CDCl₃): δ = 4.98 (s, 1H), 5.85 (brs, 1H), 6.96 (brs, 1H), 7.09–7.50 (m, 10H), 7.77–7.84 (m, 2H), 8.28 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃): δ = 75.42 (d), 114.20 (d), 114.42 (d, J_C-F = 21.72 Hz), 125.70 (d), 126.53 (d), 127.26 (d), 128.90 (d), 128.98 (d, J_C-F = 8.75 Hz), 130.16 (s), 137.64 (s), 160.39 (d), 163.25 (s, J_C-F = 252.51 Hz), 172.55 (s) ppm. Anal. calcd. for C_{15}H_{13}N_{2}OF: C, 70.30 %; H, 5.10 %; N, 10.90 %. Found: C, 70.38 %; H, 5.14 %; N, 10.83 %. MS (CI): m/z = 257 [M + H⁺].
(2R)-2-[(E)-(2-chlorophenyl)methylidene]amino]-2-phenyl acetamide (3.12): (colorless needles, 97 % yield). m.p. 170.3–171.0 °C. 1H-NMR (200MHz, CDCl3): δ = 5.05 (s, 1H), 6.20 (brs, 1H), 6.94 (brs, 1H), 7.26–7.51 (m, 8H), 8.13 (d, J = 6.10 Hz, 1H), 8.76 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 75.84 (d), 125.52 (d), 125.68 (d), 126.66 (d), 126.87 (d), 127.28 (d), 128.66 (d), 130.87 (d), 134.53 (s), 137.85 (s), 158.65 (d), 172.42 (s) ppm. Anal. calcd. for C15H13N2OCl: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.92 %; H, 4.81 %; N, 10.31 %. MS (CI): m/z = 273 (100.0) [M + H+], 275 (34.5) [M + H+].

(2R)-2-[(E)-(3-chlorophenyl)methylidene]amino]-2-phenyl acetamide (3.13): (colorless plates, 98 % yield). m.p. 119.4–120.9 °C. 1H-NMR (300MHz, CDCl3): δ = 4.94 (s, 1H), 5.83 (brs, 1H), 6.90 (brs, 1H), 7.21–7.42 (m, 7H), 7.56 (d, J = 7.33 Hz, 1H), 7.80 (s, 1H), 8.29 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 76.90 (d), 127.08 (d), 127.16 (d), 127.77 (d), 128.08 (d), 128.78 (d), 129.99 (d), 124.94 (s), 131.46 (d), 133.07 (s), 138.86 (s), 161.88 (d), 173.64 (s) ppm. Anal. calcd. for C15H13N2OCl: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.77 %; H, 4.89 %; N, 10.36 %. MS (CI): m/z = 273 (100.0) [M + H+], 275 (36.1) [M + H+].

(2R)-2-[(E)-(4-chlorophenyl)methylidene]amino]-2-phenyl acetamide (3.14): (pale yellow plates, 95 % yield). m.p. 153.4–154.2 °C. 1H-NMR (200MHz, CDCl3/[D6]DMSO): δ = 4.83 (s, 1H), 6.28 (brs, 1H), 6.83 (brs, 1H), 7.12–7.36 (m, 7H), 7.63 (d, J = 8.55 Hz, 2H), 8.15 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 75.49 (d), 125.65 (d), 126.34 (d), 127.10 (d), 127.38 (d), 128.11 (d), 132.31 (d), 135.80 (s), 137.66 (s), 160.23 (d), 172.09 (s) ppm. Anal. calcd. for C15H13N2OCl: C, 66.05 %; H, 4.80 %; N, 10.27 %. Found: C, 65.76 %; H, 4.93 %; N, 10.25 %. MS (CI): m/z = 273 (100.0) [M + H+], 275 (34.8) [M + H+].

(2R)-2-[(E)-(2-bromophenyl)methylidene]amino]-2-phenyl acetamide (3.15): (pale yellow needles, 99 % yield). m.p. 168.3–168.7 °C. 1H-NMR (300MHz, CDCl3/[D6]DMSO): δ = 5.02 (s, 1H), 5.22 (brs, 1H), 6.88 (brs, 1H), 7.21–7.36 (m, 5H), 7.43 (d, J = 6.95 Hz, 2H), 7.54 (dd, J = 8.06 Hz, 1H), 8.07 (dd, J = 7.69, J = 1.83 Hz, 1H), 8.65 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 76.54 (d), 124.57 (s), 127.43 (d), 127.47 (d), 128.00 (d), 128.36 (d), 129.30 (d), 132.94 (d), 133.07 (d), 133.73 (s), 140.01 (s), 160.90 (d), 172.20 (s) ppm. Anal. calcd. for C15H13N2OBr: C, 56.80 %; H, 4.13 %; N, 8.83%.
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

Found: C, 56.89 %; H, 4.22 %; N, 9.08 %. MS (CI): m/z = 317 (100.0) [M + H⁺], 319 (98.3) [M + H⁺].

(2R)-2-[(E)-(3-bromophenyl)methylidene]amino]-2-phenyl acetamide (3.16): (colorless plates, 98 % yield). m.p. 135.0–136.3 °C. ¹H-NMR (300MHz, CDCl₃): δ = 4.94 (s, 1H), 5.68 (bs, 1H), 6.90 (bs, 1H), 7.20–7.33 (m, 5H), 7.41 (d, J = 6.95 Hz, 1H), 7.54 (d, J = 8.61 Hz, 1H), 7.61 (d, J = 7.69 Hz, 1H), 7.96 (s, 1H), 8.20 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃): δ = 74.45 (d), 120.54 (s), 124.73 (d), 125.06 (d), 125.62 (d), 126.32 (d), 127.28 (d), 128.28 (d), 131.89 (d), 134.81 (s), 136.42 (s), 159.29 (d), 171.36 (s) ppm. Anal. calcd. for C₁₅H₁₃N₂OBr: C, 56.80 %; H, 4.13 %; N, 8.83 %. Found: C, 56.65 %; H, 4.12 %; N, 8.82 %. MS (CI): m/z = 317 (100.0) [M + H⁺], 319 (99.3) [M + H⁺].

(2R)-2-[(E)-(4-bromophenyl)methylidene]amino]-2-phenyl acetamide (3.17): (colorless prisms, 99 % yield). m.p. 164.0–165.3 °C. ¹H-NMR (300MHz, CDCl₃/[D₆]DMSO): δ = 4.68 (s, 1H), 6.37 (bs, 1H), 6.69 (bs, 1H), 6.98–7.21 (m, 5H), 7.27 (d, J = 8.44 Hz, 2H), 7.43 (d, J = 8.44 Hz, 2H), 8.01 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃/[D₆]DMSO): δ = 74.43 (d), 123.02 (s), 124.59 (d), 125.12 (d), 125.90 (d), 127.26 (d), 129.15 (d), 131.71 (s), 136.71 (s), 159.11 (d), 170.81 (s) ppm. Anal. calcd. for C₁₅H₁₃N₂OBr: C, 56.80 %; H, 4.13 %; N, 8.83 %. Found: C, 56.70 %; H, 4.22 %; N, 8.86 %. MS (CI): m/z = 317 (97.8) [M + H⁺], 319 (100.0) [M + H⁺].

(2R)-2-[(E)-[1,1'-biphenyl]-2-ylmethylidene]amino]-2-phenyl acetamide (3.18): (white solid, 85 % yield). m.p. 152.4–152.6 °C. ¹H-NMR (300MHz, CDCl₃): δ = 4.55 (s, 1H), 6.27 (bs, 1H), 6.81 (bs, 1H), 6.97–7.92 (m, 14H), 7.95 (d, J = 6.22 Hz, 1H), 8.02 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃): δ = 76.58 (d), 127.16 (d), 127.30 (d), 127.30 (d), 127.76 (d), 128.13 (d), 129.28 (d), 129.86 (s), 130.42 (d), 132.36 (s), 138.52 (s), 139.03 (s), 143.01 (s), 161.92 (d), 173.48 (s) ppm. Anal. calcd. for C₂₁H₁₈N₂O: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.02 %; H, 5.71 %; N, 8.91 %. MS (CI): m/z = 315 [M + H⁺].
(2R)-2-[(E)-[1,1'-biphenyl]-3-ylmethylidene]amino]-2-phenyl acetamide (3.19): (white solid, 89 % yield). m.p. 145.7–146.4 °C. \( ^1\)H NMR (300MHz, CDCl\(_3\)): \( \delta = 4.99 \text{ (s, 1H)}, 6.78 \text{ (brs, 1H)}, 7.04 \text{ (brs, 1H)}, 7.24–7.49 \text{ (m, 11H)}, 7.59 \text{ (dd, } J = 6.59, J = 1.10 \text{ Hz, 2H)}, 7.66 \text{ (d, } J = 6.59 \text{ Hz, 1H)}, 7.73 \text{ (d, } J = 6.59 \text{ Hz, 1H)}, 7.99 \text{ (d, } J = 1.10 \text{ Hz, 1H}), 8.31 \text{ (s, 1H) ppm.} \)

\( ^{13}\)C NMR (50MHz, CDCl\(_3\)): \( \delta = 76.79 \text{ (d), 126.85 (d), 126.93 (d), 127.01 (d), 127.20 (d), 127.32 (d), 127.59 (d), 127.82 (d), 128.60 (d), 128.76 (d), 129.03 (d), 130.08 (d), 135.76 (s), 139.13 (s), 140.13 (s), 141.64 (s), 163.12 (d), 174.46 (s) ppm. Anal. calcd. for C\(_{21}\)H\(_{18}\)N\(_2\)O: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.29 %; H, 5.82 %; N, 8.84 %. MS (Cl): \( m/z = 315 \text{ [M + H\textsuperscript{+}]} \).

(2R)-2-[(E)-[1,1'-biphenyl]-4-ylmethylidene]amino]-2-phenyl acetamide (3.20): (white solid, 95 % yield). m.p. 176.5–177.0 °C. \( ^1\)H NMR (300MHz, CDCl\(_3\)): \( \delta = 4.96 \text{ (s, 1H)}, 5.79 \text{ (brs, 1H)}, 7.00 \text{ (brs, 1H)}, 7.24–7.25 \text{ (m, 2H)}, 7.31 \text{ (t, } J = 7.33 \text{ Hz, 2H)}, 7.36–7.46 \text{ (m, 4H)}, 7.57 \text{ (d, } J = 7.33 \text{ Hz, 2H)}, 7.62 \text{ (d, } J = 8.06 \text{ Hz, 2H)}, 7.82 \text{ (d, } J = 8.06 \text{ Hz, 2H)}, 8.30 \text{ (s, 1H) ppm.} \)

\( ^{13}\)C NMR (50MHz, CDCl\(_3\)): \( \delta = 76.68 \text{ (d), 126.58 (d), 126.80 (d), 127.33 (d), 127.46 (d), 128.15 (d), 128.43 (d), 128.50 (d), 129.75 (s), 139.08 (s), 139.52 (s), 143.54 (s), 162.17 (d), 173.49 (s) ppm. Anal. calcd. for C\(_{21}\)H\(_{18}\)N\(_2\)O: C, 80.23 %; H, 5.77 %; N, 8.91 %. Found: C, 80.35 %; H, 5.84 %; N, 8.88 %. MS (Cl): \( m/z = 315 \text{ [M + H\textsuperscript{+}]} \).

(2R)-2-[(E)-[2-nitrophenyl]methylidene]amino]-2-phenyl acetamide (3.21): (pale yellow needles, 97 % yield). m.p. 165.0–165.4 °C. \( ^1\)H-NMR (300MHz, CDCl\(_3\)/[D\(_6\)]DMSO): \( \delta = 4.90 \text{ (s, 1H)}, 6.43 \text{ (brs, 1H)}, 6.73 \text{ (brs, 1H)}, 7.14–7.23 \text{ (m, 3H)}, 7.31 \text{ (d, } J = 6.96 \text{ Hz, 2H)}, 7.48 \text{ (dt, } J = 7.46 \text{ Hz, 1H)}, 7.56 \text{ (dt, } J = 7.46 \text{ Hz, 1H)}, 7.83 \text{ (dd, } J = 7.46, J = 0.72 \text{ Hz, 1H)}, 7.92 \text{ (dd, } J = 7.46, J = 0.72 \text{ Hz, 1H)}, 8.55 \text{ (s, 1H) ppm.} \)

\( ^{13}\)C-NMR (50MHz, CDCl\(_3\)/[D\(_6\)]DMSO): \( \delta = 76.90 \text{ (d), 123.91 (d), 126.92 (d), 127.68 (d), 128.38 (d), 129.53 (s), 129.73 (d), 131.18 (d), 132.99 (d), 138.34 (s), 148.46 (s), 158.69 (d), 172.75 (s) ppm. Anal. calcd. for C\(_{15}\)H\(_{13}\)N\(_3\)O\(_3\): C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.55 %; H, 4.57 %; N, 14.78 %. MS (Cl): \( m/z = 284 \text{ [M + H\textsuperscript{+}]} \).
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(2R)-2-[(E)-(3-nitrophenyl)methylidene]amino]-2-phenyl acetamide (3.22): (pale yellow plates, 98 % yield). m.p. 174.0–174.9 °C. 1H-NMR (300MHz, CDCl3/[D6]DMSO): δ = 4.73 (s, 1H), 6.50 (brs, 1H), 6.72 (brs, 1H), 6.96–7.07 (m, 3H), 7.16–7.21 (m, 2H), 7.35 (t, J = 7.97 Hz, 1H), 7.83 (dd, J = 7.97, J = 1.81 Hz, 1H), 7.99 (dd, J = 7.97, J = 1.81 Hz, 1H), 8.13 (s, 1H), 8.38 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 75.84 (d), 121.42 (d), 124.28 (d), 125.96 (d), 126.65 (d), 127.36 (d), 128.55 (d), 133.10 (d), 135.70 (s), 137.67 (s), 147.12 (s), 159.37 (s), 171.73 (s) ppm. Anal. calcd. for C15H13N3O3: C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.50 %; H, 4.84 %; N, 14.79 %. MS (CI): m/z = 284 [M + H+].

(2R)-2-[(E)-(4-nitrophenyl)methylidene]amino]-2-phenyl acetamide (3.23): (pale yellow prisms, 92 % yield). m.p. 168.1–168.3 °C. 1H-NMR (300MHz, CDCl3): δ = 5.07 (s, 1H), 5.81 (brs, 1H), 6.86 (brs, 1H), 7.30–7.46 (m, 3H), 7.98 (d, J = 8.79 Hz, 2H), 8.30 (d, J = 8.79 Hz, 2H), 8.41 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 77.27 (d), 124.01 (d), 127.21 (d), 128.35 (d), 128.95 (d), 129.22(d), 138.47 (s), 140.57 (s), 149.51 (s), 161.21 (d), 173.06 (s) ppm. Anal. calcd. for C15H13N3O3: C, 63.60 %; H, 4.63 %; N, 14.83 %. Found: C, 63.36 %; H, 4.62 %; N, 14.83 %. MS (CI): m/z = 284 [M + H+].

(2R)-2-[(E)-(2-hydroxyphenyl)methylidene]amino]-2-phenyl acetamide (3.24): (colorless plates, 97 % yield). m.p. 147.1–148.2 °C. 1H-NMR (200MHz, CDCl3): δ = 5.05 (s, 1H), 5.73 (brs, 1H), 6.12 (brs, 1H), 6.89–7.02 (m, 2H), 7.26–7.49 (m, 7H), 8.45 (s, 1H), 12.45 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 75.70 (d), 115.56 (d), 116.96 (s), 117.84 (d), 125.74 (d), 126.98 (d), 127.58 (d), 130.81 (d), 131.92 (d), 136.23 (s), 159.06 (s), 166.33 (d), 171.04 (s) ppm. Anal. calcd. for C15H14N2O2: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.57 %; H, 5.57 %; N, 10.92 %. MS (CI): m/z = 255 [M + H+].

(2R)-2-[(E)-(3-hydroxyphenyl)methylidene]amino]-2-phenyl acetamide (3.25): (pale yellow plates, 98 % yield). m.p. 146.2–147.2 °C. 1H-NMR (300MHz, CDCl3/[D6]DMSO): δ = 4.57 (s, 1H), 6.44 (brs, 1H), 6.60 (d, J = 3.29 Hz, 1H), 6.69 (brs, 1H), 6.88–7.20 (m, 8H), 7.89 (s, 1H), 8.85 (brs, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 80.28 (d), 117.93 (d), 122.19 (d), 123.30 (d), 130.54 (d), 130.98 (d), 131.79 (d), 132.89 (d), 139.99 (s), 142.92 (s), 160.94 (s), 166.33 (d), 177.19 (s) ppm. Anal. calcd. for...
Chapter 3

C₁₅H₁₄N₂O₂: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.52 %; H, 5.57 %; N, 10.94 %.
MS (Cl): m/z = 255 [M + H⁺].

(2R)-2-[(E)-(4-hydroxyphenyl)methylidene] amino]-2-phenyl acetamide (3.26): (colorless crystals, 92 % yield).
m.p. 132.5–132.9 °C. ¹H-NMR (200MHz, CDCl₃/[D₆]DMSO): δ = 4.70 (s, 1H), 6.24 (brs, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.89 (brs, 1H), 7.05–7.28 (m, 5H), 7.46 (d, J = 8.7 Hz, 2H), 7.99 (s, 1H), 9.31 (brs, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃/[D₆]DMSO): δ = 74.34 (d), 113.07 (d), 124.39 (s), 124.60 (d), 124.93 (d), 125.80 (d), 127.55 (d), 137.34 (s), 157.98 (s), 159.76 (d), 171.54 (s) ppm. Anal. calcd for C₁₅H₁₄N₂O₂: C, 70.85 %; H, 5.55 %; N, 11.02 %. Found: C, 70.52 %; H, 5.57 %; N, 10.94 %. MS (Cl): m/z = 255 [M + H⁺].

(2R)-2-[(E)-1,3-benzodioxol-5-ylmethylidene] amino]-2-phenyl acetamide (3.27): To a suspension of (R)-phenylglycine amide (15.0 gram, 100 mmol) in CHCl₃, was added piperonal (15.0 gram, 100 mmol) and a catalytic amount of p-TolSO₃H (0.3 g). The mixture was refluxed for 2 hours. Magnesium sulphate was added and the mixture was filtered. The filtrate was evaporated and the residue was recrystallized from diethyl ether. (colorless powder, 85 % yield). m.p. 138.0–139.0 °C. ¹H-NMR (200 MHz, CDCl₃): δ = 4.94, (s, 1H), 5.86 (brs, 1H), 6.02 (s, 1H), 6.03 (s, 1H), 6.81–6.86 (m, 1H), 7.00 (brs, 1H), 7.11–7.16 (m, 1H), 7.26–7.49 (m, 6H), 8.17 (s, 1H) ppm. ¹³C-NMR (50 MHz, CDCl₃): δ = 75.24 (d), 100.14 (t), 104.97 (d), 106.64 (d), 123.94 (d), 125.79 (d), 126.39 (d), 127.20 (s), 128.78 (s), 138.03 (d), 146.56 (s), 149.04 (s), 160.79 (d), 173.19 (s) ppm. Anal. calcd for C₁₆H₁₄N₂O₃: C, 68.08 %; H, 5.00 %; N, 9.92 %. Found: C, 67.74 %; H, 5.07 %; N, 9.97 %. MS (Cl): m/z = 283 [M + H⁺].

(2R)-2-[(E)-1-naphthylmethylidene] amino]-2-phenyl acetamide (3.28): Recrystallized from acetone/hexane (1:20). (white needles, 83 % yield). m.p. 166.5–166.8 °C. ¹H-NMR (300MHz, CDCl₃/[D₆]DMSO): δ = 5.04 (s, 1H), 5.59 (brs, 1H), 6.96 (brs, 1H), 7.27 (d, J = 7.32 Hz, 1H), 7.34 (t, J = 7.32 Hz, 2H), 7.47–7.60 (m, 5H), 7.86 (d, J = 8.05 Hz, 1H), 7.92 (t, J = 6.59 Hz, 2H), 8.83 (d, J = 8.32 Hz, 1H), 8.92 (s, 1H) ppm. ¹³C-NMR (50MHz, CDCl₃/[D₆]DMSO): δ = 77.97 (d), 123.40 (d), 124.69 (d), 125.74 (d), 126.81 (d), 127.03 (d), 127.36 (d), 128.20
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(2R)-2-[(E)-2-naphthylmethylidene]amino]-2-phenylacetamide (3.29): (white solid, 91% yield) m.p. 179.6–182.0 °C. 1H-NMR (300MHz, CDCl3/[D6]DMSO): δ = 5.06 (s, 1H), 7.26-7.43 (m, 6H), 7.51 (d, J = 7.69 Hz, 1H), 7.57–7.60 (m, 2H), 7.97–8.03 (m, 3H), 8.20 (d, J = 8.42 Hz, 1H), 8.27 (s, 1H), 8.60 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3/[D6]DMSO): δ = 76.84 (d), 126.78 (d), 127.49 (d), 127.85 (d), 128.34, 128.41 (d), 128.69 (d), 130.69 (d), 132.65 (s), 133.48 (s), 134.42 (s), 140.39 (s), 162.62 (d), 172.77 (s) ppm. MS (CI): m/z = 289 [M + H+].

Typical procedure for the preparation of phenyl-substituted benzaldehydes 3.30–3.32 via a Pd–C catalyzed Suzuki coupling. A solution of sodium carbonate (17.88 gram, 168.7 mmol, 1.25 equiv.) in water (100 mL) was added carefully to a stirred suspension of 25.00 gram 2-bromobenzaldehyde (135 mmol, 1.0 equiv.), phenylboronic acid (18.13 gram, 149 mmol, 1.1 equiv.), 10 % palladium on charcoal (2.67 mmol, 2 mol %) in i–propanol (30 mL) and water (100 mL). The reaction was stirred for two days at 65 °C,[20] then it was cooled to ambient temperature and diluted with 70:15:1 i–propanol/H2O/2N NaOH solution (50 mL). The catalyst was removed by filtration under suction of the reaction mixture over Celite and the residue was washed with the same solvent mixture (3 × 50 mL). The i–propanol was removed in vacuo and the residual mixture was extracted with dichloromethane (3 × 30 mL). The aqueous phase was neutralized with 10 % HCl and extracted with dichloromethane (3 × 30 mL) and with diethyl ether (3 × 30 mL). The combined organic phases were dried over Na2SO4. Evaporation of the solvent yielded the biaryl compounds 3.30–3.32 as the only products.

[1,1′-Biphenyl]-2-carboxaldehyde (3.30): (yellow oil, 93 % yield). 1H-NMR (300MHz, CDCl3): δ = 7.31–7.34 (m, 2H), 7.38–7.46 (m, 5H), 7.58 (dt, J = 7.69, J = 1.47 Hz, 1H), 7.99 (dd, J = 7.69, J = 1.10 Hz, 1H), 9.94 (s, 1H) ppm. 13C-NMR (50MHz, CDCl3): δ = 127.64 (d), 127.99 (d), 128.30 (d), 129.97 (d), 130.65 (d), 133.44 (d), 133.55 (s), 137.58 (s), 145.81 (s), 192.28 (d) ppm. Anal. calcld for C13H10O: C, 85.69 %; H, 5.53 %. Found: C, 85.61 %; H, 5.45 %. MS (Cl): m/z = 183 [M + H+].
[1,1’-Biphenyl]-3-carboxaldehyde (3.31): (yellow oil, 94 % yield). 

$^1$H-NMR (300MHz, CDCl$_3$): \( \delta = 7.35–7.45 \) (m, 3H), \( 7.53–7.58 \) (m, 3H), 
\( 7.77–7.81 \) (m, 2H), \( 8.05 \) (s, 1H), \( 10.02 \) (s, 1H) ppm. 

$^{13}$C-NMR (50MHz, CDCl$_3$): \( \delta = 126.92 \) (d), \( 127.84 \) (d), \( 127.93 \) (d), \( 128.42 \) (d), \( 128.82 \) (d), \( 129.29 \) (d), \( 132.79 \) (d), \( 136.72 \) (s), \( 139.42 \) (s), \( 141.86 \) (s), \( 192.08 \) (d) ppm.

Anal. calcd for C$_{13}$H$_{10}$O: C, 85.69 %; H, 5.53 %. Found: C, 85.38 %; H, 5.57 %. MS (CI): \( \text{m/z} = 183 \ [M + H]^+ \).

[1,1’-Biphenyl]-4-carboxaldehyde (3.32): (white solid, 95 % yield).

$^1$H-NMR (300MHz, CDCl$_3$): \( \delta = 7.34–7.47 \) (m, 3H), \( 7.59 \) (dd, \( J = 9.05 \), \( J = 1.28 \) Hz, 2H), \( 7.70 \) (d, \( J = 9.25 \) Hz, 2H), \( 7.90 \) (d, \( J = 9.25 \) Hz, 2H), \( 10.00 \) (s, 1H) ppm. 

$^{13}$C-NMR (50MHz, CDCl$_3$): \( \delta = 127.35 \) (d), \( 127.67 \) (d), \( 128.45 \) (d), \( 129.00 \) (d), \( 130.25 \) (d), \( 135.18 \) (s), \( 139.70 \) (s), \( 147.19 \) (s), \( 191.91 \) (d) ppm.

Anal. calcd for C$_{13}$H$_{10}$O: C, 85.69 %; H, 5.53 %. Found: C, 85.50 %; H, 5.55 %. MS (CI): \( \text{m/z} = 183 \ [M + H]^+ \).

Typical procedure for the allylation of (R)-PGA imines 3.2–3.29. A solution of allylzinc bromide (1.5 equiv.) was prepared by adding allyl bromide (38.5 mL, 438 mmol) to finely cut zinc-wool (28.6 gram, 438 mmol) in THF (250 mL). The solution of allylzinc bromide was cooled to 0 °C and the imine (292 mmol) in THF (150 mL) was added batch-wise maintaining this temperature. The reaction mixture was allowed to warm to room temperature and was then poured into water (500 mL). Ethyl acetate (200 mL) was added and the mixture was stirred vigorously. After filtration over Celite, the organic phase was separated and the water layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulphate and concentrated in vacuo to furnish the homoallylamine as a colorless oil, which in almost all cases crystallized on standing. In all cases, the dr could be increased to more than 99:1 by recrystallization from acetone/hexane (1:20).

Typical procedure for the allylation of (R)-PGA imines 3.2–3.11, 3.18–3.20 and 3.28–3.29 under Barbier conditions. To a flask, fitted with a cooler and charged with THF (250 mL) was added successively the imine (292 mmol) and zinc-wool (28.6 gram, 438 mmol). To the stirred mixture was added allyl bromide (438 mmol, 38.5 mL, 1.5 equiv.) in 50 mL THF at 0 °C. The reaction mixture was allowed to warm to ambient temperature. Work-up was performed as described above.
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

**(2R)-2-phenyl-2-\{[(1R)-1-phenyl-3-butenyl]amino\} ethanamide (3.33):** (colorless crystals, >99 % yield, >99:1 dr) m.p. 89.0–90.0 °C. $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.41 (dd, $J$ = 6.96 Hz, 2H), 3.69 (t, $J$ = 6.96 Hz, 1H), 3.95 (s, 1H), 5.01−5.09 (m, 2H), 5.66−5.78 (m, 1H), 6.95 (brs, 1H), 7.05 (brs, 1H), 7.14−7.31 (m, 10H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 40.09 (t), 59.19 (d), 61.83 (d), 115.35 (t), 124.64 (d), 124.83 (d), 125.01(d), 125.59 (d), 126.16 (d), 126.35 (d), 122.53 (d), 123.93 (d), 124.49 (d), 124.77 (d), 125.62 (d), 126.35 (d), 128.12 (d), 132.50 (d), 136.90 (s), 136.89 (s), 138.26 (s), 173.67 (s) ppm. Anal. calcd for C$_{18}$H$_{20}$N$_2$O: C, 77.11 %; H, 7.19 %; N, 9.99 %. Found: C, 76.95 %; H, 7.22 %; N, 9.92 %. MS (CI): $m/z$ = 281 [M + H$^+$].

**(2R)-2-\{[(1R)-1-(2-methylphenyl)-3-butenyl]amino\}-2-phenyl ethanamide (3.34):** (colorless plates, 93 % yield, 99:1 dr) m.p. 104.3−104.6 °C. $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.25 (s, 3H), 2.31-2.37 (m, 1H), 3.89 (s, 1H), 4.01 (d, $J$ = 6.23 Hz, 1H), 5.02−5.11 (m, 2H), 5.68-5.82 (m, 1H), 6.12 (bns, 1H), 7.10−7.25 (m, 10H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 16.95 (q), 39.32 (t), 54.21 (d), 61.96 (d), 115.32 (t), 122.53 (d), 123.93 (d), 124.49 (d), 124.77 (d), 125.62 (d), 126.35 (d), 128.12 (d), 132.53 (d), 133.65 (s), 136.89 (s), 138.26 (s), 173.53 (s) ppm. Anal. calcd for C$_{19}$H$_{22}$N$_2$O·½ H$_2$O: C, 75.22 %; H, 7.64 %; N, 9.23 %. Found: C, 75.18 %; H, 7.59 %; N, 9.12 %. MS (CI): $m/z$ = 295 [M + H$^+$].

**(2R)-2-\{[(1R)-1-(3-methylphenyl)-3-butenyl]amino\}-2-phenyl ethanamide (3.35):** (yellow oil, >99 % yield, >99:1 dr) m.p. 79.0–80.3 °C. $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.11 (bns, 1H), 2.30 (s, 3H), 2.39 (d, $J$ = 6.96 Hz, 2H), 3.65 (t, $J$ = 6.96 Hz, 1H), 3.96 (s, 1H), 5.03−5.10 (m, 2H), 5.69−5.83 (m, 1H), 6.96−7.06 (m + bns, 3H), 7.11 (bns, 1H), 7.16−7.29 (m, 7H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 18.60 (q), 42.35 (t), 61.53 (d), 64.17 (d), 114.75 (t), 123.76 (d), 127.07 (d), 127.69 (d), 127.82 (d), 128.58 (d), 134.87 (d), 137.93 (s), 139.26 (s), 142.40 (s), 175.88 (s) ppm. Anal. calcd for C$_{19}$H$_{22}$N$_2$O·½ H$_2$O·0.5 H$_2$O: C, 75.22 %; H, 7.64 %; N, 9.23 %. Found: C, 75.52 %; H, 7.45 %; N, 9.35 %. MS (CI): $m/z$ = 295 [M + H$^+$].

**(2R)-2-\{[(1R)-1-(4-methylphenyl)-3-butenyl]amino\}-2-phenyl ethanamide (4.36):** (colorless oil, which crystallizes on standing, 97 % yield, >99:1 dr) m.p. 120.3–121.4 °C. $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.04 (bns, 1H), 2.30 (s, 3H), 2.38 (d, $J$ = 6.96 Hz, 2H), 3.63 (t, $J$ = 6.96 Hz, 1H), 3.95 (s, 1H), 5.01−5.08 (m, 2H), 5.67−5.81 (m, 1H), 6.12 (bns, 1H),
Chapter 3

7.05–7.11 (m, 5H), 7.16–7.24 (m, 5H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 18.60\) (q), 40.04 (t), 58.96 (d), 61.86 (d), 115.22 (t), 124.42 (d), 124.75 (d), 125.61 (d), 126.33 (d), 126.80 (d), 132.56 (d), 134.59 (s), 136.81 (s), 136.92 (s), 173.67 (s) ppm. Anal. calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O: C, 77.52 %; H, 7.53 %; N, 9.52 %. Found: C, 77.43 %; H, 7.42 %; N, 9.34 %. MS (Cl): \(m/z = 295\) [M + H\(^+\)].

(2R)-2-[(1R)-1-(2-methoxyphenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.37): (pale yellow solid, 98 % yield, >99:1 dr). m.p. 63.1–63.8 °C. \(^1\)H-NMR (300MHz, CDCl\(_3\)): \(\delta = 2.38\) (d, \(J = 6.96\) Hz, 2H), 3.62 (t, \(J = 6.96\) Hz, 1H), 3.76 (s, 3H), 3.95 (s, 1H), 5.00–5.07 (m, 2H), 5.65–5.79 (m, 2H), 5.97 (bri, 1H), 6.81 (d, \(J = 8.61\) Hz, 2H), 7.03 (bri, 1H), 7.07 (d, \(J = 8.61\) Hz, 2H), 7.14–7.26 (m, 3H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 40.22\) (t), 54.88 (q), 64.71 (d), 110.72 (d), 117.07 (t), 120.45 (d), 127.17 (d), 127.85 (d), 128.38 (d), 128.62 (d), 129.49 (s), 135.65 (d), 139.43 (s), 157.33 (s), 176.32 (s) ppm. Anal. calcd. for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_2\)·\(\frac{1}{2}\)H\(_2\)O: C, 71.45 %; H, 7.26 %; N, 8.77 %. Found: C, 71.43 %; H, 6.88 %; N, 8.76 %. MS (Cl): \(m/z = 311\) [M + H\(^+\)].

(2R)-2-[(1R)-1-(3-methoxyphenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.38): (pale yellow solid, 99 % yield, >99:1 dr). m.p. 96.6–97.2 °C. \(^1\)H-NMR (300MHz, CDCl\(_3\)): \(\delta = 2.08\) (bri, 1H), 2.38 (d, \(J = 6.96\) Hz, 1H), 3.62 (t, \(J = 6.96\) Hz, 1H), 3.73 (s, 3H), 3.97 (s, 1H), 5.02–5.09 (m, 2H), 5.68–5.81 (m, 1H), 5.98 (bri, 1H), 6.70–6.77 (m, 3H), 6.99 (bri, 1H), 7.17–7.26 (m, 6H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 42.24\) (t), 54.81 (q), 61.29 (d), 63.97 (d), 112.35 (d), 112.51 (d), 116.37 (t), 119.05 (d), 126.96 (d), 127.68 (d), 129.44 (d), 134.65 (d), 139.17 (s), 144.23 (s), 159.51 (s), 175.70 (s) ppm. Anal. calcd. for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_2\)·\(\frac{1}{2}\)H\(_2\)O: C, 71.45 %; H, 7.26 %; N, 8.77 %. Found: C, 71.45 %; H, 6.90 %; N, 8.79 %. MS (Cl): \(m/z = 311\) [M + H\(^+\)].

(2R)-2-[(1R)-1-(4-methoxyphenyl)-3-butenyl] amino]-2-phenyl ethanamide (3.39): (pale yellow solid, 99 % yield, >99:1 dr). m.p. 92.2–92.7 °C. \(^1\)H-NMR (300MHz, CDCl\(_3\)): \(\delta = 2.38\) (d, \(J = 6.96\) Hz, 2H), 3.62 (t, \(J = 6.96\) Hz, 1H), 3.76 (s, 3H), 3.95 (s, 1H), 5.00–5.07 (m, 2H), 5.65–5.79 (m, 2H), 5.97 (bri, 1H), 6.81 (d, \(J = 8.61\) Hz, 2H), 7.03 (bri, 1H), 7.07 (d, \(J = 8.61\) Hz, 2H), 7.14–7.26 (m, 3H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 42.13\) (t), 54.96 (q), 60.92 (d), 63.88 (d), 113.69 (t), 117.43 (t), 127.06 (d), 127.82 (d), 127.95 (d), 128.55 (d), 134.00 (s), 134.66 (d), 138.86 (s), 158.62 (s), 175.95 (s) ppm. Anal. calcd. for C\(_{19}\)H\(_{22}\)N\(_2\)O: C, 73.52 %; H, 6.95 %; N, 9.04 %. Found: C, 73.70 %; H, 6.95 %; N, 9.04 %. MS (Cl): \(m/z = 311\) [M + H\(^+\)].
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(2R)-2-[(1R)-1-(2-fluorophenyl)-3-butenyl]amino]-2-phenylethanamide (3.40): (pale yellow oil, which became a semi-solid on standing, >99 % yield, 98:2 dr). 1H-NMR (300MHz, CDCl3): δ = 2.20 (brs, 1H), 2.46 (dt, J = 6.96 Hz, 2H), 3.94 (s, 1H), 3.99 (t, J = 6.96 Hz, 1H), 5.02–5.09 (m, 2H), 5.69–5.83 (m, 1H), 6.95-7.08 (m, 3H), 7.13–7.28 (m, 8H) ppm. 13C-NMR (50MHz, CDCl3): δ = 40.91 (t), 56.26 (d), 64.63 (d), 115.58 (d, 2JCF = 21.97 Hz), 117.76 (t), 124.06 (d, 2JCF = 3.66 Hz), 127.02 (d), 127.91 (d), 128.34 (d, 3JCF = 4.88 Hz), 128.62 (d), 128.77 (d), 129.20 (s, 3JCF = 12.20 Hz), 134.57 (d), 139.12 (s), 160.91 (s, 1JCF = 245.38 Hz), 175.62 (s) ppm. Anal. calcd. for C18H19FN2·½H2O: C, 70.34 %; H, 6.56 %; N, 9.11 %. Found: C, 70.63 %; H, 6.17 %; N, 9.39 %. MS (CI): m/z = 299 [M + H+].

(2R)-2-[(1R)-1-(3-fluorophenyl)-3-butenyl]amino]-2-phenylethanamide (3.41): (yellow oil, which became a semi-solid on standing, 97 % yield, 98:2 dr). 1H-NMR (300MHz, CDCl3): δ = 2.20 (brs, 1H), 2.37 (d, J = 6.96 Hz, 2H), 3.68 (t, J = 6.96 Hz, 1H), 3.92 (s, 1H), 5.01–5.07 (m, 2H), 5.63–5.76 (m, 1H), 6.71 (brs, 1H), 6.87–6.95 (m, 4H), 7.15–7.26 (m, 6H) ppm. 13C-NMR (50MHz, CDCl3): δ = 42.32 (t), 61.12 (d), 64.31 (d), 113.66 (d, 2JCF = 20.8 Hz), 114.15 (d, 2JCF = 22.0 Hz), 118.04 (t), 122.70 (d, 2JCF = 2.4 Hz), 127.09 (d), 128.06 (d), 128.76 (d), 129.98 (d, 3JCF = 8.6 Hz), 134.36 (d), 139.00 (s), 145.49 (s, 1JCF = 7.3 Hz), 162.95 (s, 1JCF = 246.6 Hz), 175.57 (s) ppm. Anal. calcd. for C18H19FN2: C, 72.46 %; H, 6.42 %; N, 9.39 %. Found: C, 72.19 %; H, 6.30 %; N, 9.51 %. MS (CI): m/z = 299 [M + H+].

(2R)-2-[(1R)-1-(4-fluorophenyl)-3-butenyl]amino]-2-phenylethanamide (3.42): (yellow oil, which became a semi-solid on standing, 94 % yield, 99:1 dr). 1H-NMR (300MHz, CDCl3): δ = 2.14 (brs, 2H), 2.35 (t, J = 6.96 Hz, 2H), 3.65 (t, J = 6.95 Hz, 1H), 3.88 (s, 1H), 4.99–5.05 (m, 2H), 5.58–5.69 (m, 1H), 6.44 (brs, 1H), 6.96 (t, J = 8.70 Hz, 2H), 7.08–7.12 (m, 4H), 7.18–7.22 (m, 4H) ppm. 13C-NMR (50MHz, CDCl3): δ = 42.32 (t), 61.32 (d), 64.28 (d), 115.45 (d, 2JCF = 13.8 Hz), 118.17 (t), 127.22 (d), 128.34 (d), 128.68 (d, 2JCF = 5.7 Hz), 134.29 (d), 137.72 (s), 138.61 (s), 162.07 (s, 1JCF = 162.7 Hz), 175.72 (s) ppm. MS (CI): m/z = 299 [M + H+].
Chapter 3

(2R)-2-[[((1R)-1-(2-chlorophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.43): (pale yellow oil, which crystallizes on standing, 98% yield, 97:3 dr). m.p. 110.4–111.0 °C. 1H-NMR (300MHz, CDCl₃): δ = 2.32–2.52 (m + brs, 3H), 3.89 (s, 1H), 4.25 (t, \(J = 6.78\) Hz, 1H), 4.99–5.10 (m, 2H), 5.68–5.82 (m, 1H), 6.55 (brs, 1H), 7.04 (brs, 1H), 7.12–7.30 (m, 9H) ppm. 13C-NMR (50MHz, CDCl₃): δ = 40.72 (t), 58.20 (d), 64.49 (d), 118.12 (t), 126.96 (d), 127.17 (d), 127.70 (d), 128.12 (d), 128.40 (d), 128.79 (d), 129.90 (d), 133.76 (s), 134.40 (d), 139.35 (s), 175.64 (s) ppm. Anal. calcd. for C₁₈H₁₉ClN₂O: C, 68.67%; H, 6.08%; N, 8.90%. Found: C, 68.51%; H, 6.29%; N, 8.75%. MS (CI): \(m/z = 315\) (100.0) [M + H⁺], 317 (35.8) [M + H⁺].

(2R)-2-[[((1R)-1-(3-chlorophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.44): (white plates, 83% yield, 98:2 dr). m.p. 39.2–40.3 °C. 1H-NMR (200MHz, CDCl₃): δ = 2.15 (brs, 1H), 2.33 (d, \(J = 6.84\) Hz, 2H), 3.63 (t, \(J = 6.84\) Hz, 1H), 3.88 (s, 1H), 4.97–5.05 (m, 2H), 5.55–5.75 (m, 1H), 6.54 (brs, 1H), 6.82 (brs, 1H), 6.97–7.24 (m, 8H) ppm. 13C-NMR (50MHz, CDCl₃): δ = 42.35 (t), 61.26 (d), 64.34 (d), 118.17 (t), 125.22 (d), 127.13 (d), 127.55 (d), 128.15 (d), 128.82 (d), 129.79 (d), 134.21 (d), 134.42 (s), 138.87 (s), 144.77 (s), 175.53 (s) ppm. Anal. calcd. for C₁₈H₁₉ClN₂O: C, 68.67%; H, 6.08%; N, 8.90%. Found: C, 68.32%; H, 6.16%; N, 8.76%. MS (CI): \(m/z = 315\) (100.0) [M + H⁺], 317 (35.0) [M + H⁺].

(2R)-2-[[((1R)-1-(4-chlorophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.45): (yellow solid, 98% yield, >99:1 dr). 1H-NMR (300MHz, CDCl₃): δ = 2.33–2.47 (m + brs, 3H), 3.71 (t, \(J = 6.96\) Hz, 1H), 3.97 (s, 1H), 5.58–5.72 (m, 1H), 6.54 (brs, 1H), 6.82 (brs, 1H), 7.06–7.13 (m, 4H), 7.21–7.24 (m, 5H) ppm. 13C-NMR (50MHz, CDCl₃): δ = 42.22 (t), 61.33 (d), 64.30 (d), 118.38 (t), 127.22 (d), 128.41 (d), 128.53 (d), 128.77 (d), 129.00 (d), 133.25 (s), 124.13 (d), 138.45 (s), 140.48 (s), 175.47 (s) ppm. Anal. calcd. for C₁₈H₁₉ClN₂O: C, 68.67%; H, 6.08%; N, 8.90%. Found: C, 68.24%; H, 5.88%; N, 8.63%. MS (CI): \(m/z = 315\) (100.0) [M + H⁺], 317 (35.7) [M + H⁺].

(2R)-2-[[((1R)-1-(2-bromophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.46): (pale yellow oil, 98% yield, >99:1 dr). 1H-NMR (300MHz, CDCl₃): δ = 2.24–2.50 (m + brs, 3H), 3.88 (s, 1H), 4.24 (dd, \(J = 8.06\), \(J = 5.13\) Hz, 1H), 5.05–5.15 (m, 2H), 5.71–5.83 (m, 1H), 6.45 (brs, 1H), 6.99 (brs, 1H), 7.06 (dt, \(J = 7.51\), \(J =...
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

1.83 Hz, 1H), 7.16–7.24 (m, 7H), 7.49 (d, J = 7.69 Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 38.64 (t), 57.72 (d), 62.02 (d), 115.72 (d), 121.87 (d), 124.77 (d), 125.17 (t), 125.49 (d), 125.62 (d), 126.27 (d), 126.34 (d), 130.74 (d), 132.08 (d), 136.77 (s), 138.86 (s), 173.11 (s) ppm. MS (CI): $m/z$ = 359 (39.8) [M + H$^+$], 361 (39.4) [M + H$^+$].

(2R)-2-[(1R)-1-(3-bromophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.47): (pale yellow oil, 99 % yield, >99:1 dr). $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.27 (brs, 1H), 2.41 (dt, J = 6.96 Hz, 2H), 3.66 (t, J = 6.96 Hz, 1H), 3.94 (s, 1H), 5.02–5.13 (m, 2H), 5.61–5.74 (m, 1H), 6.26 (brs, 1H), 6.84 (brs, 1H), 7.08–7.30 (m, 8H), 7.33 (dd, J = 7.69, J = 1.1 Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 42.29 (t), 61.35 (d), 64.27 (d), 118.24 (t), 122.69 (s), 124.39 (d), 125.76 (d), 128.19 (d), 128.84 (d), 130.08 (d), 130.51 (d), 134.13 (d), 138.71 (s), 175.56 (s) ppm. Anal. calcd. for C$_{18}$H$_{19}$BrN$_2$O: C, 60.18 %; H, 5.33 %; N, 7.80 %. Found: C, 59.84 %; H, 5.21 %; N, 7.67 %. MS (CI): $m/z$ = 359 (100.0) [M + H$^+$], 361 (99.3) [M + H$^+$].

(2R)-2-[(1R)-1-(4-bromophenyl)-3-butenyl]amino]-2-phenyl ethanamide (3.48): (white solid, 95 % yield, >99:1 dr). m.p. 115.6–116.5 °C. $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 2.24 (brs, 1H), 2.31–2.48 (m, 2H), 3.68 (t, J = 6.78 Hz, 1H), 3.93 (s, 1H), 5.01–5.07 (m, 2H), 5.60–5.73 (m, 1H), 6.30 (brs, 1H), 7.03 (d, J = 8.24 Hz, 2H), 7.11–7.14 (m, 2H), 7.22–7.24 (m, 3H), 7.39 (d, J = 8.24 Hz, 2H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 42.27 (t), 61.25 (d), 64.31 (d), 118.28 (t), 121.23 (s), 127.19 (d), 128.29 (d), 128.85 (d), 128.93 (d), 131.67 (d), 134.21 (d), 138.69 (s), 141.31 (s), 175.62 (s) ppm. Anal. calcd. for C$_{18}$H$_{19}$BrN$_2$O: C, 60.18 %; H, 5.33 %; N, 7.80 %. Found: C, 59.75 %; H, 5.37 %; N, 7.72 %. MS (CI): $m/z$ = 359 (100.0) [M + H$^+$], 361 (99.3) [M + H$^+$].

(2R)-2-[(1R)-1-[1,1'-biphenyl]-2-y1-3-butenyl]amino]-2-phenyl ethanamide (3.49): (pale yellow solid, 89 % yield, >99:1 dr). $^1$H-NMR (500MHz, CDCl$_3$): $\delta$ = 2.16 (brs, 1H), 2.28–2.41 (m, 2H), 3.99 (dt, J = 5.41, J = 2.95 Hz, 1H), 4.01 (s, 1H), 4.99–5.04 (m, 2H), 5.64–5.73 (m, 1H), 5.78 (brs, 1H), 7.04 (brs, 1H), 7.23–7.25 (m, 5H), 7.29–7.41 (m, 9H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 42.22 (t), 56.89 (d), 64.64 (d), 125.26 (d), 126.73 (d), 127.03 (d), 127.17 (d), 127.79 (t), 128.00 (d), 128.08 (d), 128.74 (d), 129.23 (d), 130.07 (d), 134.96 (d), 139.44 (s), 140.18 (s), 140.68 (s), 142.53 (s), 175.25 (s) ppm. MS (CI): $m/z$ = 357 [M + H$^+$].
(2R)-2-[(1R)-1-[1,1'-biphenyl]-3-yl-3-butenyl]amino]-2-phenylethanamide (3.50): (yellow oil, 85% yield, >99:1 dr). 1H-NMR (300MHz, CDCl3): δ = 2.37 (brs, 1H), 2.50 (t, J = 6.55 Hz, 2H), 3.83 (t, J = 6.55 Hz, 1H), 4.08 (s, 1H), 5.03–5.16 (m, 2H), 5.74–5.87 (m, 1H), 7.00 (brs, 1H), 7.08 (brs, 1H), 7.19–7.24 (m, 6H), 7.33–7.45 (m, 5H), 7.51 (d, J = 7.69 Hz, 1H), 7.57 (dd, J = 7.69, J = 1.10 Hz, 2H) ppm. 13C-NMR (50MHz, CDCl3): δ = 42.34 (t), 61.61 (d), 64.17 (d), 117.72 (t), 125.65 (d), 125.80 (d), 126.02 (d), 126.91 (d), 127.09 (d), 127.17 (d), 127.85 (d), 128.60 (d), 128.81 (d), 134.63 (d), 139.05 (s), 140.64 (s), 141.22 (s), 142.97 (s), 175.88 (s) ppm. MS (CI): m/z = 357 [M + H+].

(2R)-2-[(1R)-1-[1,1'-biphenyl]-4-yl-3-butenyl]amino]-2-phenylethanamide (3.51): (pale green oil, 99% yield, >99:1 dr). 1H-NMR (300MHz, CDCl3): δ = 2.27 (brs, 1H), 2.45 (t, J = 6.59 Hz, 2H), 3.75 (t, J = 6.59 Hz, 1H), 4.02 (s, 1H), 5.04–5.12 (m, 2H), 5.73–5.84 (m, 1H), 6.75 (brs, 1H), 7.04 (brs, 1H), 7.22–7.33 (m, 8H), 7.40 (t, J = 7.32 Hz, 2H), 7.52 (d, J = 8.06 Hz, 2H), 7.56 (d, J = 7.32 Hz, 2H) ppm. 13C-NMR (50MHz, CDCl3): δ = 42.37 (t), 61.21 (d), 64.52 (d), 117.70 (t), 125.68 (d), 125.82 (d), 126.02 (d), 126.91 (d), 127.09 (d), 127.17 (d), 127.85 (d), 128.60 (d), 128.81 (d), 134.63 (d), 139.15 (s), 140.12 (s), 140.52 (s), 141.53 (s), 175.72 (s) ppm. MS (CI): m/z = 357 [M + H+].

(2R)-2-[(1R)-1-(2-nitrophenyl)-3-butenyl]amino]-2-phenylethanamide (3.52): (orange oil, >99% yield, >99:1 dr). 1H-NMR (300MHz, CDCl3/D6DMSO): δ = 2.35–2.45 (m, 1H), 2.49–2.57 (m, 1H), 2.96 (brs, 1H), 3.93 (s, 1H), 4.35 (dd, J = 5.12, J = 2.93 Hz, 1H), 5.06–5.12 (m, 2H), 5.75–5.89 (m, 1H), 7.00 (brs, 1H), 7.19–7.28 (m + brs, 5H), 7.39–7.44 (m, 2H), 7.60 (t, J = 7.33 Hz, 1H), 7.78 (d, J = 8.06 Hz, 1H), 7.86 (d, J = 7.33 Hz, 1H) ppm. 13C-NMR (50MHz, CDCl3/D6DMSO): δ = 41.98 (t), 54.94 (d), 63.10 (d), 117.78 (t), 123.69 (d), 126.94 (d), 127.19 (d), 128.09 (d), 128.84 (d), 133.01 (d), 134.71 (d), 137.90 (s), 139.96 (s), 149.93 (s), 173.75 (s) ppm. Anal. calcd. for C18H19N3O3: C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.06 %; H, 5.97 %; N, 12.72 %. MS (CI): m/z = 326 [M + H+].

(2R)-2-[(1R)-1-(3-nitrophenyl)-3-butenyl]amino]-2-phenylethanamide (3.53): (orange oil, which became a semi-solid on standing, 96% yield, >99:1 dr). 1H-NMR (200MHz, CDCl3): δ = 2.46–2.62 (m + brs, 3H), 3.92 (t, J = 6.84 Hz, 1H), 4.09 (s, 1H), 5.06–5.15 (m, 2H), 5.61–5.82 (m, 1H), 6.02 (brs, 1H), 6.06–6.19 (m, 2H), 7.00–7.08 (m, 1H), 7.18–7.44 (m, 5H), 7.51 (d, J = 8.06 Hz, 2H), 7.56 (d, J = 8.06 Hz, 2H), 7.60 (d, J = 7.33 Hz, 1H), 7.78 (d, J = 8.06 Hz, 1H), 7.86 (d, J = 7.33 Hz, 1H) ppm. 13C-NMR (50MHz, CDCl3/D6DMSO): δ = 41.98 (t), 54.94 (d), 63.10 (d), 117.78 (t), 123.69 (d), 126.94 (d), 127.19 (d), 128.09 (d), 128.84 (d), 133.01 (d), 134.71 (d), 137.90 (s), 139.96 (s), 149.93 (s), 173.75 (s) ppm. Anal. calcd. for C18H19N3O3: C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.06 %; H, 5.97 %; N, 12.72 %. MS (CI): m/z = 326 [M + H+].
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

6.57 (brs, 1H), 7.15–7.27 (m, 5H), 7.42–7.57 (m, 2H), 8.06–8.11 (m, 2H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 42.32 \) (t), 61.42 (d), 64.72(d), 118.96 (t), 122.07 (d), 122.52 (d), 127.32 (d), 128.46 (d), 129.01 (d), 133.42 (d), 135.58 (d), 138.29 (s), 144.75 (s), 148.37 (s), 174.96 (s) ppm. Anal. calcd. for C\(_{18}\)H\(_{19}\)N\(_3\)O\(_3\): C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.21 %; H, 5.80 %; N, 12.82 %.

\[\text{(2R)-2-[[1(R)-1-(4-nitrophenyl)-3-butenyl] amino]-2-phenyl ethanamide (3.54):} \]

(2R)-2-[[1(R)-1-(4-nitrophenyl)-3-butenyl] amino]-2-phenyl ethanamide (3.54): (orange oil, 93 % yield, 99:1 dr). \(^{1}\)H-NMR (300MHz, CDCl\(_3\)): \(\delta = 2.38–2.47 \) (m, 1H), 2.54–2.63 (m, 1H), 2.75 (brs, 1H), 3.93 (t, \(J = 6.23 \) Hz, 1H), 4.07 (s, 1H), 4.97–5.02 (m, 2H), 5.49–5.63 (m, 1H), 6.58 (brs, 1H), 6.77 (brs, 1H), 7.07–7.18 (m, 5H), 7.29 (d, \(J = 8.61 \) Hz, 2H), 8.03 (d, \(J = 8.61 \) Hz, 2H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)): \(\delta = 41.77 \) (t), 61.71 (d), 64.28 (d), 119.09 (t), 123.72 (d), 124.26 (d), 127.40 (d), 128.75 (d), 129.14 (d), 133.01 (d), 137.43 (s), 147.28 (s), 149.05 (s), 176.29 (s) ppm. Anal. calcd. for C\(_{18}\)H\(_{19}\)N\(_3\)O\(_3\): C, 66.45 %; H, 5.89 %; N, 12.91 %. Found: C, 66.32 %; H, 5.90 %; N, 12.88 %.

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{O}_2\text{N} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]

\[\text{HN} \quad \text{Ph} \quad \text{CONH}_2 \]

\[\text{H} \quad \text{OH} \]
ppm. Anal. calcd for C_{18}H_{20}N_{2}O_{2}·H_{2}O: C, 68.77 %; H, 7.05 %; N, 8.91 %. Found: C, 69.57 %; H, 6.51 %; N, 9.64 %. MS (CI): \textit{m/z} = 297 [M + H^+].

(2R)-2-[[1R]-1-(4-hydroxyphenyl)-3-butenyl] amino]-2-phenyl ethanamide (3.57): (colorless solid, 97 % yield, 99:1 \textit{dr}). m.p. 158.0–159.0 °C. \textit{H}-NMR (300MHz, CDCl\textsubscript{3}/[D\textsubscript{6}]DMSO): \(\delta = 2.21\) (dt, \(J = 6.96\) Hz, 2H), 3.42 (t, \(J = 6.96\) Hz, 1H), 3.81 (s, 1H), 4.83–4.90 (m, 2H), 5.50–5.61 (m, 1H), 6.01 (brs, 1H), 6.60 (d, \(J = 8.43\) Hz, 2H), 6.86 (d, \(J = 8.43\) Hz, 2H), 7.05–7.21 (m + brs, 6H), 8.55 (brs, 1H) ppm.

\textit{13C-NMR} (50MHz, CDCl\textsubscript{3}/[D\textsubscript{6}]DMSO): \(\delta = 41.20\) (t), 59.12 (d), 62.12 (d), 113.78 (d), 115.62 (t), 125.54 (d), 126.02 (d), 126.47 (d), 126.90 (d), 131.77 (s), 133.80 (d), 138.24 (s), 173.69 (s) ppm. Anal. calcd for C_{18}H_{20}N_{2}O_{2}: C, 72.95 %; H, 6.80 %; N, 9.45 %. Found: C, 72.90 %; H, 6.84 %; N, 9.45 %. MS (CI): \textit{m/z} = 297 [M + H^+].

(2R)-2-[[1R]-1-(1,3-benzodioxol-5-yl)-4-pentenyl] amino]-2-phenyl ethanamide (3.58): (colorless crystals, 81 % yield, \textgreater 99:1 \textit{dr}). m.p. 110.0–111.0 °C. \textit{H}-NMR (200 MHz, CDCl\textsubscript{3}): \(\delta = 2.34–2.39\) (dd, \(J = 6.96\) Hz, 2H), 3.60 (t, \(J = 6.96\) Hz, 1H), 3.99 (s, 1H), 5.00–5.07 (m, 2H), 5.64–5.74 (m, 2H), 5.90 (s, 2H), 6.61–6.72 (m, 3H), 6.93 (brs, 1H), 7.21–7.23 (m, 5H) ppm. \textit{13C-NMR} (50 MHz, CDCl\textsubscript{3}): \(\delta = 41.12\) (t), 59.92 (d), 69.92 (d), 99.51 (t), 105.47 (d), 106.64 (d), 116.25 (d), 119.03 (t), 125.72 (d), 126.56 (d), 127.31 (d), 133.47 (s), 135.21 (d), 137.87 (s), 145.30 (s), 146.46 (s), 174.24 (s) ppm. Anal. calcd for C_{19}H_{20}N_{2}O_{3}: C, 70.35 %; H, 6.21 %; N, 8.64 %. Found: C, 70.28 %; H, 6.33 %; N, 8.59 %. MS (CI): \textit{m/z} = 325 [M + H^+].

(2R)-2-[[1R]-1-(1-naphthyl)-3-butenyl]amino]-2-phenyl ethanamide (3.59): (pale yellow solid, which was recrystallized from acetone/hexane, 95 % yield, \textgreater 99:1 \textit{dr}) m.p. 103.0–103.8 °C. \textit{H}-NMR (300MHz, CDCl\textsubscript{3}/[D\textsubscript{6}]DMSO): \(\delta = 2.41–2.51\) (m + brs, 2H), 2.59–2.67 (m, 1H), 3.99 (s, 1H), 4.64 (dt, \(J = 7.69, J = 5.13\) Hz, 1H), 5.05–5.15 (m, 2H), 5.75–5.89 (m, 1H), 6.34 (brs, 1H), 6.96 (brs, 1H), 7.21–7.24 (m, 5H), 7.35–7.50 (m, 4H), 7.74 (d, \(J = 7.32\) Hz, 1H), 7.85 (d, \(J = 7.69\) Hz, 1H), 8.11 (d, \(J = 7.32\) Hz, 1H) ppm. \textit{13C-NMR} (50MHz, CDCl\textsubscript{3}/[D\textsubscript{6}]DMSO): \(\delta = 41.69\) (t), 63.93 (d), 117.64 (t), 122.43 (d), 122.82 (d), 125.02 (d), 125.28 (d), 125.83 (d), 126.93 (d), 127.43 (d), 127.67 (d), 128.43 (d), 128.66 (d), 131.31 (s), 133.63 (s), 134.63 (d), 137.97 (s), 139.03 (s), 175.77 (s) ppm. Anal. calcd for C_{22}H_{22}N_{2}O: C, 79.97 %; H, 6.71 %; N, 8.48 %. Found: C, 79.72 %; H, 6.76 %; N, 8.58 %. MS (CI): \textit{m/z} = 331 [M+1].
Chapter 3

Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(2R)-2-\{(1R)-1-(2-naphthyl)-4-pentenyl\}[amino]-2-phenyl ethanamide (3.60): (pale yellow solid, which was recrystallized from acetone/hexane, 73 % yield, >99:1 d.r) m.p. 105.8–108.0 °C. \(^{1}\)H-NMR (300MHz, CDCl\(_3\), \[^{1}D_{2}\]DMSO): \(\delta = 2.45\) (brs, 1H), 2.49 (t, \(J = 6.78 \) Hz, 2H), 3.86 (t, \(J = 6.78 \) Hz, 1H), 3.99 (s, 1H), 5.03–5.12 (m, 2H), 5.71–5.84 (m, 1H), 6.43 (brs, 1H), 6.99 (brs, 1H), 7.16–7.23 (m, 5H), 7.31 (d, \(J = 8.42 \) Hz, 1H), 7.41–7.48 (m, 2H), 7.63 (s, 1H), 7.75–7.81 (m, 3H) ppm. \(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta = 42.24\) (t), 61.45 (d), 64.07 (d), 117.61 (t), 124.32 (d), 125.59 (d), 125.99 (d), 126.10 (d), 127.03 (d), 127.43 (d), 127.58 (d), 127.75 (d), 128.30 (d), 128.53 (d), 132.67 (s), 133.01 (s), 134.71 (d), 139.20 (d), 139.86 (s), 175.74 (s) ppm. Anal. calcd for C\(_{22}\)H\(_{22}\)N\(_{2}\)O: C, 79.97 %; H, 6.71 %; N, 8.48 %. Found: C, 80.08 %; H, 6.75 %; N, 8.35 %. MS (Cl): m/z = 331 [M+1].

2-\{(2-methyl-1-phenyl-3-butenyl)amino\}-2-phenyl ethanamide (3.61): A solution of crotylzinc bromide (1.5 equiv.) was prepared by adding crotylbromide (62.6 mmol, 6.4 mL) to finely cut zinc-wool (62.6 mmol, 4.0 g) in THF (50 mL). The solution of crotylzinc bromide was cooled to room temperature and was added dropwise to a solution of 3.2 (41.7 mmol, 10.0 gram) in THF (30 mL) at 0°C. Workup was performed as described above. Evaporation of the solvent provided a mixture of isomers ((R,R,R):(R,R,S)=1:1.3), (orange oil, 98 % yield). \(^{1}\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 0.78\) (d, \(J = 6.59 \) Hz, 3H), 0.92 (d, \(J = 6.95 \) Hz, 3H), 2.31–2.41 (m, 1H), 2.41–2.65 (m, 1H), 3.36 (d, \(J = 8.42 \) Hz, 1H), 3.70 (d, \(J = 5.13 \) Hz, 1H), 3.89 (s, 1H), 3.97 (s, 1H), 4.46–5.58 (m, 1H), 4.98–5.15 (m, 2 × 2H), 5.72–5.84 (m, 1H), 6.44 (brs, 1H), 6.69 (brs, 1H), 6.99–7.29 (m, 2 × 10H) ppm. \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta = 15.0\) (q), 16.3 (q), 42.2 (d), 43.2 (d), 62.5 (d), 62.6 (d), 64.9 (d), 65.3 (d), 114.6 (t), 115.3 (t), 125.8 (d), 126.1 (d), 126.2 (d), 126.3 (d), 126.7 (d), 126.8 (d), 127.0 (d), 127.3 (d), 127.6 (d), 136.9 (s), 137.5 (d), 138.0 (d), 139.7 (s), 139.9 (s), 175.2 (s), 175.5 (s) ppm.

(2R)-2-\{(1R)-3-methyl-1-phenyl-3-butenyl\}[amino]-2-phenyl ethanamide (3.62): A solution of methallylzinc bromide (1.5 equiv.) was prepared by adding methallylbromide (62.6 mmol, 6.30 mL) to finely cut zinc-wool (4.0 gram, 62.6 mmol) in THF (50 mL). The solution of methallylzinc bromide was cooled to room temperature and was added dropwise to a solution of 3.2 (10 gram, 41.7 mmol) in THF (30 mL) at 0°C. The reaction mixture was warmed to room temperature and was poured into water (100 mL). Ethylacetate (30 mL) was added and the mixture was stirred vigorously. After filtration through a glass filter, the organic phase was separated and the water layer was extracted
with ethylacetate (2 x 30 mL). The combined organic phase was dried on magnesium sulphate and the ethylacetate was evaporated furnishing 31 that can be crystallized from diethyl ether (colorless solid, 98 % yield). m.p. 104.0–109.0 °C. 1H-NMR (200 MHz, CDCl₃): δ = 1.72 (s, 3H), 2.27–2.43 (m, 2H), 3.75–3.80 (m, 1H), 4.00 (s, 1H), 4.73 (s, 1H), 4.80 (s, 1H), 5.76 (brs, 1H), 6.95 (brs, 1H), 7.14–7.30 (m, 10H) ppm. 13C-NMR (50 MHz, CDCl₃): δ = 21.1 (q), 44.9 (t), 62.5 (d), 63.7 (d), 112.4 (t), 125.7 (d), 125.9 (d), 126.2 (d), 126.8 (d), 127.2 (d), 127.4 (d), 136.9 (d), 140.5 (s), 140.7 (s), 175.1 (s) ppm.

Typical Procedure for the Catalytic Hydrogenation of (R)-PGA Homoallylamines 3.24–3.33 and 3.40. The PGA homoallylamine (15.0 mmol) was dissolved in i-propanol (75 mL). Water (75 mL), acetic acid (100 mL), and Pd–C (10 %) (0.6 gram, cat.) were added successively. After two vacuum/H₂ cycles to remove air from the reaction flask, the stirred mixture of the substrate was hydrogenated at ambient pressure of H₂ at room temperature for 5 days. After filtration, the i-propanol was evaporated under reduced pressure. The residue was diluted with water (50 mL) and while acidic, the reaction mixture was washed once with diethyl ether to remove any by-products. The aqueous phase was brought to pH 10 with 10 % NaOH and was extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layers were washed with brine and dried over sodium sulphate. After evaporation of the dichloromethane, pentane was added to the residue. Filtration through a glass filter yielded crystalline phenyl acetamide as the by-product. Evaporation of the pentane of the filtrate yielded the primary substituted (R)-arylbutylamine as an oil.

(1R)-1-phenylbutylamine (3.64): (colorless oil which crystallizes into white needles on standing, 70 % yield). [α]D²⁷ = +18.3 (c = 1.06, CHCl₃). 1H-NMR (300MHz, CDCl₃): δ = 0.86 (t, 3H, J = 7.32 Hz), 1.14–1.37 (m, 2H), 1.58 (brs, 2H), 1.50–1.77 (m, 2H), 3.84 (t, J = 6.96 Hz, 1H), 7.17–7.31 (m, 5H) ppm. 13C-NMR (50MHz, CDCl₃): δ = 13.87 (q), 19.58 (t), 41.72 (t), 55.84 (d), 126.14 (d), 126.64 (d), 128.22 (d), 146.67 (s) ppm. Anal. calcd for C₁₀H₁₅N: C, 80.48 %; H, 10.13 %; N, 9.39 %. Found: C, 79.95 %; H, 10.01 %; N, 9.21 %. MS (CI): m/z = 150 [M + H⁺].

(1R)-1-(2-methylphenyl)butylamine (3.65): (yellow oil, 95 % yield). [α]D²⁵ = +32.8 (c = 2.08, CHCl₃). 1H-NMR (300MHz, CDCl₃): δ = 0.89 (t, J = 7.33 Hz, 3H), 1.20–1.44 (m, 2H), 1.52 (brs, 2H), 1.46–1.63 (m, 2H), 2.31 (s, 3H), 4.14 (t, J = 6.59 Hz, 1H), 7.09 (dd, J = 4.39 Hz, 2H), 7.14–7.22 (m, 1H), 7.37 (d, J = 7.33 Hz, 1H) ppm. 13C-NMR (50MHz, CDCl₃): δ = 13.81 (q), 19.55 (t), 21.21 (q), 41.58 (t), 55.73 (d), 123.12 (d), 126.76 (d), 127.31 (d), 128.03 (d), 137.67 (s), 146.53 (s) ppm. Anal. calcd. for C₁₁H₁₇N: C, 80.48 %; H, 10.13 %; N, 8.58 %. Found: C, 80.69 %; H, 10.62 %; N, 8.46 %. MS (CI): m/z = 164 [M + H⁺].
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(1R)-1-(3-methylphenyl)butylamine (3.66): (yellow oil, 92 % yield). $\left[\alpha\right]_D^{25} = +13.59$ (c = 1.13, CHCl$_3$). $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 0.88 (t, $J$ = 7.33 Hz, 3H), 1.18–1.38 (m, 2H), 1.44 (brs, 2H), 1.56–1.64 (m, 2H), 2.31 (s, 3H), 3.80 (t, $J$ = 6.96 Hz, 1H), 7.00 (d, $J$ = 7.51 Hz, 1H), 7.05 (d, $J$ = 7.51 Hz, 1H), 7.09 (s, 1H), 7.17 (t, $J$ = 7.51 Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 13.79 (q), 19.53 (t), 21.19 (q), 41.60 (t), 55.71 (d), 123.10 (d), 126.73 (d), 127.25 (d), 127.99 (d), 137.61 (s), 146.55 (s) ppm. MS (CI): $m/z$ = 164 [M + H$^+$].

(1R)-1-(4-methylphenyl)butylamine (3.67): (yellow oil, which crystallizes on standing, 91 % yield). m.p. 55.0–56.5 °C. $\left[\alpha\right]_D^{25} = +19.34$ (c = 2.23, CHCl$_3$). $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 0.85 (t, $J$ = 7.32 Hz, 3H), 1.13–1.34 (m, 2H), 1.70 (brs, 2H), 1.75–1.50 (m, 2H), 2.26 (s, 3H), 3.77 (t, $J$ = 6.96 Hz, 1H), 7.06 (d, $J$ = 8.06 Hz, 2H), 7.13 (d, $J$ = 8.06 Hz, 2H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 13.56 (q), 19.27 (t), 20.50 (q), 41.35 (t), 55.19 (d), 125.73 (d), 128.55 (d), 135.68 (s), 143.24 (s) ppm. MS (CI): $m/z$ = 164 [M + H$^+$].

(1R)-1-(2-methoxyphenyl)butylamine (3.68): (colorless oil, which crystallizes on standing, 87 % yield). m.p. 56.8–57.6 °C. $\left[\alpha\right]_D^{25} = +4.49$ (c = 3.45, CHCl$_3$). $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 0.88 (t, $J$ = 7.32 Hz, 3H), 1.15–1.39 (m, 2H), 1.53–1.90 (m + brs, 3H), 3.76 (s, 3H), 4.10 (t, $J$ = 6.95 Hz, 1H), 6.80 (d, $J$ = 8.06 Hz, 1H), 6.87 (t, $J$ = 7.33 Hz, 1H), 7.15 (dt, $J$ = 8.06, $J$ = 1.83 Hz, 1H), 7.21 (dd, $J$ = 7.33, $J$ = 1.83 Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 13.98 (q), 19.87 (t), 39.66 (t), 50.49 (d), 55.07 (q), 110.39 (d), 120.47 (d), 126.59 (d), 127.36 (d), 134.71 (s), 156.75 (s) ppm. Anal. calcd for C$_{11}$H$_{17}$NO: C, 73.70 %; H, 9.56 %; N, 7.81 %. Found: C, 73.40 %; H, 9.96 %; N, 7.54 %. MS (CI): $m/z$ = 180 [M + H$^+$].

(1R)-1-(3-methoxyphenyl)butylamine (3.69): (pale yellow oil, 89 % yield). $\left[\alpha\right]_D^{25} = +16.4$ (c = 3.68, CHCl$_3$). $^1$H-NMR (300MHz, CDCl$_3$): $\delta$ = 0.80 (t, $J$ = 7.32 Hz, 3H), 1.12–1.29 (m, 2H), 1.39 (brs, 2H), 1.49–1.56 (m, 2H), 3.68 (s, 3H), 3.74 (t, $J$ = 6.96 Hz, 1H), 6.66 (dd, $J$ = 8.06, $J$ = 1.84 Hz, 1H), 6.77–6.79 (m, 2H), 7.12 (t, $J$ = 8.06 Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta$ = 13.70 (q), 19.38 (t), 41.49 (t), 54.72 (d), 55.67 (q), 111.61 (d), 111.69 (d), 118.33 (d), 128.99 (d), 148.33 (s), 159.37 (s) ppm. Anal. calcd for C$_{11}$H$_{17}$NO: C, 73.70 %; H, 9.56 %; N, 7.81 %. Found: C, 73.59 %; H, 9.54 %; N, 7.81 %. MS (CI): $m/z$ = 180 [M + H$^+$].

89

Chapter 3
Chapter 3

(1R)-1-(4-methoxyphenyl)butylamine (3.70): (yellow oil, 89% yield). \([\alpha]_{D}^{27} = +12.57\) (c = 7.39, CHCl3). \(^1\)H-NMR (300MHz, CDCl3): \(\delta = 0.87\) (t, \(J = 7.08\) Hz, 3H), 1.14–1.36 (m, 2H), 1.44 (brs, 2H), 1.50–1.69 (m, 2H), 3.76 (s, 3H), 3.82 (t, \(J = 6.84\) Hz, 1H), 6.84 (d, \(J = 8.79\) Hz, 2H), 7.20 (d, \(J = 8.79\) Hz, 2H) ppm. \(^1\)C-NMR (50MHz, CDCl3): \(\delta = 13.86\) (q), 19.60 (t), 41.77 (t), 55.18 (d), 113.53 (d), 127.14 (d), 138.78 (s), 158.25 (s) ppm. Anal. calcd. for C11H17NO: C, 73.70%; H, 9.56%; N, 7.81%. Found: C, 73.58%; H, 9.47%; N, 7.67%. MS (CI): \(m/z = 180\) [M+H^+].

(1R)-1-(2-fluorophenyl)butylamine (3.71): (pale yellow oil, 58% yield). \([\alpha]_{D}^{27} = +9.39\) (c = 3.21, CHCl3). \(^1\)H-NMR (300MHz, CDCl3): \(\delta = 0.82\) (t, \(J = 7.32\) Hz, 3H), 1.11–1.36 (m, 2H), 1.45 (brs, 2H), 1.56–1.63 (m, 2H), 4.10 (t, \(J = 6.96\) Hz, 1H), 6.87–6.93 (m, 1H), 7.04 (dt, \(J = 7.32, J = 1.10\) Hz, 1H), 6.98–7.13 (m, 1H), 7.27 ppm. \(^1\)C-NMR (50MHz, CDCl3): \(\delta = 13.72\) (q), 19.47 (t), 40.35 (t), 49.49 (d), 115.14 (d, \(J_{C-F} = 23.20\) Hz), 123.94 (d, \(J_{C-F} = 3.66\) Hz), 127.30 (d, \(J_{C-F} = 8.49\) Hz), 127.78 (d, \(J_{C-F} = 8.45\) Hz), 133.39 (s, \(J_{C-F} = 14.65\) Hz), 160.27 (s, \(J_{C-F} = 294.16\) Hz) ppm. MS (CI): \(m/z = 168\) [M+H^+].

(1R)-1-(3-fluorophenyl)butylamine (3.72): (pale yellow oil, 79% yield). \([\alpha]_{D}^{25} = +9.39\) (c = 3.21, CHCl3). \(^1\)H-NMR (300MHz, CDCl3): \(\delta = 0.80\) (t, \(J = 7.03\) Hz, 3H), 1.06–1.32 (m, 2H), 1.41 (brs, 2H), 1.44–1.57 (m, 2H), 3.77 (t, \(J = 6.96\) Hz, 1H), 6.79 (dt, \(J = 8.06\) Hz, 1H), 6.95 (dt, \(J = 8.32\) Hz, 2H), 7.15 (dd, \(J = 13.92, J = 8.06\) Hz, 1H) ppm. \(^1\)C-NMR (50MHz, CDCl3): \(\delta = 11.40\) (q), 17.03 (t), 39.24 (t), 53.06 (d), 110.56 (d, \(J_{C-F} = 21.97\) Hz), 110.99 (d, \(J_{C-F} = 21.97\) Hz), 119.46 (d, \(J_{C-F} = 2.44\) Hz), 127.21 (d, \(J_{C-F} = 7.33\) Hz), 147.11 (s, \(J_{C-F} = 6.10\) Hz), 160.46 (s, \(J_{C-F} = 245.38\) Hz) ppm. MS (CI): \(m/z = 168\) [M+H^+].

(1R)-1-(4-fluorophenyl)butylamine (3.73): (pale yellow oil, 70% yield). \(^1\)H-NMR (300MHz, CDCl3): \(\delta = 0.83\) (t, \(J = 7.33\) Hz, 3H), 1.08–1.32 (m, 2H), 1.50 (brs, 2H), 1.45–1.61 (m, 2H), 3.81 (t, \(J = 6.96\) Hz, 1H), 6.92 (dd, \(J = 8.79, J_{H-F} = 8.42\) Hz, 2H), 7.20 (dd, \(J = 5.49, J_{H-F} = 8.42\) Hz, 2H) ppm. \(^1\)C-NMR (50MHz, CDCl3): \(\delta = 13.76\) (q), 19.45 (t), 41.73 (t), 55.12 (d), 114.86 (d, \(J_{C-F} = 20.98\) Hz), 127.61 (d, \(J_{C-F} = 7.63\) Hz), 142.20 (s, \(J_{C-F} = 3.60\) Hz), 161.51 (s, \(J_{C-F} = 244.53\) Hz) ppm. MS (CI): \(m/z = 168\) [M+H^+].
Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide

(1R)-1-[(1,1'-biphenyl)-2-yl]butylamine (3.74): (yellow oil, 87 % yield). $[\alpha]_D^{25} = +16.17$ (c = 2.18, CHCl$_3$). $^1$H-NMR (300MHz, CDCl$_3$): $\delta = 0.73$ (t, $J = 7.32$ Hz, 3H), 0.98–1.28 (m, 2H), 1.47 (brs, 2H), 1.52–1.63 (m, 2H), 1.63 (d, $J = 6.95$ Hz, 1H), 7.16 (d, $J = 7.69$ Hz, 1H), 7.20–7.33 (m, 5H), 7.36 (d, $J = 6.96$ Hz, 2H), 7.52 (d, $J = 7.69$ Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta = 13.80$ (q), 19.63 (t), 41.49 (t), 50.69 (d), 125.47 (d), 126.15 (d), 126.77 (d), 127.80 (d), 129.24 (d), 129.79 (d), 141.21 (s), 141.38 (s), 144.07 (s) ppm. MS (CI): $m/z = 226$ [M + H$^+$].

(1R)-1-(2-phenol)butylamine (3.79): The ortho-bromo-substituted PGA allylamine 3.46 (15.0 mmol) was dissolved in i-propanol (75 mL). Water (75 mL), acetic acid (100 mL), and Pd-C (10 %) (0.6 gram, cat.) were added successively. After two vacuum/H$_2$ cycles to remove air from the reaction flask, the mixture was hydrogenated at ambient pressure of H$_2$ and room temperature and stirred for 7 days. After filtration, the i-propanol was evaporated under reduced pressure. The residue was diluted with water (50 mL) and carefully adjusted to pH 7. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic phase was washed with brine, dried over sodium sulphate and filtered. After evaporation of the dichloromethane, pentane was added to the residue. Filtration through a glass filter yielded crystalline phenyl acetamide. Evaporation of the pentane of the filtrate yields 3.79 as a colorless oil, which solidifies on standing (83 % yield). $^1$H-NMR (300MHz, CDCl$_3$): $\delta = 0.87$ (t, $J = 7.33$ Hz, 3H), 1.08–1.49 (m, 3H), 1.52–1.79 (m, 2H), 4.05 (t, $J = 6.96$ Hz, 1H), 6.70 (t, $J = 7.33$ Hz, 1H), 5.68 (d, $J = 7.33$ Hz, 1H), 6.86 (d, $J = 7.33$ Hz), 7.08 (dt, $J = 7.33$, $J = 1.46$ Hz, 1H) ppm. $^{13}$C-NMR (50MHz, CDCl$_3$): $\delta = 13.86$ (q), 19.48 (t), 38.90 (t), 56.54 (d), 117.17 (d), 118.71 (d), 127.13 (s), 128.08 (d), 128.36 (d), 157.60 (s) ppm. Anal. calcd. for C$_{10}$H$_{15}$NO·½H$_2$O: C, 68.93 %; H, 9.26 %; N, 8.04 %. Found: C, 68.85 %; H, 9.35 %; N, 7.90 %. MS (CI): $m/z = 166$ [M + H$^+$].

(1R)-1-(1,3-benzodioxol-5-yl)butylamine (3.82): (colorless oil, 88 % yield). $[\alpha]_D^{25} = +10.9$ (c = 1.01, CHCl$_3$). $^1$H-NMR (200MHz, CDCl$_3$): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.18–1.26 (m, 2H), 1.58–1.63 (m, 2H), 3.80 (m, 1H), 5.92 (s, 2H), 6.74 (s, 2H), 6.83 (s, 1H) ppm. $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta = 12.44$ (q), 18.15 (t), 40.30 (t), 54.22 (d), 99.22 (t), 105.00 (d), 106.32 (d), 117.85 (d), 139.35, 144.67 (s), 146.08 (s) ppm. MS (CI): $m/z = 194$ [M + H$^+$].
3.7 References


Diastereoselective Allylation of Imines derived from (R)-Phenylglycine Amide


Chapter 3


[19] The ee of the chiral auxiliary is determined after acidic hydrolysis of imines 3.33, 3.39 and 3.54, and found to be unchanged.

[20] Temperatures higher than 65 °C lead to considerable amounts of the Cannizzaro products.


[25] In all cases the addition of 1.5 equiv. of *pre-formed* allylmagnesium bromide to a solution of the imine in THF at ambient temperature failed to produce the adducts.

[26] Crotyl bromide was used consisting of a cis/trans (1:13) mixture (85 %) and 3-bromo-1-butene (15 %).

[27] X-ray data for 3.57 is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.; fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk, and was allocated the deposition number CCDC 154389.


[30] Compound 3.75 was obtained by a NaBH₄ reduction (4 equiv.) of imine 3.2 in refluxing methanol.


The occurrence of intermediate 3.83 was confirmed by mass analysis, $^1$H- and $^{13}$C-NMR.

IUPAC-name of (R)-α-3-piperonylbutylamine 3.82: (1R)-1-(1,3-benzodioxol-5-yl)butylamine.

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