Asymmetric Strecker Synthesis via a Crystallization-Induced Asymmetric Transformation using a Chiral Auxiliary

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Introduction

The synthesis of L-amino acids is important because they are used extensively in pharmaceuticals, agrochemicals, and as chiral ligands. The Strecker reaction is historically one of the most versatile ways to synthesize L-amino acids, but this method yields only 50% of a single enantiomer. Higher yields can be achieved by using chiral auxiliaries, but auxiliaries are often high in cost and low in availability.

Overview. To solve these problems, we present the first example of a crystallization-induced asymmetric transformation using optically pure (R)-phenylglycine amide 1 as a chiral auxiliary. The (R,S)-3 diastereomer precipitates out of solution in 76-93% yield with a diastereomeric ratio (dr) > 99/1.

Experimental Section (cont.)

The synthesis of amino nitrile (R,S)-3.

\[
\begin{align*}
\text{Ph} & \quad \text{NaCN, HOAc} \\
\text{NH} & \quad \text{solvent, time, temp} \\
\text{CN} & \quad \text{Ph}
\end{align*}
\]

- A stirred suspension of 1 (400 mmol) in H₂O (400 mL) was added to pivaldehyde 2 (419 mmol) and stirred for 30 min.
- NaN₃/HOAc was added at 23–28 °C. The mixture was heated to 70 °C and stirred for 24 h.
- After cooling to 30 °C, the product was filtered, washed (500 mL H₂O), dried, and analyzed by ¹H NMR.
- (R,S)-3 formed as a colorless solid (92.4%, dr > 99/1).

Results (cont.)

- Optimization trials (Table 1) showed that water at 70 °C for 24 h produced (R,S)-3 in 93% yield (dr > 99/1).

<table>
<thead>
<tr>
<th>Solvent(s)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>dr (R,S)-3</th>
<th>dr (R,R)-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH/H₂O</td>
<td>rt</td>
<td>20</td>
<td>80</td>
<td>84</td>
<td>86/12</td>
</tr>
<tr>
<td>2-PrOH</td>
<td>rt</td>
<td>20</td>
<td>80</td>
<td>86/12</td>
<td></td>
</tr>
<tr>
<td>2-PrOH/H₂O</td>
<td>rt</td>
<td>20</td>
<td>69</td>
<td>81/18</td>
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<tr>
<td>H₂O</td>
<td>55</td>
<td>24</td>
<td>84</td>
<td>86/4</td>
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<tr>
<td>H₂O</td>
<td>65</td>
<td>24</td>
<td>84</td>
<td>96/4</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

A proposed mechanism is shown in Scheme 1. The re-facial attack of CN⁻ to the intermediate imine 3 appears to be preferred, forming (R,S)-3. (R,S)-3 is less soluble and precipitates out of solution; (R,R)-3 is more soluble and epimerizes in solution via the imine 4.

Conclusions

(R)-phenylglycine amide 1 is an excellent chiral auxiliary in the asymmetric Strecker reaction of pivaldehyde 2. In water at 70 °C, the (R,S)-3 product was isolated in 93% yield and dr > 99/1. Work is underway to convert (R,S)-3 to (S)-tart-leucine and thereby complete the asymmetric Strecker reaction.