Enantioselective Catalytic Hydrogenation of 
α-Acetylaminoacrylic Acids

Wolfgang Bergstein, Axel Kleemann, Jürgen Martens
Degussa, Fachbereich Forschung Chemie Organisch, Postfach 1345,
D-6450 Hanau 1, Germany

Substantial quantities of optically active amino acids are used in 
the drug industry and as building blocks for peptide synthesis. 
In recent years, the increased interest in new sources of nutri-
tional protein has made the asymmetric synthesis of amino acids 
an area of vital concern.

Homogeneous asymmetric hydrogenation\textsuperscript{1-3} of prochiral α-acyl-
aminoacrylic acids\textsuperscript{6} with hydrogen and soluble chiral rhodium complexes furnished N-acyl-α-amino acids in noteworthy 
optical yields. The enantiomeric enrichment in such reactions 
has proven to be particularly high when chiral ditertiary phosphines 
are used as ligands which form rigid five-membered chela-
tate rings\textsuperscript{6} \textsuperscript{11}.

The development of methods for the synthesis of chiral ditertiary phosphines forming rigid five-membered chelate rings using 
inexpensive optically active natural products as reaction com-
ponents is an attractive objective. We describe here the synthesis of
the two optically active ditertiary bis-phosphine ligands \textsuperscript{4a} and 
\textsuperscript{4b} from (S)-phenylalanine and (S)-valine, respectively.
The optical yields obtained in the reduction 6-7 are good and excellent. The reaction sequence has been carried out using separate catalysts and all by-products are carried out under an atmosphere.

The formation of the chiral rhodium complexes 5a and 5b containing ligands 4a and 4b

Table. Asymmetric Hydrogenation of (Z)-2-Acylamino-2-alkenoic Acids (6) at 20 °C to give N-Acyl-α-amino Acids (7), using separately prepared Catalyst 5a or in situ prepared Catalyst 5b

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Catalyst [(R)-S]</th>
<th>Ratio 6 : catalyst</th>
<th>Solvent</th>
<th>H₂ Pressure [bar]</th>
<th>Product 7</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>[α]D₀ of pure 7</th>
<th>Optical yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃</td>
<td>5a</td>
<td>1550</td>
<td>ethanol/benzene 2/1</td>
<td>14.8</td>
<td>(S)-Ac-Ala-OH</td>
<td>99</td>
<td>123°</td>
<td>122-123°</td>
<td>[α]D₀: -56.0° (c 2, H₂O)</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>5b</td>
<td>1276</td>
<td>ethanol</td>
<td>1</td>
<td>(S)-Ac-Ala-OH</td>
<td>99</td>
<td>120-122°</td>
<td>[α]D₀: -99.1° (c 2, H₂O)</td>
<td>88.6</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>5a</td>
<td>1800</td>
<td>ethanol/benzene 2/1</td>
<td>20</td>
<td>(S)-Ac-Phe-OH</td>
<td>99</td>
<td>173°</td>
<td>170-171°</td>
<td>[α]D₀: +46.8° (c 1, 95% ethanol)</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>5a</td>
<td>6800</td>
<td>ethanol</td>
<td>15</td>
<td>(S)-Ac-Phe-OH</td>
<td>99</td>
<td>172°</td>
<td>[α]D₀: +43.5° (c 1, 95% ethanol)</td>
<td>92.0</td>
</tr>
<tr>
<td>C₄H₅</td>
<td>5b</td>
<td>680</td>
<td></td>
<td>ethanol</td>
<td>20</td>
<td>(S)-Az-Phe-OH</td>
<td>98</td>
<td>142°</td>
<td>142-143°</td>
<td>[α]D₀: -38.3° (c 1, methanol)</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>5a</td>
<td>1440</td>
<td>ethanol</td>
<td>21</td>
<td>(S)-Ac-Tyr(3)-Ac-OH</td>
<td>99</td>
<td>172°</td>
<td>170-20</td>
<td>[α]D₀: +49.4° (c 1, methanol)</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>5b</td>
<td>910</td>
<td>ethanol/benzene 2/1</td>
<td>14.9</td>
<td>(S)-Ac-Phe-(3-OCH₃, 4-OAc)-OH</td>
<td>99</td>
<td>171°</td>
<td>[α]D₀: +36.8° (c 1, methanol)</td>
<td>90.4</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>5a</td>
<td>540</td>
<td>ethanol</td>
<td>6.6</td>
<td>(S)-Ac-Phe-(3-OCH₃, 4-OAc)-OH</td>
<td>98</td>
<td>[α]D₀: +35.5° (c 1, methanol)</td>
<td>88.0</td>
<td></td>
</tr>
</tbody>
</table>

* Yield of isolated product.
* Reaction performed with 0.89 g of 6 in 10 ml of solvent.
* [α]D₀: +40.7° (c 1, methanol).
lowed by the addition of dichloromethane (200 ml). The organic layer is separated, washed with dilute hydrochloric acid (3 x 50 ml) to remove pyridine, then with water (3 x 50 ml). It is dried with sodium sulfate and evaporated to give 3 as a crystalline product: yield: 91 g (99%); [α]D202 = −26.6° (c 1, chloroform).

(CiH4O3S)2, calc. C 59.96 H 5.25 S 13.92
(406.6)
found 59.75 5.38 14.04

(R)-1,2-Bis[diphenylphosphino]-3-phenylpropane [4; (R)-Phos-Phos]: A solution of (S)-1,2-ditosyloxy-3-phenylpropane (3. 257 g, 0.0547 mol) in tetrahydrofuran (100 ml) is added to a stirred solution of sodium diphosphinophosphate (37.8 g, 0.181 mol) in tetrahydrofuran (450 ml) at −10 °C to −15 °C, and stirring is continued for 480 min. The precipitate is filtered off and washed with tetrahydrofuran. The combined filtrates are stirred with water (200 ml), most of the tetrahydrofuran is removed at reduced pressure, and the resultant oily aqeeous residue is extracted with ether (3 x 100 ml). The organic extract is dried with sodium sulfate and the solvent removed at reduced pressure to give 4a: yield: 25.2 g (92%); [α]D20 = +45.9° (c 1.4 chloroform).

C16H16P2, calc. C 81.13 H 6.19 P 12.68
(488.5)
found 81.08 6.26 12.56

Rhodium Complex 5a: (R)-1,2-Bis[diphenylphosphino]-3-phenylpropane (4a; 1.52 g, 3.1 mmol) is stirred with bis[cyclooctadiene]rhodium chloride[RhCODCl2] (0.75 g, 0.0031 mol) and sodium tetrafluoroborate (0.75 g, 0.0068 mol) in methanol. The resultant precipitate is isolated by suction; yield: 1.2 g (73%); yellow crystalline product.

C12H10BF3P2Rh, calc. C 62.62 H 5.38
(786.4)
found 62.36 5.79

(R)-1,2-Bis[diphenylphosphino]-3-methylbutane [4b, (R)-Val-Phos]19:
This ligand is prepared starting from (S)-valine following the procedure described for the synthesis of ligand 4a; yield: 48%; m.p. 77.8 °C; [α]D20 = +98.1° (c 0.626, chloroform).

C12H18P2, calc. C 79.07 H 6.87 P 14.06
(440.5)
found 78.89 7.00 14.12

Asymmetric Hydrogenation of 2-Acylamino-2-alkenoic Acids (6) to N-Acyl-α-amino Acids (7): Typical Procedure:
The 2-acylamino-2-alkenoic acid (6; 0.128 mol) is dissolved either in deoxygenated ethanol (50 ml) or in a 2:1 ethanol/ benzene (60 ml). The catalyst (for amount, see Table) is added as such or prepared in situ by mixing (R)-Val-Phos (4b; 0.1814 g, 0.00041 mol) and bis[cyclooctadiene]rhodium chloride (0.1 g, 0.00041 mol) and adding this mixture to the solution. The reaction mixture is transferred into an autoclave and then hydrogenated under a hydrogen pressure of 1-21 bar (see Table) for ~2 h.

After the theoretical amount of hydrogen has been taken up, the hydrogenation is stopped and the mixture shaken with an acidic ion-exchange resin to remove the catalyst. The mixture is then filtered and the clear filtrate evaporated to dryness at reduced pressure to leave the acid 7 in a purity of generally 98.5-99% (as determined by H.L.C. analysis). The products may be further purified by recrystallization from suitable solvents.

Received: April 14, 1980
(Revised form: May 30, 1980)

12. For the synthesis of this catalyst, see: J. Organomet. Chem. in prepa-