The Ru(II)-catalyzed hydrogenation of α-amino-β-keto esters as their hydrochloride salts affords preparation of the corresponding anti α-amino-β-hydroxy esters under mild conditions with high diastereoselectivities and enantioselectivities via dynamic kinetic resolution.

Ruthenium-promoted hydrogenation via Dynamic Kinetic Resolution (DKR) has turned out to be an elegant and powerful method of simultaneously controlling two adjacent stereogenic centers with high levels of selectivity in a single chemical operation. This reaction was first reported independently by Noyori et al. 1 and Genet et al. 2 in 1989 for the synthesis of threonine. The hydrogenation of α-acetamido-β-keto esters and more generally of non-cyclic α-amido-β-keto esters 4 with Ru(II)-catalysts affords, under optimized conditions, the corresponding syn β-hydroxy esters with excellent diastereoisomeric and enantiomeric excesses. The stereochemical course of the hydrogenation reaction is highly dependent on the nature of the configurationally labile group borne at the α-position of the β-keto ester. α-Chloro-5 or cyclic α-alkyl-1,2-anti-β-keto esters were reduced to the anti α-substituted β-hydroxy esters. The first example of an efficient DKR of an α-alkyl-β-keto ester was observed by our group during preliminary studies on Dolastatin 10. 6 The anti β-hydroxy-α-methyl ester was isolated with high stereoselectivity after hydrogenation under mild conditions of the β-keto ester derived from the hydrochloride salt of (S)-proline.

Inspired by these encouraging results and as part of our continuing interest in stereoselective hydrogenation, we set out to continue our interest in stereoselective hydrogenation, we set out to synthesize one specific isomer of medically important compounds. For substrate 3a, the hydrochloride salt was formed by adding hydrochloric acid to the intermediate α-tert-butoxycarbonyl-β-keto ester.

Following our previous results obtained with the β-keto-α-methyl ester derived from (S)-proline hydrochloride, 7 the preliminary hydrogenation reactions were run in an alcoholic solvent (ROH) with compounds 3c and 3d as representative precursors of 3-hydroxyoctanolic and dihydroxypropionic acid, respectively. The trials were performed under mild conditions: 12 bar of hydrogen at 50 °C for 24 h (Table 1, entries 1 and 4), in the presence of the in situ generated chiral catalyst 11 [RuMeO–BIPHEP]Br 2. The anti configuration of the resulting α-amino-β-hydroxy ester, isolated with good yield after reprotention of the crude hydrogenated product with benzoic anhydride, was determined by comparison with the well-known syn products and authentic samples. 12 The main results are summarized in Table 1.

For substrate 3d, an excellent diastereoselectivity (98%) and a significant level of enantioselectivity (87%) were observed in ethanol (entry 1). These results remained unchanged regardless of the hydrogen pressure (50 or 100 bar, entries 2 and 3). The hydrogenation proceeded smoothly with high diastereoselectivity (93%) even with the long-chain substrate 3c though the enantioselectivity was poor (39%, entry 4). Higher hydrogen pressure (50
Table 1 Hydrogenation reaction of compounds 3c and 3d in alcoholic solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent (R’OH)</th>
<th>%Yield</th>
<th>d.e. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3d R=Pr</td>
<td>EtOH</td>
<td>12</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>3d R=Pr</td>
<td>EtOH</td>
<td>50</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>3d R=Pr</td>
<td>EtOH 100%</td>
<td>50</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>3c R=C2H5</td>
<td>MeOH</td>
<td>50</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>3c R=C2H5</td>
<td>MeOH</td>
<td>50</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

**Notes and references**


