Asymmetric Hydrogenation of Indolizines and 1,2,3-Triazolo[1,5-a]pyridines

**Significance:** The indolizidine motif, which is characterized by fused six- and five-membered rings containing a bridgehead nitrogen atom, is widely distributed as a core structure in bioactive alkaloids. The authors reported the direct asymmetric hydrogenation of the challenging N-bridged heterocycles, represented by substituted indolizine and 1,2,3-triazolo[1,5-a]pyridine derivatives. High enantioselectivities and yields were achieved by the application of a chiral ruthenium–NHC complex for the completely regioselective and asymmetric hydrogenation. Additionally, access to indolizidine scaffolds is demonstrated by the efficient synthesis of (−)-monomorine via hydrogenation of the remaining pyrrole ring under Jefford’s conditions.

**Comment:** The high regioselectivity is explained by the unusual aromatic structure of the fused N-bridged heterocycle, where the six-membered ring reacts more like a reactive diene rather than a pyridine, furnishing partially hydrogenated products in high yields. Interestingly, the chiral induction is influenced strongly by the substitution pattern on the substrate. In the case of alkyl groups on the 3- and 5-position, high ee values are observed. A similar trend was obtained for substrates substituted with aryl or ester groups on the 2-position. Alkyl groups on the 6-, 7- and 8-position caused no reaction or diminished enantioselectivities. The potential of the procedure was demonstrated by the short two-step synthesis of an alkaloid in an overall yield of 98%.

**Selected examples:**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>X</th>
<th>Y</th>
<th>[Ru] (5 mol%)</th>
<th>ligand (10 mol%)</th>
<th>KOt-Bu (15 mol%)</th>
<th>H2 (100 bar)</th>
<th>16–24 h, r.t.</th>
<th>13 (+ 2) examples up to 99% yield er up to 97:3 (0.3 mmol scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>5-Me, 5-Et, 5-Pr, 5-C5H11, 5-(CH2)2Ph, 5-C11H23, 6-Me, 7-Me, 8-Me</td>
<td>R1</td>
<td>R2</td>
<td>[Ru] N N BF4– ligand</td>
<td></td>
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<tr>
<td>R2</td>
<td>H, 2-CO2Et, 2-Ph, 2-(4-FC6H4), 2-(4-MeOC6H4), 3-Bu</td>
<td>X = Y = CR2, N</td>
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</tbody>
</table>

99% yield er = 97:3 99% yield er = 91:9 99% yield er = 95:5 no reaction 99% yield er = 75:25 99% yield er = 62:38

99% yield er = 83:17 99% yield er = 78:22 99% yield er = 83:17

99% yield dr = 91:5:2:1

ent-monomorine

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