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%.

SYNFACTS Contributors: Mark Lautens, Marcel Sickert
Synfacts 2013, 9(11), 1183 Published online: 18.10.2013
DOI: 10.1055/s-0033-1339948; Reg-No.: L12413SF