Asymmetric Hydrogenation

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Ruthenium–NHC-Catalyzed Asymmetric Hydrogenation of Indolizines: Access to Indolizidine Alkaloids**

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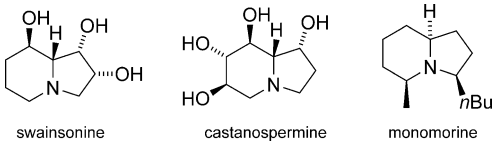
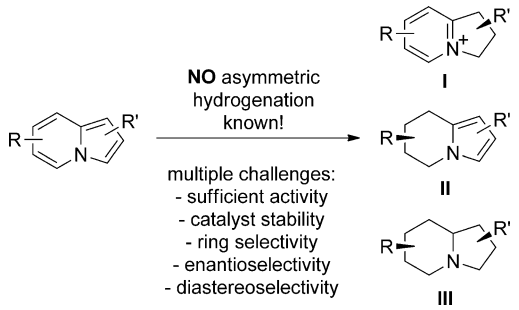
Dedicated to the Bayer company on the occasion of its 150th anniversary

Indolizidine alkaloids constitute a very important class of natural products. These metabolites derived from lysine can be isolated from diverse sources, like fungi, bacteria, higher plants, invertebrates, and vertebrates. Their core structure is characterized by fused six- and five-membered rings, with a bridgehead nitrogen atom, and is found in 25–30% of all naturally occurring alkaloids.[1] The most important types of indolizidines are plant-derived polyhydroxylated indolizidines, like swainsonine[2] and castanospermine,[3] which are glycosidase inhibitors with activity against HIV, as well as alkylindolizidines, like monomorine (**3**),[4] which is isolated from ants (*Monomorium pharaonis*) and from the skin of amphibians (*Melanophryniscus stelzneri*), and is believed to serve in their defense against predators (Scheme 1).



Scheme 1. Selected indolizidine natural products.

Due to their diverse activities and profusion in nature, interest in indolizidine alkaloids extends far beyond natural product chemistry and has been the motivation behind the development of new synthetic methods. Thus, countless reports concerning the synthesis of such bicyclic systems in racemic or asymmetric fashion can be found in literature.[5] Surprisingly, even though the hydrogenation of the corresponding aromatic indolizine precursor seems to be a straightforward approach, it has hardly been used. Only a few reports using heterogeneous catalysis have been published, starting from partially saturated precursors through the reduction of the remaining pyrrole ring.[6] The fact that asymmetric hydrogenation starting from indolizines has not been accomplished yet (Scheme 2) reflects the difficulty of the selective



Scheme 2. Untapped potential of the asymmetric hydrogenation of indolizines.

reduction of this substrate class, arising from the nitrogen atom in the bridgehead position of the fused pyridine and pyrrole units. In the last years, the asymmetric hydrogenation of aromatic and heteroaromatic compounds has emerged as one of the most promising methods for the asymmetric synthesis of saturated or partially saturated cyclic molecules.[7] Mostly N-heterocycles like (iso)quinolines,[8] quinoxalines,[9] and indoles[10] have been successfully hydrogenated to the corresponding tetrahydro(iso)quinolines, tetrahydroquinoxalines and indolines, respectively. Recently, the asymmetric hydrogenation of challenging N-free substrates like benzofurans,[11] benzothiophenes, and thiophenes[12] as well as carbocyclic aromatic rings[13] has also been achieved. Key to success in these latter cases was the development of robust and more selective catalysts. In the last three years we have developed a new catalyst for the asymmetric hydrogenation of (hetero)aromatics.[11c,d,12,13] This system consists of a well-defined chiral ruthenium N-heterocyclic carbene[14] (NHC) complex, which can react under mild conditions with high levels of regio- and enantioselectivity. In our program focused on the application of this new catalytic system to the hydrogenation of more challenging substrates, we envisioned that it could be applied to the yet unsolved asymmetric hydrogenation of indolizines, to obtain the corresponding

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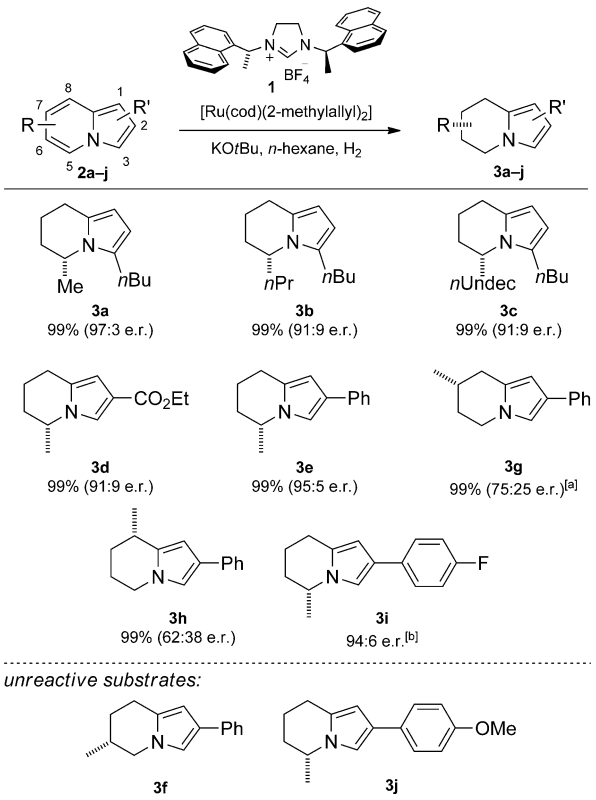
indolizidines and consequently provide easy access to many types of natural products (Scheme 1). Herein we report, to the best of our knowledge, the first high-yielding and completely regioselective and asymmetric hydrogenation of challenging N-bridged heterocycles, represented by substituted indolizine and 1,2,3-triazolo[1,5-*a*]pyridine derivatives.

Our study started with the hydrogenation of 3-butyl-5-methylindolizine (**2a**) as a model substrate, with the ultimate goal of a direct synthesis of the alkaloid monomorine. When we applied our catalytic system to this aromatic precursor under 60 bar of hydrogen and at 80 °C, we observed that the six-membered ring was selectively reduced, giving **3a** with 81 % yield and 94:6 e.r. Even though the fully reduced indolizidine core **III** (Scheme 2) was not observed, we envisioned that the completely hydrogenated system could be obtained by a second hydrogenation using a heterogeneous catalyst (vide infra). The reaction reached full conversion and a good e.r. of 97:3 was obtained when the reaction was performed at room temperature and 100 bar of hydrogen.[15] Solvent screening revealed that *n*-hexane is best suited for this reaction. Other solvents such as toluene and *t*-amyl alcohol are also suitable, but yields and e.r. values were not highly reproducible. The use of an unsaturated NHC derivative led to similar results in conversion and regioselectivity but a significant decrease in the enantiomeric ratio. Other NHCs were tested, but in all cases either no reaction occurred or only the racemic product was formed.

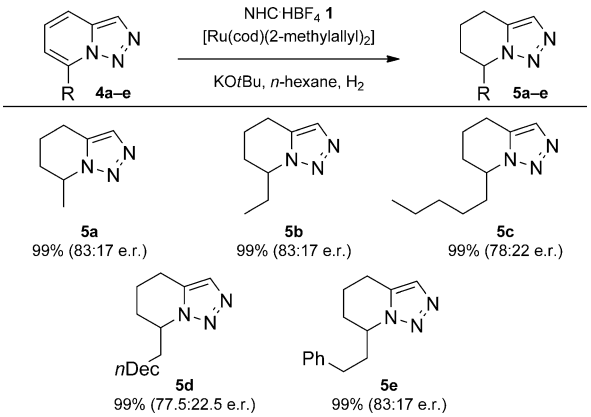
Having established the optimized reaction conditions, we tested a variety of indolizines. As shown in Scheme 3, when we increased the length of the substituent in position 5, the enantiomeric ratio decreased slightly, while perfect conversion to the desired product (**3b**,**c**) was maintained. The reaction tolerates the presence of esters. Thus, **2d** reacts smoothly, yielding **3d** with full conversion and 91:9 e.r. without any reduction of the ester. In order to investigate the effect of the position of the substituent in the six-membered ring, we prepared a series of methyl-2-phenylindolizines (**2e**–**h**). With these substrates, the best e.r. was obtained for 5-methyl-2-phenylindolizine (**2e**). Surprisingly, 6-methyl-2-phenylindolizine (**2f**) did not react, even when we applied harsher conditions like higher pressure, temperature, and catalyst loading. In the case of the 7-methyl-2-phenylindolizine (**2g**) we obtained full conversion to the desired product only when the temperature was increased to 40 °C, albeit the e.r. was only 75:25. Changing the position of the methyl group to position 8 (**2h**) led to a drop in the enantioselectivity to 62:38, but perfect regioselectivity and complete conversion were still maintained. We also observed that the electronics of the phenyl ring in position 2 play a key role for the hydrogenation.[16] While the unsubstituted phenyl ring of substrate **2e** has no adverse effects on the hydrogenation in terms of reactivity and enantioselectivity, when a fluorine atom is present in the *para* position (**2i**), partial over-reduction of the substrate was observed, yielding a mixture of products impossible to separate for characterization. However, HPLC analysis of the mixture indicates that enantiomeric ratio (94:6) is almost the same as that observed for **3e**. In contrast, the *p*-methoxyphenyl-substituted indolizine **2j** gave no hydrogenation product; the starting material was completely recovered, even under higher pressure, temperature, and catalyst loading.



Scheme 3. Scope for the asymmetric hydrogenation of indolizines **2a**–**j**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol; cod = cyclooctadiene), KO*t*Bu (0.045 mmol), and **1** (0.03 mmol) were stirred at 70 °C in *n*-hexane (2 mL) for 12 h, after which the reaction mixture was added to **2a–j** (0.30 mmol), and hydrogenation was performed at 100 bar and room temperature for 24 h. Yields of isolated products are given. Enantiomeric ratios were determined by HPLC on a chiral stationary phase. The absolute configuration of **3a** was determined by hydrogenation to monomorine (see Scheme 5). [a] Reaction carried out at 100 bar and 40 °C. [b] **3i** was obtained accompanied with over-reduction products and was impossible to purify for characterization.

We also explored the asymmetric hydrogenation of 1,2,3-triazolo-[1,5-*a*]pyridines (Scheme 4). This core can be found in many biologically active compounds. The selective reduction of 1,2,3-triazolo-[1,5-*a*]pyridines could be an easy way to access new and more active derivatives, and therefore is highly interesting for medicinal chemistry research.[17] The hydrogenation of different alkyl-substituted substrates proceeded with perfect conversion and moderate enantioselectivity (**4a**–**d**). We noticed that the enantiomeric ratio decreased slightly when the length of the alkyl chain was increased, while perfect conversion to the desired product was maintained. The reaction of 7-phenethyl-1,2,3-triazolo[1,5-*a*]pyridine (**4e**) also gave the desired product with an e.r. value of 83:17.

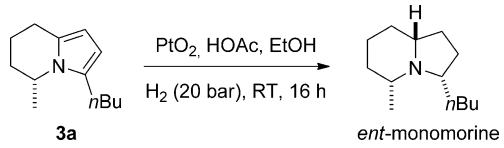
In the transformation presented here the regioselectivity of the hydrogenation reaction can be explained by the unusual aromatic structure of the fused N-bridged heterocycle: While the five-membered ring still corresponds to an intact pyrrole unit, the six-membered ring resembles a diene



Scheme 4. Scope of the asymmetric hydrogenation of 1,2,3-triazolo-[1,5-*a*]pyridines **4a–e**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO*t*Bu (0.045 mmol), and **1** (0.03 mmol) were stirred at 70 °C in *n*-hexane (2 mL) for 12 h, after which the reaction mixture was added to **4a–e** (0.30 mmol), and hydrogenation was performed at 100 bar and room temperature for 16 h. Yields of isolated products are given. Enantiomeric ratios were determined by HPLC on a chiral stationary phase.

rather than a pyridine, which makes the latter less aromatic and therefore less stable and more amenable to hydrogenation. In addition, N-substituted pyridines are generally more susceptible to hydrogenation reactions.

Finally, we explored the hydrogenation of the remaining pyrrole ring to access the corresponding indolizidines, using an achiral heterogeneous catalyst. In particular, we explored the hydrogenation of **3a** to obtain the natural product monomorine. After testing several heterogeneous catalysts, we obtained best results by following a procedure by Jefford et al., which provided the desired indolizidine in 99% yield and a ratio of 91:5:2:1 for different diastereomers.[18] After chromatographic separation and comparison with the reported data, we could confirm that the major product is (−)-monomorine, the enantiomer of the natural product (Scheme 5).[19] Due to the unfavorable steric interaction between the surface of the PtO_2 catalyst and the methyl group in the 5-position, the opposite face of the molecule approaches the catalyst surface preferably.



Scheme 5. Synthesis of unnatural (−)-monomorine.

In conclusion, we have successfully applied a chiral ruthenium–NHC complex for the high-yielding and completely regioselective and asymmetric hydrogenation of substituted indolizines and 1,2,3-triazolo-[1,5-*a*]pyridines. We also applied this methodology for the synthesis of a natural product in a straightforward manner. We achieved the synthesis of the alkaloid (−)-monomorine in only two steps from the corresponding indolizine precursor after the reduction of the pyrrole ring. We hope that our results will trigger increased interest in the asymmetric hydrogenation of these heteroaromatic substrates. Further studies focusing on catalyst characterization, mechanistic aspects of this reaction, and the hydrogenation of other challenging substrates are ongoing.

Experimental Section

General procedure: A flame-dried screw-capped tube equipped with magnetic stirring bar was charged with [Ru(cod)(2-methylallyl)$_2$] (4.8 mg, 0.015 mmol, 0.05 equiv), imidazolium salt **1** (14.1 mg, 0.03 mmol, 0.1 equiv), and dry KO*t*Bu (5.0 mg, 0.045 mmol, 0.15 equiv) in a glove box. The mixture was suspended in *n*-hexane (2 mL) and stirred at 70 °C for 12 h. Then the mixture was transferred under argon to a glass vial containing the corresponding indolizine **2a–j** and 1,2,3-triazolo-[1,5-*a*]pyridine **4a–e** (0.3 mmol, 1.0 equiv), respectively, and a magnetic stirring bar. The glass vial was placed in a 150 mL stainless-steel reactor. The autoclave was pressurized/depressurized with hydrogen gas three times before the indicated pressure was adjusted. The reaction mixture was stirred at 25 °C or 40 °C for 16 h. After the autoclave was depressurized, the crude mixture was filtered through a plug of silica using a mixture of *n*-pentane/EtOAc (9:1), yielding the corresponding, analytically pure compound **3a–j** and **5a–e**, respectively. The enantiomeric ratio of all compounds was determined by HPLC on a chiral stationary phase.

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