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Pd-Catalyzed Asymmetric Hydrogenation of Unprotected Indoles Activated by Brønsted Acids
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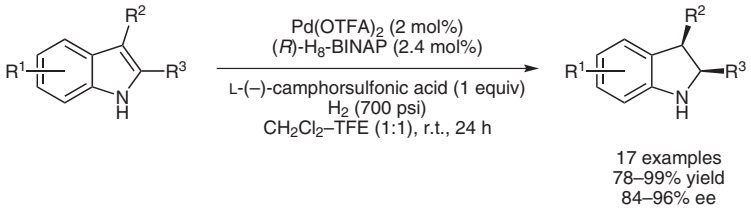
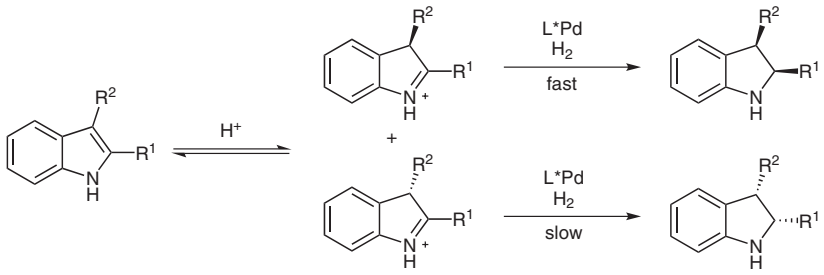
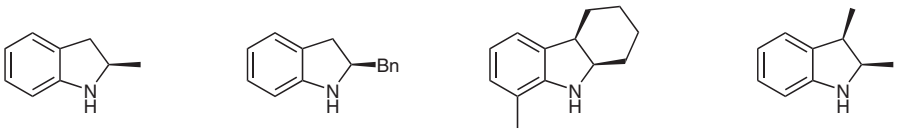
Asymmetric Hydrogenation of Unprotected Indoles



Proposed mechanism:



Selected examples:



Significance: Chiral indolines are often found in natural products and other biologically active molecules. Many groups have explored asymmetric hydrogenation of indoles as a method to access this family. While success has been achieved with reduction of protected indoles, the use of unprotected substrates would provide a more direct route. The authors present the first example of a general, enantioselective hydrogenation of unprotected indoles to synthesize chiral indolines. Key to this finding was the use of a palladium catalyst under a high pressure of hydrogen gas in the presence of one equivalent of L-(–)-camphorsulfonic acid (L-CSA).

Comment: Both 2-substituted and 2,3-disubstituted indolines can be accessed with high yields and enantioselectivity. Deuterium-labeling studies suggest an initial protonation of indole followed by hydrogenation of the iminium salt. If the indole is unsubstituted at the 3-position, the hydrogenation is the enantio-discriminating step. If it is 3-substituted, reversible protonation forms a chiral imine, which undergoes dynamic kinetic resolution. Only alkyl substituents were shown to work, with no examples of 2- or 3-aryl indoles. Interestingly, L-CSA gave higher yields and enantioselectivities than D-CSA, suggesting a possible matched/mismatched effect in the chiral iminium salt.

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