S. LI, X. LIU, C.-H. TUNG, L. LIU* (SHANDONG UNIVERSITY, JINAN, P. R. OF CHINA)
Late-Stage Chemo- and Enantioselective Oxidation of Indoles to C3- Monosubstituted Oxindoles
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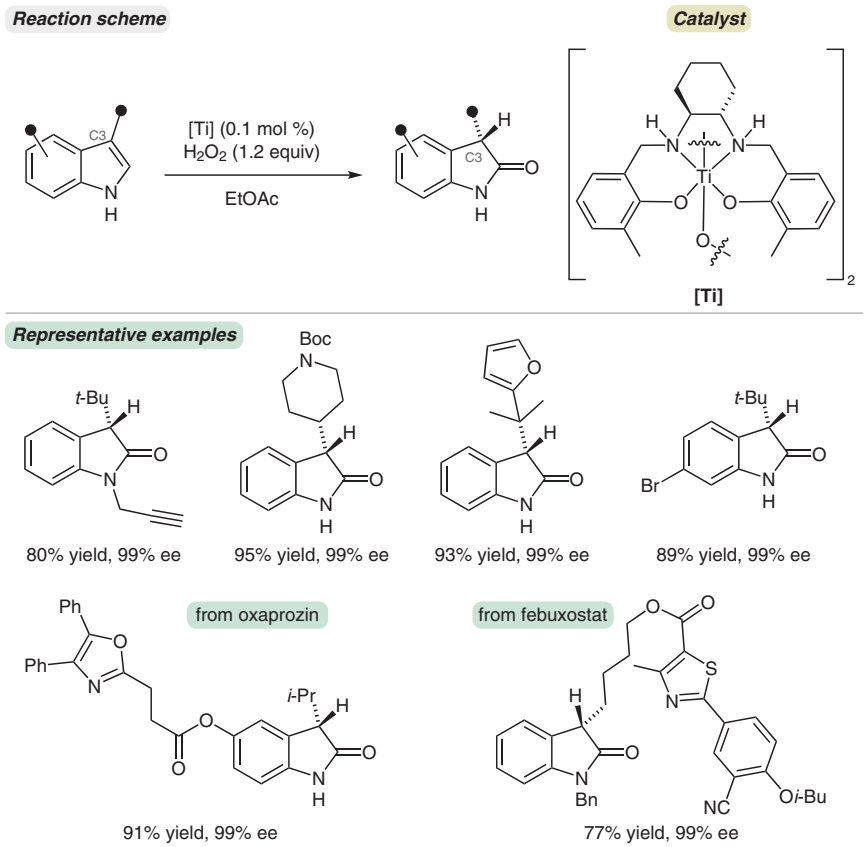
Enantioselective Indole C3 Oxidation



Significance: Indole cores are found in a range of natural products and pharmaceuticals featuring a wide variety of bioactivities. Substitution of the 2- and 3-positions can dramatically affect the properties of the indole. While oxindoles with 3,3-disubstitution can be accessed by numerous methods, synthetic approaches to *chiral 3-monosubstituted oxindoles* are limited. One major challenge is the ease of racemization, since the 3-position is alpha to the amide carbonyl as well as benzylic. Liu et al. demonstrate a simple catalytic protocol for accessing these desirable substitution patterns with high ee (>90%, often 99%) and in only one step from common 3-substituted indoles.

Comment: To achieve the one-step synthesis of chiral, monosubstituted 3-oxindoles directly from 3-indoles, the authors envisioned an enantioselective epoxidation and a 2,3-hydride migration sequence. From a screen of known asymmetric epoxidation catalysts, sharpless-type titanium catalysts were found to exhibit the best performance; subsequent ligand optimization found the salan family of ligands to be optimal. Up to gram scale, enantiomeric excesses were routinely >97% ee. The protocol tolerates a range of sensitive functional groups (thiophenes, furans, amides, alkynes), and as such, late-stage functionalization of several drug analogues was possible.

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Category
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