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Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing α,β-Unsaturated Acylammonium Salts

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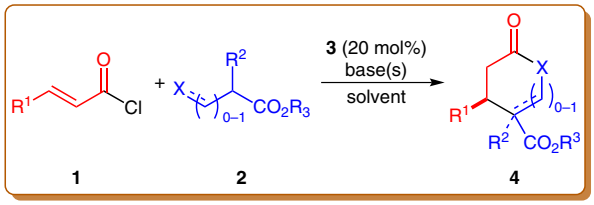
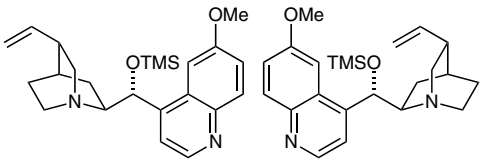
Asymmetric Organocatalytic Synthesis of Lactams and Lactones

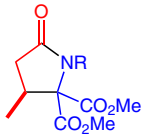




3c = $(DHQ)_2PHAL$

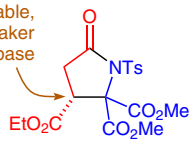
Selected examples: pyrrolidinones and piperidinones

catalyst: **3b**
bases:
LiHMDS (1 equiv)
DBU (1 equiv)
solvent: THF
conditions: –30 °C, 18 h

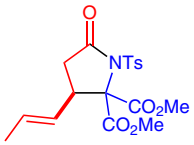


R = Bz 78% yield, 86% ee (gram scale)
Ts 73% yield, 93% ee

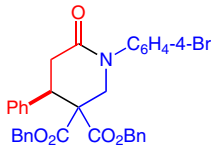
epimerizable, requires weaker base



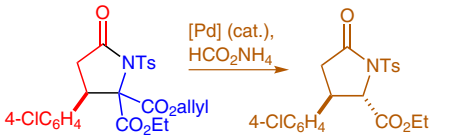
72% yield, 98% ee
catalyst: **3c**, bases: LiHMDS and DIPEA



80% yield, 93% ee
used 2 equiv of **1**, –10 °C



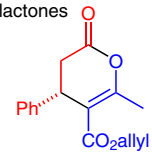
40% yield, 93% ee
used 2 equiv of **1**, –15 °C



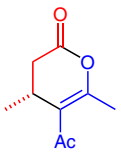
74% yield, –15 °C
71% yield, 99% ee, dr = 19:1
gram-scale synthesis of drug intermediate

Selected examples: enol δ-lactones

catalyst: **3a**, **3c**
bases:
LiHMDS (1 equiv)
DBU (1 equiv)
solvent: THF
conditions: –30 °C, 18 h



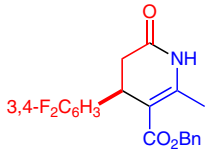
52% yield, 90% ee
catalyst **3c**



48% yield, 89% ee
catalyst **3c**, 0 °C

Example: 3,4-dihydro-2-pyridinones

catalyst **3b**
base: DIPEA (3 equiv)
additive: LiCl (1 equiv)
4 Å MS
solvent: PhMe
conditions: 23 °C, 20 h



78% yield, 92% ee

Significance: The reported method for the synthesis of lactams and lactones **4** employs quinine- and quinidine-derived catalysts **3** to activate α,β-unsaturated acid chlorides **1** toward reaction with bisnucleophiles **2**. A variety of heterocycles relevant to medicinal and natural product chemistry were obtained, including 2-pyrrolidinones, 2-piperidinones, enol δ-valerolactones, and 3,4-dihydro-2-pyridinones. The yields are modest to good and enantioselectivity is good to excellent. The method was demonstrated to provide two intermediates for drug synthesis (one on a gram scale).

Comment: For success of the reported method, significant tuning of the reaction conditions to the substrate, including the use of excess reactant; the choice of base, catalyst, and temperature; and the use of additives, is required. Catalyst **3b** affords products of opposite configuration to those obtained using **3a** or **3c**; although, in our opinion, the publication relies too heavily on assumptions in drawing this conclusion. In the synthesis of piperidinones, a retro-aza Michael side reaction results in low yields of the desired product. Interestingly, Michael addition, not acylation, appears to be the first mechanistic step, a fact essential to explaining the enantioselectivity.

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