Asymmetric Organocatalytic Synthesis of Lactams and Lactones

Significance: The reported method for the synthesis of lactams and lactones employs quinine- and quinidine-derived catalysts to activate \( \alpha, \beta \)-unsaturated acid chlorides toward reaction with bisnucleophiles. A variety of heterocycles relevant to medicinal and natural product chemistry were obtained, including 2-pyrrolidinones, 2-piperidinones, enol \( \delta \)-lactones, 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.

Selected examples:
- **pyrrolidinones and piperidinones**
  - Catalyst: \( 3b \)
  - Bases: LiHMDS (1 equiv), DBU (1 equiv)
  - Solvent: THF
  - Conditions: \(-30^\circ C, 18\) h
  - 80% yield, 93% ee used 2 equiv of \( 1, -10^\circ C \)
  - 40% yield, 93% ee used 2 equiv of \( 1, -15^\circ C \)

- **enol \( \delta \)-lactones**
  - Catalyst: \( 3a, 3c \)
  - Bases: LiHMDS (1 equiv), DBU (1 equiv)
  - Solvent: THF
  - Conditions: \(-30^\circ C, 18\) h
  - 52% yield, 90% ee catalyst \( 3c \)
  - 48% yield, 89% ee catalyst \( 3c, 0^\circ C \)

Example: 3,4-dihydro-2-pyridinones
- Catalyst: \( 3b \)
- Base: DIPEA (3 equiv), LiCl (1 equiv)
- Additive: \( 4^\circ \) MS
- Solvent: PhMe, \( 23^\circ C, 20\) h
- 78% yield, 92% ee

SYNFACTS Contributors: Victor Snieckus, Benjamin N. Rocke (Pfizer)