Asymmetric Organocatalytic Synthesis of Lactams and Lactones

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-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 °C, 18 h
  - Product: 3a (DHQ)2PHAL
  - R = Bz: 78% yield, 86% ee (gram scale)
  - R = Ts: 73% yield, 93% ee
  - 80% yield, 93% ee used 2 equiv of 1, –10 °C

- **Enol δ-lactones**
  - Catalyst: 3a, 3c
  - Bases: LiHMDS (1 equiv), DBU (1 equiv)
  - Solvent: THF
  - Conditions: –30 °C, 18 h
  - 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
    - 80% yield, 93% ee

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