Asymmetric Organocatalytic Synthesis of Lactams and Lactones

**Selected examples:** pyrrolidinones and piperidinones

- Catalyst: 3b
- Bases: LiHMDS (1 equiv), DBU (1 equiv)
- Solvent: THF
- Conditions: –30 °C, 18 h

**Selected examples:** 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

**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 enantioreselectivity 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.