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 α,β-unsaturated acid chlorides toward reaction with bisnucleophiles. A variety of heterocycles relevant to medicinal and natural product chemistry were obtained, including 2-pyrrolidinones and piperidinones, enol δ-lactones, and 3,4-dihydro-2-pyridinones. The yields are modest to good, and enantioselectivity is 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 affords products of opposite configuration to those obtained using or ; 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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