Organocatalytic Trifluoromethylthiolation of β-Keto Esters

Significance: A highly enantioselective trifluoromethylthiolation of β-keto esters is reported by Shen and co-workers. The reaction is catalyzed by quinine 1 or the quinine-derived phase-transfer catalyst 2. Good to excellent yields and enantioselectivities are obtained by utilizing different catalysts for different ring sizes of the β-keto esters. The free hydroxyl group of the catalyst is crucial for reactivity, and the SCF₃-substituted quaternary ammonium pathway was ruled out by control experiments. The proposed reaction pathway involves a dual activation, in which the catalyst activates both the β-keto ester and the SCF₃ reagent via a double hydrogen bonding.

Comment: The introduction of fluorine functional groups into different molecules is of great importance for the pharmaceutical and agrochemical industries. Here, the authors report a practical procedure for highly enantioselective trifluoromethylthiolation of β-keto esters. This methodology provides a straightforward way to build quaternary carbon centers with a SCF₃ group, which potentially could lead to useful drug candidates. At the same time, Rueping and co-workers report a very similar study, but utilizing different SCF₃ sources (T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping Angew. Chem. Int. Ed. 2013, 52, 12860–12864).

Selected examples:

- **R = H, OMe, halogen**
  - 90% yield, er = 96:4
  - 95% yield, er = 97:3
  - 93% yield, er = 90:10
  - 88% yield, er = 98:2

- **n = 2, 3**
  - 8 examples
  - 49–93% yield er from 60:40 to 98:2

- **n = 1**
  - 12 examples
  - 81–97% yield er from 93:7 to 97:3

Reaction pathway:

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