Chiral γ-Lactams by Enantioselective Cyclopropane Functionalization

Significance: Cyclopropanes are important components of many biologically active molecules and they can be found fused to a pyrrolidine ring in certain medicines. The authors present a new approach to this ring system using an enantioselective C–H functionalization of a cyclopropane, enabled by a Pd/TADDOL catalyst. This work constitutes a notable advance in the field of C(sp³)–C(sp³) bond formation by C–H activation.

Comment: The reaction shows good functional group tolerance and allows the synthesis of a library of diverse cyclopropane-fused pyrrolidines in high yield and with high enantioselectivity. The substrates can be accessed in a sequence by using a variant of the Kulinkovich reaction. The authors also demonstrate that the catalyst can efficiently activate methyl C–H groups in other substrates.

Selected examples:

- **Pd(dba)₂ (5 mol%)**
  - ligand (10 mol%)
  - AdCO₂H (5 mol%)
  - Cs₂CO₃ (1.5 equiv)
- PhMe, 70 °C
- 17 examples up to 99% yield er up to 98:2

- **Pd(dba)₂ (10 mol%)**
  - ligand (20 mol%)
  - AdCO₂H (10 mol%)
  - Cs₂CO₃ (1.5 equiv)
- PhMe, 110 °C
- 75% yield er = 79.21

Additional examples:

- **Pd(dba)₂ (5 mol%)**
  - ligand (10 mol%)
  - AdCO₂H (5 mol%)
  - Cs₂CO₃ (1.5 equiv)
- PhMe, 70 °C
- 92% yield er = 96.5:3.5
- 99% yield er = 95:4.5
- 89% yield er = 95.5:4.5
- 99% yield er = 96:4
- 78% yield er = 98:2
- 94% yield er = 98.2
- 92% yield er = 96.5:3.5
- 93% yield er = 97.5:2.5 (gram scale)

- **Pd(dba)₂ (10 mol%)**
  - ligand (20 mol%)
  - AdCO₂H (10 mol%)
  - Cs₂CO₃ (1.5 equiv)
- PhMe, 110 °C
- 99% yield er = 98.2
- 90% yield er = 91.5:8.5
- 99% yield er = 92.5:7.5
- 99% yield er = 95:5
- 65% yield er = 98.2 (at 35 °C)
- 76% yield er = 97.5:2.5
- 89% yield er = 97.5:2.5

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