Asymmetric Phosphoric Acid Catalyzed Four-Component Ugi Reaction

Significance: The Houk and Tan groups report an asymmetric phosphoric acid catalyzed Ugi reaction furnishing $\alpha$-aminoacylaminoamides from four achiral building blocks in excellent yields and high enantioselectivities. DFT calculations support imine activation accomplished by phosphoric acid carboxylic acid heterodimer catalysis through a bi-functional activation mode.

Comment: Asymmetric Ugi reactions, which are highly atom- and step-economical transformations, remain challenging partially due to the requirement of suppressing the Passerini reaction. The authors have developed two chiral phosphoric acids, based on STRIP (I. Ćorić, S. Müller, B. List J. Am. Chem. Soc. 2010, 132, 17370) that fully suppress the Passerini reaction while providing a broad substrate scope.

Key words: Ugi reaction, acylamino amides, chiral phosphoric acids

Selected examples:

- $R_1 = \text{Alk}$
  - $82\%$ yield $\text{er} = 96:4$
- $R_1 = \text{Ar}$
  - $93\%$ yield $\text{er} = 95:5$
- $R_1 = \text{Het}$
  - $54\%$ yield $\text{er} = 97:3$
- $R_1 = \text{Het}$
  - $89\%$ yield $\text{er} = 97:3$
- $R_1 = \text{Het}$
  - $84\%$ yield $\text{er} = 93.5:6.5$

DFT-optimized transition-state structure and computed activation energy for the nucleophilic addition of the isocyanide to the imine:

- $\Delta G^\ddagger = 15.7 \text{ kcal/mol}$
  - lowest barrier among the considered transition states