



Catalytic Enantioselective Ugi and Passerini Multicomponent Reactions

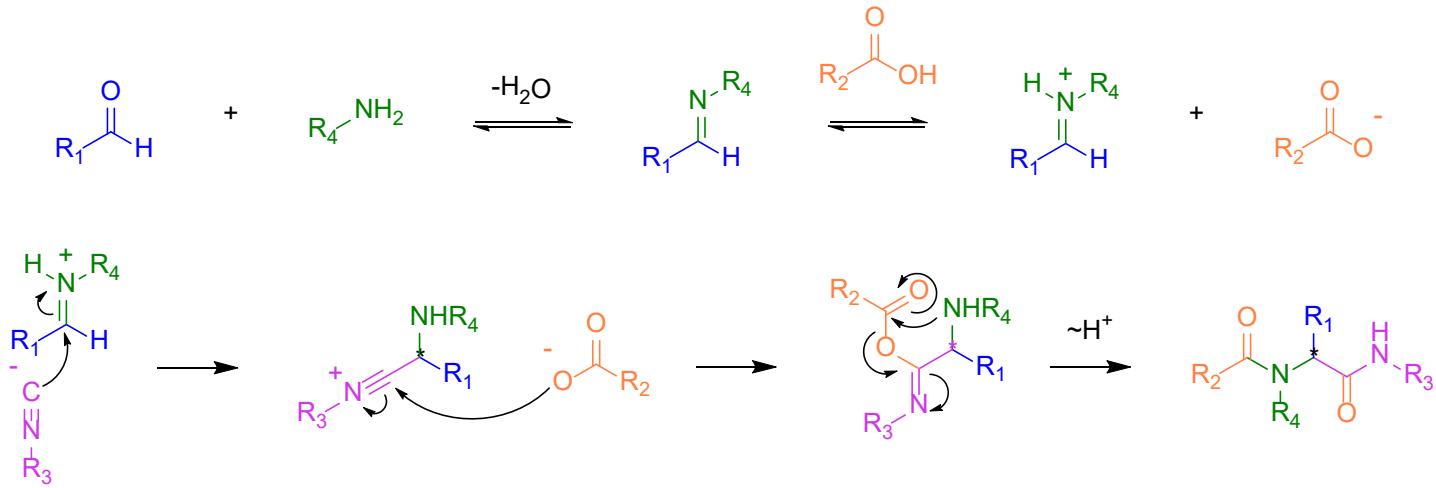
Matthew Albritton

Group Meeting

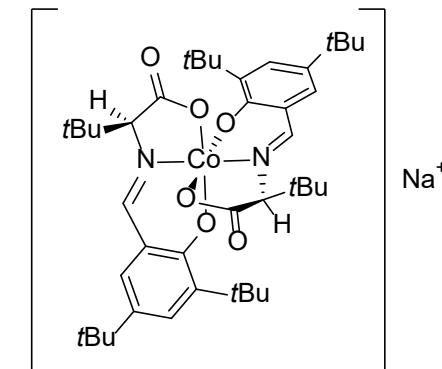
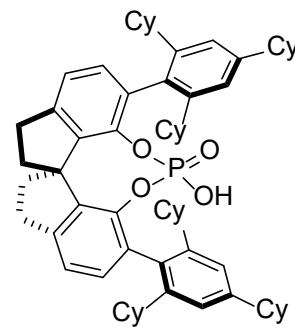
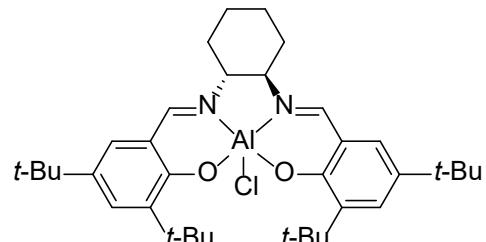
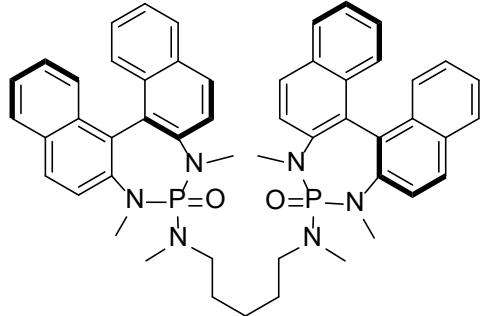
May 16, 2023

Outline

Mechanism and Related Reactions



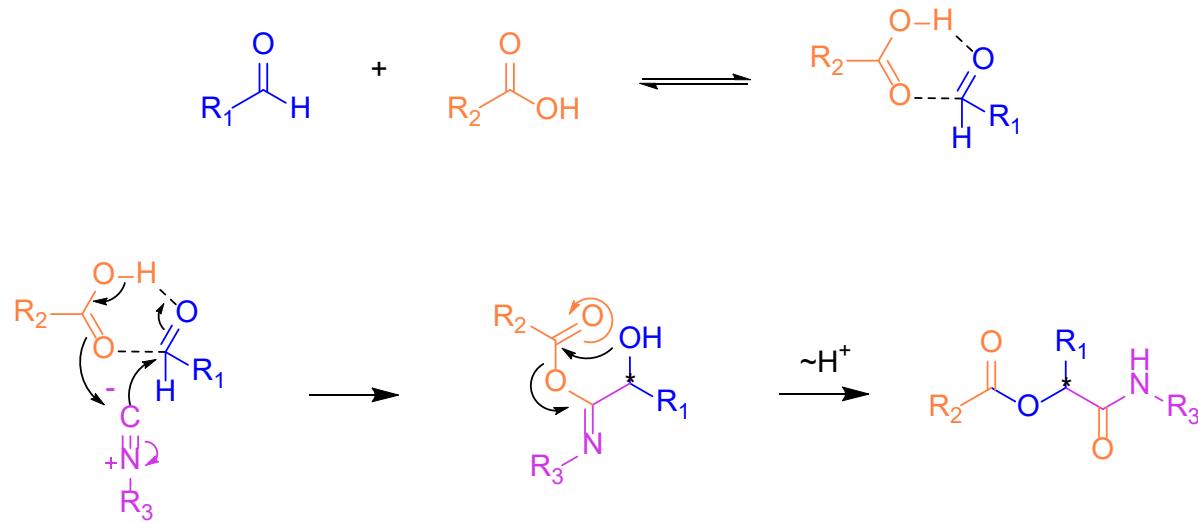
Development of Catalytic Enantioselective Reactions



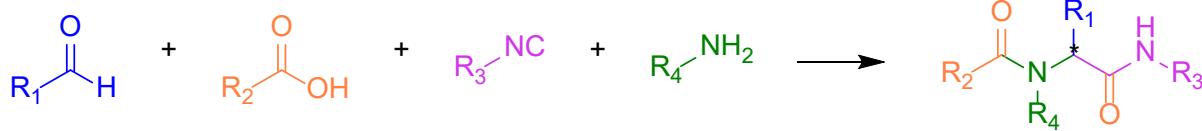
The Passerini 3-Component Reaction



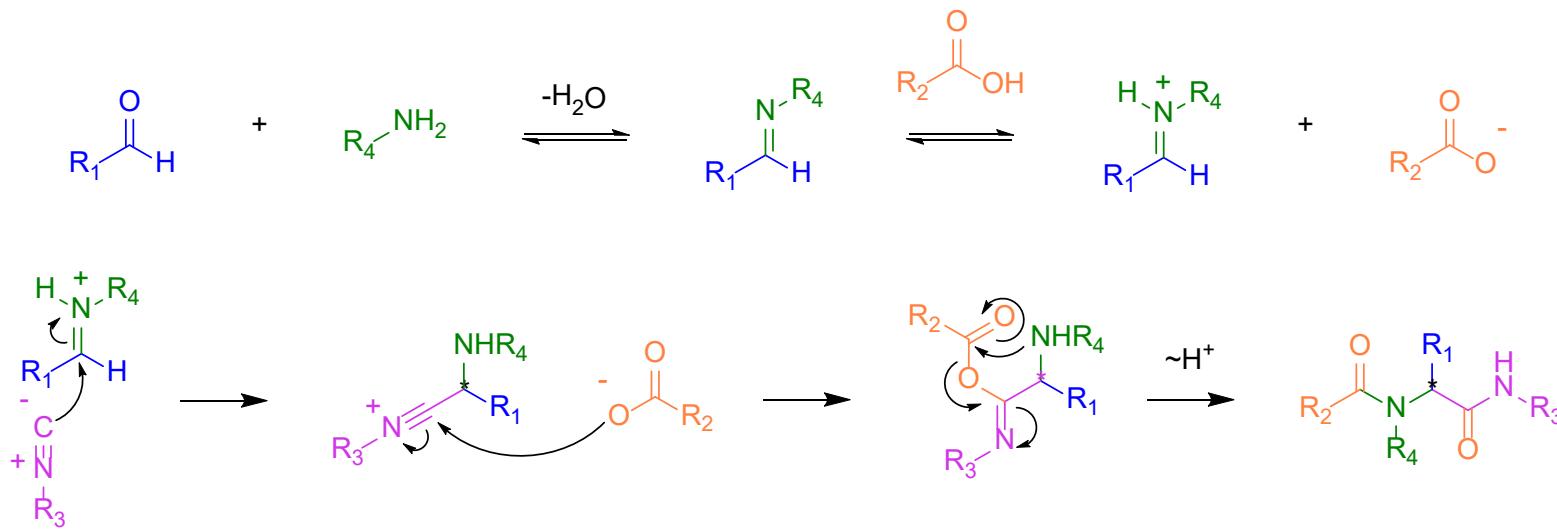
- Discovered in 1921 by Mario Passerini at the University of Florence
- Student of Ugo Schiff



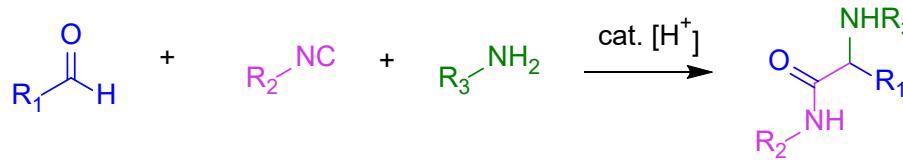
The Ugi 4-Component Reaction



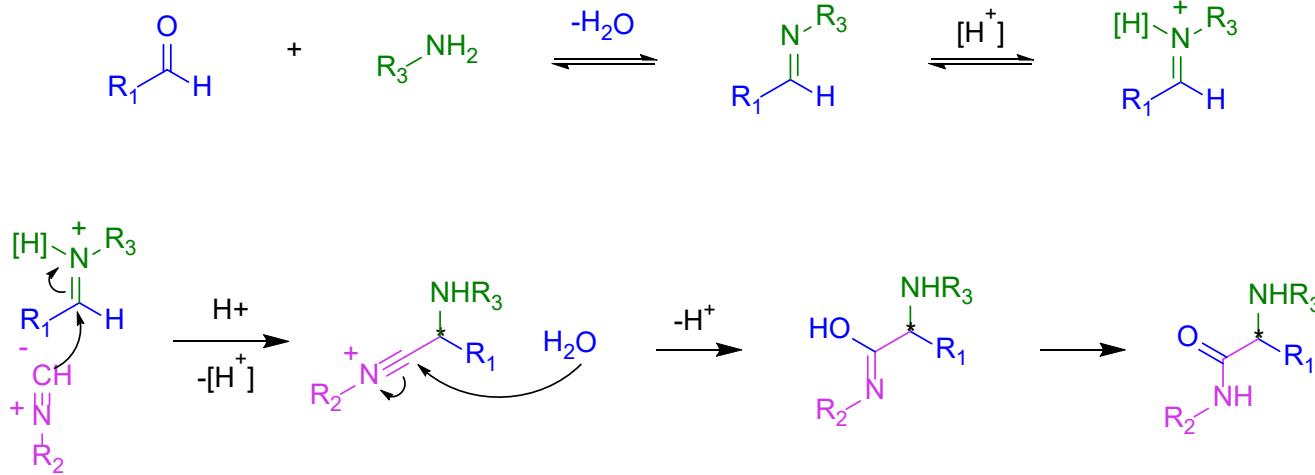
- Discovered in 1959 by Ivar Karl Ugi at the Ludwig Maximilian University of Munich



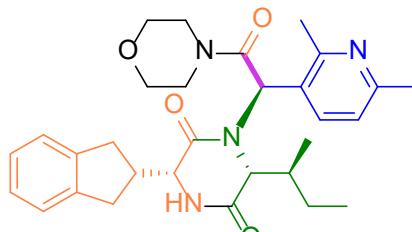
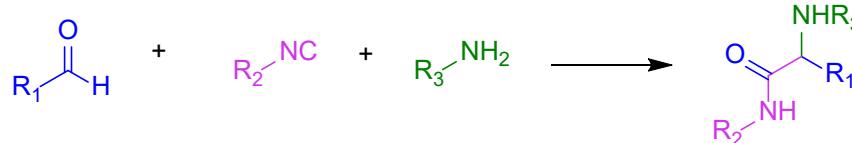
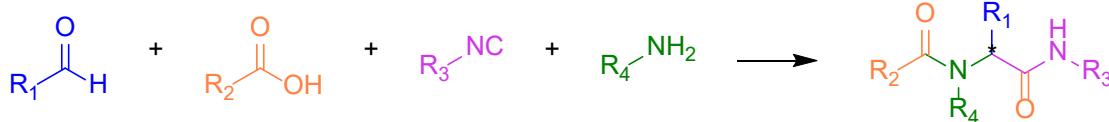
The Ugi 3-Component Reaction



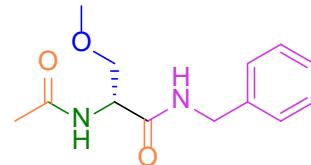
Brønsted or Lewis acid-catalyzed



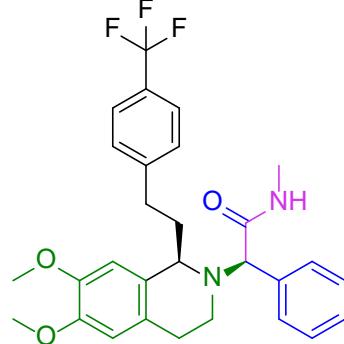
Synthetic utility



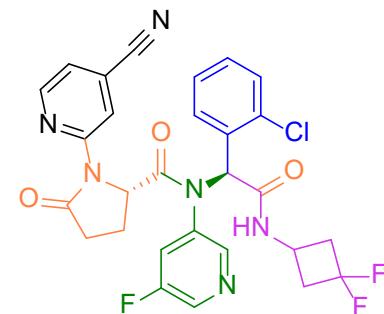
Epelsiban



Lacosamide

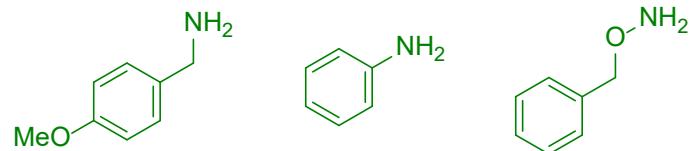
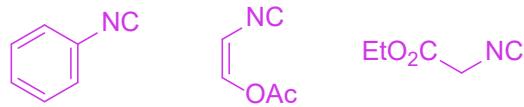
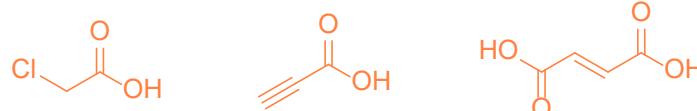
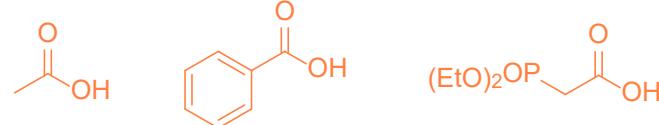
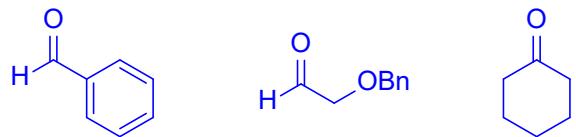
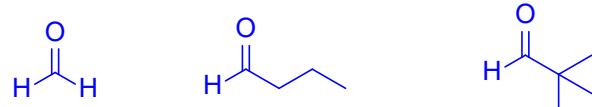


Almorexant

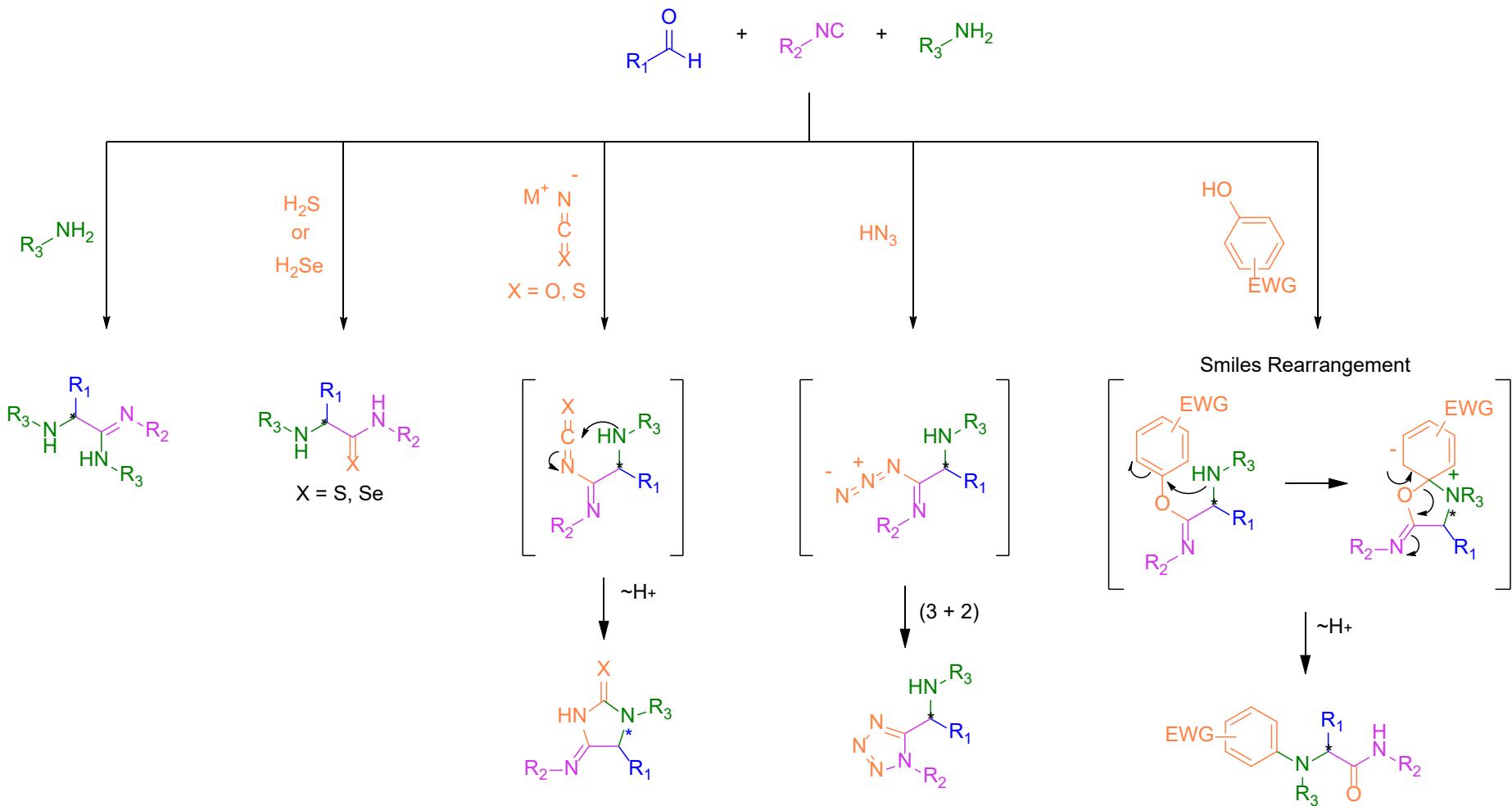


Ivosidenib

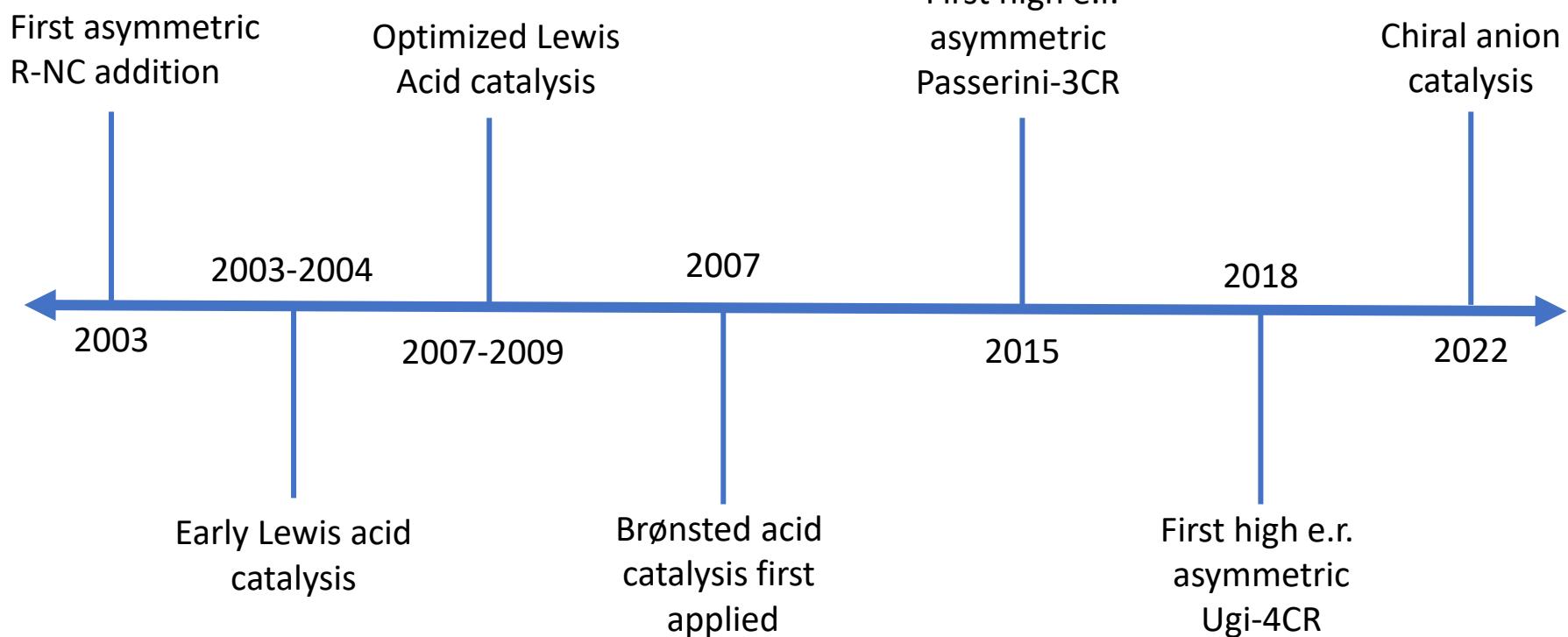
General Scope



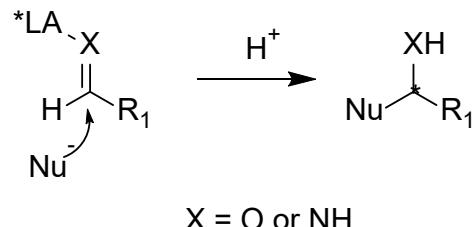
Other Variants



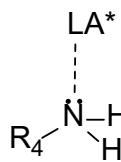
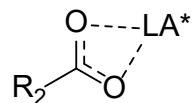
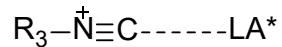
Outline



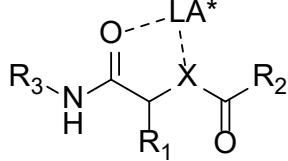
Asymmetric Ugi and Passerini Reactions



Competing Lewis basic sites

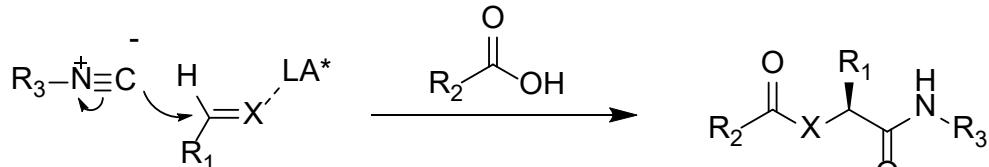


Bidentate product inhibition

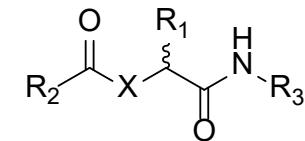
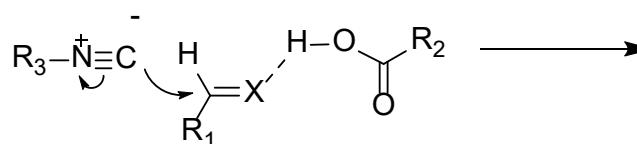


$\text{X} = \text{O}$ or NR_4

Competitive background reaction

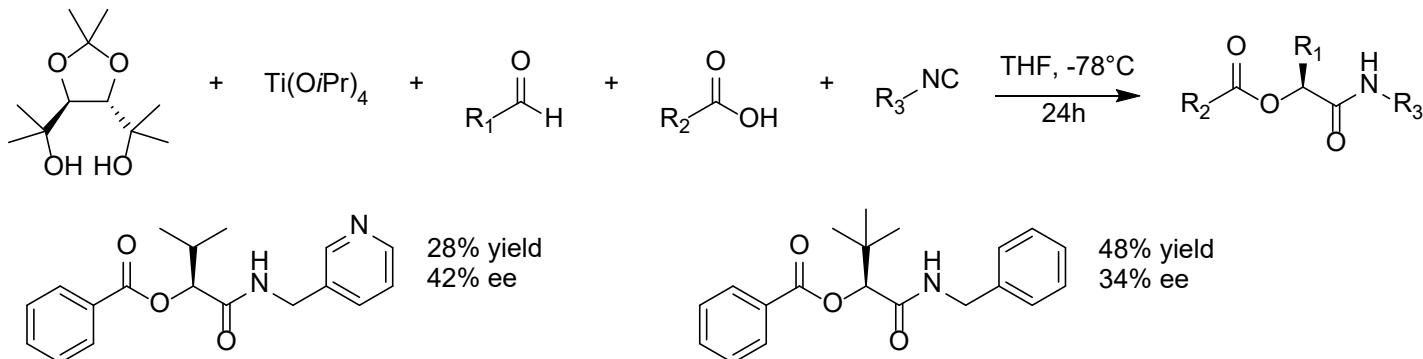


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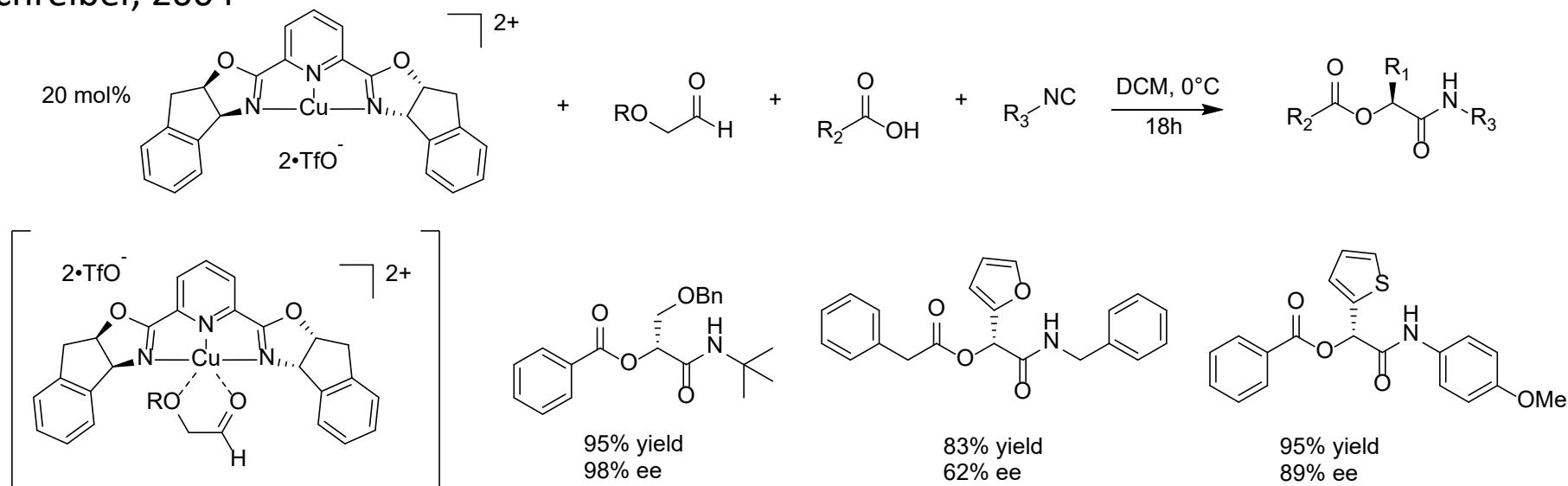


Early Attempts: Passerini Reaction

Dömling, 2003



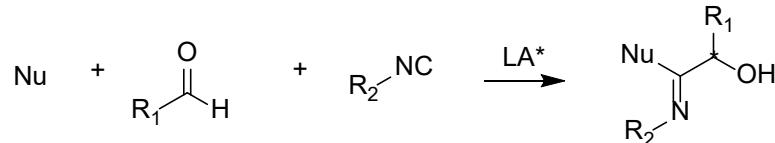
Schreiber, 2004



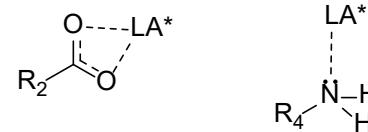
Alternative Nucleophiles

Removing the carboxylic acid eliminates several issues...

More control over carbonyl activation

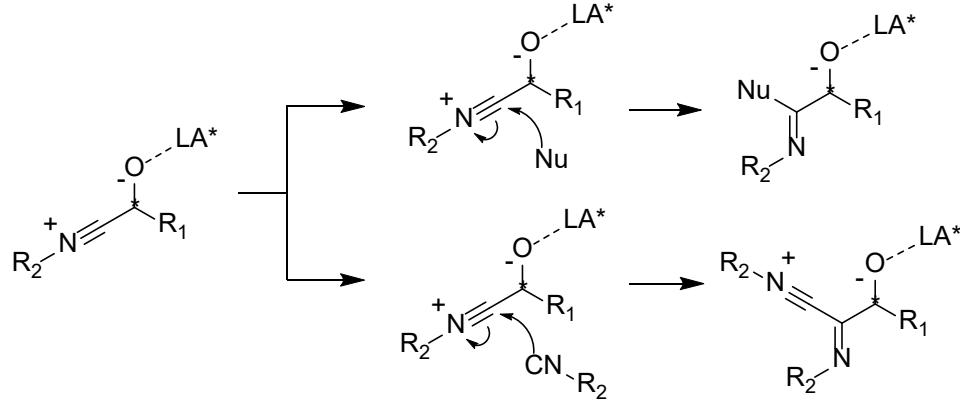


Less competing Lewis bases

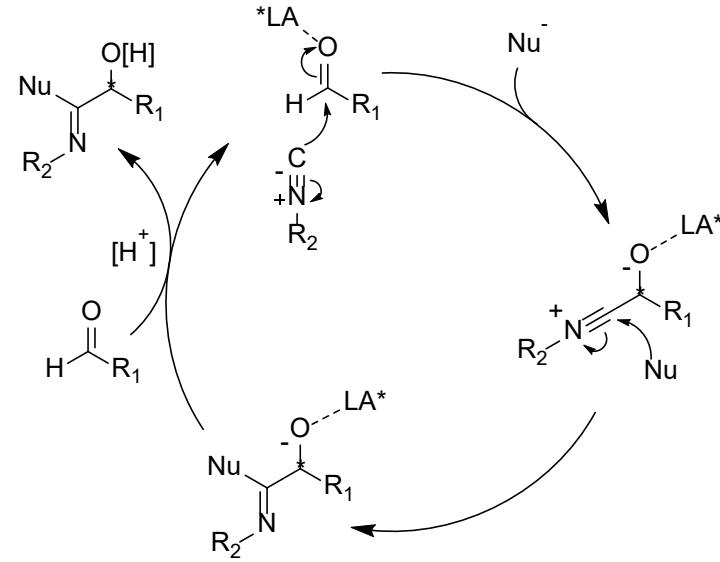


...but introduces new challenges.

Nucleophile must outcompete isocyanide overaddition

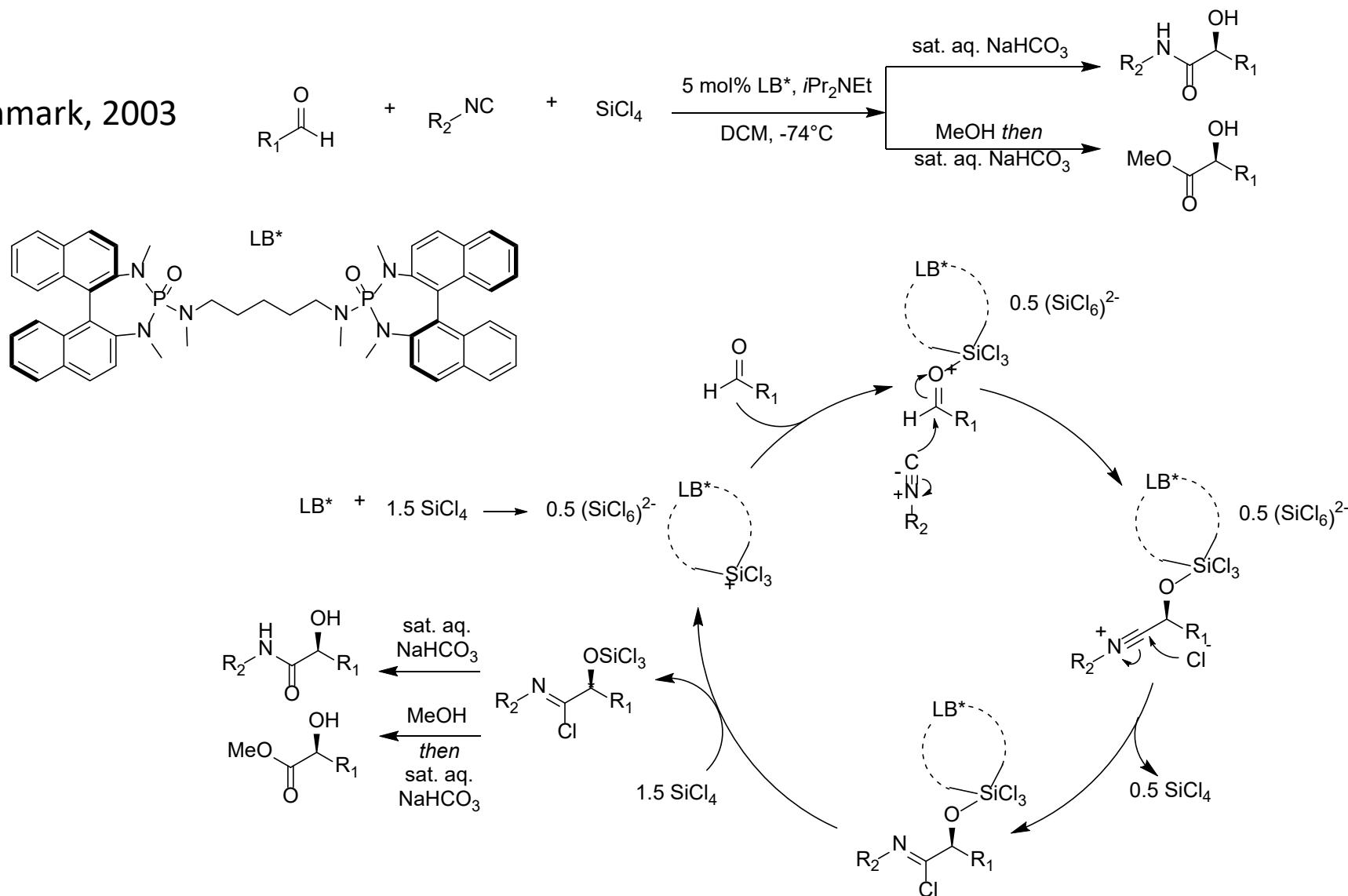


Catalyst turnover requires suitable alkoxide counterion

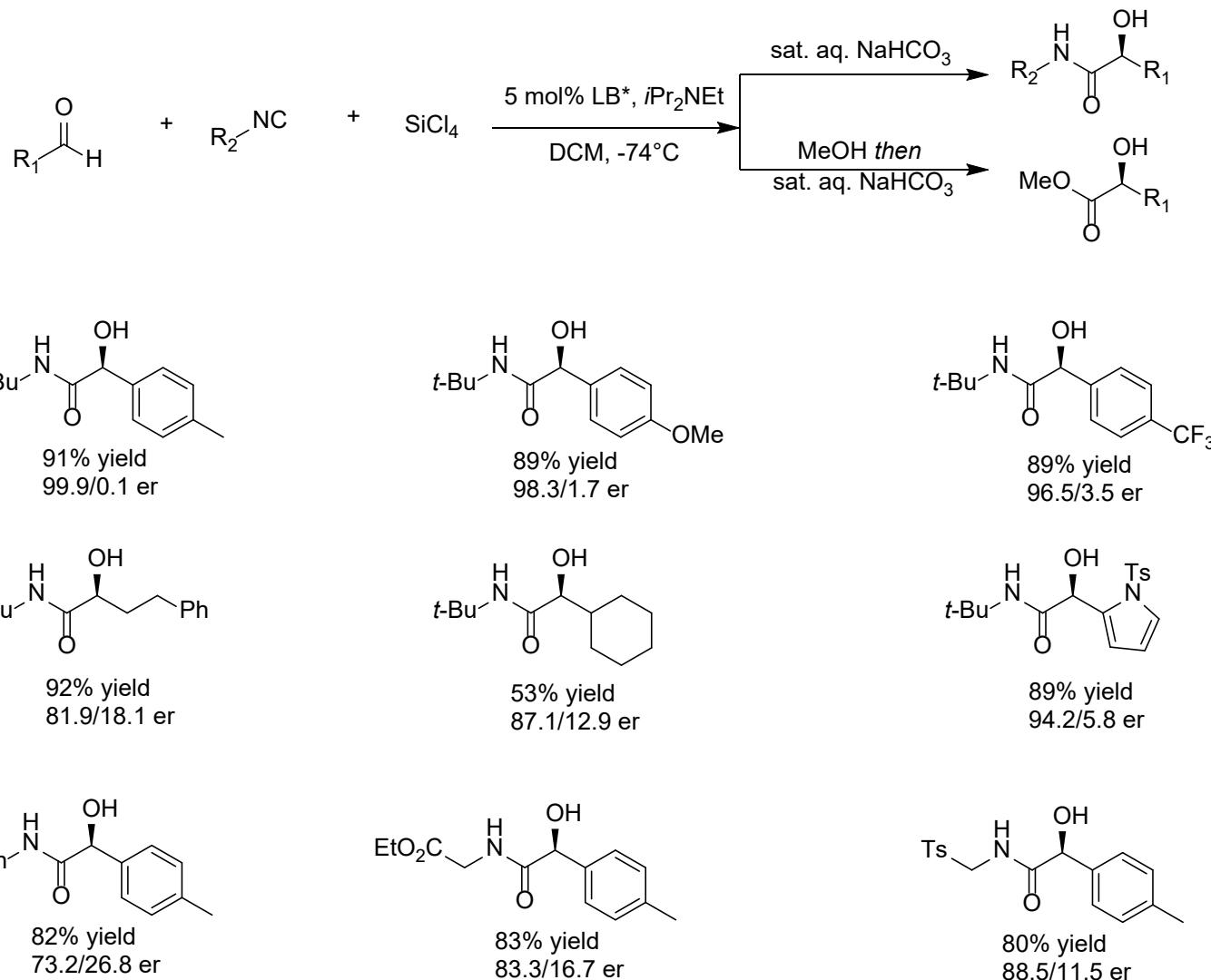


Asymmetric Ugi and Passerini Reactions

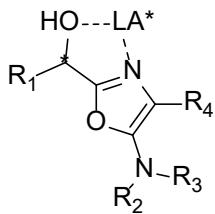
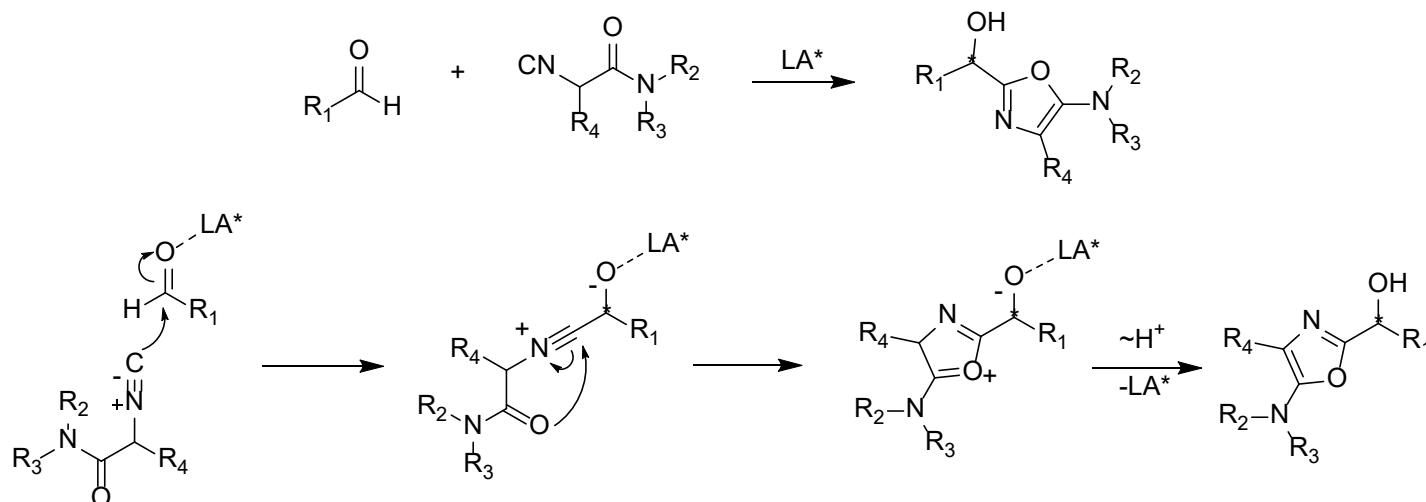
Denmark, 2003



Asymmetric Ugi and Passerini Reactions

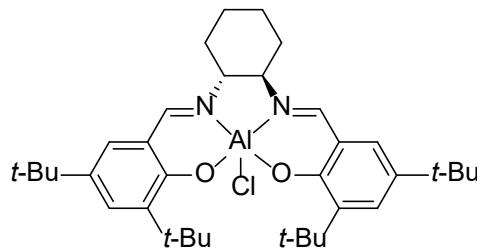


Asymmetric Ugi and Passerini Reactions



Bidentate product still complicates turnover

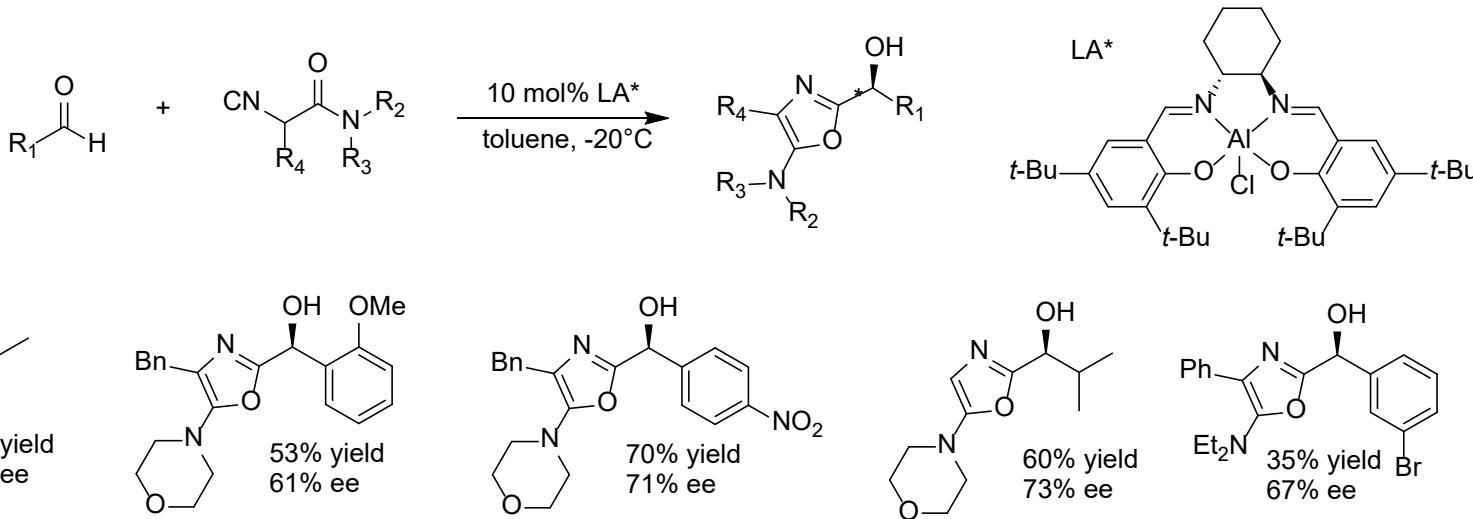
Single coordination site



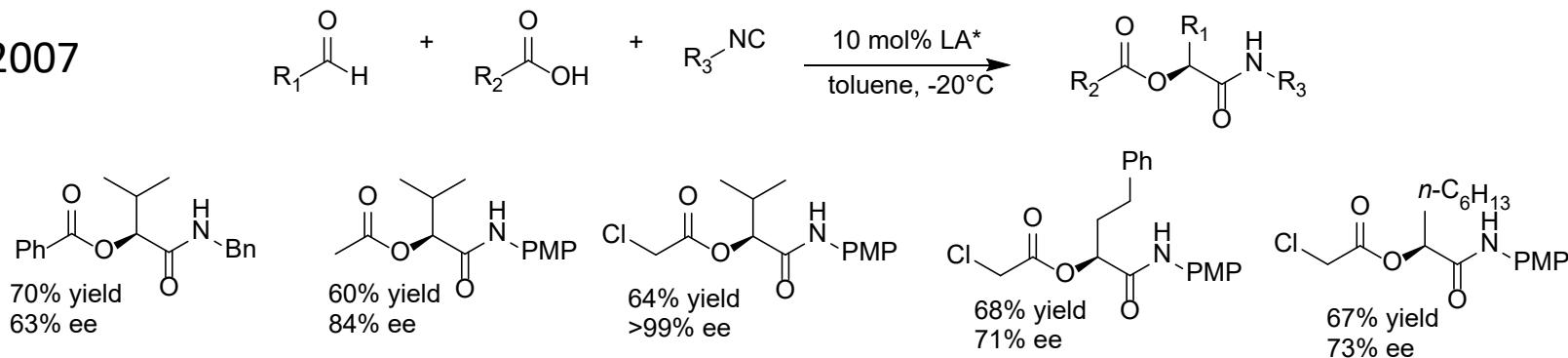
Zhu, 2007

Asymmetric Ugi and Passerini Reactions

Zhu, 2007

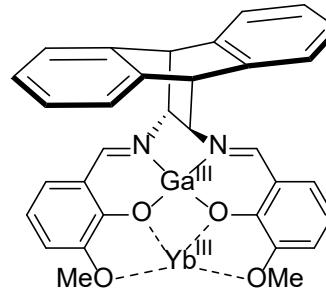
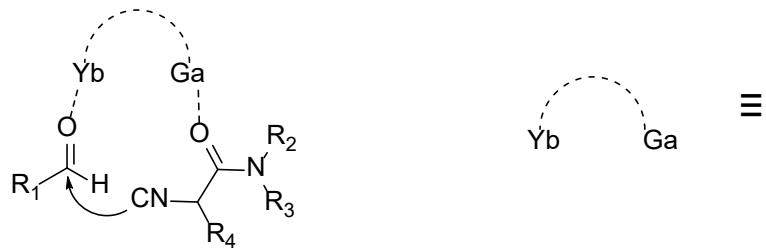
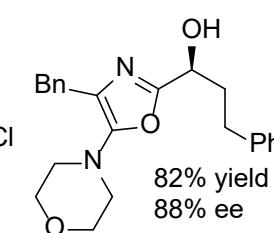
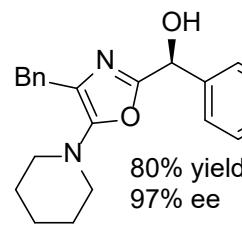
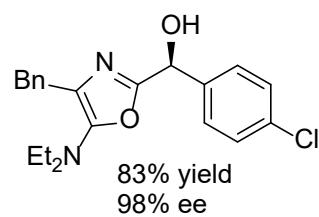
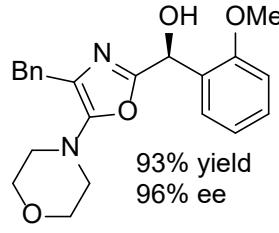
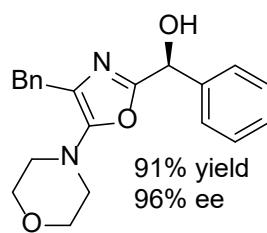
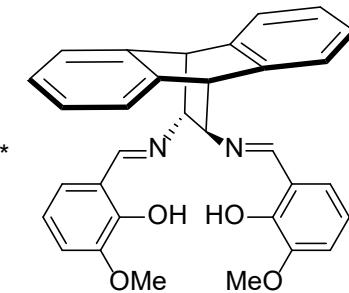
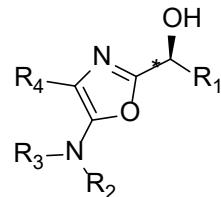
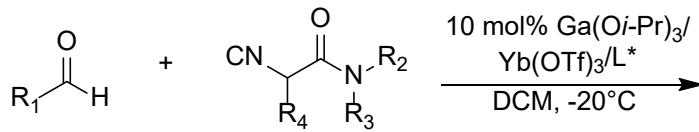


Zhu, 2007



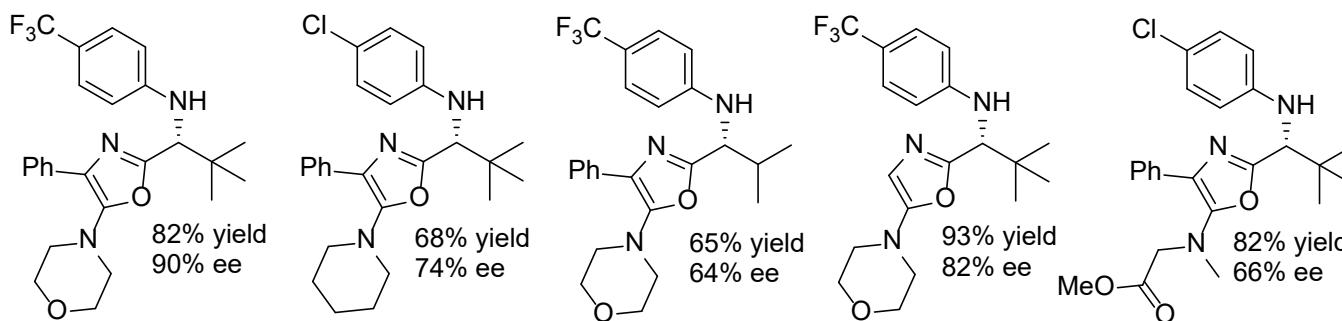
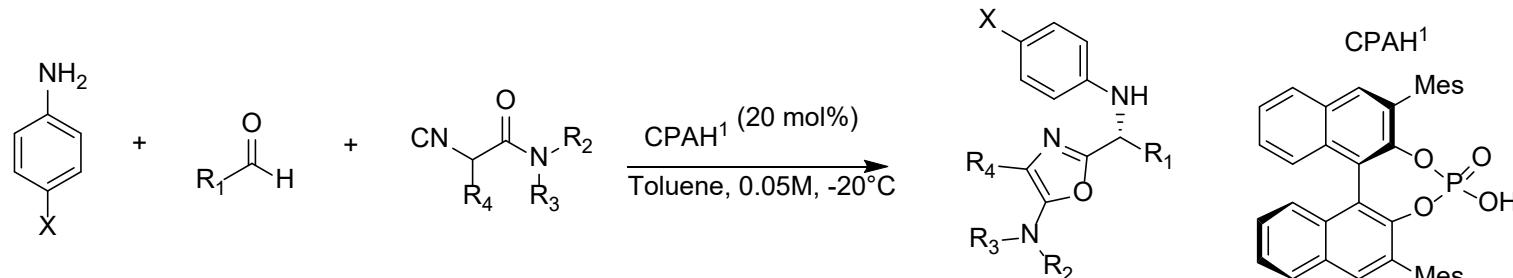
Asymmetric Ugi and Passerini Reactions

Shibasaki, 2009

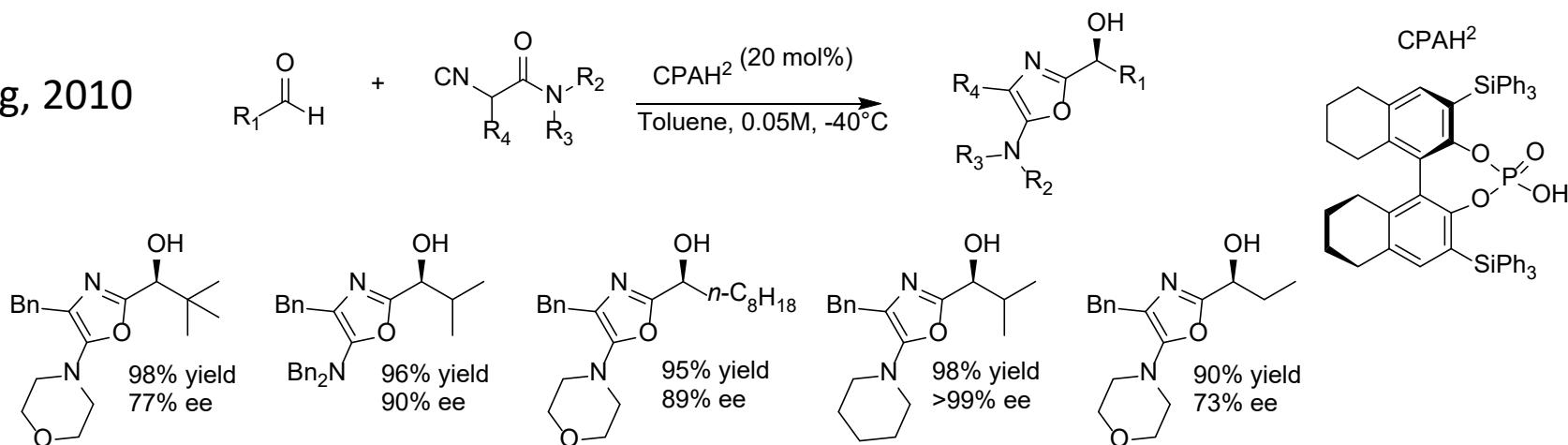


Asymmetric Ugi and Passerini Reactions

Zhu, 2009

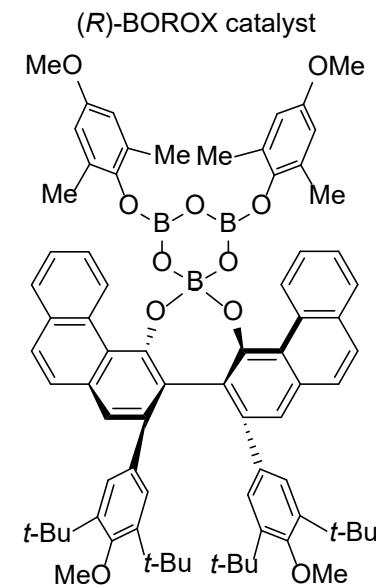
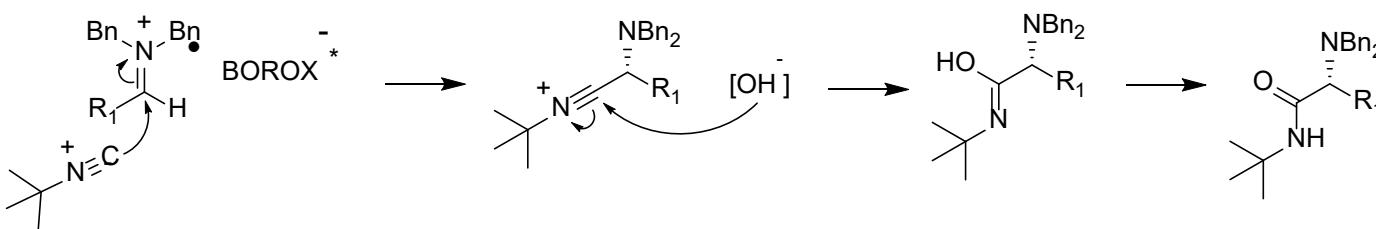
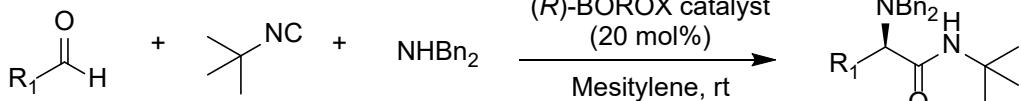


Zhong, 2010



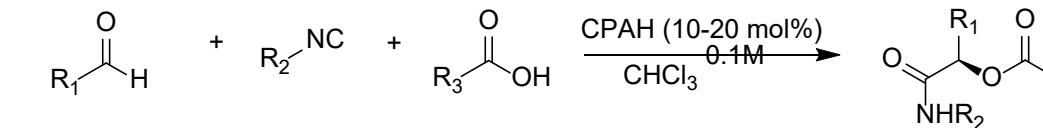
Asymmetric Ugi and Passerini Reactions

Wulff, 2014

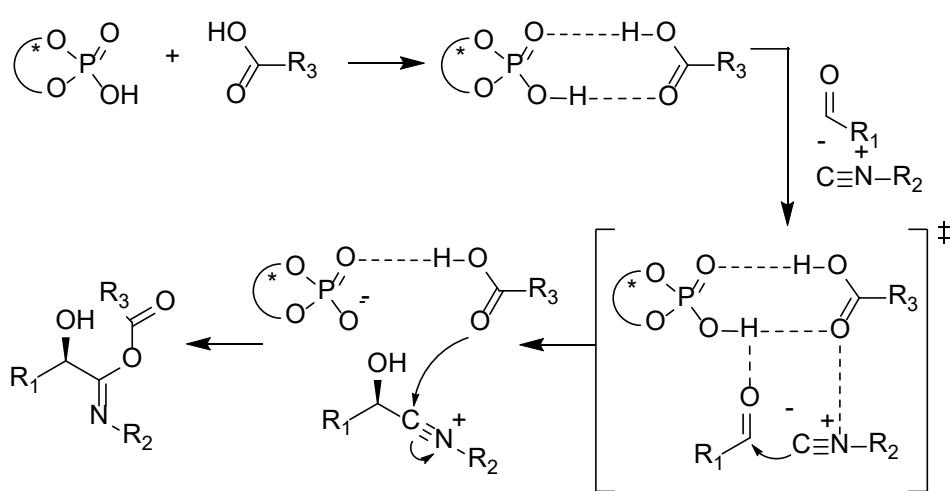
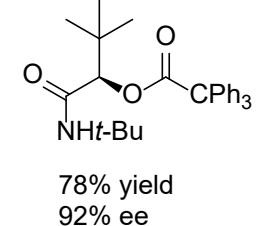
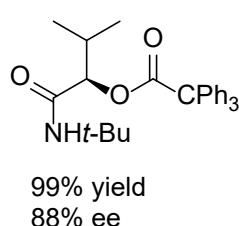
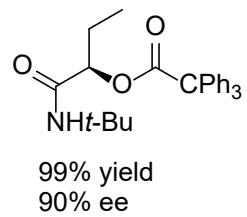
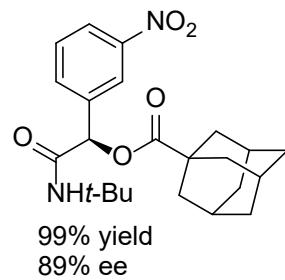
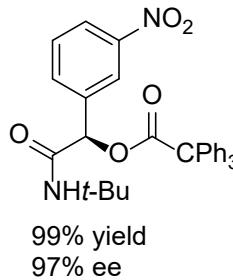
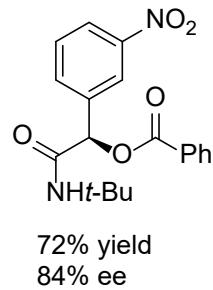
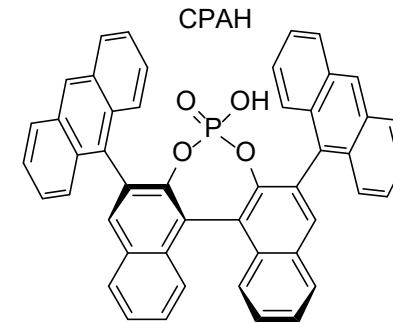
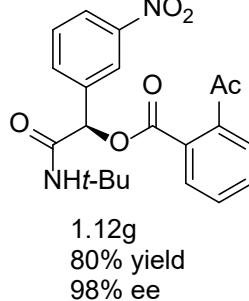
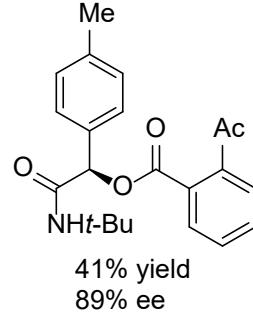
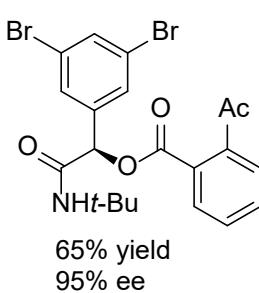
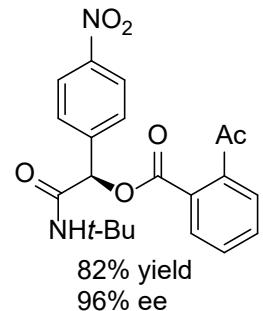


76% yield 78:22 er	80% yield 90:10 er	83% yield 84:16 er	84% yield 88:12 er	83% yield 93:7 er

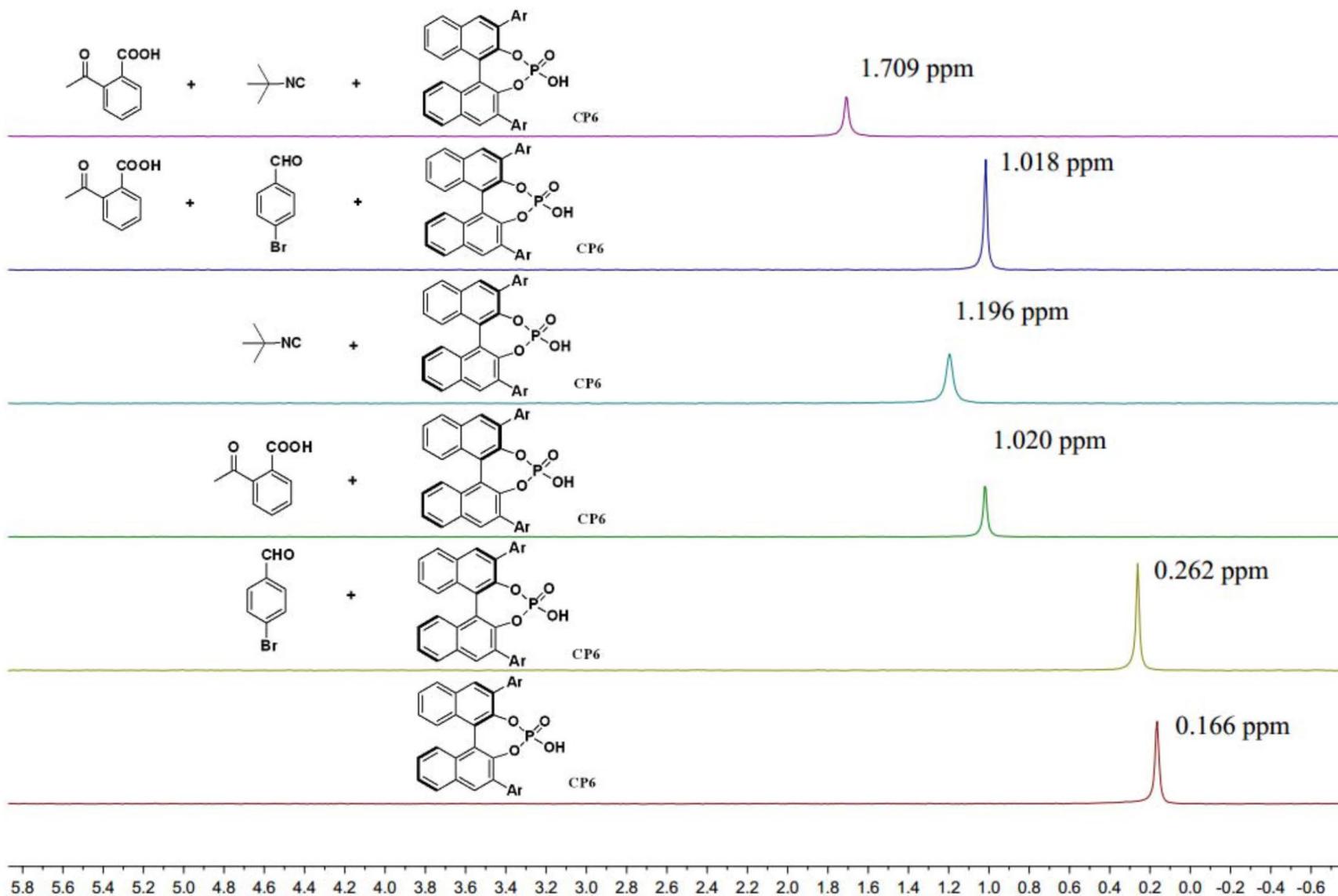
Asymmetric Ugi and Passerini Reactions



Tan, 2015

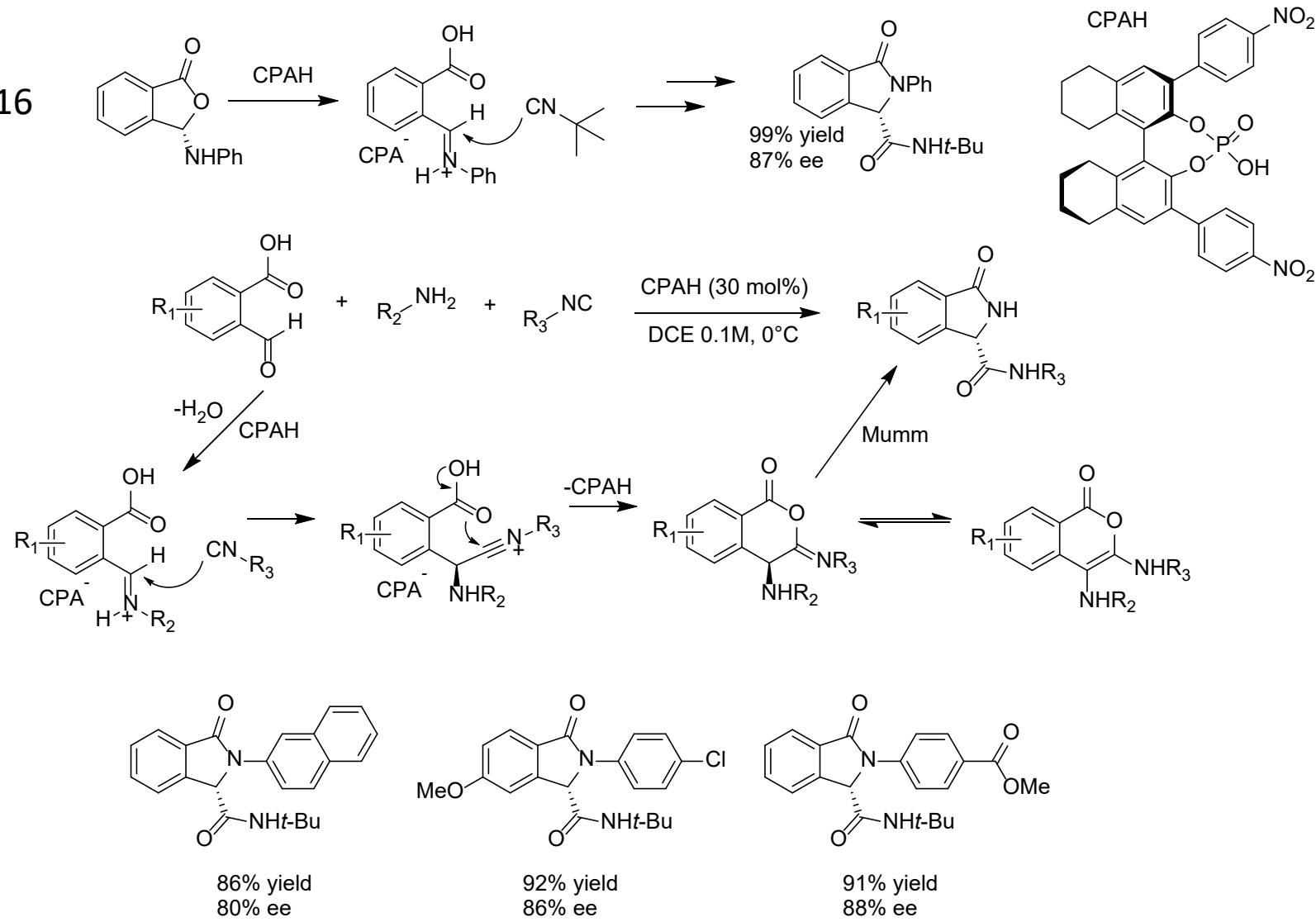


Asymmetric Ugi and Passerini Reactions



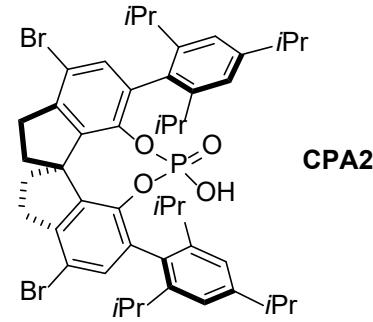
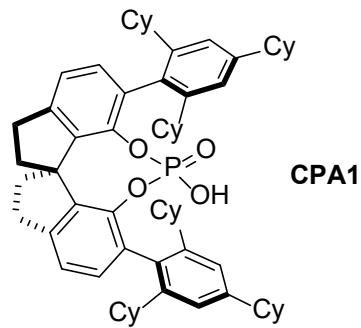
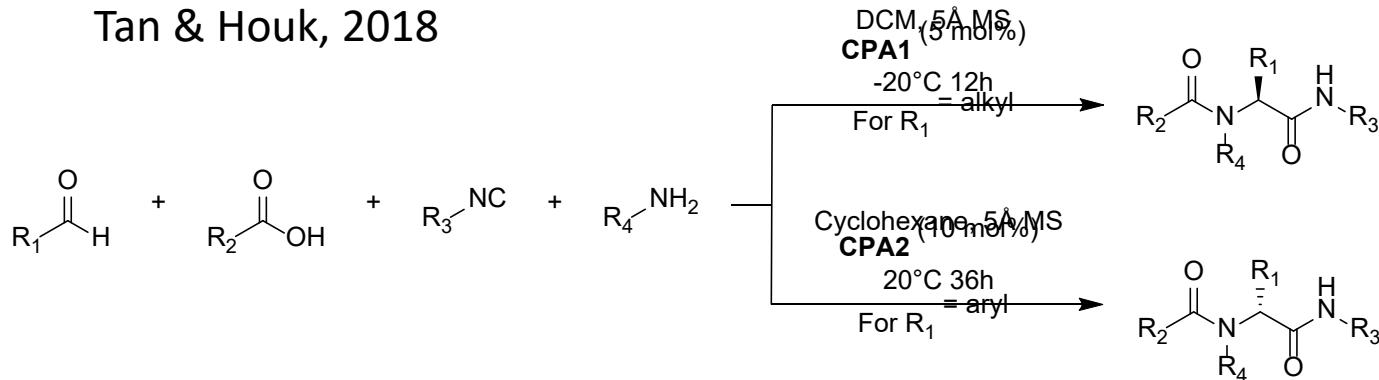
Asymmetric Ugi and Passerini Reactions

Zhu, 2016

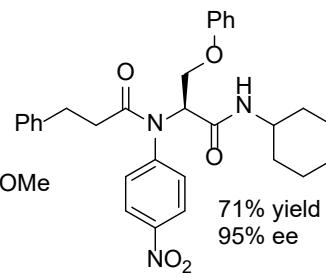
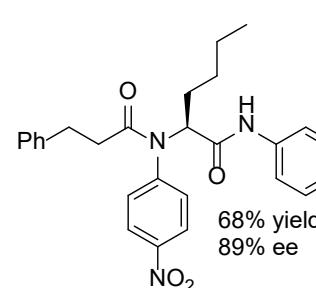
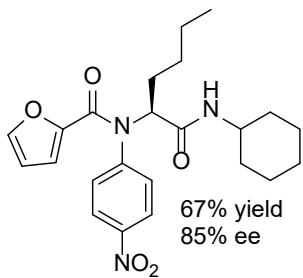
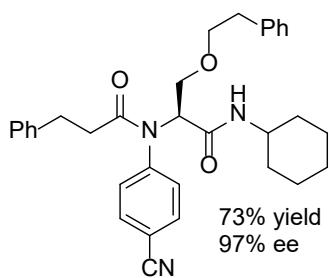
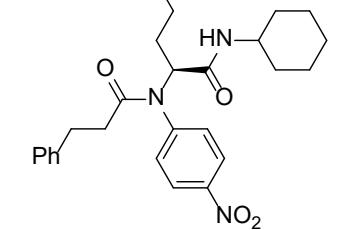
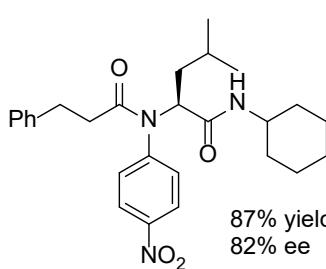
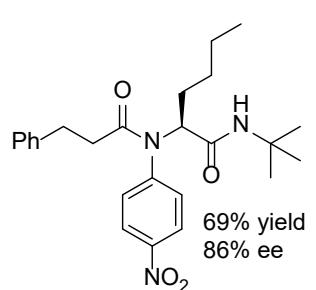
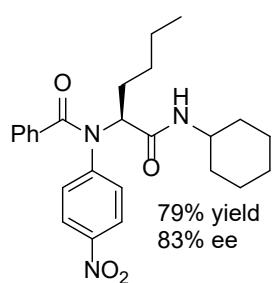
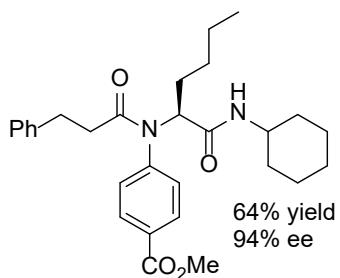
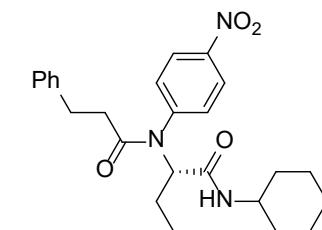
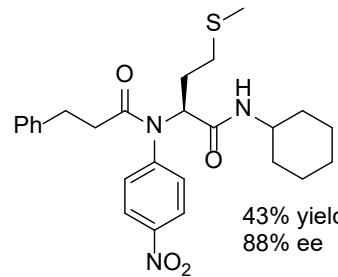
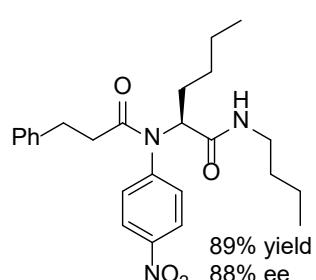
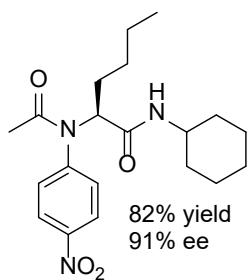
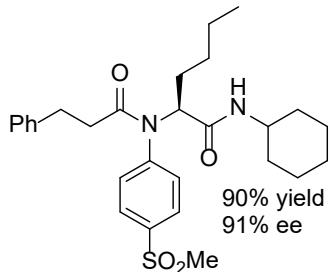
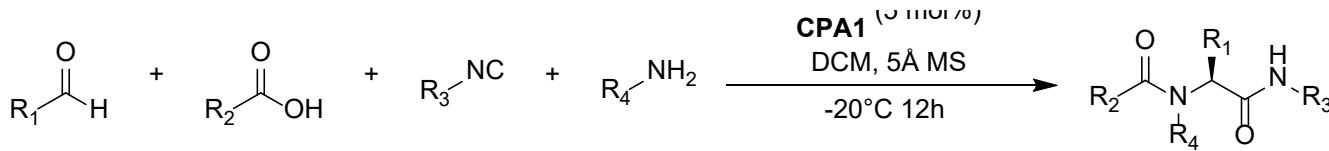


Asymmetric Ugi and Passerini Reactions

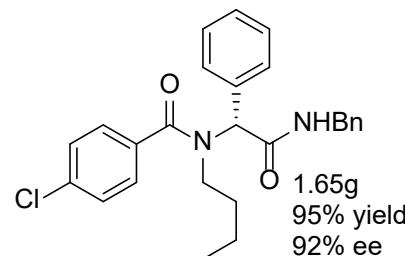
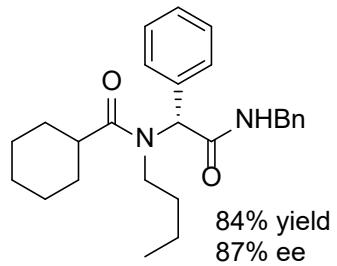
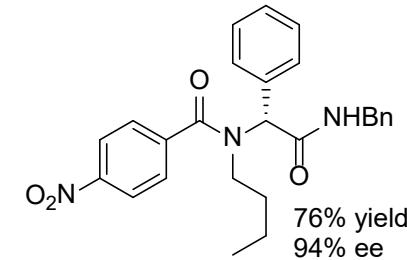
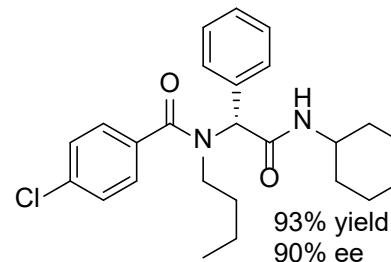
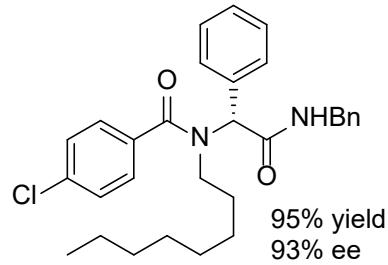
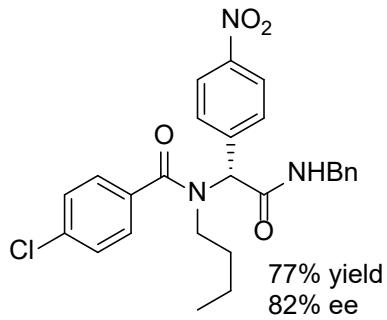
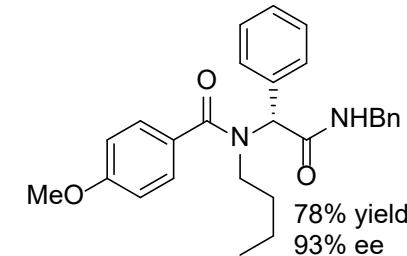
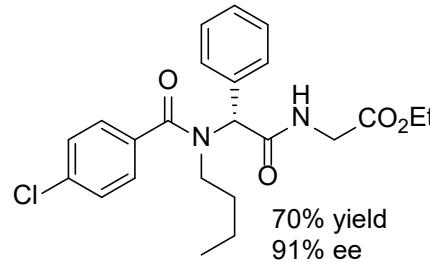
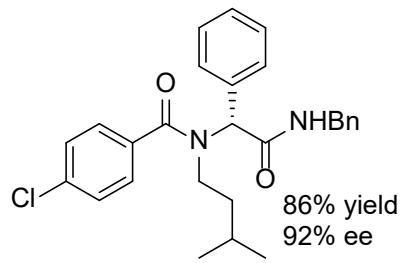
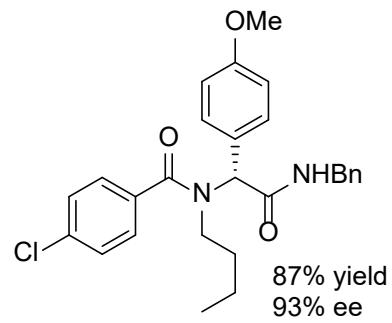
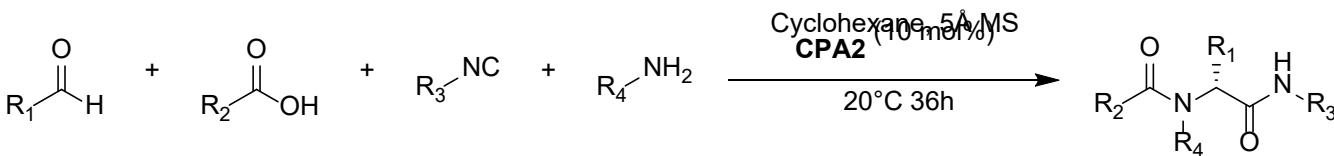
Tan & Houk, 2018



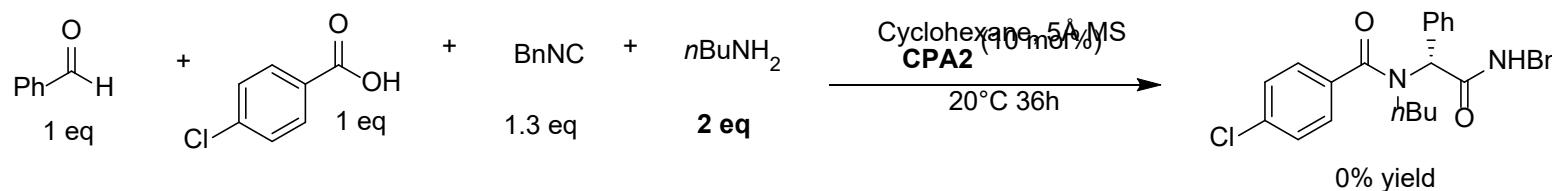
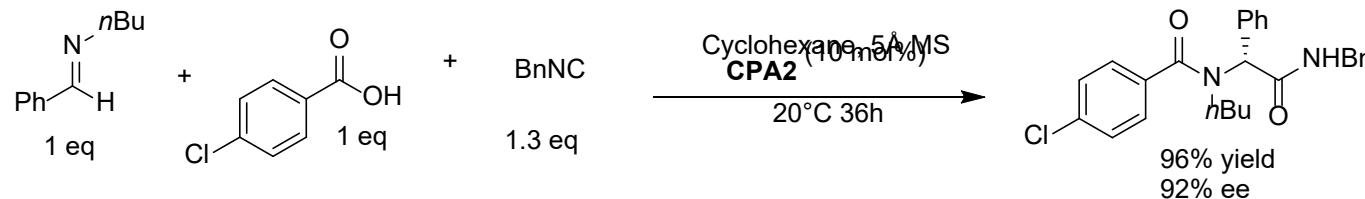
Asymmetric Ugi and Passerini Reactions



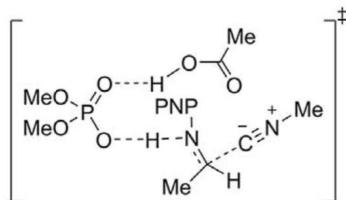
Asymmetric Ugi and Passerini Reactions



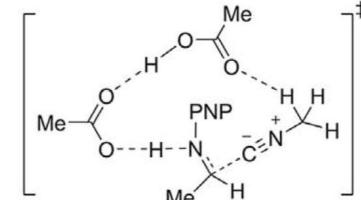
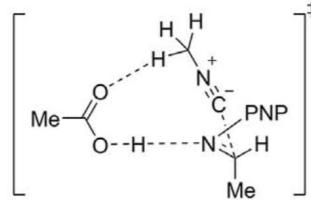
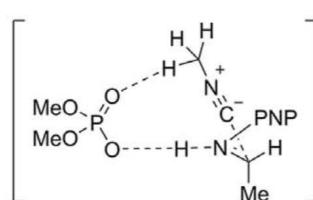
Asymmetric Ugi and Passerini Reactions



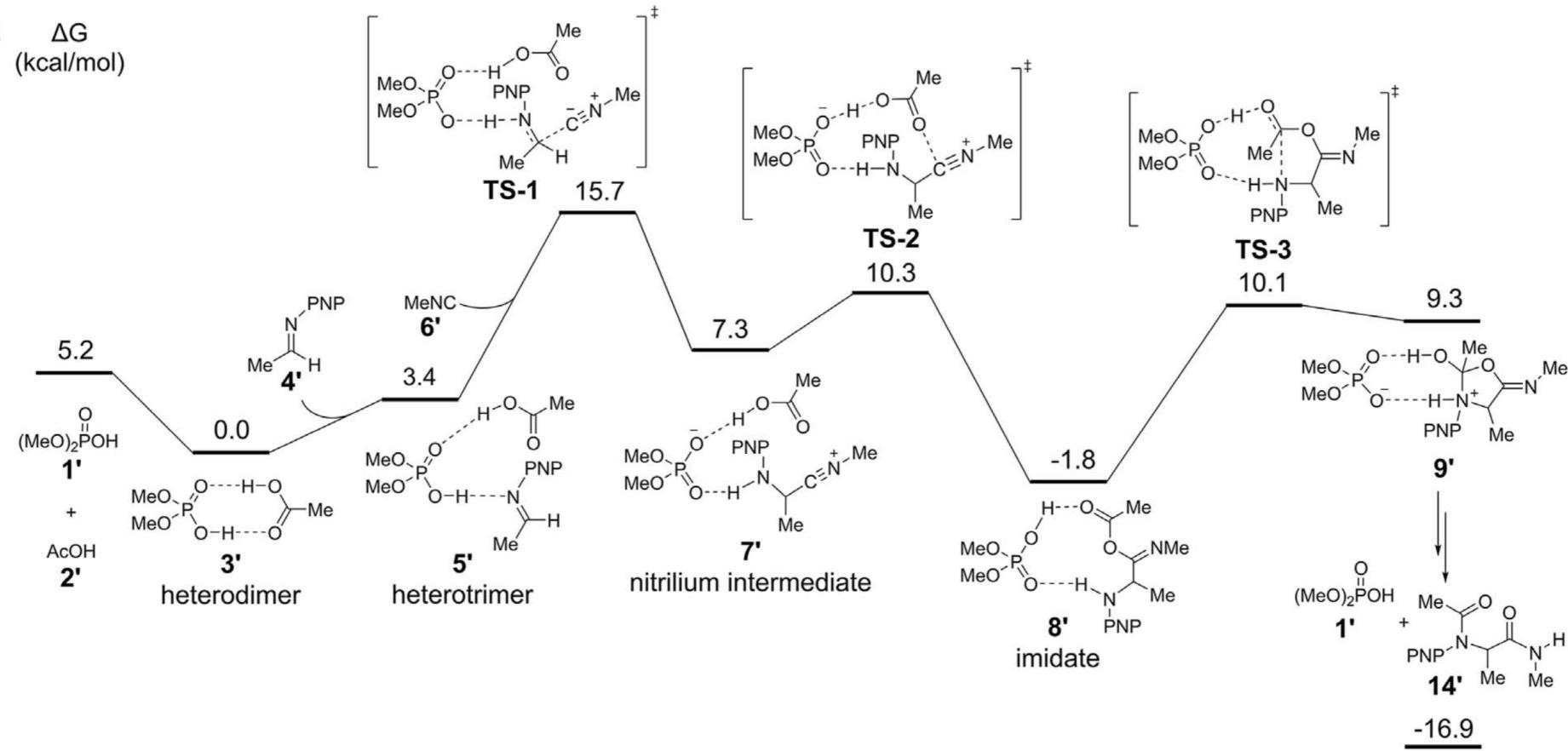
Active catalyst is protonated CPA2



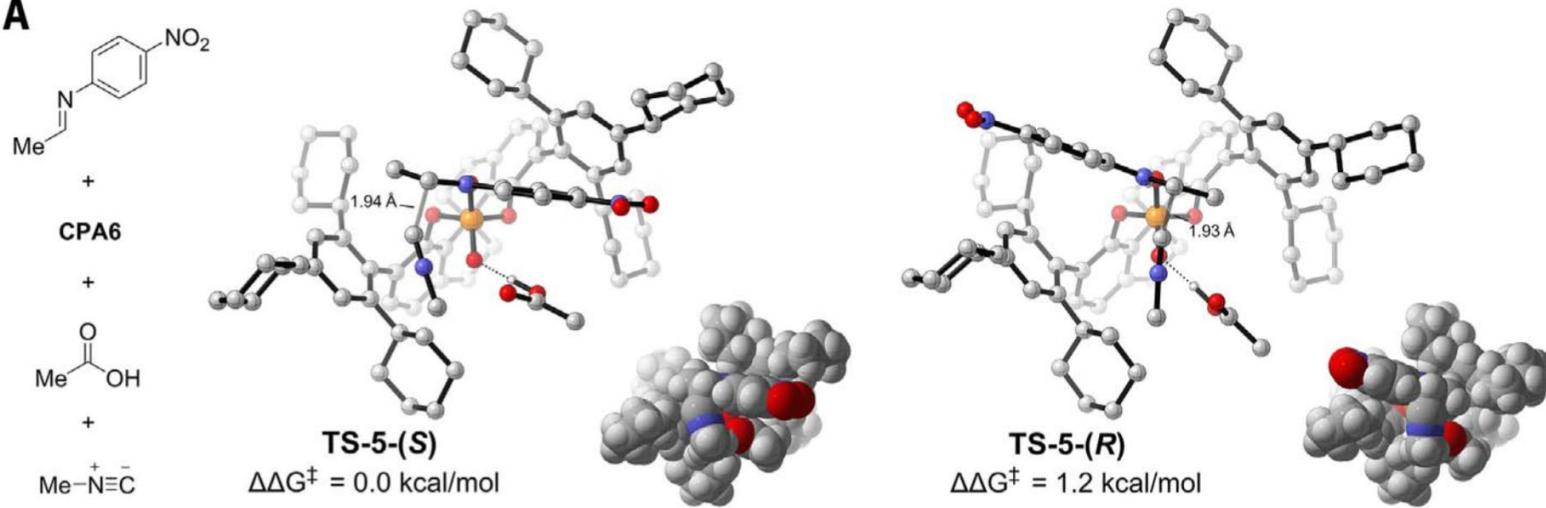
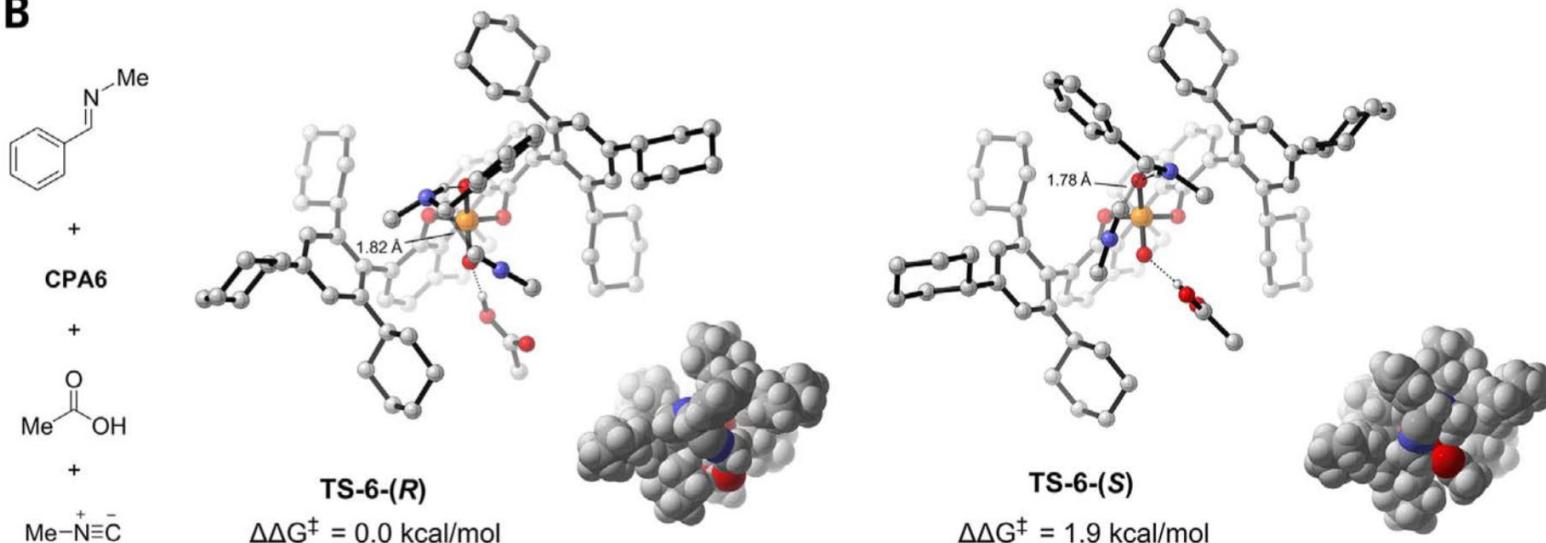
Acid-heterodimer-catalyzed
 $\Delta G^\ddagger = 15.7 \text{ kcal/mol}$
lowest barrier



Asymmetric Ugi and Passerini Reactions

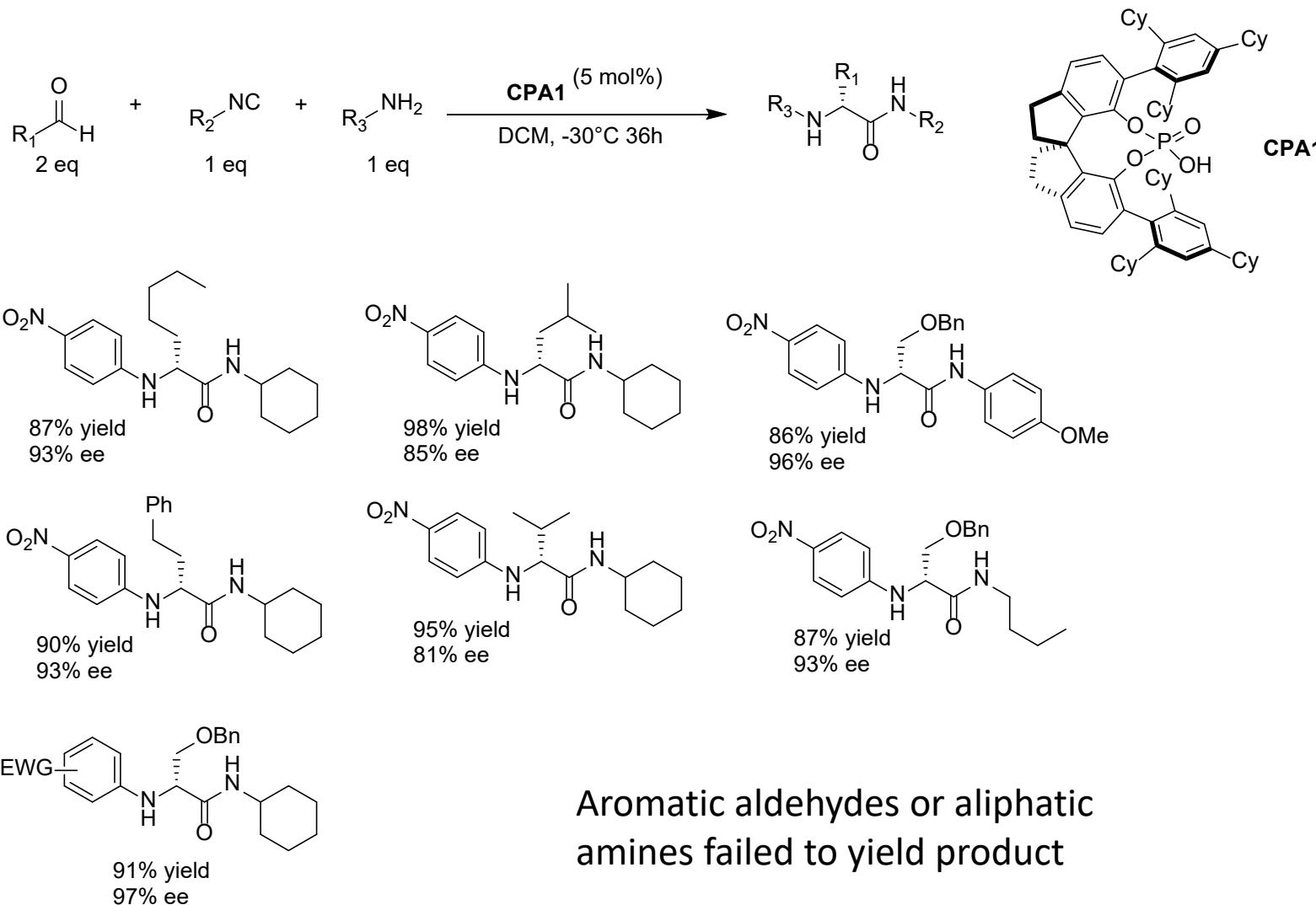


Asymmetric Ugi and Passerini Reactions

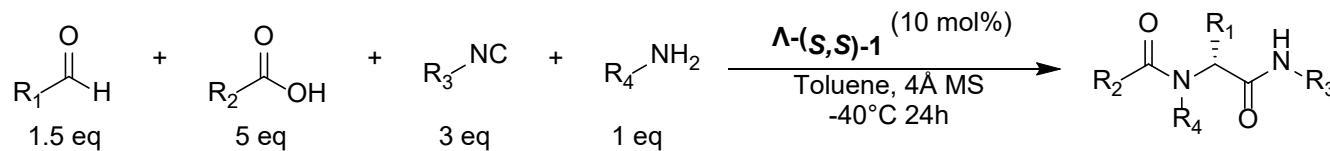
A**B**

Asymmetric Ugi and Passerini Reactions

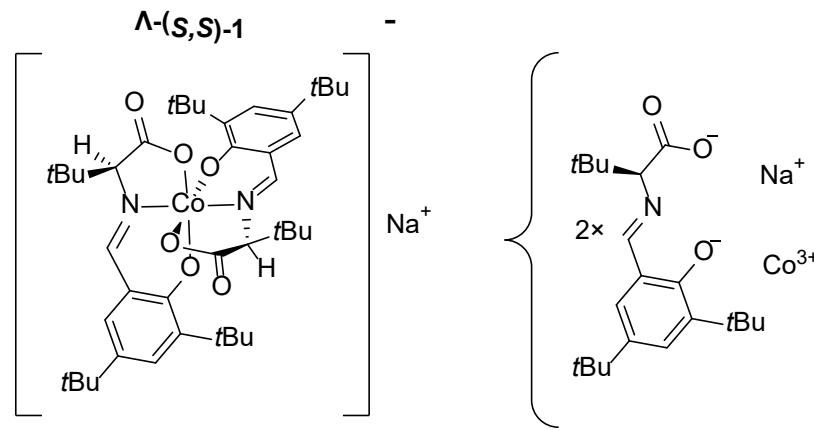
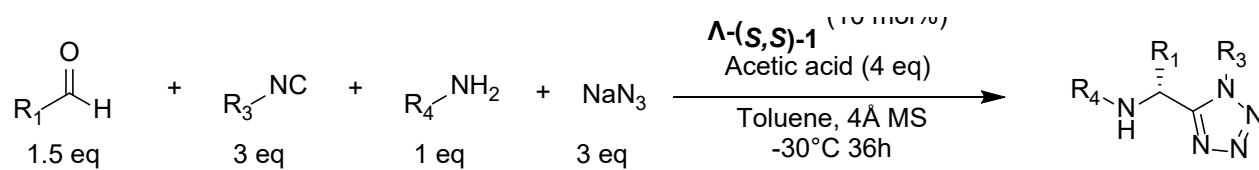
Tan, 2020



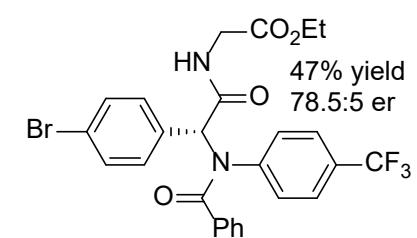
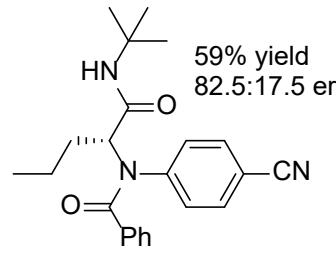
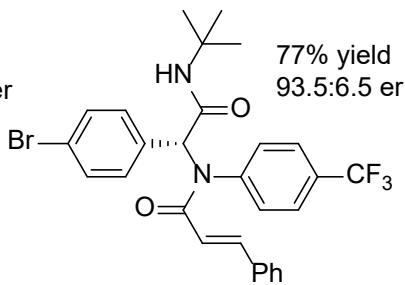
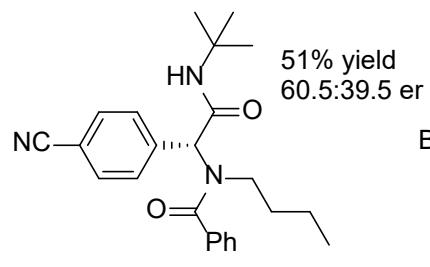
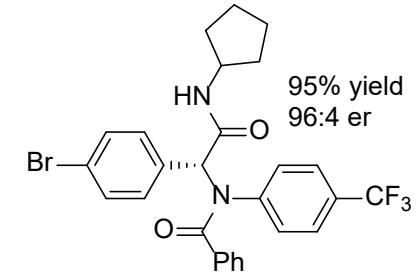
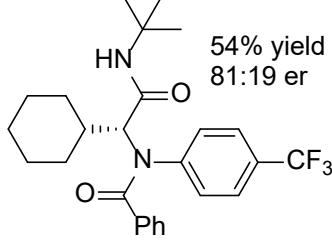
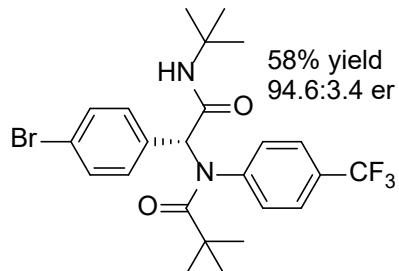
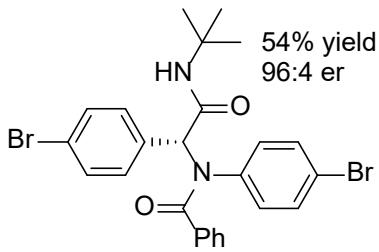
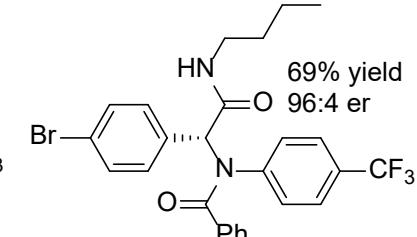
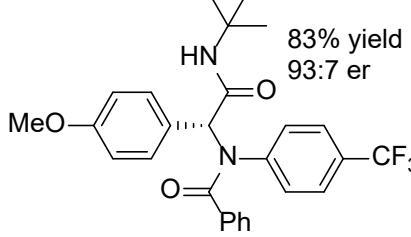
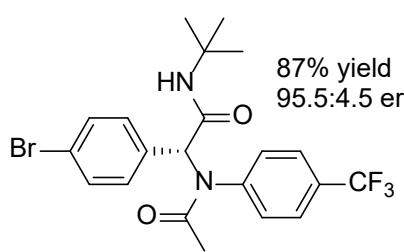
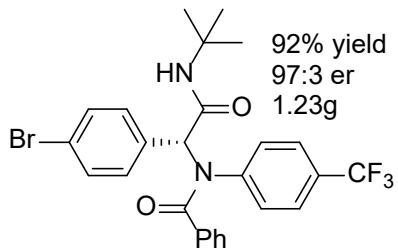
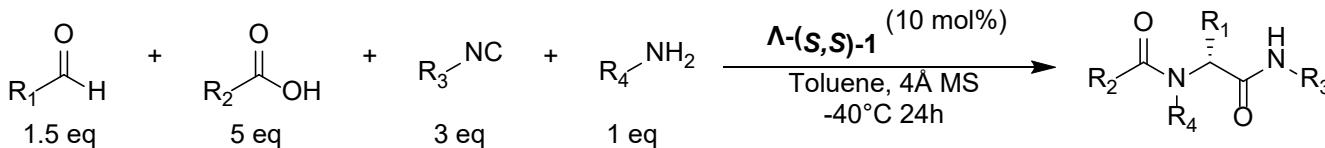
Asymmetric Ugi and Passerini Reactions



Yu, 2022

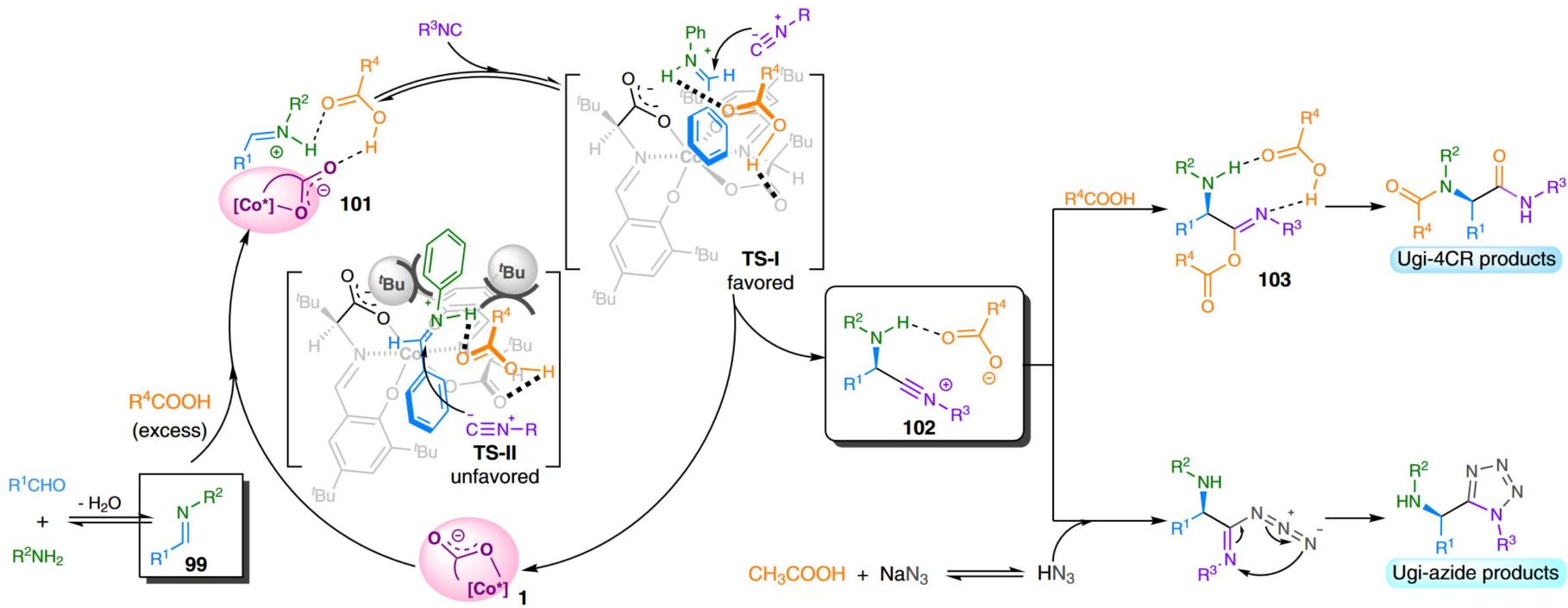
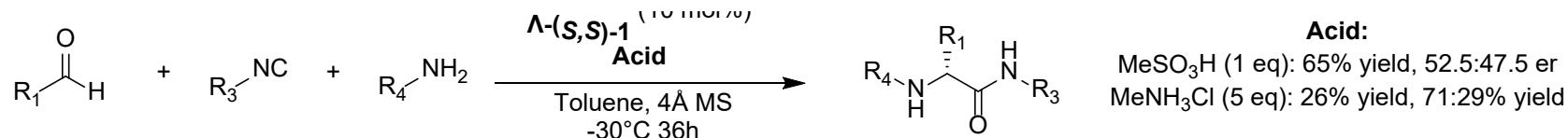


Asymmetric Ugi and Passerini Reactions

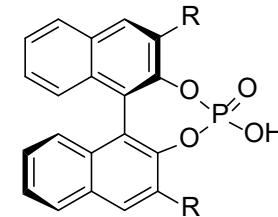
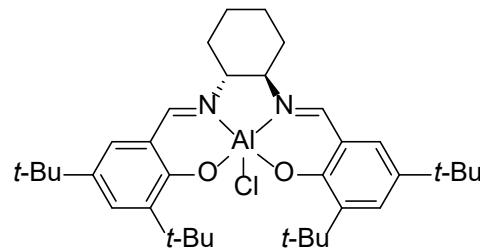


Asymmetric Ugi and Passerini Reactions

- Both Ugi and Ugi-azide reactions are $\sim 1^{\text{st}}$ order in imine, carboxylic acid, and catalyst
- Ugi-azide is 0 order in azide

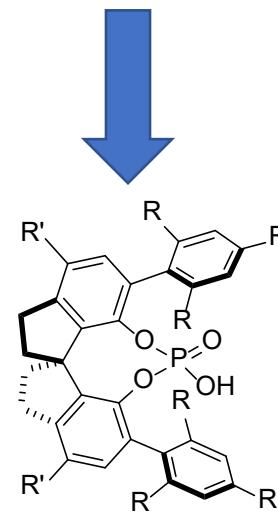
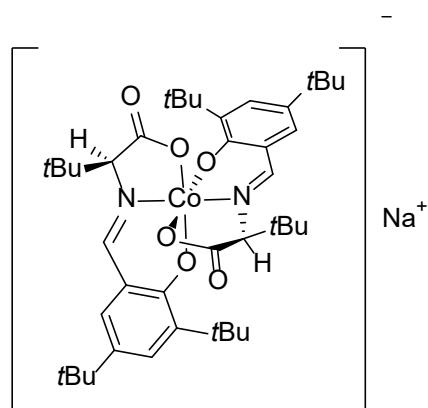


Summary



Intramolecular Passerini-type Reactions

Asymmetric Passerini and Intramolecular Ugi-4CR



Asymmetric Ugi-4CR

Asymmetric Ugi-4CR and Ugi-3CR

Questions?