"Copper(II)-Catalyzed Highly Enantioselective Addition of Enamides to Imines: The Use of Enamides as Nucleophiles in Asymmetric Catalysis"

Matsubara, R.; Nakamura, Y.; Kobayashi, S.
Angew. Chem. Int. Ed. **2004**, *43,* 1679-1681.

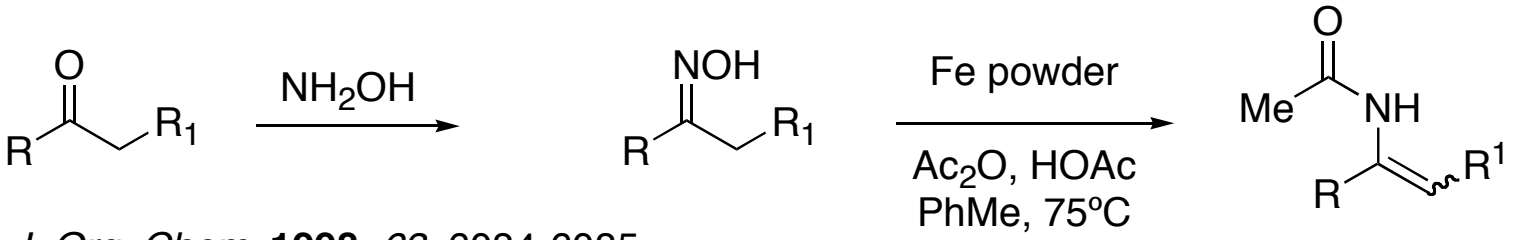
Current Literature
Tyler Benedum
3.27.04

Outline

- General preparation of enamides
- Enamide-use in organic synthesis
- Overview of current literature
- Mechanistic studies
- Synthetic utility
- Applications
- Highlights and lowlights
- Future endeavors

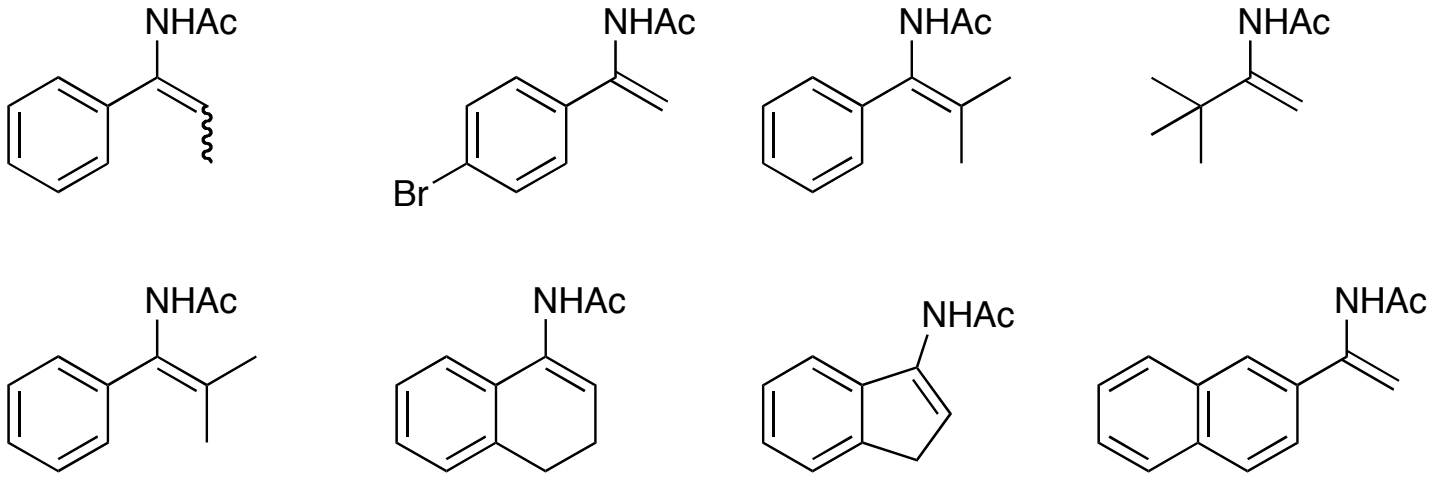
Preparation of Enamides

- Enamides
  - Easily prepared, handled, and stored



J. Org. Chem. **1998**, *63*, 6084-6085.

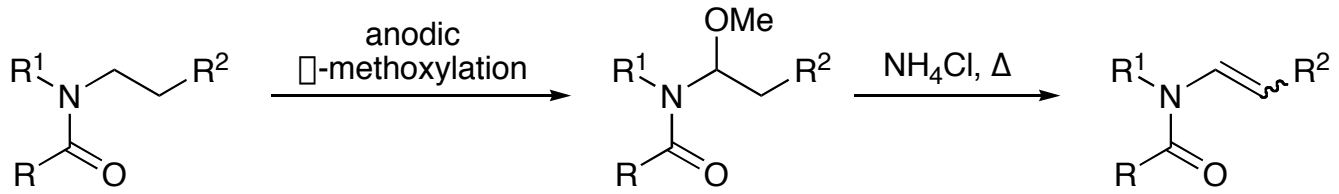
(*E/Z* mixture)



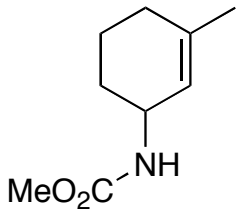
Preparation of Enamides

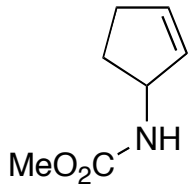
- An alternative route:

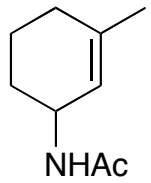
J. Am. Chem. Soc. **1982** *104*, 6697-6703.

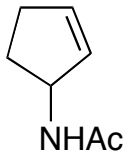


R = OMe, OBn, Me, Ph, or H
R^1, R^2 = alkyl



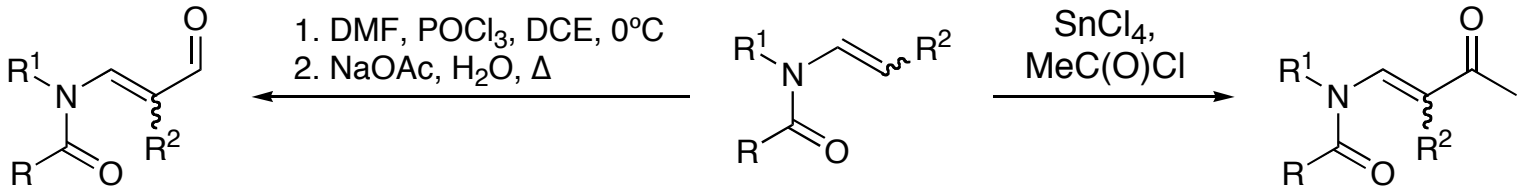






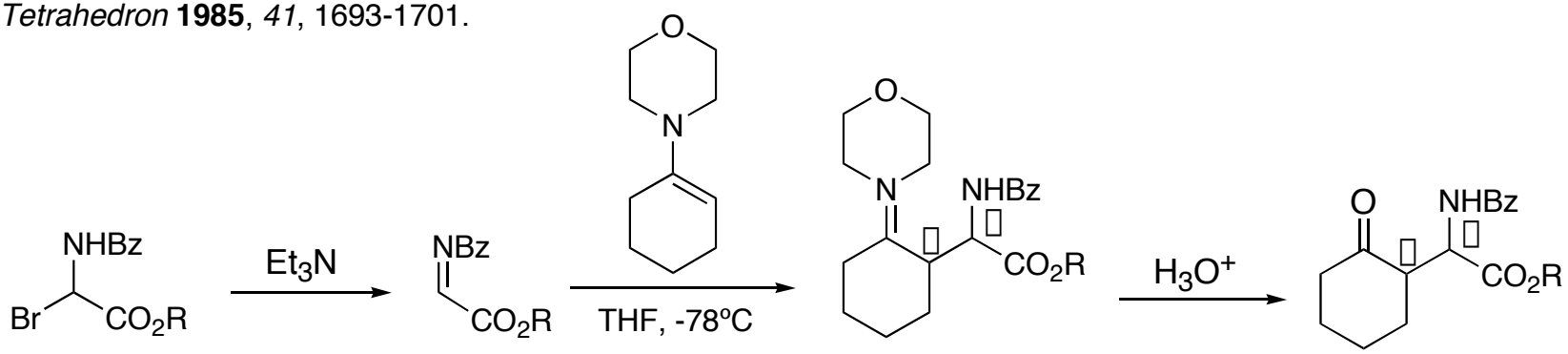
Enamides in Organic Synthesis

J. Am. Chem. Soc. **1982** *104*, 6697-6703.



Previous Work by Steglich and Enders

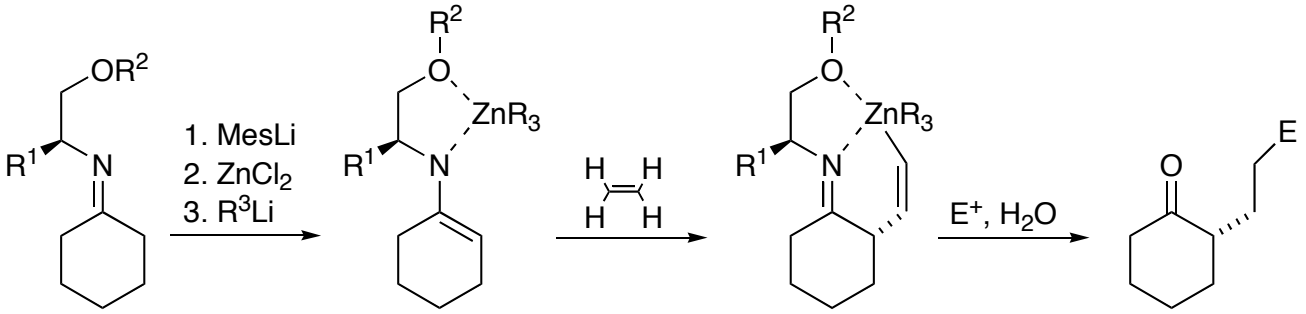
Tetrahedron **1985**, *41*, 1693-1701.



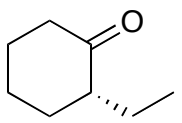
R = Me
Et
(-)-menthyl
(+)-menthyl

Previous Work by Nakamura, M.

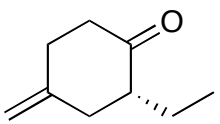
J. Am. Chem. Soc. **2003** *125*, 6362-6363.



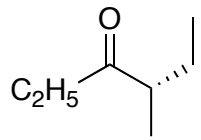
R^1 = *i*-Pr, *t*-Bu, or Ph
R^2 = Me, Me_3Si, or *t*-$BuMe_2Si$
R^3 = Me, *t*-Bu, *n*-Bu, or Mesityl



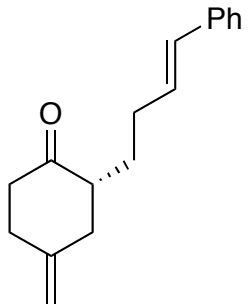
(95%ee, 91% yield)



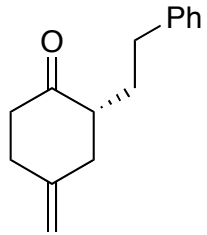
(91%ee, 93% yield)



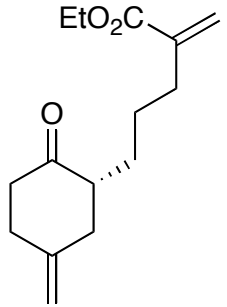
(58%ee, 81% yield)



(97%ee, 90% yield)



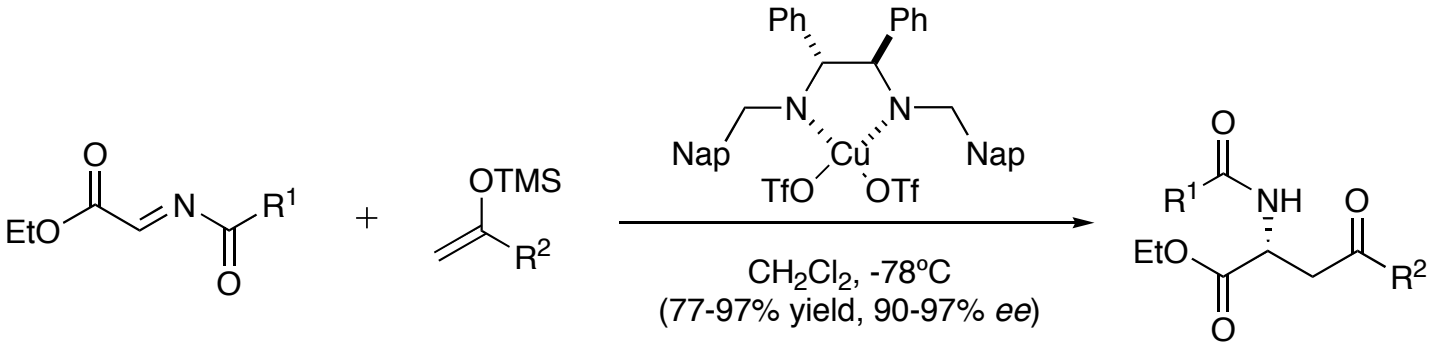
(97%ee, 83% yield)



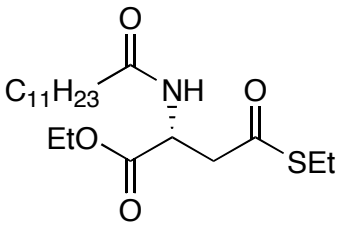
(87%ee, 84% yield)

Previous Work by Kobayashi

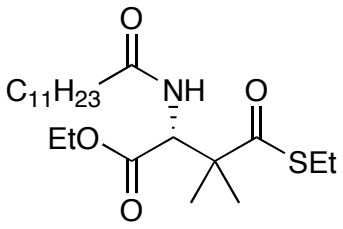
- Varied copper salts, diamine ligands, reaction conditions, enolate substituents



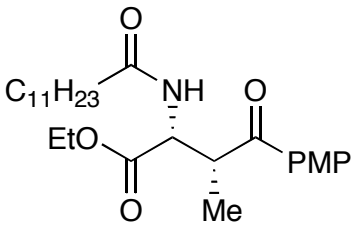
R^1 = $C_{11}H_{23}$, Me, or Ph
R^2 = Ph, MeOPh, ClPh, MeO, or EtS



(6% ee, 89% yield)



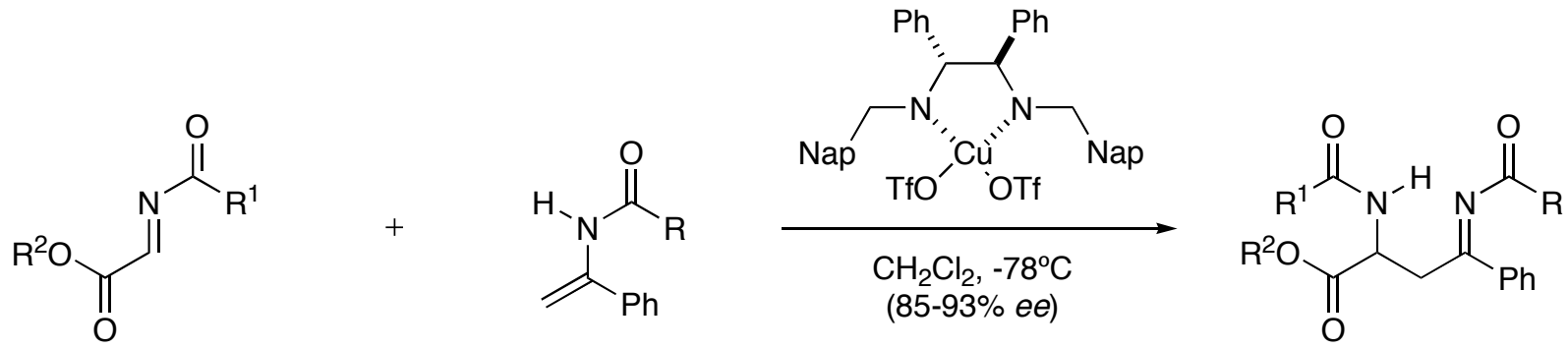
(90% ee, 92% yield)



(94% ee, 92% yield)

The Current Literature

- Original studies:

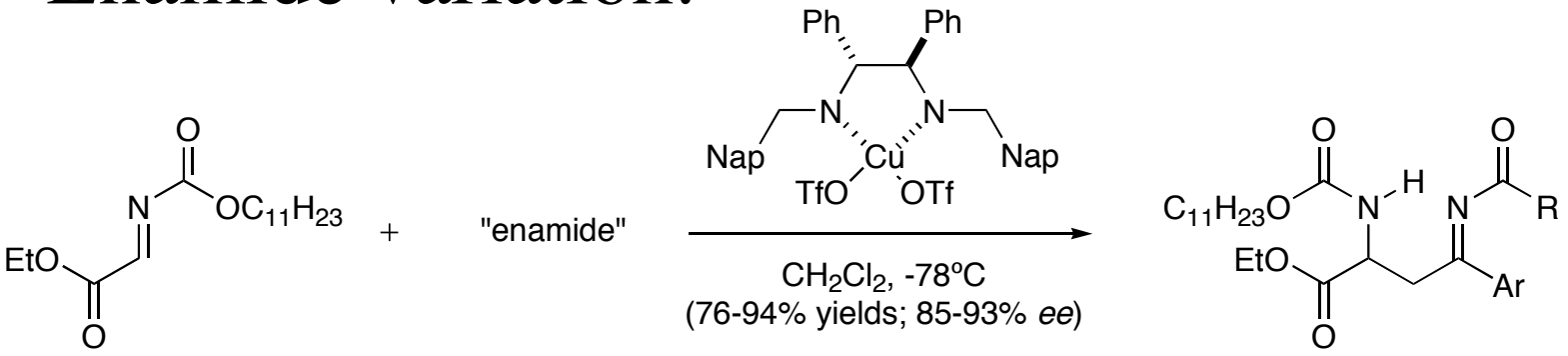


R^1 = $C_{11}H_{23}$, Me,or O*t*-Bu
R^2 = Et or Bn

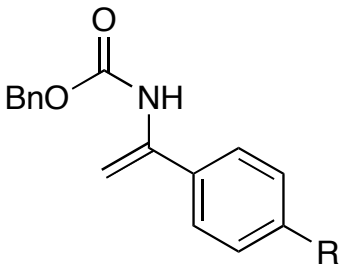
R = Me, OEt, O*t*-Bu, or OBn

The Current Literature

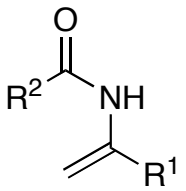
- Enamide variation:



Enamide =

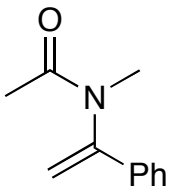


R = OMe, Cl, Me



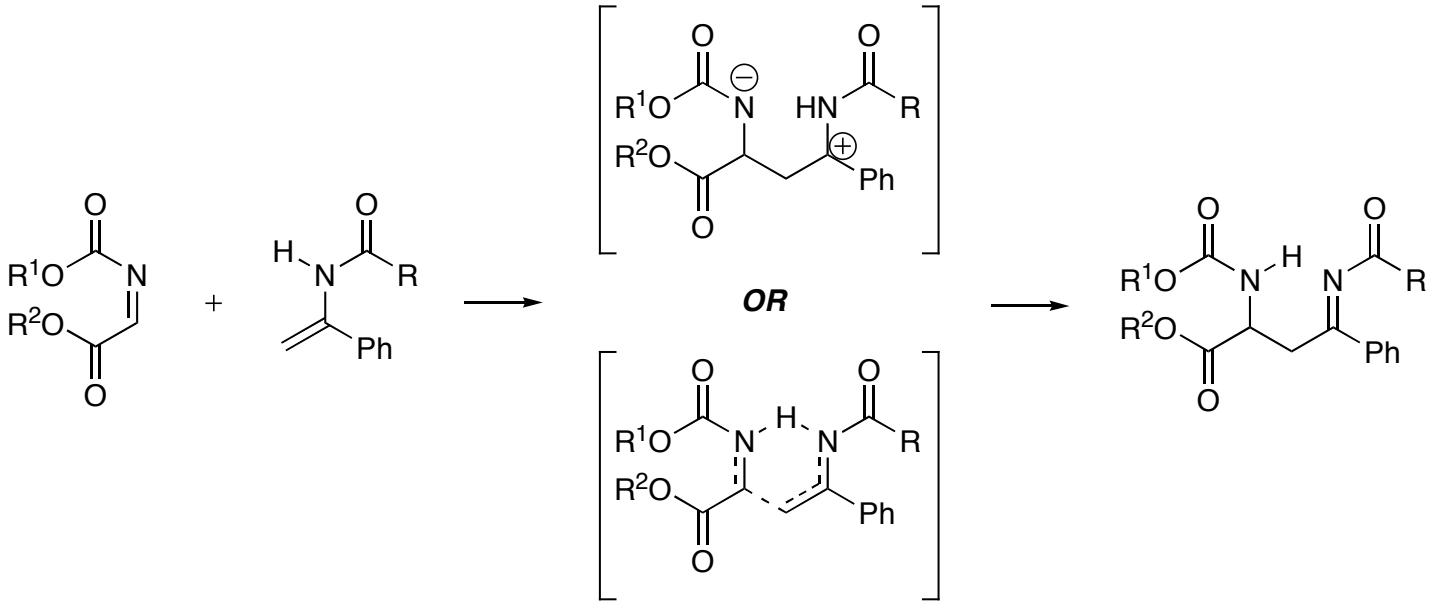
R^1 = 2-naphthyl
R^2 = OBn

R^1 = Me
R^2 = Et



Mechanistic Studies

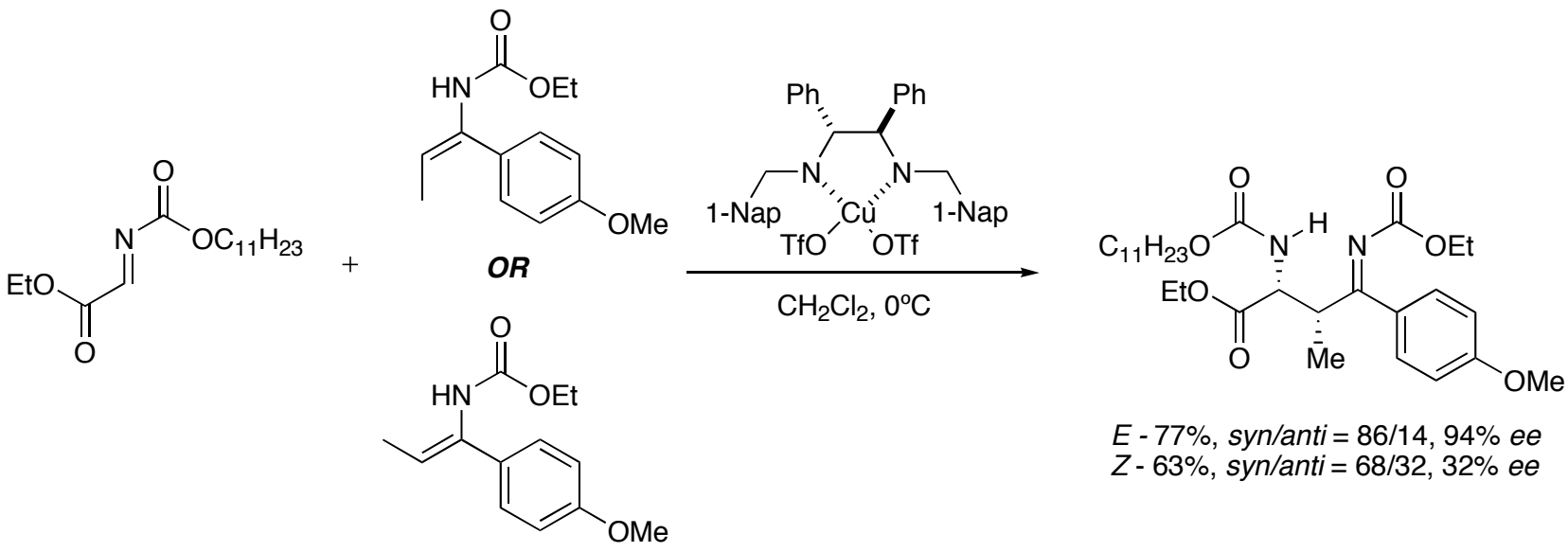
- Concerted or stepwise pathway?



- Unclear, but studies are underway

Support for Acyclic T.S.

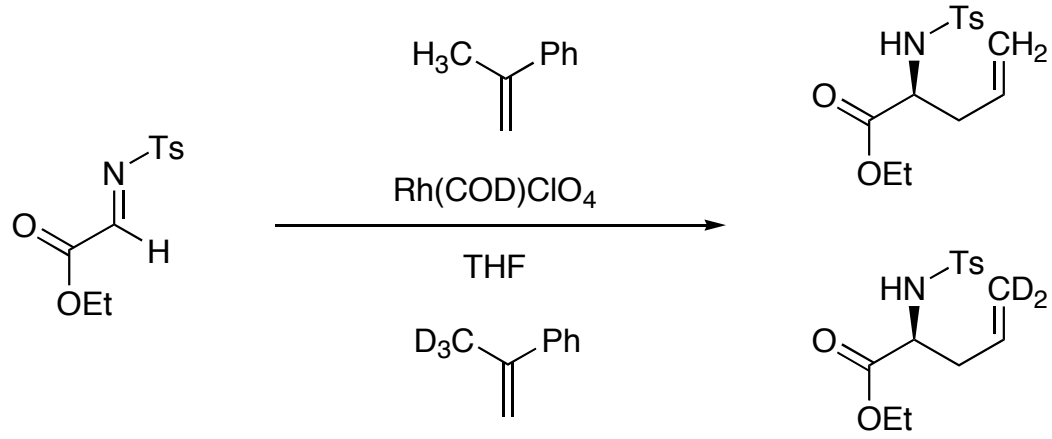
- Possibly stepwise mechanism…



E - 77%, *syn/anti* = 86/14, 94% *ee*
Z - 63%, *syn/anti* = 68/32, 32% *ee*

Related Mechanistic Studies

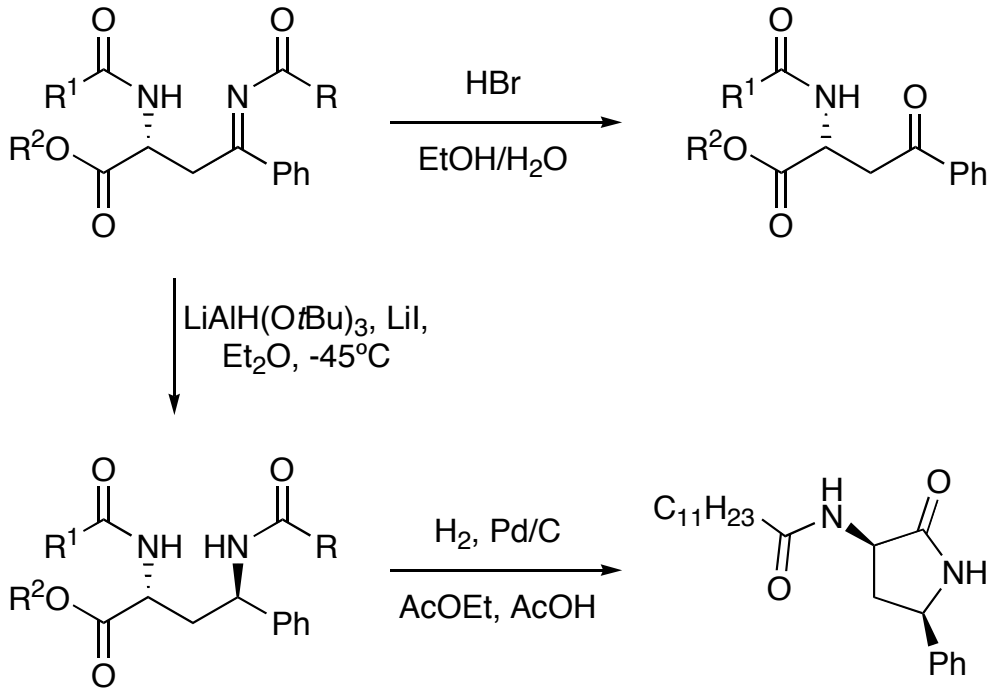
- Kinetic isotope studies



- $k_H/k_D = 4.4$
  - consistent with transfer of H(D) in transition state

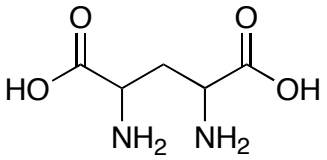
Synthetic Utility

- Optically active amino acids
- 1,3-Diamino substrates
- Lactams

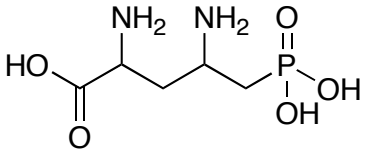


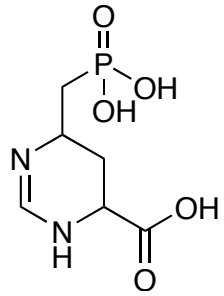
Applications

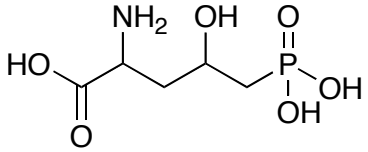
- Diaminoglutamic acids
  - Identifying and mapping role of glutamic acid receptors for possible treatment of brain disorders such as Alzheimer's and schizophrenia



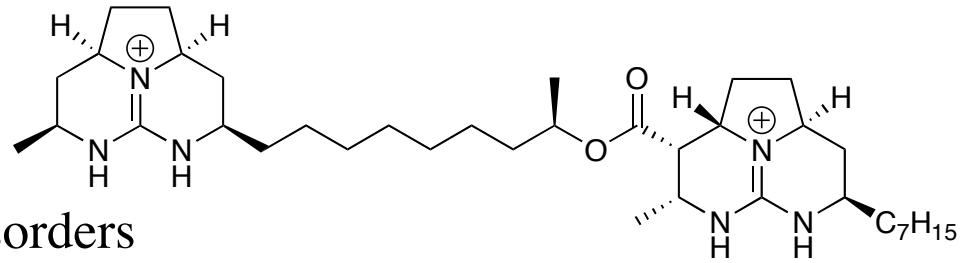
- *N*-Methyl-D-aspartate receptor antagonists







- Batzelladine F
  - induce dissociation of protein tyrosine kinase p56
  - used to treat autoimmune disorders



Highlights

- Enamides are easily:
  - Prepared, handled, stored
- Possibility to obtain similar products as aldol reactions (but considerable work needs to be done)
- First enantioselective enamide addition to imines using chiral catalyst
  - □-aminoimines, □-aminoketones, 1,3-diamines
- Yields (70-97%) and *ee*'s (83-93%)

Future Endeavors

- Functional group tolerance
- Improve 1,3-diamine *syn*/*anti*-selectivity
- Increase selectivity with (*E*)- and (*Z*)-2-methyl-substituted enamides
- Elucidate reaction mechanism and catalyst structure