The Biginelli and Related (Passerini and Ugi) Reactions

Mike DeMartino

Group Meeting: August 27, 2003

Overview

- How these reactions are related
- The Biginelli Reaction
  - Mechanism
  - Modifications and chemical manipulation
  - Biology
  - Synthetic examples
- The Passerini Reaction
  - Mechanism
  - Synthetic examples
- The Ugi Reaction
  - Mechanism
  - Synthetic Reactions
- Concluding Remarks

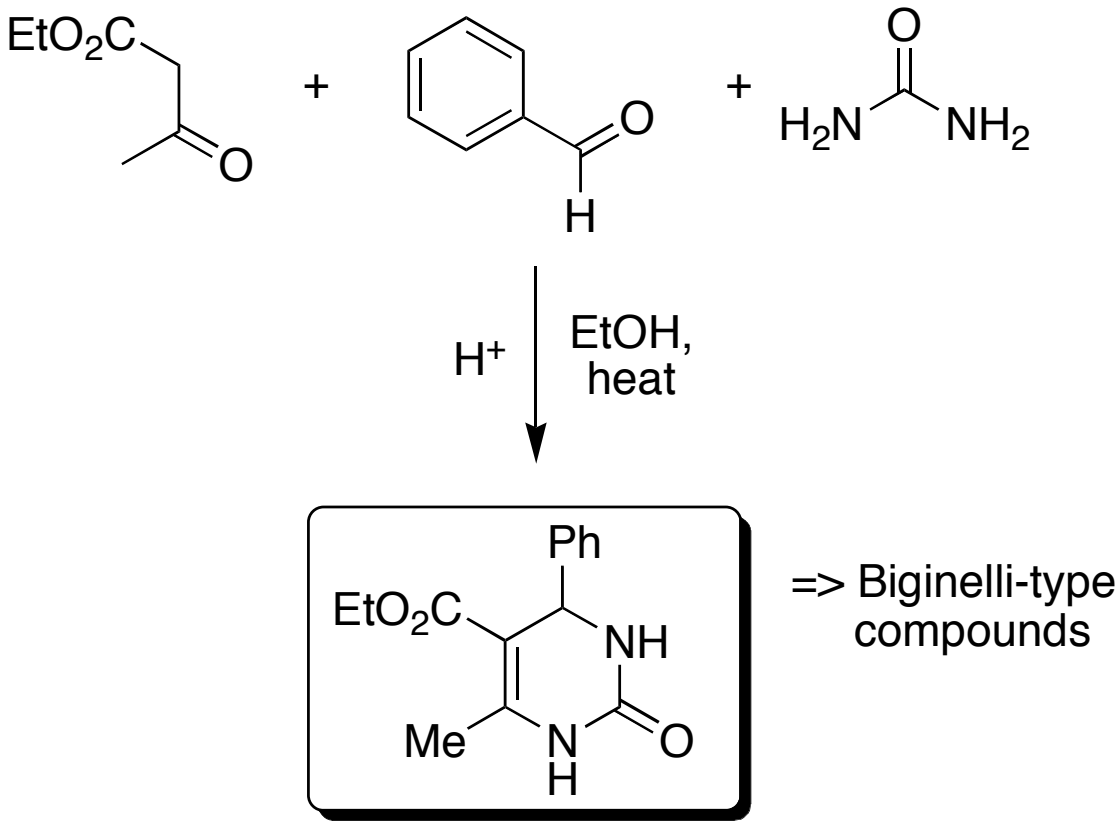
Similarities

- All are multicomponent Reactions (MCRs)
  - In MCRs, “three or more reactants come together in a single reaction vessel to form products that contain portions of all the components.”
    - » Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
  - Has advantages over traditional linear syntheses.
- Manifestations in a variety of chemical sects.

The Biginelli Reaction

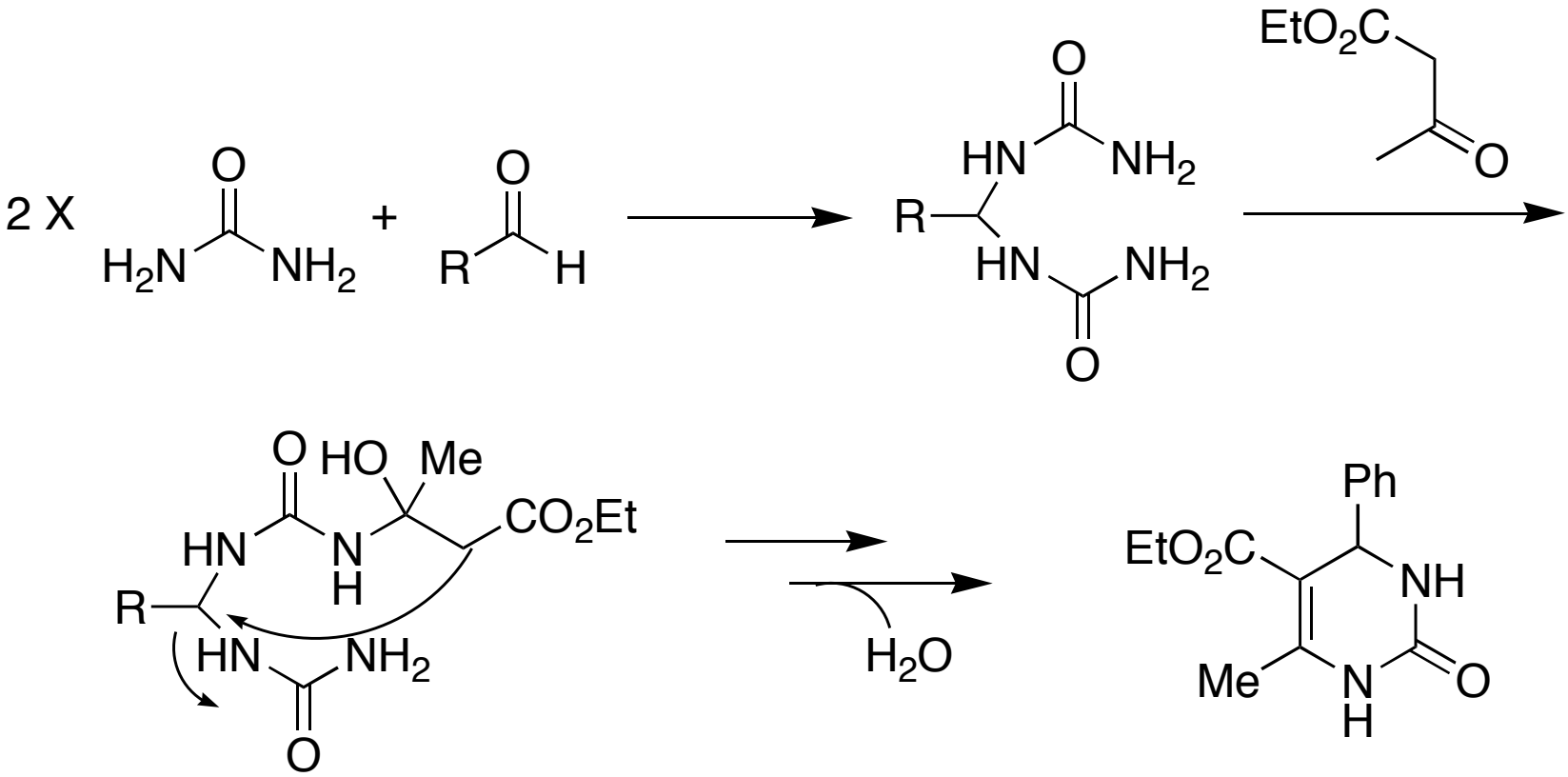
The Biginelli Reaction

- Synthesis of 3,4-dihydropyrimidin-2(1H)-ones was discovered in 1893 by Pietro Biginelli
  - » Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.



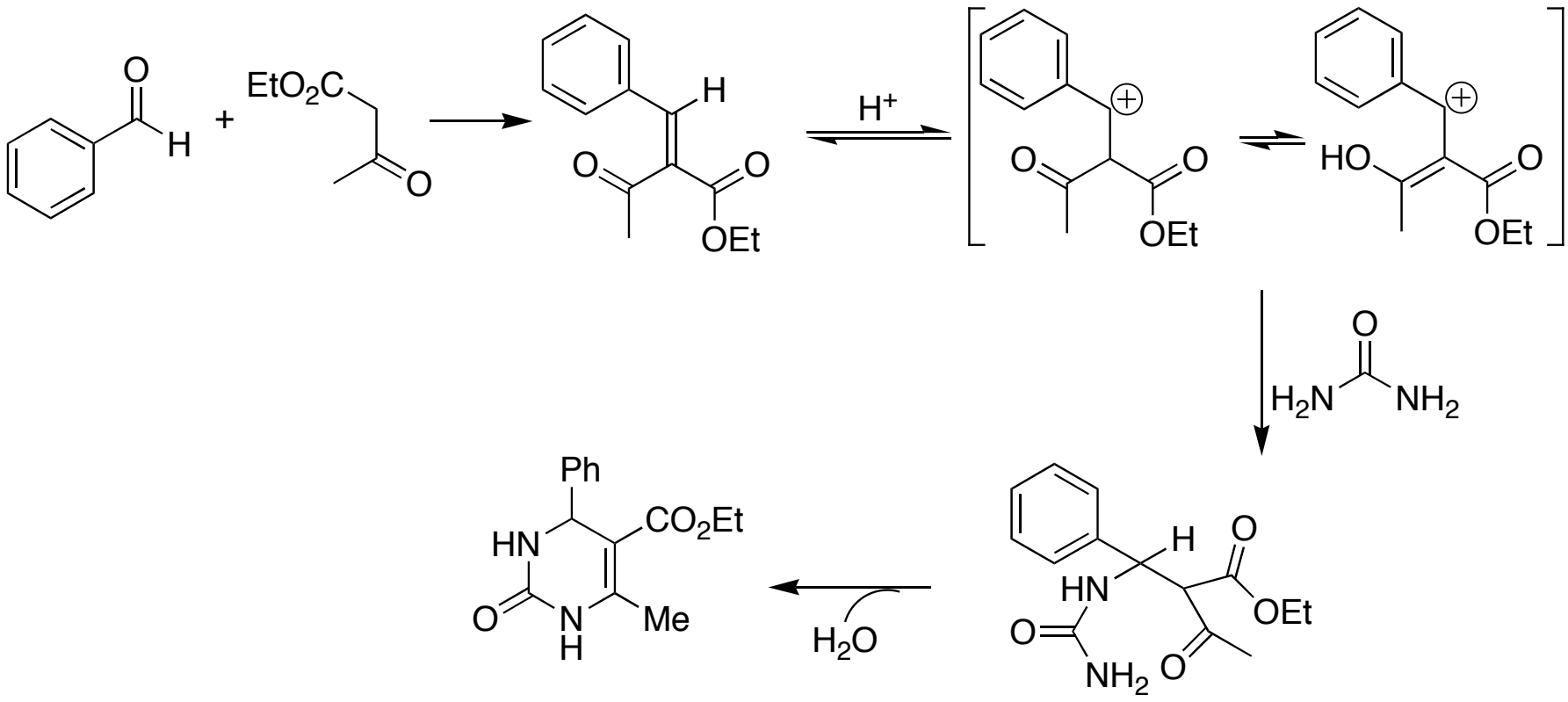
The Mechanism: a Century of Uncertainty

- First proposal in 1933
  - » Folkers, K., Johnson, T.B. *J. Am. Chem. Soc.* **1933**, *55*, 3784.



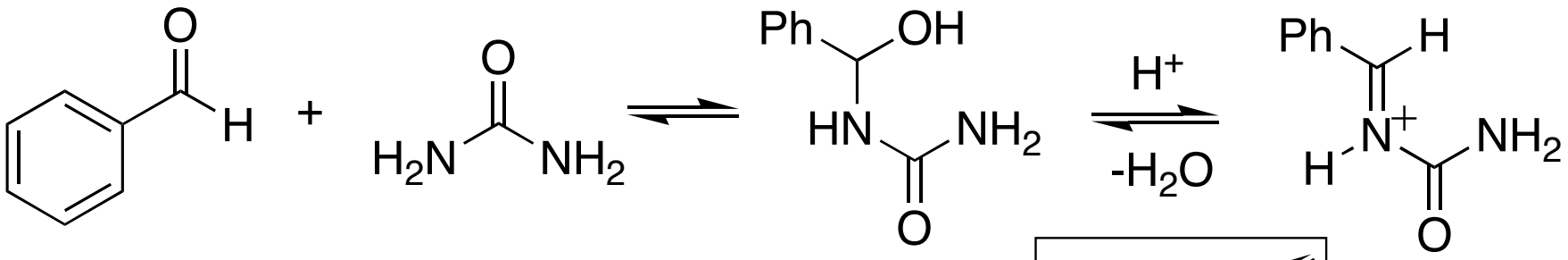
The Mechanism: a Century of Uncertainty

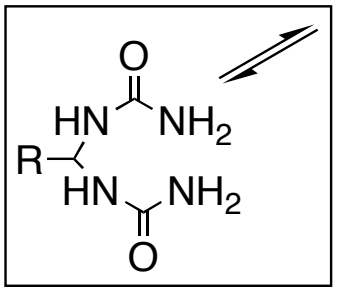
- Second proposal in 1973
  - » Sweet, F., Fissekis, J.D.. *J. Am. Chem. Soc.* **1973**, *95*, 8741.

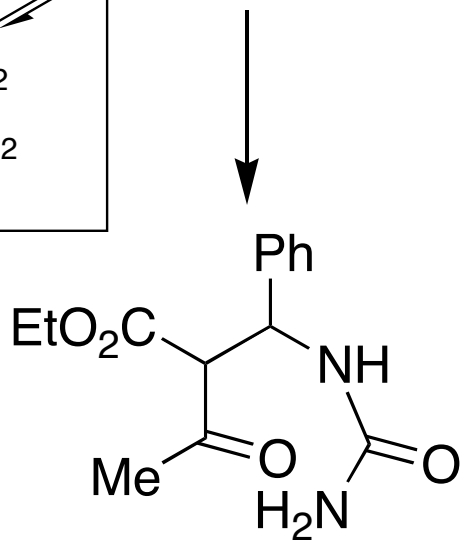


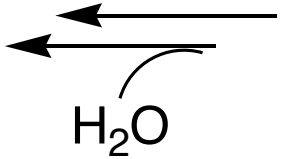
The Mechanism: a Century of Uncertainty

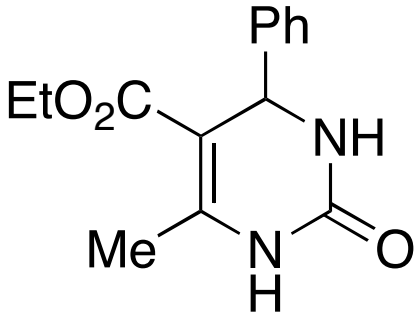
- Latest proposal in 1997
  - » Kappe, C.O. *J. Org. Chem.* **1997**, *62*(21), 7203.

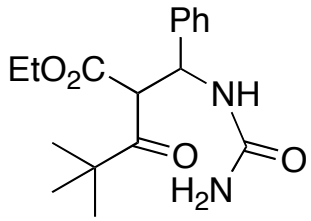








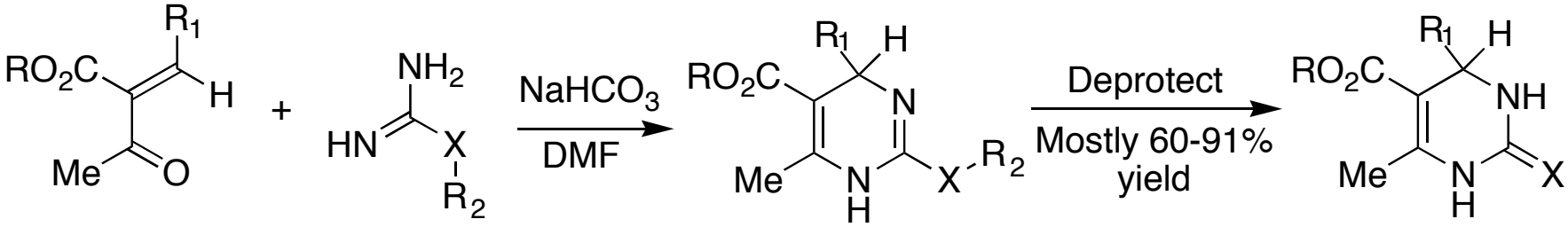




Hu, E.H., *et.al.*
J. Org. Chem. **1998**. *63*, 3454.

The Atwal* modification

- Brought about by the need for better yields:
  - Ortho-substituted aryl aldehydes
  - Aliphatic aldehydes



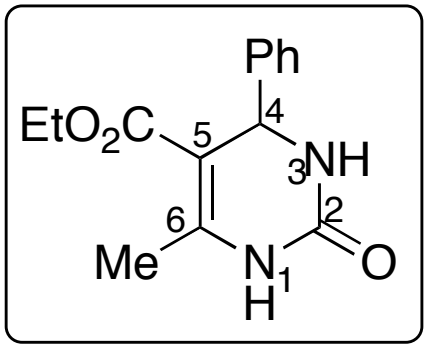
X = O, S (With an appropriate protecting group)

- Since R_1 can be significantly varied w/little affect on yield, the "finicky" aldehyde problem can be circumvented.

*Atwal, K. S., *et. al.* *J. Org. Chem.* **1989**, *54*, 5898.

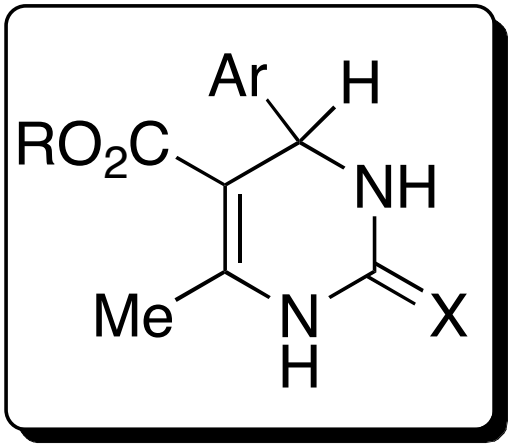
Synthetic Manipulation

- So, with the dihydropyrimidine in hand, what can be done?
  - Partial of full oxidation (not trivial)
  - Reduction of the ring to the hexahydropyrimidine
  - Alkylation and acylation of the heteroatoms
  - Manipulation of the ester at C(5)
  - Manipulation of the methyl group at C(6) (halogenation, nitration, etc.)
  - Ring condensing reactions to make bi,tri-cycles



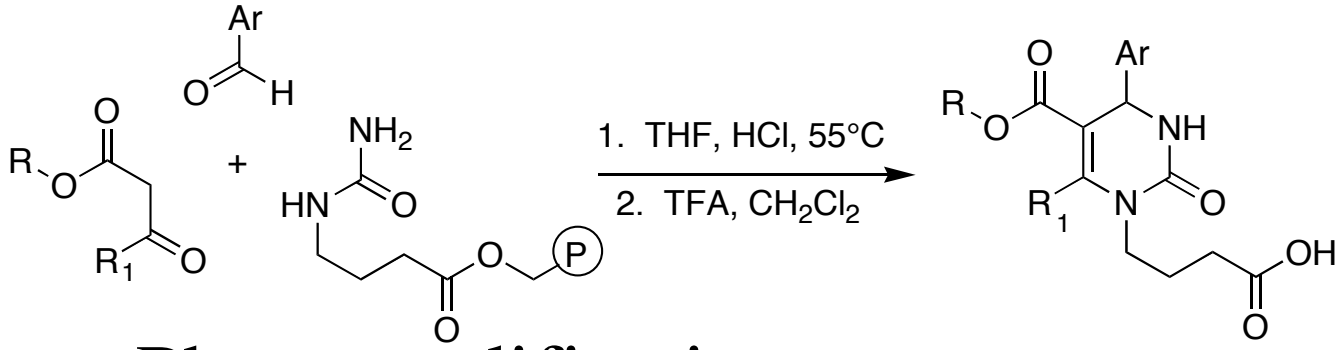
Biology

- The biological activity is what make these pyrimdines such attractive targets
  - (A 1930 patent for use of a Biginelli cmpd for protection of wool from moths!?!)
  - Antiviral activity
  - Antibacterial activity
  - Antitumor
  - Antiinflammatiry
  - Analgesic
  - Blood palette aggregation inhibitor
  - Cardiovascular activity
  - Potent calcium channel blockers
  - Etc.

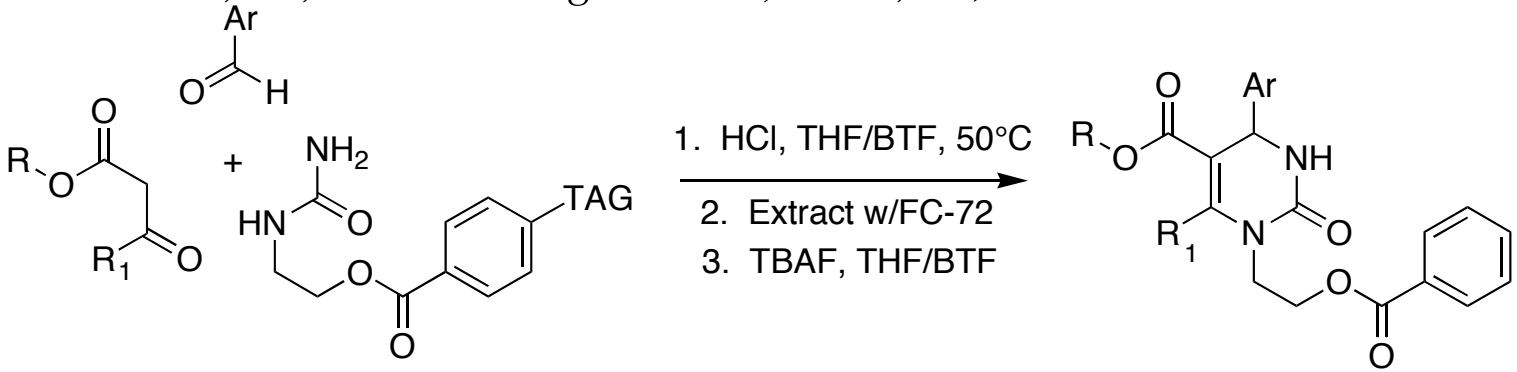


Synthetic Examples

- Solid phase synthesis for combinatorial scaffolds of Biginelli compounds
  - First example: Wipf, P., Cunningham, A. *Tet. Lett.* **1995**, *36*, 7819.



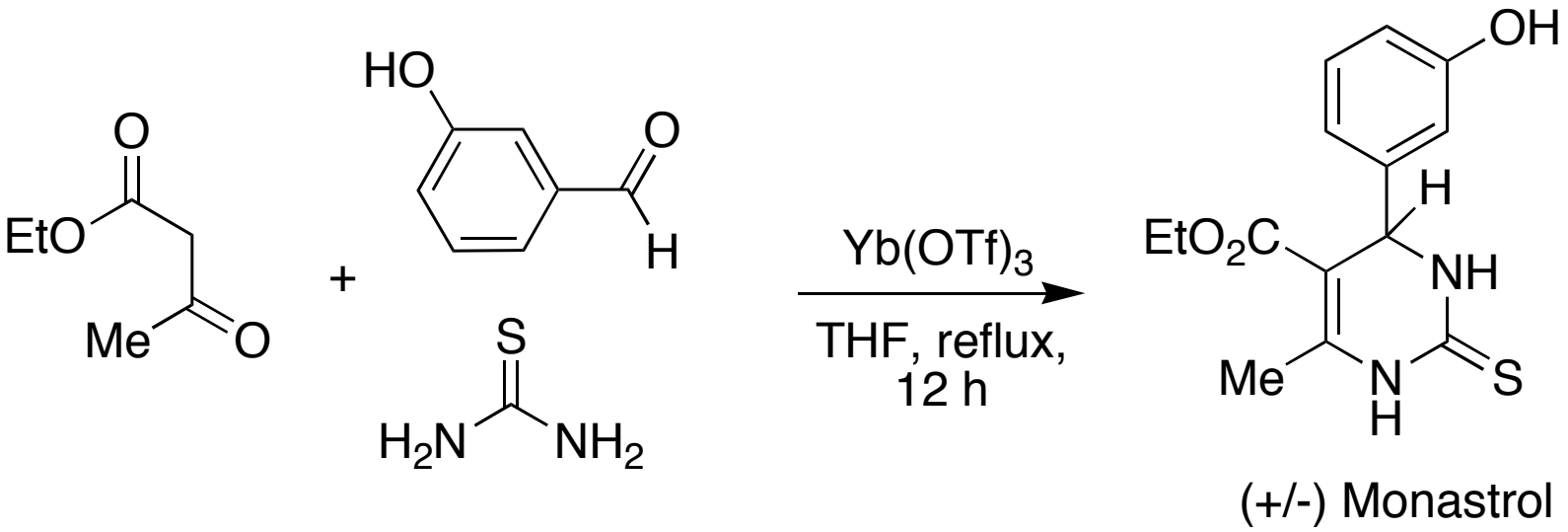
- Fluorous-Phase modifications
  - Studer, A., *et. al. J. Org. Chem.*, **1997**, *62,* 2917.



Tag = $Si(CH_2CH_2C_{10}F_{21})_3$

Synthetic Examples

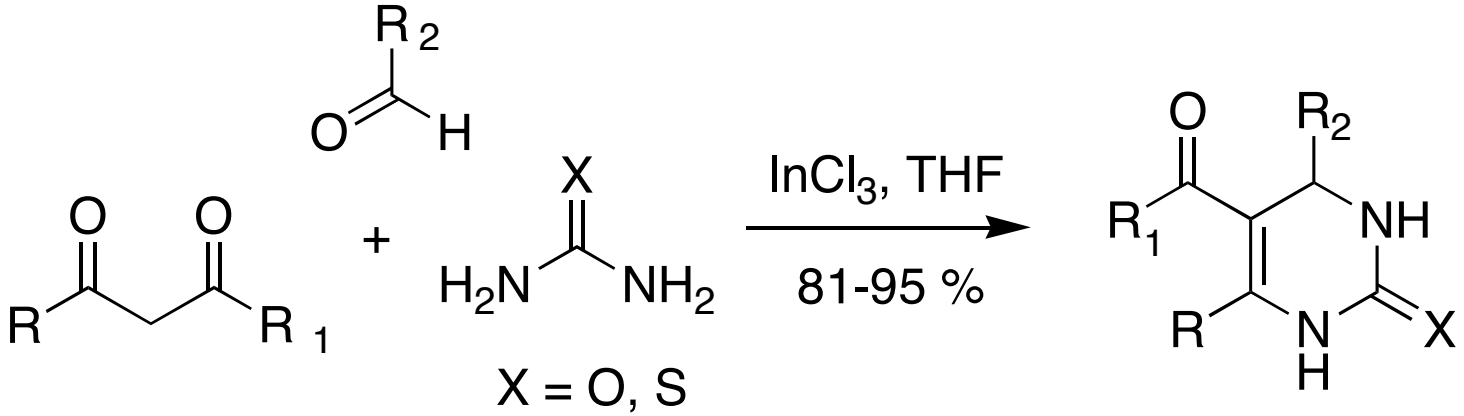
- Synthesis of *rac*-Monastrol
  - Mitosis blocker by kinase Eg5 inhibition
  - Utilization and extension (to thioureas) of the $Yb(OTf)_3$ catalysis work
    - » Dondoni, A., *et. al. Tet. Lett.* **2001**, *43*, 5913



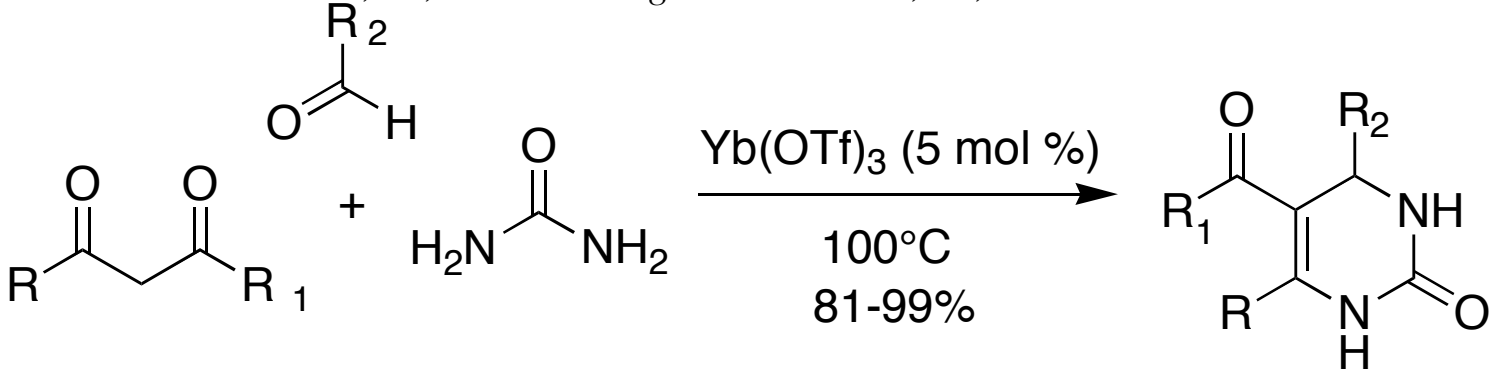
(+/-) Monastrol

Synthetic Examples

- Inorganic catalysis
  - Indium(III) Chloride mediated Biginelli reactions
    - » Brindaban, C. R., *et. al. J. Org. Chem.* **2000**, *65*, 6270

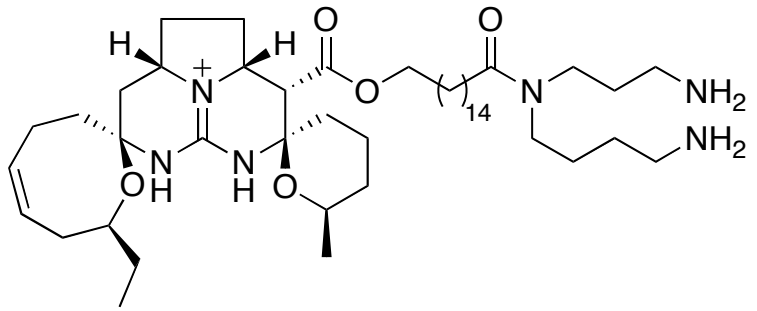


- Heavy-Metal catalysis
  - » Ma, Y., *et. al. J. Org. Chem.* **2000**, *65*, 3864

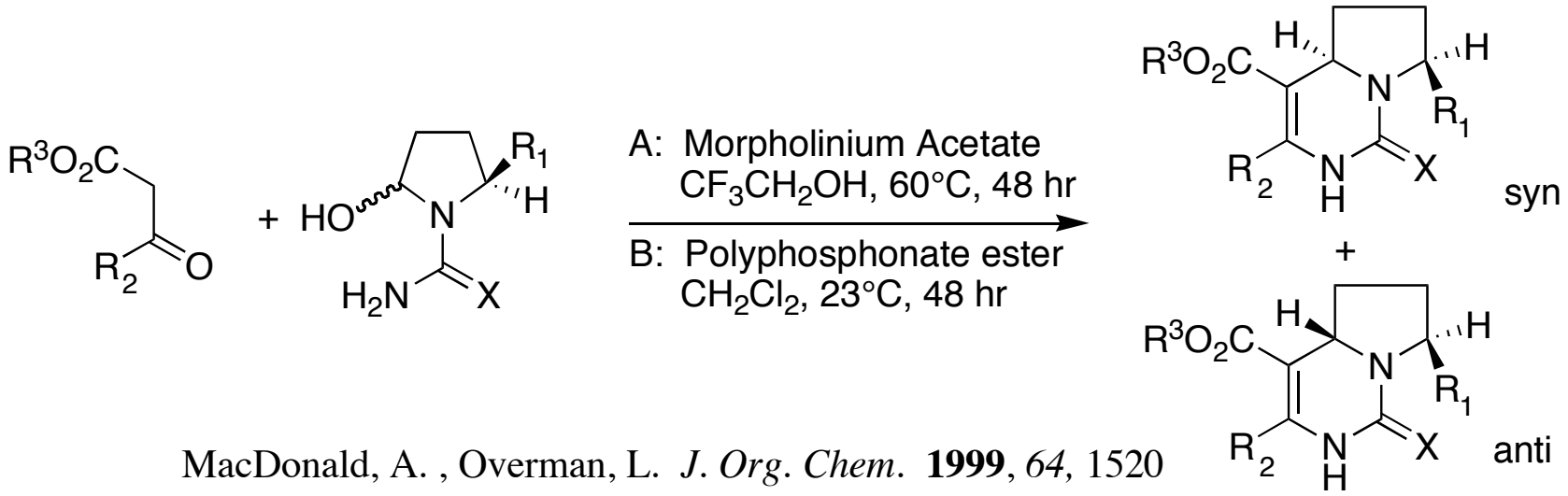


Synthetic Examples

- Natural Product Synthesis
  - The use of tethered Biginelli condensations for syntheses of structurally diverse guanidine alkaloids
    - (–)-Ptilomycalin A:



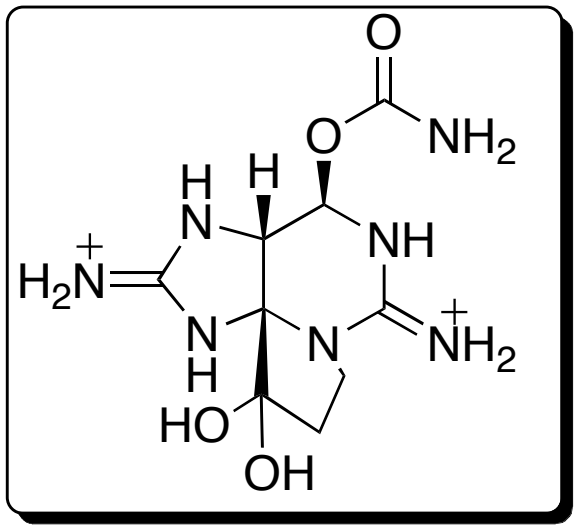
Overman, L., *et. al. J. Am. Chem. Soc.* **1995**, *117,* 2657



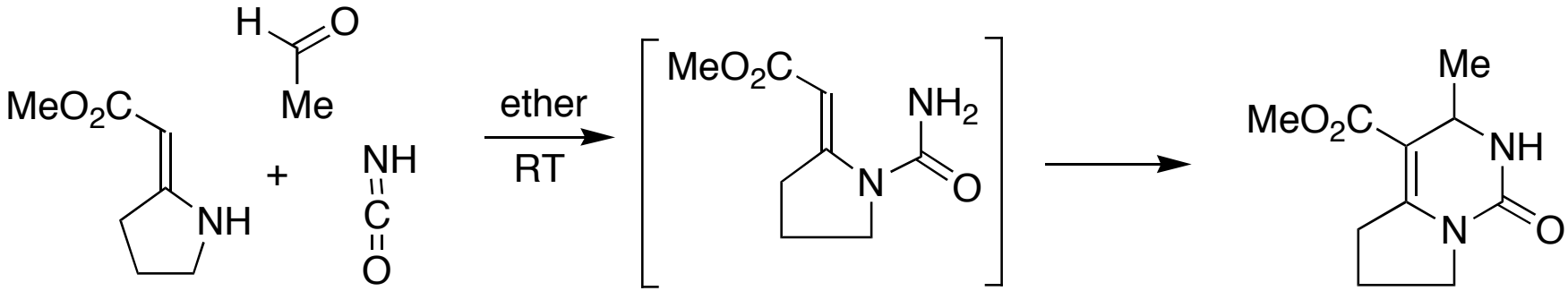
MacDonald, A. , Overman, L. *J. Org. Chem.* **1999**, *64,* 1520

Synthetic Examples

- Total synthesis of the HIGHLY POTENT NEUROTOXIN: Saxitoxin
  - Tanini, H. *et. al., J. Am. Chem. Soc.* **1977**, *99*, 2818



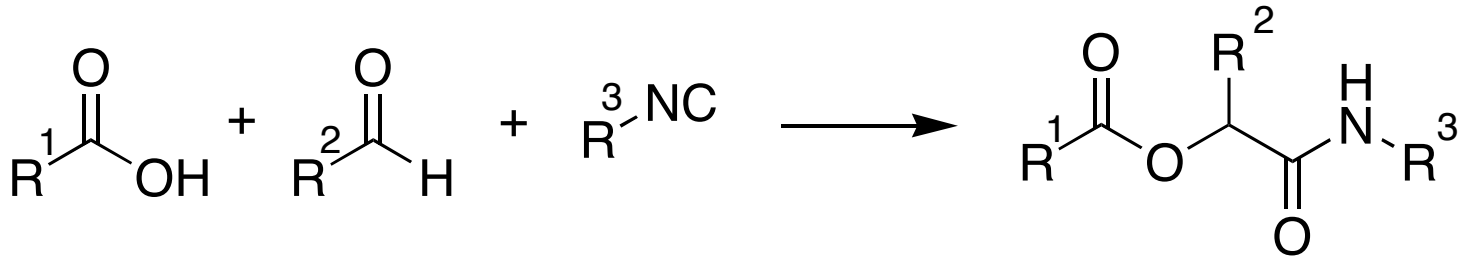
Key Step:



The Passerini Reaction

Details of the Passerini Reaction

- Discovered in 1921 by Passerini
  - » Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
- A three component reaction involving:
  - Aldehyde (or ketone)
  - Carboxylic Acid
  - Isocyanide
- Generally,



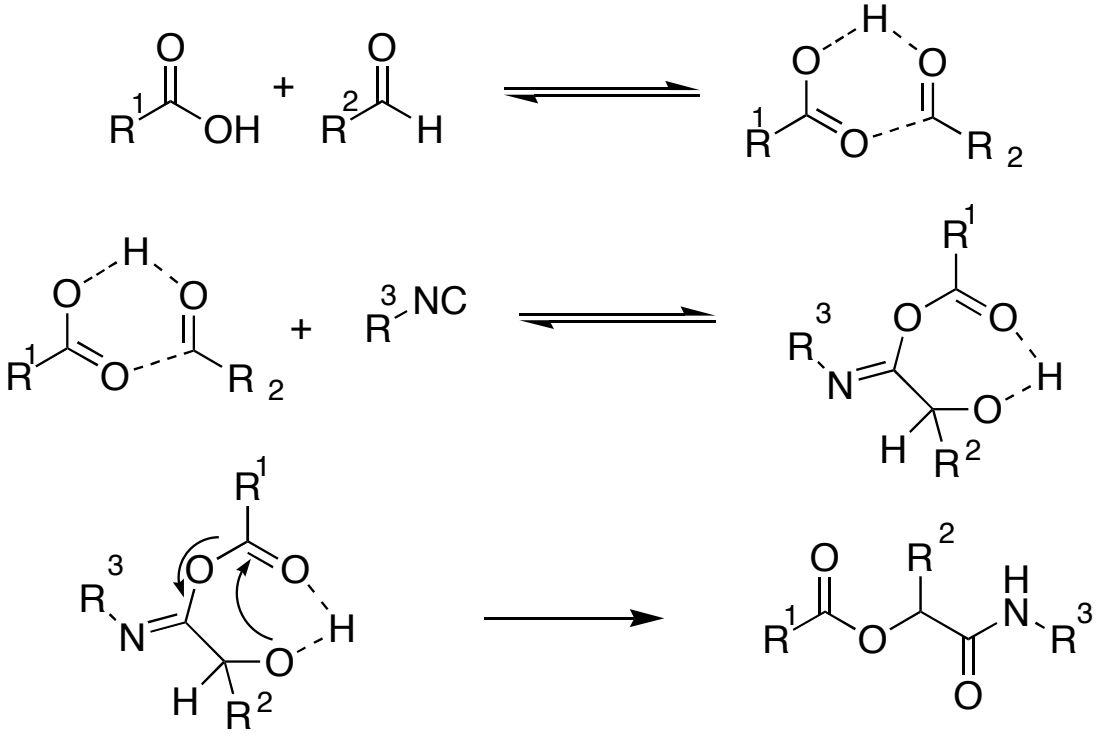
More on Isocyanides

- Only stable organic functionality with divalent carbon
- Found in many natural products

- Preparation: Dehydration of *N*-monosubstituted formamides with phosgene or derivatives thereof
- Like carbenes, isocyanides can react with both neucleophiles and electrophiles at the same carbon center
- Used heavily in the synthesis of various heterocycles

Mechanism

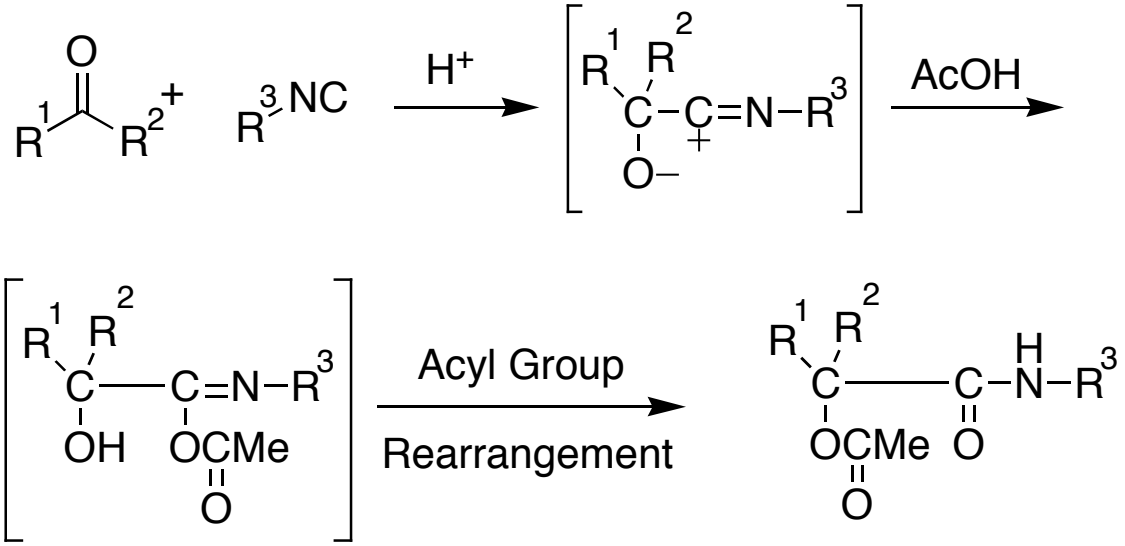
- Mechanism is still a subject of uncertainty
  - Kinetic studies were conducted
    - Termolecular reaction (3rd order rate law), first order in each of the reactants
      - » Baker, R.H., Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699.
  - Ugi discovered that the reaction is accelerated in aprotic solvents (indicating a non-ionic mechanism)
    - Based on this work (Ugi, I., Meyr, R., *Chem. Ber.* **1961**, *94*, 2229) and on the work of Baker *et. al.*, Ugi postulated the following mechanism:



Mechanism continued

- Most of the many suggested mechanisms suggest some sort of electrophilic activation of the carbonyl, followed by neucleophilic attack of the isocyanide.
- One exception:

» Saegusa, N., *et. al. Tet.* **1968**, *24*, 3795

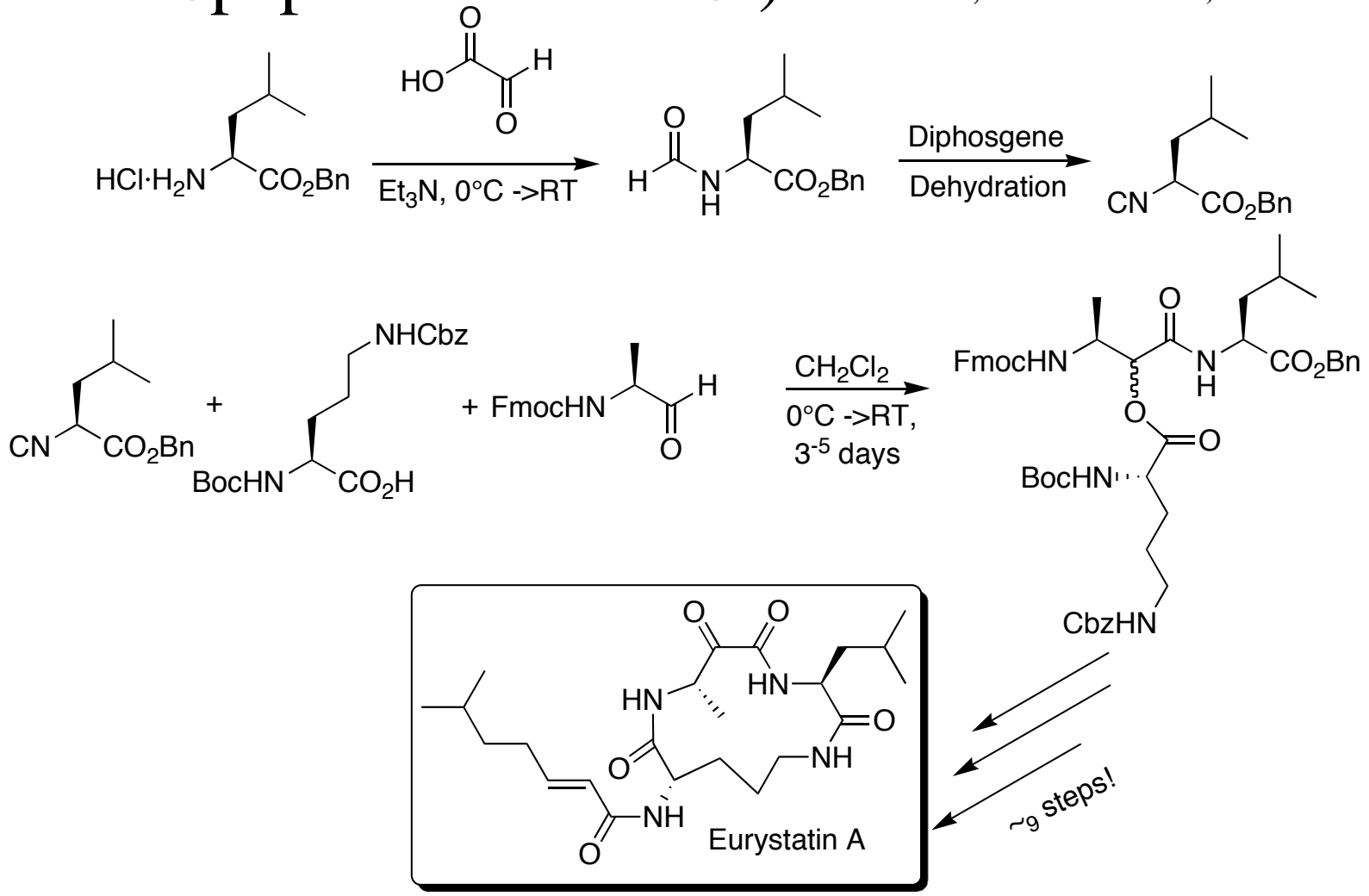


Details of the Reaction

- Done at high reactant concentration
- Done at low temperature
- Little limitations on the aldehyde/ketone used (extremely sterically bulky ketones)

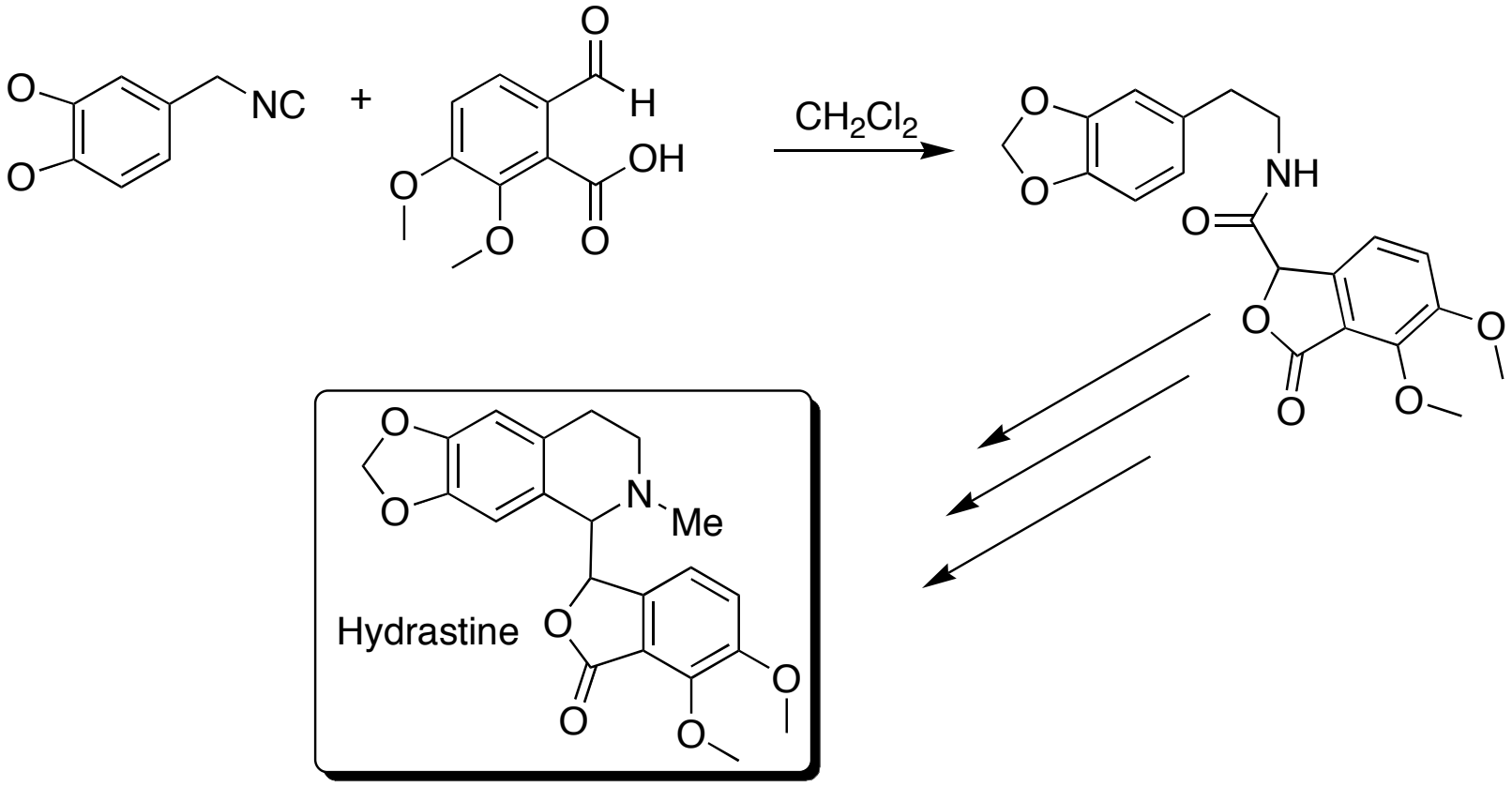
Synthetic Examples

- Total synthesis of Eurystatin A (a prolyl endopeptidase inhibitor) -- Owens, T.D. *et. al. Tet, Lett*. **2001**, 6271



Synthetic Examples

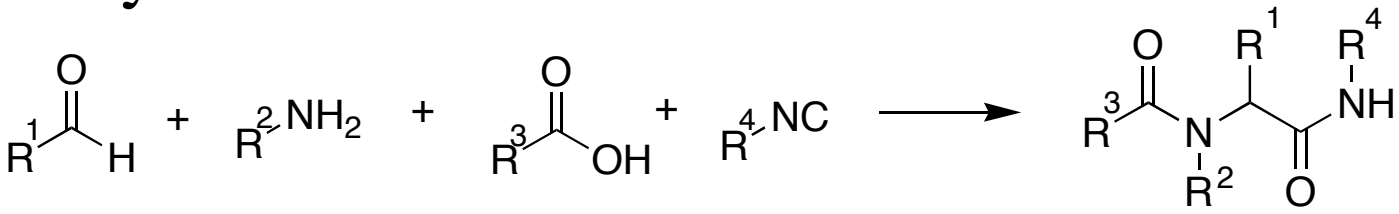
- Total synthesis of hydrastine, a phthalideisoquinoline alkaloid, using a an intramolecular Passerini reaction
  - » Zeigler, T., *et. al. Tet. Lett.* **1981**, *22*, 619



The Ugi Reaction

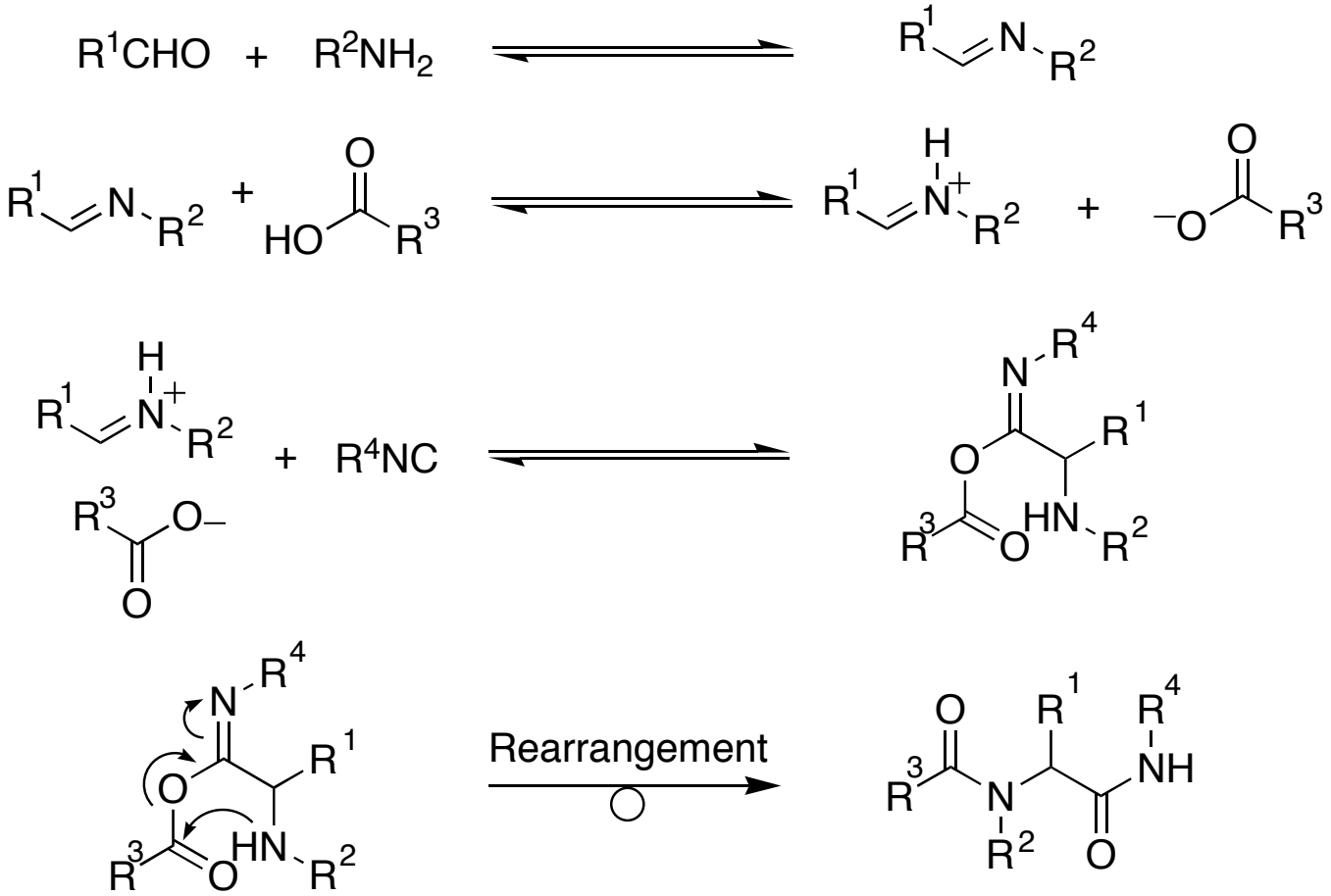
Details of the Ugi Reaction

- Discovered in 1959
  - » Ugi, I., *et. al. Angew. Chem.* **1959**, *71*, 386
- Four component condensation involving:
  - Amine (secondary or primary)
  - Aldehyde (or ketone)
  - Carboxylic Acid
  - Isocyanide
- Generally:



- Mechanism involves linear and parallel sequences first and second order reactions (no third or above!)

Mechanism

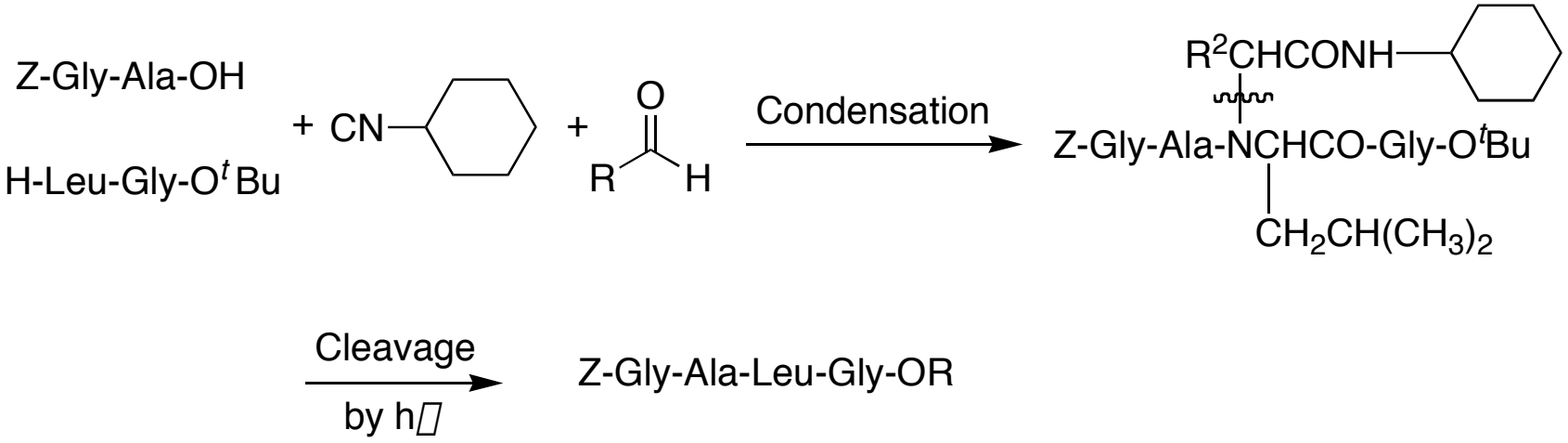


Generally Observed Properties of the Ugi Reaction

- Rxn is exothermic and usually complete in seconds-minutes at room temperature
- Aprotic, polar solvents are best, though the low-molecular weight alcohols have been used
- Can be performed in biphasic media
- High (0.5-2M) reactant concentrations are best
- By virtue of the mechanism, Lewis acids can accelerate the reaction
- Precondensation of the amine and the carbonyl (preformation of the Schiff base) can increase yields.

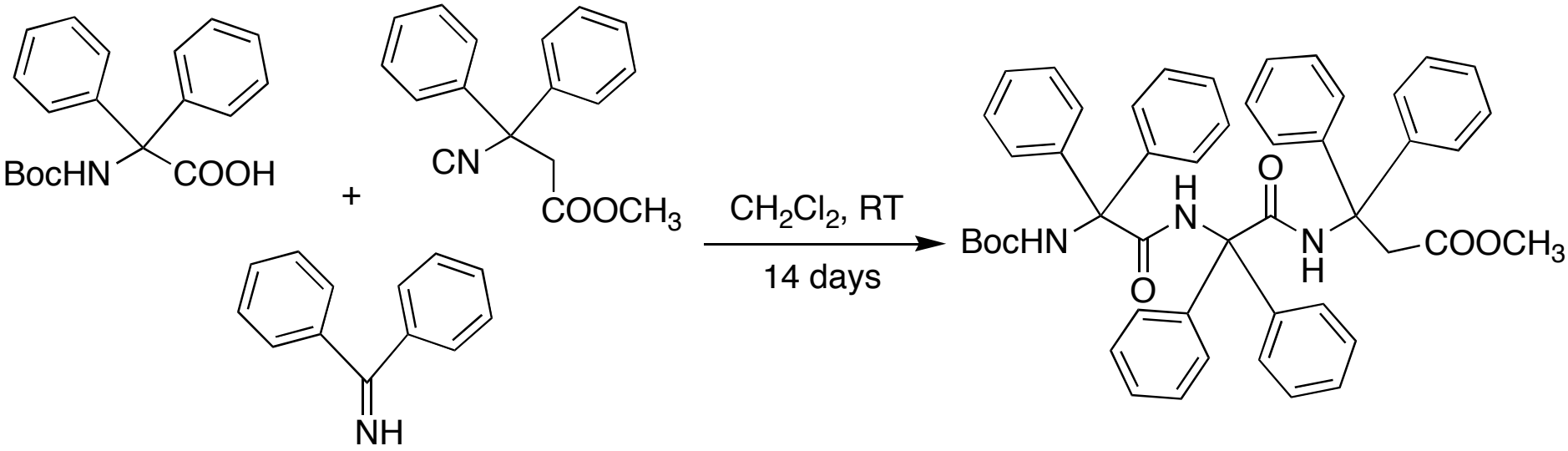
Synthetic Examples of the Ugi Reaction

- The Ugi reaction can be utilized to make peptides and peptoids
  - Tripeptides in one pot
  - Couple two peptide fragments
    - » Waki, M., Meienhofer, J. *J. Am. Chem. Soc.* **1977**., *99*, 6075



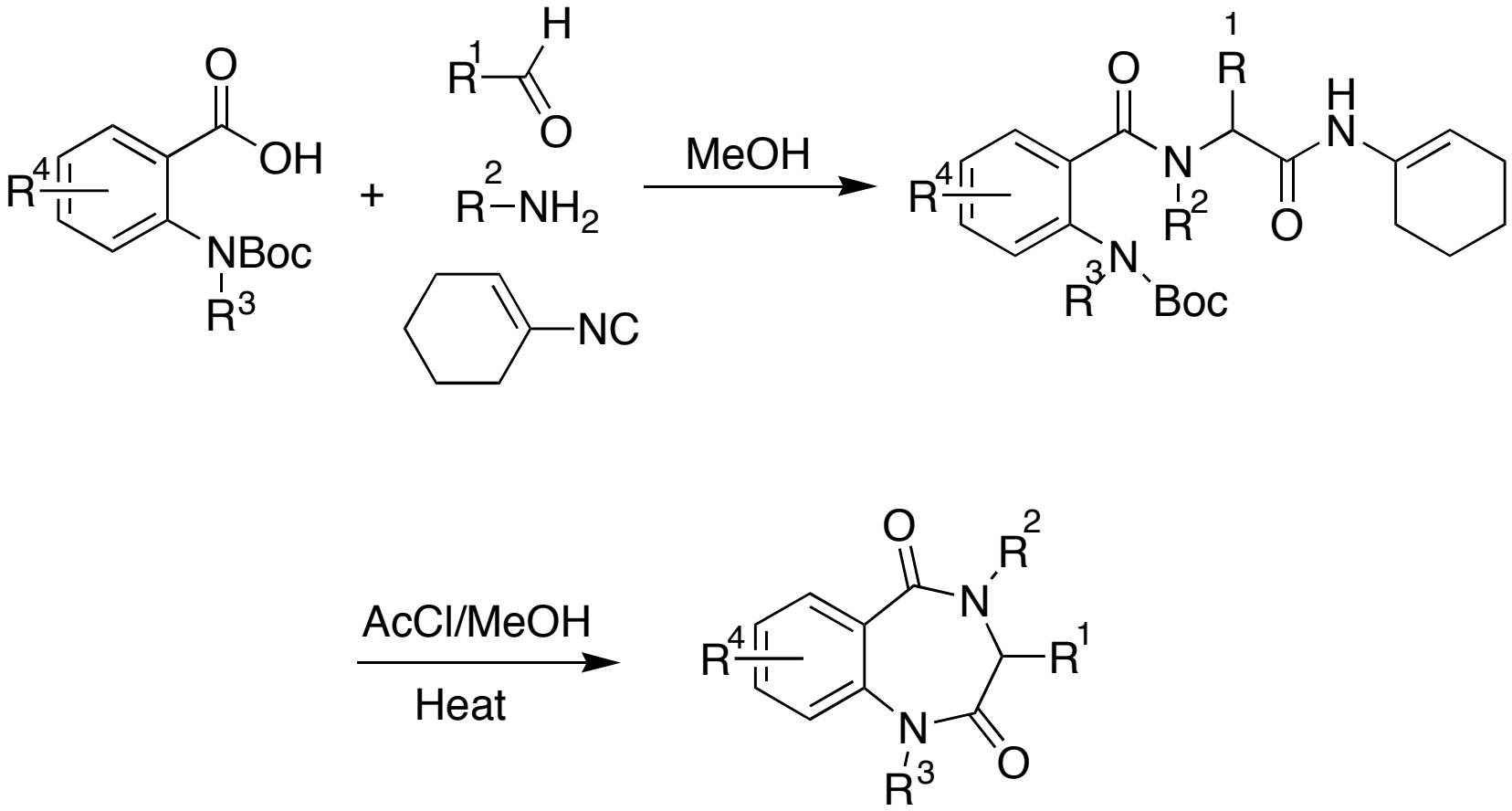
Synthetic Examples of the Ugi Reaction

- Synthesis of non-natural amino acids
  - Yamada, T. *et. al.* *Synthesis*. **1998**, 991



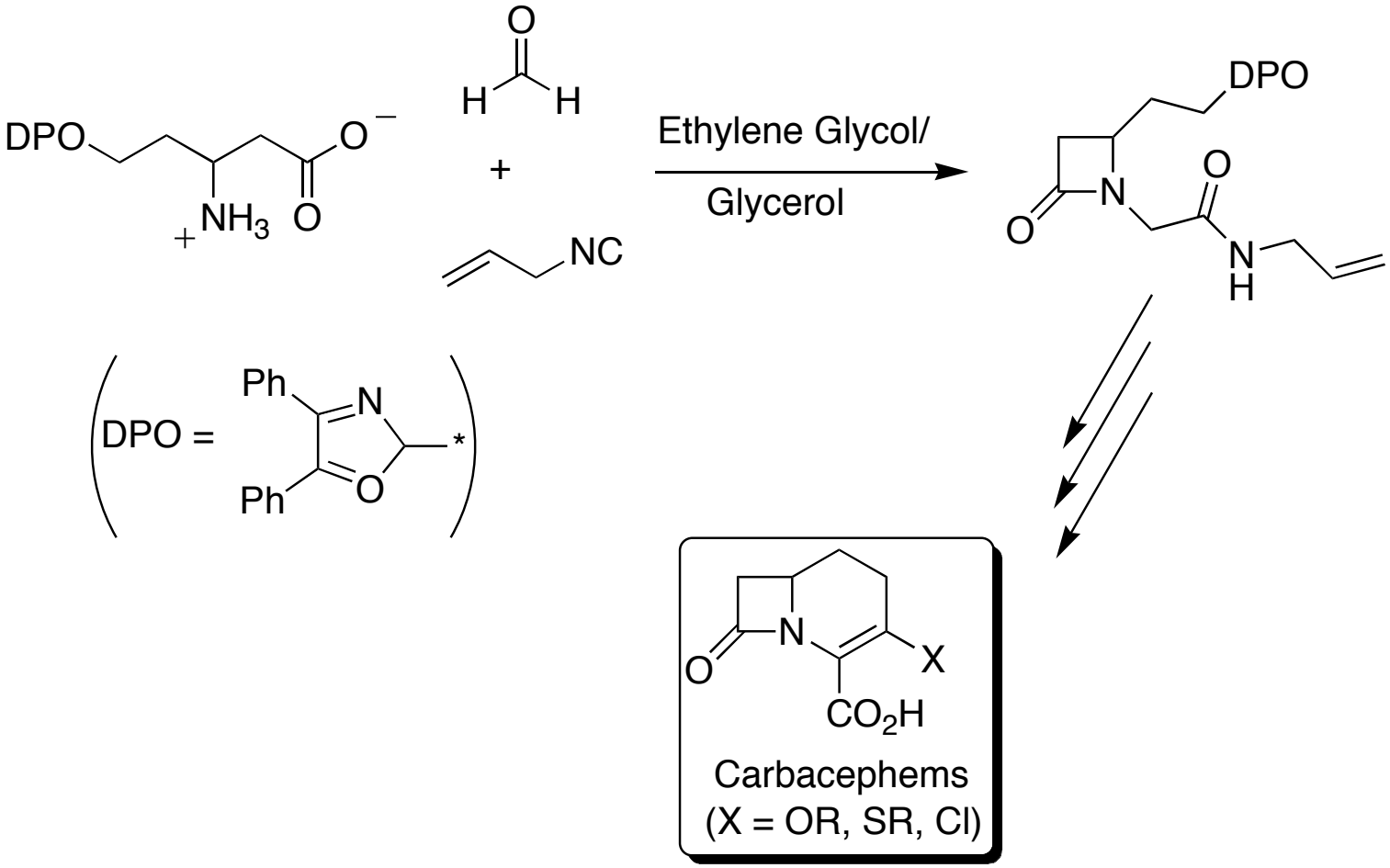
Synthetic Examples

- Concise synthesis of benzodiazepines
  - » Hulme, C., *et. al. J. Org. Chem.* **1998**, *63*, 8021



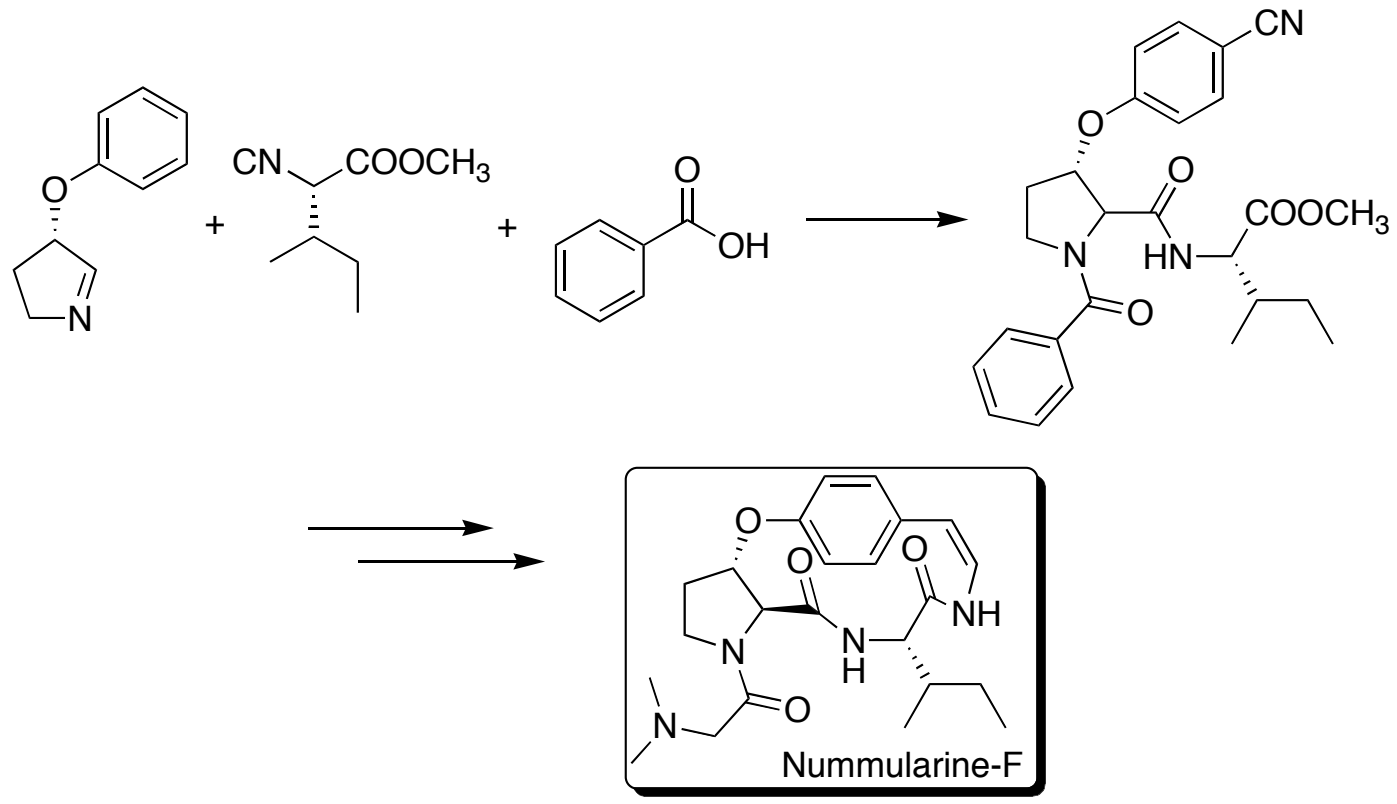
Synthetic Examples

- Synthesis of the carbacephems containing a β-lactam moiety commonly found in antibiotics
  - » Neyer, G., Achtaz, J., Danzer, B. Ugi, I. *Heterocycles*, **1990,** *30*, 863

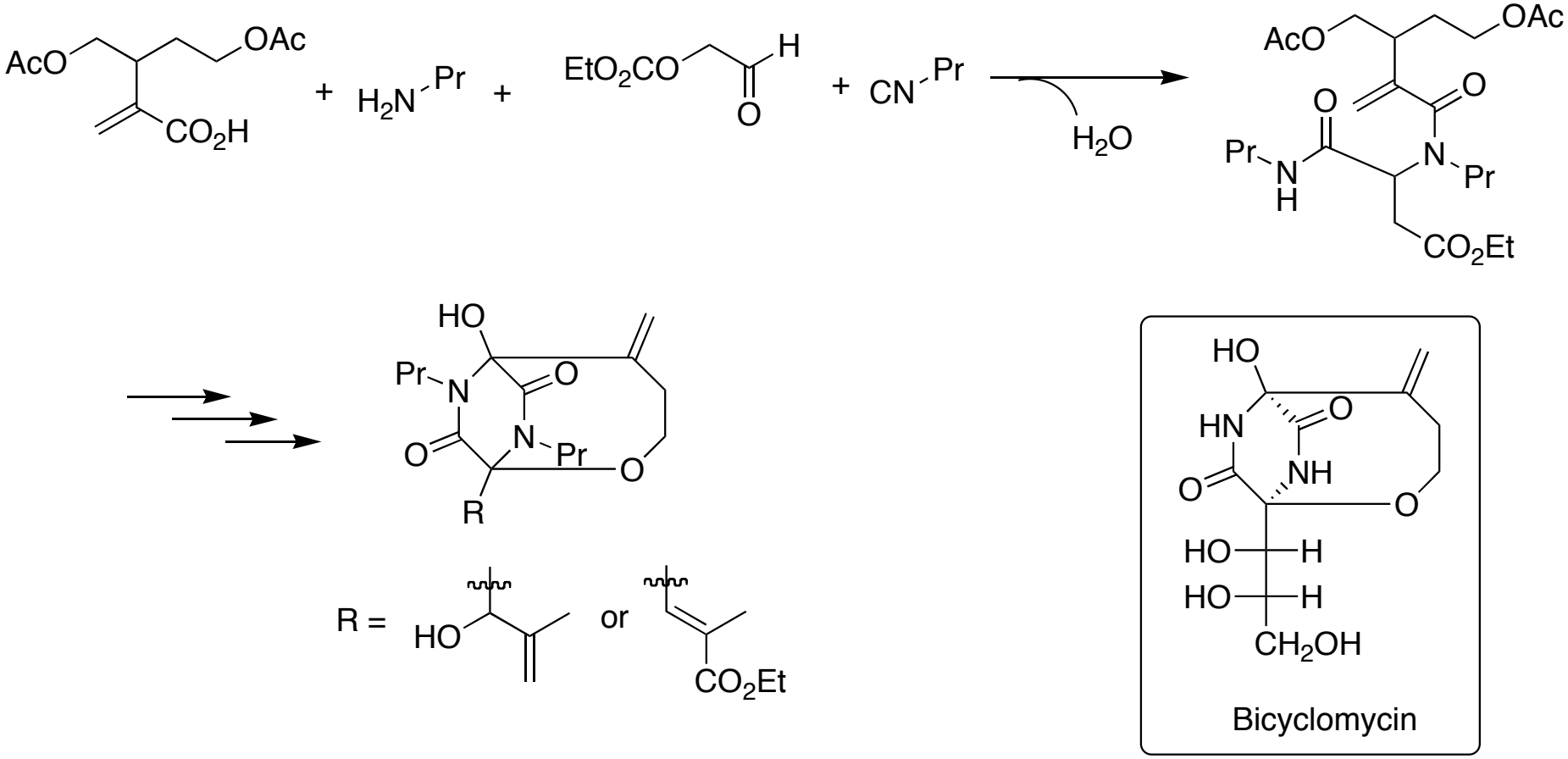


Synthetic Examples of the Ugi Reaction

- Total synthesis of the cyclopeptidic alkyloid natural product: Nummularine - F
  - » Bowers, M.M., *et. al. J. Chem. Soc. Perkin Trans. 1,* **1989,** 857



Synthetic Examples of the Ugi Reaction



-T. Fukuyama, *et. al. Tet. Lett.* **1981**, *22*, 4155

Concluding Remarks

- The Biginelli, Passerini, and Ugi reactions are all multicomponent reactions that are manifested in many facets of chemistry

- The Biginelli and Passerini reactions were discovered very early on and were underappreciated and underutilized until the late 1950s

- All three reactions have interesting mechanistic and synthetic problems associated with them, some having been solved, some yet to be

Synthetic Examples

- Titanium Tetrachloride assisted Passerini reaction
  - Carofiglio, T., *et. al. Organomett.*, **1993**, *12*, 2726