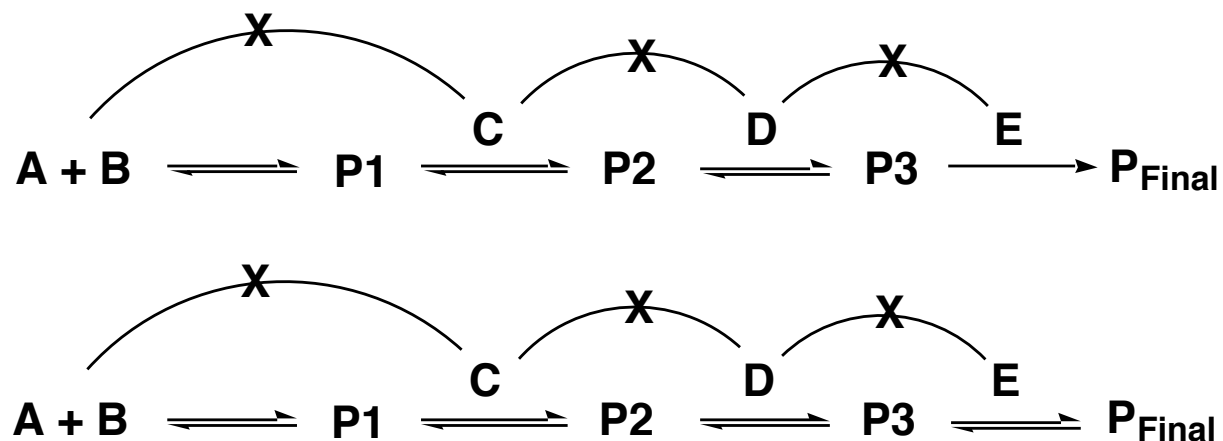


Multicomponent Reaction (MCR)

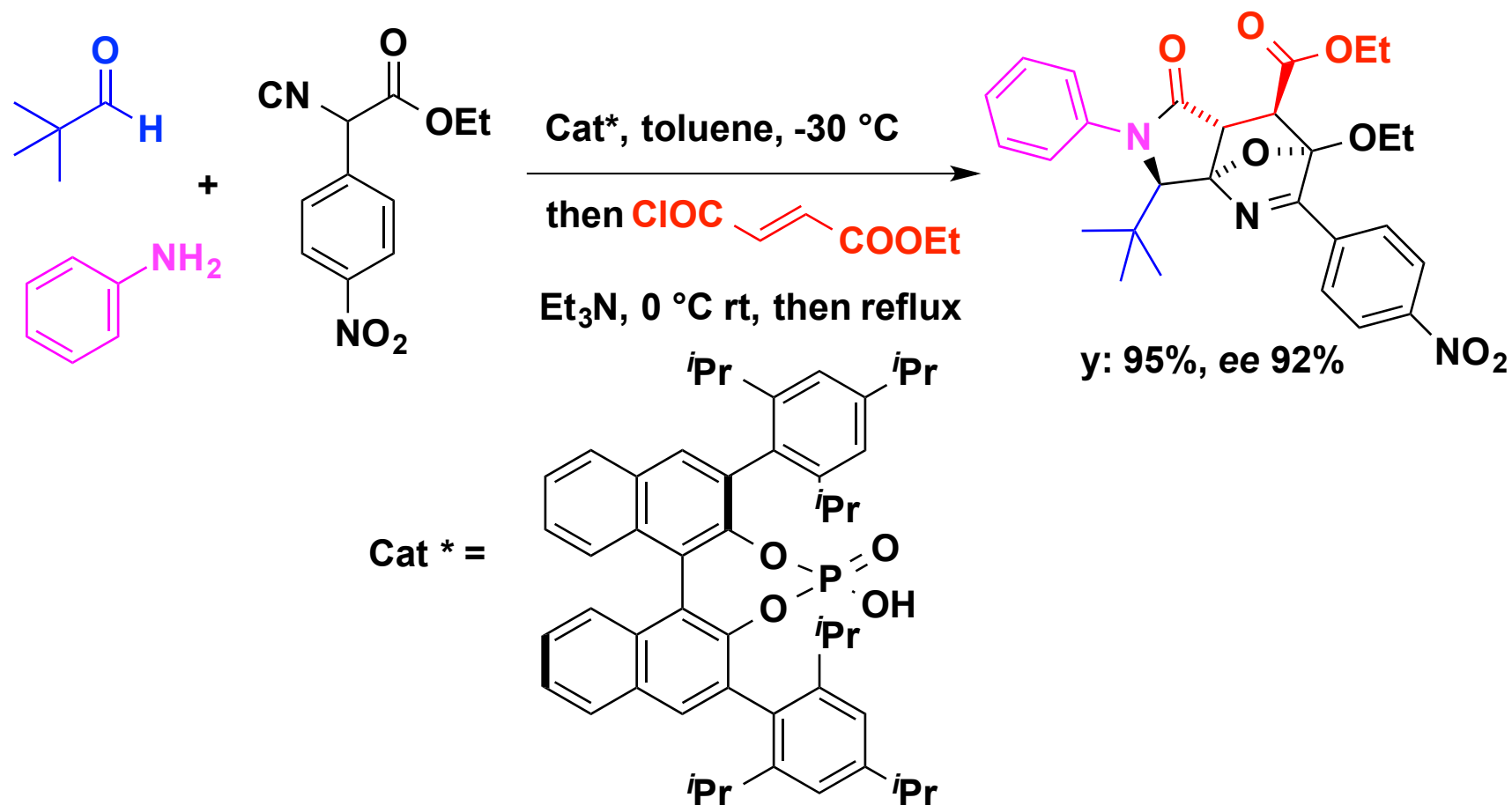
Definition and Principle

A process in which three or more reactants are combined in a single reaction vessel to produce a product that incorporates substantial portions of all the components. A sequence of bimolecular events that proceed according to the Domino principle, i.e., the subsequent reactions result as a consequence of the functionality formed in the previous step.



Monographs: a) "**Multicomponent Reaction**" Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
b) "**Multicomponent reactions in Organic Synthesis**" Wiley VCH,
Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014**.

Multicomponent Synthesis of Heterocycles



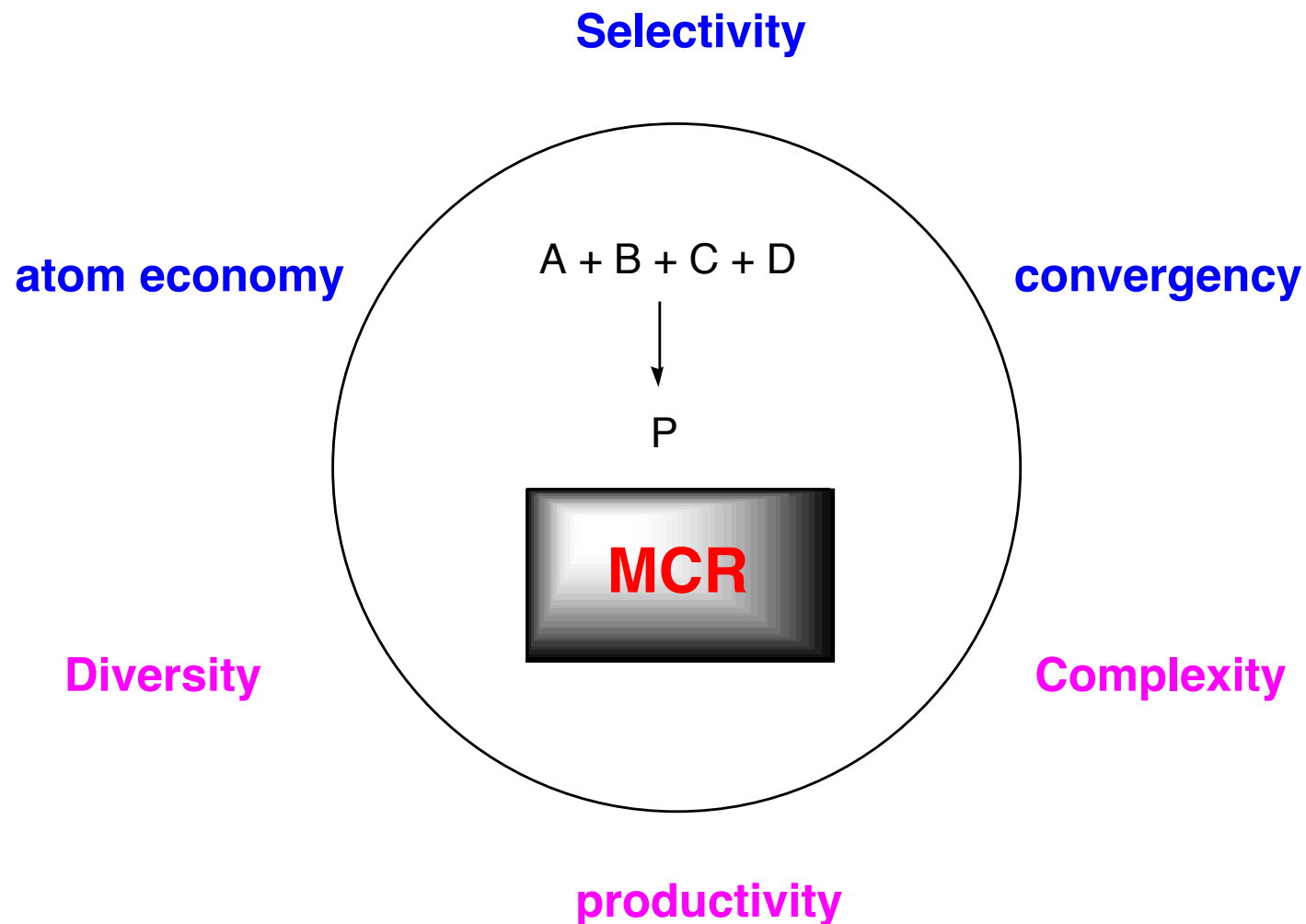
1 C-O, 2 C-N, 3 C-C bonds formed (total 6)

5 contiguous stereocenters including 2 quaternary ones

Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, 46, 2485-2488.

Su, Y.; Bouma, M. J.; Alcaraz, L.; Stocks, M.; Furber, M.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2012**, 18, 12624-12627.

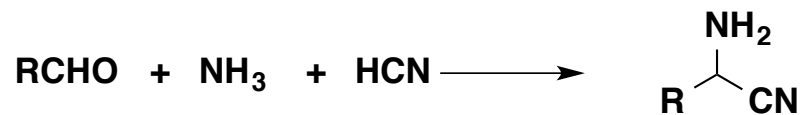
Advantages of Multicomponent Reactions



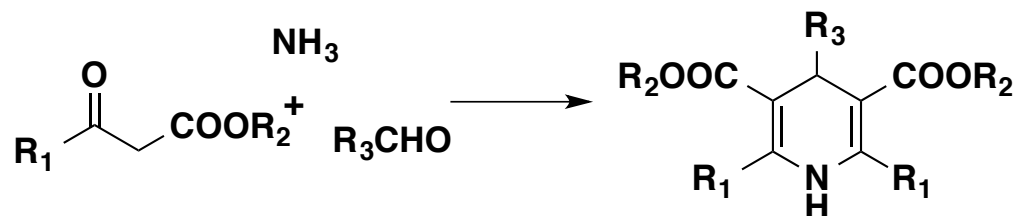
Monographs: "**Multicomponent Reaction**" Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
"**Multicomponent reactions in Organic Synthesis**" Wiley VCH, Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014**

MCR in Natural Product Synthesis: B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486.

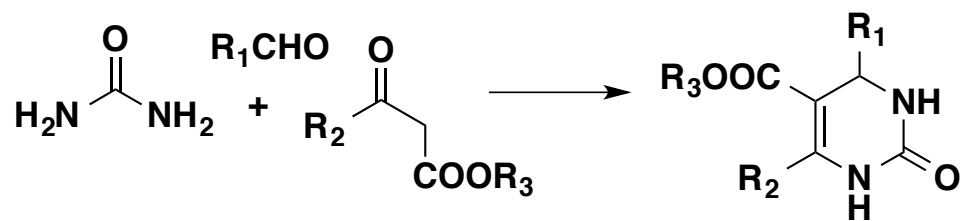
Textbook MCRs



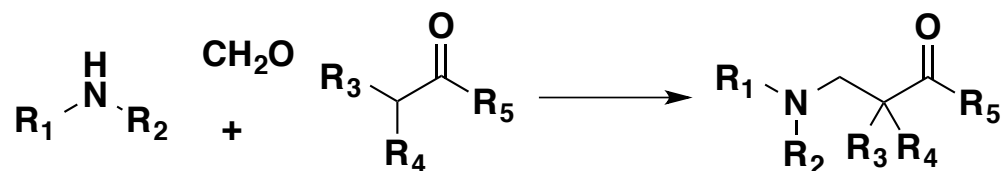
Strecker, 1850



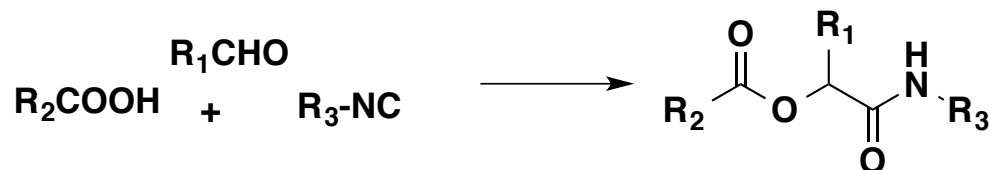
Hantzsch, 1882



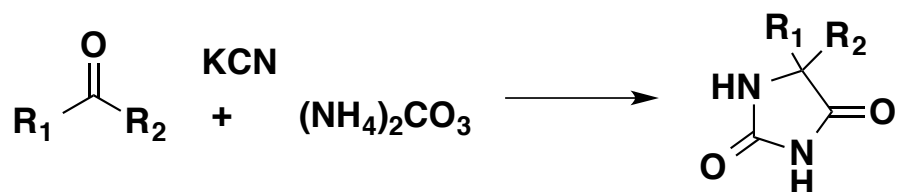
Biginelli, 1891



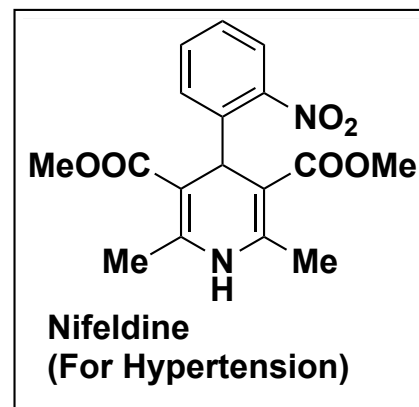
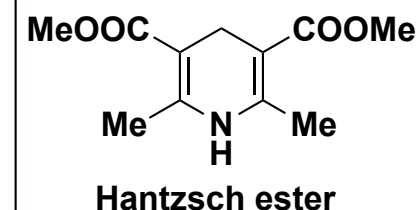
Mannich, 1912



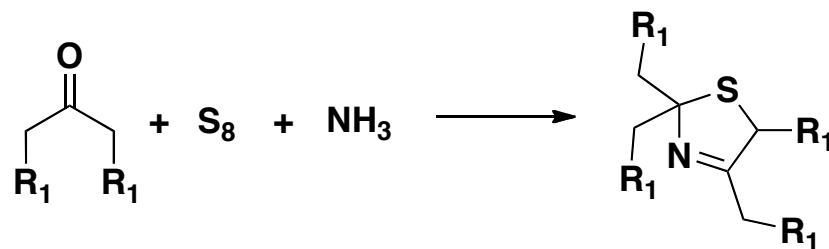
Passerini, 1921



Bucherer-Bergs 1934



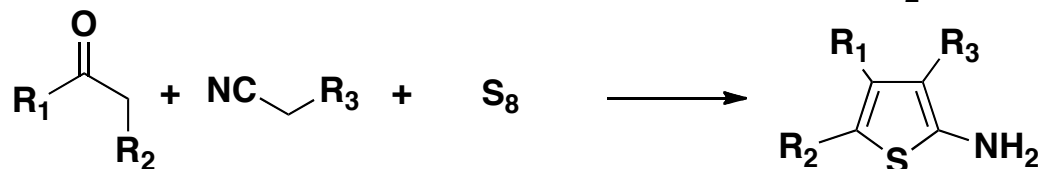
Textbook MCRs



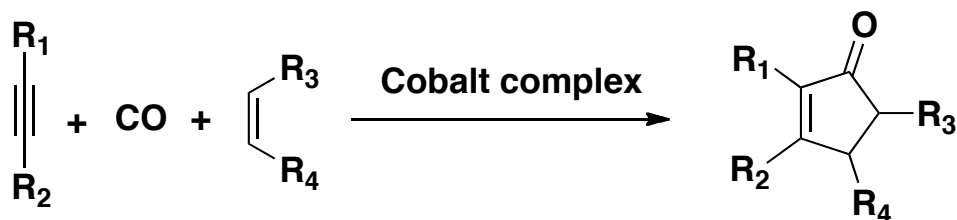
Asinger, 1956



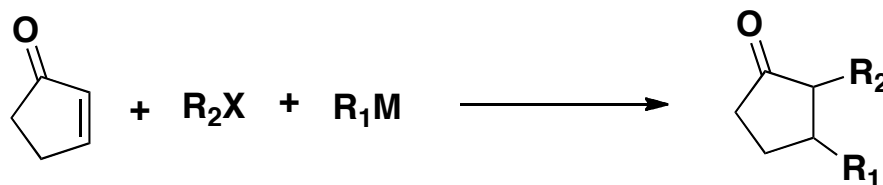
Ugi, 1959



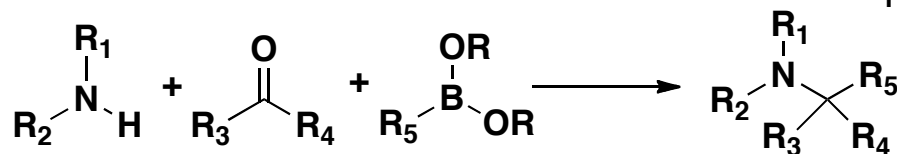
Gewald 1966



Pauson-Khand 1973

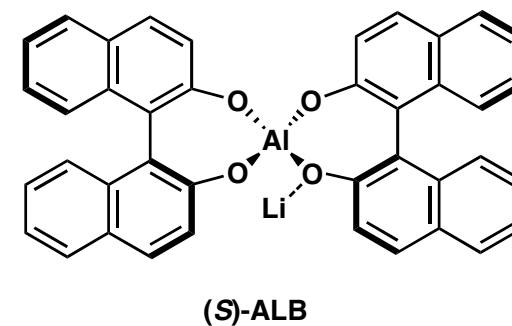
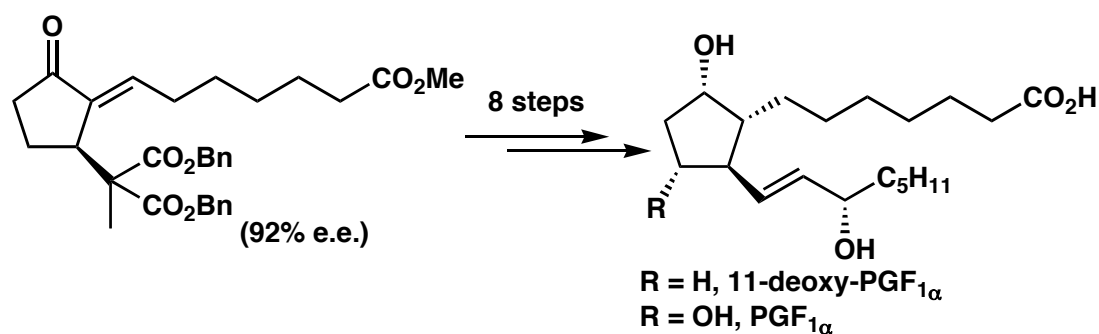
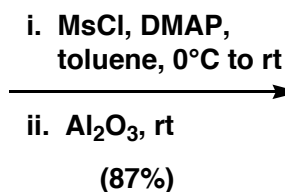
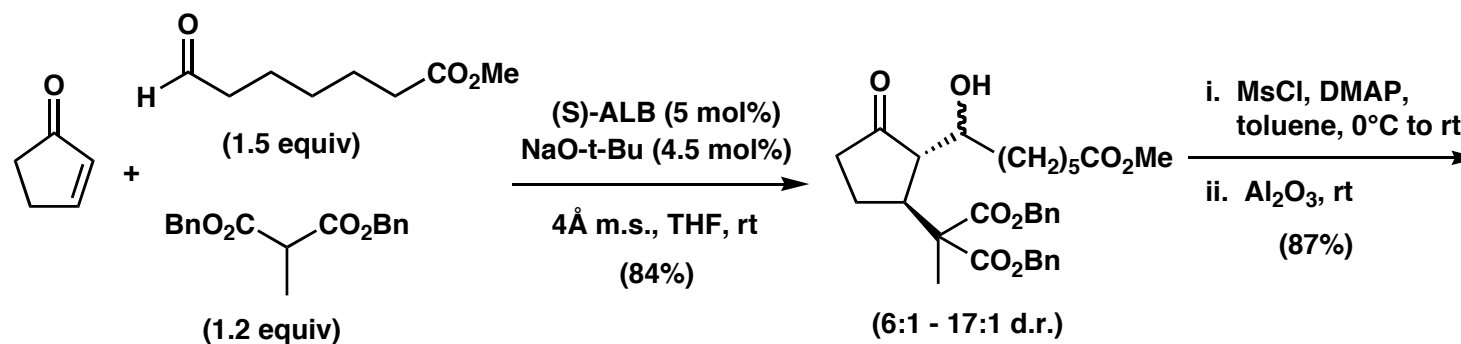
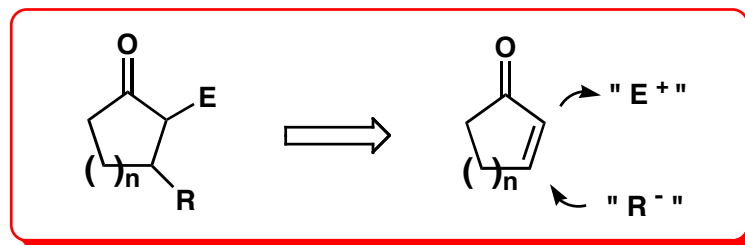


Noyori 1982



Petasis, 1993

Michael Addition/Aldol Sequence

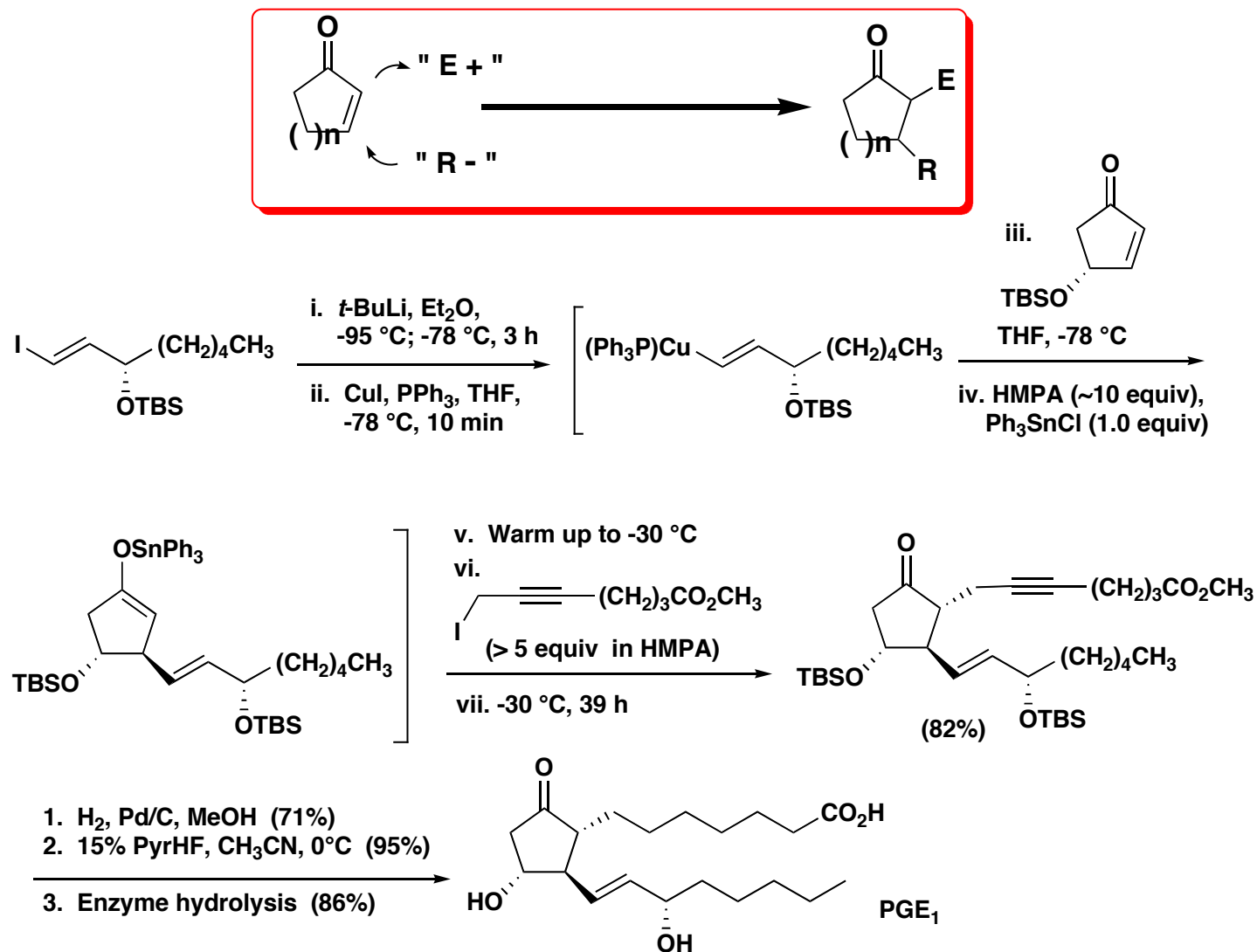


Shibasaki, *J. Org. Chem.* **1998**, *63*, 3666-3672; *Syn Org Chem JPN* **1998**, *56*, 344-356.

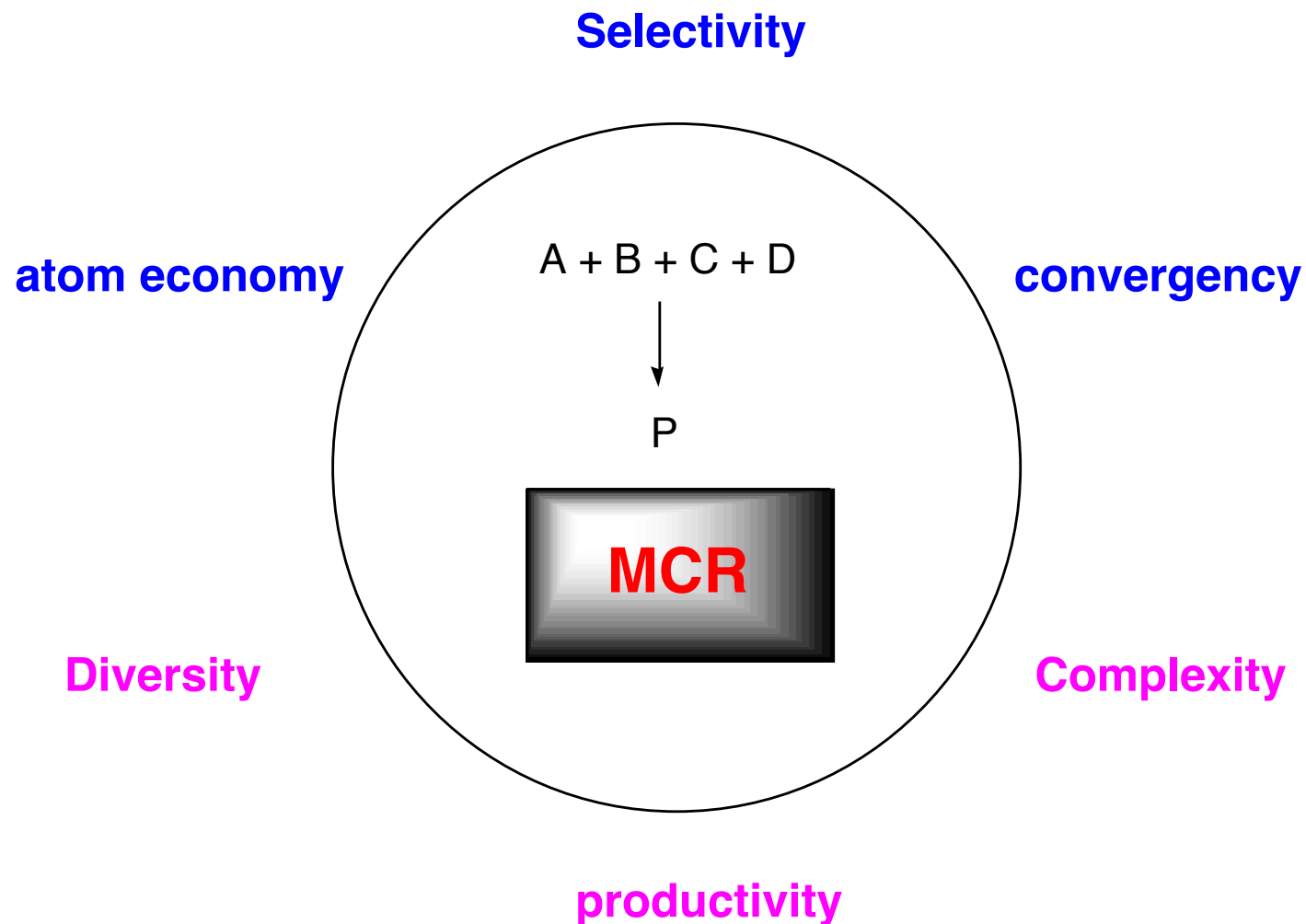
Reviews: *Org React.* **1990**, *38*, 225-653; **1992**, *41*, 135-631.

Ma, J. A. *Anegw. Chem. Int. Ed.* **2006**, *45*, 354-366.

Michael Addition/Alkylation Sequence



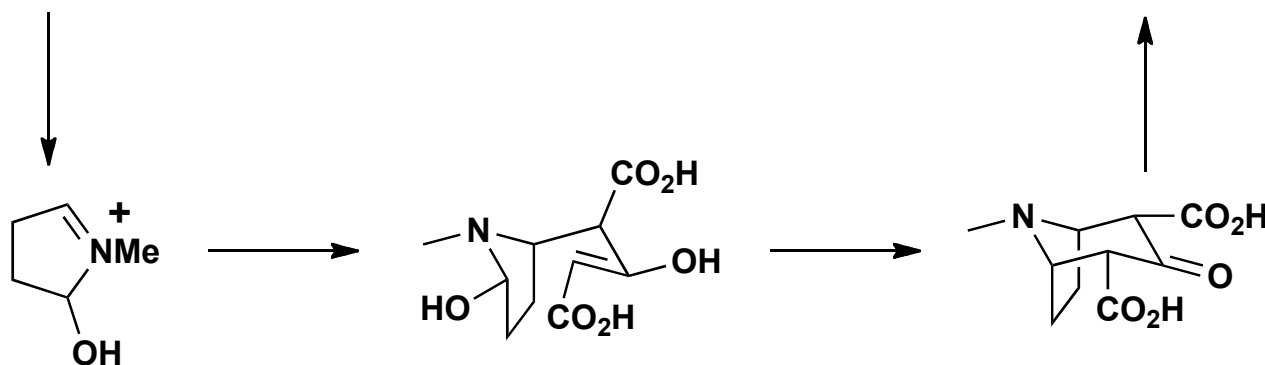
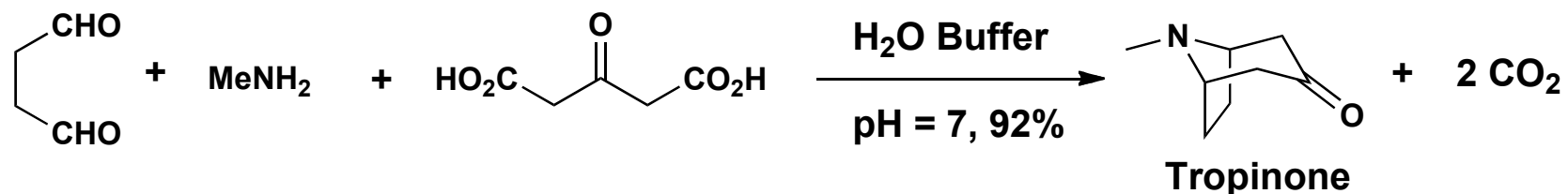
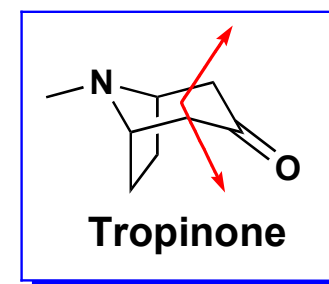
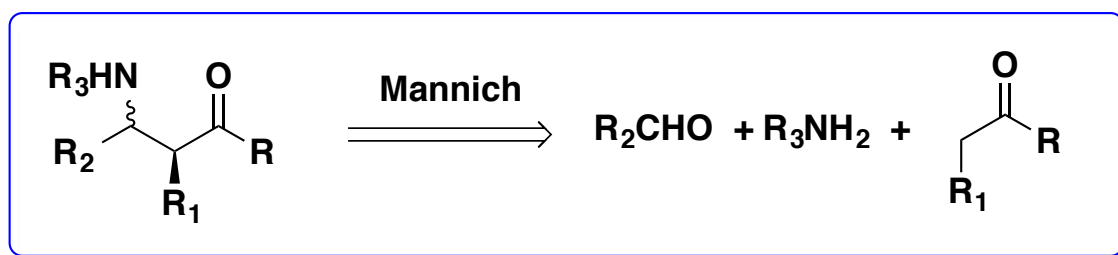
Advantages of Multicomponent Reactions



Monographs: “**Multicomponent Reaction**” Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
“**Multicomponent reactions in Organic Synthesis**” Wiley VCH, Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014**

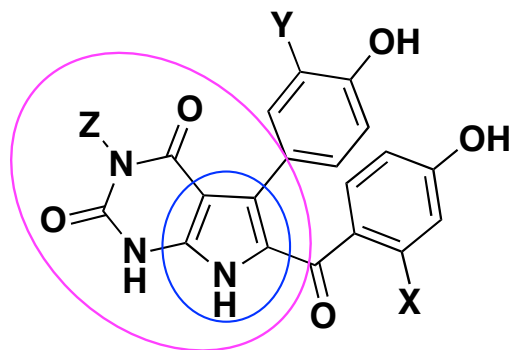
MCR in Natural Product Synthesis: B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486.

Robinson's Three-Component Synthesis of Tropinone

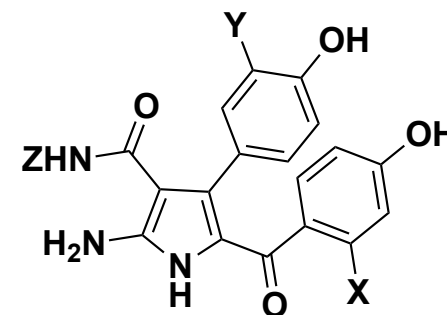


Key: Double Mannich Reactions

Rigidins



Rigidin A X = Y = Z = H
Rigidin B X = OMe, Y = Z = H
Rigidin C Y = OMe, X = Z = H
Rigidin D X = Y = OMe, Z = H
Rigidin E X = Y = H, Z = Me



Isolated from marine tunicates collected near Okinawa and New Guinea displayed potent calmodulin antagonist activities

Structural features:

Pyrrolopyrimidine

Fully substituted 2-aminopyrrole unit

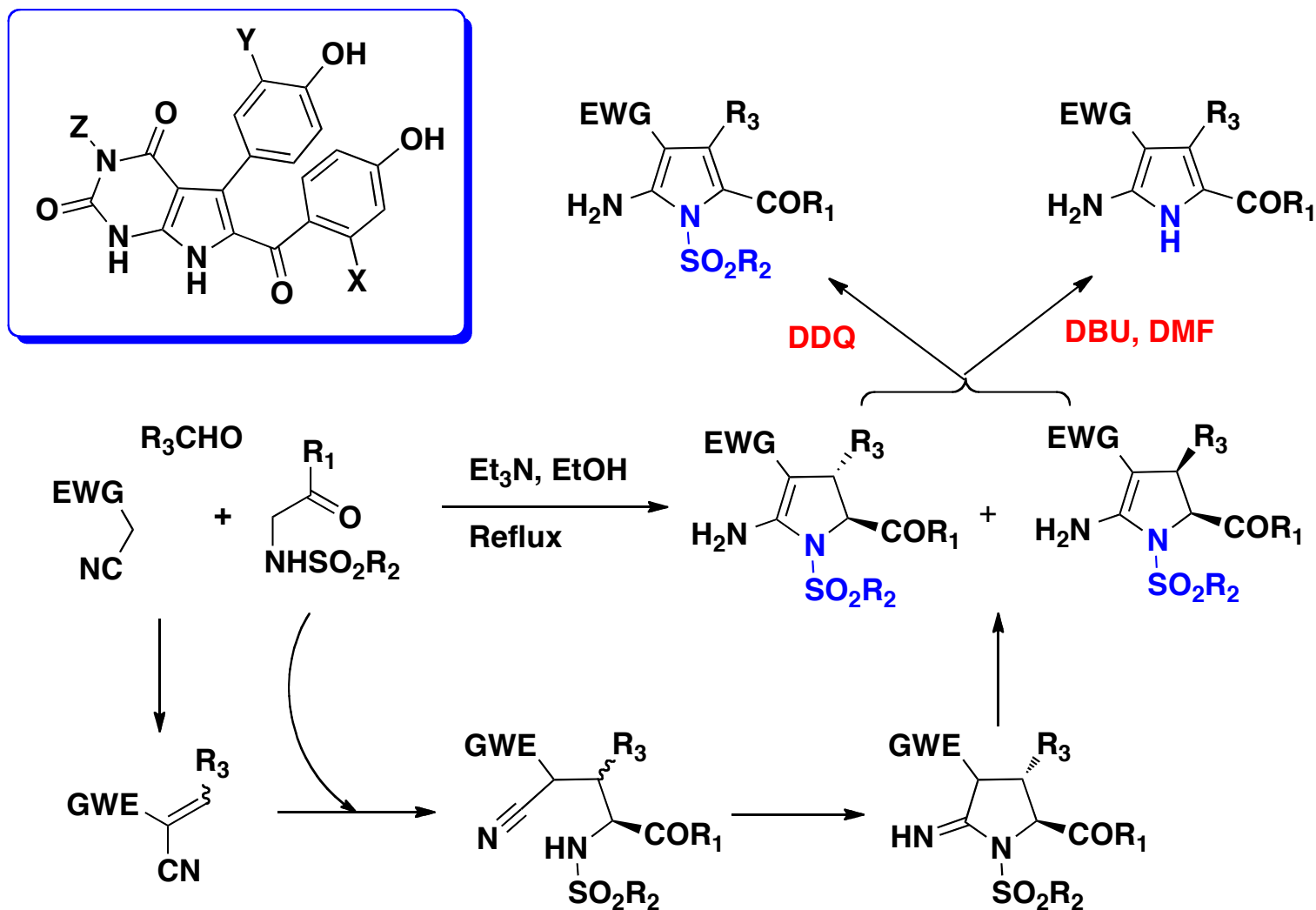
A multicomponent Synthesis???

Kobayashi, J.; Cheng, J.; Kikuchi, Y.; Ishibashi, Y.; Yamamura, S.; Ohizumi, Y.; Ohta, T.; Nozoe, S. *Tetrahedron*, **1990**, *31*, 4617-4620.

Tsuda, M.; Nozawa, K.; Shimbo, K.; Kobayashi, J. *J. Nat. Prod.* **2003**, *66*, 292-294.

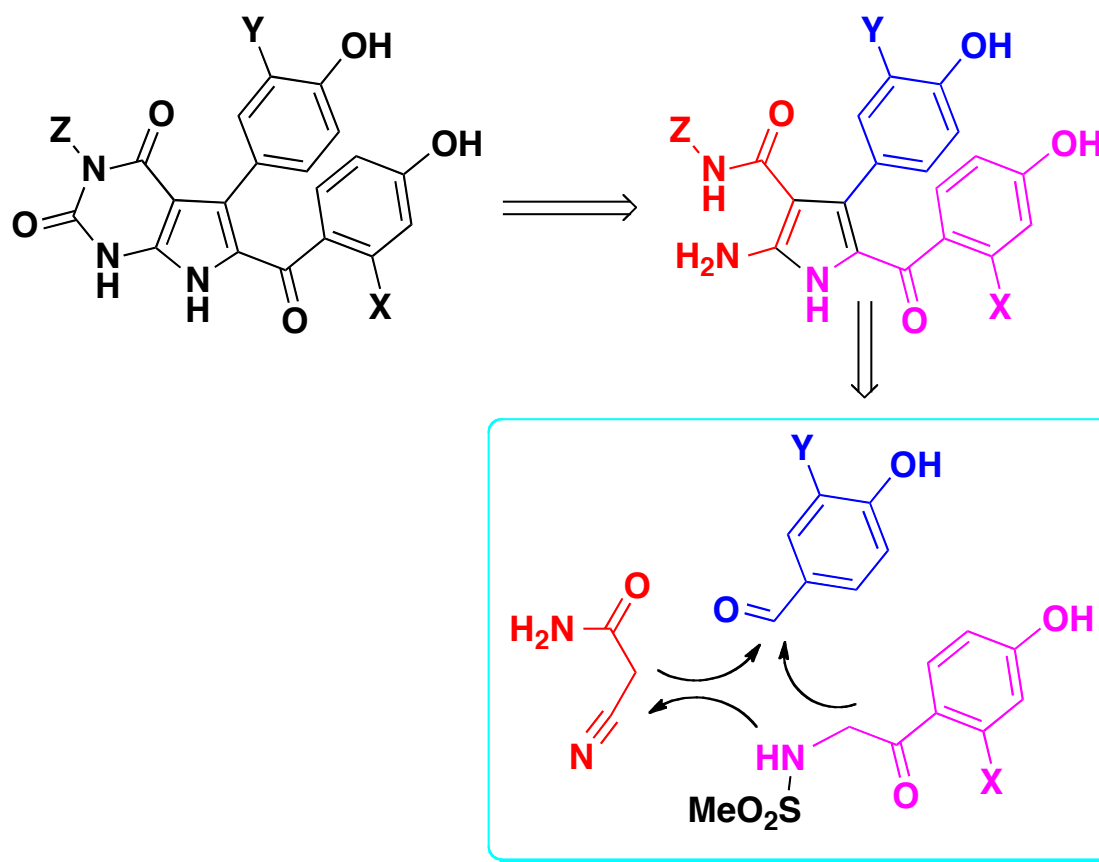
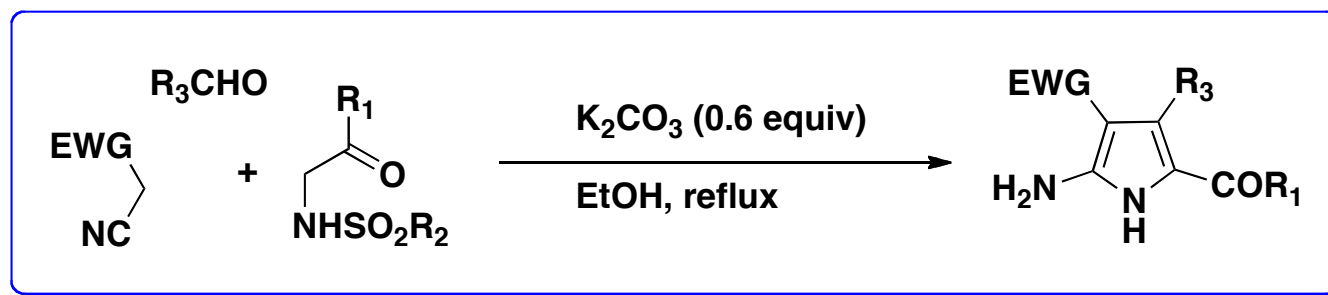
Davis, R.; Christensen, L.; Richardson, A.; da Rocha; Ireland, C. *Mar. Drugs* **2003**, *1*, 27-33

Three-component synthesis of Pyrroline and Pyrrole

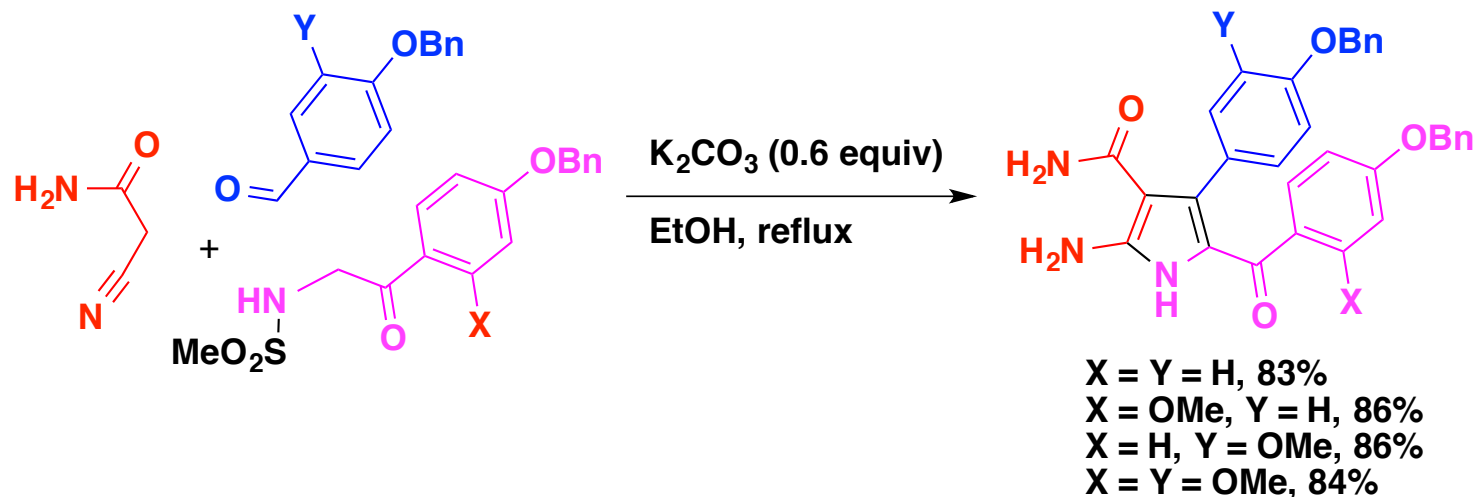


Magedov, I. V. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1392-1396.

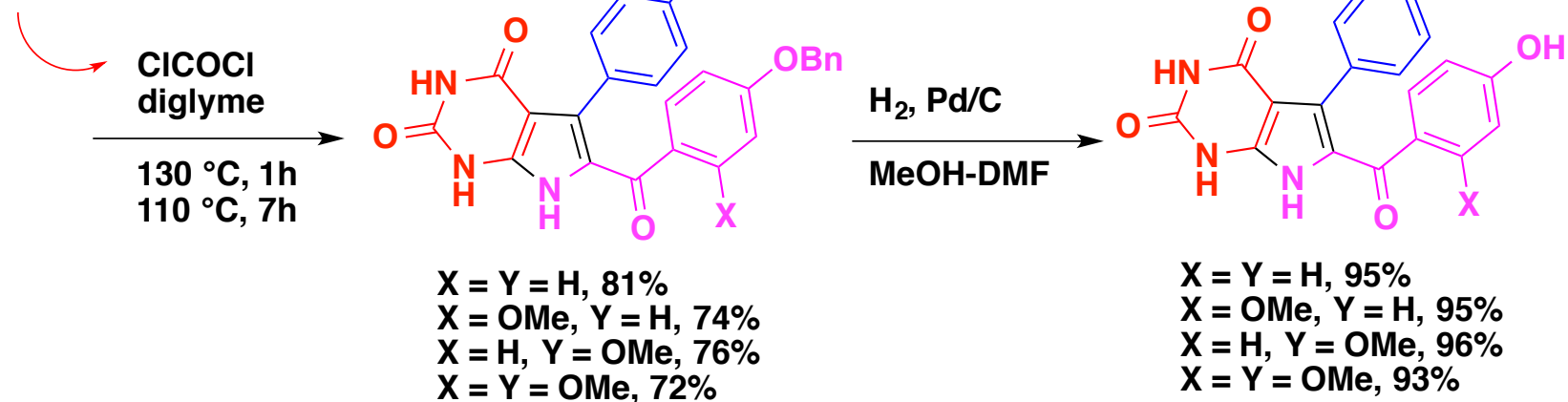
Three-component Synthesis of 2-Aminopyrrole



Three-step Total Synthesis of Regidins

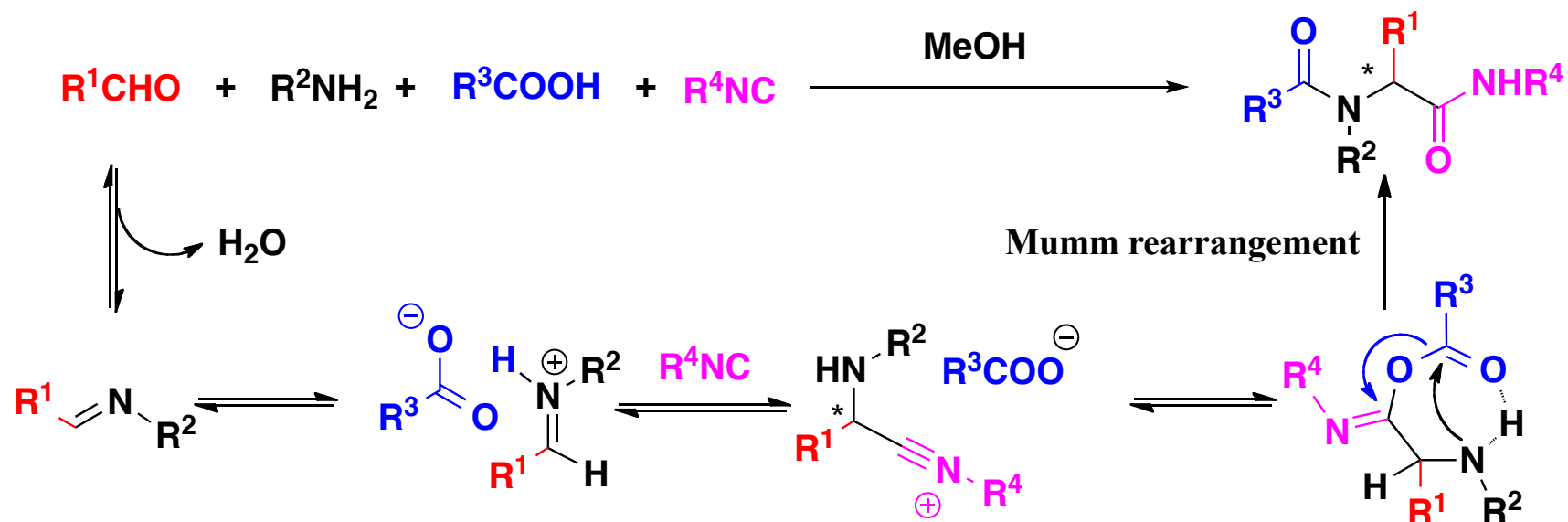


Phosgene or triphosgene



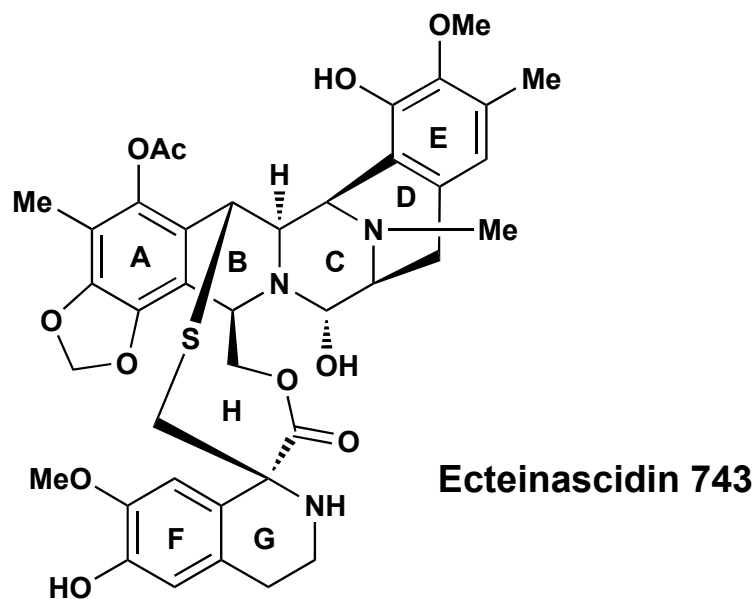
Magedov, I. V. et al. *Org. Lett.* **2011**, *13*, 1118.

Deep Insight into Structure: Ugi 4CR and Ecteinascidin-743

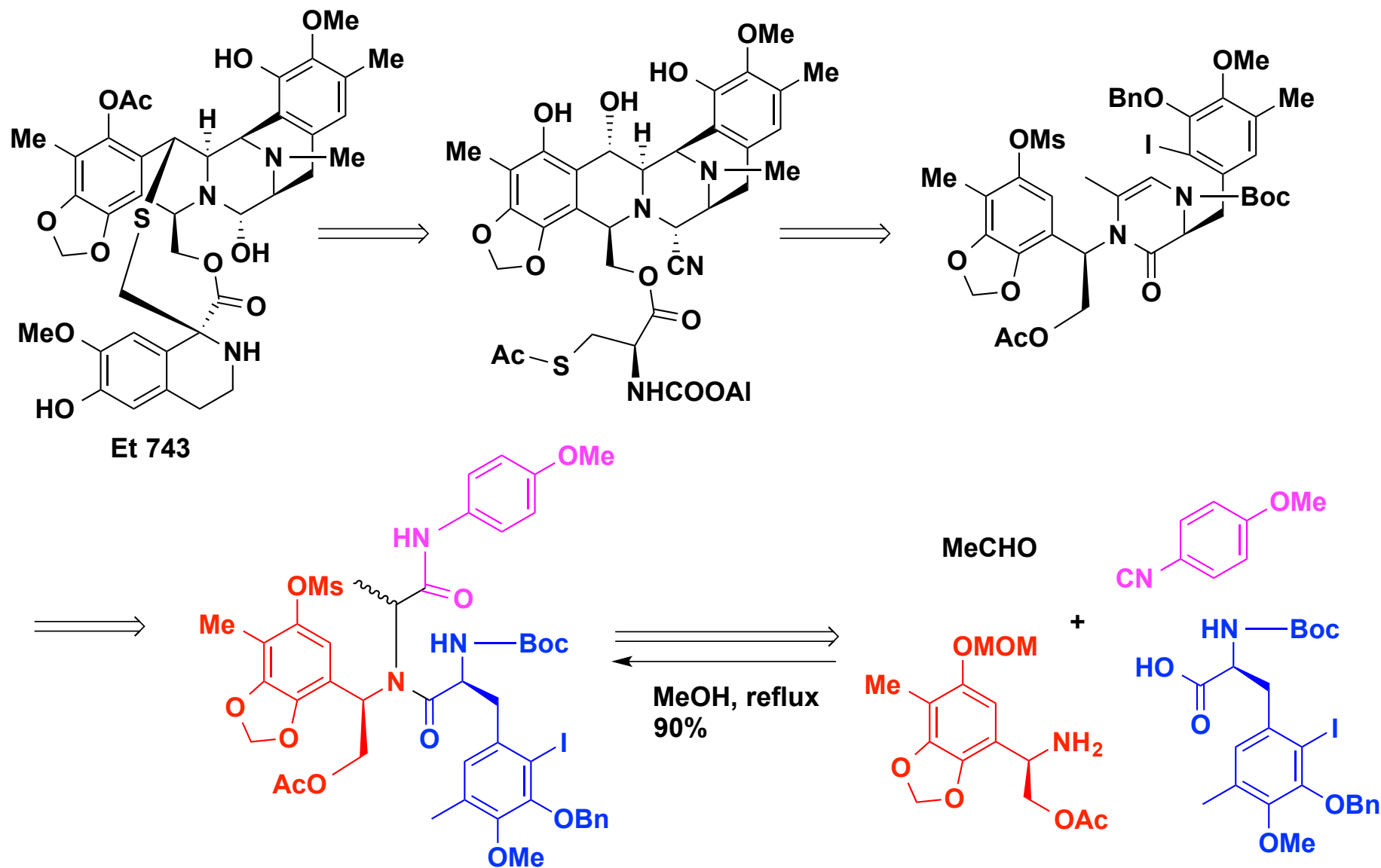


$R^1, R^2, R^3, R^4 = \text{aliphatique, aromatique}$

Rev on Isonitrile-based MCRs, see:
 Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.



Fukuyama's Synthesis of Ecteinascidin-743: Retro-Synthetic Analysis

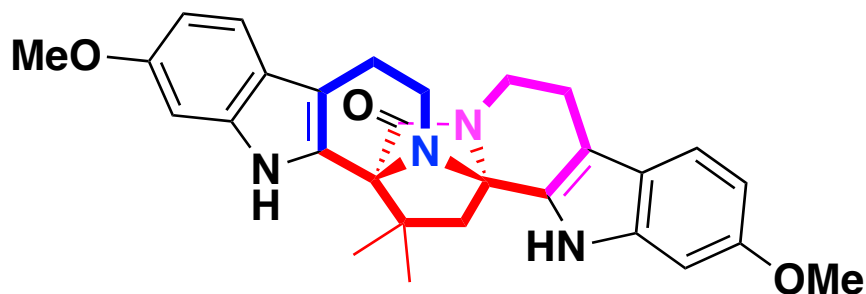


T. Fukuyama *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 6552-6554.

Two other total syntheses: Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202-9203

Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87-89.

(+)-Peganumine A: an Octacyclic Alkaloid



(+)-Peganumine A

Relative stereochemistry: by X-ray

Absolute configuration: based on CD, ECD spectroscopic studies

Bioactivity: Low μM activity against MCF-7, PC-3, HepG2 and HL-60 cancer cell lines

Isolation yield: Extremely low (3.5 mg from 15.4 kg of the seeds)

Completely new skeleton:

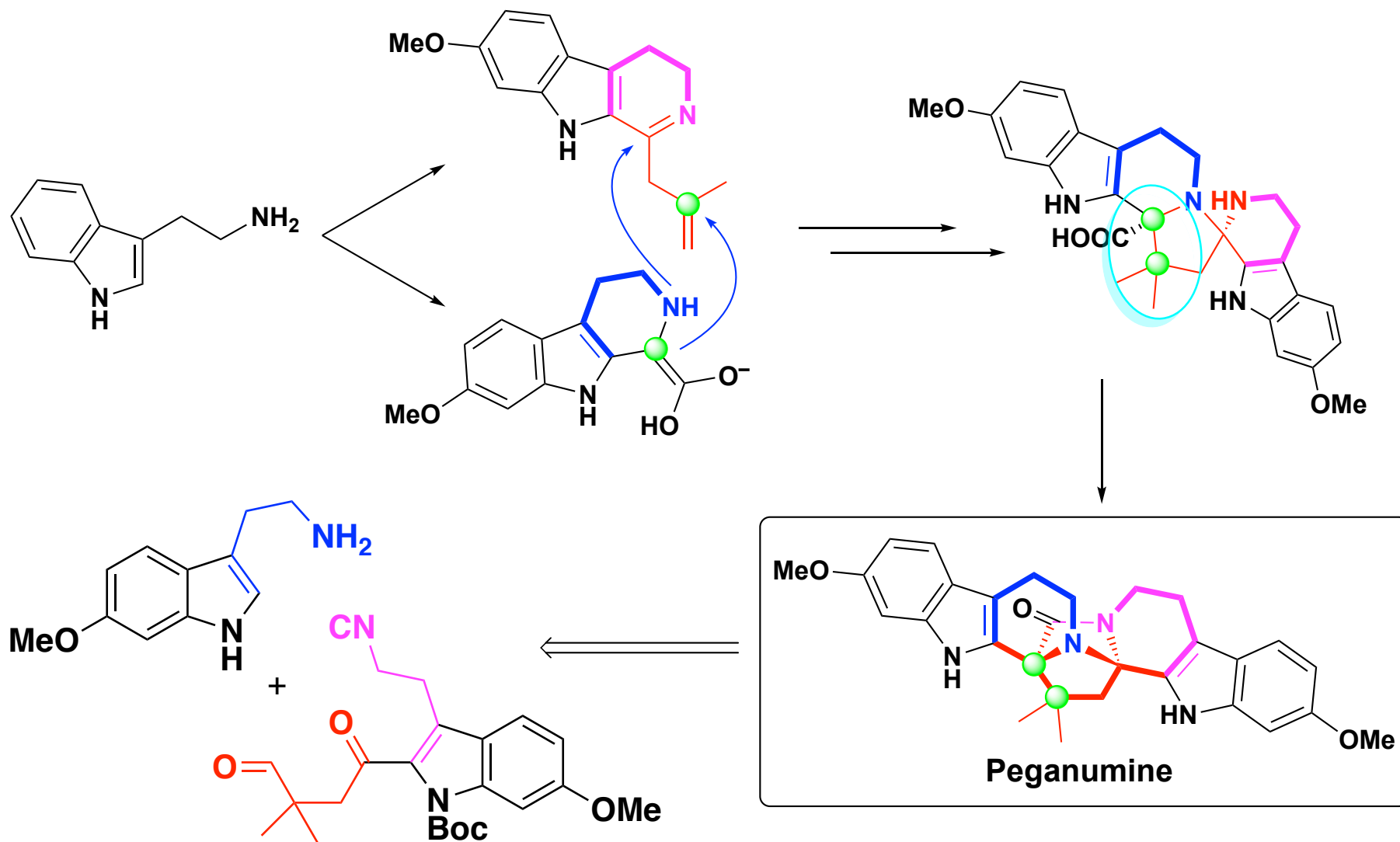
an octacyclic indole alkaloid

two quaternary stereocenters,

two spirocycles embedded in an unusual

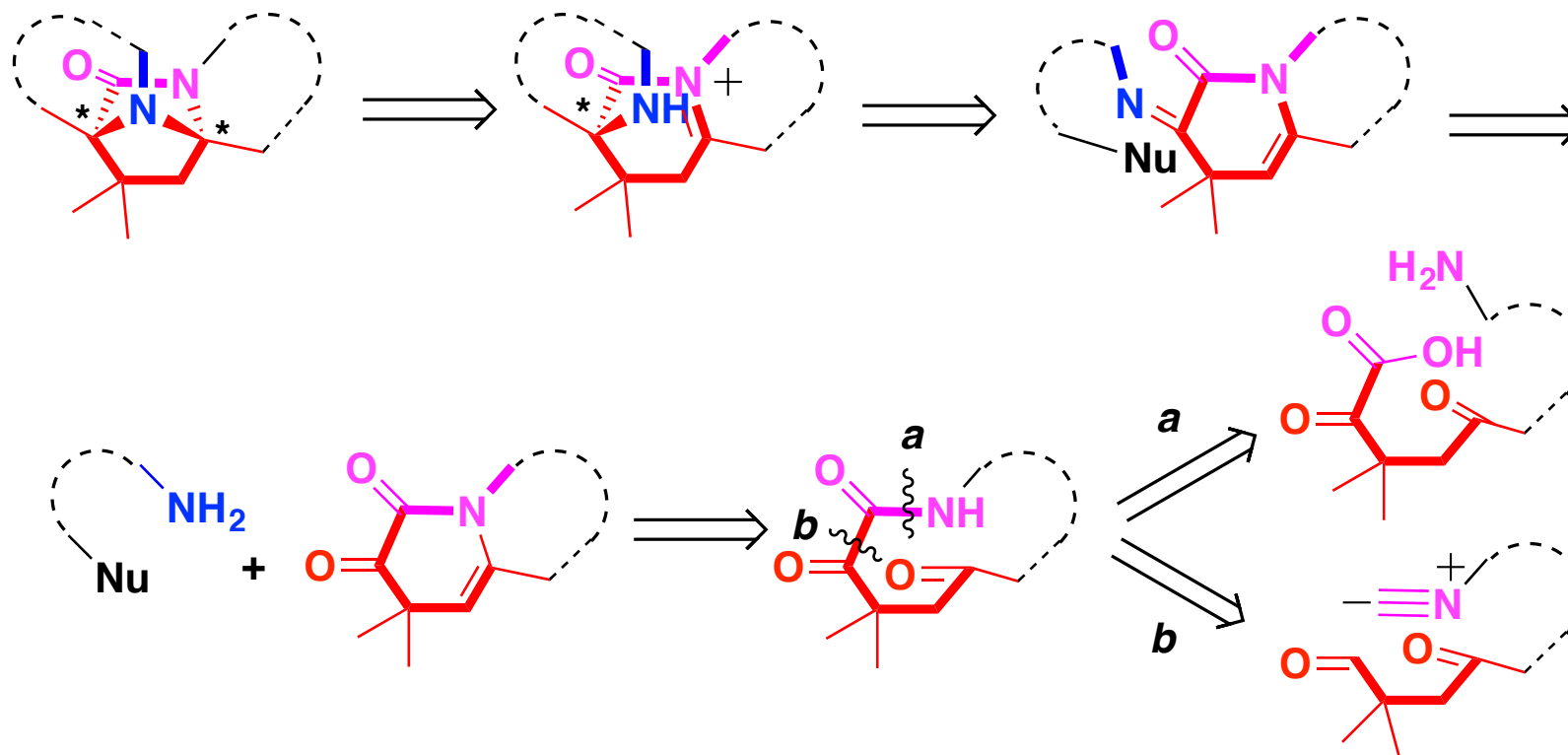
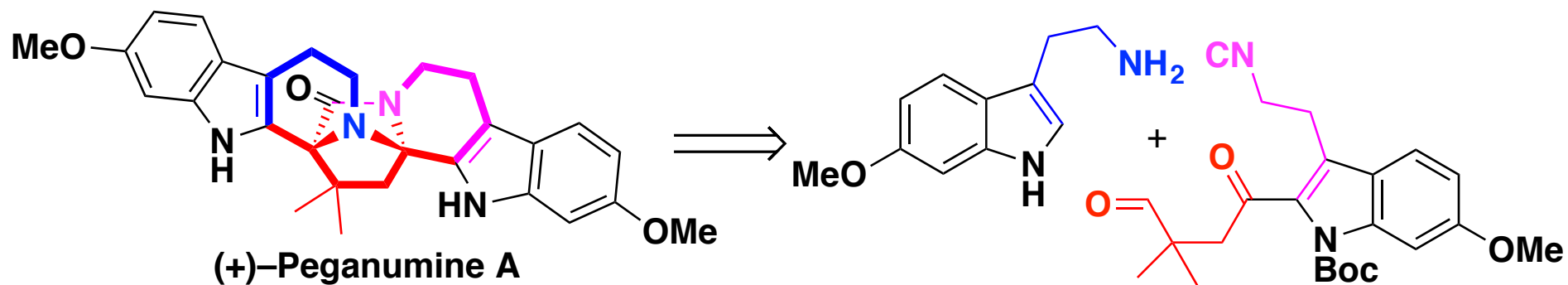
2,7-diazabicyclo[2.2.1]heptan-3-one unit

(+)-Peganumine A: Biosynthetic Hypothesis and Synthesis Design

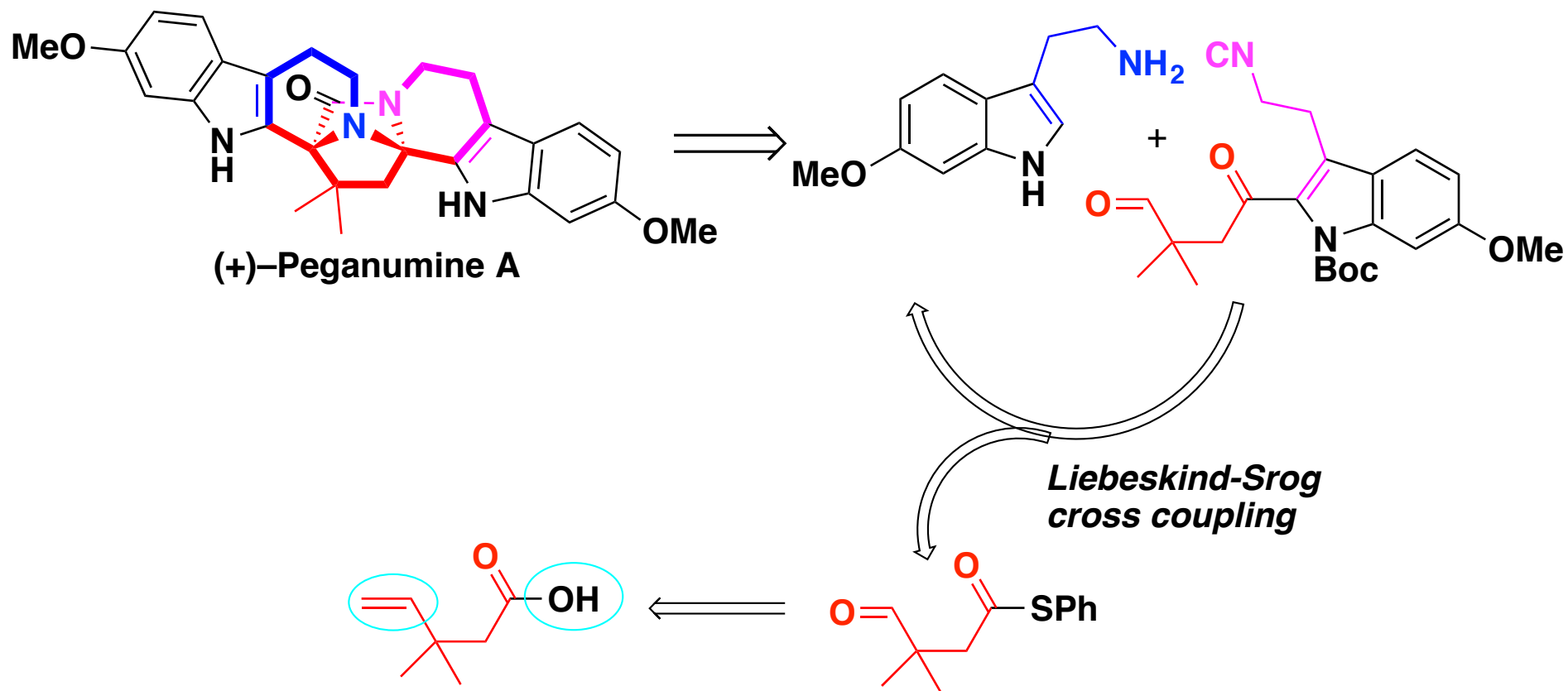


Biosynthesis hypothesis: Hua, H.-M. *et al Org. Lett.* **2014**, *16*, 4028

Peganumine A: Retro-synthetic Analysis



Peganumine A: Retro-synthetic Analysis



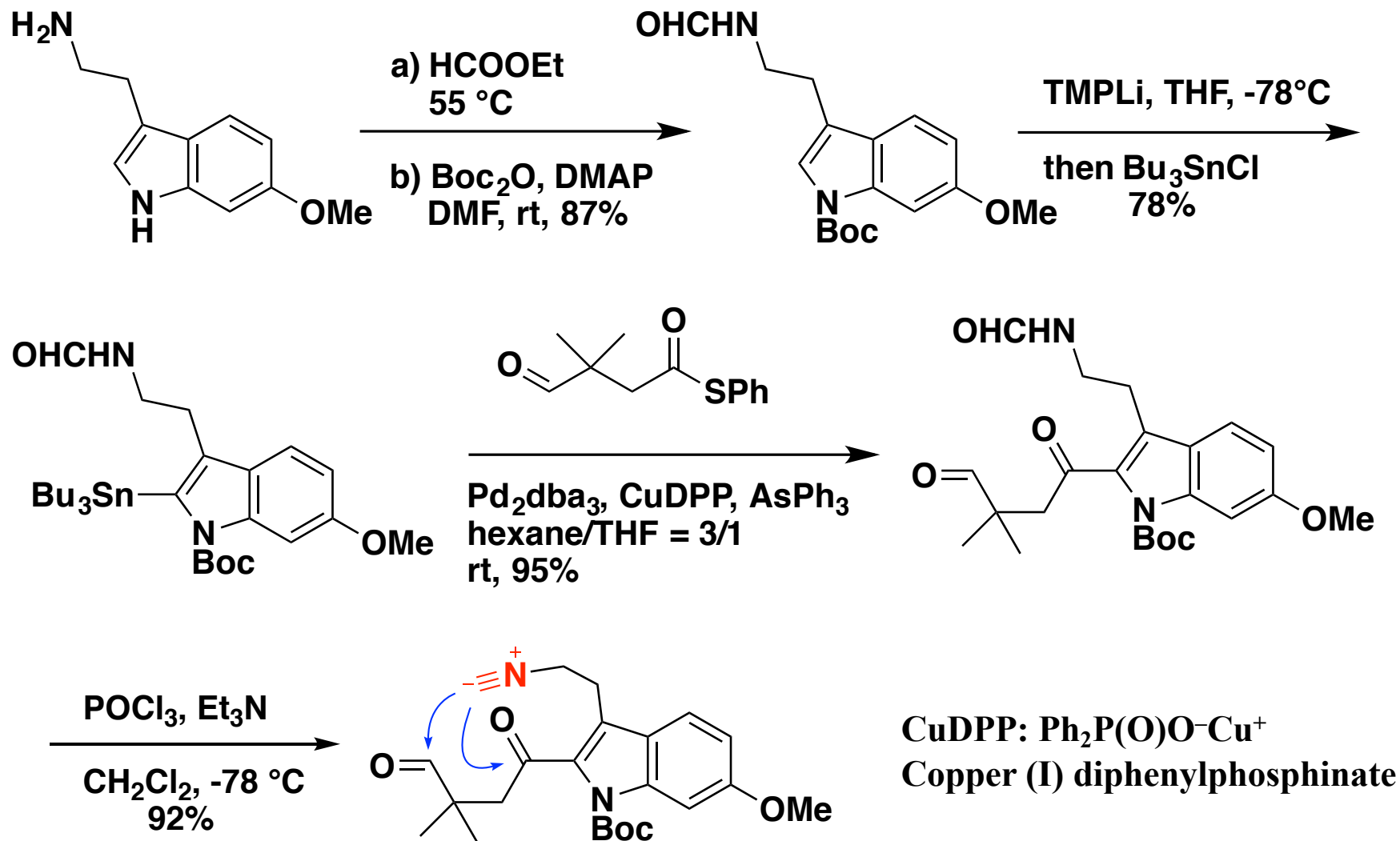
Liebeskind-Srogl cross coupling:

Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

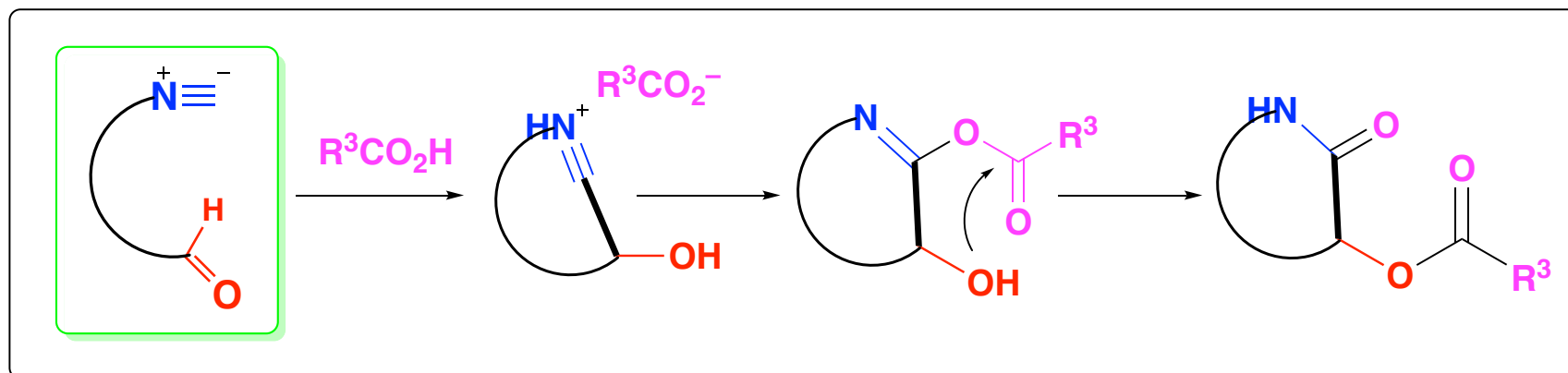
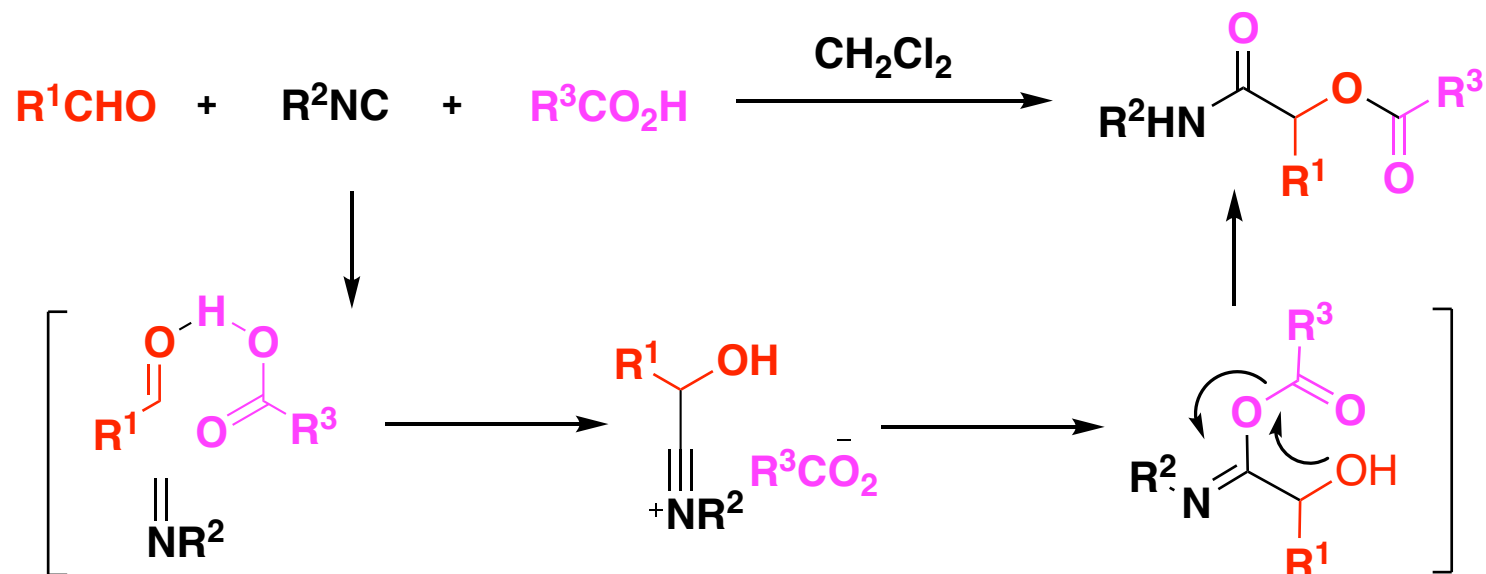
Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132

For a review, see: Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276.

Synthesis of Functionalized Tryptamine



Passerini Three-component Reaction

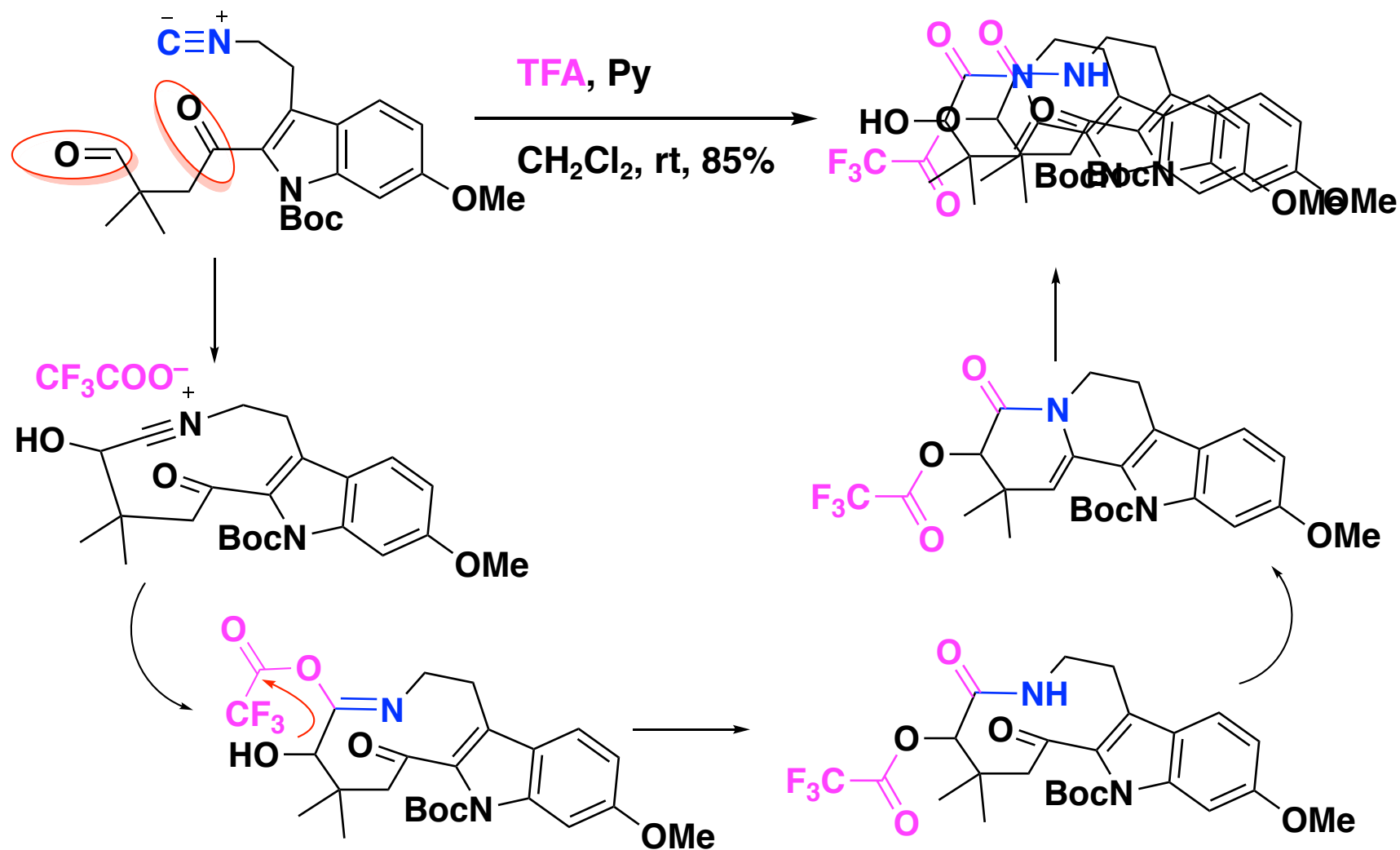


For reviews on multicomponent synthesis of macrocycles:

Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796.

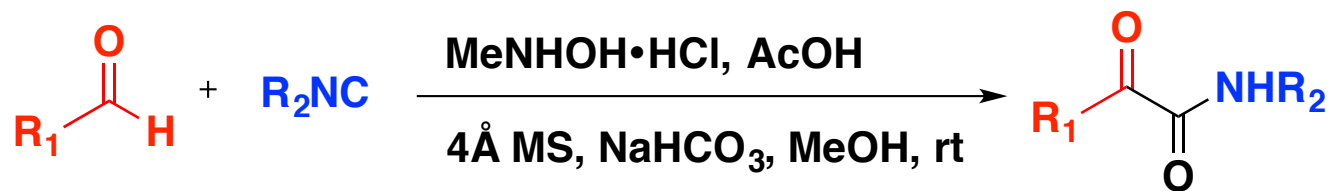
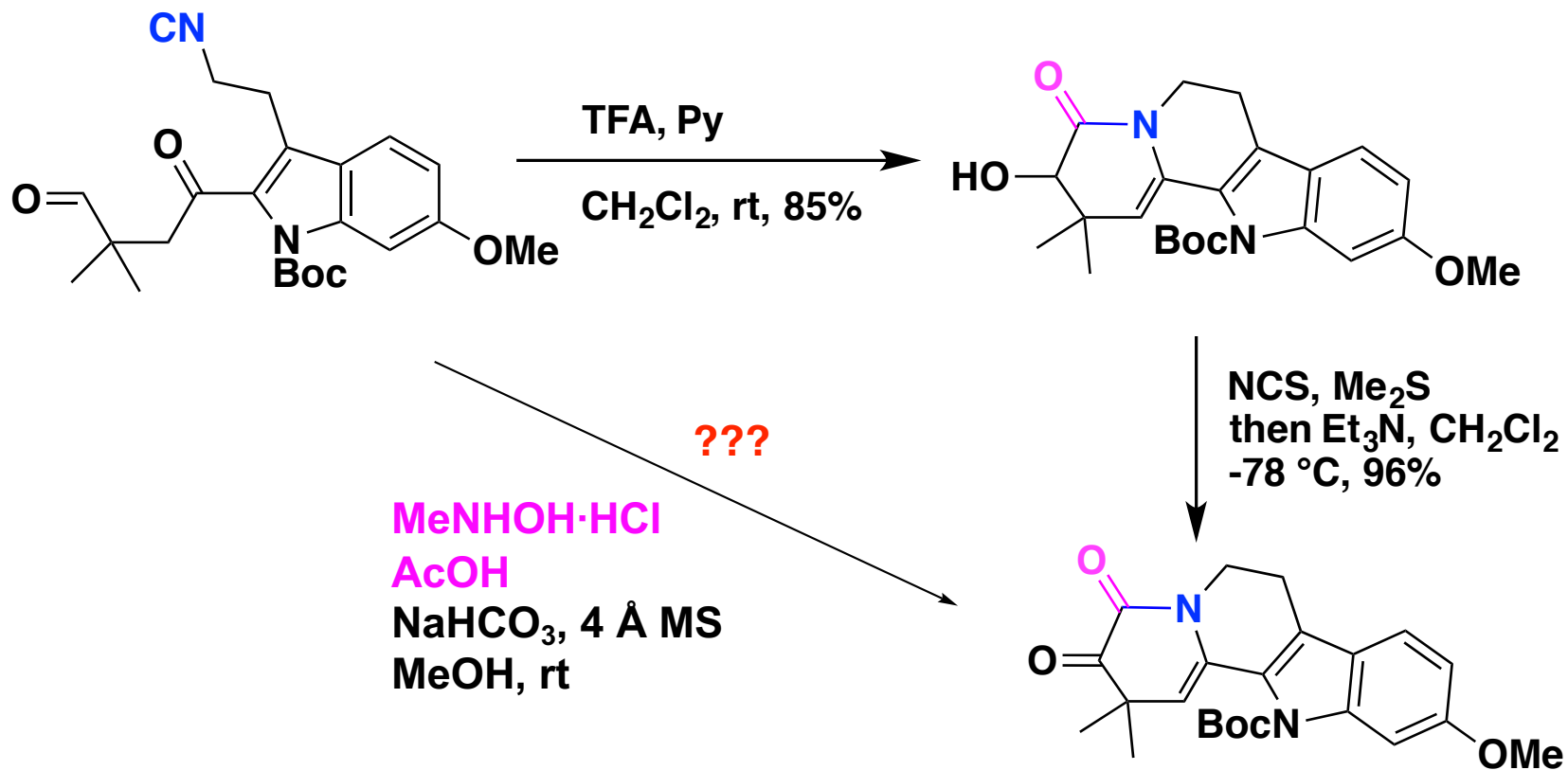
Masson, G.; Neuville, L.; Bughin, C.; Fayol, A.; Zhu, J. in *Synthesis of Heterocycles via Multicomponent Reactions II* (Eds. R. V. A. Orru, E. Ruijter), **2010**, Springer, Heidelberg.

Intramolecular Three-center-two-component Passerini Reaction



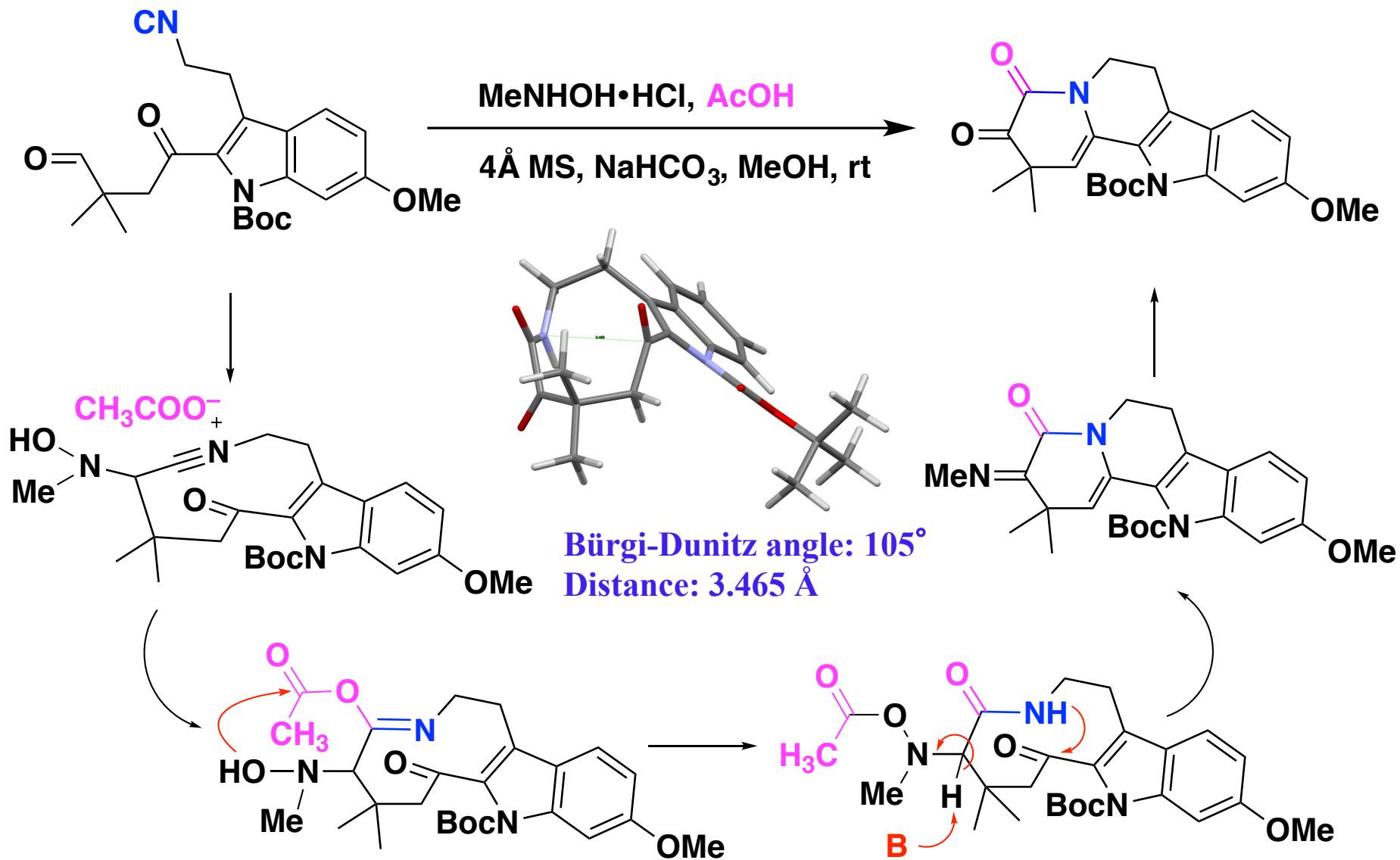
**Formation of a tetracycle, a hydroxy amide unit
with the creation of one C-N, one C=O, one C-C bonds**

Intramolecular Three-center-two-component Passerini Reaction

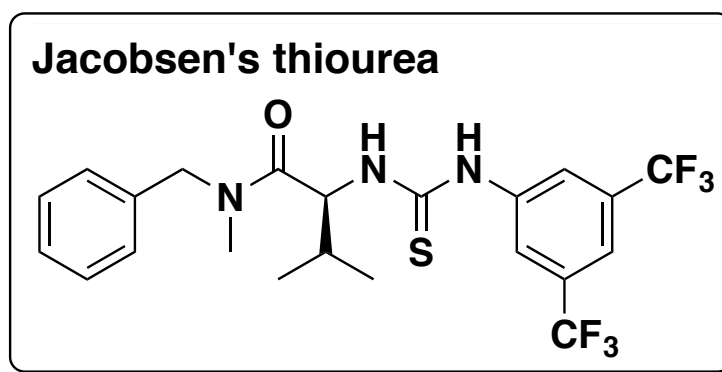
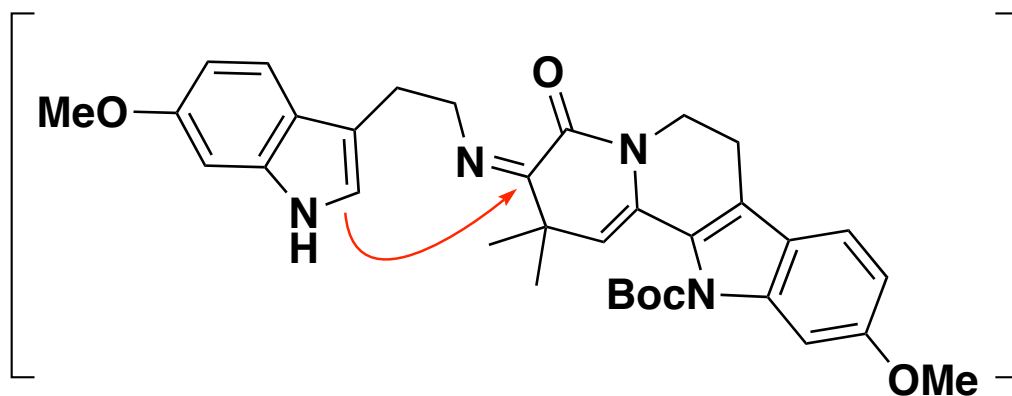
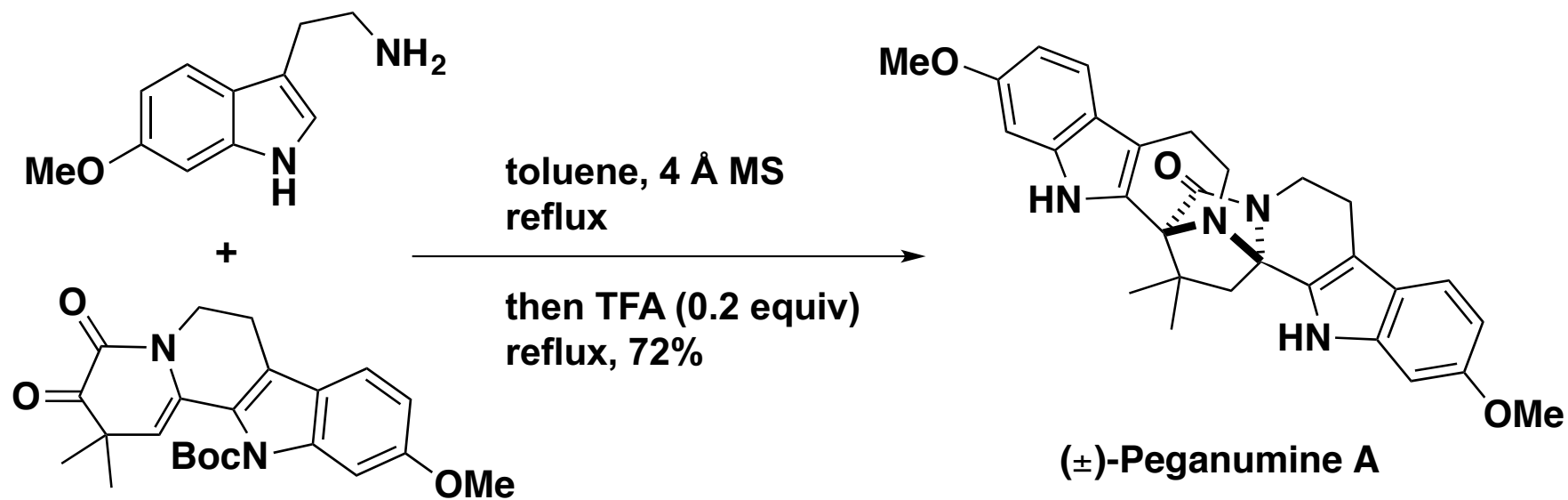


Grassot, J. M.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 947.

Hydroxyamine-mediated Oxidative Coupling of Aldehyde with Isocyanide

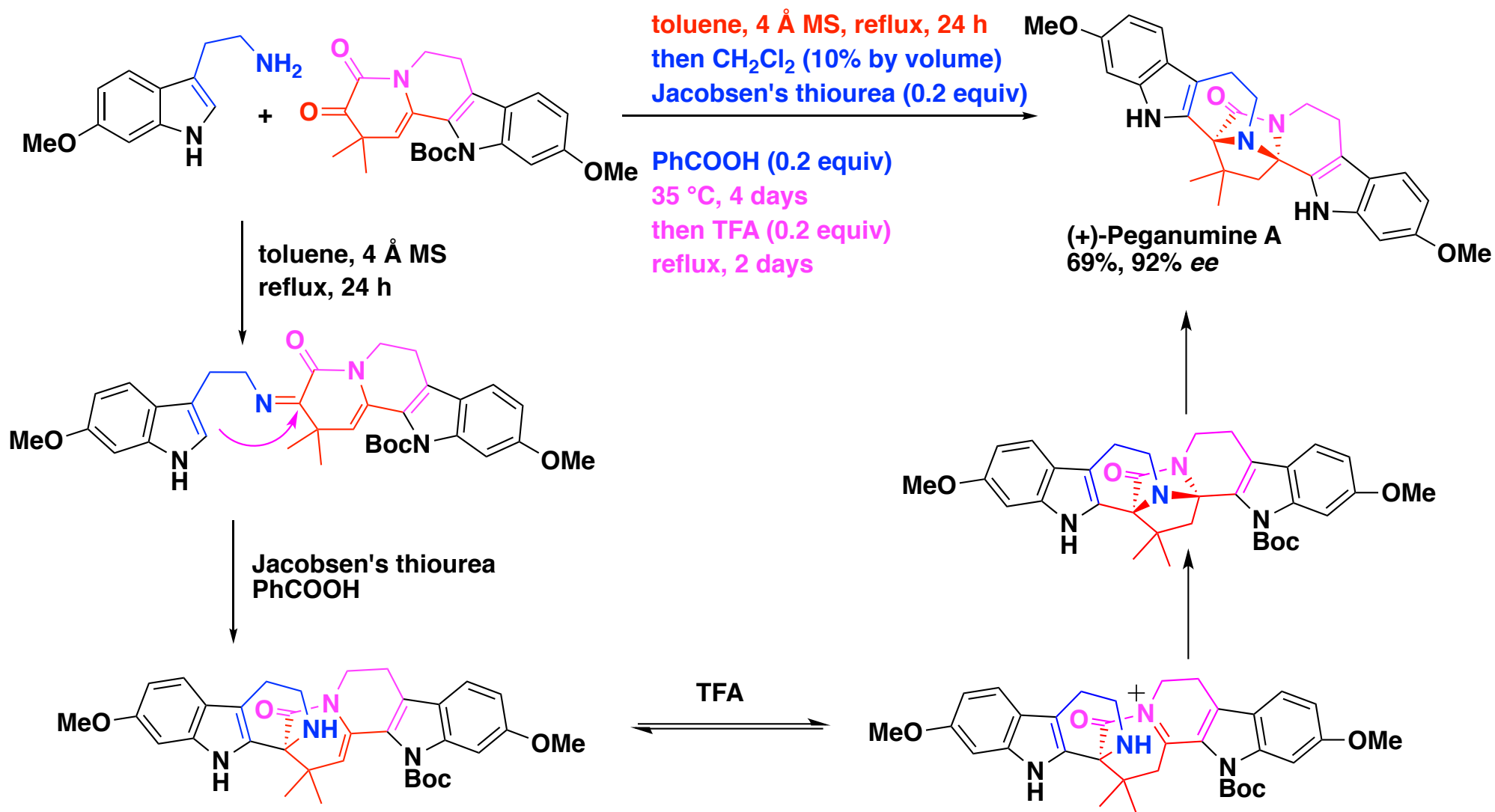


Total Synthesis of (\pm)-Peganumine A



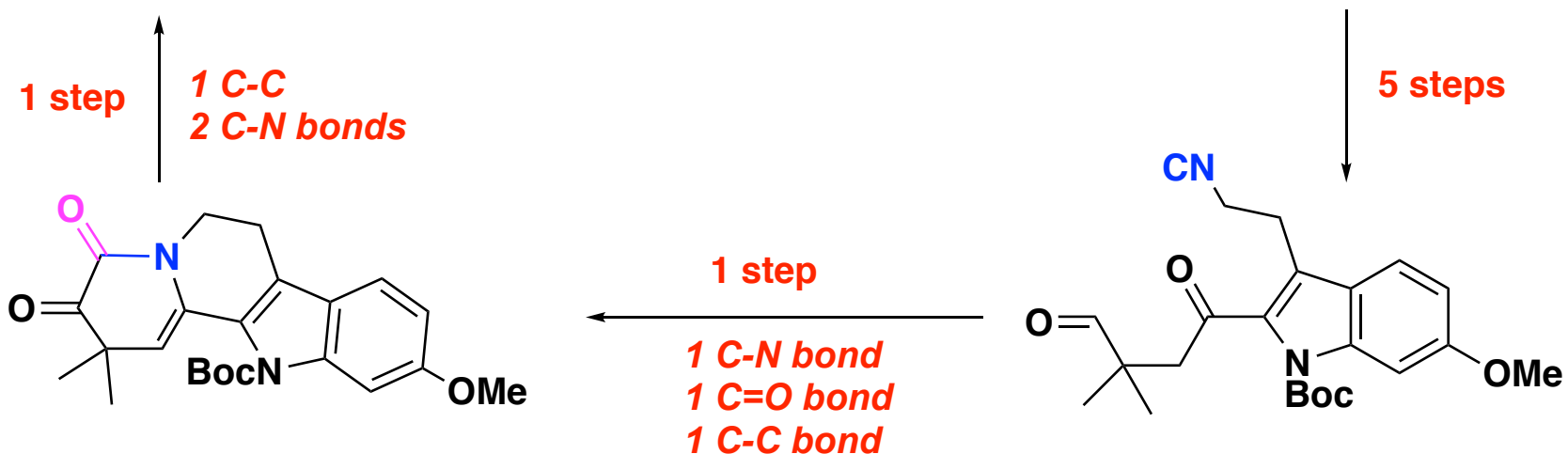
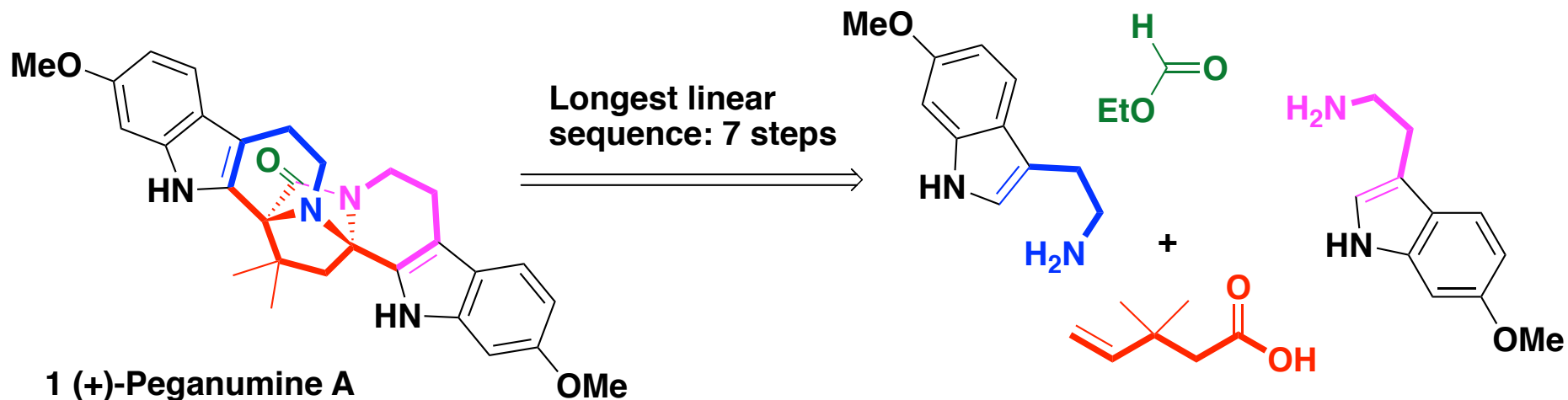
Jacobsen, E. et al. *J. Am. Chem. Soc.* **2004**, 126, 10558
Jacobsen, E. et al. *Org. Lett.* **2009**, 11, 887.

Total Synthesis of (+)-Peganumine A



1 C-C, 2 C-N bonds, two quaternary stereocenters
2 Spirocycles, concurrent formation of the 2,7-diazabicyclo[2.2.1]heptan-3-one unit

Total Synthesis of (-)-Peganumine A: Combined Use of MCR and Domino Process



Summary of Peganumine A Synthesis

- 1) Liebeskind-Sroog Cross Coupling**
- 2) Isocyanide chemistry**
- 3) Passerini three-component reaction**
- 4) Ugi four-component reaction**
- 5) Enantioselective Pictet-Spingler reaction**
- 6) Corey-Kim Oxidation of alcohol to ketone**
- 7) Transannular cyclization**

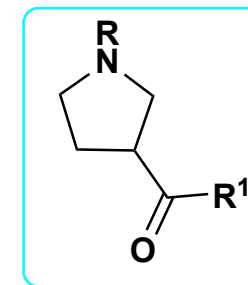
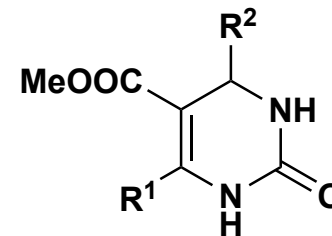
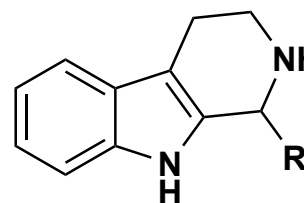
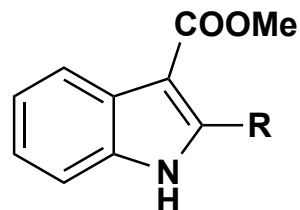
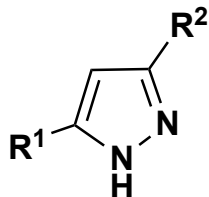
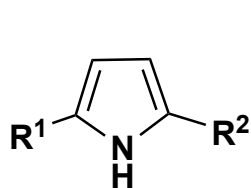
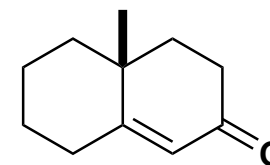
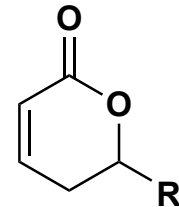
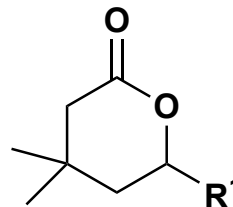
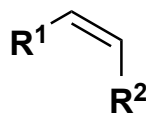
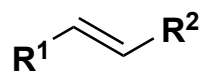
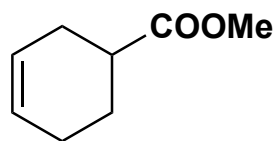
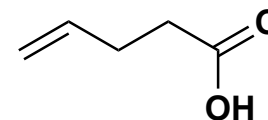
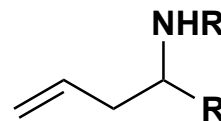
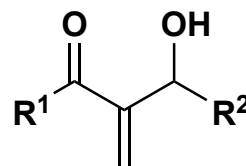
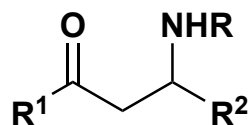
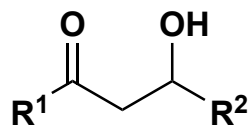
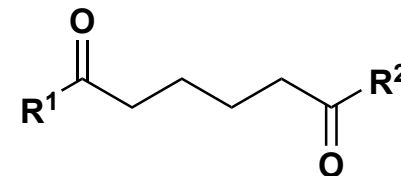
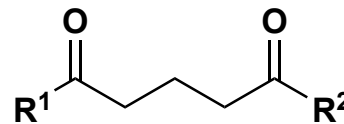
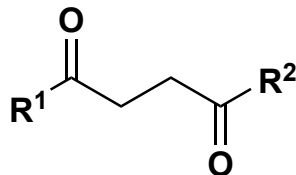
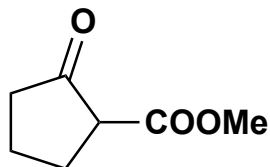
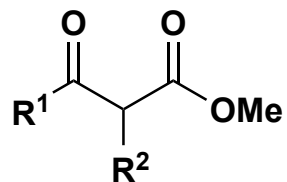
Pattern Recognition

Pattern recognition seeks to discover an exploitable substructural motif around which to organize the thought process and then the synthesis.

The most fascinating cases arise when the target itself must actually be modified leading to a more complex compound before a staple pattern is revealed

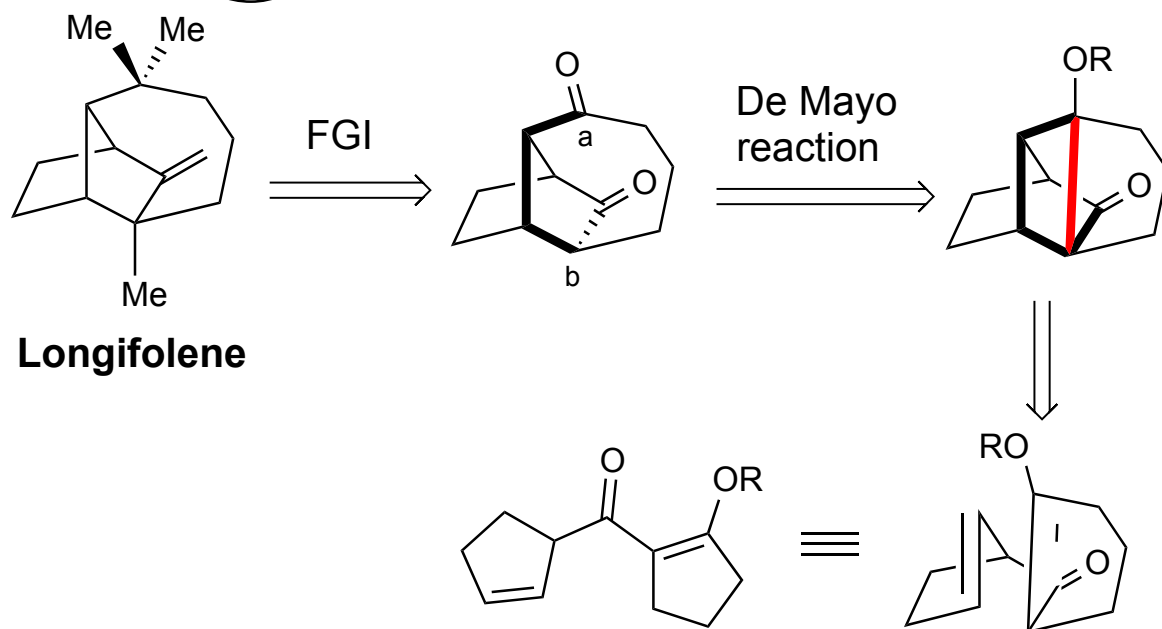
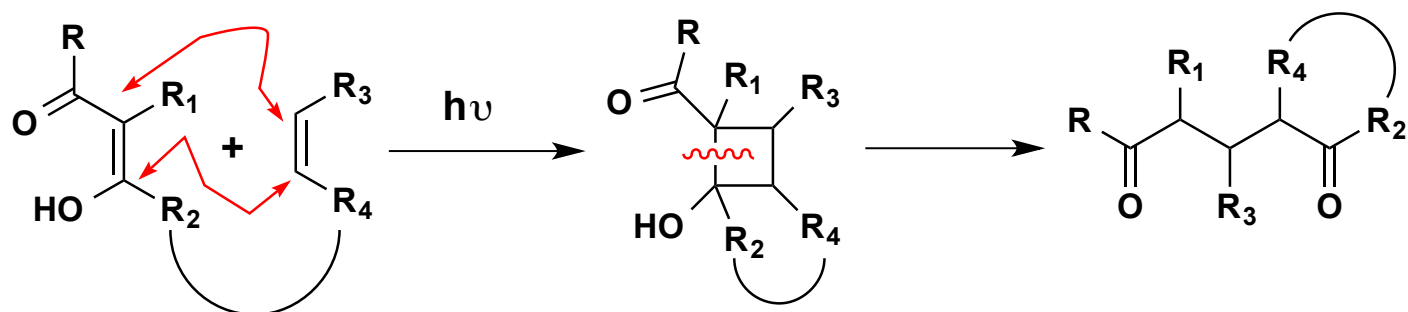
R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2007**, 72, 4293-4305.

Pattern Recognition: Simple examples



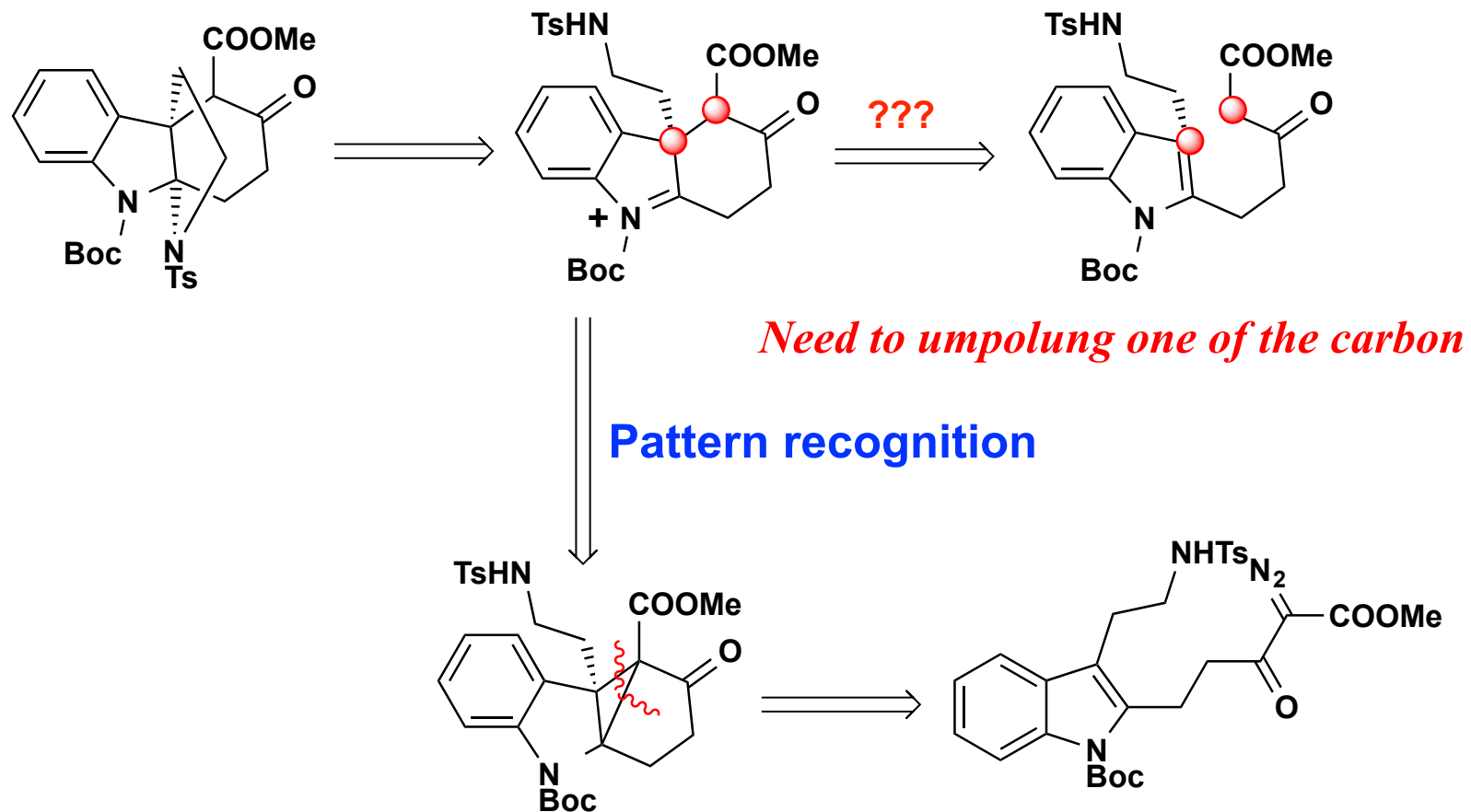
Oppolzer's Synthesis of Longifolene

De Mayo reaction



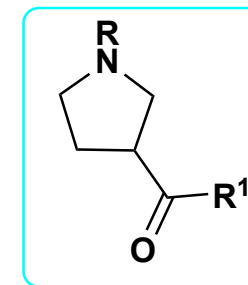
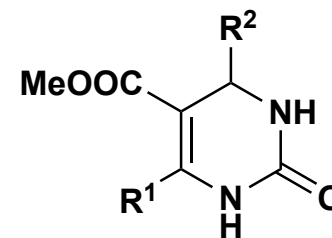
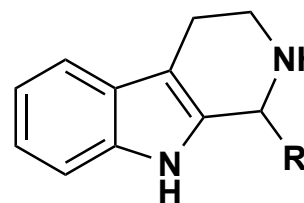
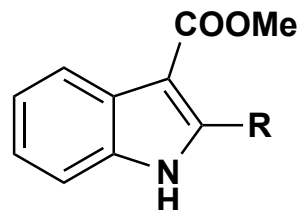
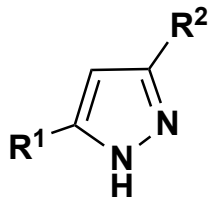
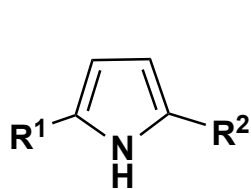
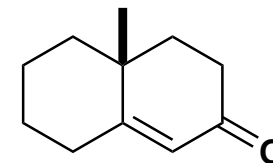
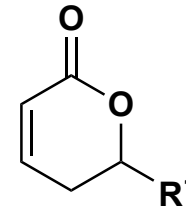
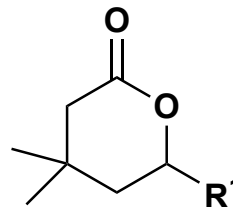
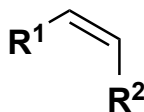
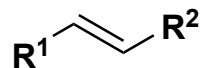
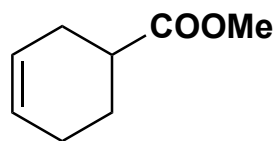
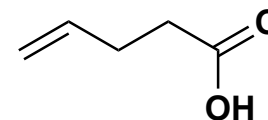
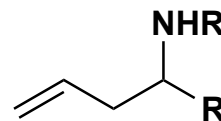
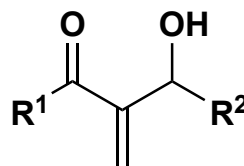
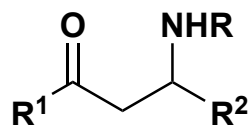
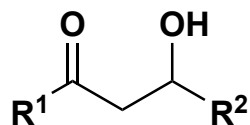
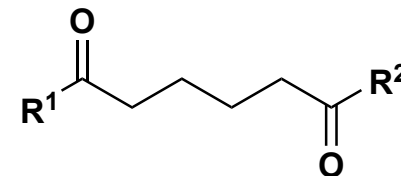
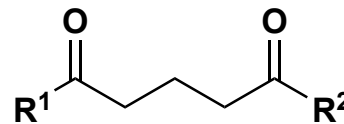
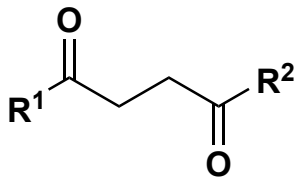
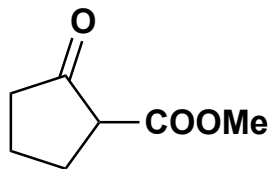
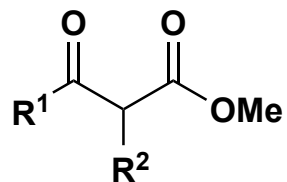
P. de Mayo, *Acc. Chem. Res.*, **1971**, *4*, 41;
W. Oppolzer, *Acc. Chem. Res.*, **1982**, *15*, 135

Qin's Synthesis of Minfiensine

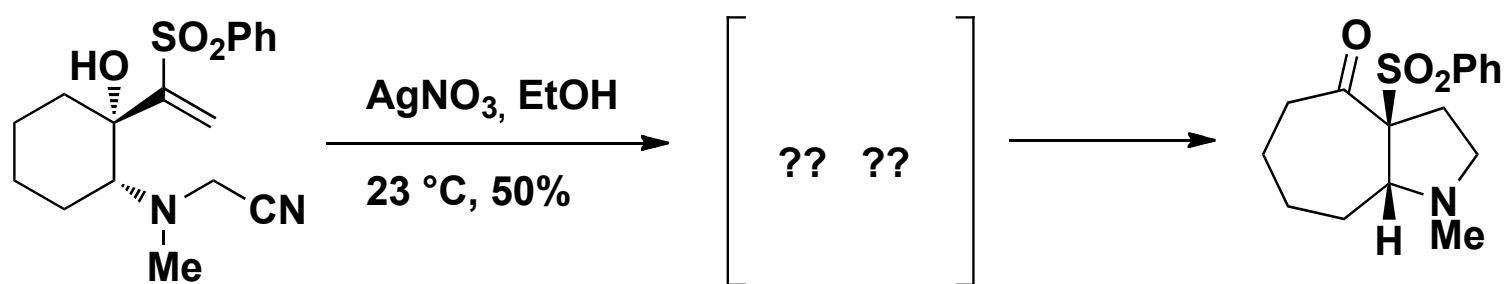
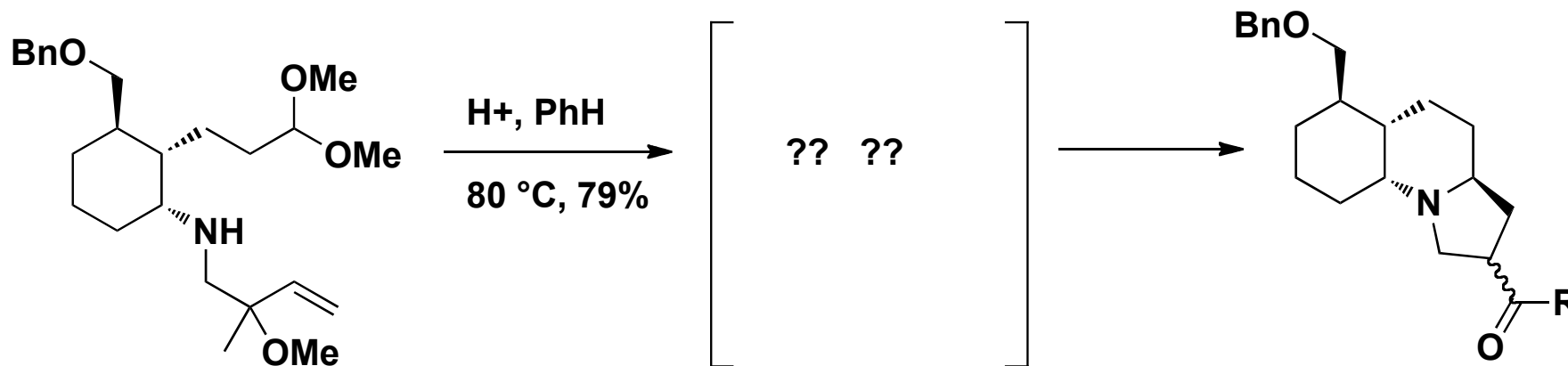
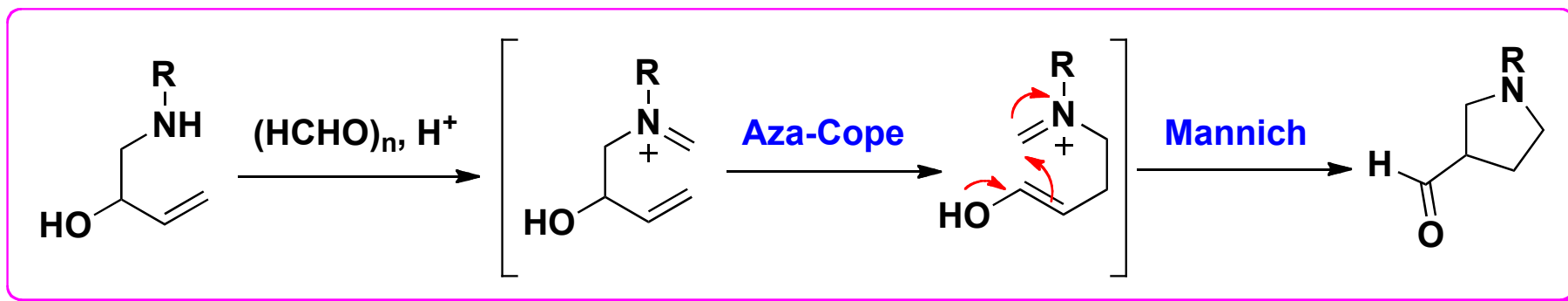


L. Shen, M. Zhang, Y. Wu, Y. Qin, *Angew. Chem. Int. Ed.* **2008**, 47, 3618-3621.

Pattern Recognition: Simple examples

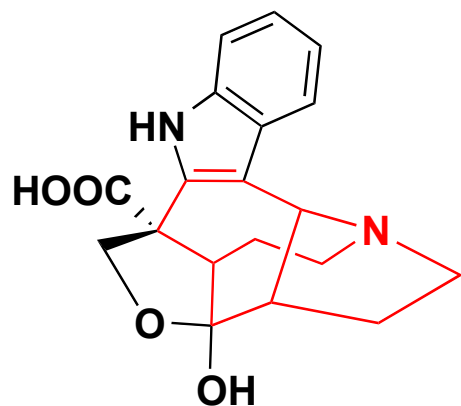


Basic of Aza-Cope/Mannich

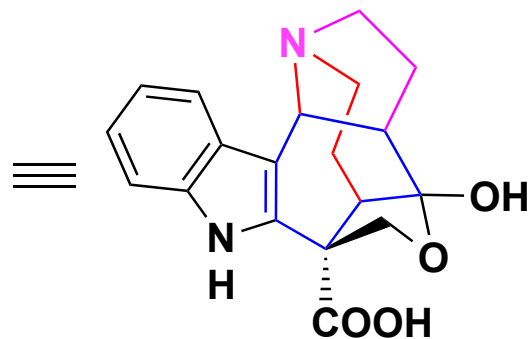


Key Motif: 3-Acyl proline!!!

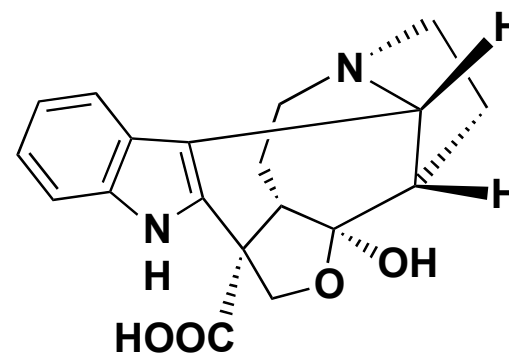
Actinophyllic acid



Actinophyllic acid



Drawing in the isolation paper

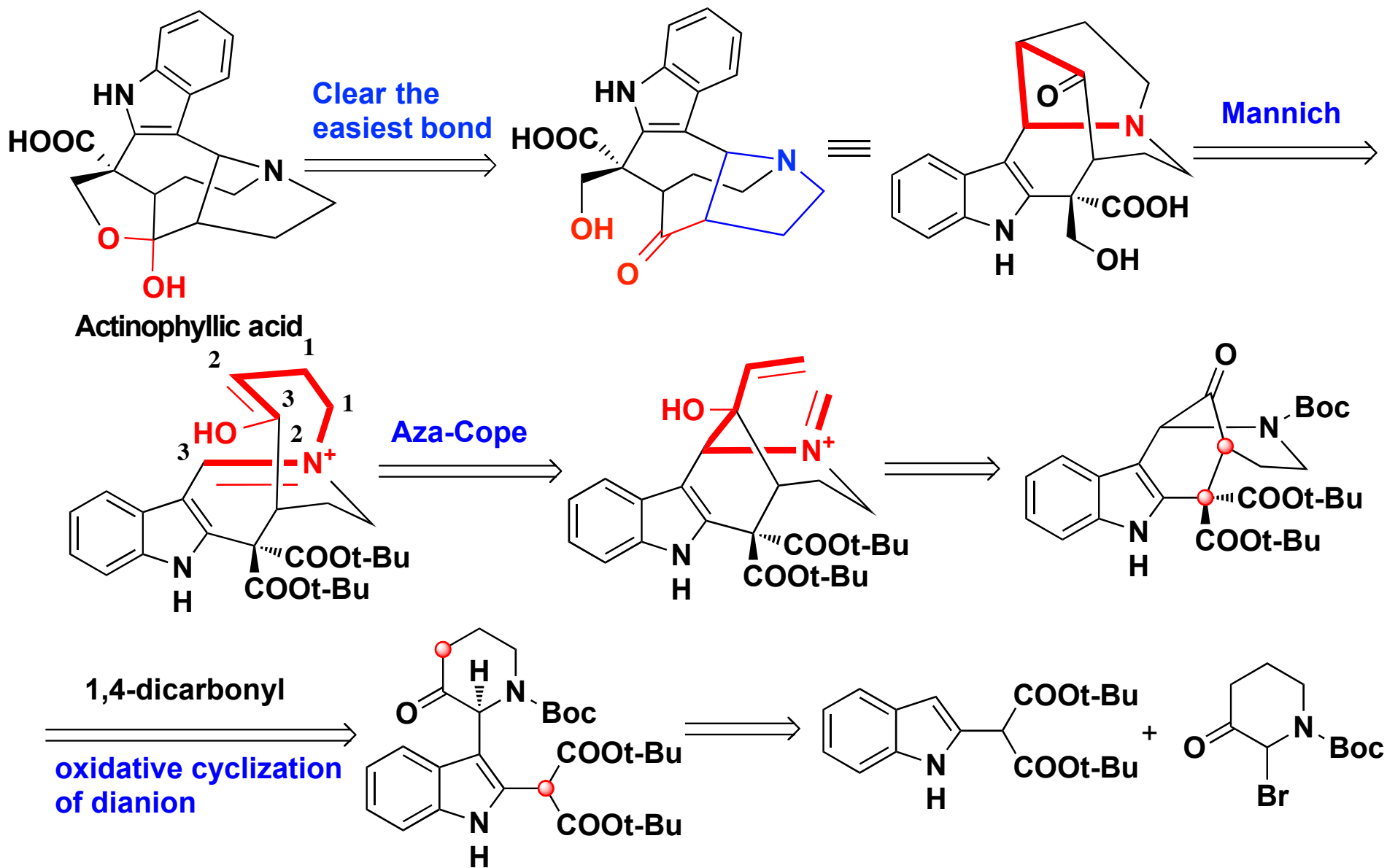


Isolated From *Alstonia actinophylla* in 2005

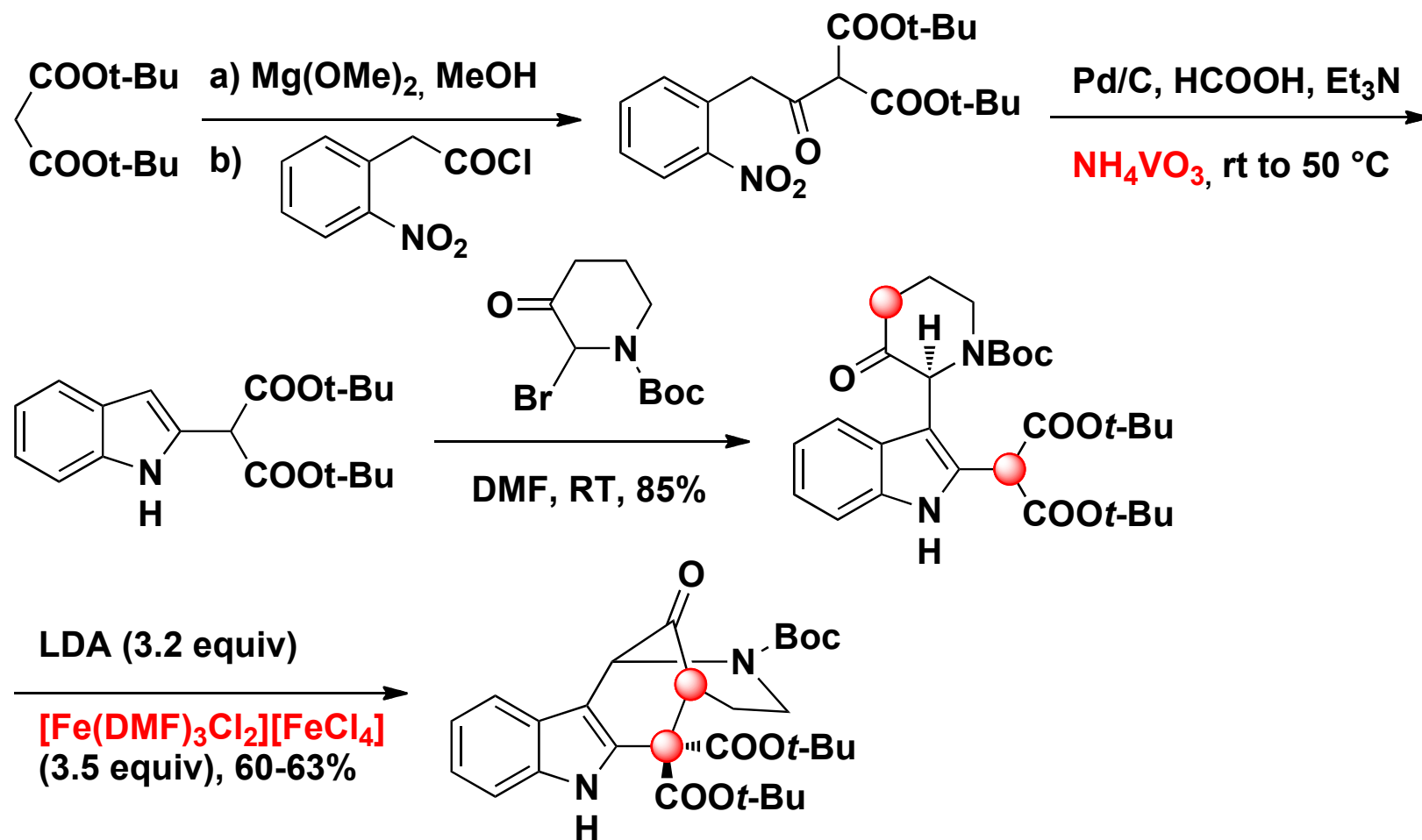
a potent inhibitor in the coupled enzyme assay
TAFIa/hippuricase (IC₅₀) 0.84 μ M).

A. R. Carroll, E. Hyde, J. Smith, R. J. Quinn, G. Guymer, P. I. Foster, *J. Org. Chem.* **2005**, *70*, 1096–1099.

Overman's Synthesis of Actinophyllic acid



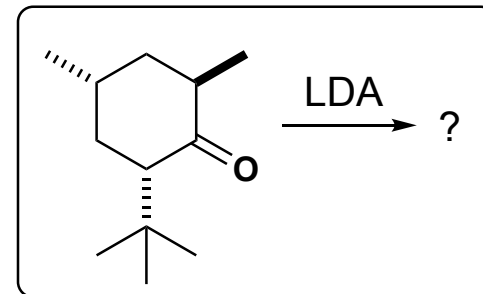
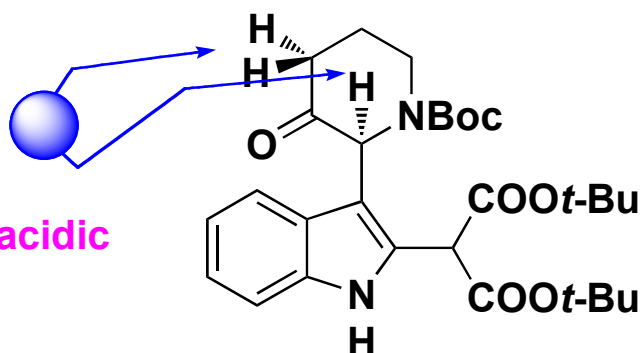
Key Oxidative dienolate cyclization



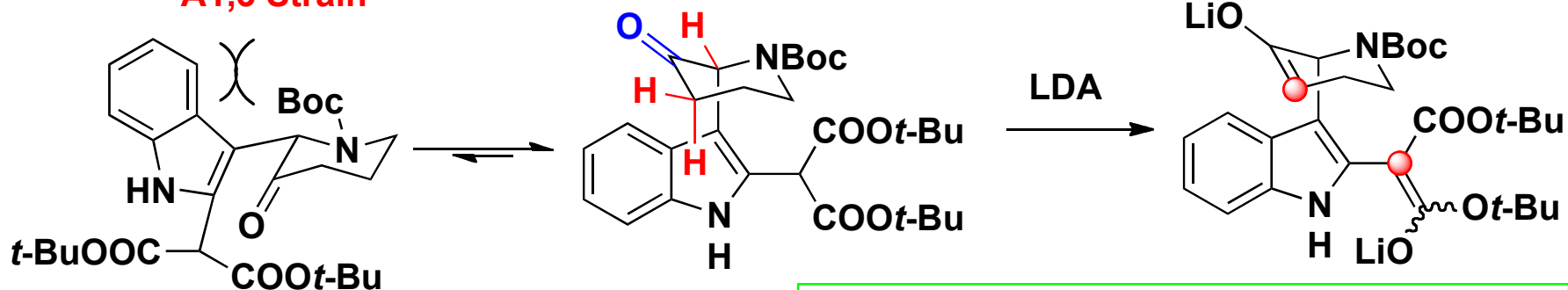
NH_4VO_3 : promote the complete reduction of nitro to aniline
 $[\text{Fe}(\text{DMF})_3\text{Cl}_2][\text{FeCl}_4]$: easily prepared by dissolving FeCl_3 in DMF,
Different bases and oxidants were tested, LDA and
 $[\text{Fe}(\text{DMF})_3\text{Cl}_2][\text{FeCl}_4]$ turned out to be the best combination.

Key Oxidative Dienolate Cyclization—Regioselectivity

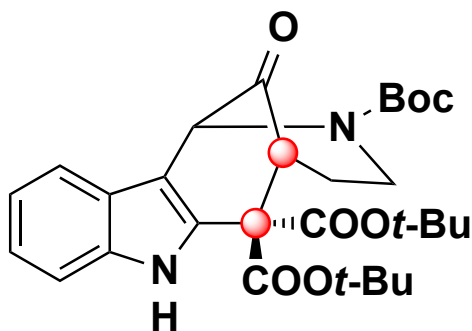
Which protons are more acidic



A1,3 Strain

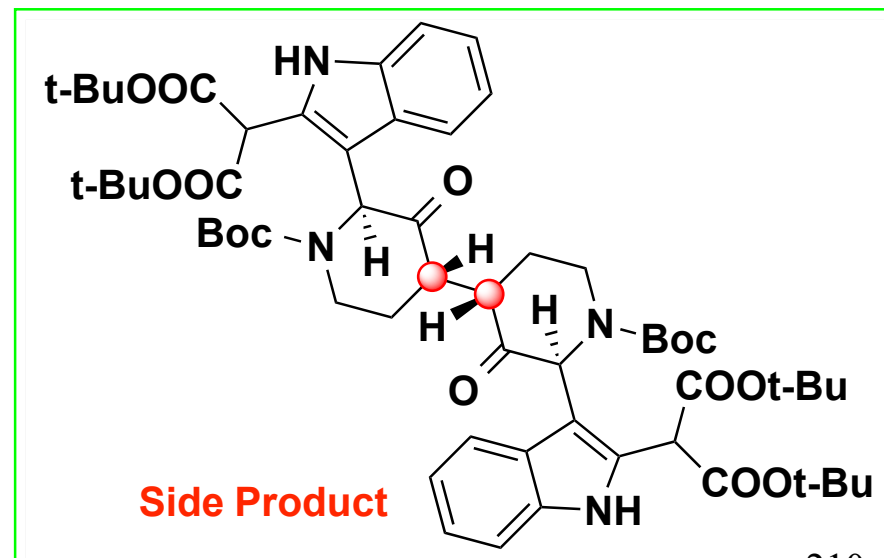


$[Fe(DMF)_3Cl_2][FeCl_4]$

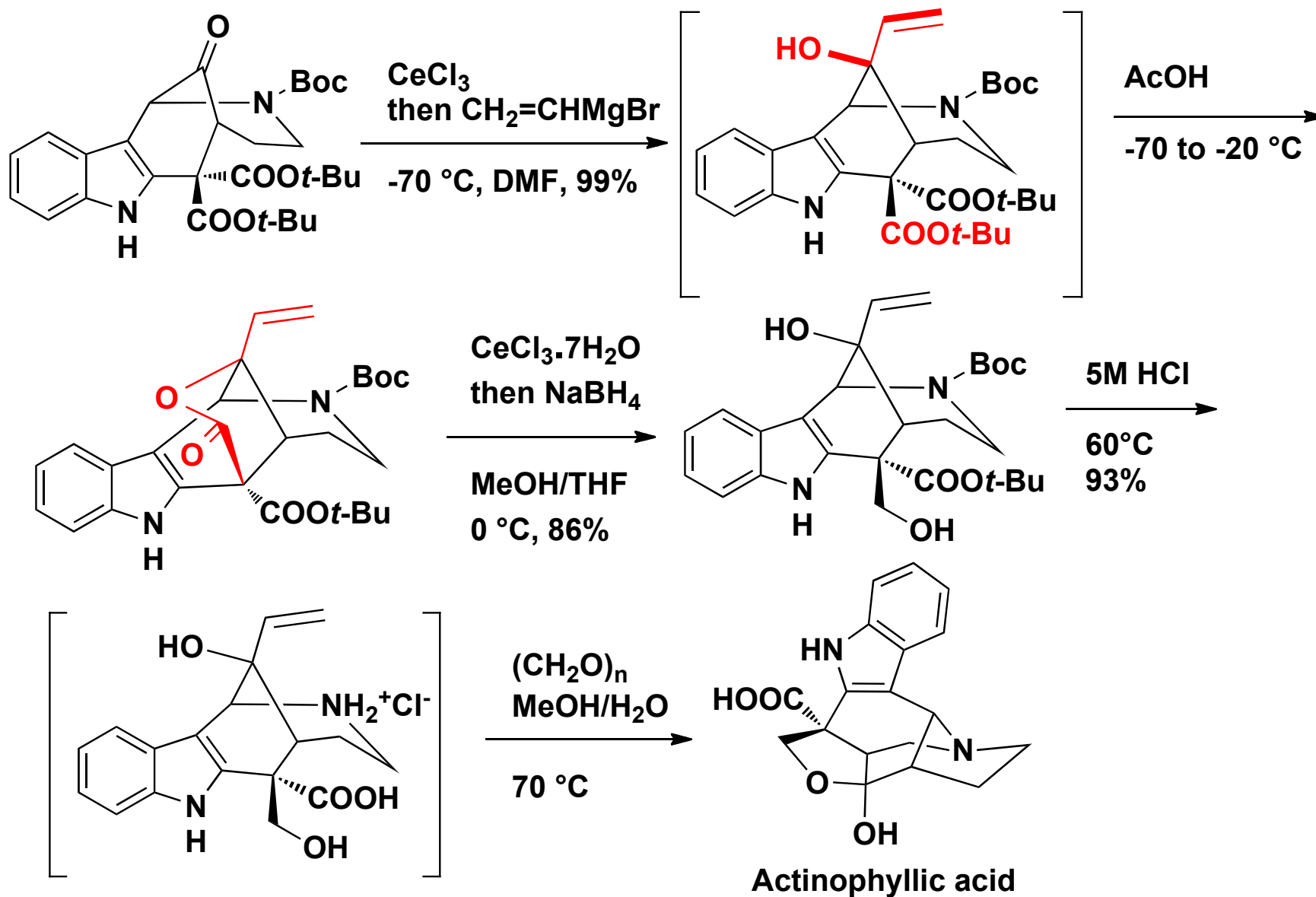


Side Product:

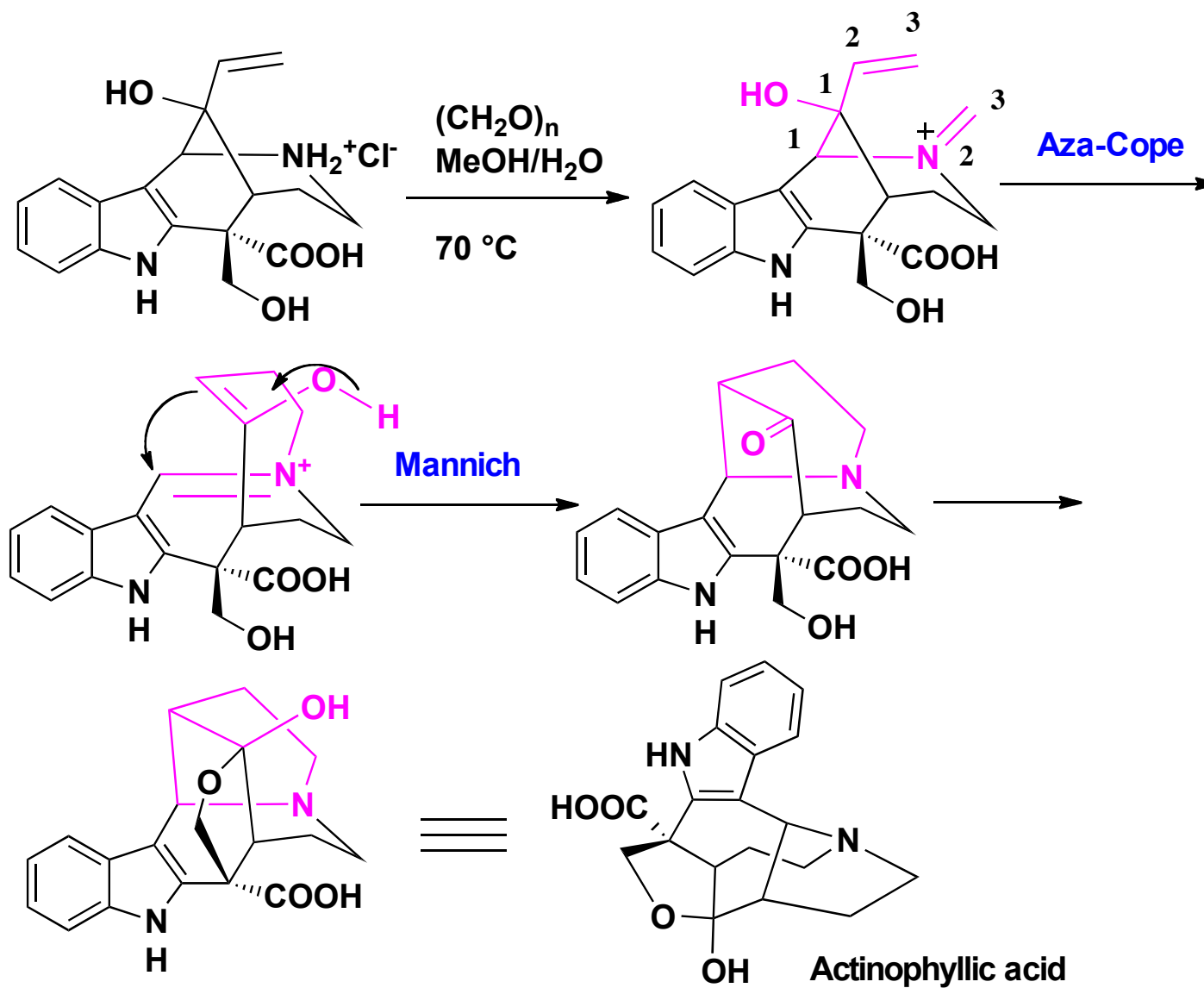
decreased as concentration of rxn mixture increased, Unusual !!!



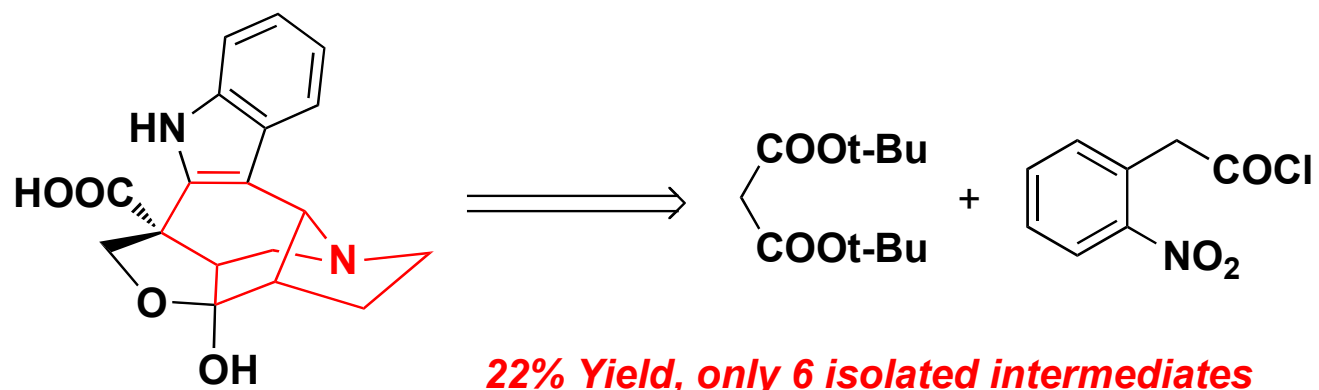
Overman's Synthesis of Actinophyllic acid: Endgame



Aza-Cope/Mannich: Pathway



Actinophyllic acid: Summary

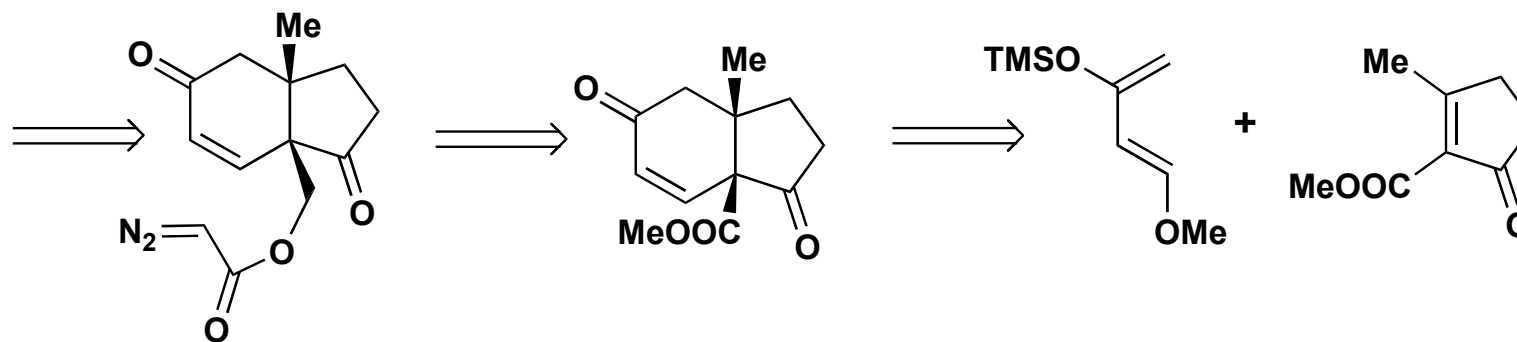
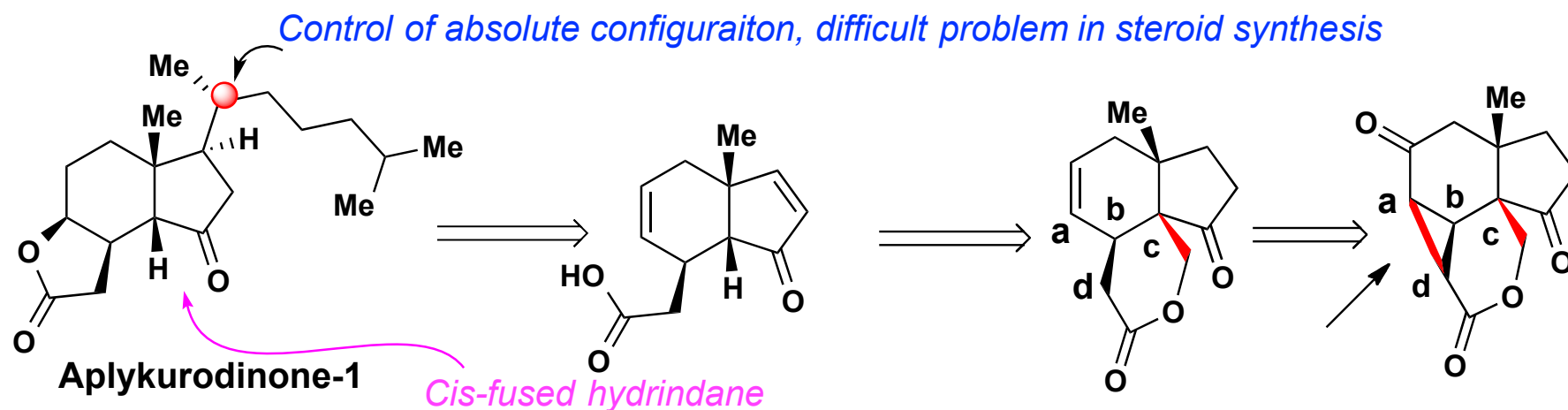


Key steps:

- Intramolecular oxidative cyclization of dienolate
- Domino Aza-Cope/Mannich sequence
- Conformation Analysis

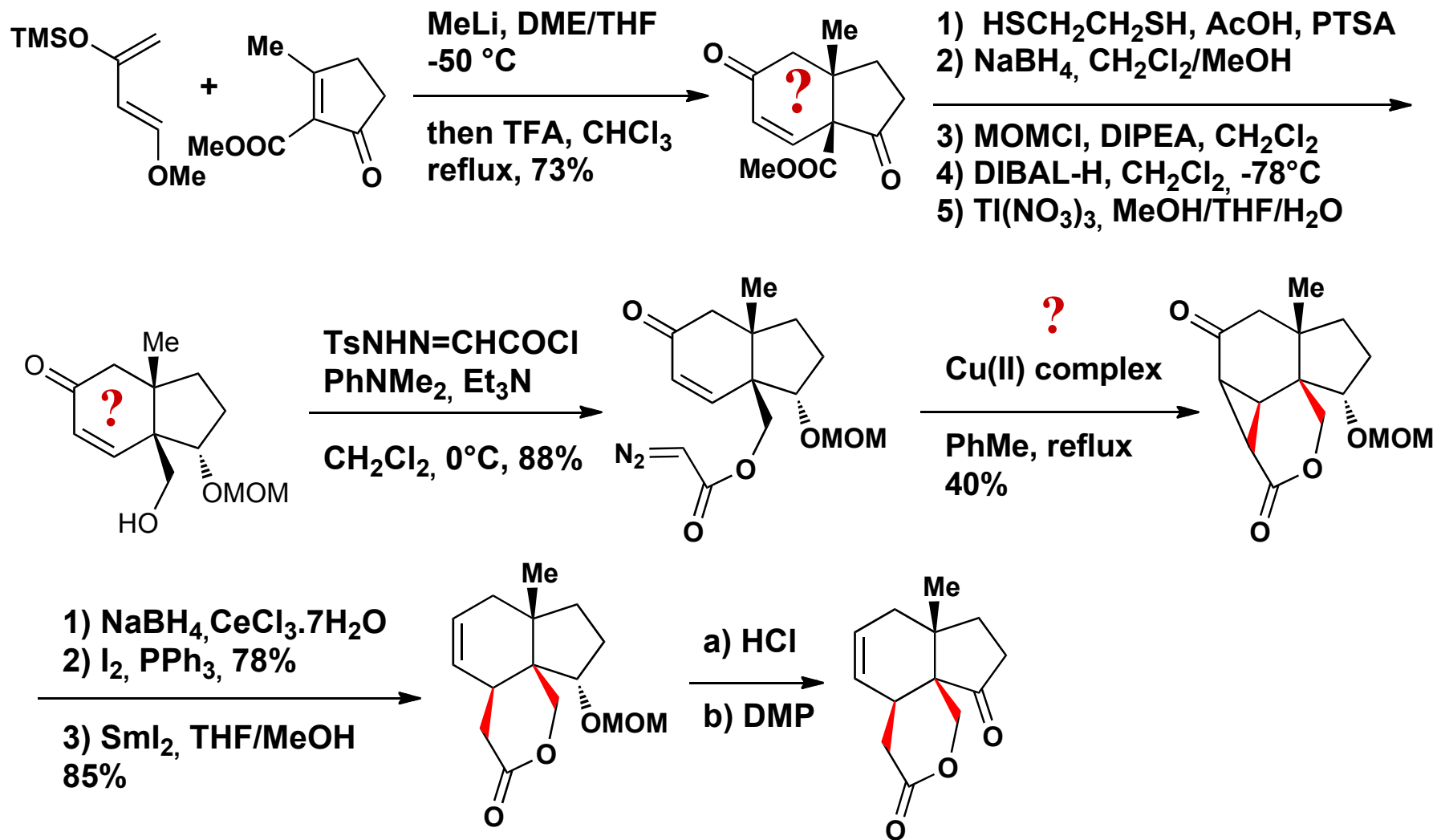
C. L. Martin, L. E. Overman, J. M. Rohde, *J. Am. Chem. Soc.* **2010**, *132*, 4894-4906.

Danishefsky's Retro Synthesis of Aplykurodinone



Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 9567-9569.

Danishefsky's Synthesis-1

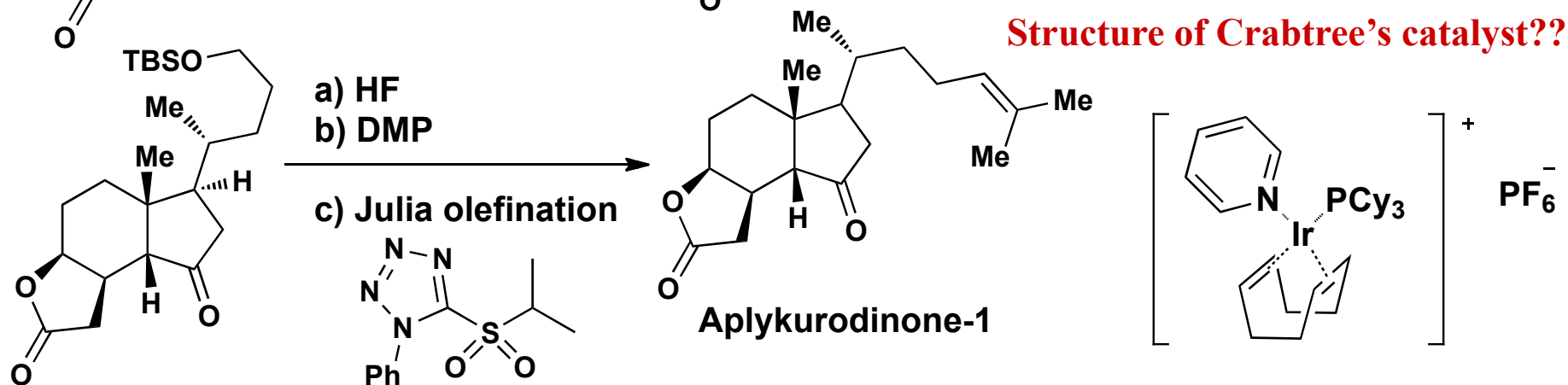
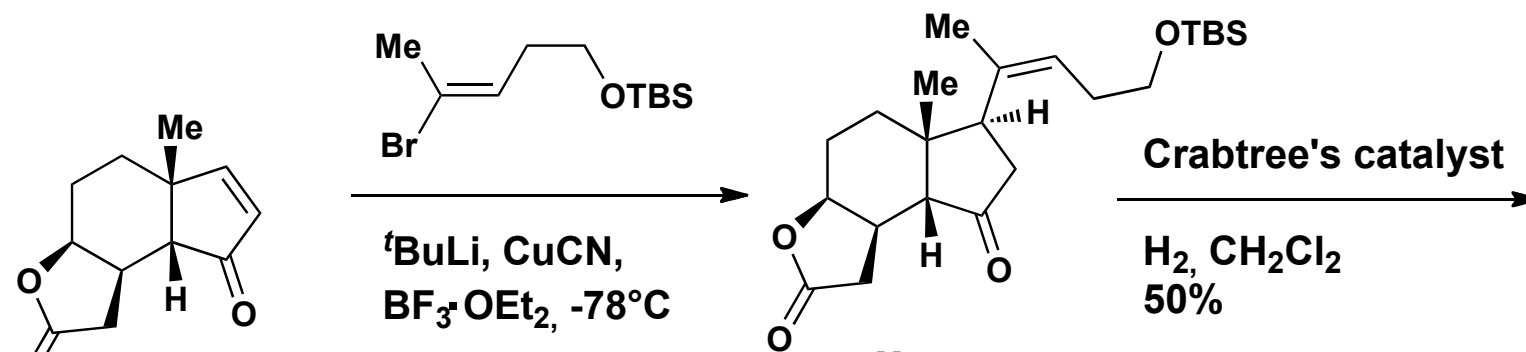
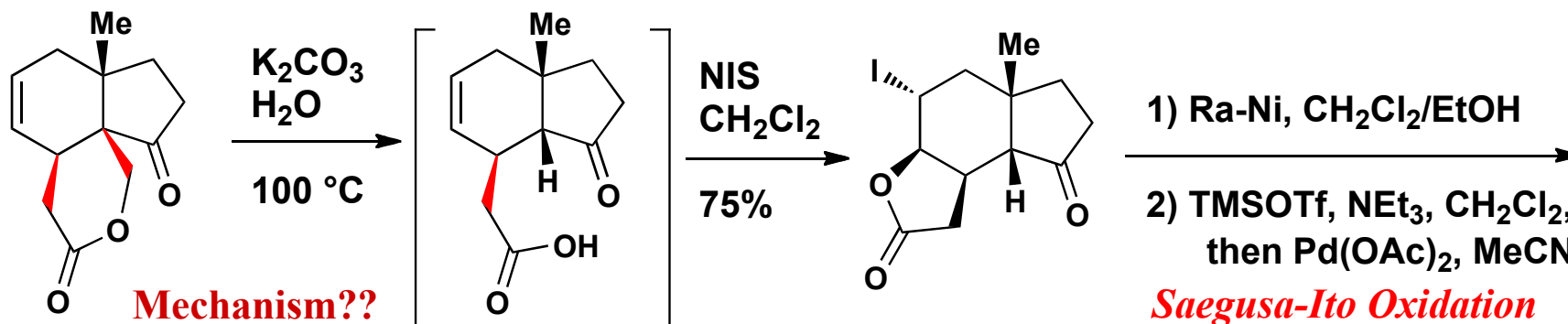


Structure of intermediate

Appel reaction

Mitsunobu reaction

Traceless Stereochemical guidance



Julia olefination; Julia-Kocienski olefination

Summary of Danishefsky's Synthesis of Aplykurodinone

- 1) Diels-Alder reaction under basic conditions**
- 2) Intramolecular cyclopropanation**
- 3) Retro-aldol**
- 4) Iodolactonization**
- 5) 1,4-Addition of cuprate to enone**
- 6) Julia reaction, Julia-Kocienski Reaction**