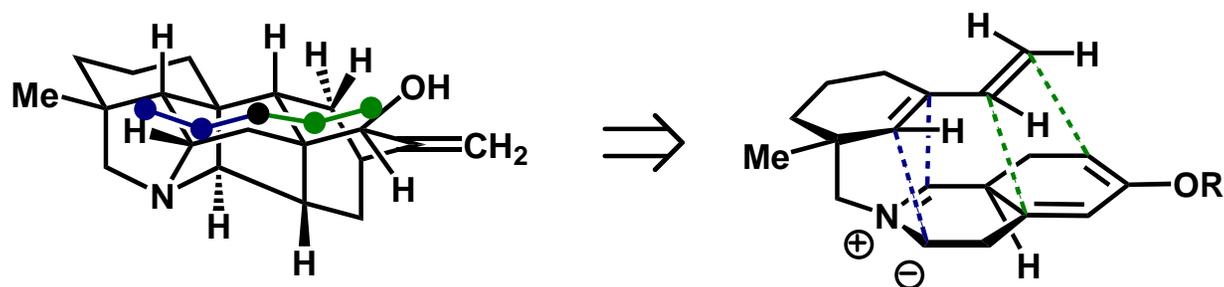


***Asymmetric Total Synthesis of (+)-Nominine:  
Development of a Dual Cycloaddition Strategy for  
the synthesis of the Hetisine Alkaloids***



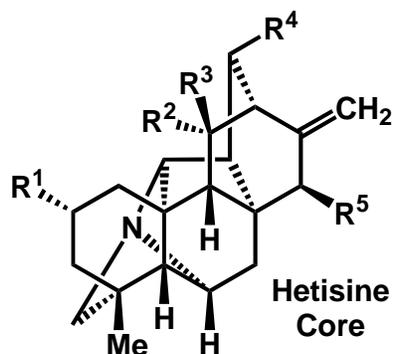
**Kevin M. Peese  
Denmark Group Meeting**

**Department of Chemistry  
University of Illinois at Urbana-Champaign  
Tuesday May 15, 2006**



## Hetisine Alkaloids: Background

- **Classification:** Family of >103 distinct natural products within the larger class of C<sub>20</sub>-diterpene alkaloids
- **Isolation:** Predominantly from *Aconitum* (monkshood) and *Delphinium* genera, but also *Rumex*, *Consolida*, and *Spiraea*
- **Pharmacology:** Active constituents of traditional Chinese medicines
- **Biological activity:** Vasodilating, immunomodulating, analgesic, and antiarrhythmic activities



**Nominine**  
(R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> = H; R<sup>5</sup> = OH)

**Kobusine**  
(R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> = H; R<sup>3</sup>, R<sup>5</sup> = OH)

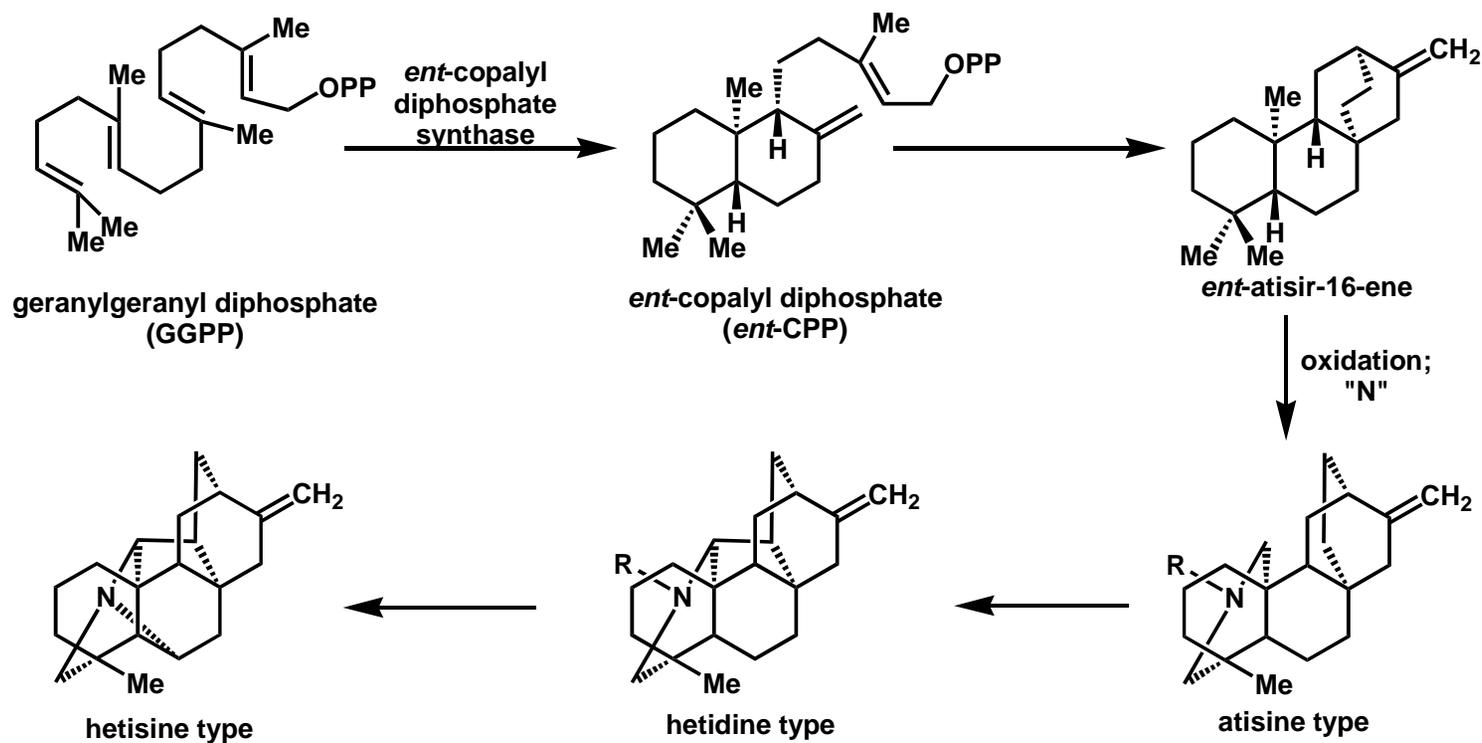
**Hetisine**  
(R<sup>3</sup>, R<sup>5</sup> = H, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> = OH)



*Aconitum sanyoense*

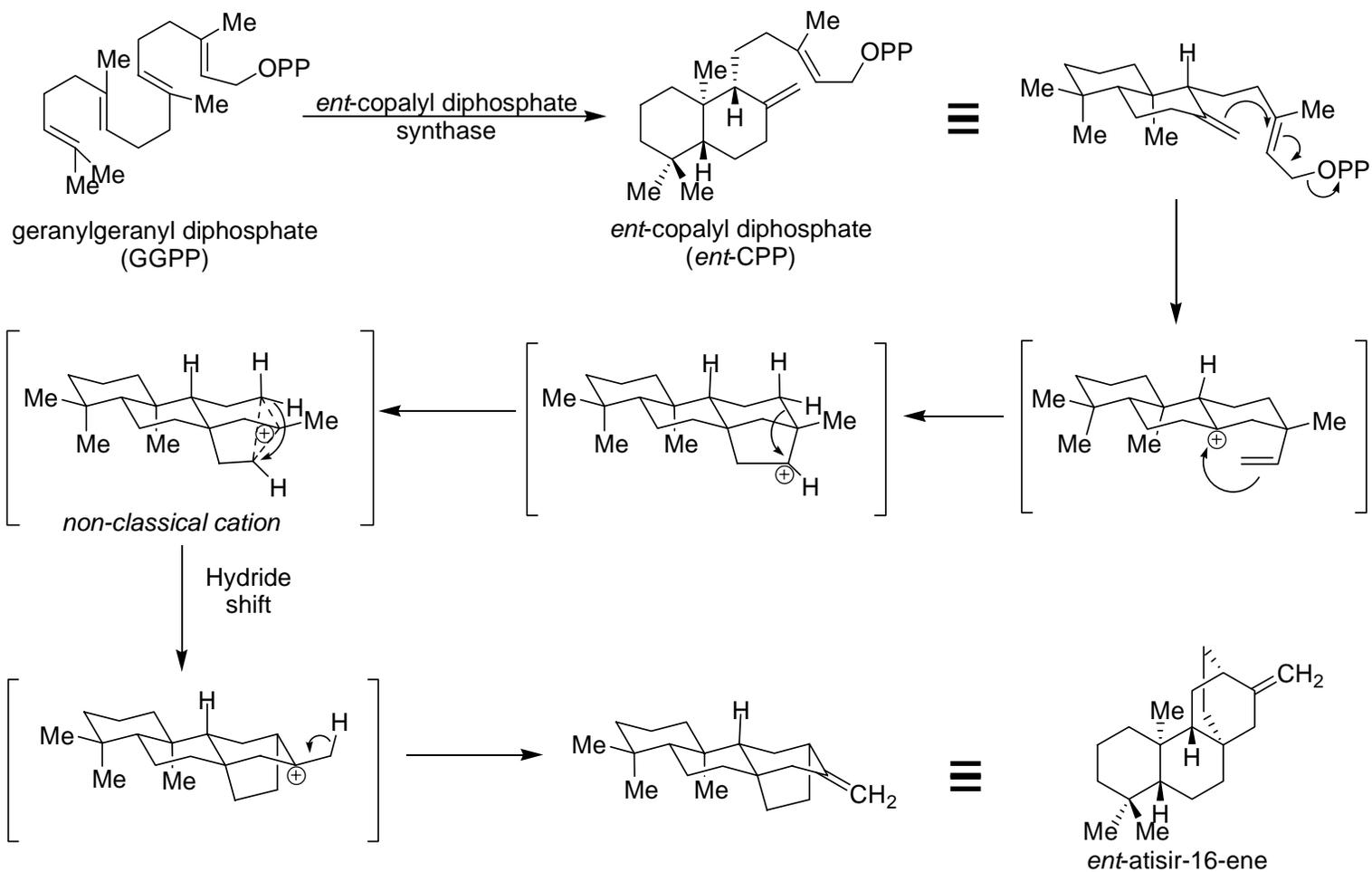


# Hetisine Alkaloids: Biosynthesis



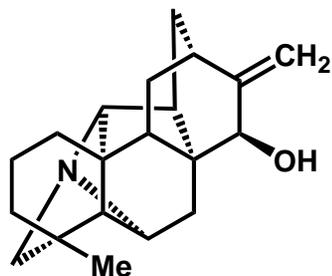


# Hetisine Alkaloids: Biosynthesis





# Hetisine Alkaloids: Previous Synthetic Approaches

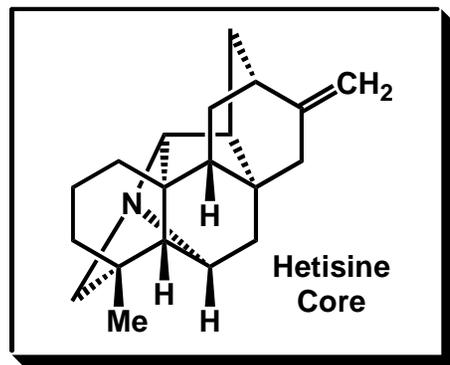


(±)-nominine (40 steps)

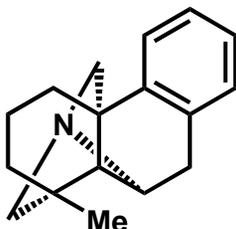
Muratake, H.; Natsume, M.

*Angew. Chem. Int. Ed.* 2004, 43, 4646-4649

*Tetrahedron Lett.* 2002, 43, 2913-2917

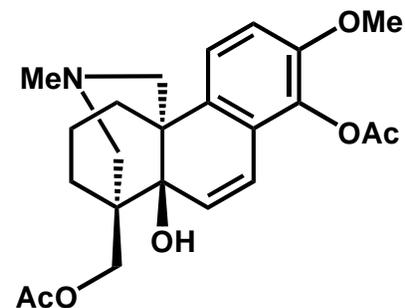


Hetisine  
Core



Shibanuma, Y.; Okamoto, T.

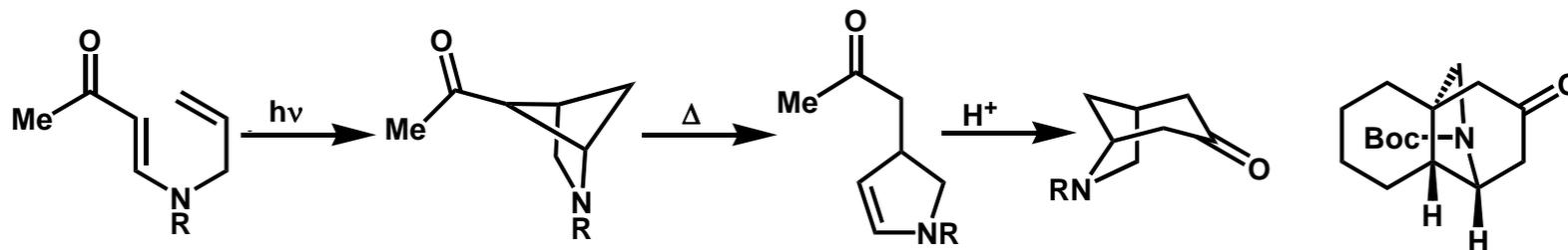
*Chem. Pharm. Bull.* 1985, 33, 3187-3194



Williams, C. M.; Mander, L. N. et al.

*Tetrahedron* 2005, 61, 3759-3769

*Org. Lett.* 2003, 5, 3499-3502



Winkler, J. D.; Kwak, Y.

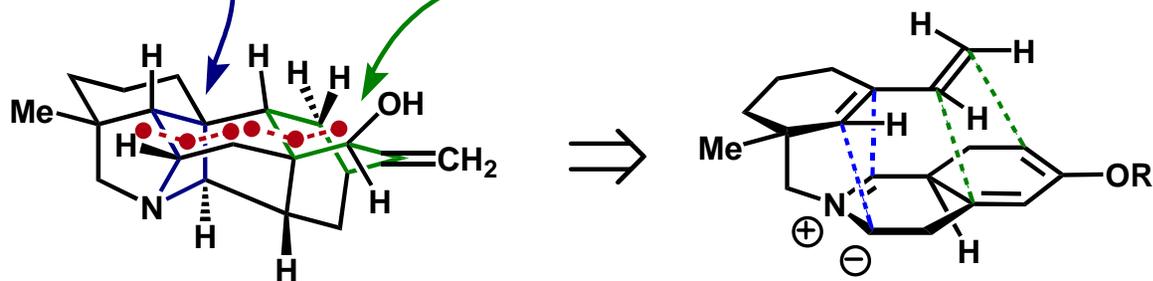
*J. Am. Chem. Soc.* 2001, 123, 7429-7430



# Synthetic Strategy

Early stage  
[3+2] Dipolar cycloaddition

Late stage  
[4+2] Diels-Alder cycloaddition

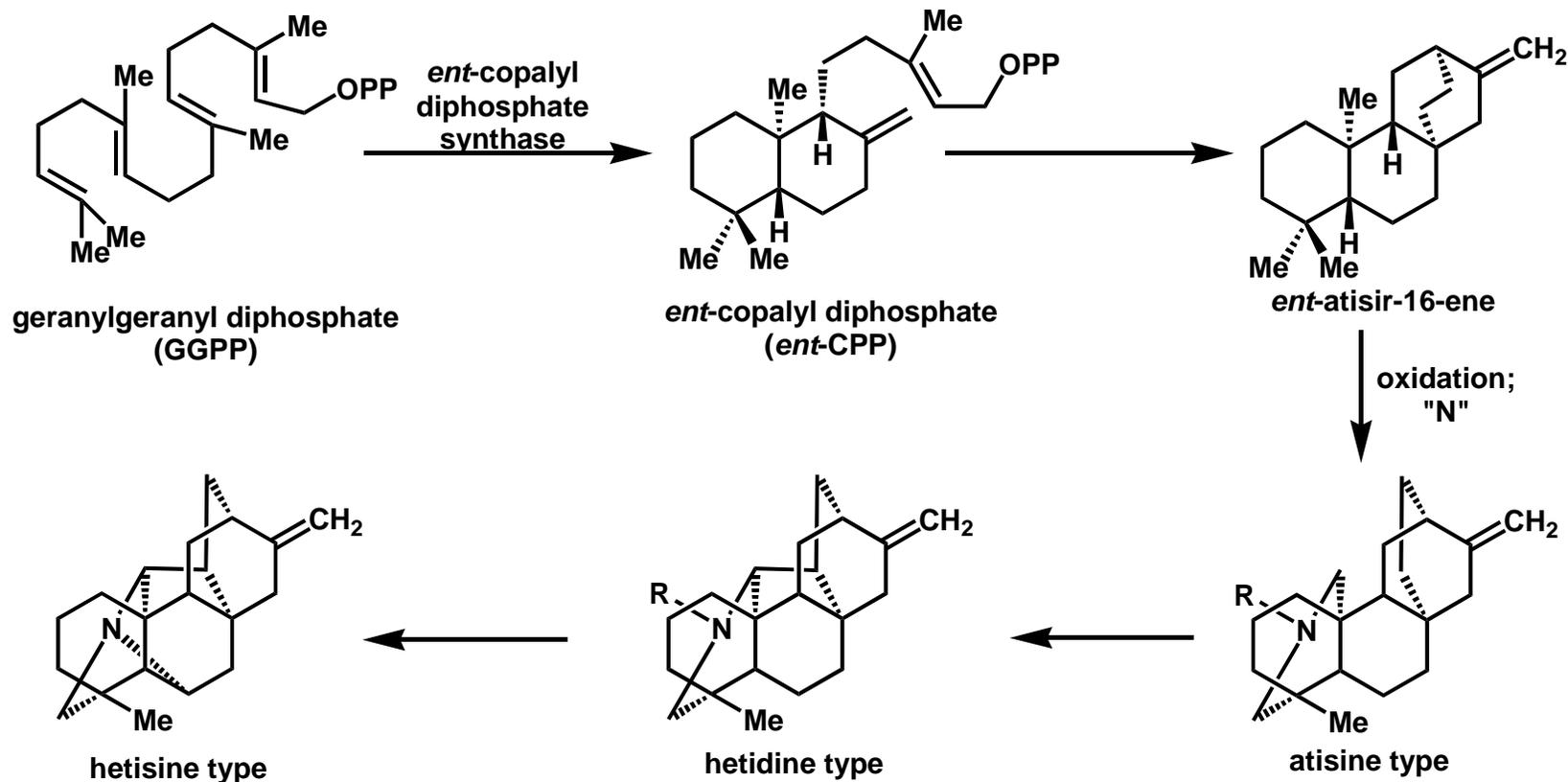


**Dual Cycloaddition Strategy:**

- 1) Early stage dipolar cycloaddition
- 2) Late stage Diels-Alder cycloaddition



# Synthetic Strategy: Biosynthetic Considerations

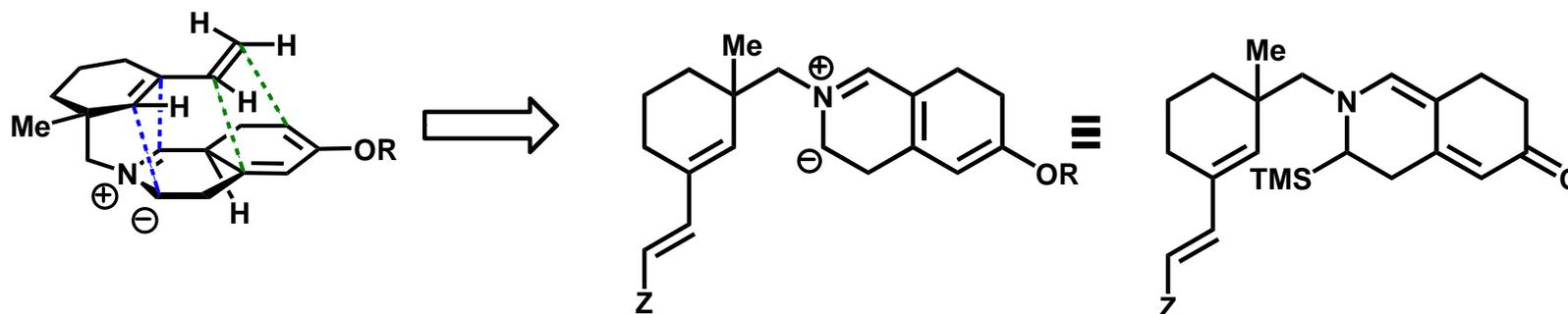


## Biosynthesis:

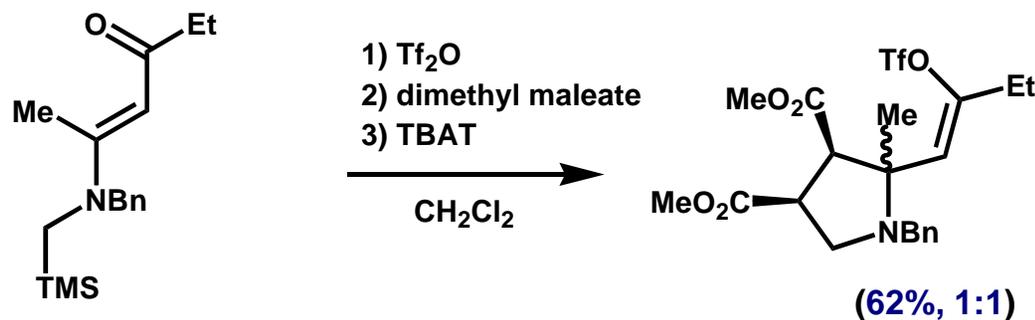
- 1) Complexity built slowly over an extended sequence
- 2) No single "key" step



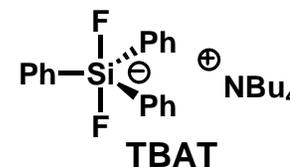
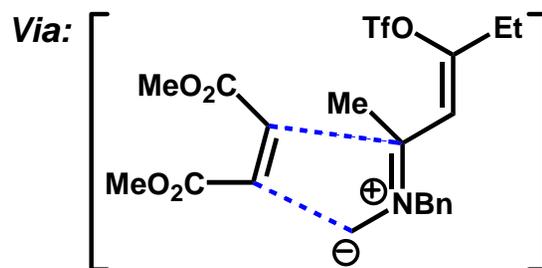
# Dipolar Cycloaddition: Vinylogous Azomethine Ylide Approach



## Vinylogous azomethine cycloadditions:

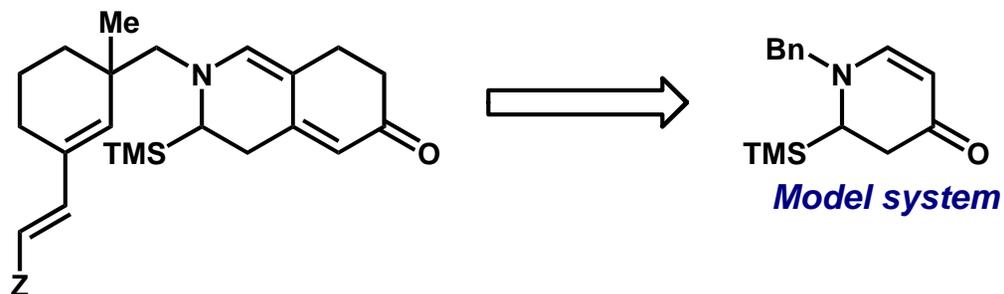


Epperson, M. T.; Gin, D. Y.  
*Angew. Chem. Int. Ed.* 2002, 41,  
1778-1780

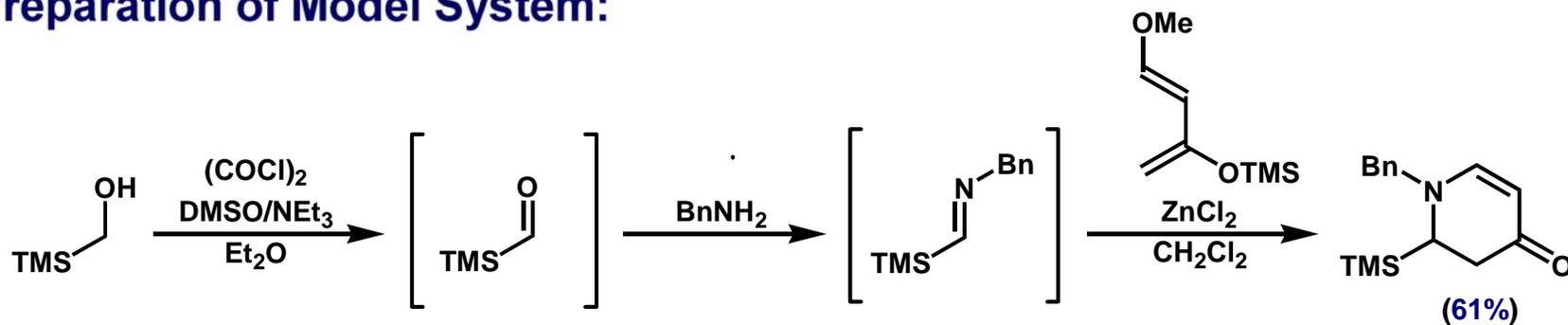




# Dipolar Cycloaddition: Azomethine Ylide Model System



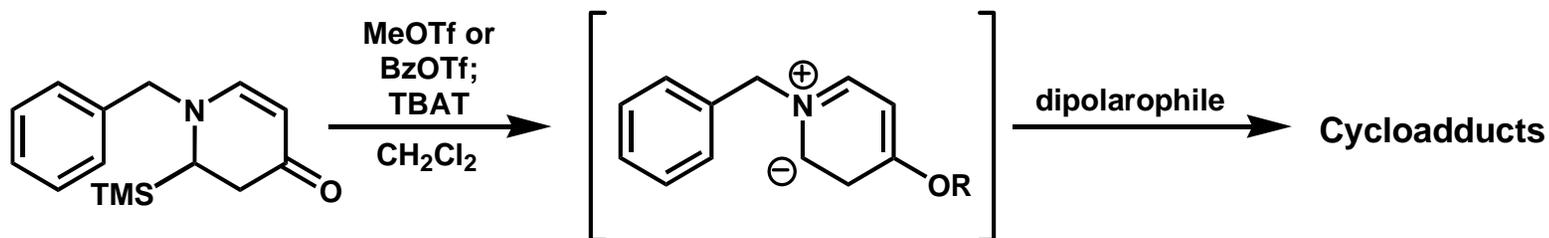
## Preparation of Model System:



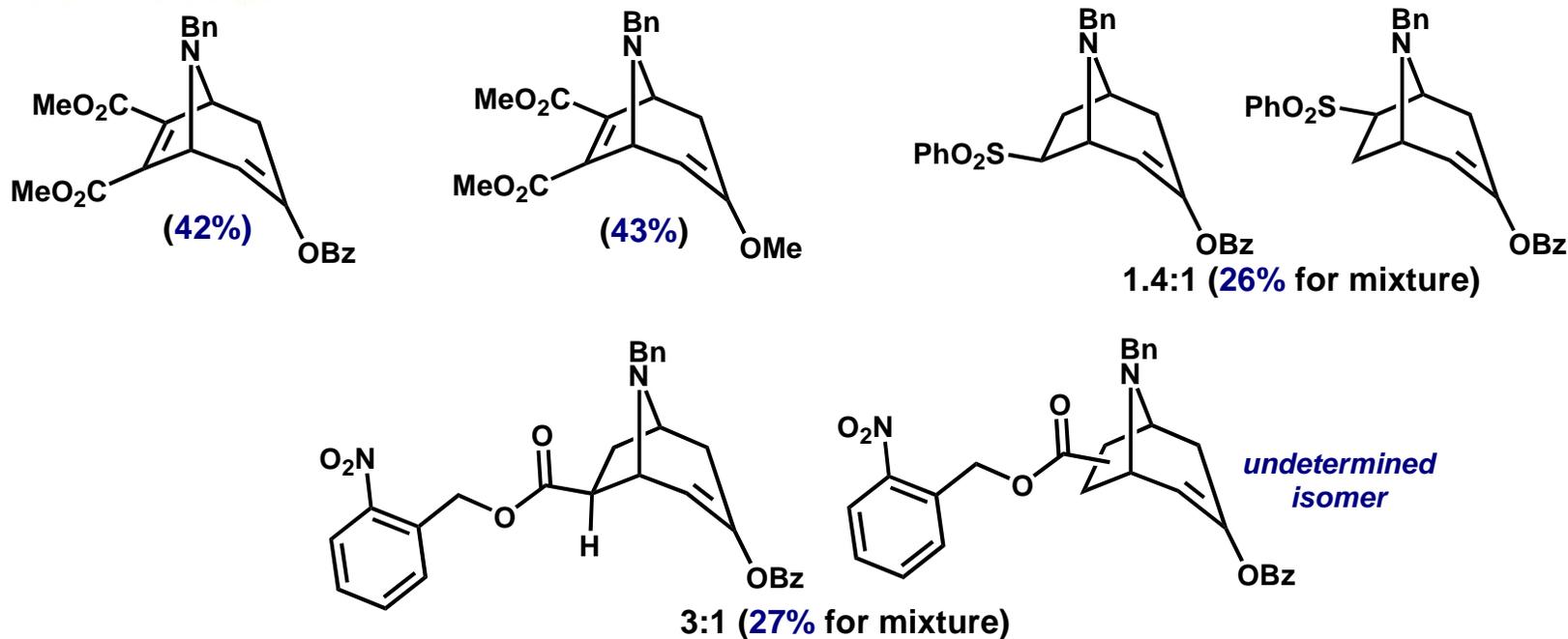
Linderman, R. J.; Suhr, Y.  
*J. Org. Chem.* 1988,  
53, 1569-1572



# Dipolar Cycloaddition: Azomethine Ylide Model System Scope

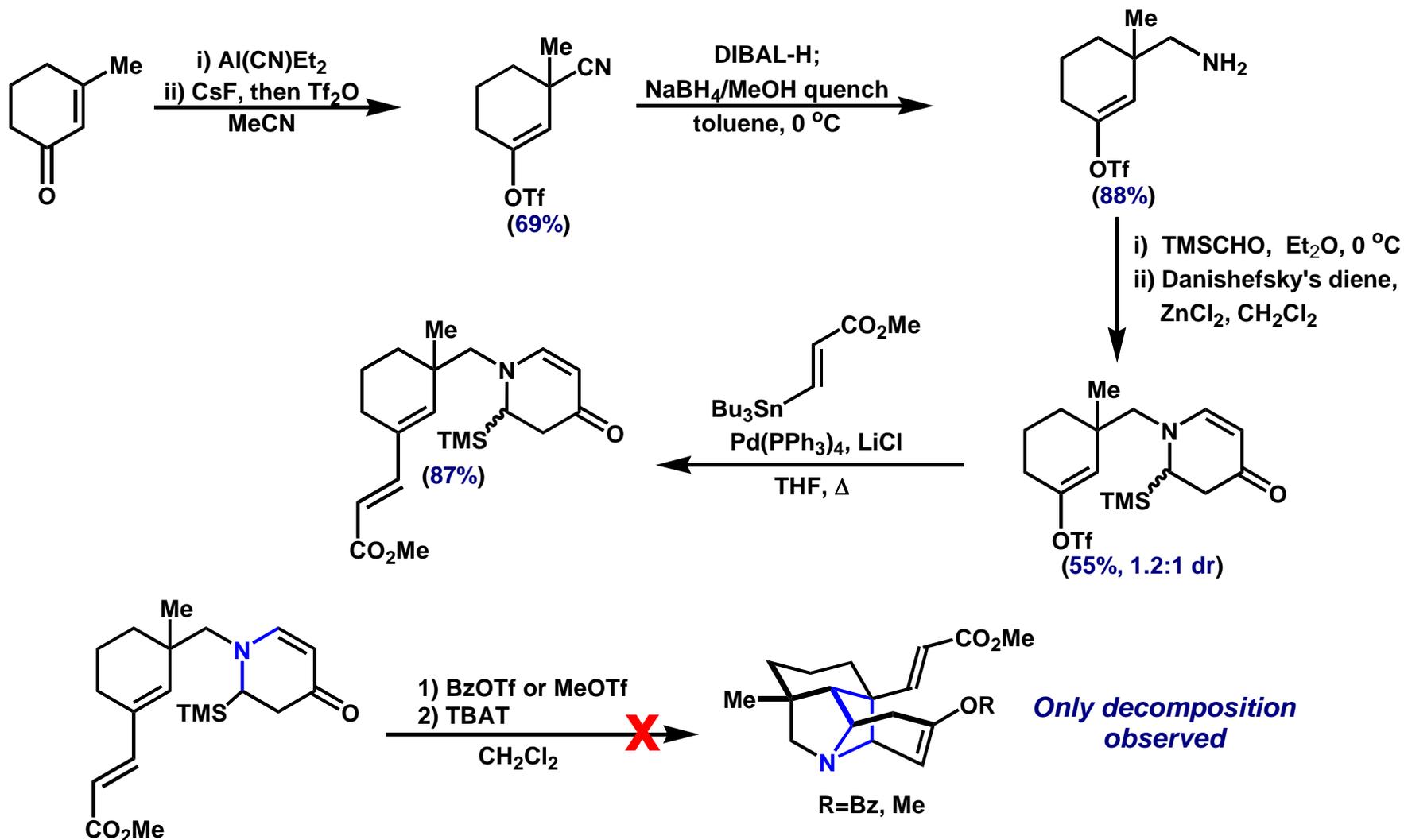


## Substrate Scope:



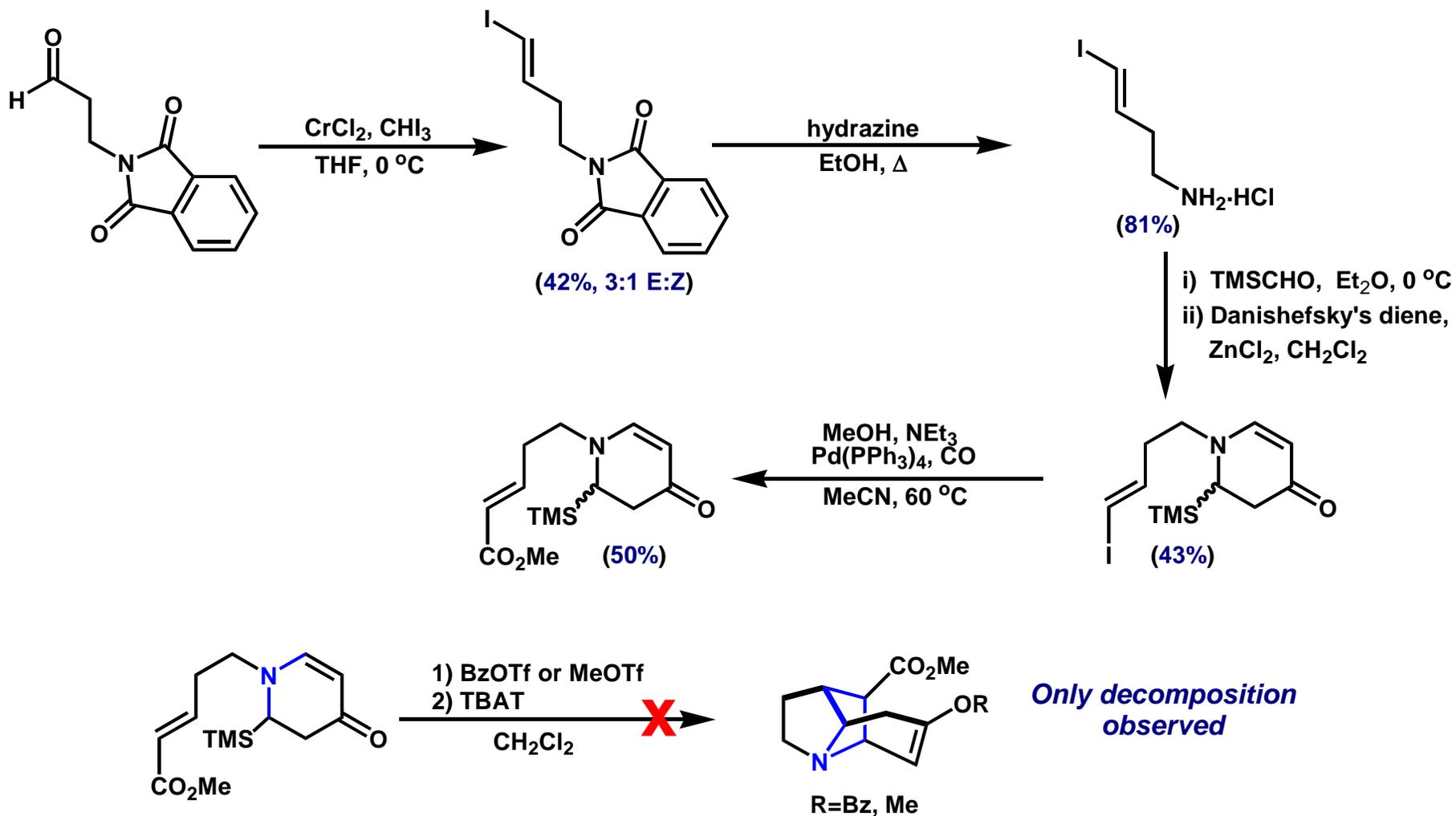


# Dipolar Cycloaddition: Application of Azomethine Ylide Model



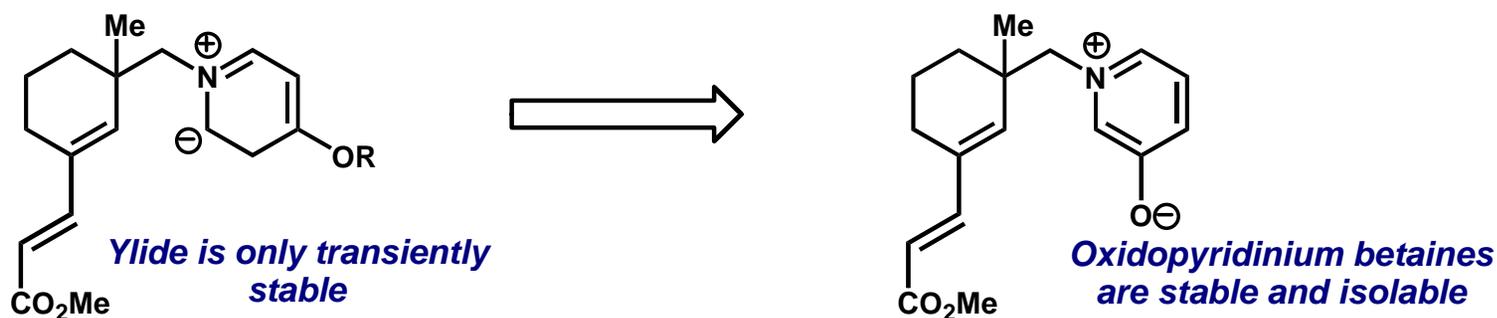


# Dipolar Cycloaddition: Application of Azomethine Ylide Model

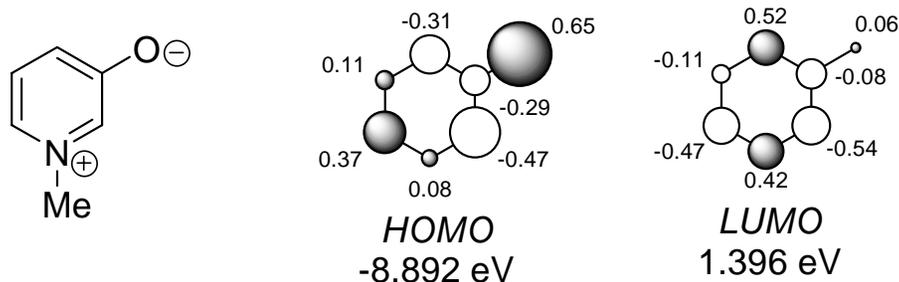




# Dipolar Cycloaddition: Evolution of Dipole



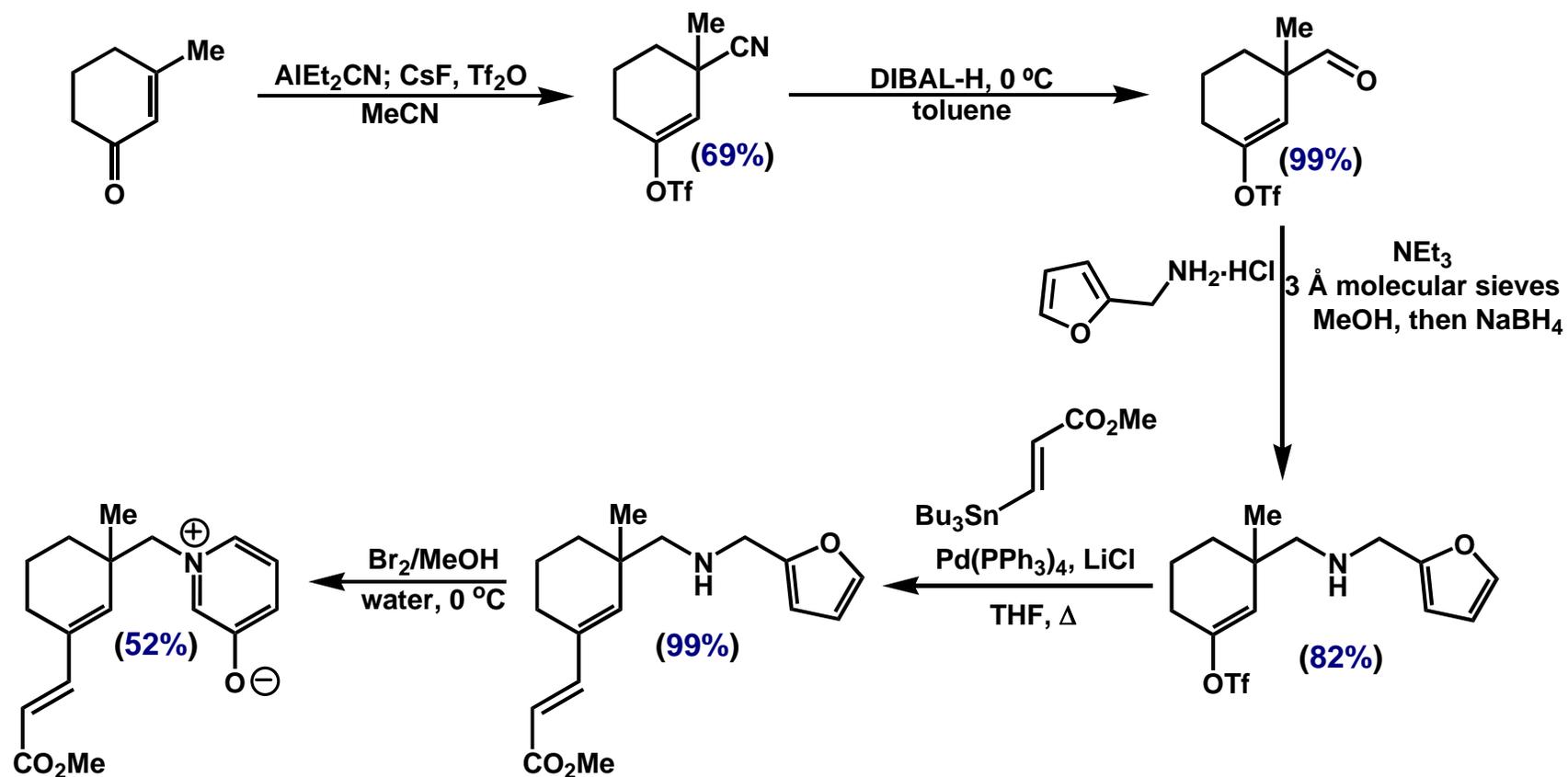
- Decomposition competitive with cycloaddition
- Decomposition makes investigation difficult
- Oxidopyridinium betaine dipoles are stable and isolable
- Stable dipole should allow more forcing conditions



Dennis, N.; Katritzky, A. R.; Takeuchi Y. *J. Am. Chem. Soc.* **1970**, *92*, 4134-4136.  
Katritzky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827-861.

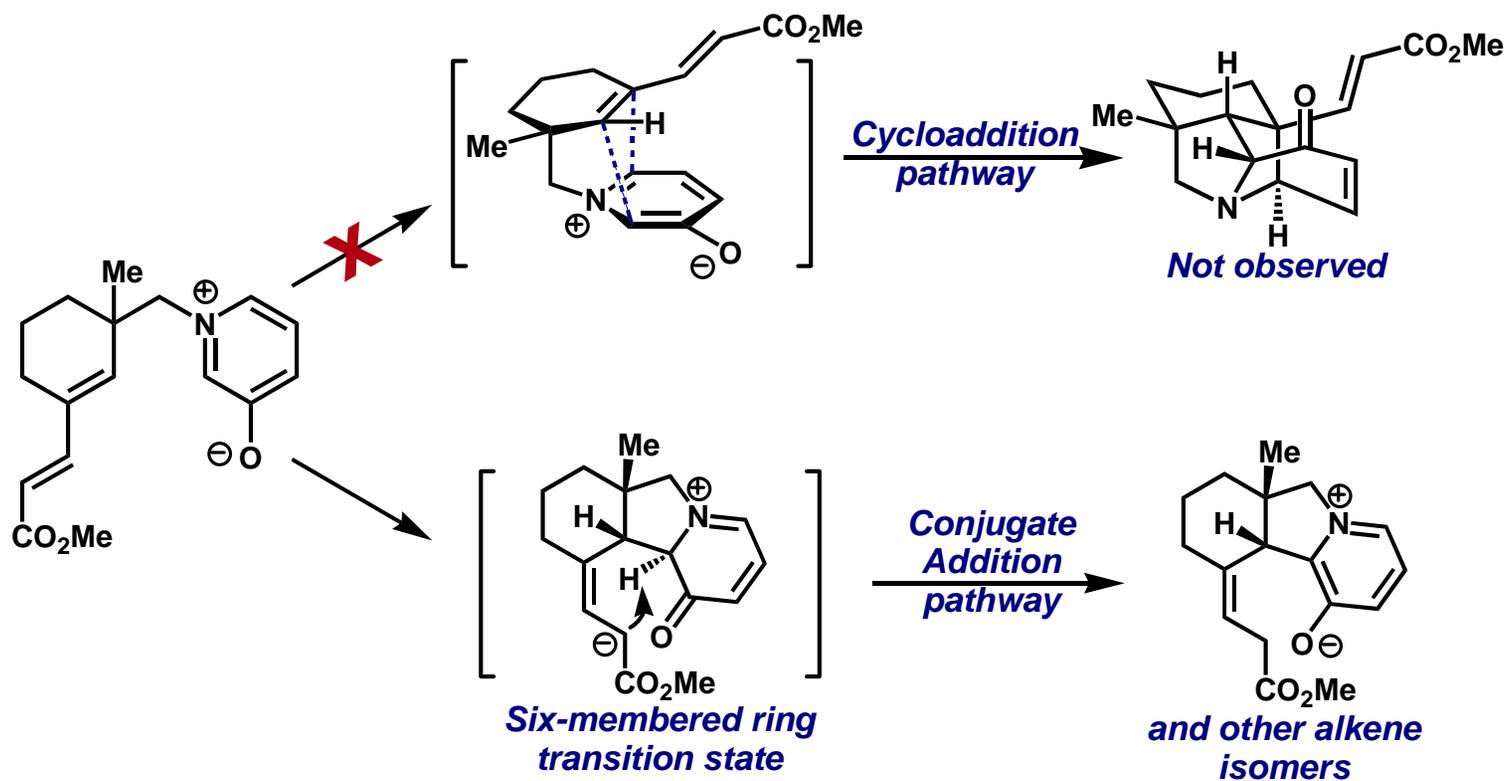


# Dipolar Cycloaddition: Diene Dipolarophile Preparation



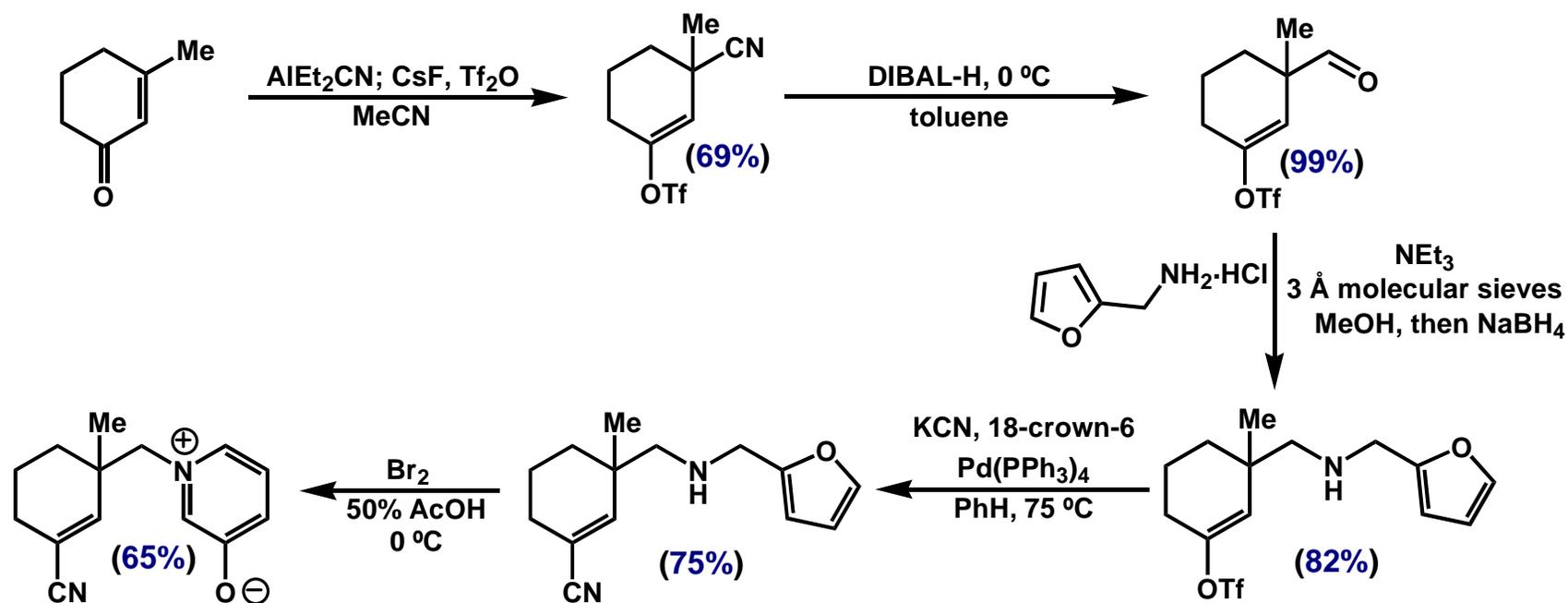


# Dipolar Cycloaddition: Diene Dipolarophile Cycloaddition



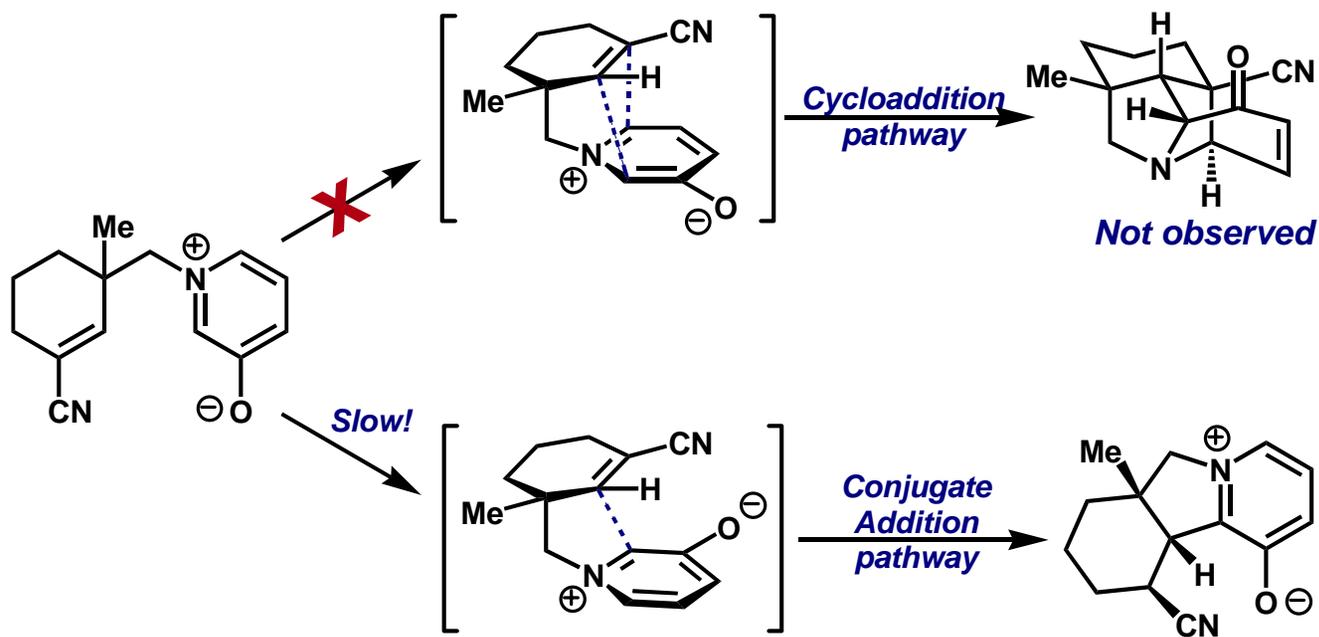


# Dipolar Cycloaddition: Ene-Nitrile Dipolarophile Preparation



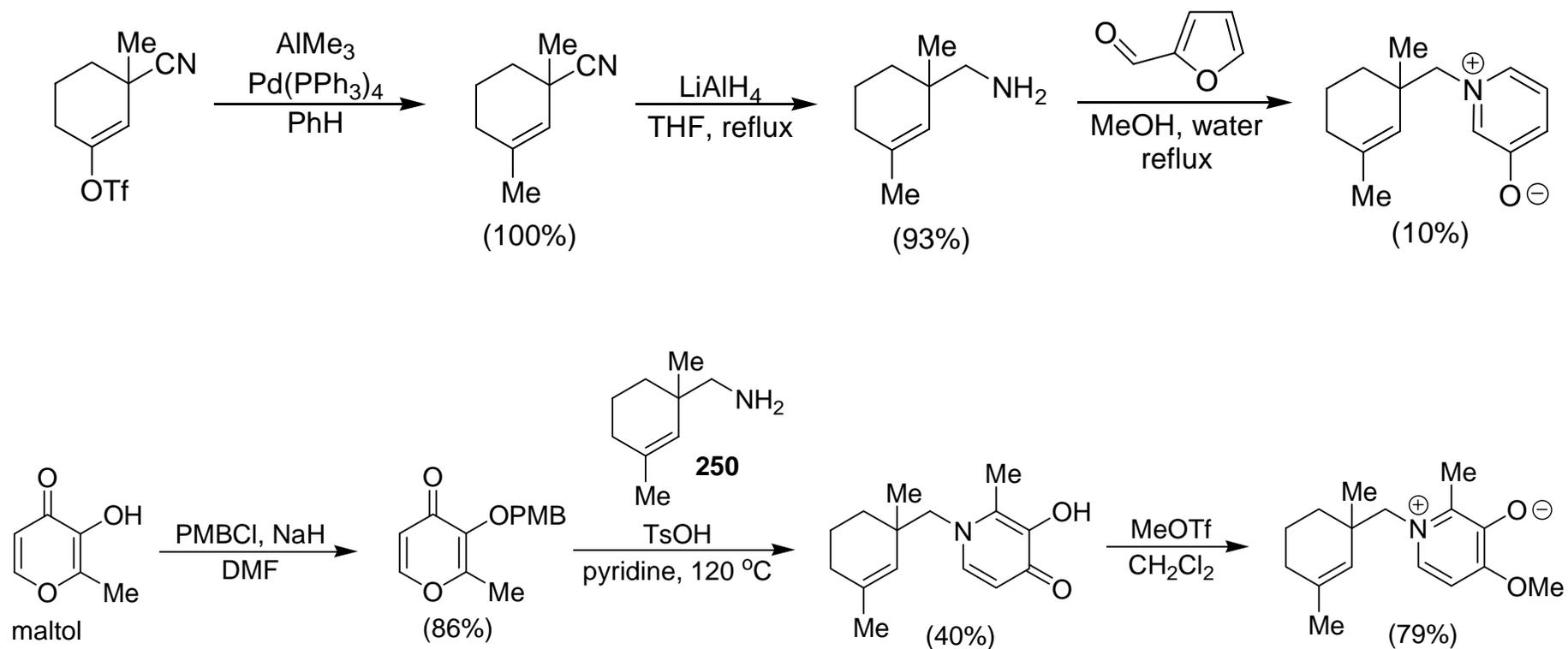


# Dipolar Cycloaddition: Ene-Nitrile Dipolarophile Cycloaddition



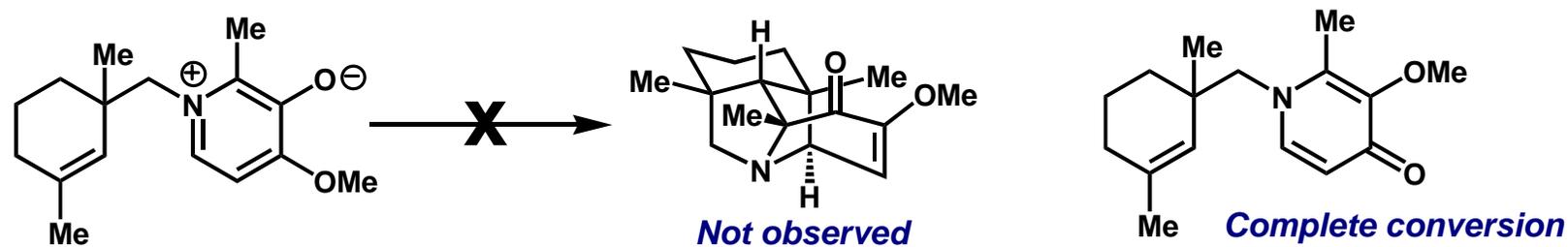
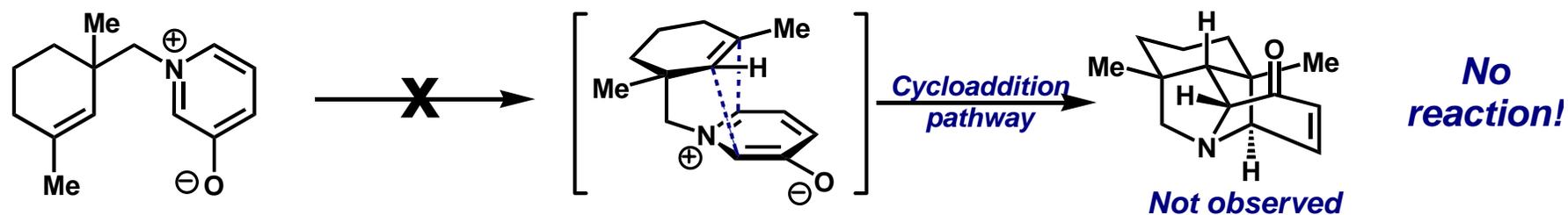


# Dipolar Cycloaddition: Unactivated Dipolarophiles



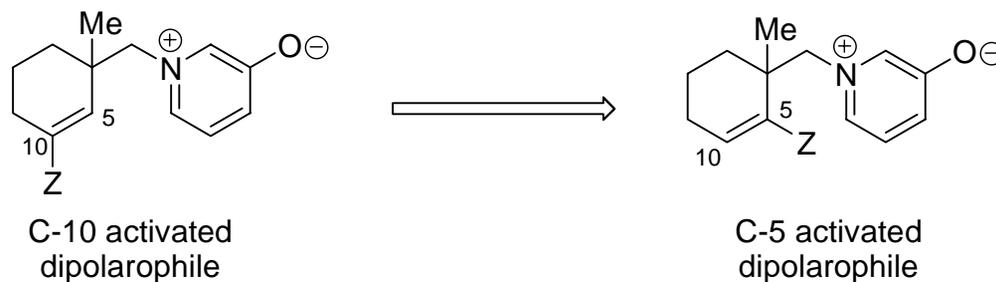


# Dipolar Cycloaddition: Unactivated Dipolarophiles

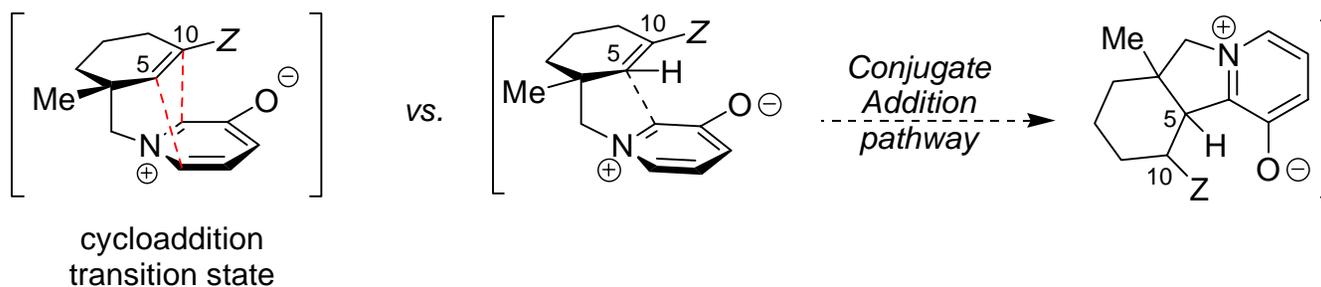




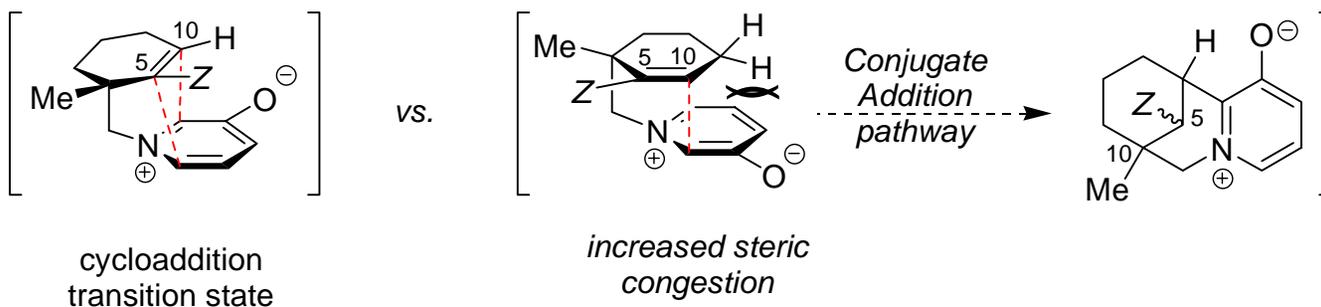
# Dipolar Cycloaddition: Reversed Dipolarophile



C-10 activated dipolarophile:

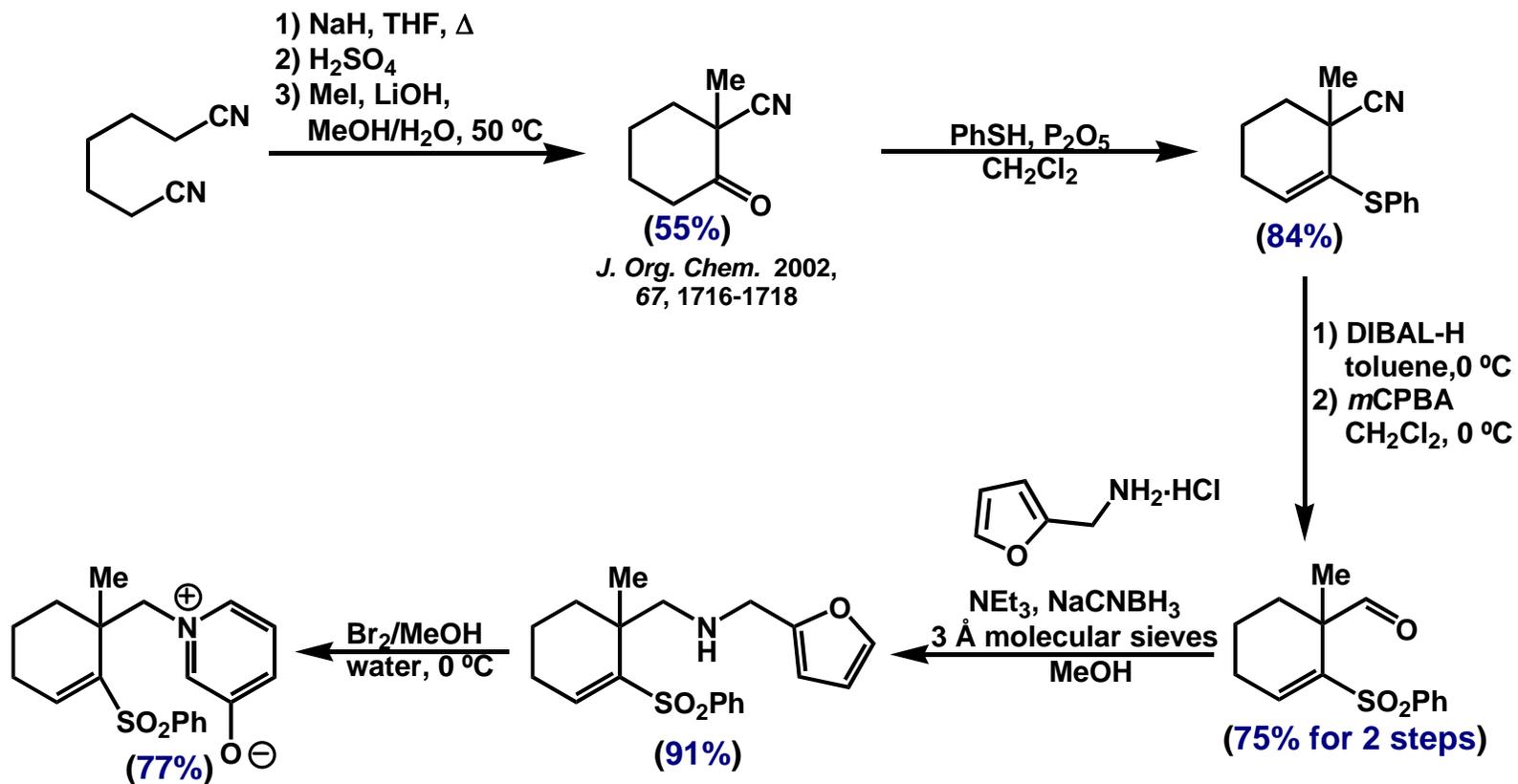


C-5 activated dipolarophile:



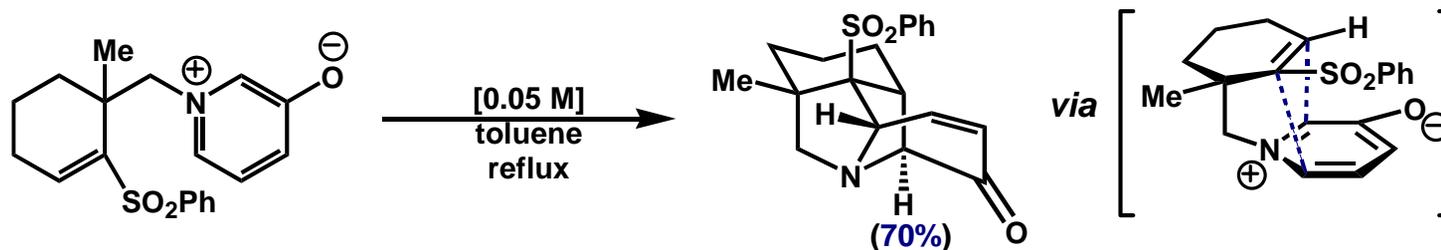


# Dipolar Cycloaddition: Ene-Sulfone Dipolarophile Cycloaddition

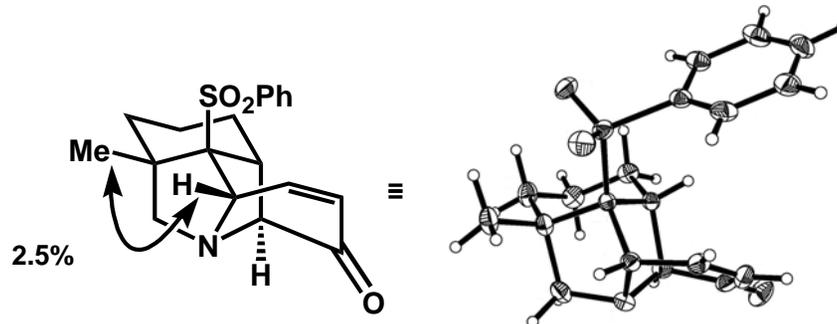




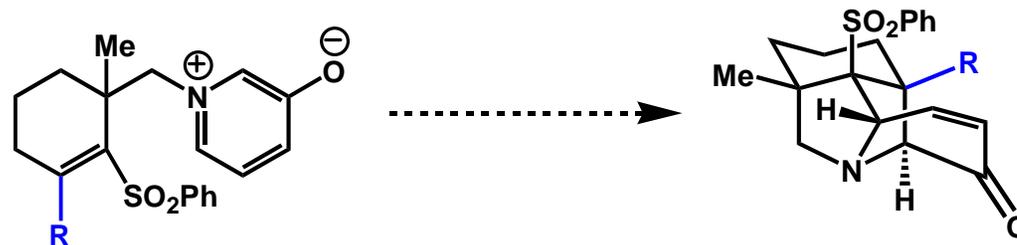
# Dipolar Cycloaddition: Ene-Sulfone Dipolarophile Cycloaddition



$^1\text{H}$ ,  $^{13}\text{C}$ , HMQC, COSY  
IR, HRMS

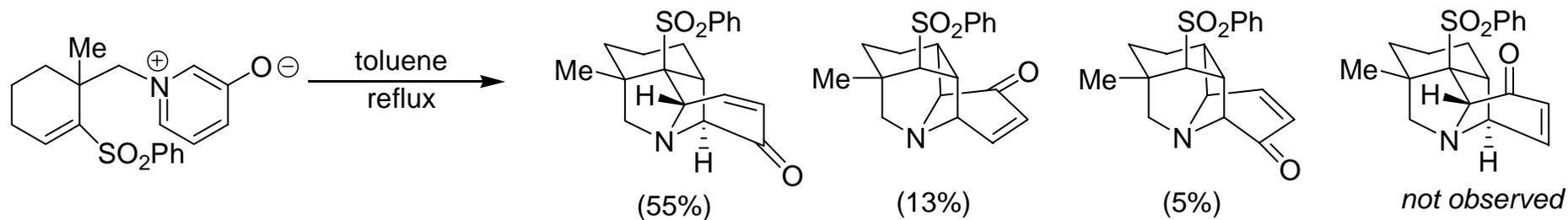


## Tetra-substituted alkene dipolarophiles:



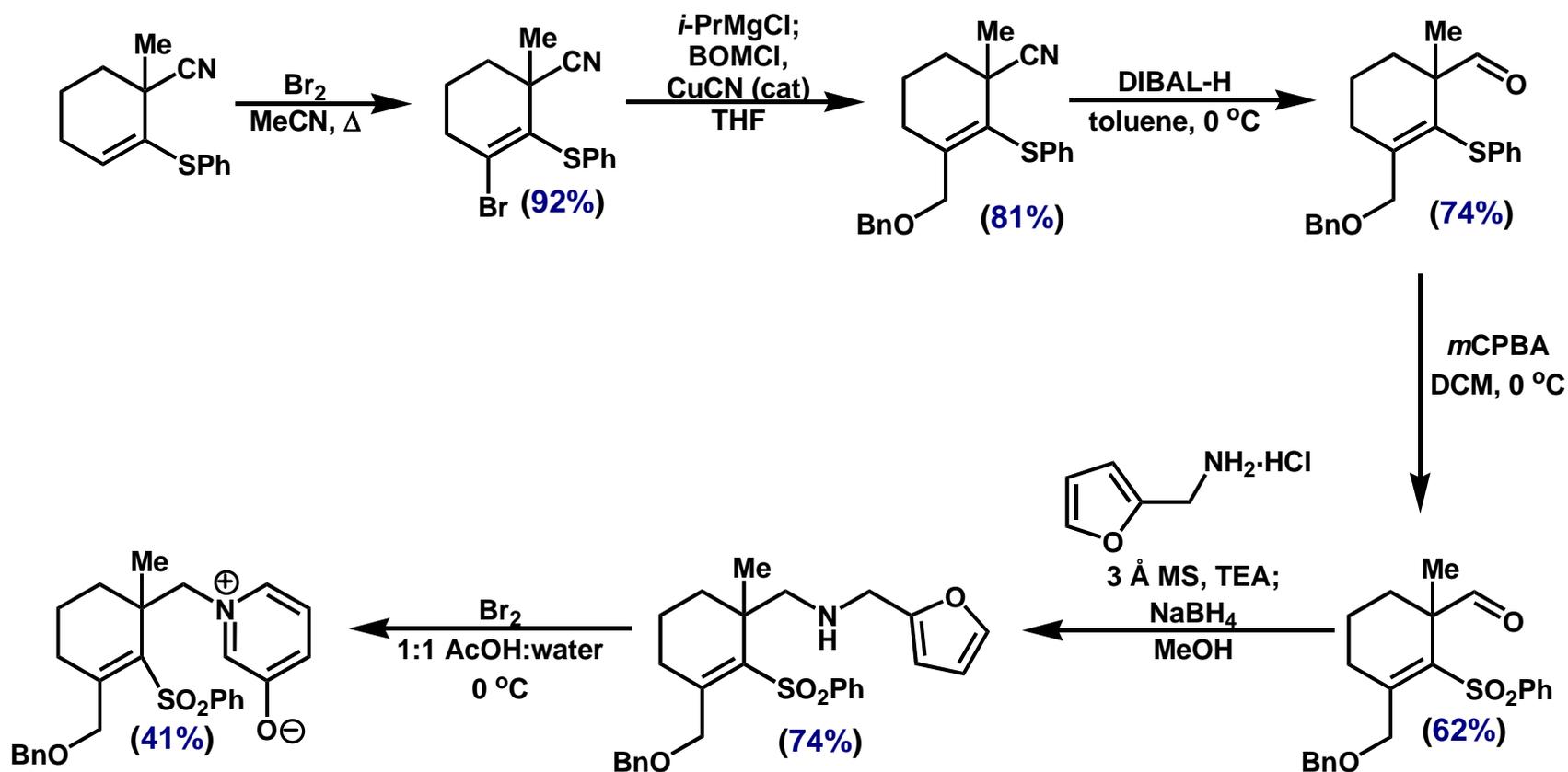


# Dipolar Cycloaddition: Ene-Sulfone Dipolarophile Cycloaddition



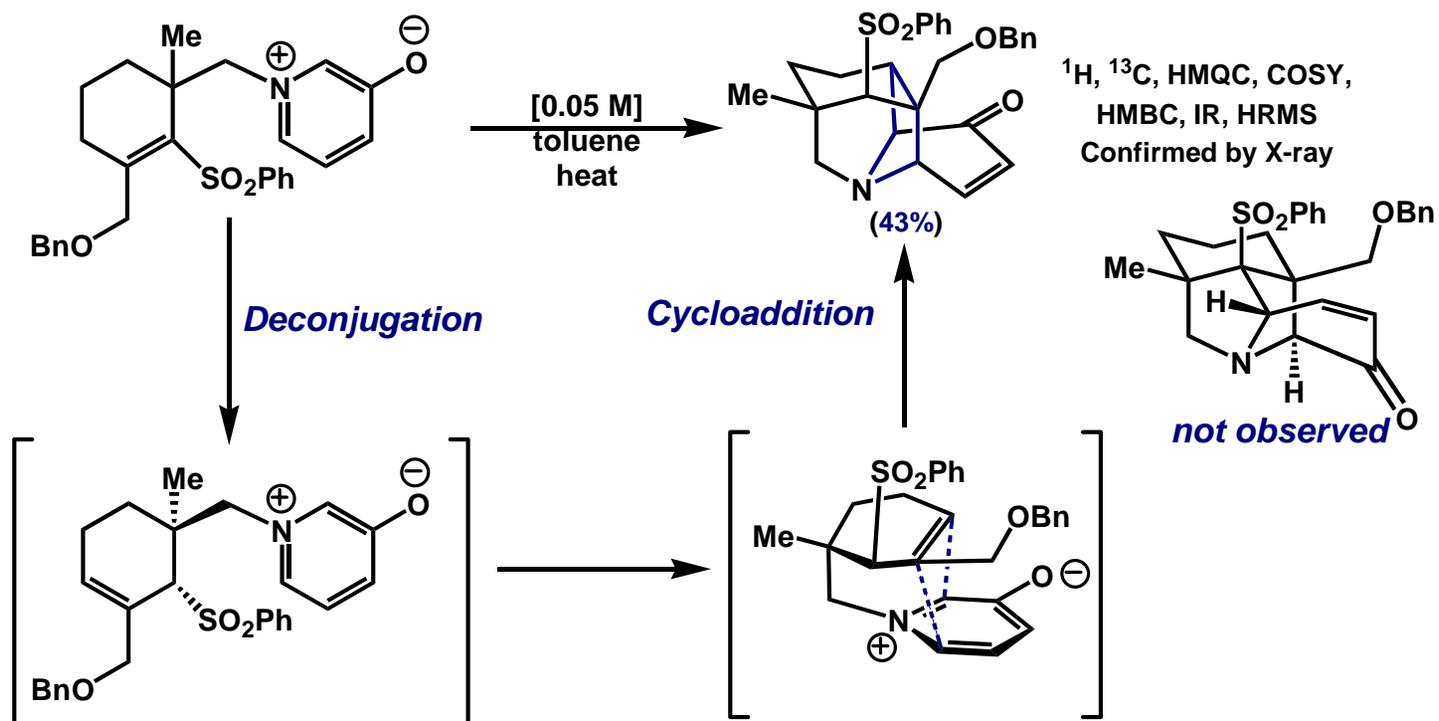


# Dipolar Cycloaddition: Ene-Sulfone Dipolarophile Preparation



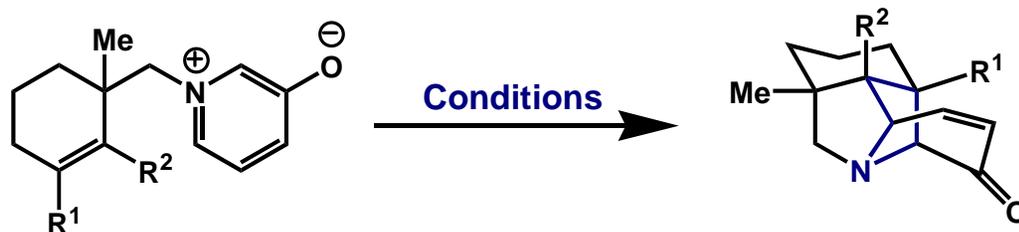


# Dipolar Cycloaddition: Ene-Sulfone Dipolarophile Cycloaddition





# Dipolar Cycloaddition: Survey of Dipolarophiles

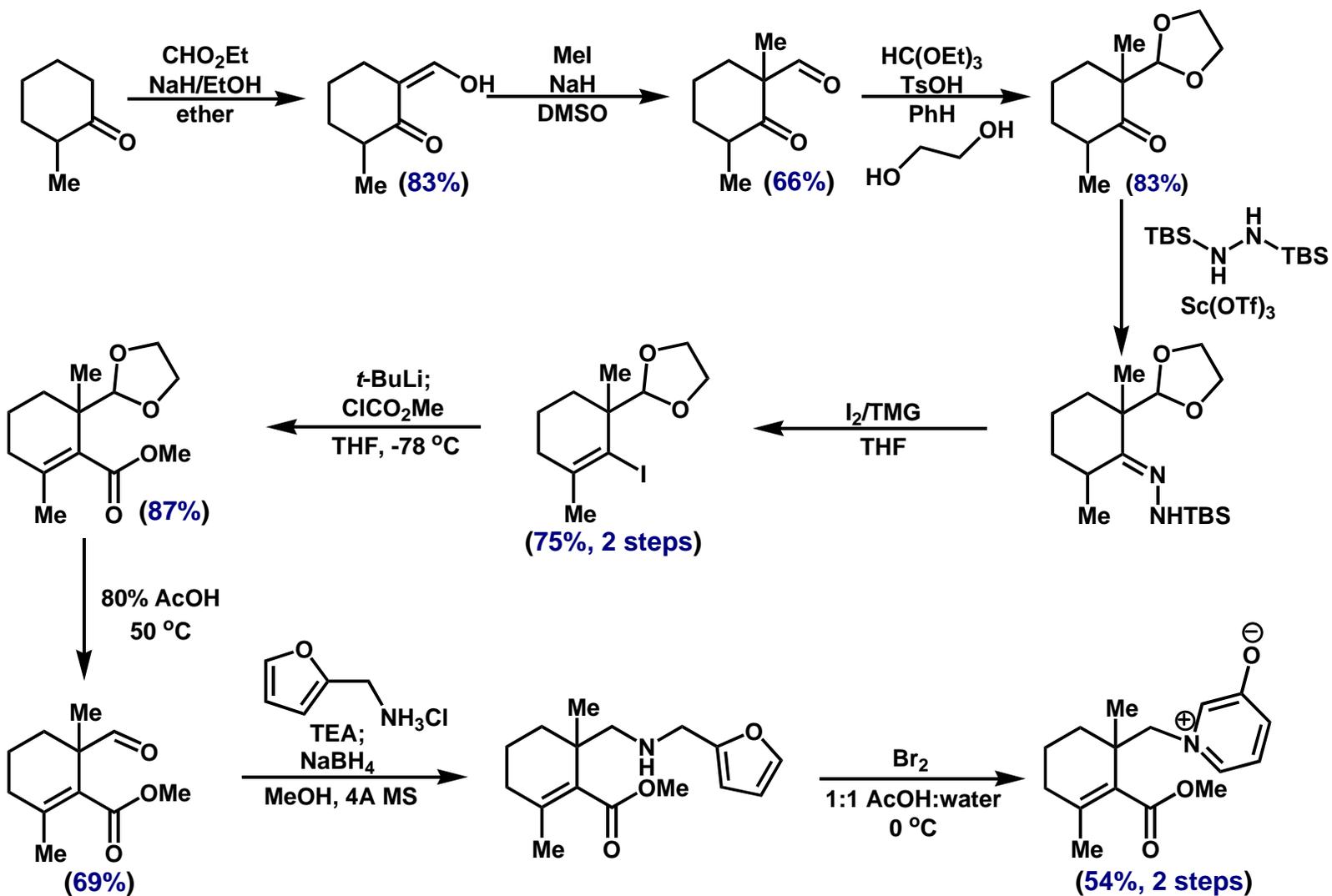


R <sup>1</sup>	R <sup>2</sup>	Conditions	Observed Result
Me	SO <sub>2</sub> Ph	toluene, 120 °C	deconjugation/cycloaddition
Br	SO <sub>2</sub> Ph	toluene, 120 °C	decomposition
CH=CH <sub>2</sub>	SO <sub>2</sub> Ph	toluene, 150 °C	decomposition
Me	SOPh	toluene, 180 °C	epimerization of SOPh
CN	SPh	toluene, 180 °C	slow decomposition

*Can the deconjugation pathway be disfavored?*

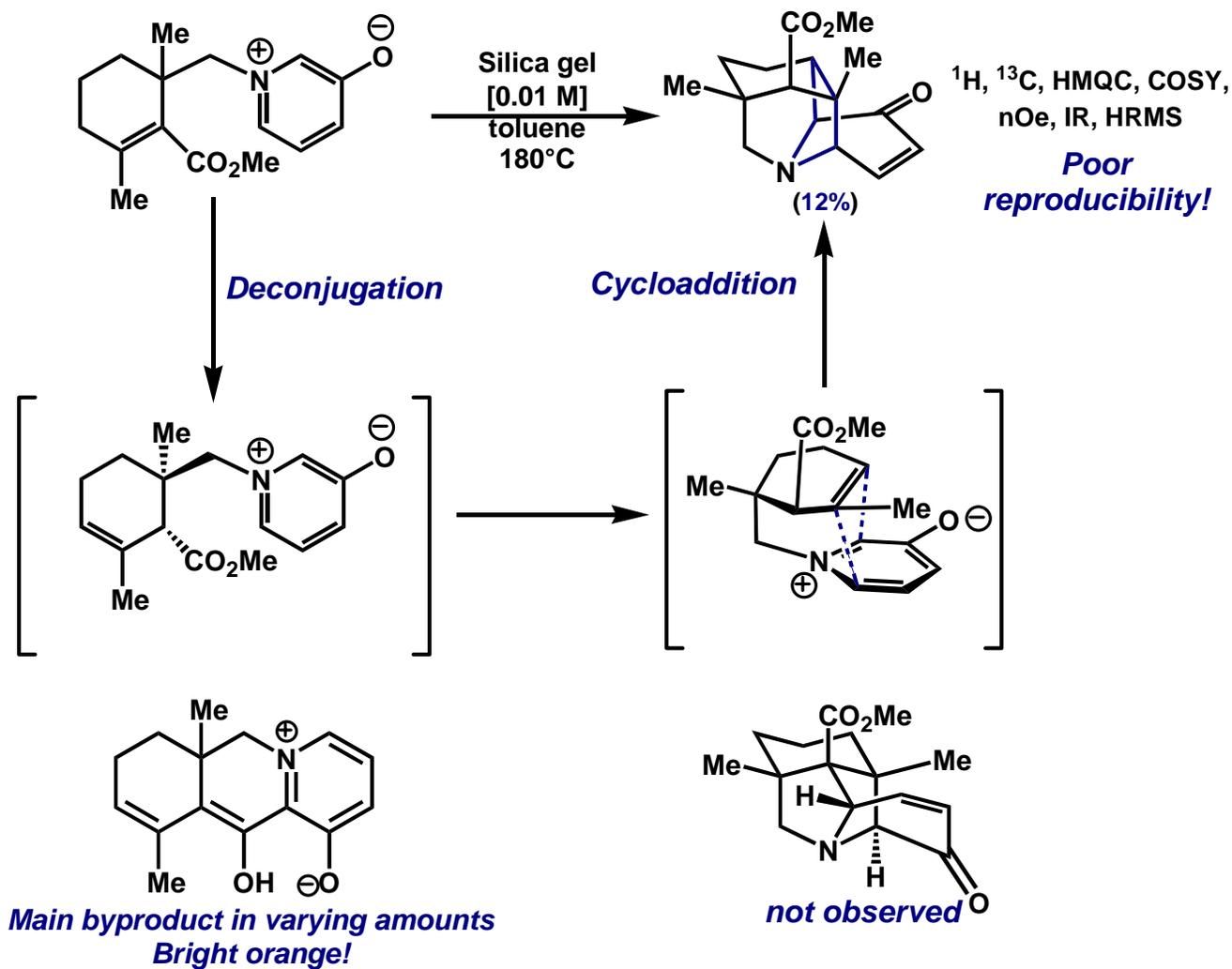


# Dipolar Cycloaddition: Enoate Dipolarophile Preparation



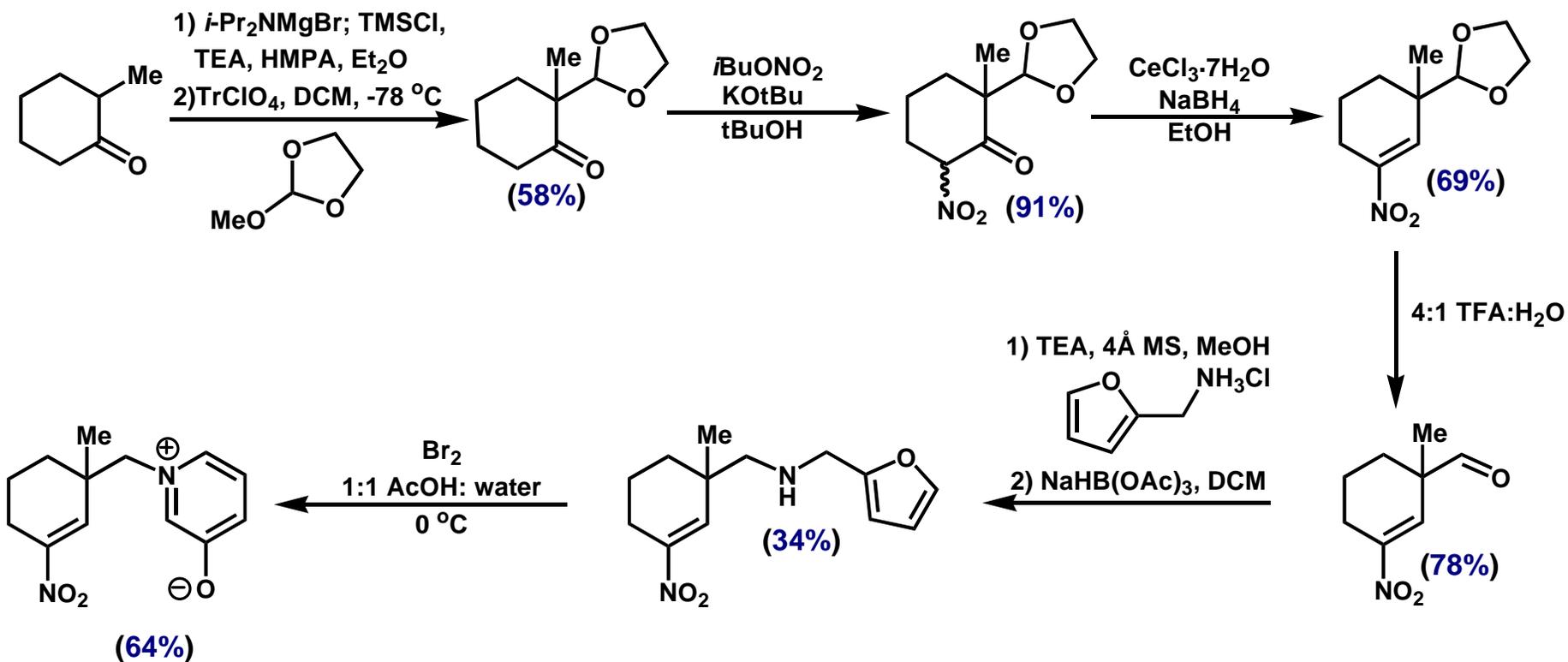


# Dipolar Cycloaddition: Enoate Dipolarophile Cycloaddition





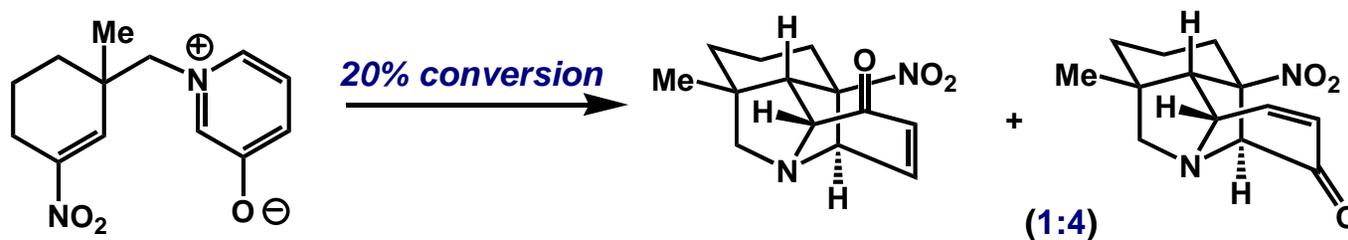
# Dipolar Cycloaddition: Nitroalkene Dipolarophile Preparation





# ***Dipolar Cycloaddition: Nitroalkene Dipolarophile Cycloaddition***

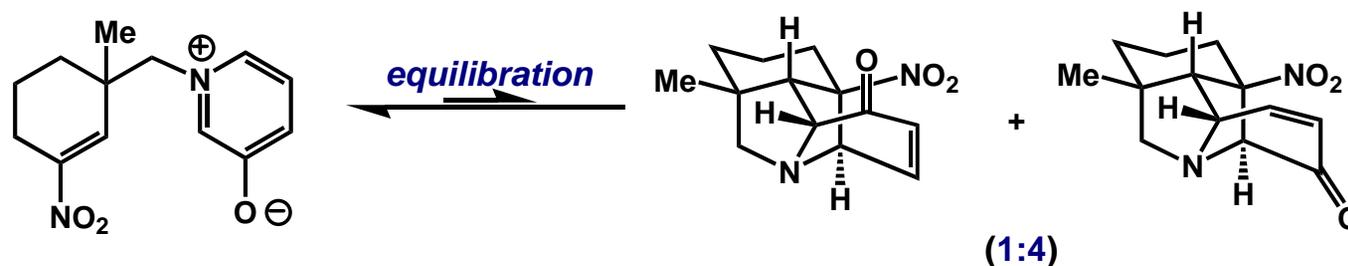
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***Reaction stalls at ~20% conversion!***



# ***Dipolar Cycloaddition: Nitroalkene Dipolarophile Cycloaddition***



***Reaction reaches thermodynamic equilibrium!***

***Are all the previous oxidopyridinium betaines in equilibrium?***



# Dipolar Cycloaddition: Summary of Oxidopyridinium Betaines

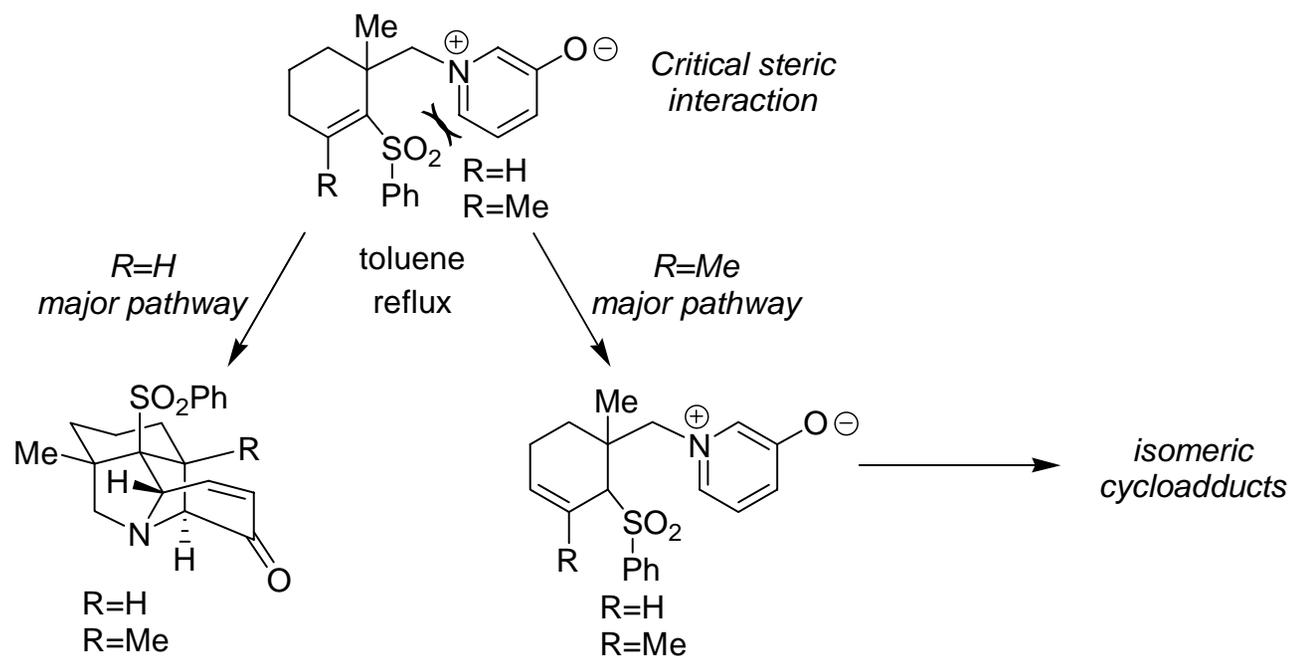
Substrate	Conditions	Observed Result	Product(s) Structure
	toluene, 160 °C	Conjugate addition	 <i>mixture of alkene isomers</i>
	toluene, 170 °C	Conjugate addition	
	toluene, 190 °C	No Reaction	
	toluene, 120 °C	Methyl group migration	
	toluene, 110 °C	Dipolar Cycloaddition	
	toluene, 120 °C	Sulfone deconjugation; dipolar cycloaddition	
	toluene, 120 °C	Sulfone deconjugation; dipolar cycloaddition	

Substrate	Conditions	Observed Result	Product(s) Structure
	toluene, 120 °C	Complex mixture	
	toluene, 150 °C	Complex mixture	
	toluene, 180 °C	No reaction except sulfoxide epimerization	
	toluene, 180 °C	No reaction	
	toluene, SiO <sub>2</sub> , 180 °C	Ester deconjugation; dipolar cycloaddition	
	toluene, 110 °C	Dipolar cycloaddition equilibrium	



# Dipolar Cycloaddition: Summary of Oxidopyridinium Betaines



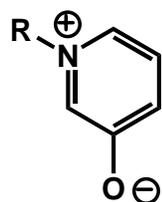


# Dipolar Cycloaddition: Shifting the Equilibrium

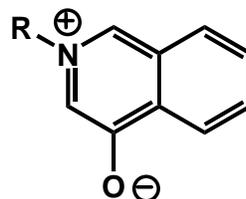
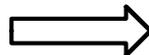
*Can the dipolar cycloaddition be made more thermodynamically favorable?*

*Lower the energetic cost of breaking aromaticity!*

Estimated energetic cost of breaking pyridinium aromaticity:



Energetic cost  
of breaking  
aromaticity  
~43.3 kcal/mol

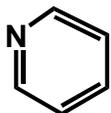


Energetic cost  
of breaking pyridine  
aromaticity  
~35.2 kcal/mol  
isoquinoline-benzene  
(81.0-45.8 kcal/mol)

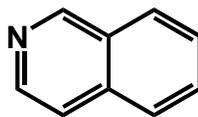
Resonance stabilization energies:



45.8 kcal/mol



43.3 kcal/mol



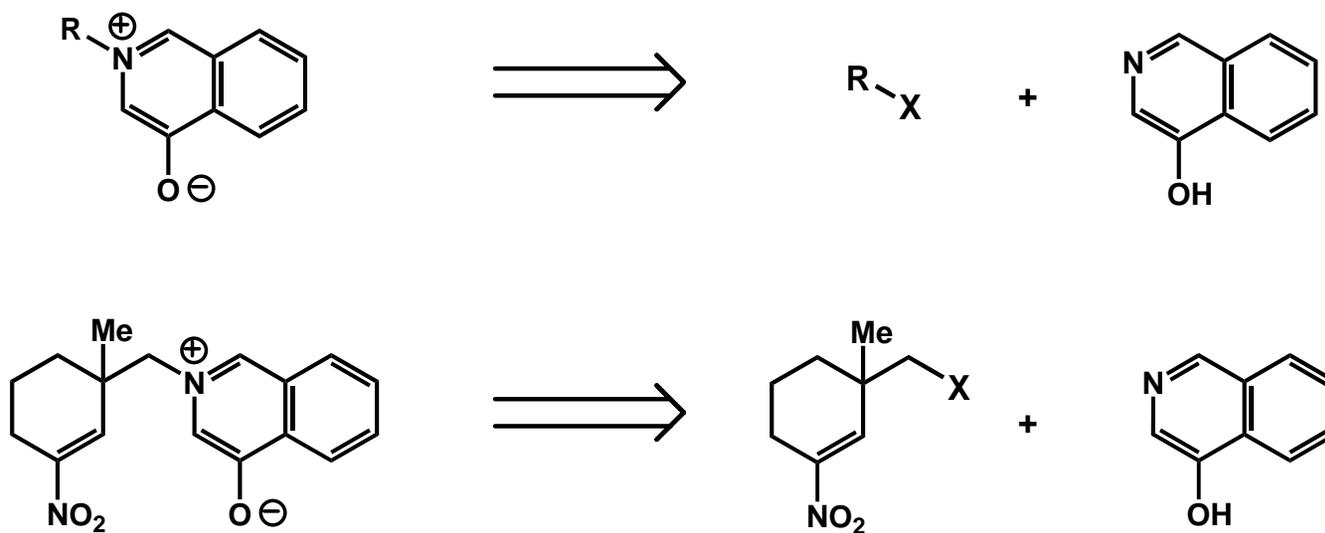
81.0 kcal/mol

Bird, C. W.  
*Tetrahedron* 1992, 48, 335-340



# *Dipolar Cycloaddition: Oxidoisoquinolinium Dipole Preparation*

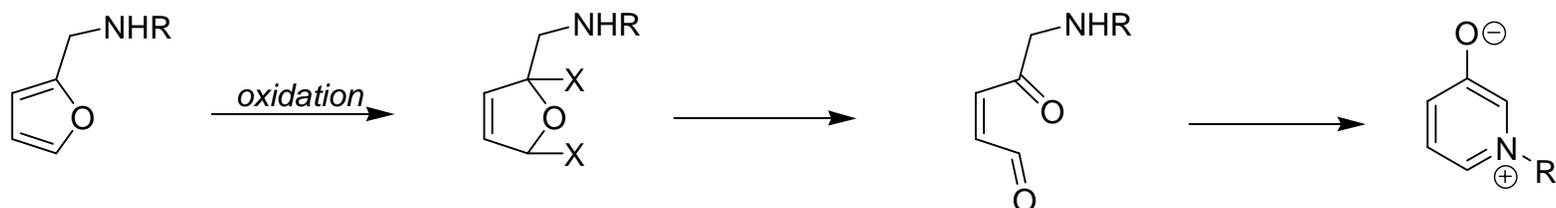
- Oxidoisoquinoliniums betaines are rare literature
- Need new method for oxidoisoquinolinium synthesis



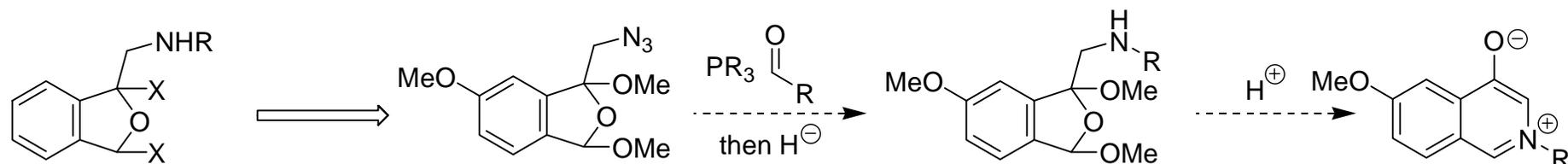
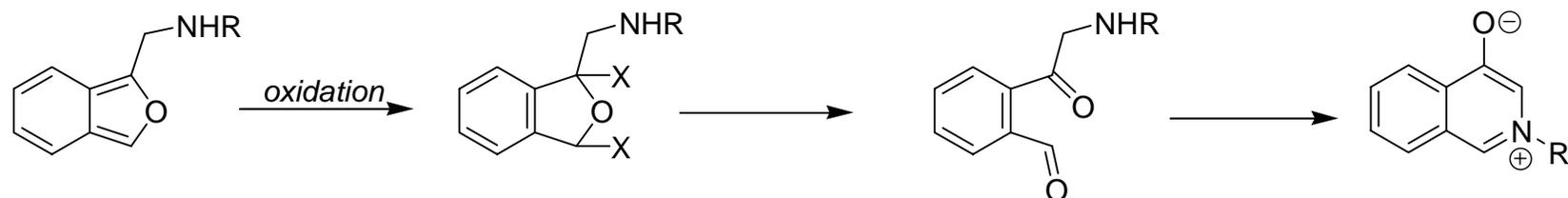


# Dipolar Cycloaddition: Oxidoisoquinolinium Aza-Achmatowicz?

Aza-Achmatowicz rearrangement for the preparation of oxidopyridinium betaines:

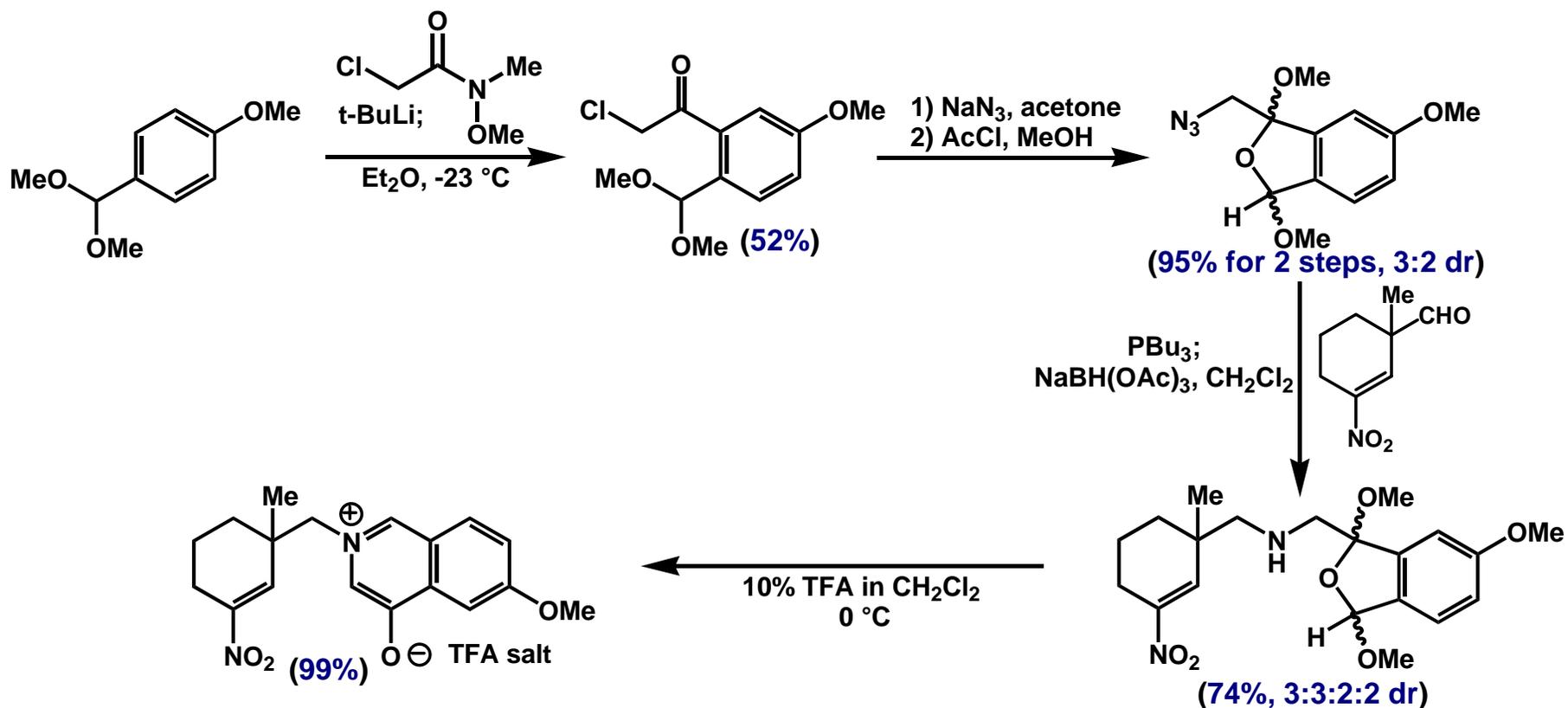


Proposed aza-Achmatowicz rearrangement for the preparation of oxidoisoquinolinium betaines:



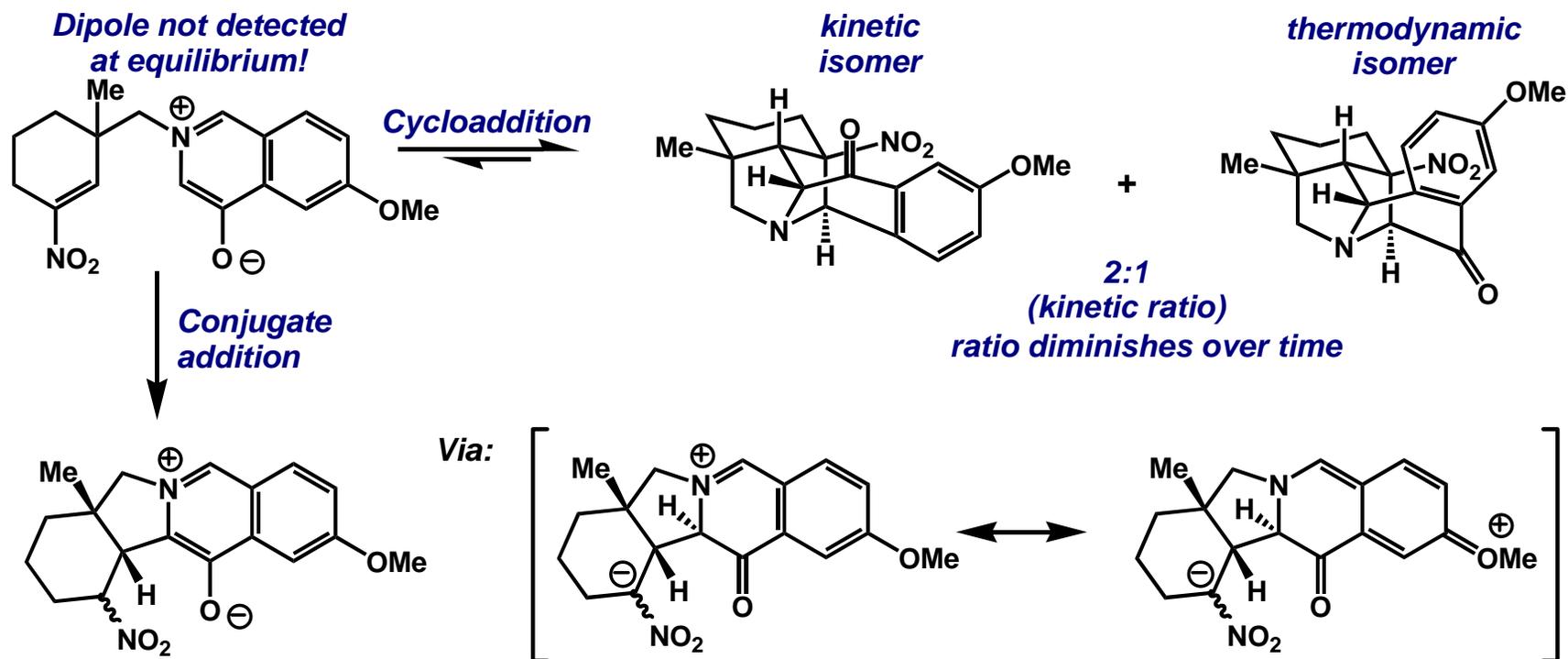


# Dipolar Cycloaddition: Oxidoisoquinolinium Dipole Preparation





# Dipolar Cycloaddition: Oxidoisoquinolinium Dipole Cycloaddition



## Success:

- Equilibrium is shifted entirely towards cycloadducts!

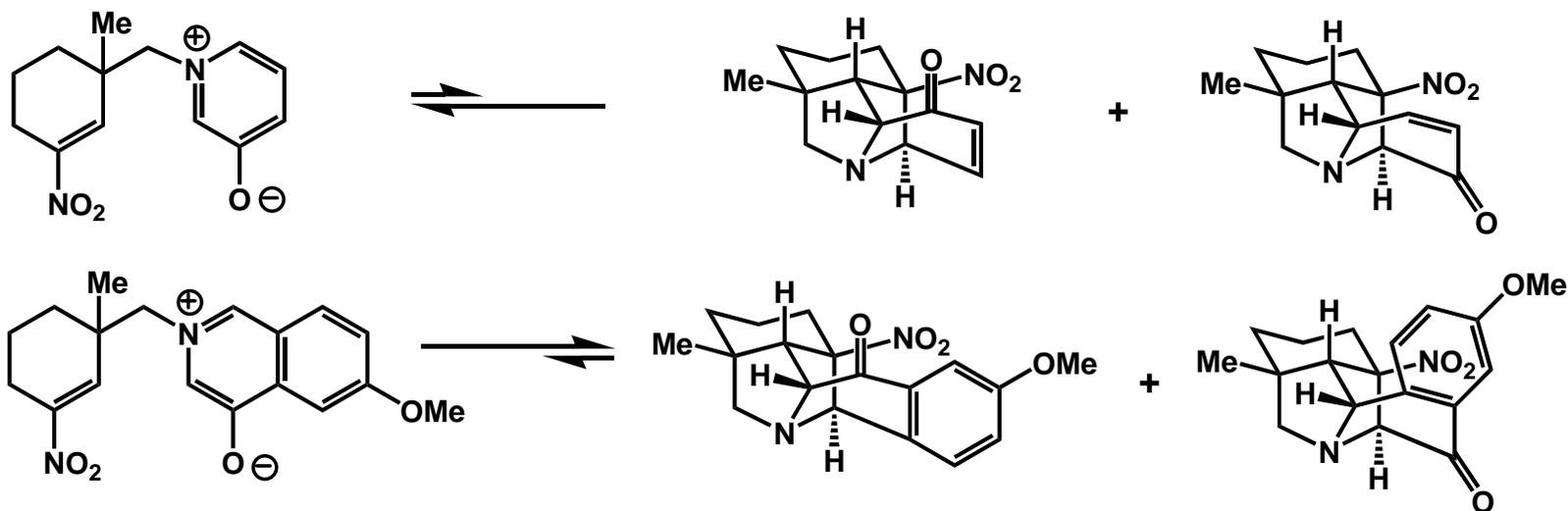
## New problems:

- Conjugate addition is main pathway and is irreversible
- Nitro group is of limited synthetic utility

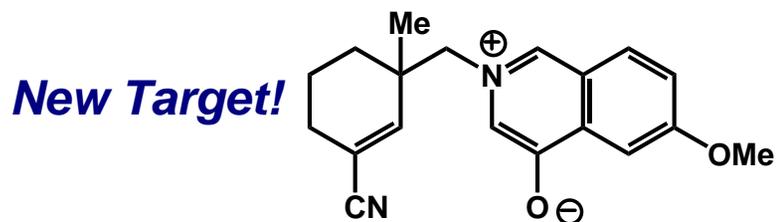


# Dipolar Cycloaddition: Analysis

- Other cycloadditions may have failed for thermodynamic reasons!
- Oxidoisoquinolinium betaines shift equilibrium towards cycloadducts

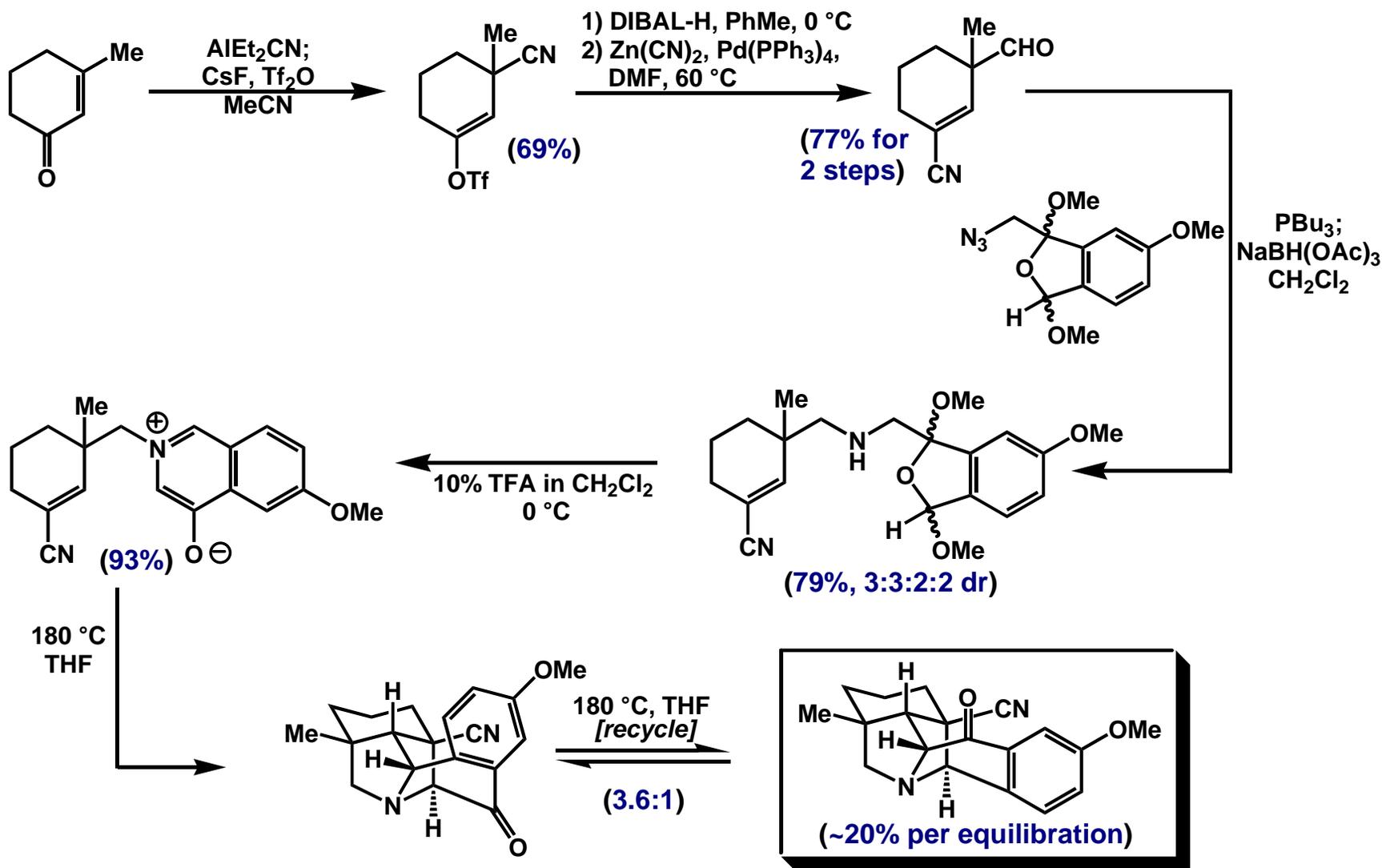


- Conjugate additions irreversible



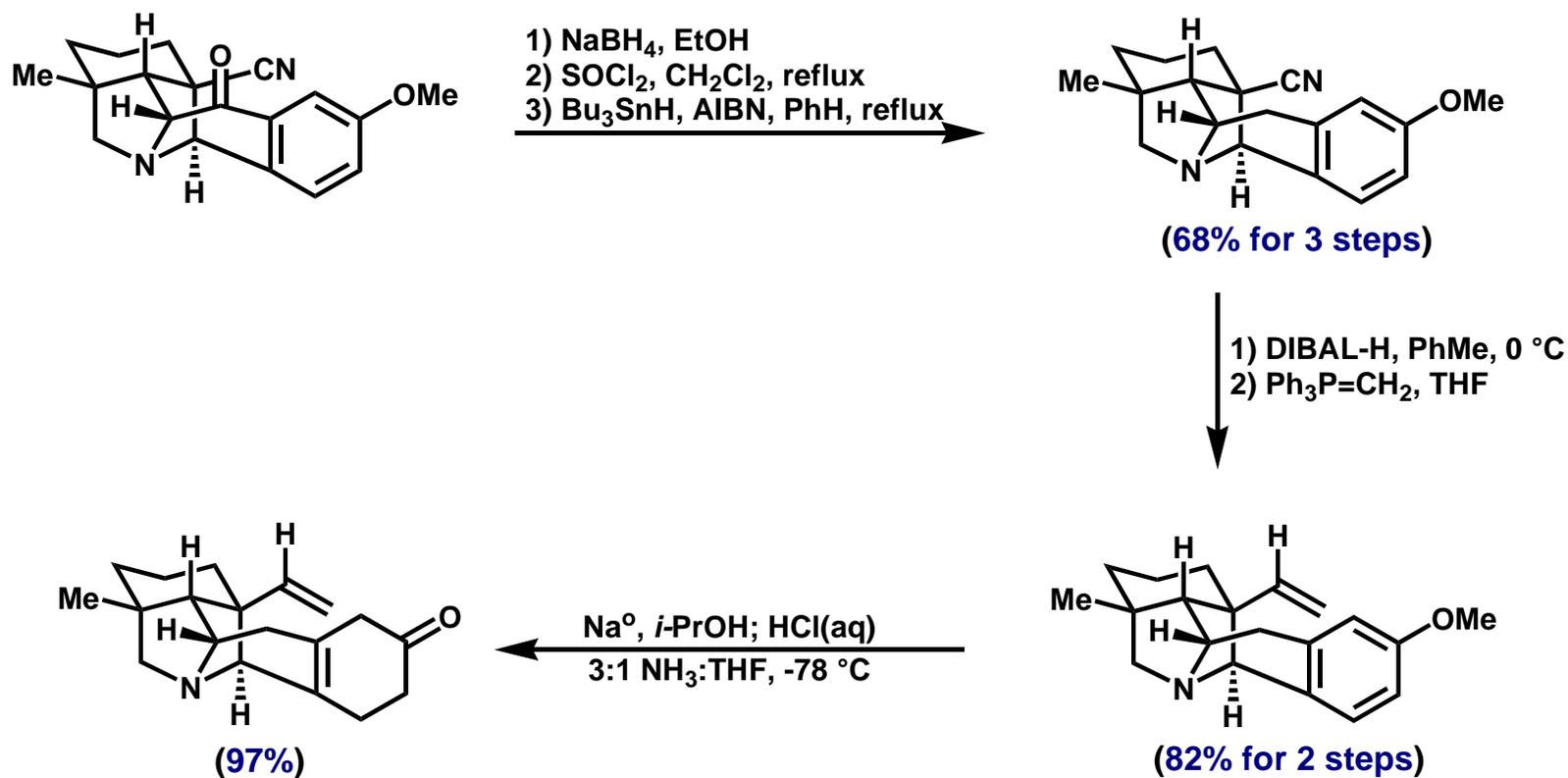


# Dipolar Cycloaddition: Ene-Nitrile Dipolarophile Revisited



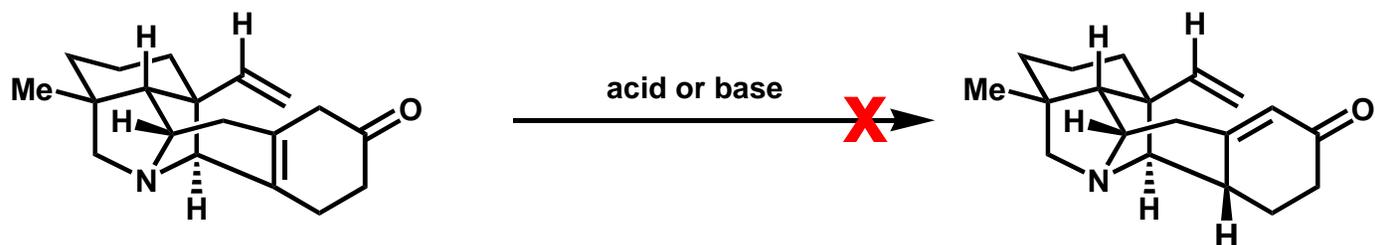


# Total Synthesis of ( $\pm$ )-Nominine: Advancement of the Synthesis

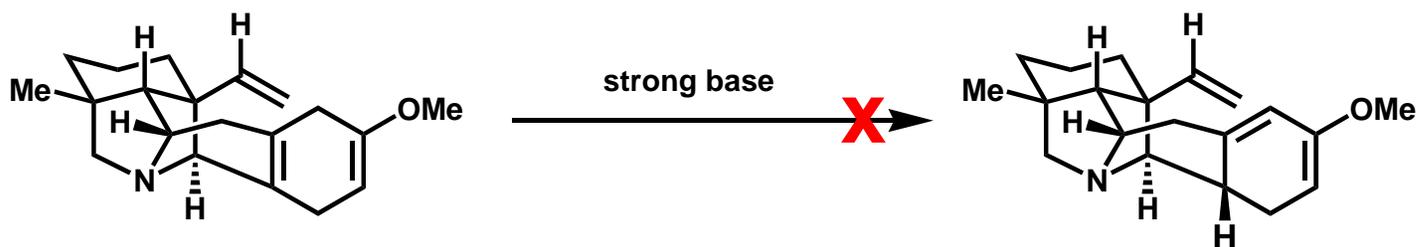




# Total Synthesis of ( $\pm$ )-Nominine: Preparation of Diene



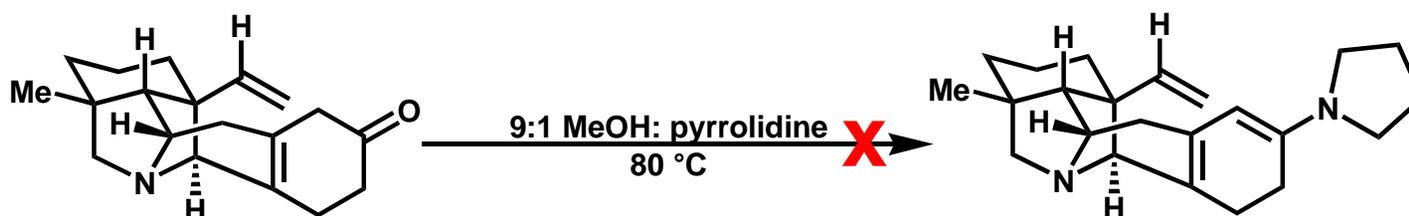
*Unconjugated enone may be the more stable isomer!*



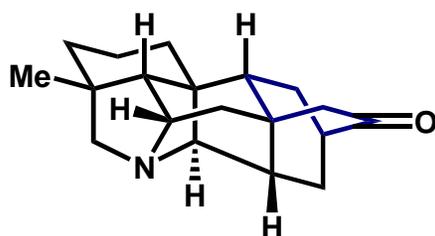
*No alkene isomerization!*



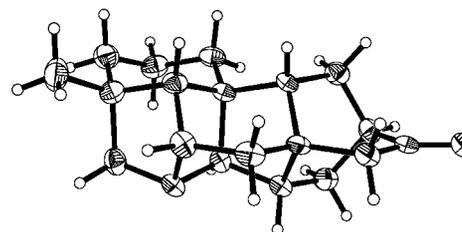
# Total Synthesis of ( $\pm$ )-Nominine: A Fortuitous Discovery



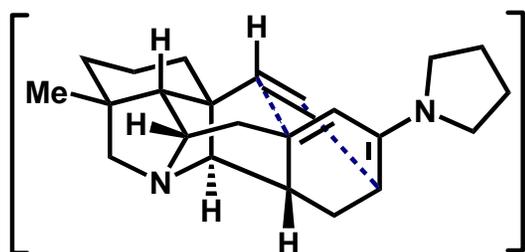
**Conversion to one spot by TLC; NMR shows complex mixture!**



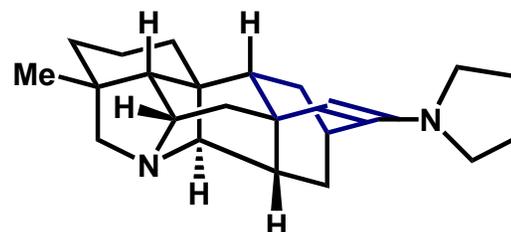
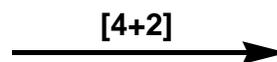
**Isolated after  
chromatography**



**Structure confirmed by X-ray**



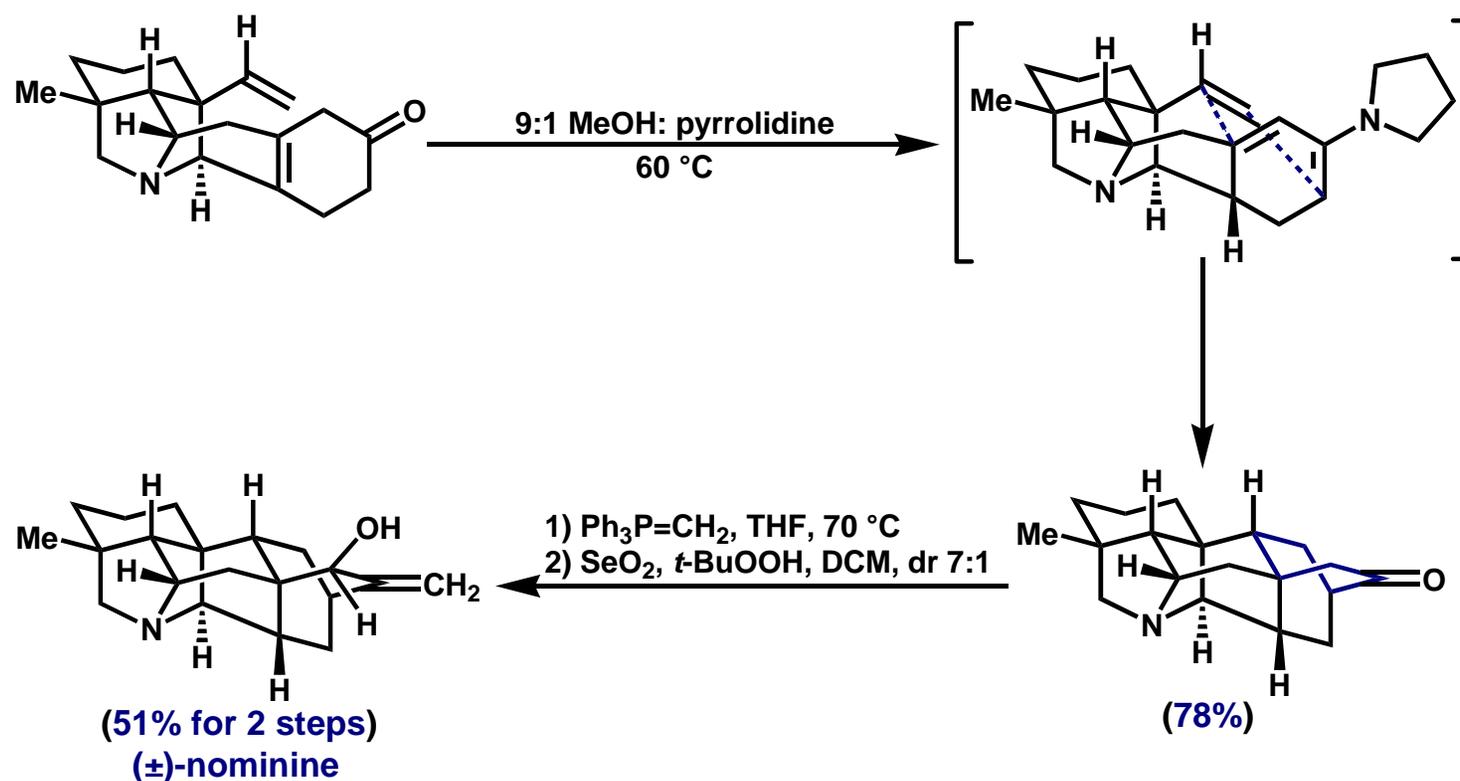
**Equilibrating mixture of  
dieneamines**



**Crude product is mixture of enamine and ketone  
Complete hydrolysis occurs on silica**

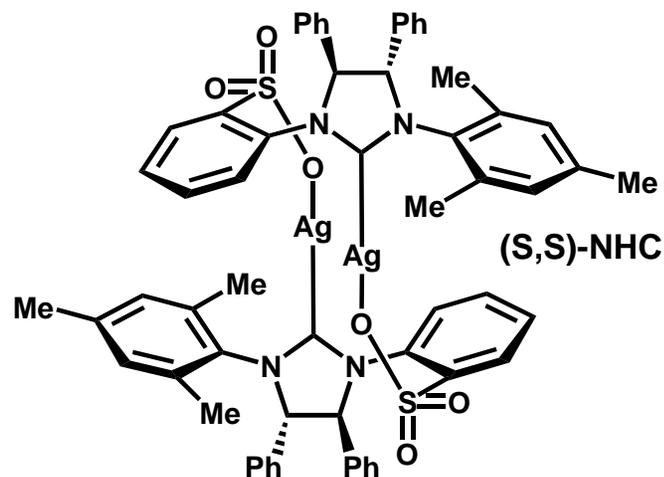
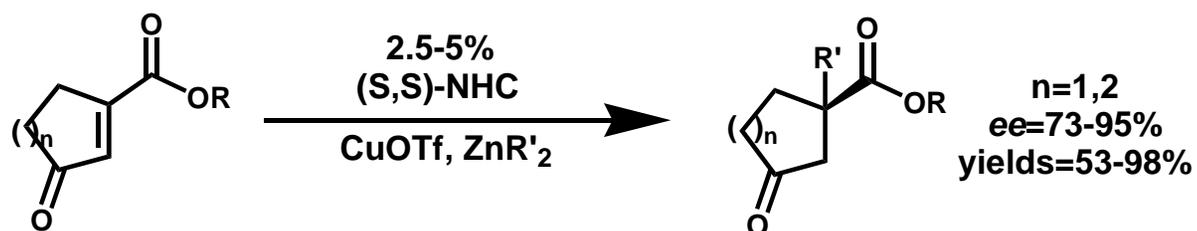


# Total Synthesis of ( $\pm$ )-Nominine: Completion of Synthesis



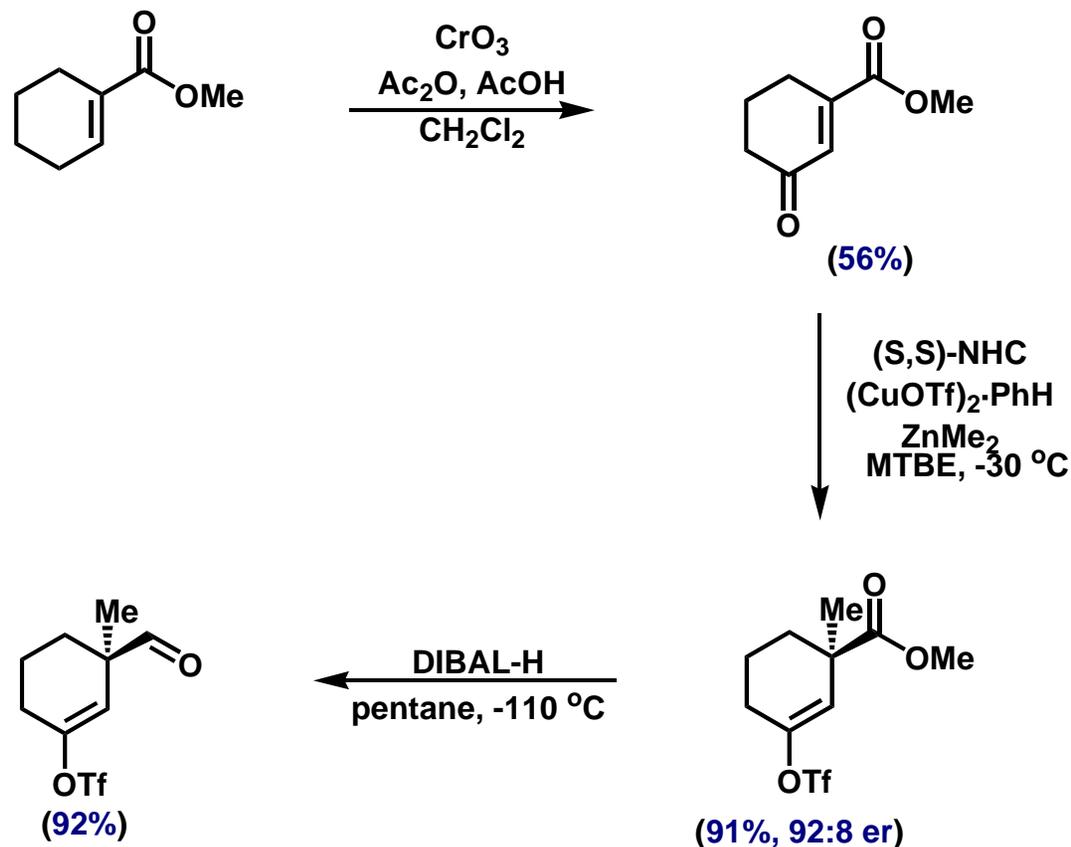


# Asymmetric Synthesis of (+)-Nominine: Hoveyda Conjugate Addition



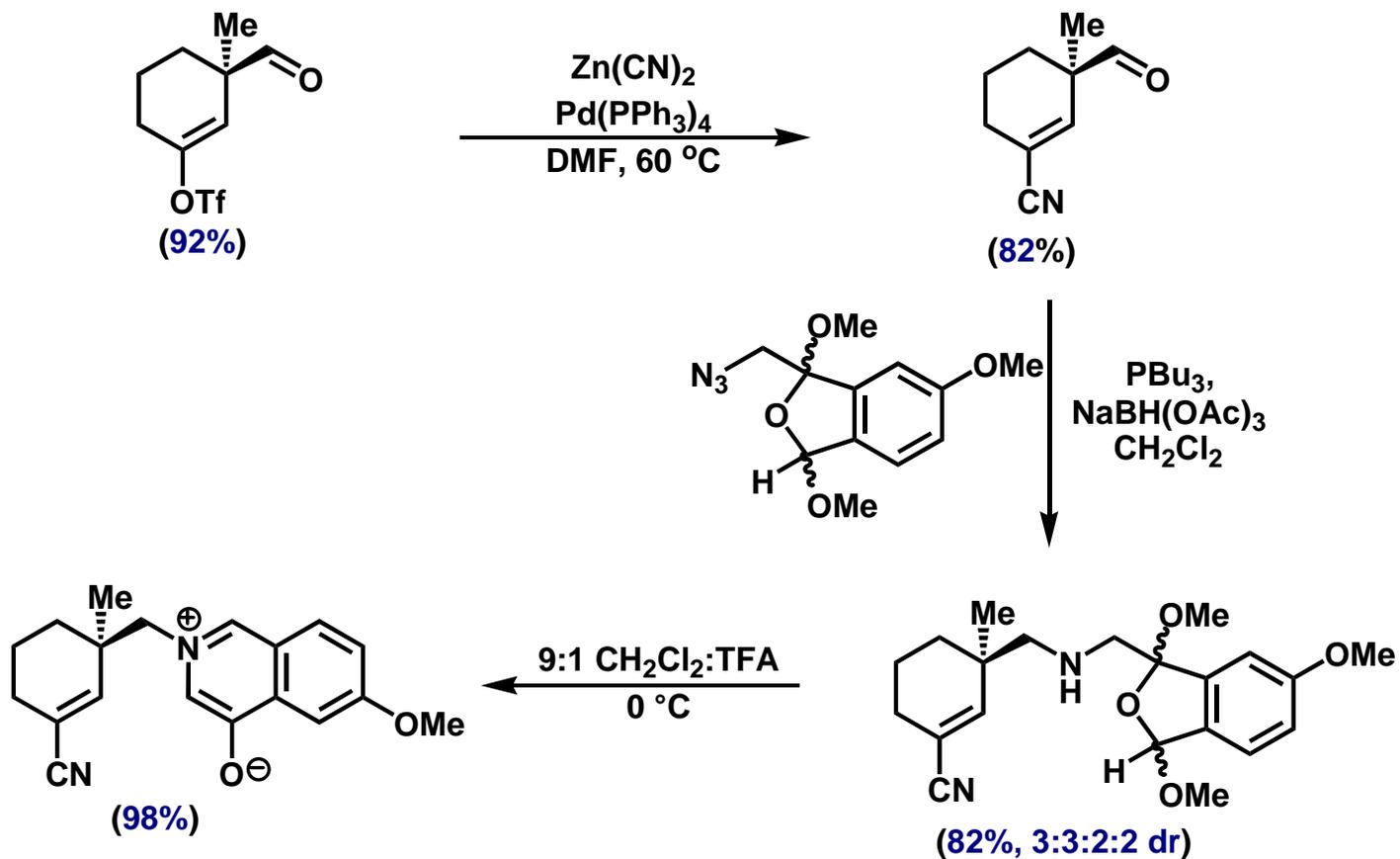


# Asymmetric Synthesis of (+)-Nominine: Application of the Hoveyda Method



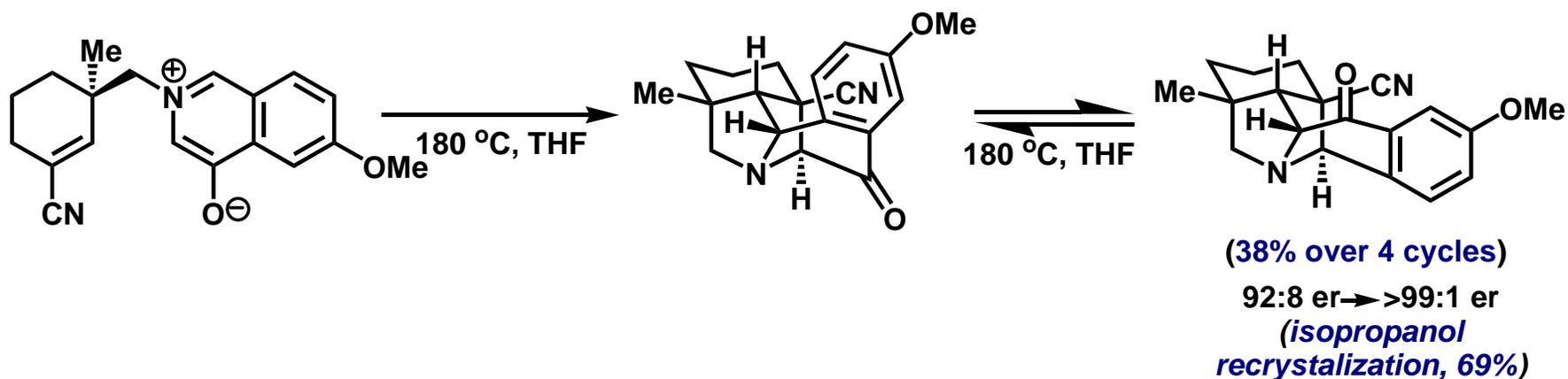


# Asymmetric Synthesis of (+)-Nominine: Advancement to the Dipole



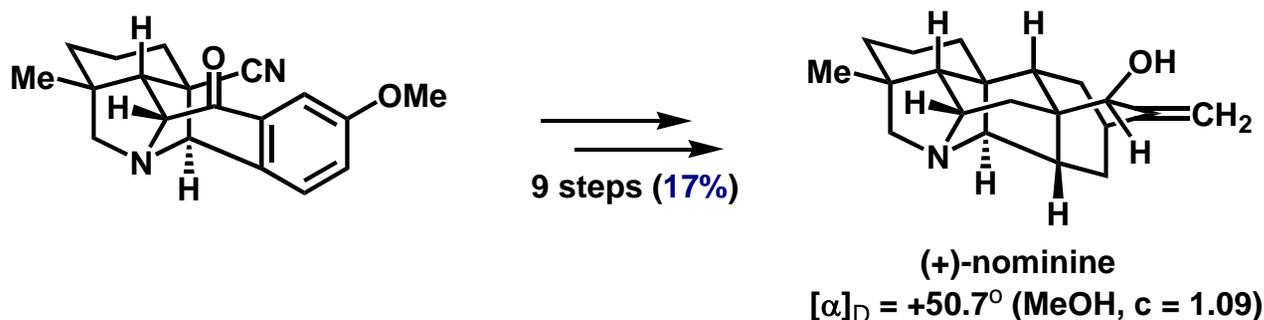


# Asymmetric Synthesis of (+)-Nominine: Cycladdition and Recrystallization





# Asymmetric Synthesis of (+)-Nominine: Completion of (+)-Nominine



Literature rotation:

$[\alpha]_D = +71.8^\circ$  (MeOH, no concentration given)

Ochiai, E.; Okamoto, T.; Sakai, S.; Saito, A. *Yakugaku Zasshi* 1956, 76, 1414-1418

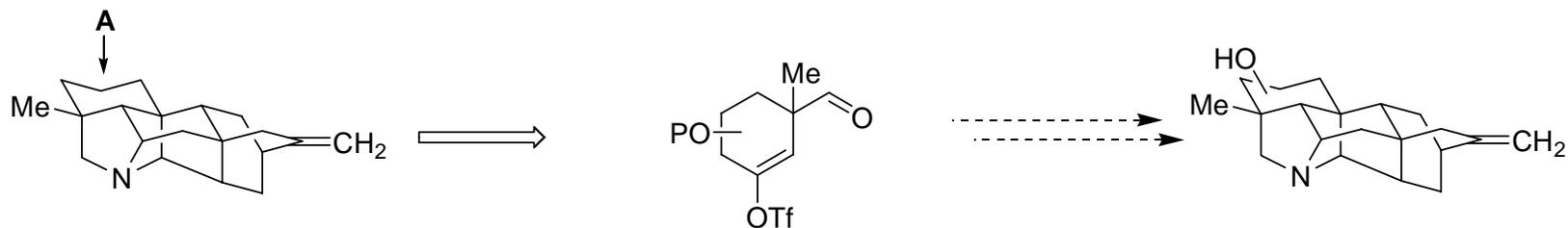
$[\alpha]_D = +53.4^\circ$  (no solvent or concentration given)

Sakai, S.; Yamamoto, I.; Yamaguchi, K.; Takayama, H.; Ito, M.; Okamoto, T. *Chem. Pharm. Bull.* 1982, 30, 4579-4582

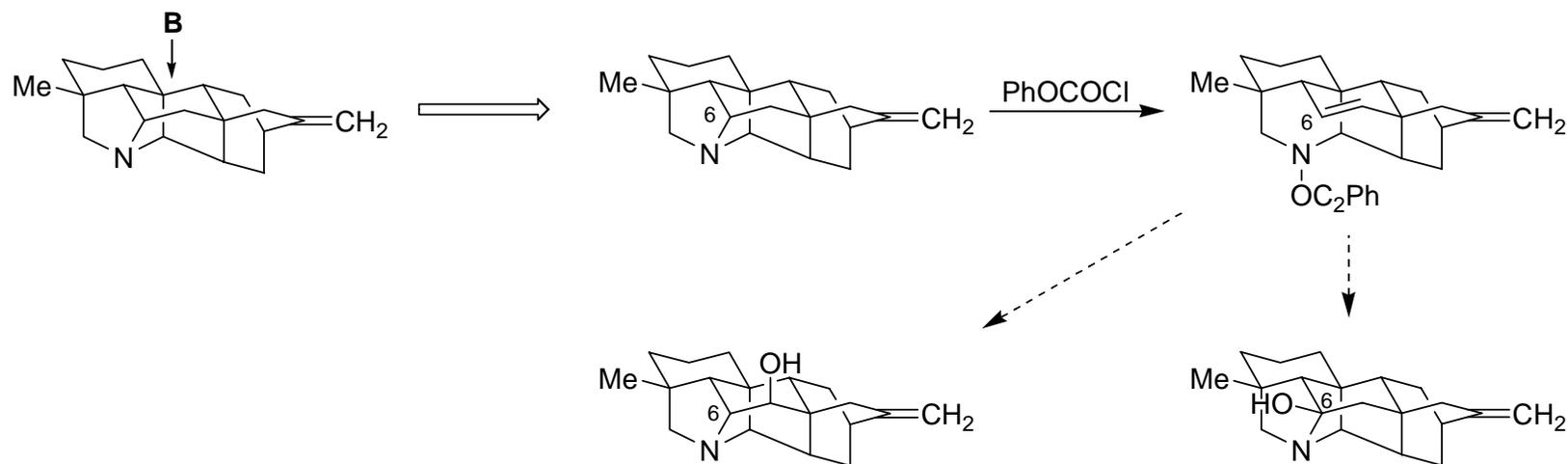


# Synthesis of Other Hetisine Alkaloids

A-ring oxygenation:



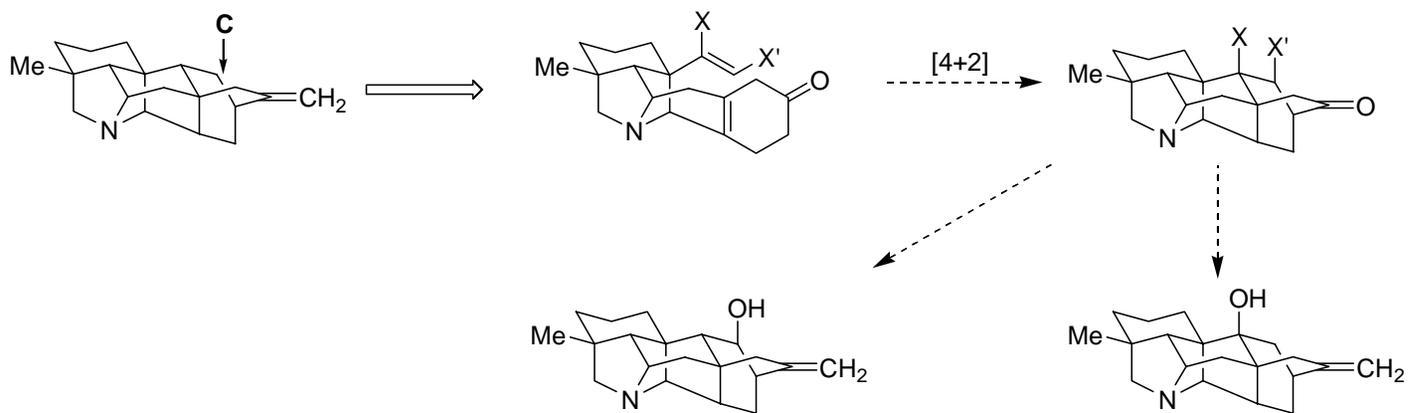
B-ring oxygenation:



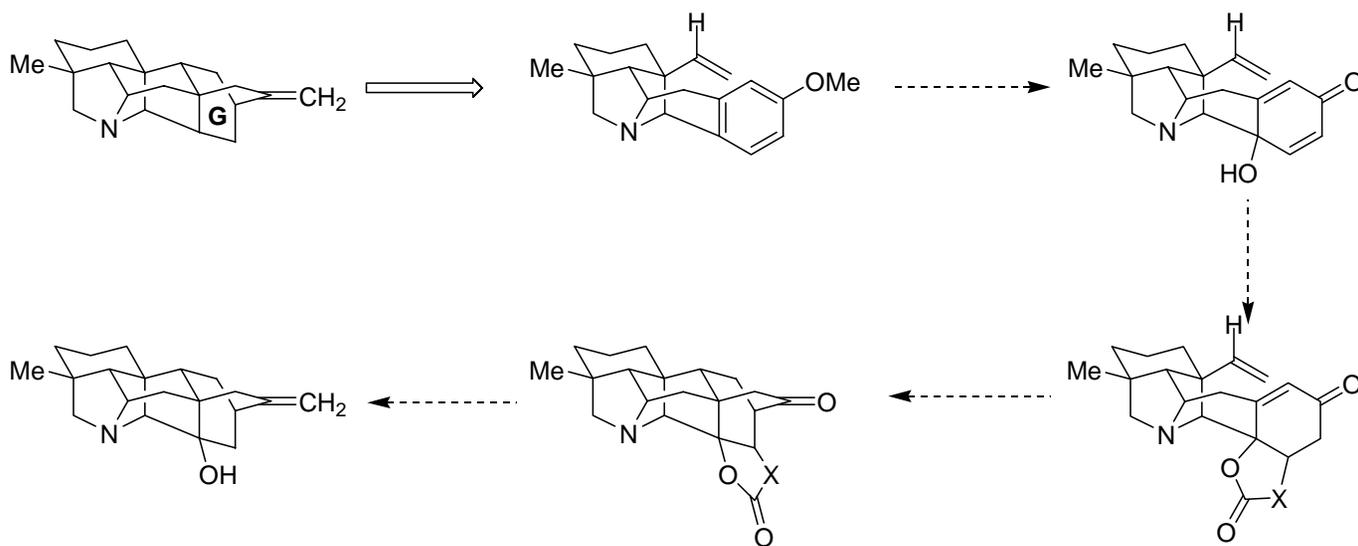


# Synthesis of Other Hetisine Alkaloids

C-ring oxygenation:



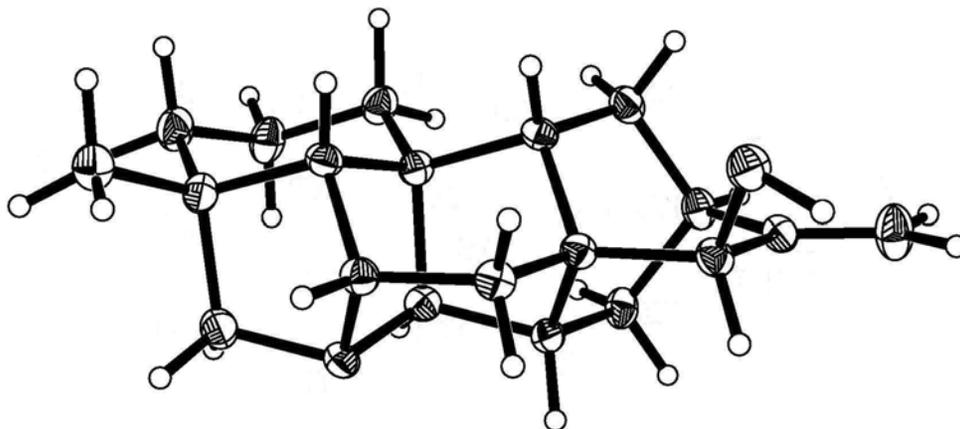
G-ring oxygenation:





## Summary

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- **Total synthesis of (+)-nominine**
  - 1.3% total, 16 steps (longest linear sequence)
- **Total synthesis of (±)-nominine**
  - 6.1% total, 15 steps (longest linear sequence)
- **Dual cycloaddition strategy**
  - Oxidoisoquinolinium betaine cycloaddition
  - Diels-Alder cycloaddition



## ***Acknowledgments***

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