

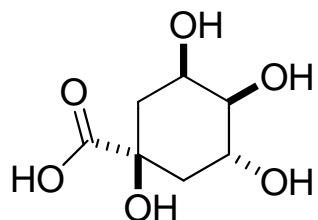
Tim Martin

7/30/08

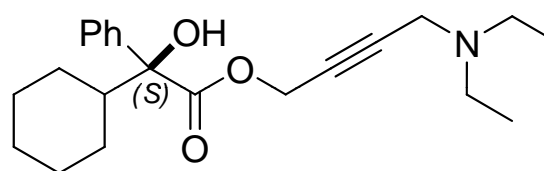
# Recent Methods for the Asymmetric Synthesis of C( $\alpha$ )-Tetrasubstituted Hydroxycarbonyls

# Why $\alpha$ -hydroxycarbonyls

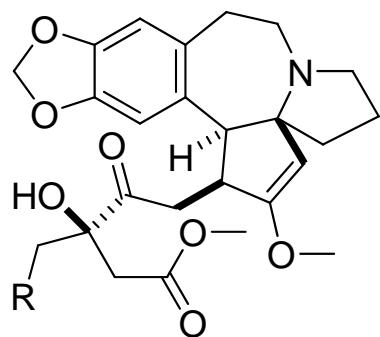
- Versatile building blocks
- Important in pharmaceuticals and natural products
- Quaternary centers are an interesting challenge



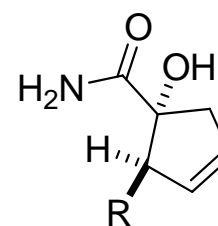
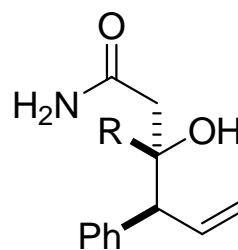
(-)-Quinic Acid



(S)-Oxybutynin



Harringtonines

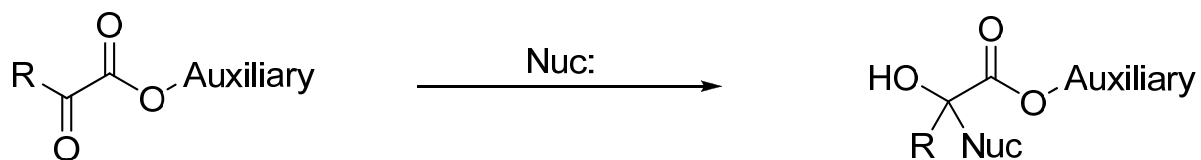


1-hydroxy amides

# Synthesis of $\alpha$ -hydroxycarbonyls

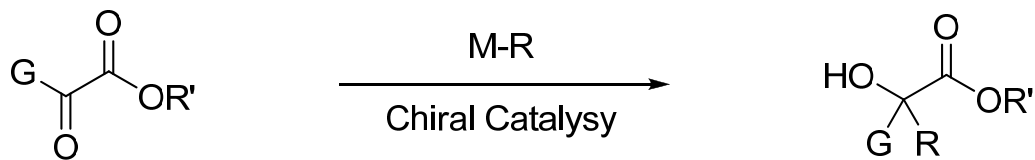
## Chiral Pool Approach

## Chiral Auxiliary Approach



*Tetrahedron*, **2002**, 58, 1541  
*Tetrahedron*, **1989**, 45, 5837  
*J. Am. Chem. Soc.*, **1975**, 97, 6908

## Metal Additions

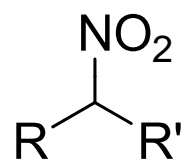


*J. Am. Chem. Soc.* **2005**, 127, 15453-15456 and references therein

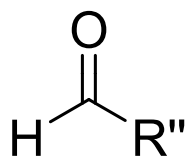
# Scope

- Formation via Henry Reaction with  $\alpha$ -ketocarboxyls
- Synthesis from *5H*-Oxazol-4-ones
- Formation through metal catalyzed reactions

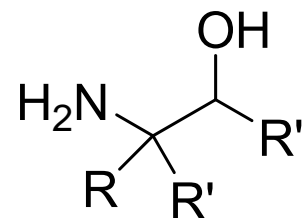
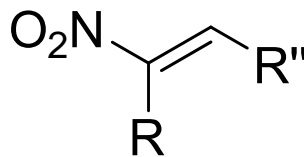
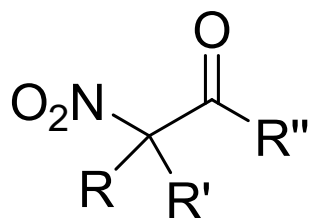
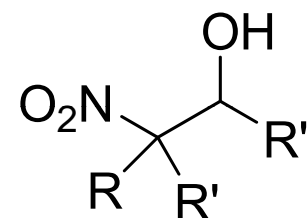
# The Henry Reaction



+

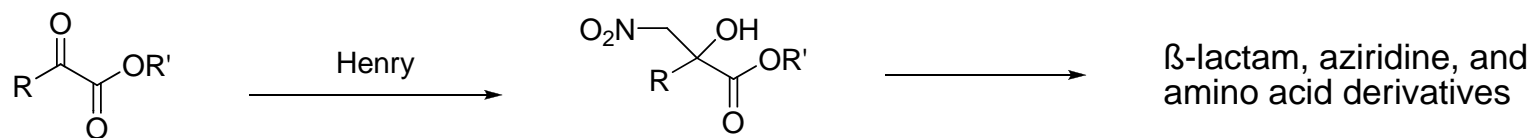


Base (cat.)

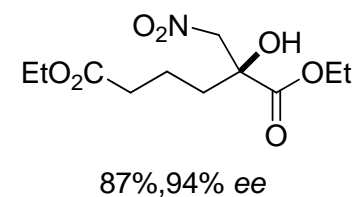
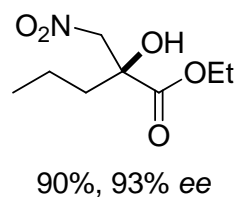
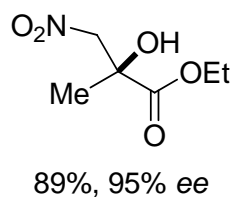
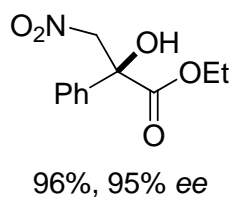
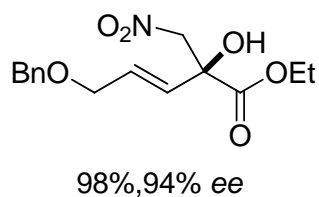
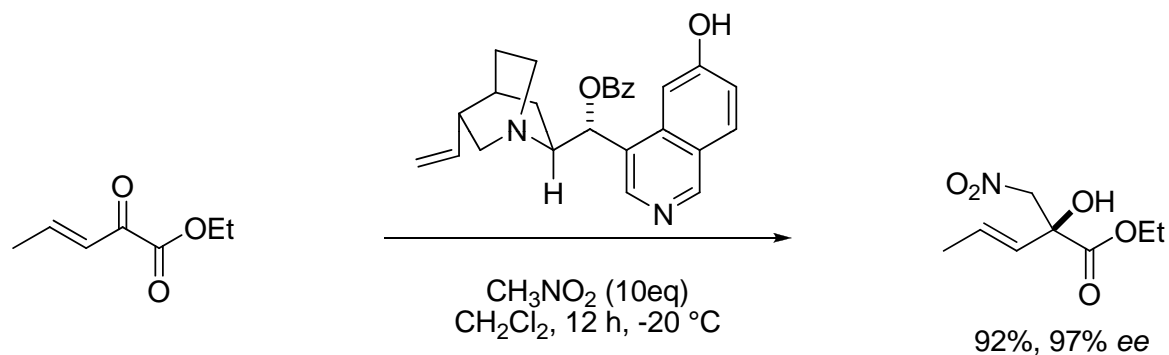


# Enantioselective Nitroaldol Reactions catalyzed by Cinchona Alkaloids

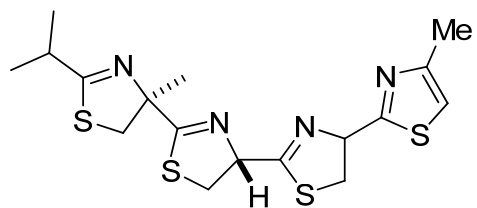
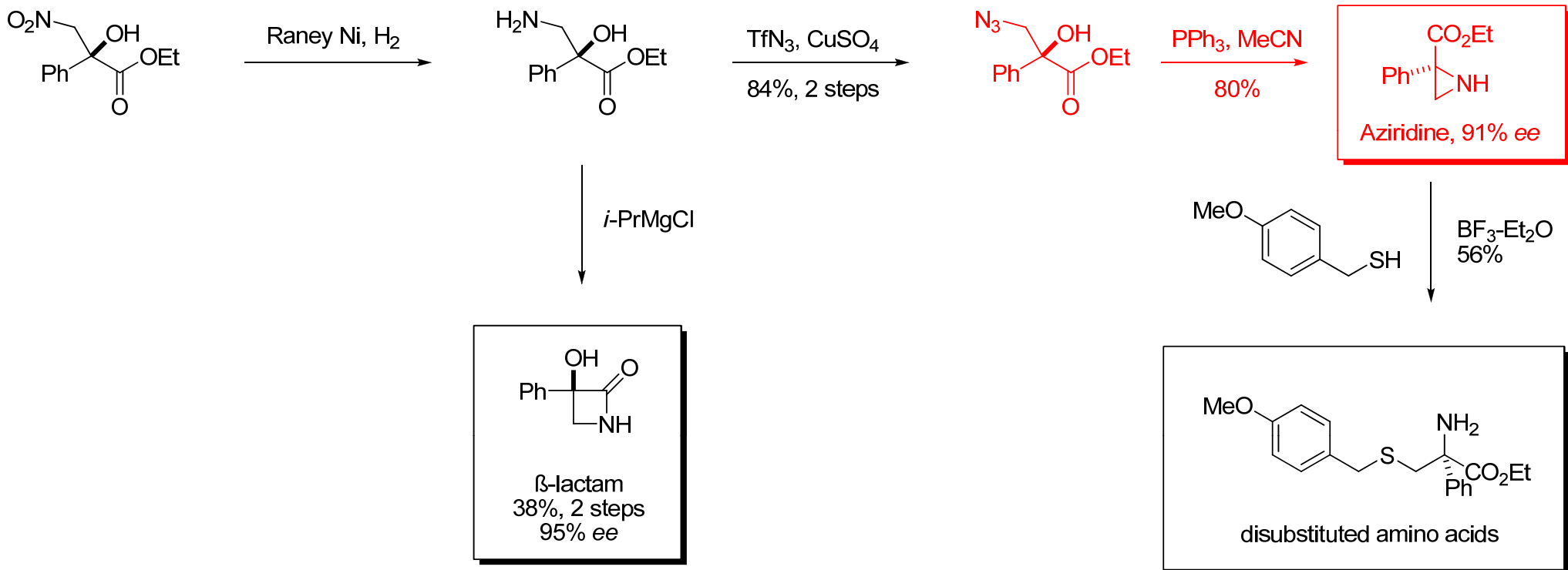
## The Approach:



## The Method:

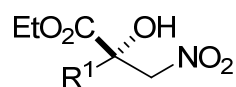
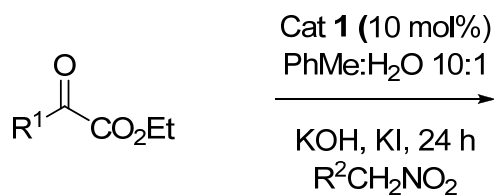


# Enantioselective Nitroaldol Reactions catalyzed by Cinchona Alkaloids

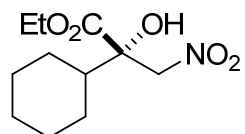
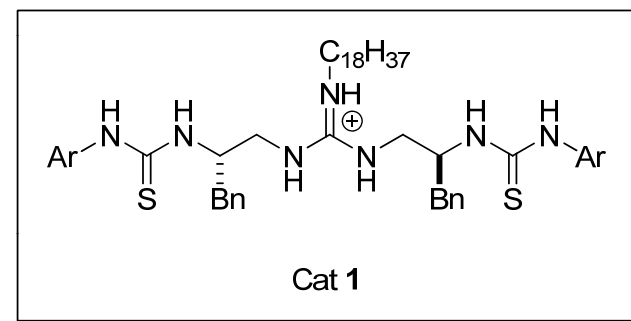
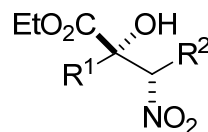


mirabazoles, antitumor and anti HIV

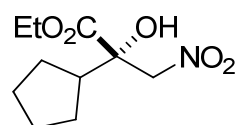
# Enantioselective Nitroaldol Reactions utilizing Bifunctional Guanidine-Thiourea Catalysts



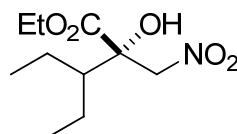
or



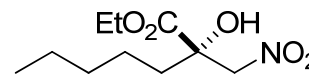
90%, 93% ee



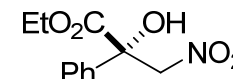
83%, 80% ee



89%, 78% ee

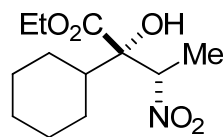


60%, 83% ee

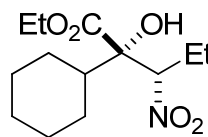


56%, 5% ee

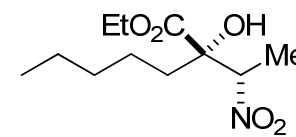
!!



45%, 91% ee  
dr 97:3



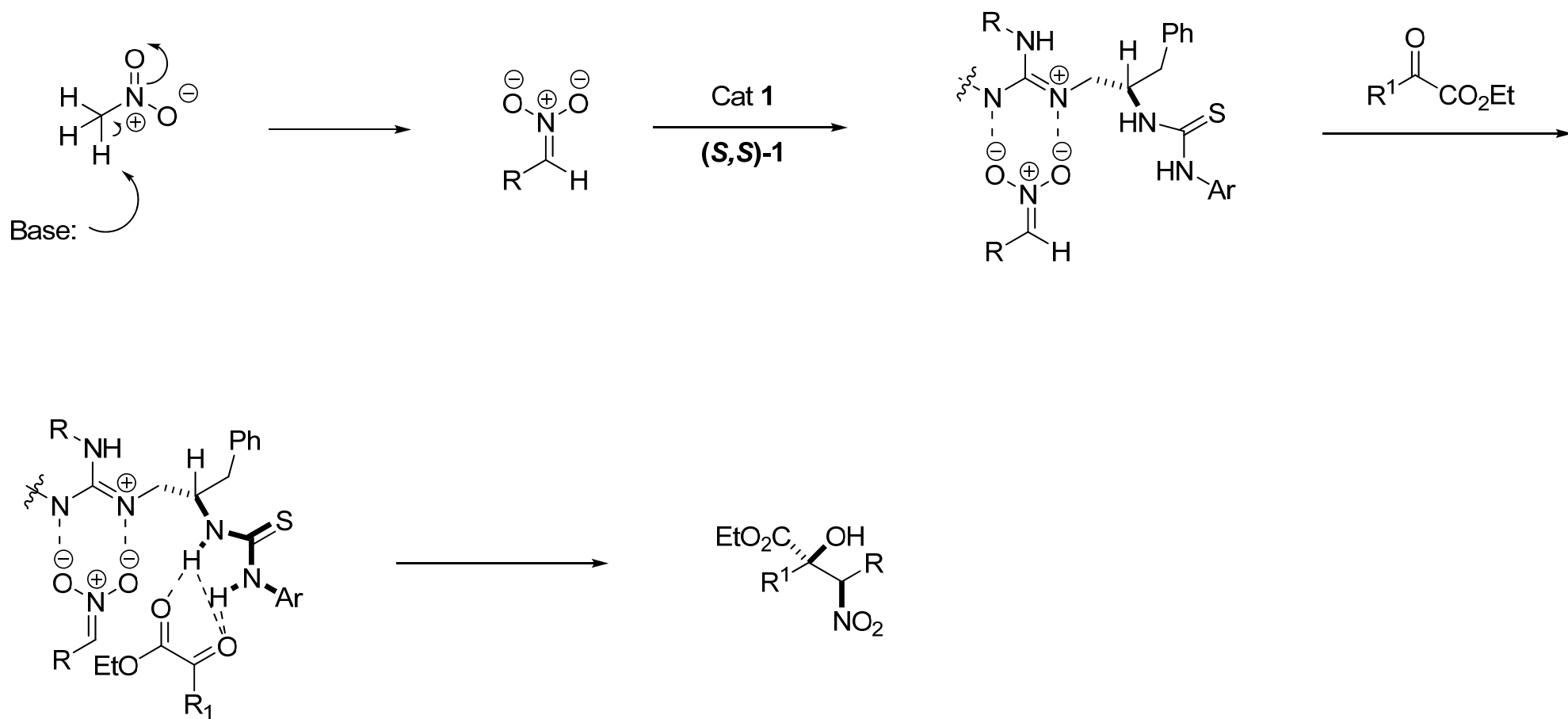
35%, 83% ee  
dr 92:8



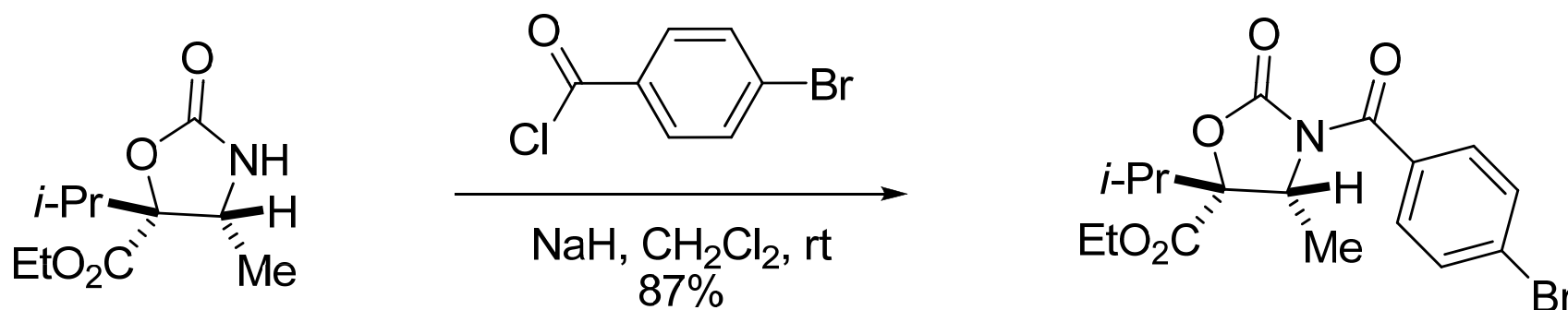
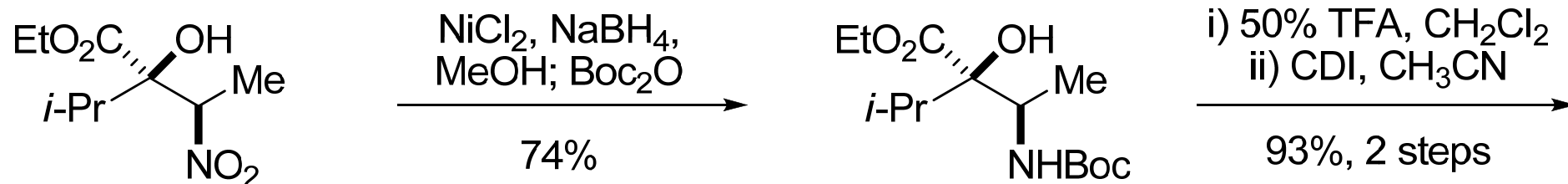
36%, 93% ee  
dr 79:21

# Enantioselective Nitroaldol Reactions utilizing Bifunctional Guanidine-Thiourea Catalysts

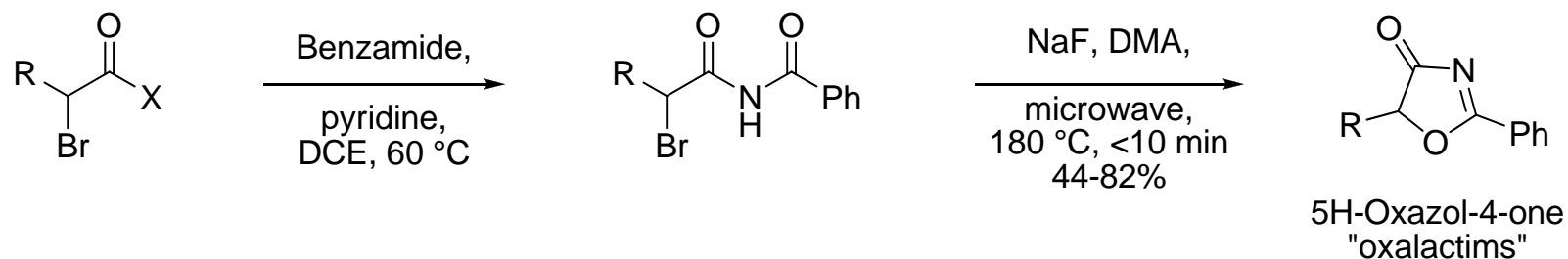
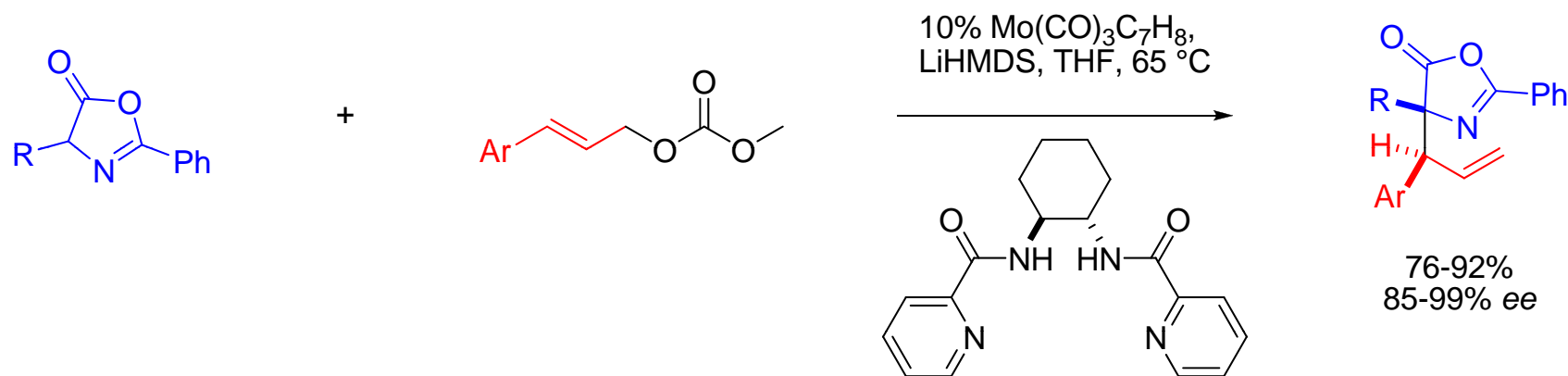
## Plausible Mechanism



# Enantioselective Nitroaldol Reactions utilizing Bifunctional Guanidine-Thiourea Catalysts

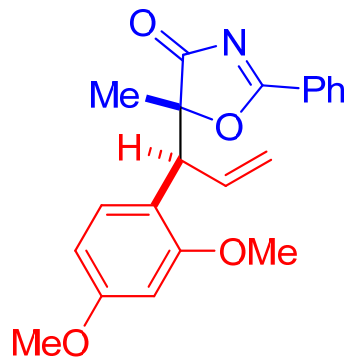
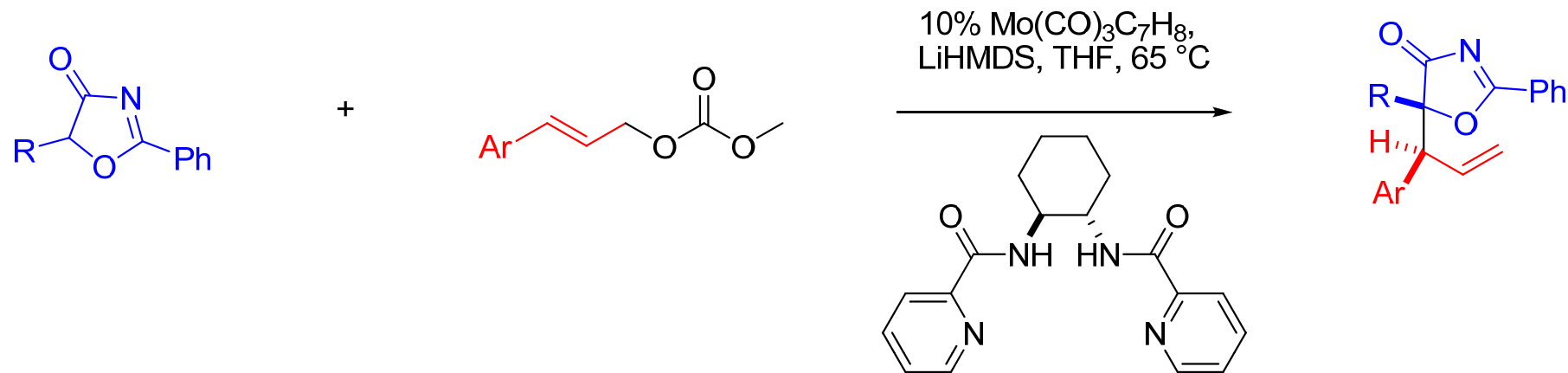


# 5H-Oxazol-4-ones as Building Blocks for $\alpha$ -hydroxycarbonyls

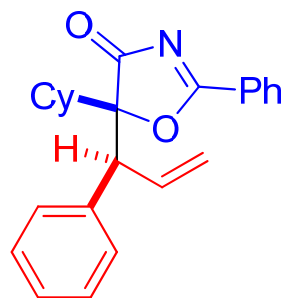


*J. Am. Chem. Soc.* **2002**, *124*, 7257;  
*J. Am. Chem. Soc.* **2004**, *126*, 1944.

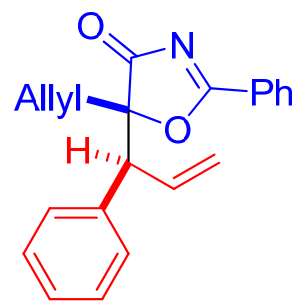
# 5*H*-Oxazol-4-ones as Building Blocks for $\alpha$ -hydroxycarbonyls



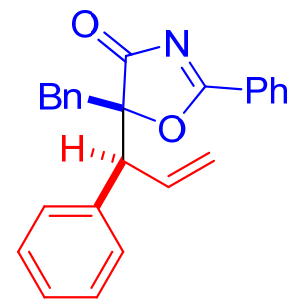
91%, >99% ee  
18:1 dr



89%, >99% ee  
12:1 dr

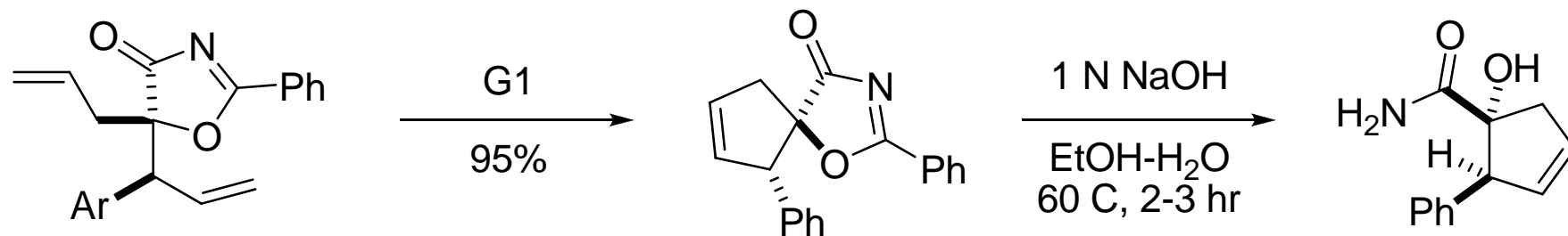
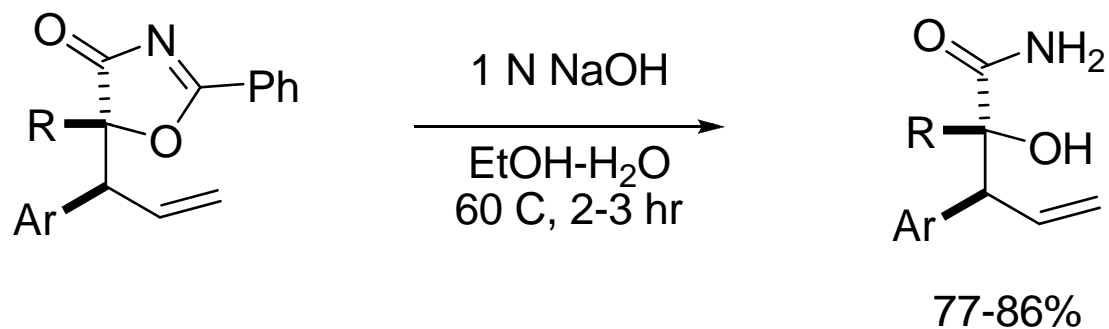


97%, >99% ee  
10:1 dr



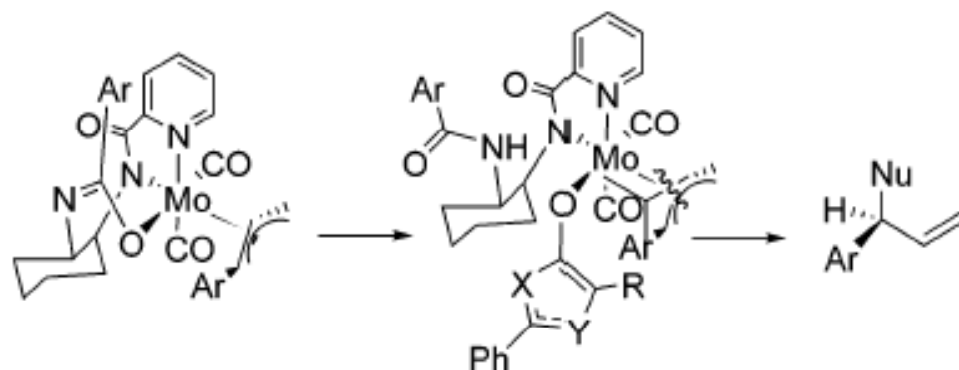
99%, >99% ee  
7.4:1 dr

# 5H-Oxazol-4-ones as Building Blocks for $\alpha$ -hydroxycarbonyls

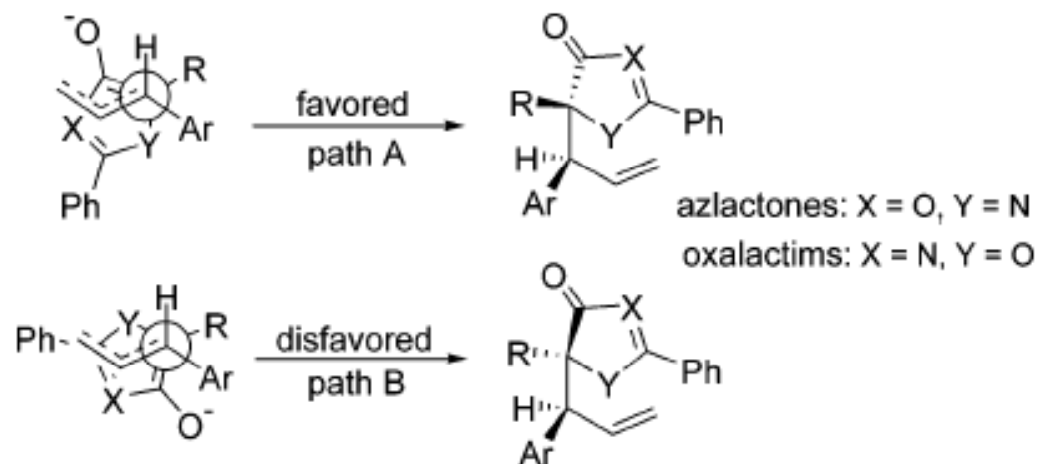


# 5*H*-Oxazol-4-ones as Building Blocks for $\alpha$ -hydroxycarbonyls

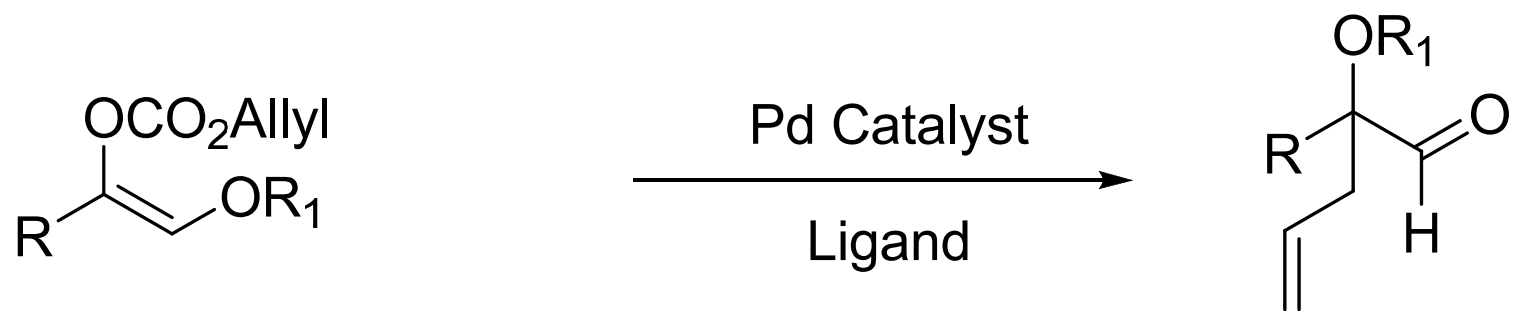
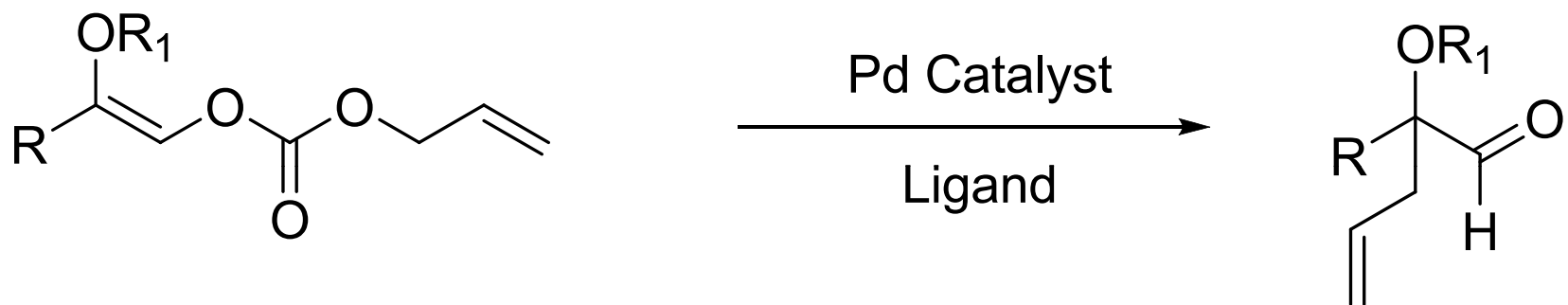
Stereochemistry at the electrophile:



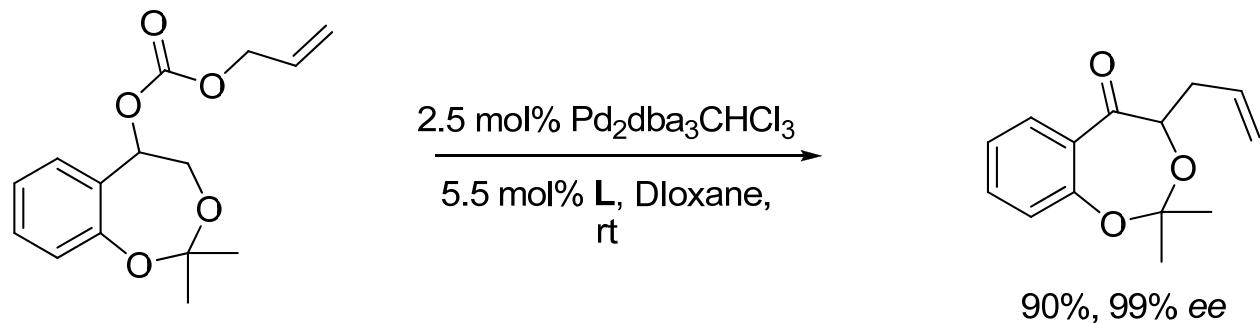
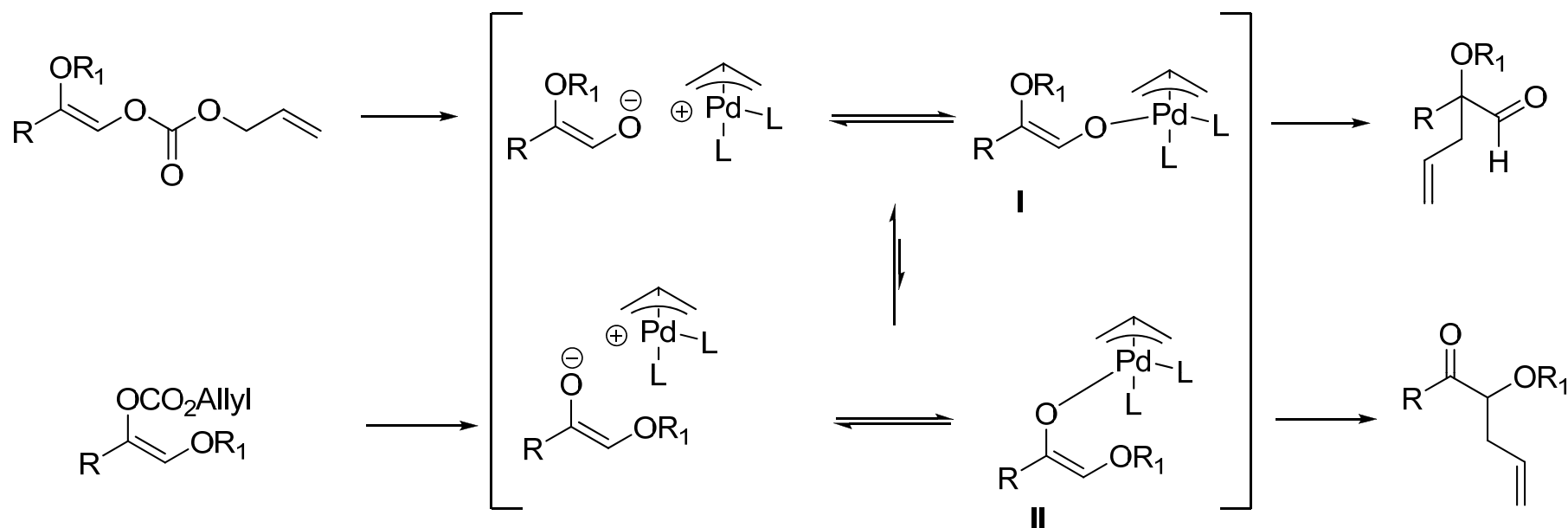
Stereochemistry at the nucleophile:



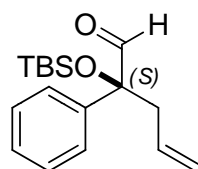
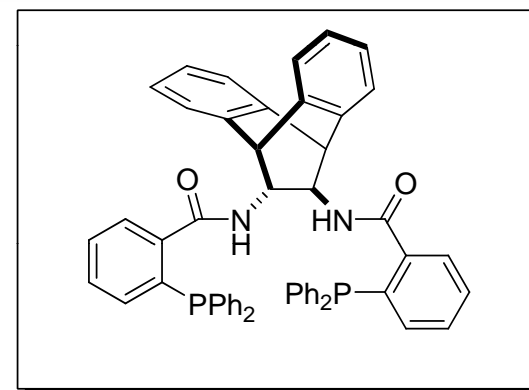
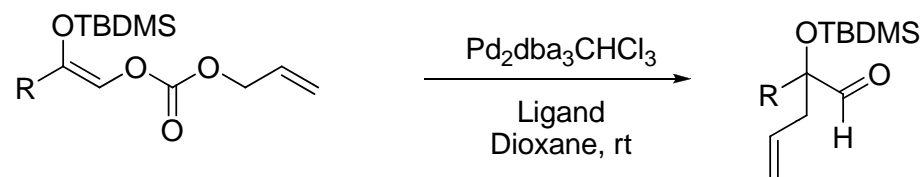
# Pd-Catalyzed Asymmetric Allylic Alkylation of Enolates



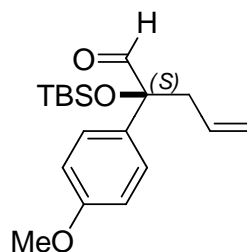
# Pd-Catalyzed Asymmetric Allylic Alkylation of Enolates



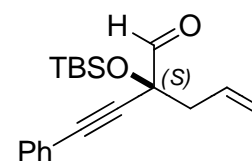
# Pd-Catalyzed Asymmetric Allylic Alkylation of Enolates



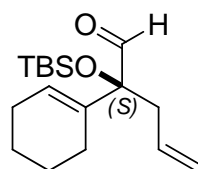
93%, 92% ee



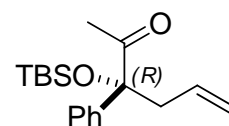
94%, 92% ee



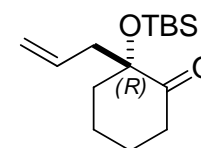
76%, 89% ee



93%, 98% ee

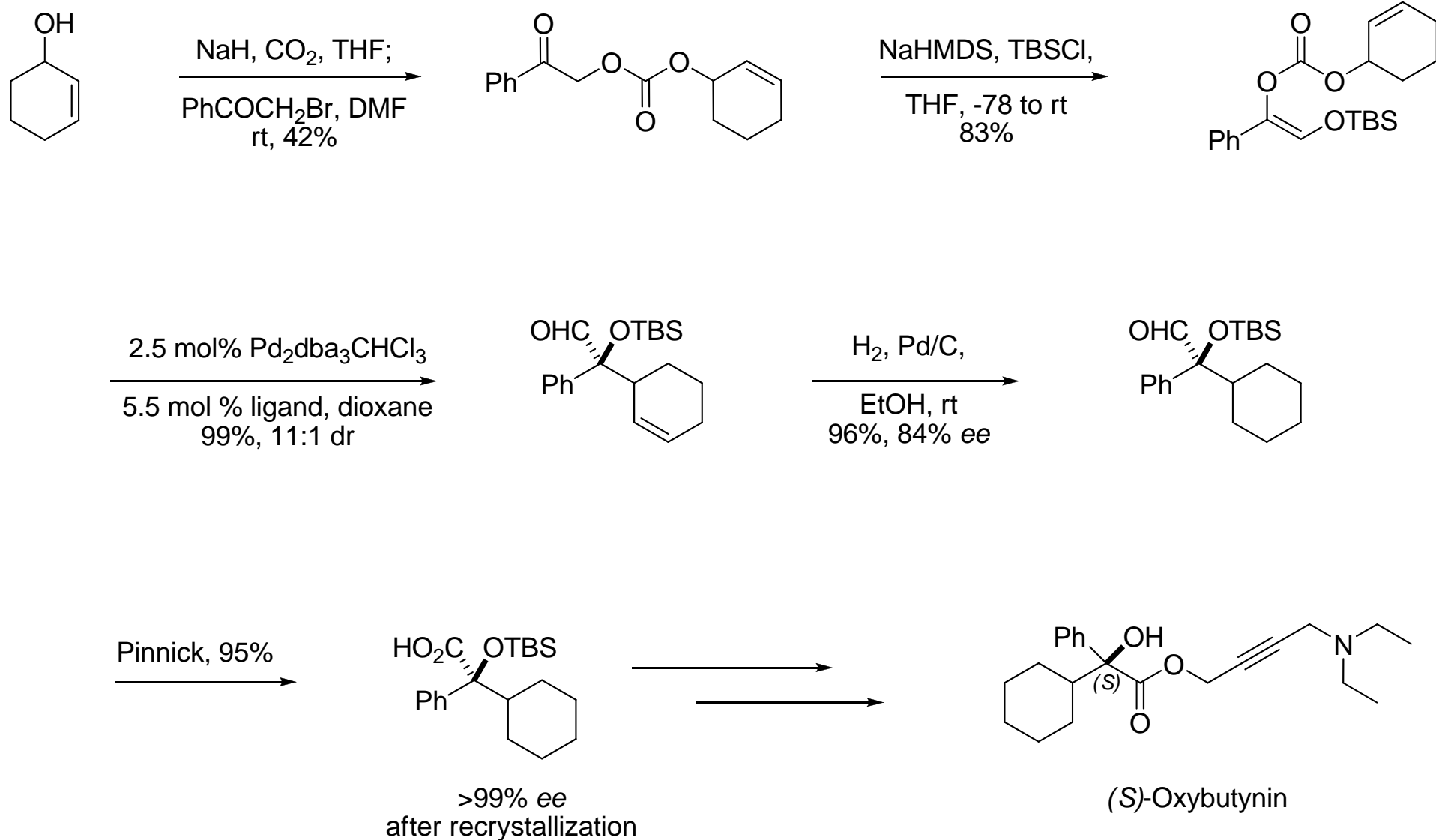


94%, 80% ee

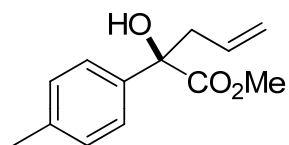
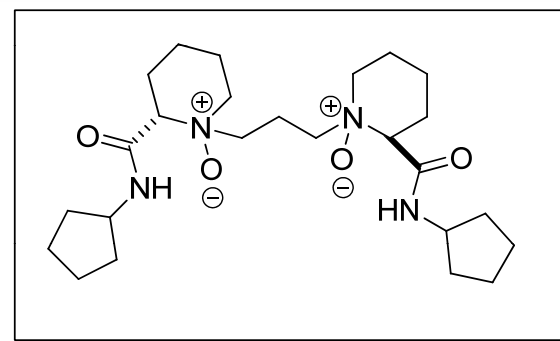
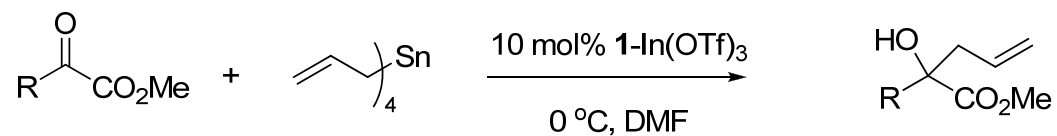


96%, 64% ee

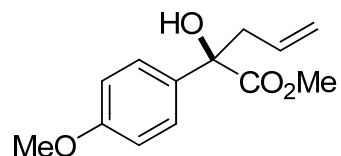
# Formal Synthesis of (S)-Oxybutynin



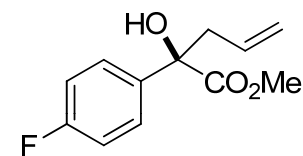
# Allylation of $\alpha$ -Ketoesters by In(III) Complexes



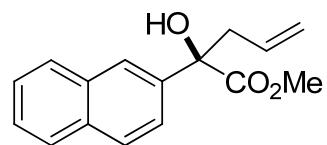
99%, 91% ee



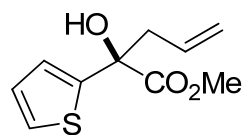
89%, 94% ee



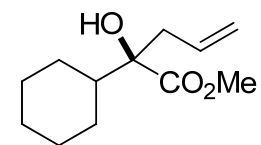
99%, 92% ee



80%, 91% ee

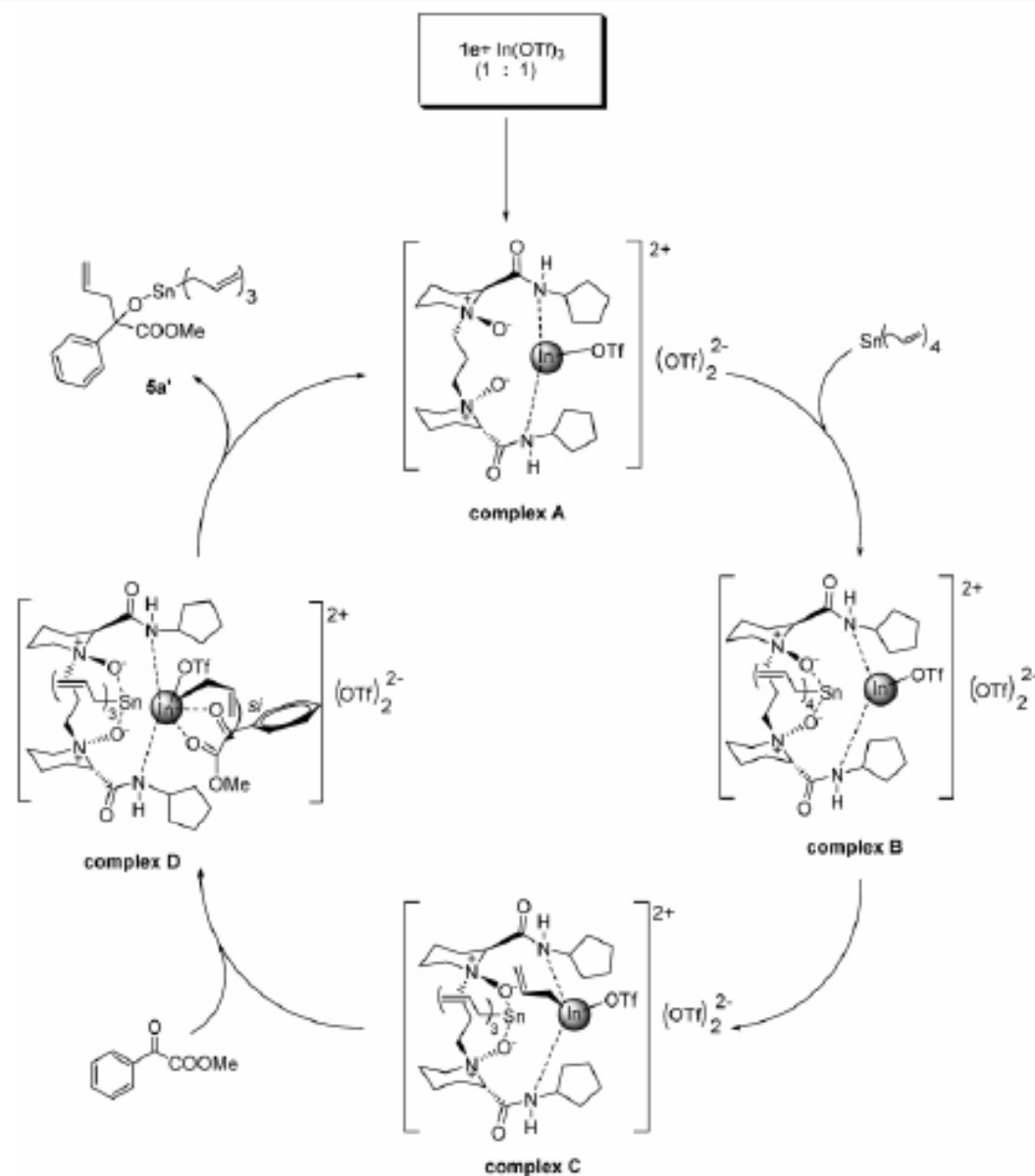


98%, 89% ee

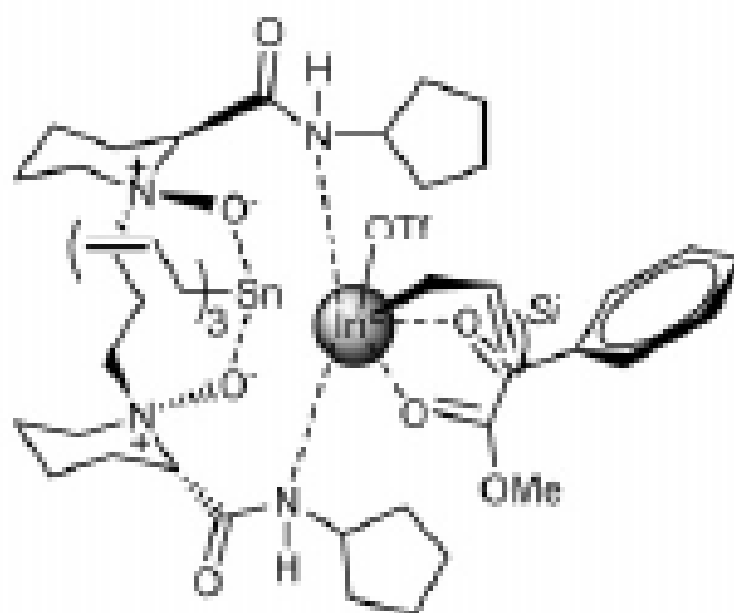


90%, 69% ee

# Allylation of $\alpha$ -Ketoesters by In(III) Complexes

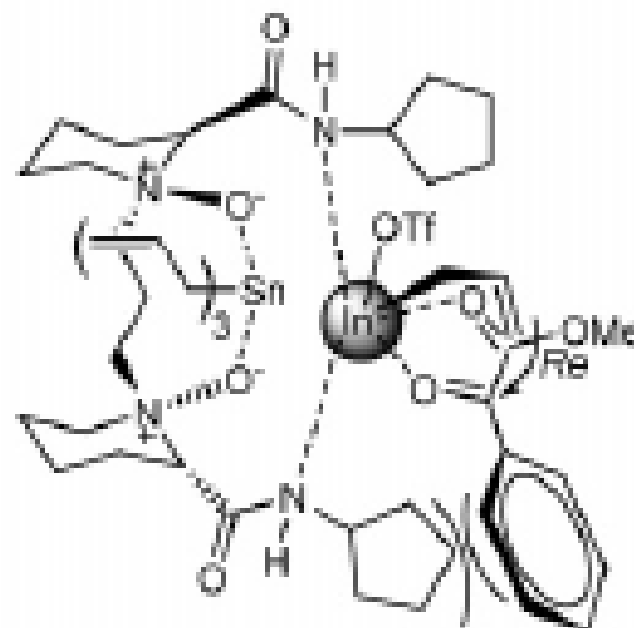


# Allylation of $\alpha$ -Ketoesters by In(III) Complexes



T.S-I

*Si* face attack  
Favored

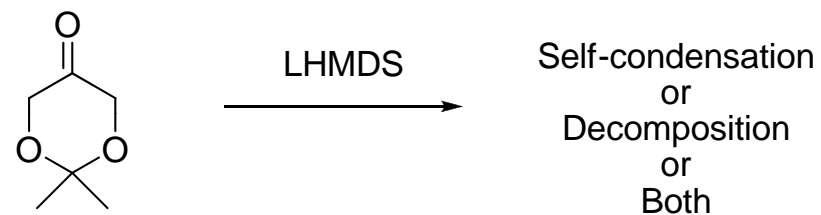
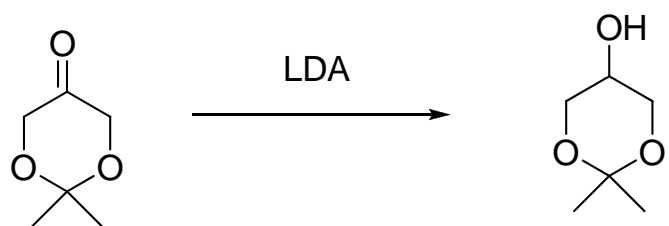


T.S-II

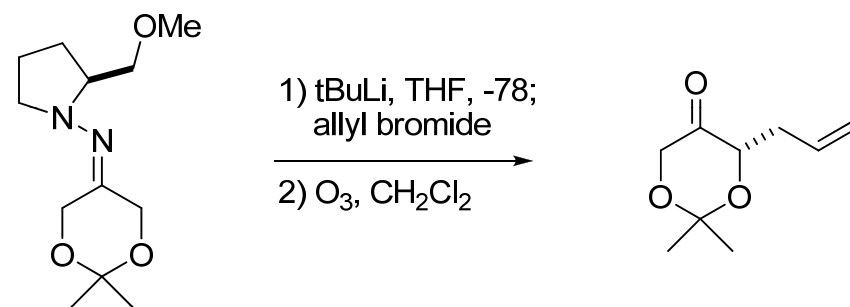
*Re* face attack  
Disfavored

# Alkylation of Substituted Dioxanone Enol Ethers

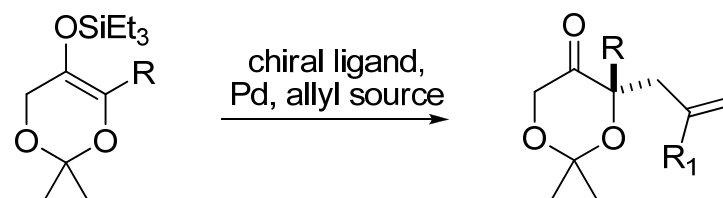
## Challenges:



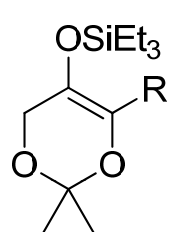
## Enders



## Stoltz

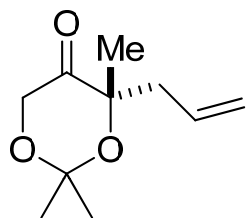
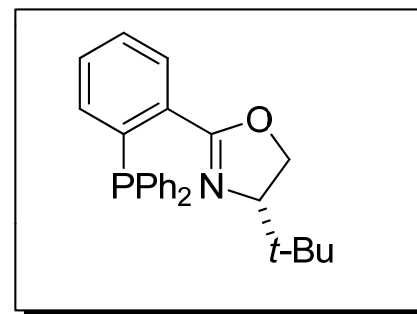
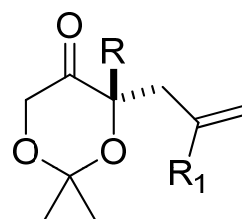


# Alkylation of Substituted Dioxanone Enol Ethers

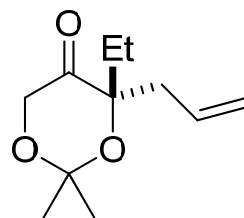


Pd(dmdba)<sub>2</sub> (5 mol%),  
L (5.5 mol%), TBAT (1 eq)  
diallyl carbonate (1.05 eq)

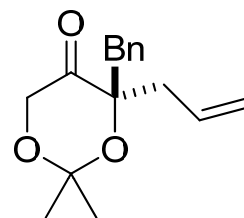
PhMe, rt



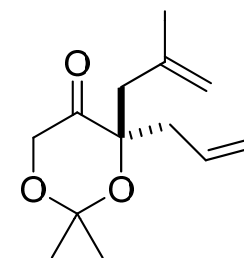
86%, 87% ee



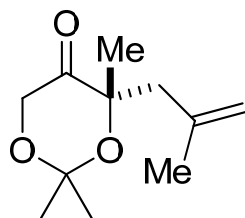
79%, 93% ee



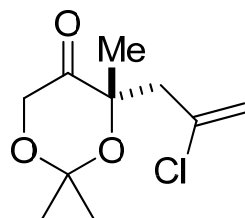
85%, 86% ee



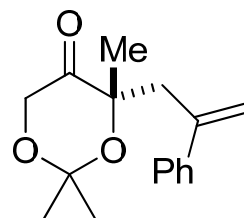
88%, 85% ee



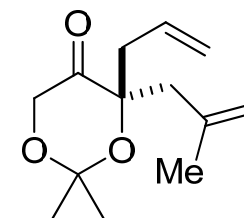
59%, 89% ee



59%, 92% ee

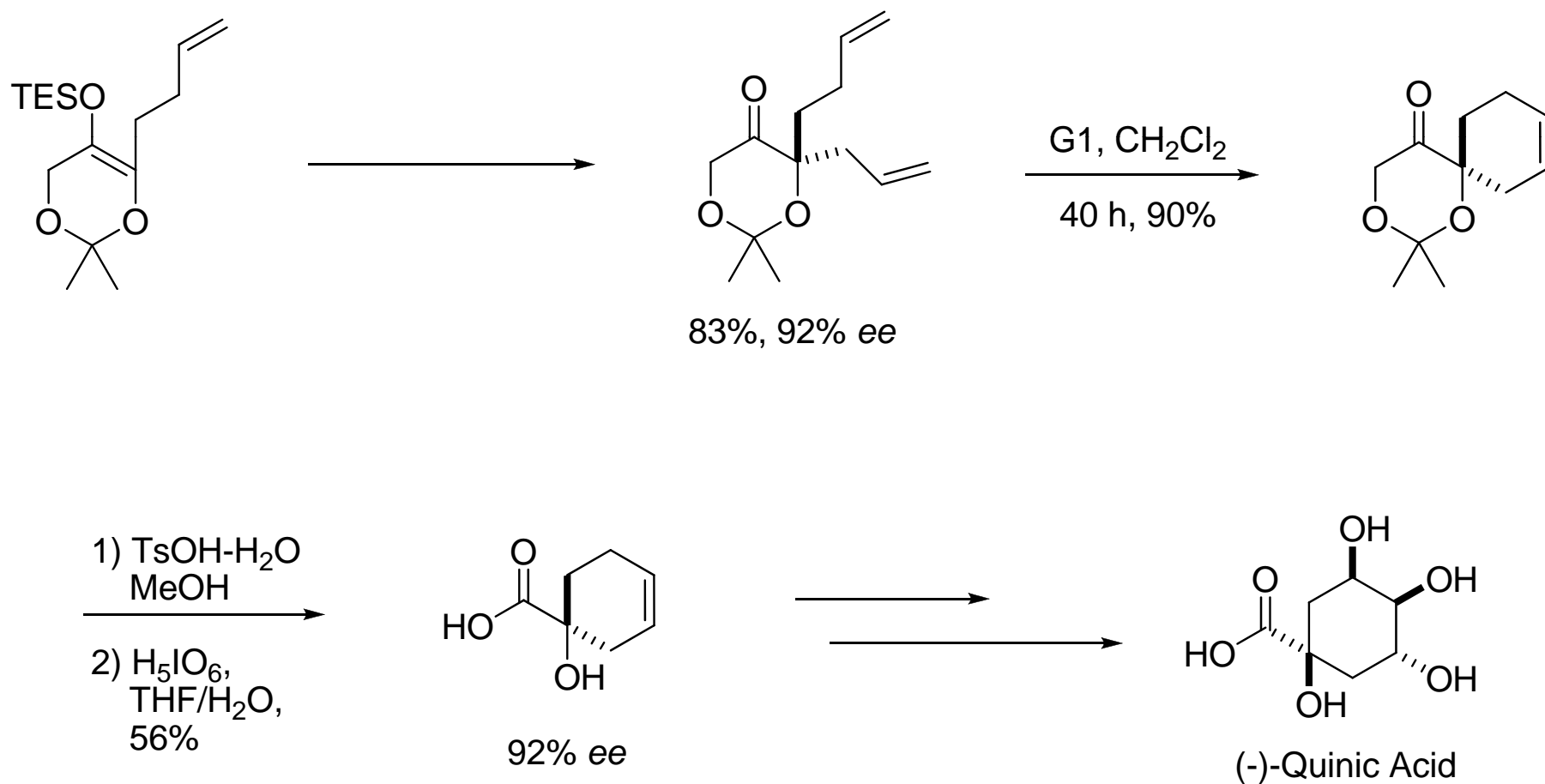


73%, 94% ee



93%, 88% ee

# Formal Synthesis of (-)-Quinic Acid



# Conclusions

- Organocatalysts (cinchona alkaloids, “peptides”) can be used as enantioselective catalysts for 1,2-addition to  $\alpha$ -ketoesters
- Chiral palladium catalysts can be used for the enantioselective construction of  $\alpha$ -tertiary hydroxycarbonyls
- $\alpha$ -tertiary hydroxycarbonyls can be very useful building blocks in organic synthesis
  - Aziridines
  - $\beta$ -lactams
  - Disubstituted amino acids
  - Natural products and biologically active compounds

# Leading References

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