

# Enantioselective Organocatalysis (I): Organic Bases

- I. Introduction
- II. Nucleophilic Additions to C=O
  - IIa. Hydrocyanation
  - IIb. Aldol reactions
  - IIc. Morita-Baylis-Hillman reaction
  - IId. Allylation reactions
  - IIE. Epoxidation of aldehydes
  - IIf. Benzoin condensation
- III. Nucleophilic Additions to C=N
  - IIIa. Strecker reaction
  - IIIb. Mannich condensation
  - IIIc. Aziridination reactions
  - IIId. Synthesis of  $\beta$ -lactams
- IV. Additions to Alkenes
  - IVa. Michael addition
  - IVb. Epoxidation reactions
- V. Cycloaddition reactions
  - Va. Diels-Alder
  - Vb. Hetero Diels-Alder
  - Vc. 1,3-Dipolar cycloadditions
- VI.  $\alpha$ -Functionalization of Carbonyl Compounds
  - VIa. Oxygenation
  - VIb. Amination
  - VIc. Halogenation
  - VId. Sulfonylation

# Enantioselective Organocatalysis (I): Organic Bases

## I. Introduction

### ADVANTAGES:

1. Reactions can be performed under aerobic atmosphere and wet solvents
2. Catalysts are inexpensive
3. Recovery is more simple than metal-based or bioorganic catalysts
4. More stable than metal-based or bioorganic analogous
5. They can be anchored to a solid support and reused

### STEREOSELECTIVITY:

Well-organized transition state by passive or dynamic binding

- passive binding: hydrophobic, van der Waals and electrostatic interactions
- dynamic binding: interaction between catalyst and substrate at the reaction center

Hydrogen bonding

# Enantioselective Organocatalysis (I): Organic Bases

## I. Introduction

### MECHANISMS:

#### 1. Phase-transfer reactions:

- The chiral catalyst forms a host-guest complex with the substrate
- The catalyst does not require parallel regeneration

#### 2. Activation of the reaction based on nucleophilic/electrophilic properties of the catalyst:

- The chiral catalyst is not consumed in the reaction
- The catalyst does not require parallel regeneration

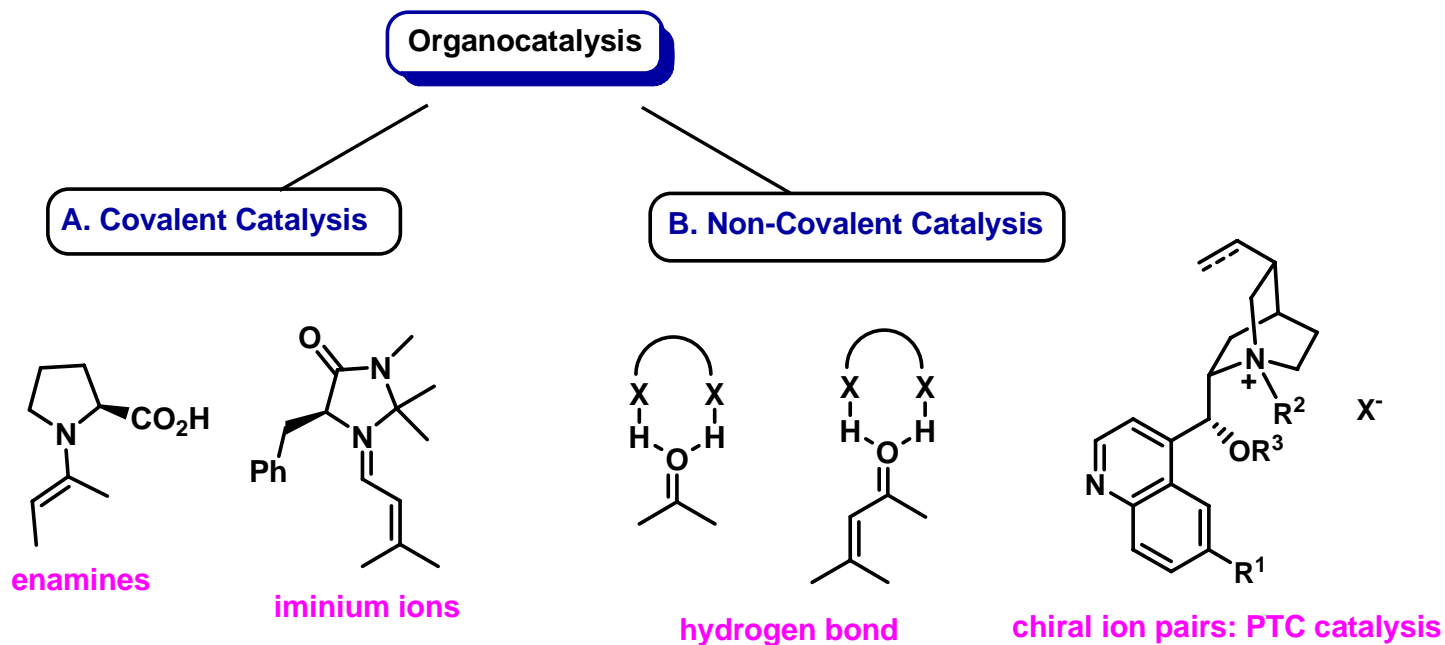
#### 3. Organic molecules form reactive intermediates:

- The chiral catalyst is consumed
- The catalyst requires regeneration in a parallel catalytic cycle

#### 4. Molecular-cavity-accelerated asymmetric transformations

# Enantioselective Organocatalysis (I): Organic Bases

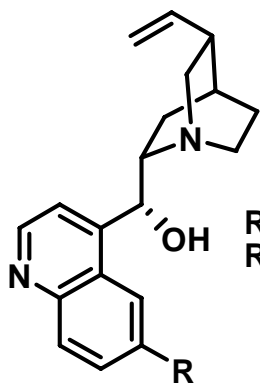
## I. Introduction



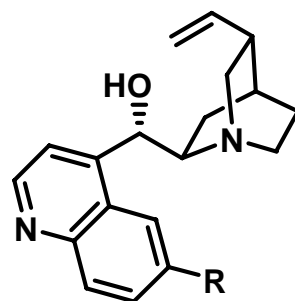
# Enantioselective Organocatalysis (I): Organic Bases

## I. Introduction: catalysts

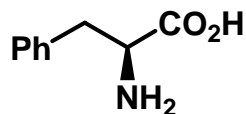
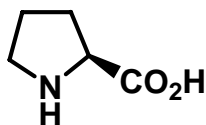
### Natural products



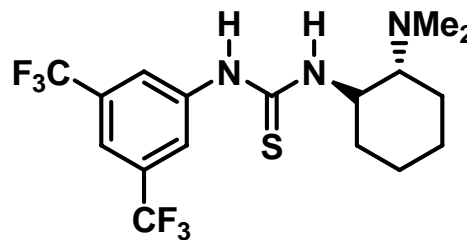
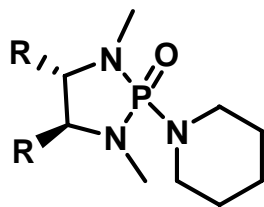
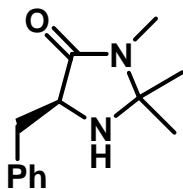
R = H; cinchonidine  
R = OMe; quinine



R = H; cinchonine  
R = OMe; quinidine



### Synthetic molecules



# Enantioselective Organocatalysis (I): Organic Bases

## II. Nucleophilic Additions to C=O

IIa. Hydrocyanation

IIb. Aldol reactions

IIc. Morita-Baylis-Hillman reaction

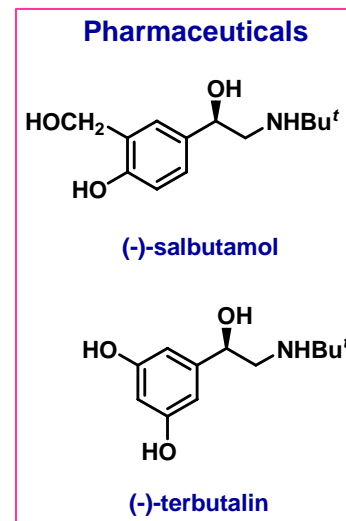
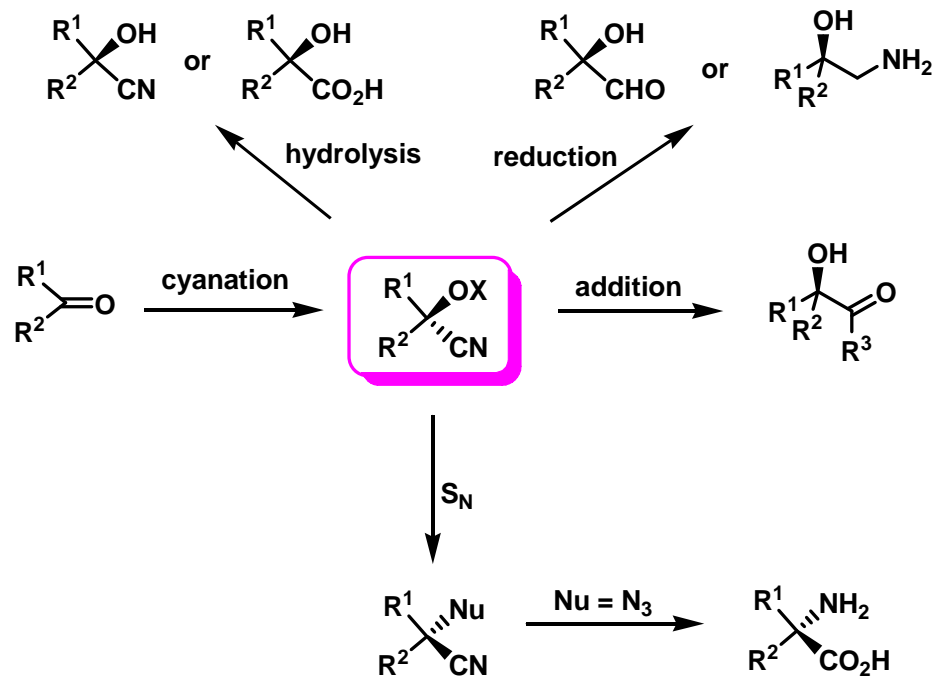
IId. Allylation reactions

IIe. Epoxidation of aldehydes

IIf. Benzoin condensation

# Enantioselective Organocatalysis (I): Organic Bases

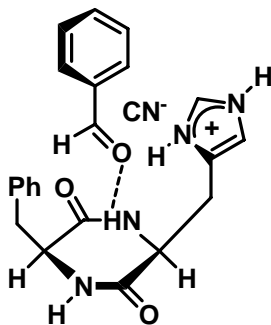
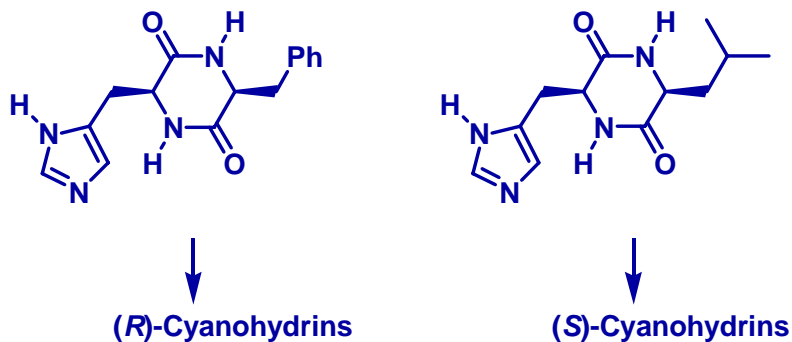
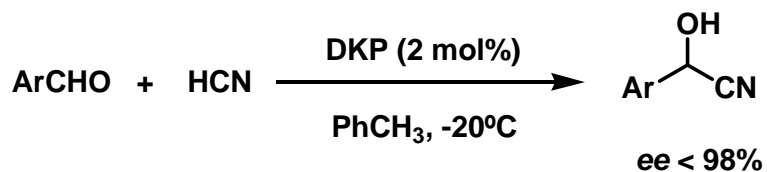
## Ia. Nucleophilic Additions to C=O: Hydrocyanation



J.-M. Brunel, I. P. Holmes, *Angew. Chem. Int. Ed.* **2004**, *43*, 2752  
M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147  
R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649

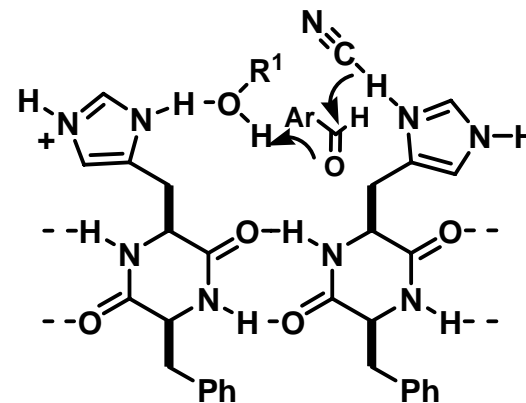
# Enantioselective Organocatalysis (I): Organic Bases

## Ila. Nucleophilic Additions to C=O: Hydrocyanation



Aromatic aldehydes only!

Ar	Ph	3-MeOC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>
Phe	97% ( <i>R</i> )	97% ( <i>R</i> )	96% ( <i>R</i> )
Leu	55% ( <i>S</i> )	56% ( <i>S</i> )	60% ( <i>S</i> )

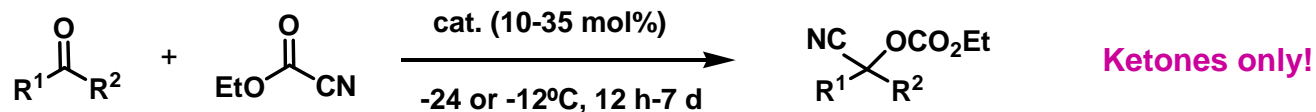


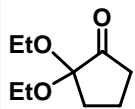
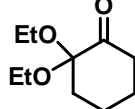
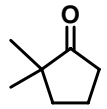
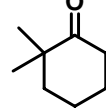
J. Oku, S. Inoue, *J. Chem. Soc., Chem. Commun.* **1981**, 229

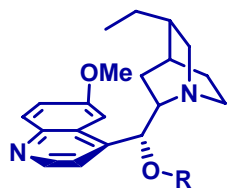
W. Hua et al., *Tetrahedron: Asymmetry* **1999**, *10*, 4715  
M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147

# Enantioselective Organocatalysis (I): Organic Bases

## Ila. Nucleophilic Additions to C=O: Hydrocyanation



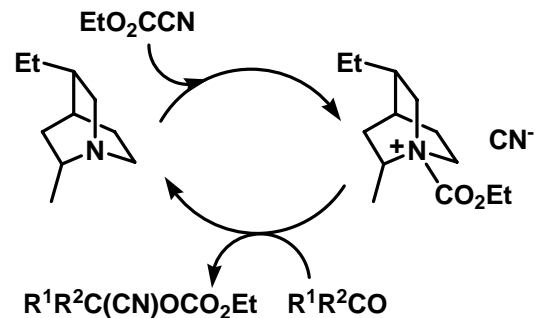
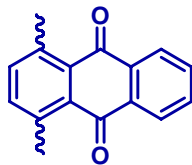
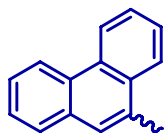
	DHQN (R = 9-phenantryl): 99% 94% ee ( <i>R</i> ) DHQD (R = 9-phenantryl): 80% 95% ee ( <i>S</i> )		DHQN (R = 9-phenantryl): 78% 96% ee ( <i>R</i> )
	DHQN (R = anthraquinone): 66% 97% ee ( <i>R</i> ) DHQD (R = anthraquinone): 76% 95% ee ( <i>S</i> )		DHQN (R = anthraquinone): 62% 91% ee ( <i>R</i> ) DHQD (R = anthraquinone): 53% 92% ee ( <i>S</i> )



DHQN

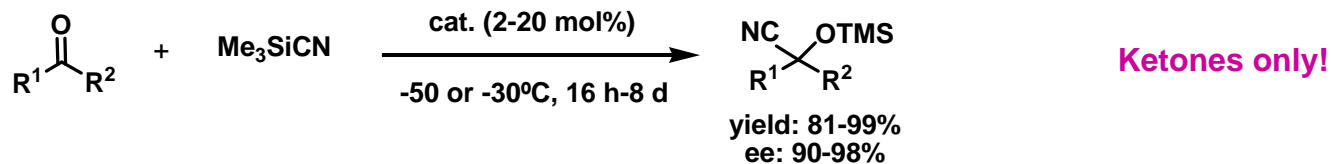


DHQD



# Enantioselective Organocatalysis (I): Organic Bases

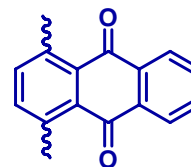
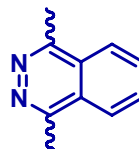
## Ila. Nucleophilic Additions to C=O: Hydrocyanation



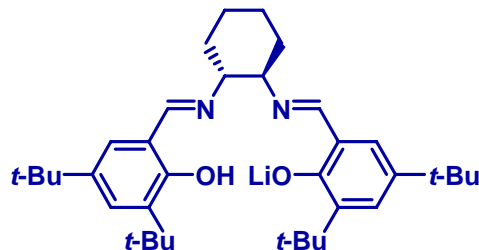
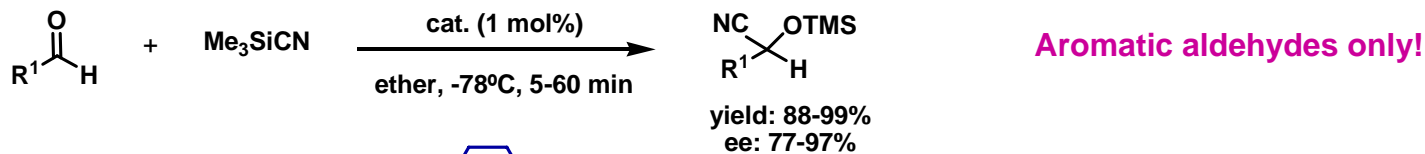
DHQN



DHQD



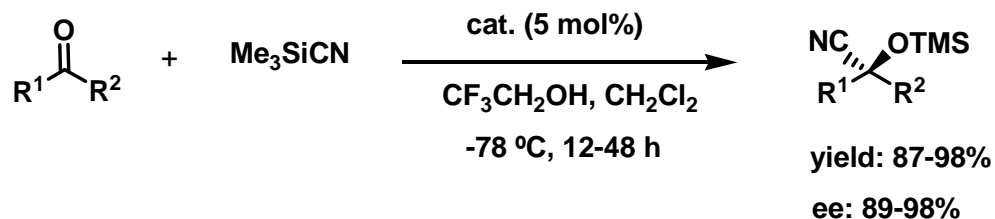
Deng et al. *J. Am. Chem. Soc.* **2003**, *125*, 9900



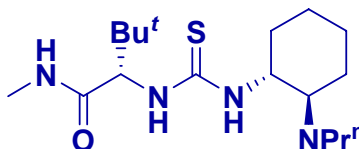
Kagan et al. *Tetrahedron Lett.* **2000**, *41*, 7453

# Enantioselective Organocatalysis (I): Organic Bases

## Ila. Nucleophilic Additions to C=O: Hydrocyanation



Aldehydes and Ketones



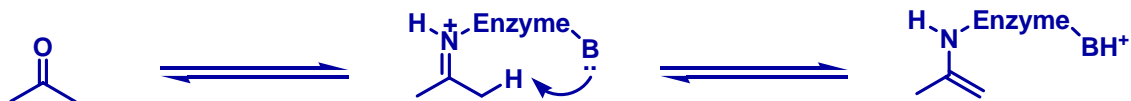
No proposal about a possible mechanism  
Catalyst recovery by column chromatography

Jacobsen et al. *J. Am. Chem. Soc.* **2005**, *127*, 8964

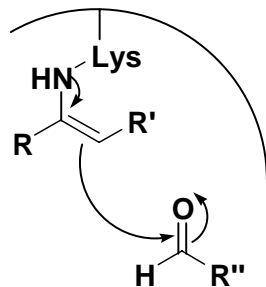
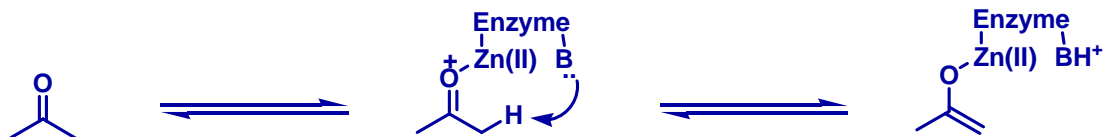
# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

Class I  
Aldolases



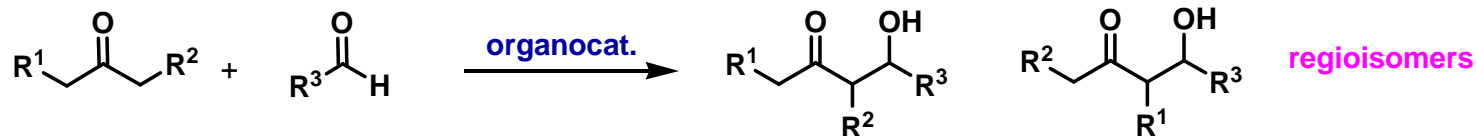
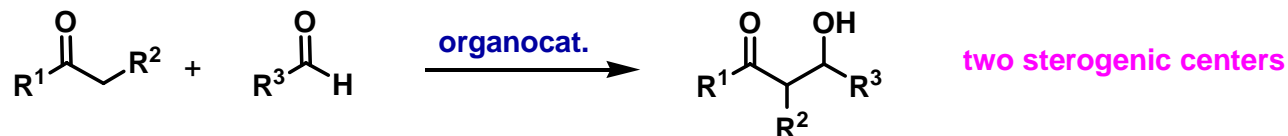
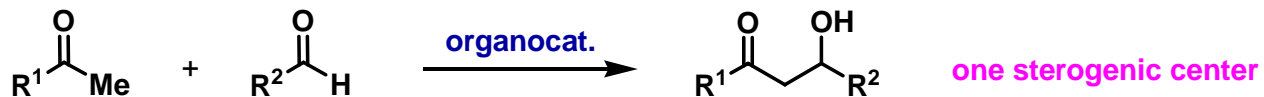
Class II  
Aldolases



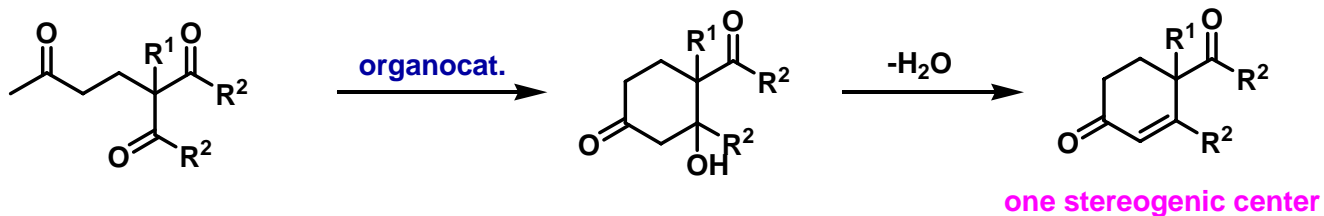
# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intermolecular direct aldol reaction



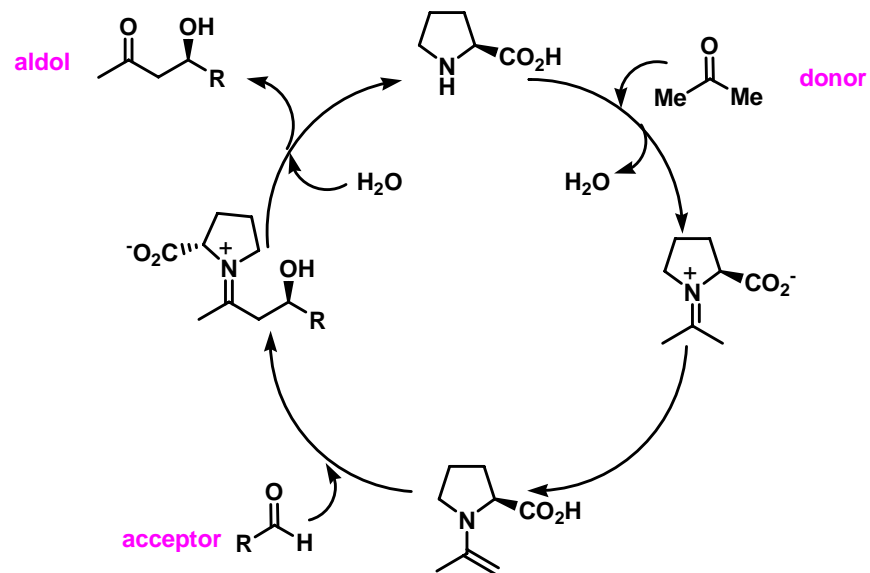
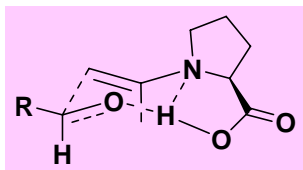
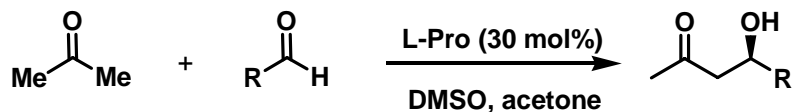
### Intramolecular direct aldol reaction



# Enantioselective Organocatalysis (I): Organic Bases

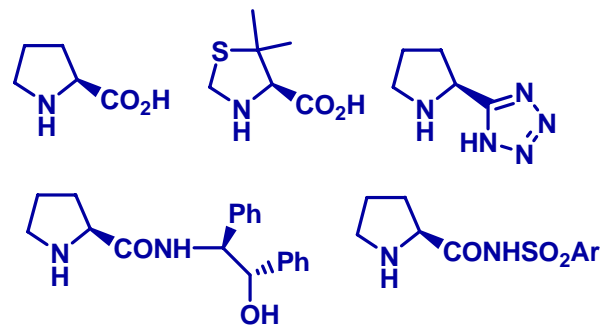
## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intermolecular direct aldol reaction



### Reaction conditions and substrates

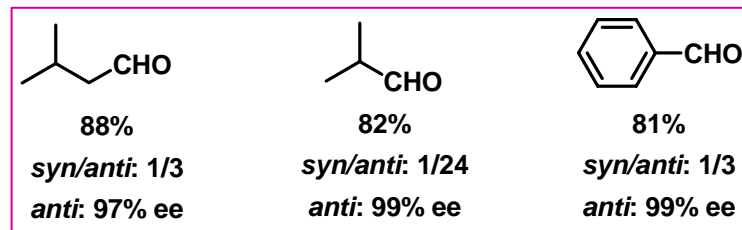
- Aromatic aldehydes: 60-70% ee
- Cyclohexanecarboxaldehyde, isobutiraldehyde: 96% ee (low yields)
- Tertiary aldehydes: 99% ee
- The presence of water accelerates the reaction
- Ketones: butanone, pentan-2-one, cycloalkanones,  $\alpha$ -hydroxyacetone (no reaction: acetophenone, pentan-3-one)



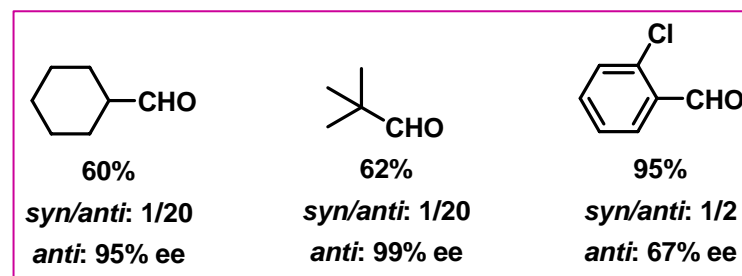
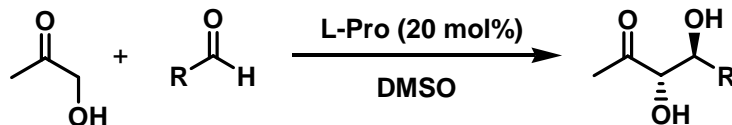
# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

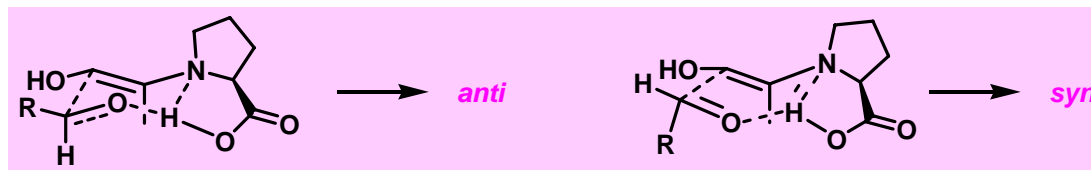
### Intermolecular direct aldol reaction



List et al. *Org. Lett.* **2001**, *3*, 573



Barbas III et al. *J. Am. Chem. Soc.* **2001**, *123*, 5260

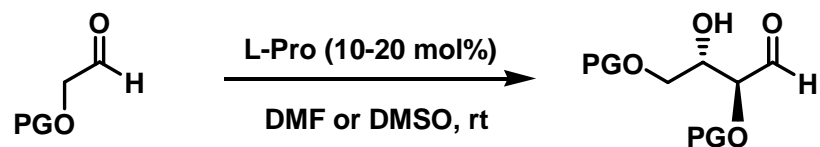


Barbas III et al. *J. Am. Chem. Soc.* **2001**, *123*, 5260  
Houk, List et al. *J. Am. Chem. Soc.* **2003**, *125*, 2475

# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

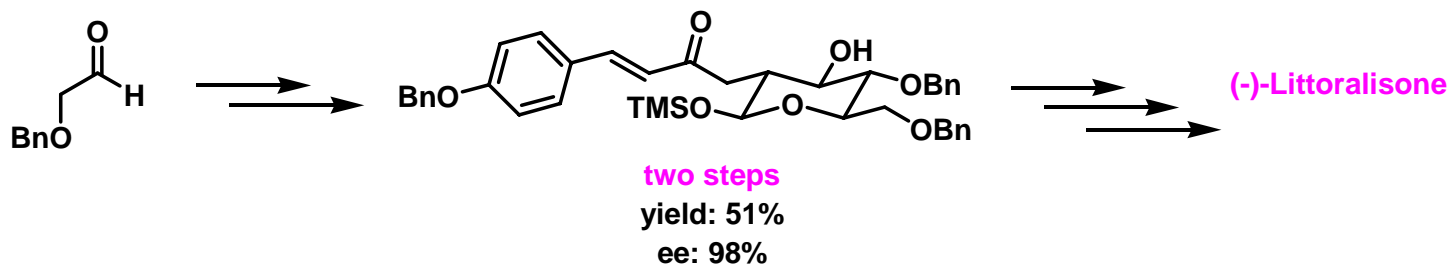
### Intermolecular aldol reaction



(PG = Bn, PMB, MOM, TBDPS, TBS)

yield: 42-92%  
anti/syn: 3/1-9/1  
ee: 88-98%

D. W. C. MacMillan, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152; *Science* **2004**, *305*, 1752

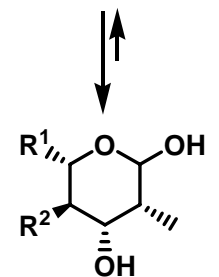
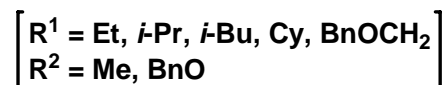
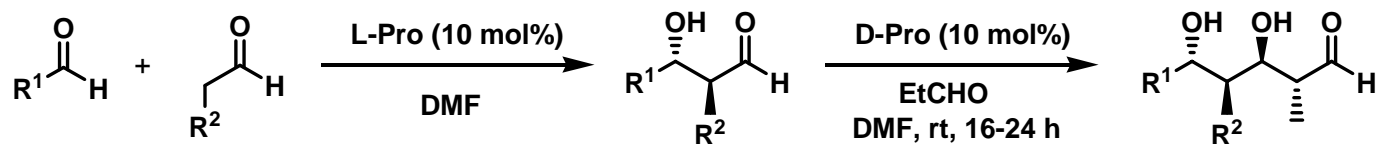


D. W. C. MacMillan, et al. *J. Am. Chem. Soc.* **2005**, *127*, 3696

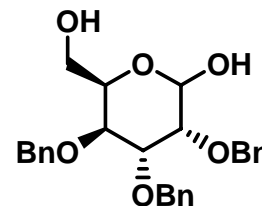
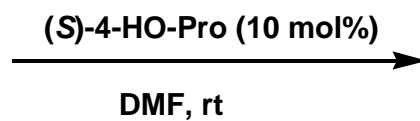
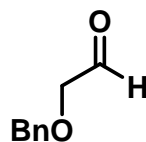
# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intermolecular twofold iterative aldol reaction



yield: 24-40%  
ee: >99%



yield: 28%  
ee: >99%

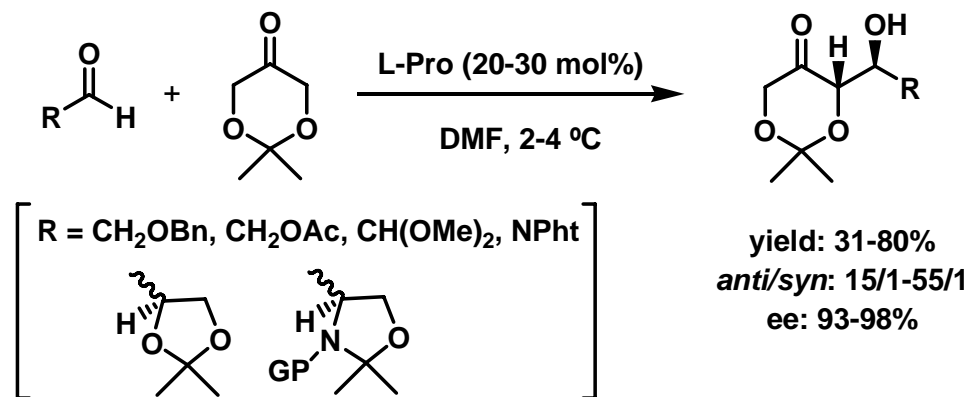
Allose

A. Córdova, et al. *Angew. Chem. Int. Ed.* **2005**, *43*, 1343

# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

Intermolecular aldol reaction: imitating nature



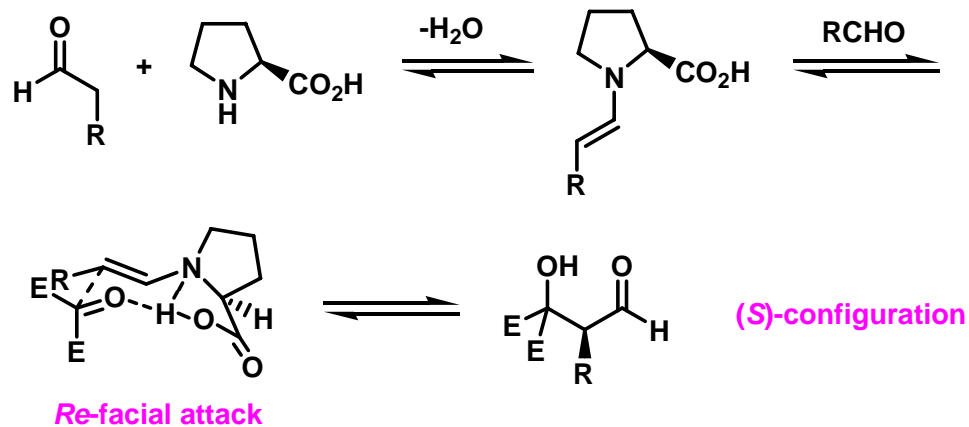
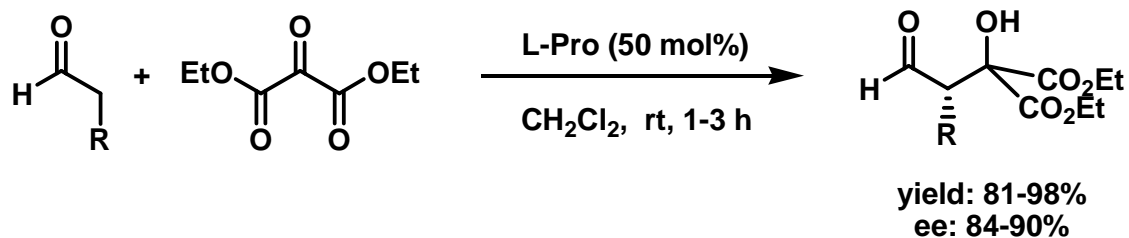
L-ribulose, L- and D-psicose, D-tagatose, 1-amino-1-deoxy-D-lyxitol

C. F. Barbas III et al. *Chem. Commun.* **2002**, 3024  
D. Enders et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210

# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

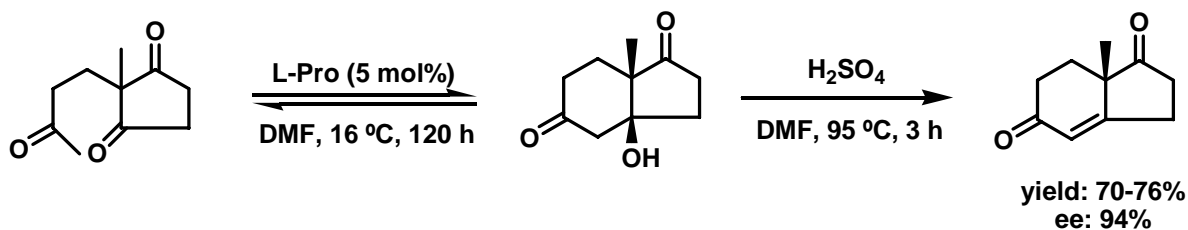
### Intermolecular direct aldol reaction: donor aldehyde



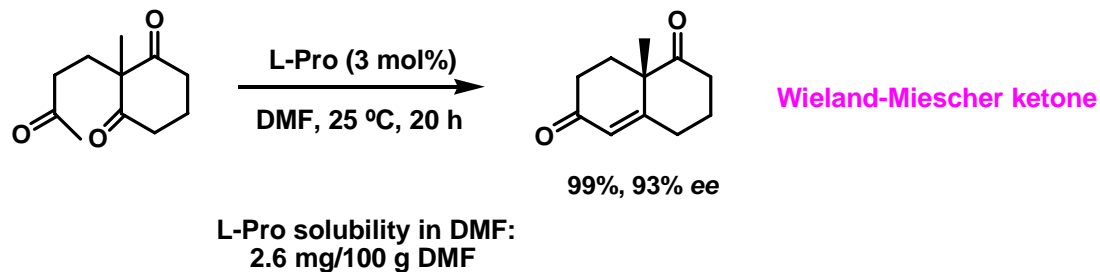
# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intramolecular direct aldol reaction: Hajos-Parrish-Eder-Sauer-Wiechert reaction



U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496

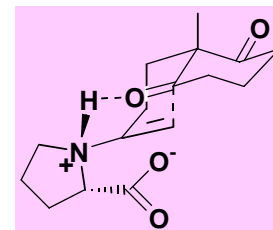
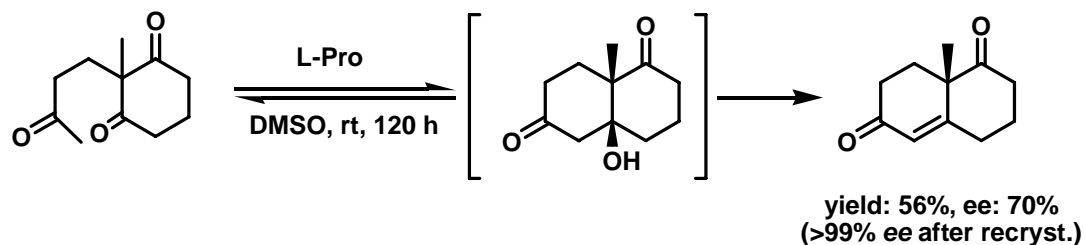


Hajos, Parrish et al. *J. Org. Chem.* **1974**, *39*, 1615

# Enantioselective Organocatalysis (I): Organic Bases

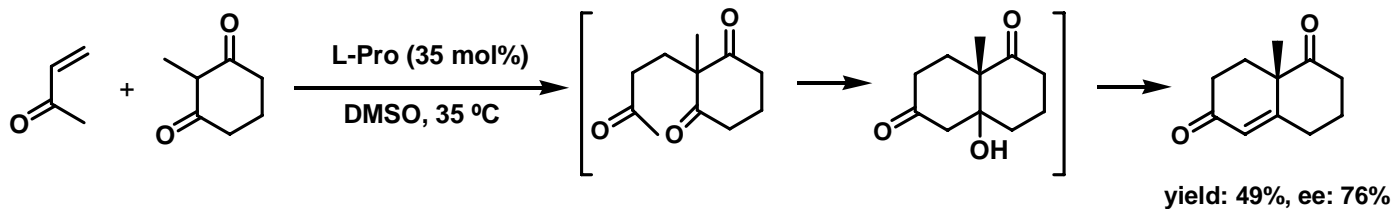
## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intramolecular direct aldol reaction: Hajos-Parrish-Eder-Sauer-Wiechert reaction



S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975;  
P. Buchschacher et al., *OS*, Vol. VI, 368

### One-step reaction!

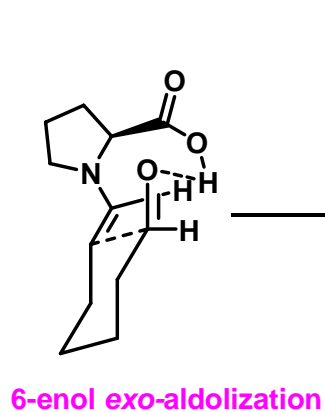
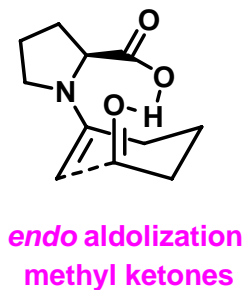
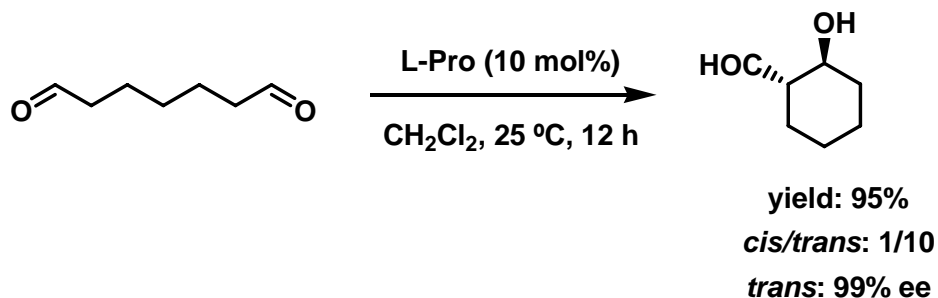


Barbas III et al. *Tetrahedron Lett.* **2000**, *41*, 6951

# Enantioselective Organocatalysis (I): Organic Bases

## IIb. Nucleophilic Additions to C=O: Aldol reactions

### Intramolecular direct aldol reaction: dialdehydes

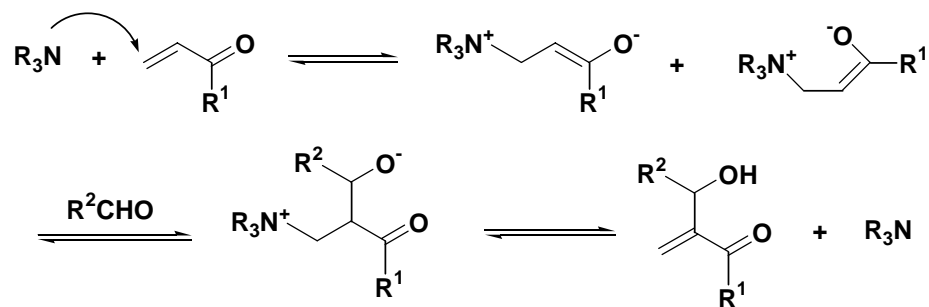


# Enantioselective Organocatalysis (I): Organic Bases

## IIc. Nucleophilic Additions to C=O: Morita-Baylis-Hillman reaction



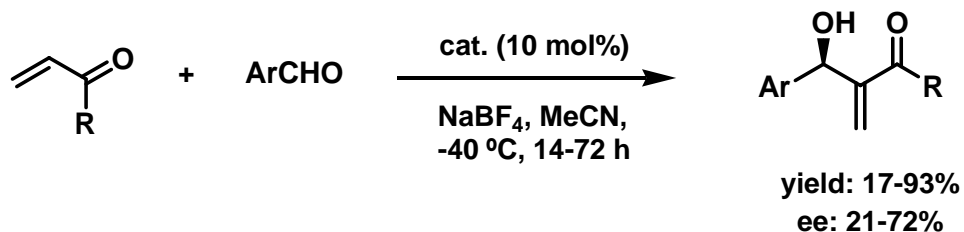
### Mechanism



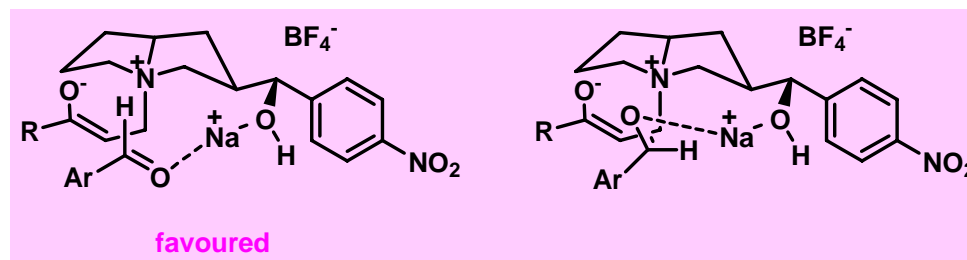
P. Langer, *Angew. Chem. Int. Ed.*, **2000**, 39, 3049

# Enantioselective Organocatalysis (I): Organic Bases

## IIc. Nucleophilic Additions to C=O: Morita-Baylis-Hillman reaction



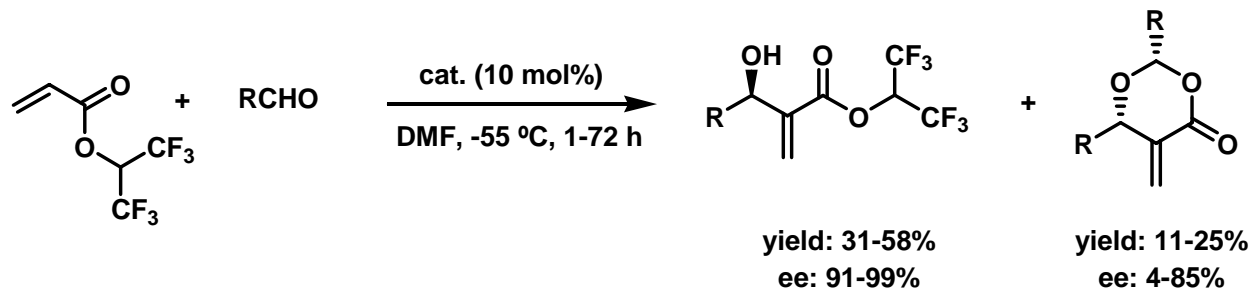
Catalyst



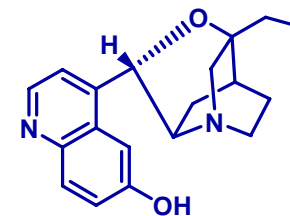
A. G. M. Barrett *et al.*, *Chem. Commun.* **1998**, 2533

# Enantioselective Organocatalysis (I): Organic Bases

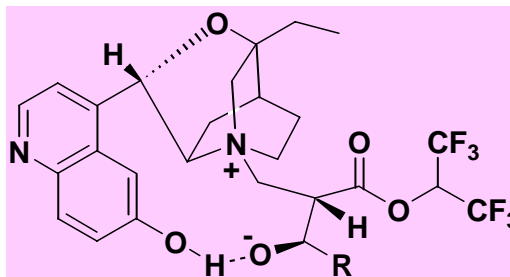
## IIc. Nucleophilic Additions to C=O: Morita-Baylis-Hillman reaction



Aliphatic and aromatic  
aldehydes



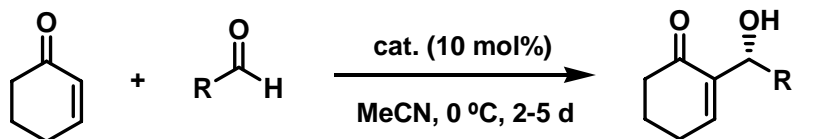
Catalyst



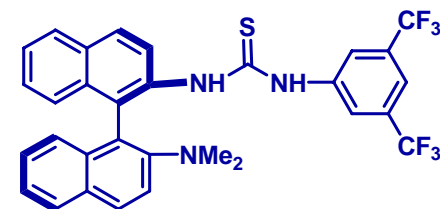
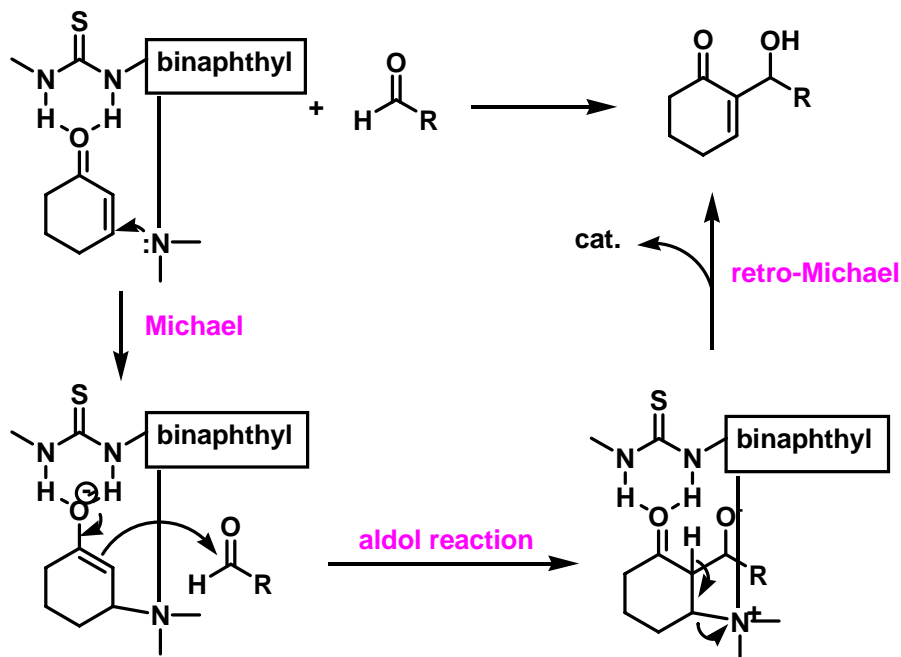
S. Hatakeyama *et al.*, *J. Am. Chem. Soc.* **1999**, *121*, 10219

# Enantioselective Organocatalysis (I): Organic Bases

## IIc. Nucleophilic Additions to C=O: Morita-Baylis-Hillman reaction



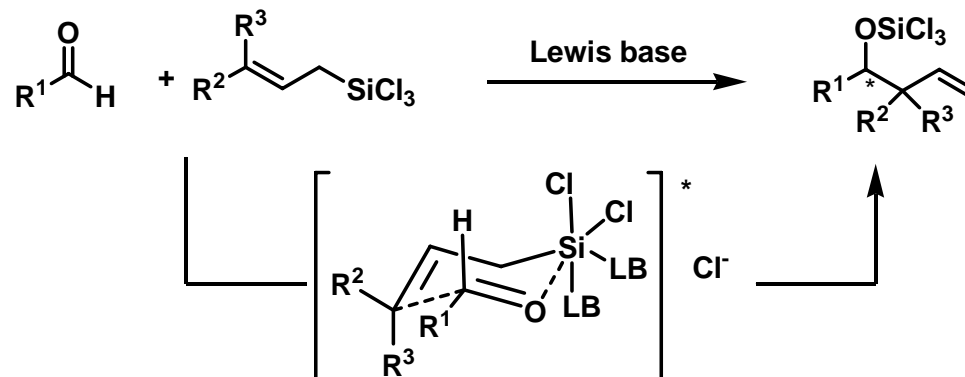
yield: 55-84%  
ee: 60-94%



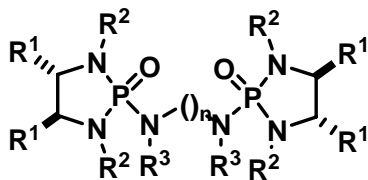
Bifunctional catalyst

# Enantioselective Organocatalysis (I): Organic Bases

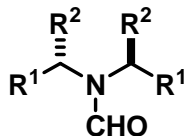
## IId. Nucleophilic Additions to C=O: allylation reactions



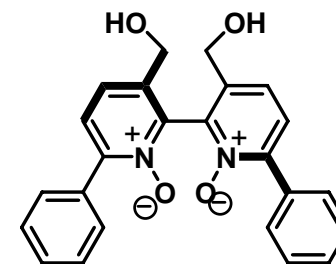
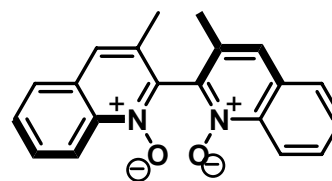
Phosphoramides



Formamides



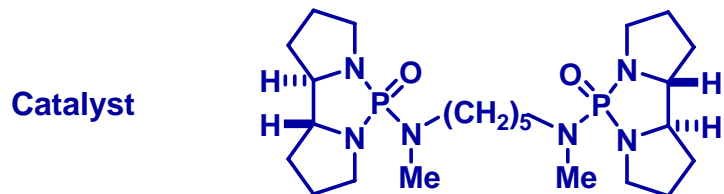
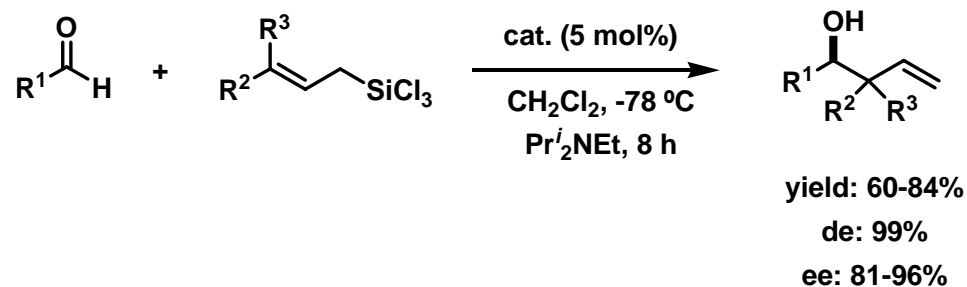
Amine N-Oxides



# Enantioselective Organocatalysis (I): Organic Bases

## IId. Nucleophilic Additions to C=O: allylation reactions

### Phosphoramidates



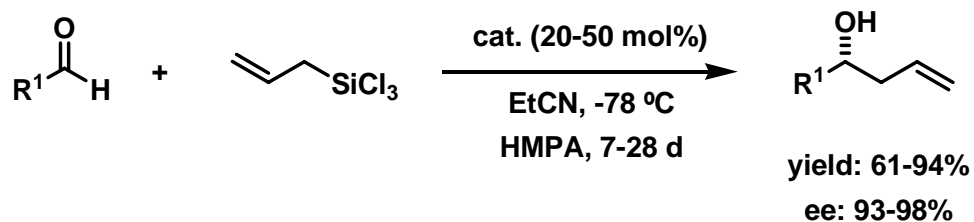
*E*-allylsilanes  $\Rightarrow$  *syn/anti*: 1/99

*Z*-allylsilanes  $\Rightarrow$  *syn/anti*: 99/1

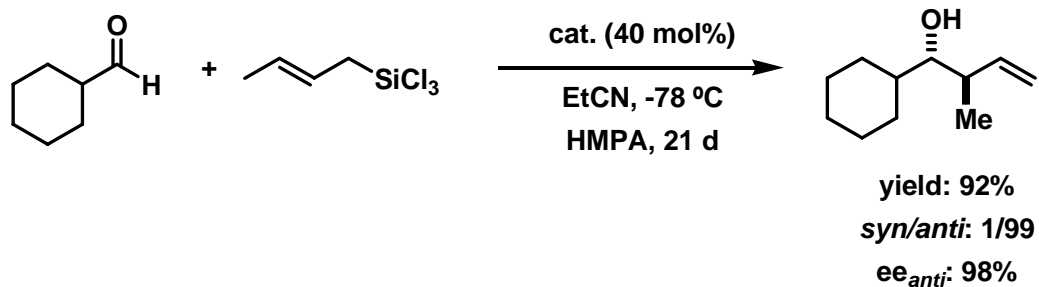
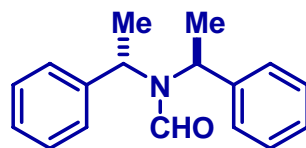
# Enantioselective Organocatalysis (I): Organic Bases

## IId. Nucleophilic Additions to C=O: allylation reactions

### Formamides



### Catalyst

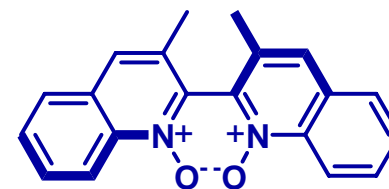
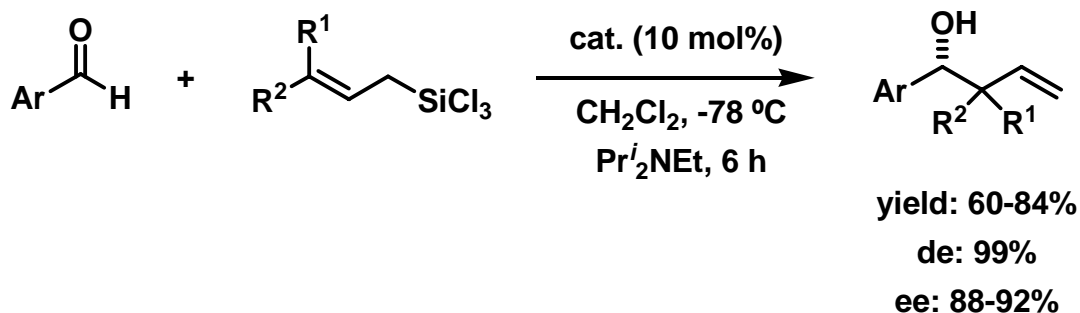


Y. Kobayashi et al., *Tetrahedron Lett.* **1998**, 39, 2767

# Enantioselective Organocatalysis (I): Organic Bases

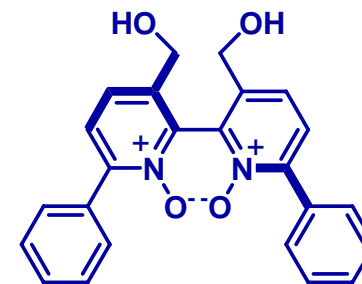
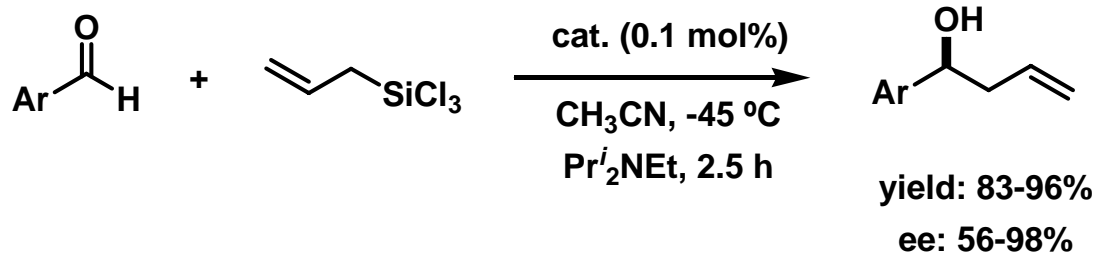
## IId. Nucleophilic Additions to C=O: allylation reactions

### Amine N-oxides



Catalyst

Nakajima et al., *J. Am. Chem. Soc.* **1998**, *120*, 6419

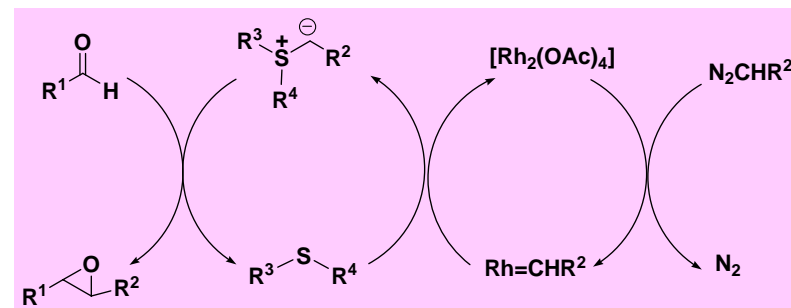
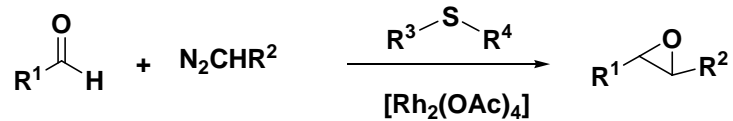
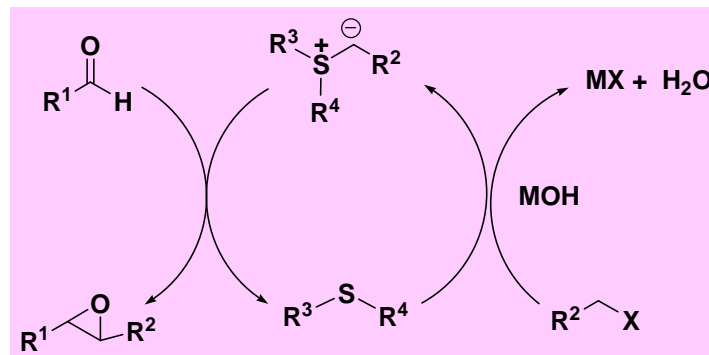
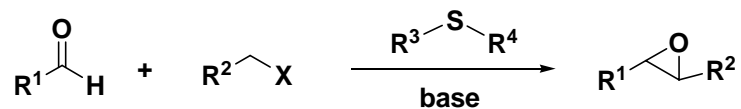


Catalyst

T. Hayashi et al., *Org. Lett.* **2002**, *4*, 2799

# Enantioselective Organocatalysis (I): Organic Bases

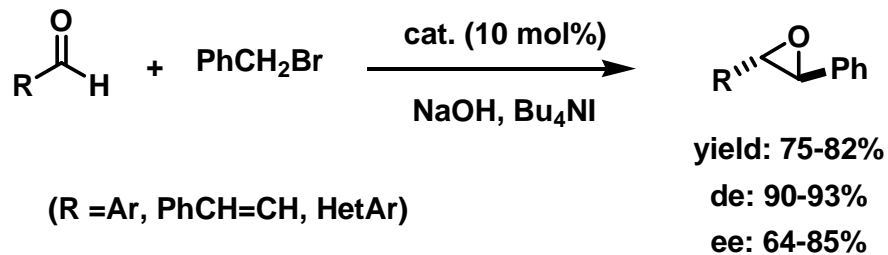
## Ile. Nucleophilic Additions to C=O: epoxidation of aldehydes



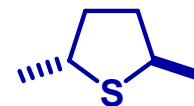
# Enantioselective Organocatalysis (I): Organic Bases

## Ile. Nucleophilic Additions to C=O: epoxidation of aldehydes

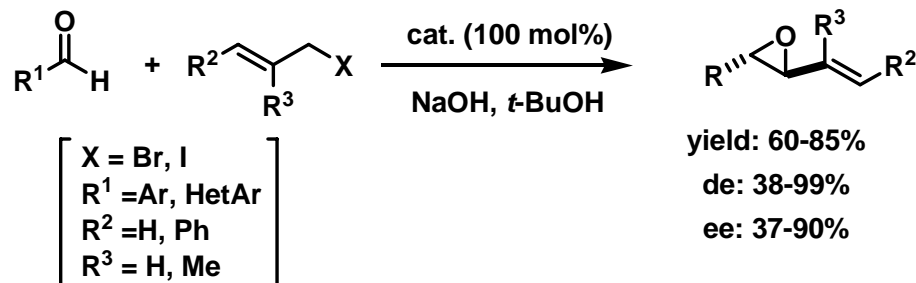
### Sulfur ylides



P. Metzner et al., *J. Chem. Soc., Perkin Trans I.* **1999**, 731; *J. Org. Chem.* **2001**, 66, 5620



Catalyst

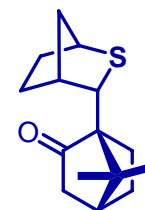
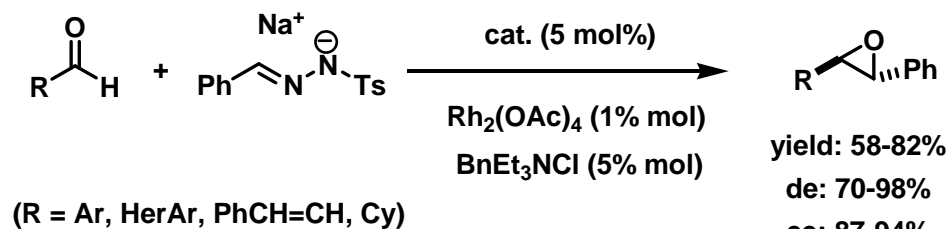


P. Metzner et al., *J. Org. Chem.* **2002**, 67, 9083

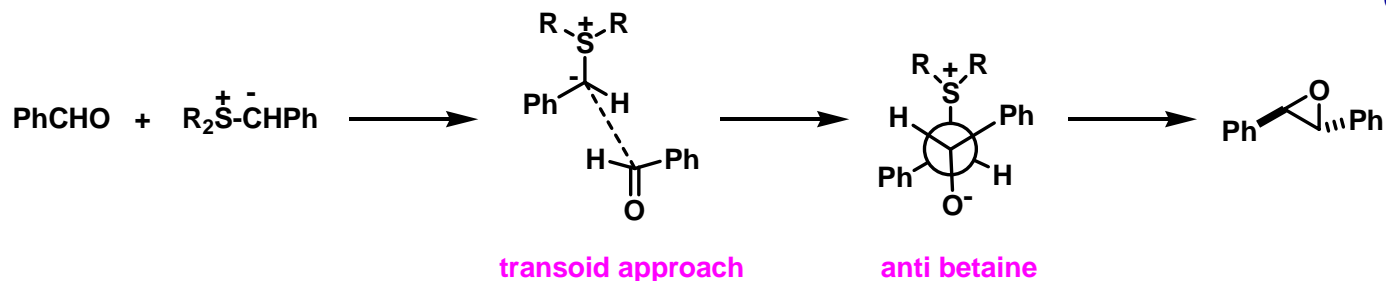
# Enantioselective Organocatalysis (I): Organic Bases

## Ile. Nucleophilic Additions to C=O: epoxidation of aldehydes

### Sulfur ylides



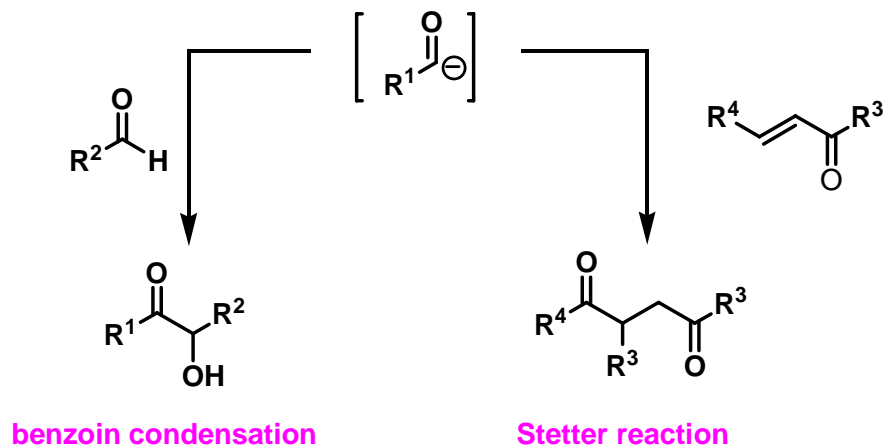
Catalyst



V. Aggarwal et al., *Angew. Chem.Int. Ed.* **2001**, *40*, 1430

# Enantioselective Organocatalysis (I): Organic Bases

## IIf. Nucleophilic Additions to C=O: benzoin condensation and Stetter reaction



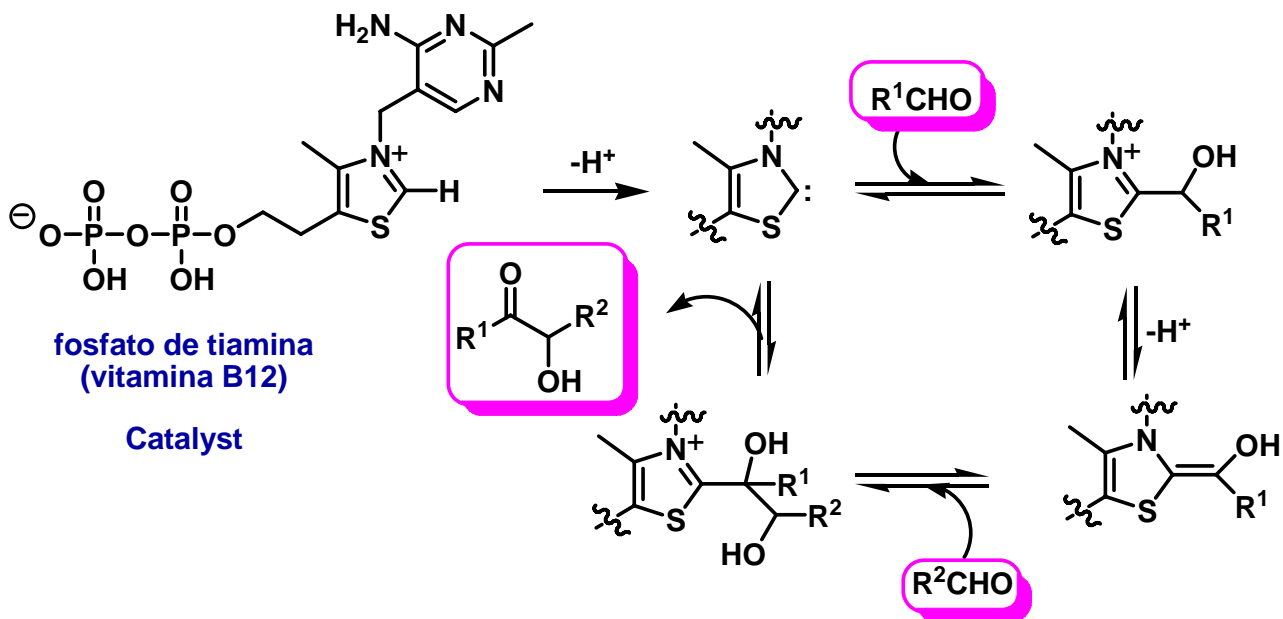
- In nature this umpolung is performed enzymatically by the cofactor thiamine pyrophosphate (vit. B12)
- Reactions catalyzed by chiral thiazolium systems
- Carbenes as catalytic species generated from heterocyclic systems

W. S. Ide, J. S. Buck, *Org. React.* **1948**, 4, 269  
H. Stetter, H. Kuhlmann, *Org. React.* **1991**, 40, 407

# Enantioselective Organocatalysis (I): Organic Bases

## II. Nucleophilic Additions to C=O: benzoin condensation and Stetter reaction

### Benzoin condensation

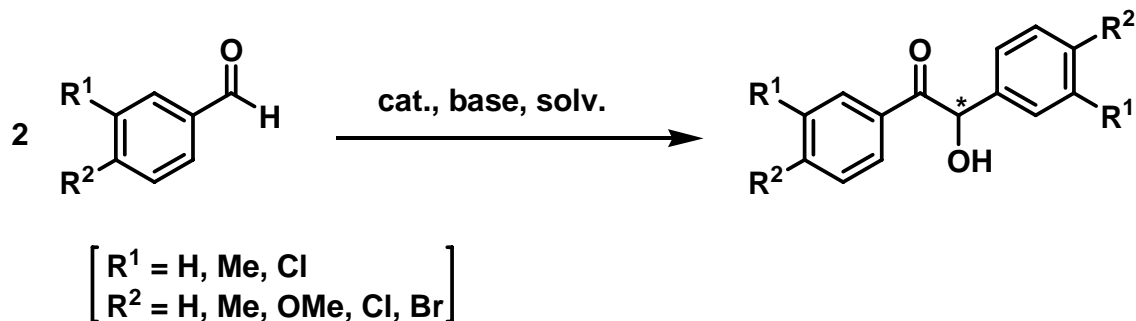


R. Breslow, *J. Am. Chem. Soc.* **1958**, 80, 3719

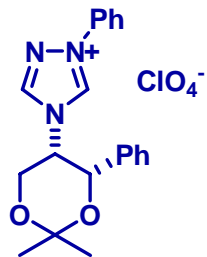
# Enantioselective Organocatalysis (I): Organic Bases

## IIf. Nucleophilic Additions to C=O: benzoin condensation and Stetter reaction

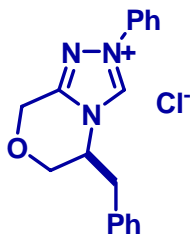
### Benzoin condensation



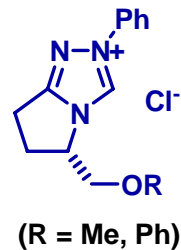
### Catalysts



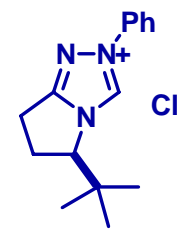
1.25 mol%  
K<sub>2</sub>CO<sub>3</sub> (0.6 mol%)  
THF  
yield: 22-66%  
ee: 20-75%



10-30 mol%  
Et<sub>3</sub>N (5-30 mol%)  
MeOH  
yield: 11-45%  
ee: 70-80%



10 mol%  
Et<sub>3</sub>N (5-30 mol%)  
MeOH  
yield: 12-38%  
ee: 48-65%

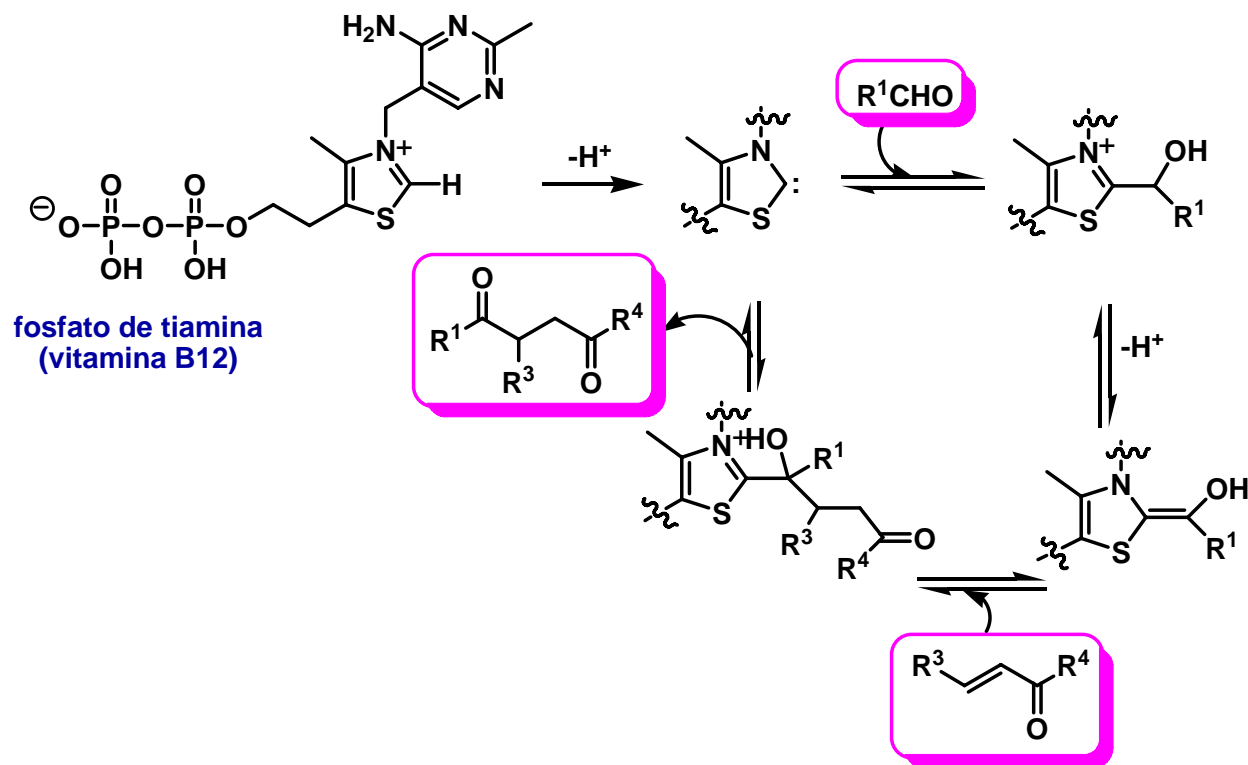


10-30 mol%  
Bu<sup>t</sup>OK (10 mol%)  
THF  
yield: 11-81%  
ee: 83-91%

# Enantioselective Organocatalysis (I): Organic Bases

## IIf. Nucleophilic Additions to C=O: benzoin condensation and Stetter reaction

### Stetter reaction

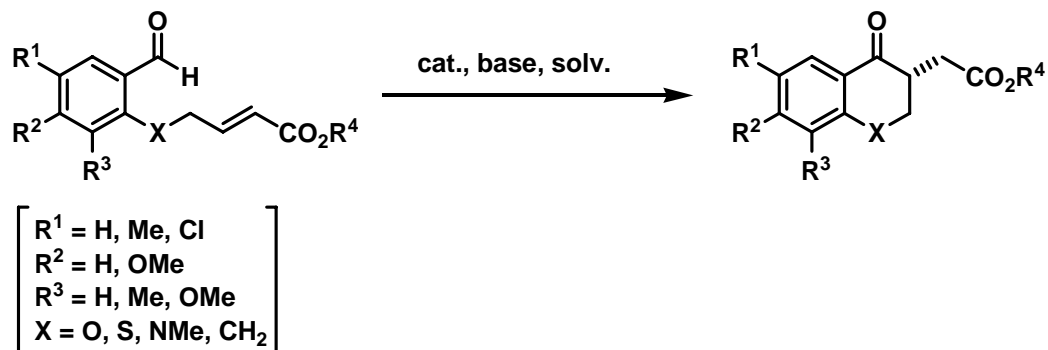


R. Breslow, *J. Am. Chem. Soc.* **1958**, 80, 3719

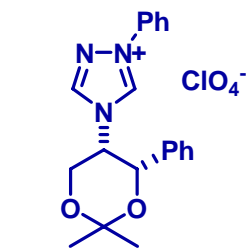
# Enantioselective Organocatalysis (I): Organic Bases

## II. Nucleophilic Additions to C=O: benzoin condensation and Stetter reaction

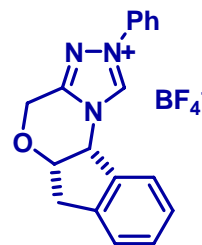
### Stetter reaction



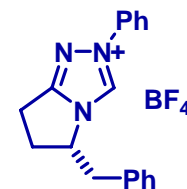
### Catalysts



20 mol%  
 $\text{K}_2\text{CO}_3$  (10 mol%)  
THF  
yield: 22-69%  
ee: 56-74%



20 mol%  
KHMDS  
xylene  
yield: 35-95%  
ee: 82-97%



20 mol%  
KHMDS  
xylene  
yield: 90%  
ee: 92%

# Enantioselective Organocatalysis (I): Organic Bases

## III. Nucleophilic Additions to C=N

IIIa. Strecker reaction

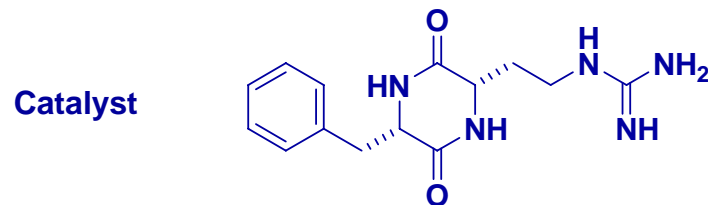
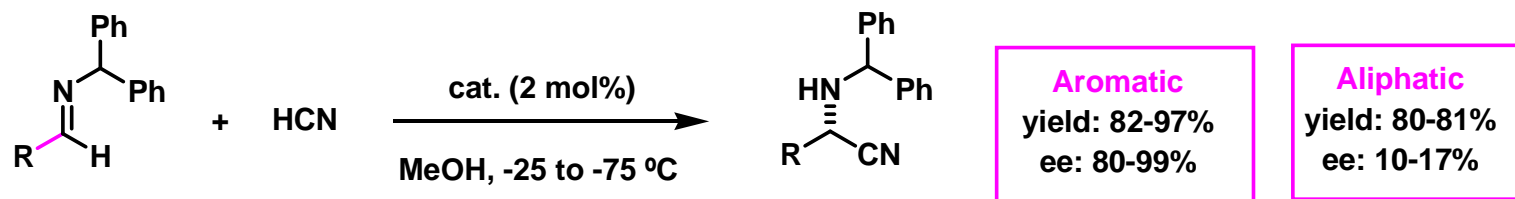
IIIb. Mannich condensation

IIIc. Aziridination reactions

IIId. Synthesis of  $\beta$ -lactams

# Enantioselective Organocatalysis (I): Organic Bases

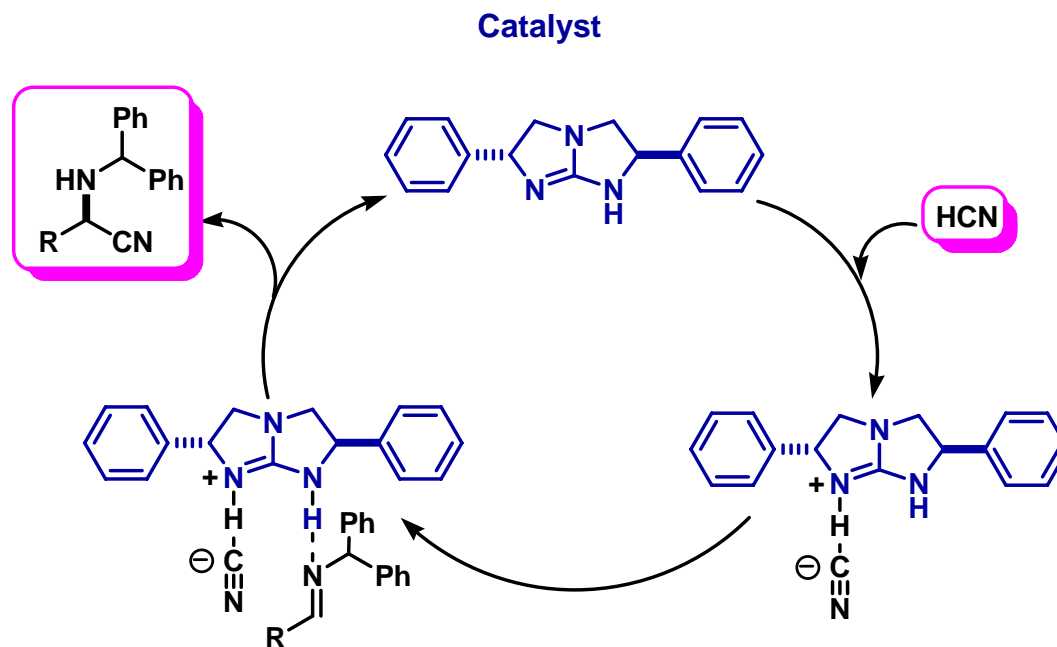
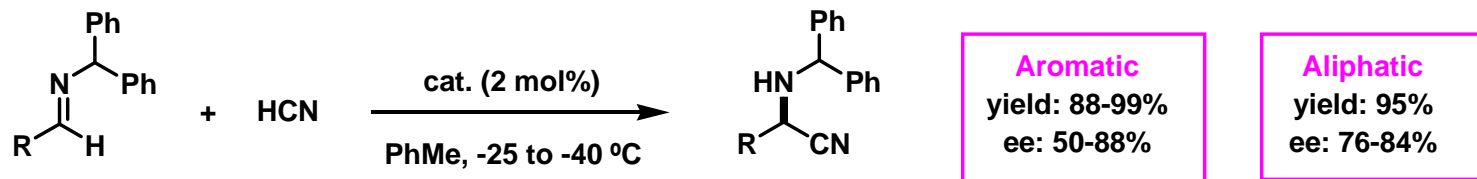
## IIIa. Nucleophilic Additions to C=N: Strecker reaction



M. Lipton et al., *J. Am. Chem. Soc.* **1996**, *118*, 4910

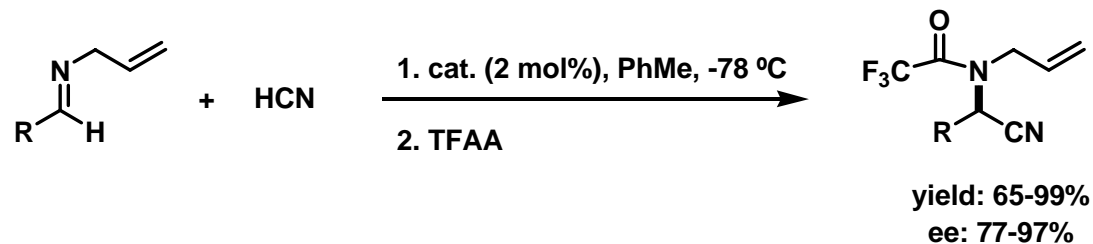
# Enantioselective Organocatalysis (I): Organic Bases

## IIIa. Nucleophilic Additions to C=N: Strecker reaction

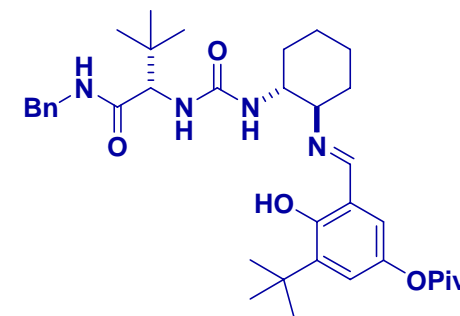


# Enantioselective Organocatalysis (I): Organic Bases

## IIIa. Nucleophilic Additions to C=N: Strecker reaction

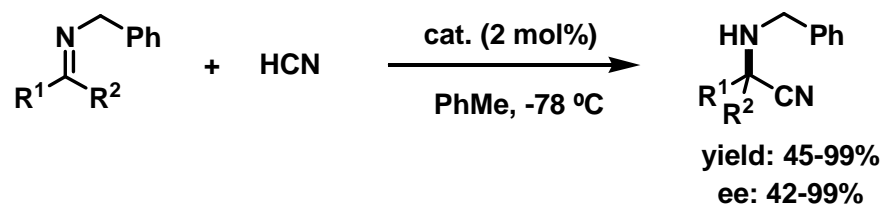


Aliphatic and aromatic aldimines

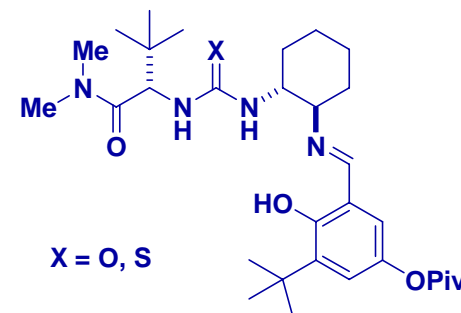


Catalyst

E. N. Jacobsen et al., *Angew. Chem. Int. Ed.* **2000**, *39*, 1279



Aliphatic and aromatic aldimines and ketimines

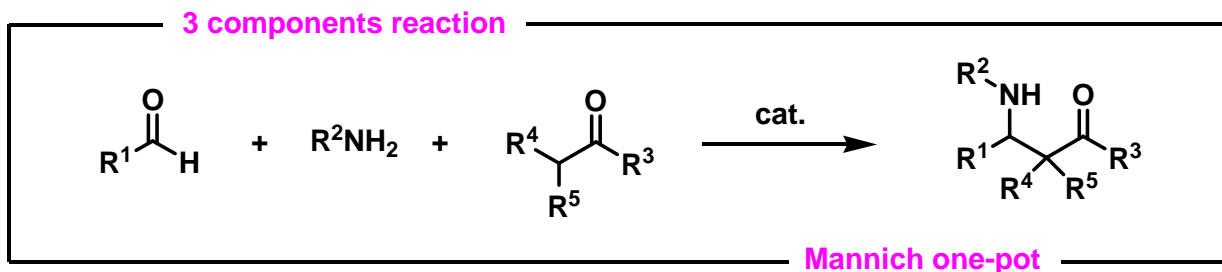


Catalysts

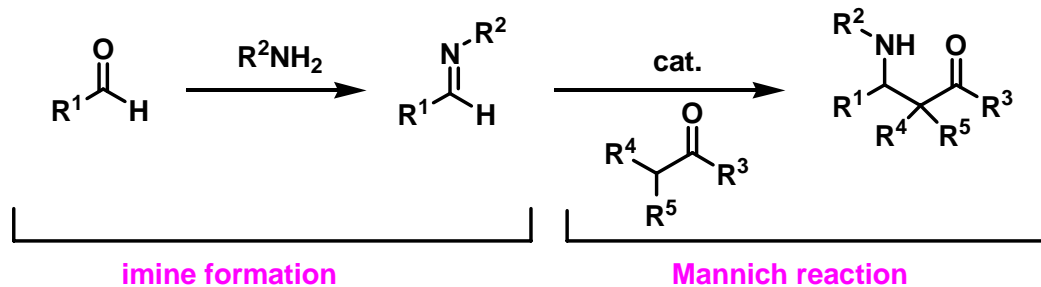
E. N. Jacobsen et al., *J. Am. Chem. Soc.* **2002**, *124*, 10012

# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

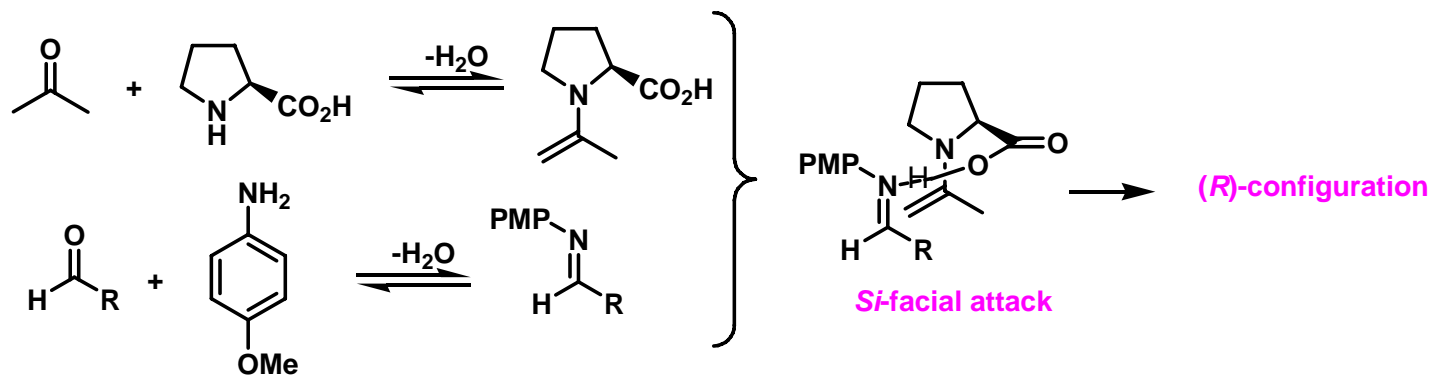
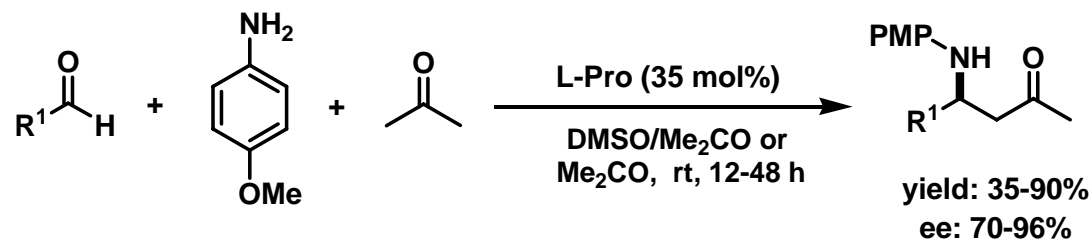


- Synthesis of β-aminocarbonyl compounds
- Proline as catalyst
- Non modified ketones (enolates, enol ethers...)



# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

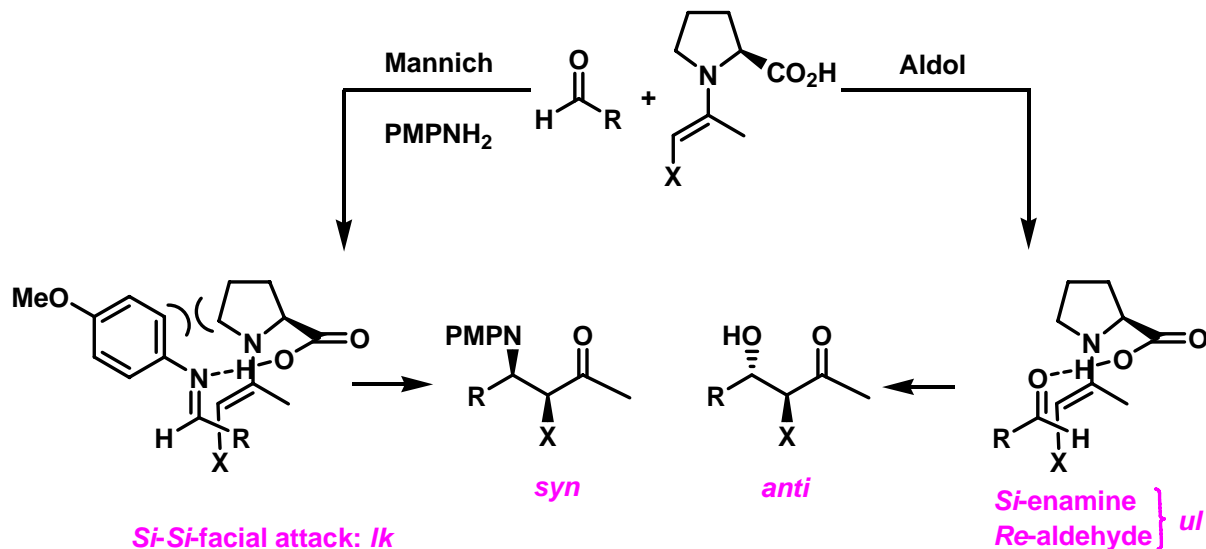
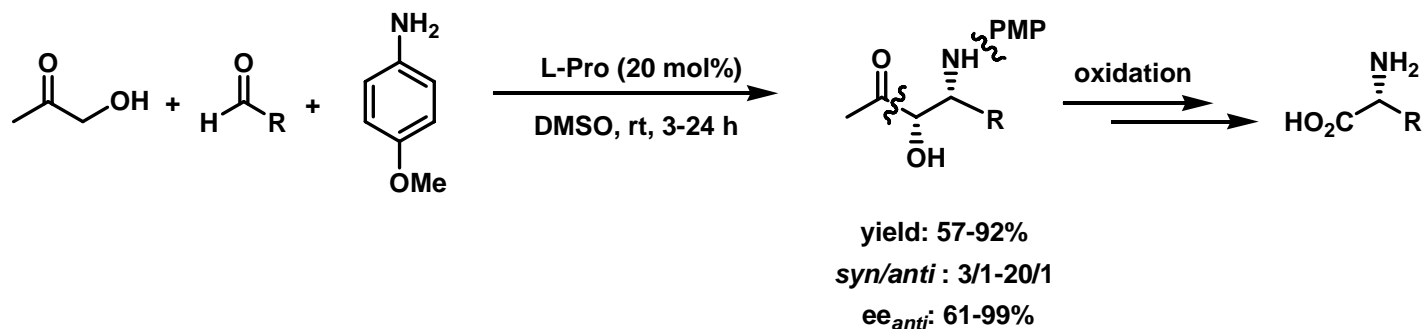


B. List et al., *J. Am. Chem. Soc.* **2000**, *122*, 9336; **2002**, *124*, 827

# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

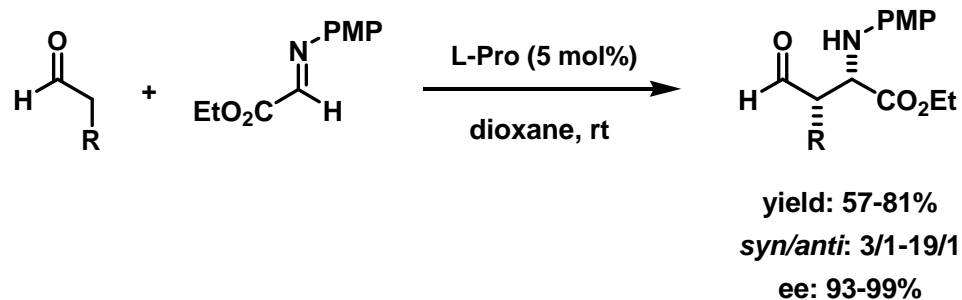
2 Sterocenters (3 components)



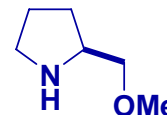
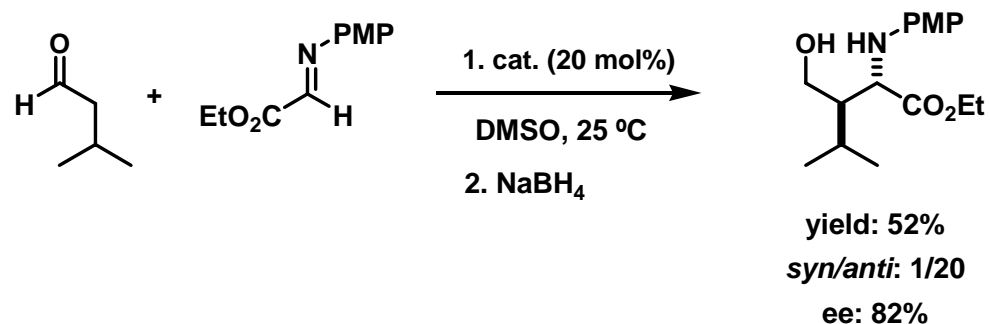
# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

2 Sterocenters (2 components)



C. F. Barbas III et al., *J. Am. Chem. Soc.* **2002**, *124*, 1842



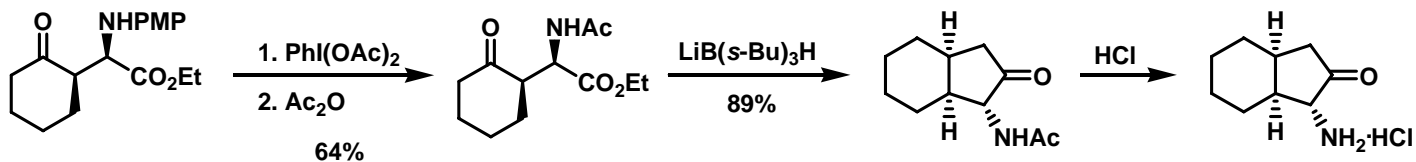
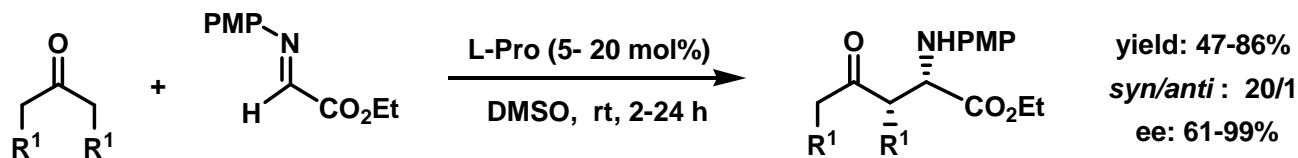
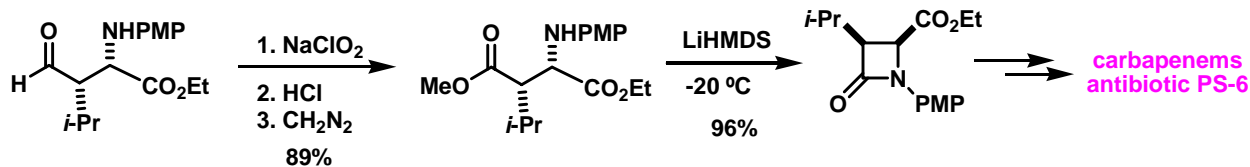
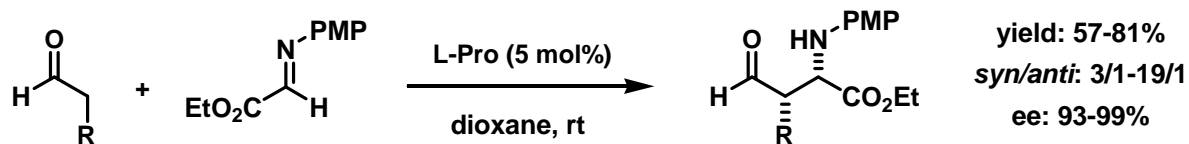
Catalyst

C. F. Barbas III et al., *Tetrahedron Lett.* **2002**, *43*, 7749

# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

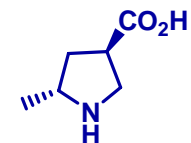
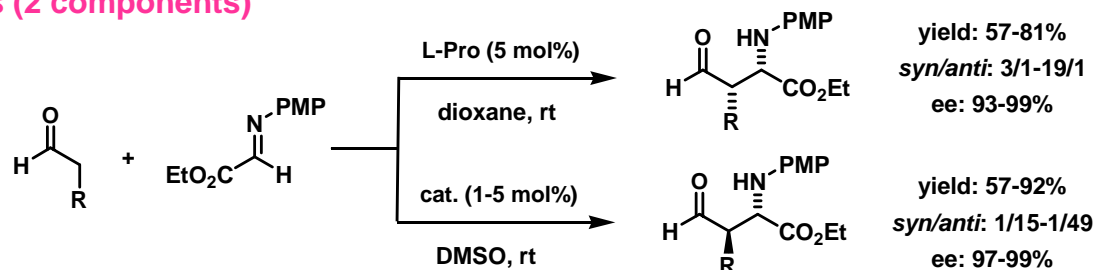
### 2 Sterocenters (2 components)



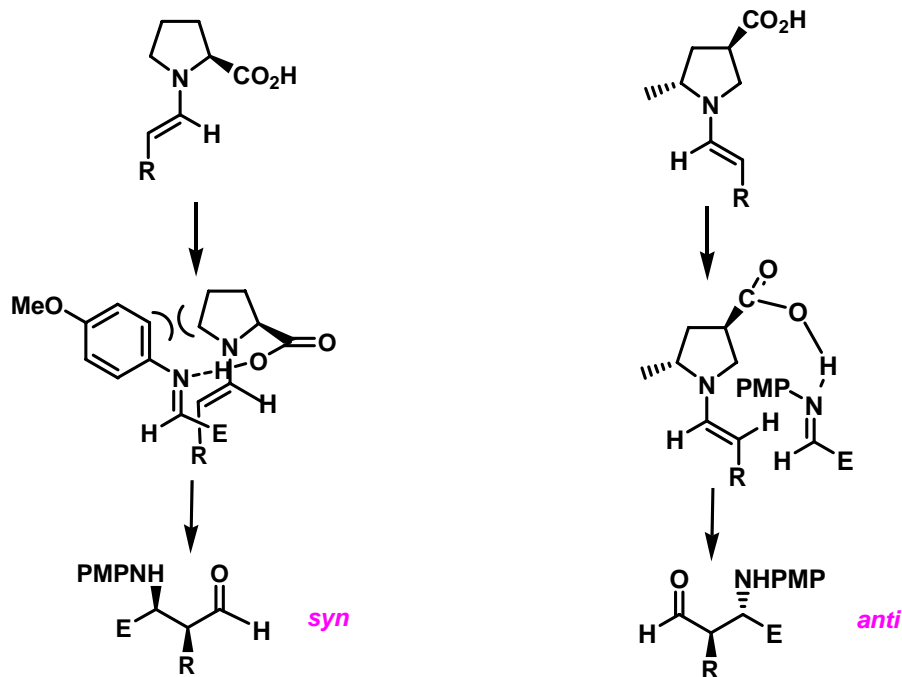
# Enantioselective Organocatalysis (I): Organic Bases

## IIIb. Nucleophilic Additions to C=N: Mannich condensation

2 Sterocenters (2 components)



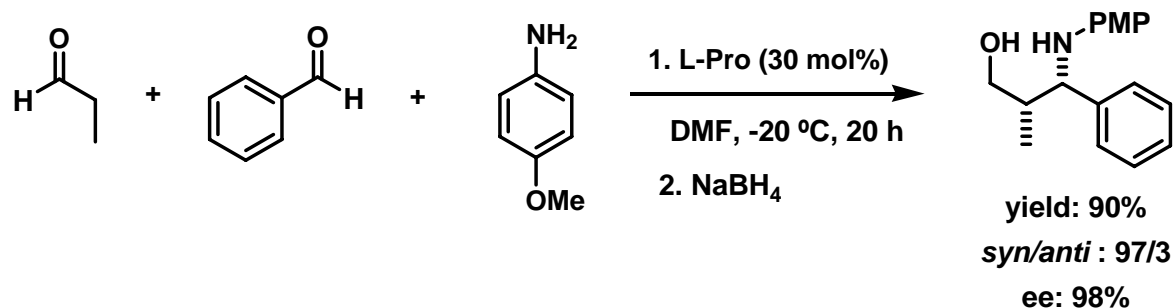
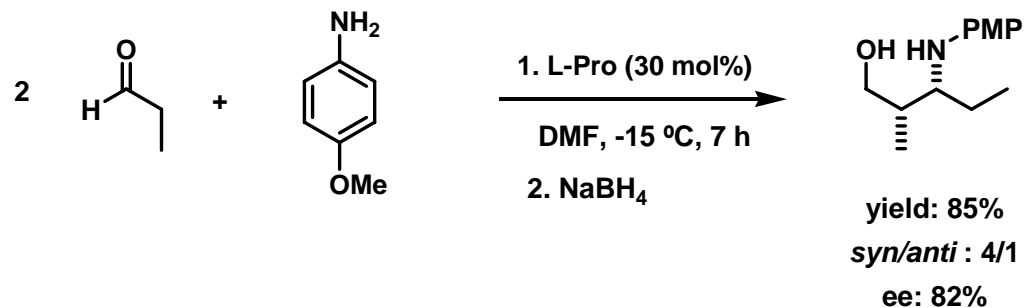
Catalyst



# Enantioselective Organocatalysis (I): Organic Bases

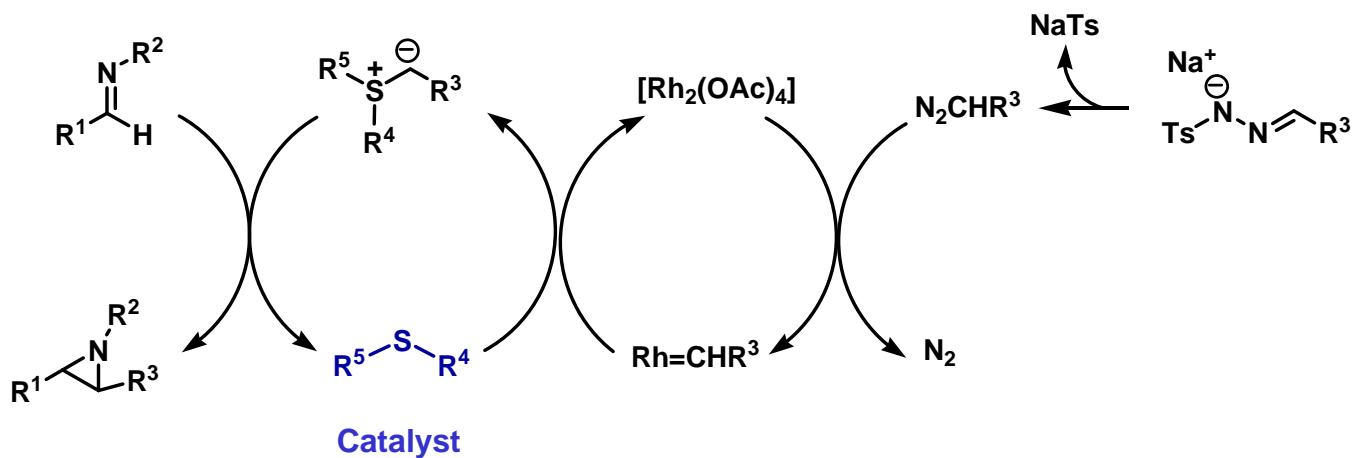
## IIIb. Nucleophilic Additions to C=N: Mannich condensation

2 Sterocenters (3 components)



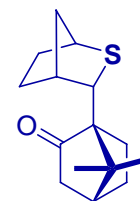
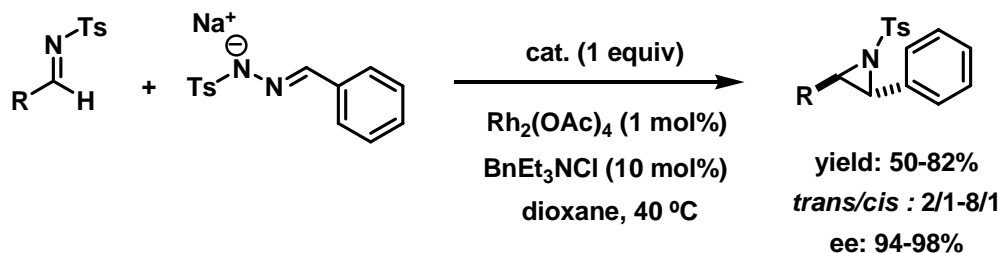
# Enantioselective Organocatalysis (I): Organic Bases

## IIIc. Nucleophilic Additions to C=N: aziridination reactions



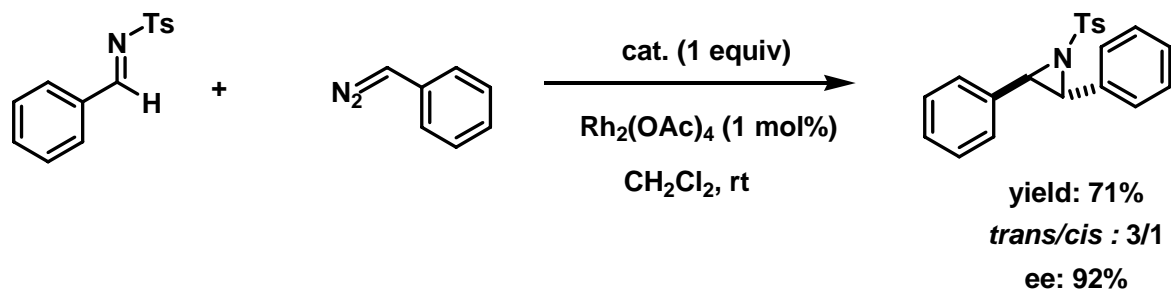
# Enantioselective Organocatalysis (I): Organic Bases

## IIIc. Nucleophilic Additions to C=N: aziridination reactions



Catalyst

Aggarwal *et al.*, *Angew. Chem. Int. Ed.* **2001**, *40*, 1433

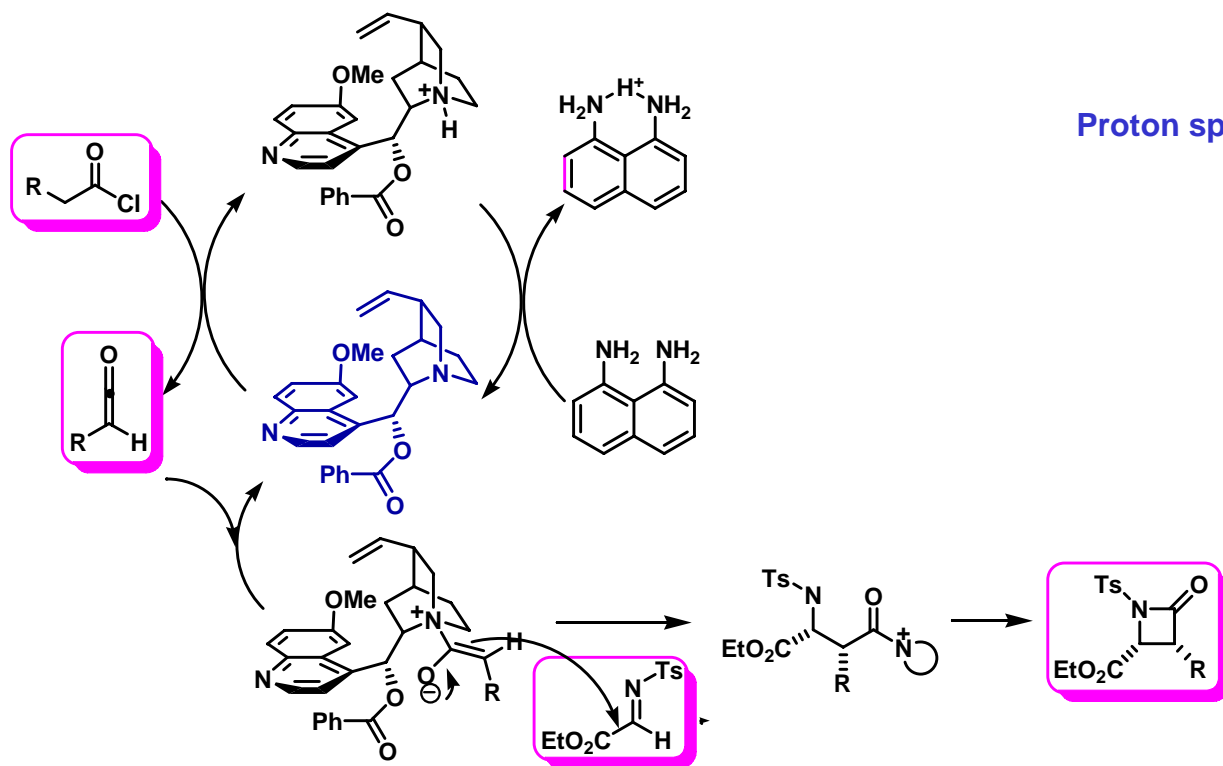
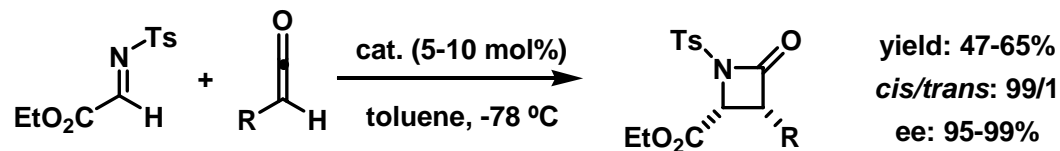


Catalyst

Aggarwal *et al.*, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635

# Enantioselective Organocatalysis (I): Organic Bases

## IIId. Nucleophilic Additions to C=N: synthesis of $\beta$ -lactams



# Enantioselective Organocatalysis (I): Organic Bases

## IV. Additions to Alkenes

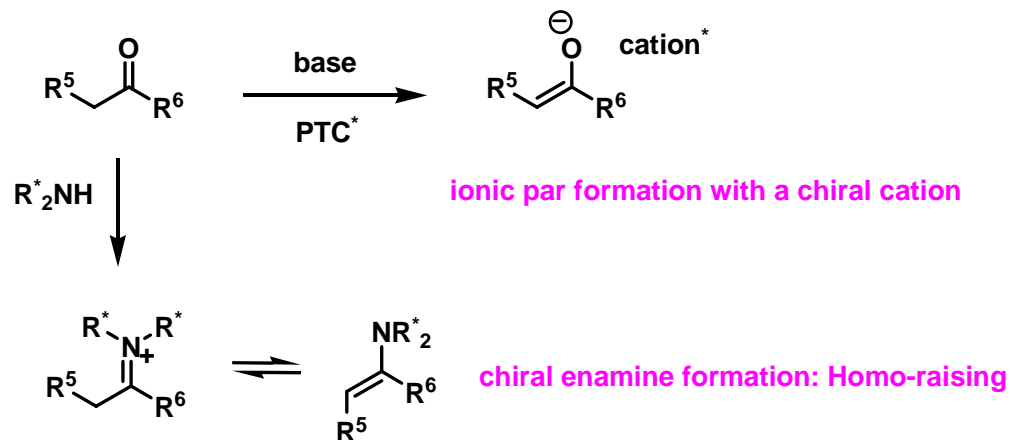
### IVa. Michael addition

### IVb. Epoxidation reactions

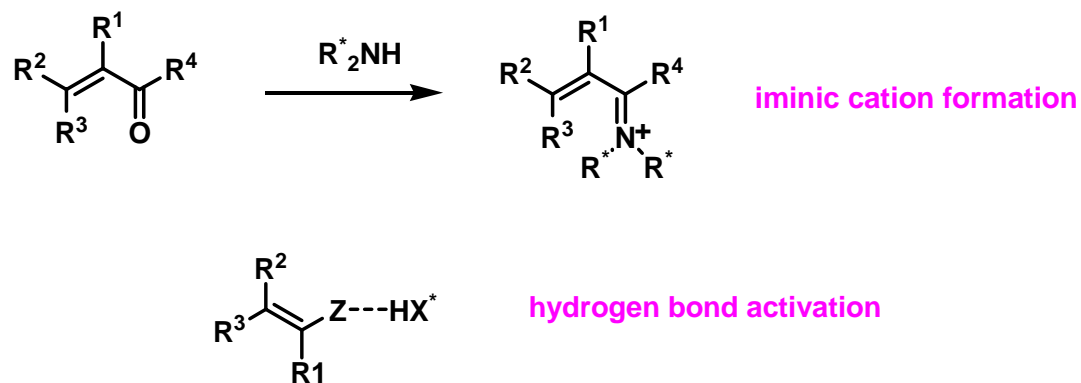
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Nucleophile activation



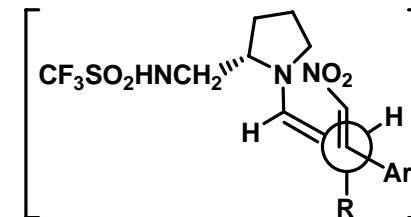
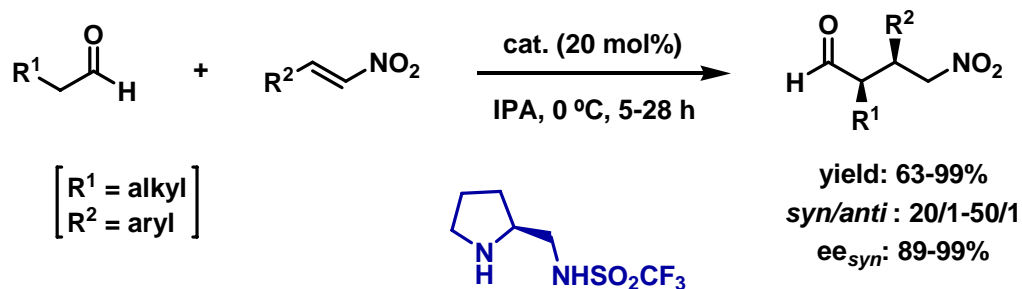
### Michael acceptor activation: LUMO-lowering



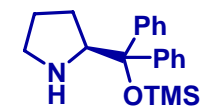
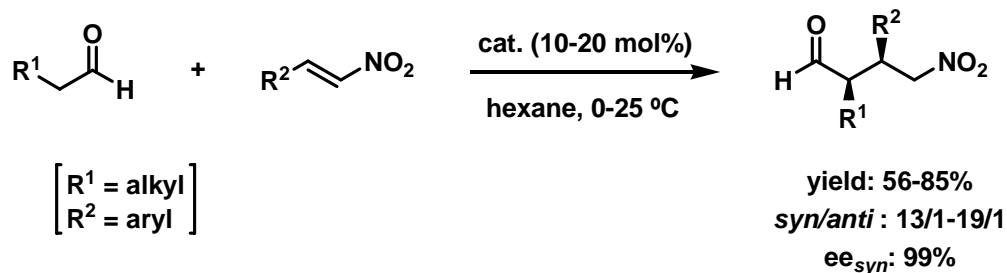
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Nucleophile activation: aldehydes



W. Wang et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 1369

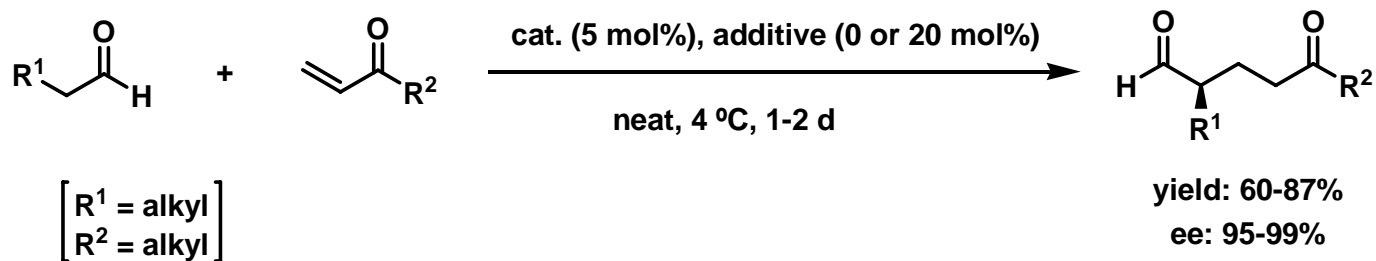


Y. Hayashi et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 4213

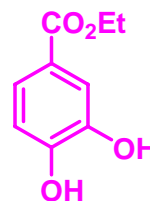
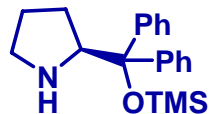
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Nucleophile activation: aldehydes



Catalyst

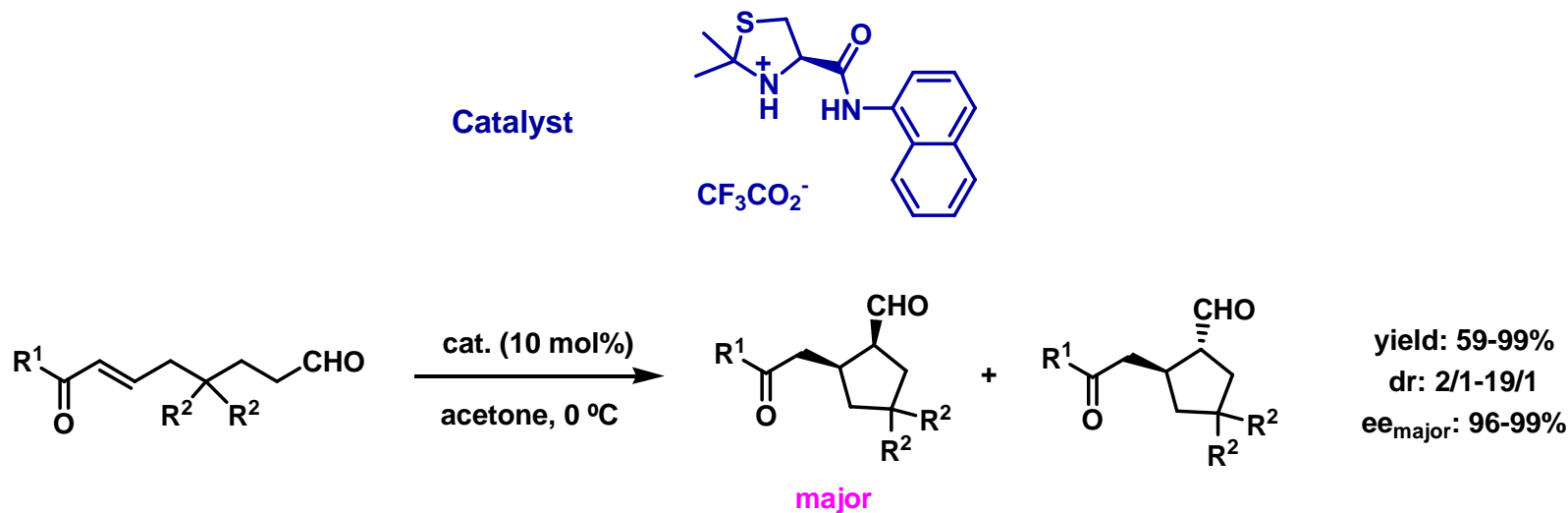
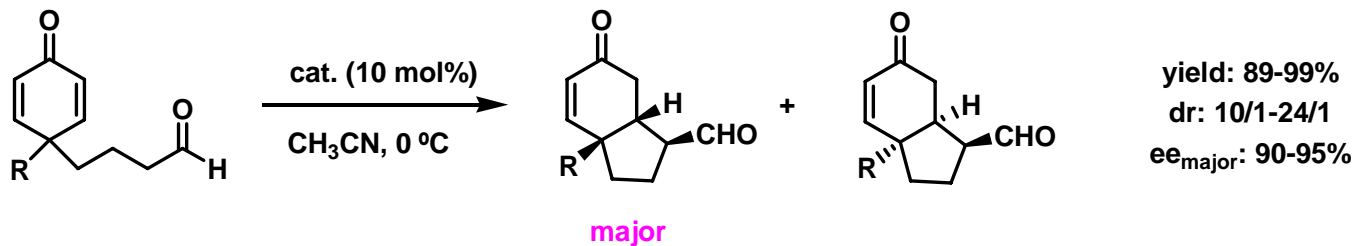


S. Gellman et al., *Org. Lett.* **2005**, 7, 4253

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

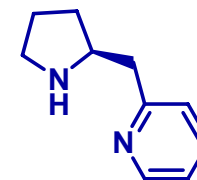
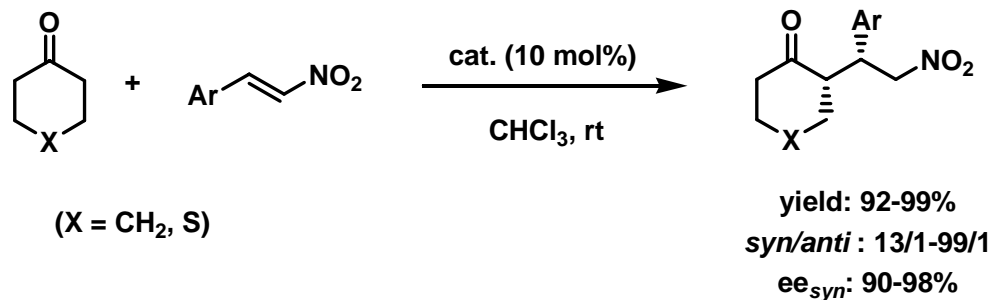
Nucleophile activation: aldehydes intramolecular



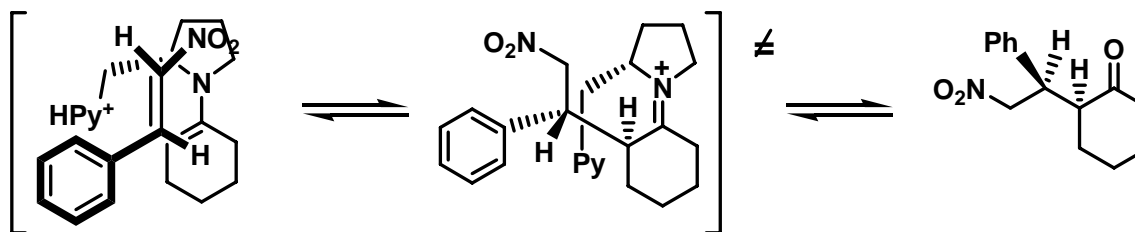
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

Nucleophile activation: ketones



Catalyst

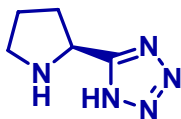
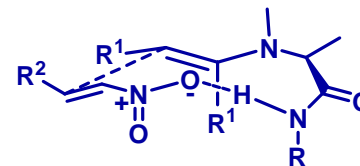
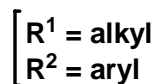
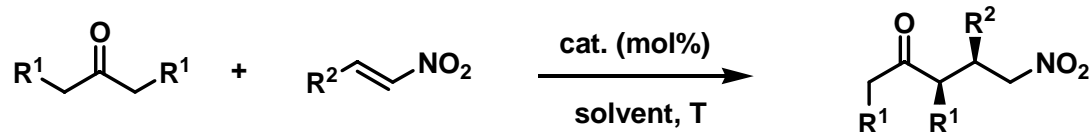


H. Kotsuki et al., *J. Am. Chem. Soc.* **2004**, 126, 9558

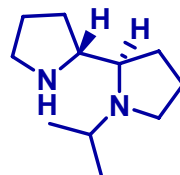
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

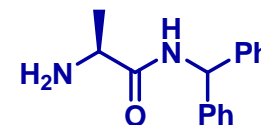
### Nucleophile activation: ketones



cat. (15 mol%)  
EtOH:IPA (1:1), rt  
yield: 47-94%  
*syn/anti* : 10/1-19/1  
*ee<sub>syn</sub>*: 40-73%



cat. (15 mol%), HCl (15 mol%)  
CHCl<sub>3</sub>, rt  
yield: 46-99%  
*syn/anti* : 2/1-19/1  
*ee<sub>syn</sub>*: 32-76%



cat. (30 mol%)  
NMP:DMSO (9:1), H<sub>2</sub>O (10eq), rt  
yield: 45-92%  
*syn/anti* : 5/1-38/1  
*ee<sub>syn</sub>*: 67-99%

A. Alexakis et al., *Org. Lett.* **2002**, 4, 3611

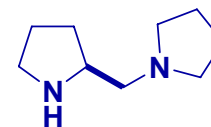
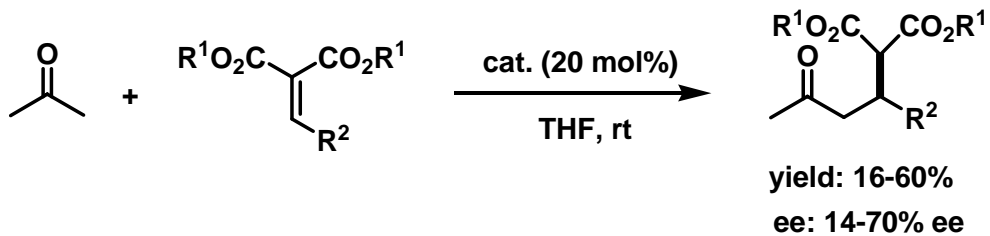
A. Córdova et al., *Chem. Commun.* **2006**, 460

S. V. Ley et al., *Org. Biomol. Chem.* **2005**, 3, 84

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

Nucleophile activation: ketones



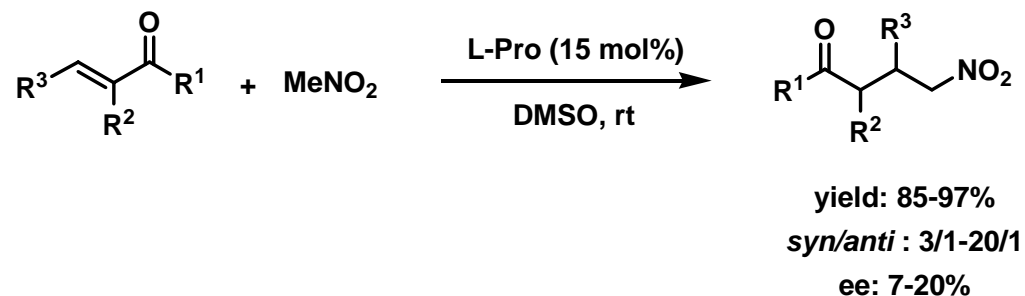
Catalyst

C. F. Barbas III et al., *Tetrahedron Lett.* **2001**, 42, 4441

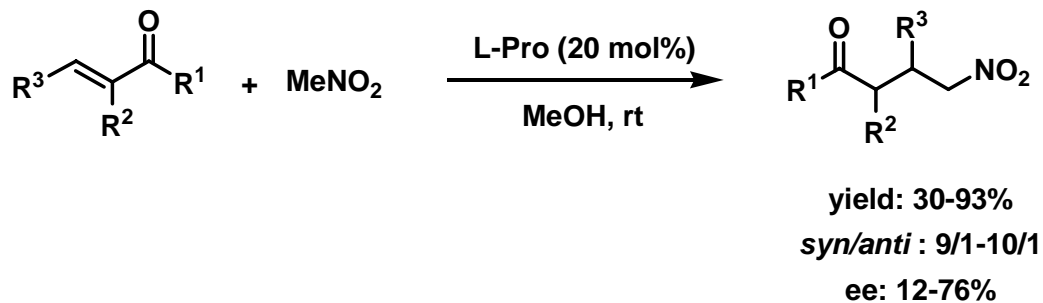
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Michael acceptor activation



B. List et al., *Org. Lett.* **2001**, 3, 2423

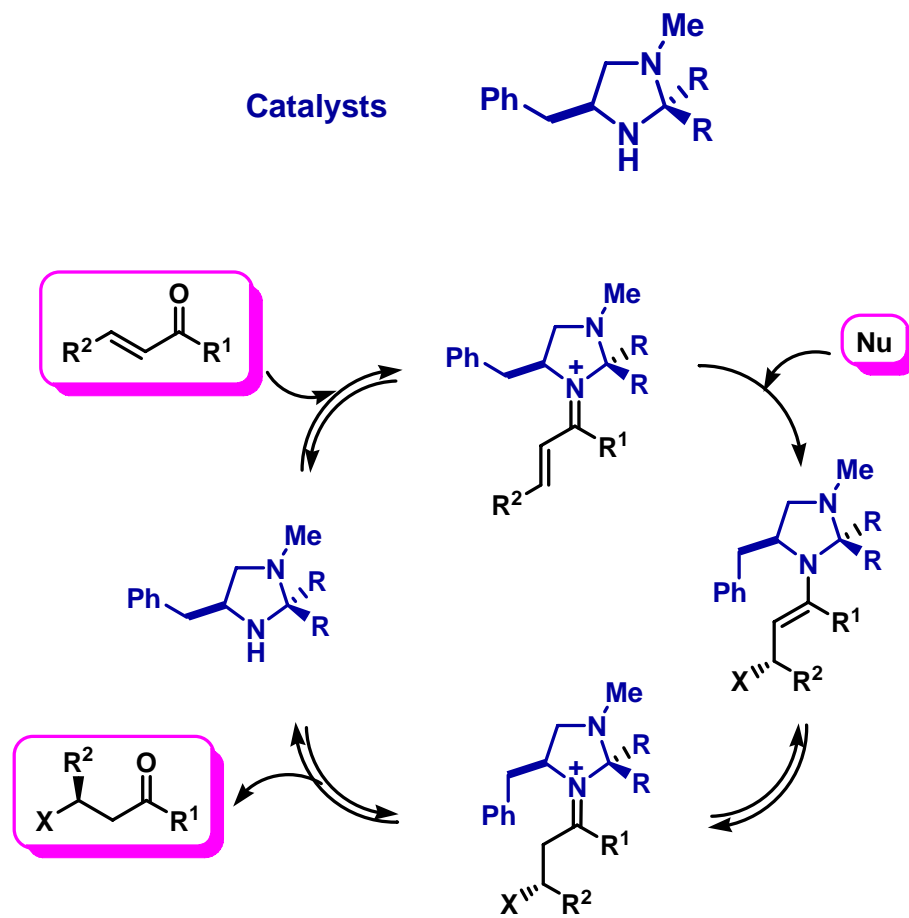


D. Enders et al., *Synlett.* **2002**, 2628

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

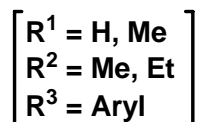
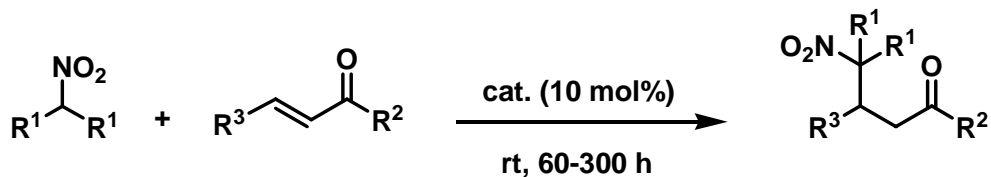
### Michael acceptor activation



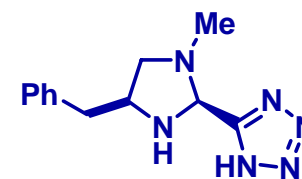
# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

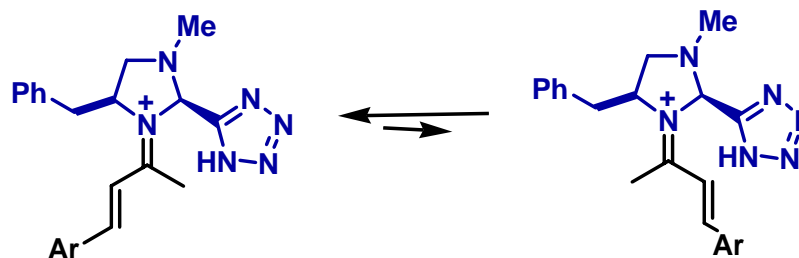
### Michael acceptor activation



yield: 48-93%  
ee: 71-92%



Catalyst

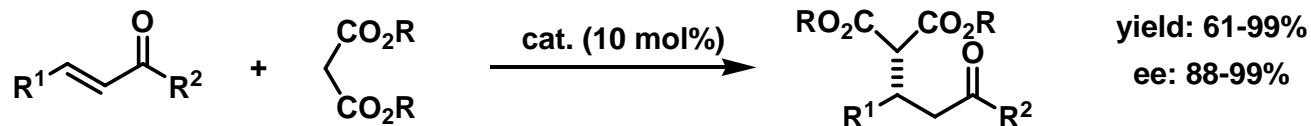


K. A. Jorgensen et al., *Org. Lett.* **2005**, 7, 3897

# Enantioselective Organocatalysis (I): Organic Bases

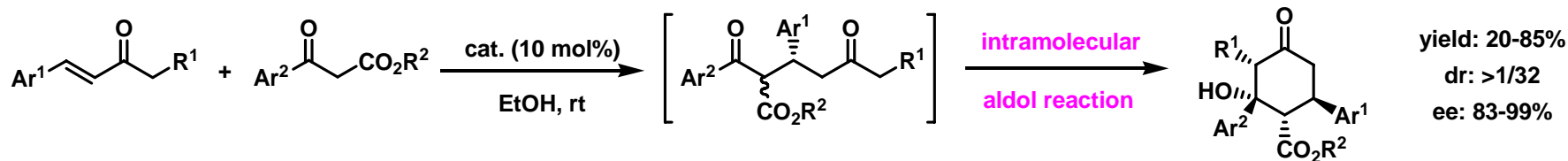
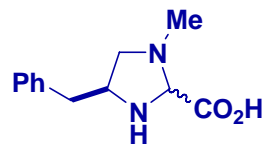
## IVa. Additions to Alkenes: Michael addition

### Michael acceptor activation



K. A. Jorgensen *et al.*, *Angew. Chem. Int. Ed.* **2003**, 42, 661

### Catalyst

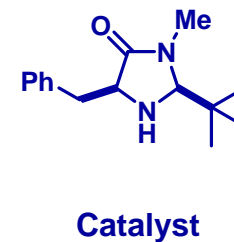
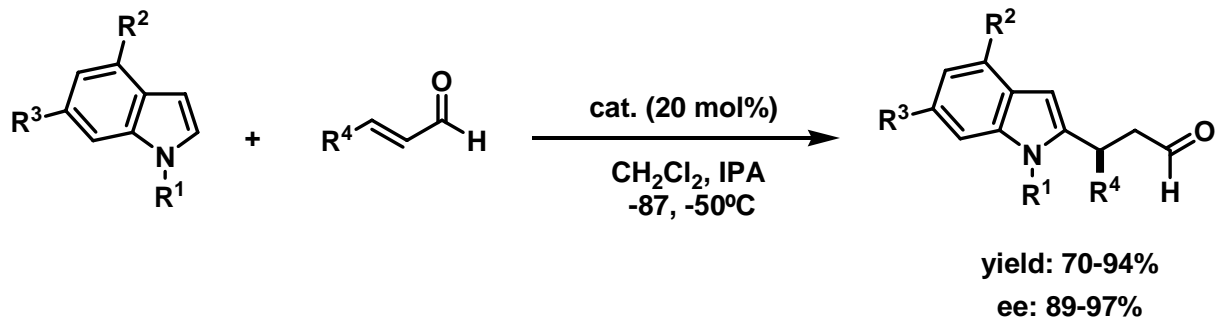
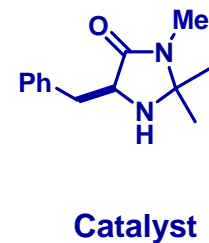
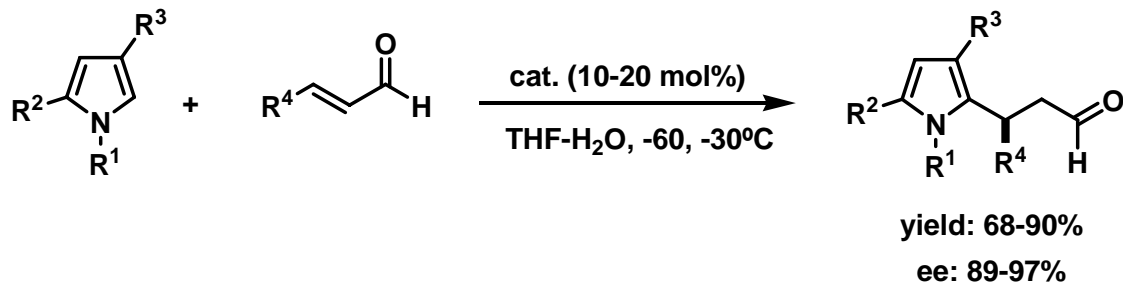


K. A. Jorgensen *et al.*, *Angew. Chem. Int. Ed.* **2004**, 43, 1272

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Michael acceptor activation

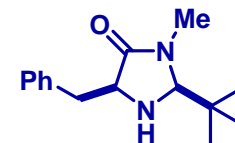
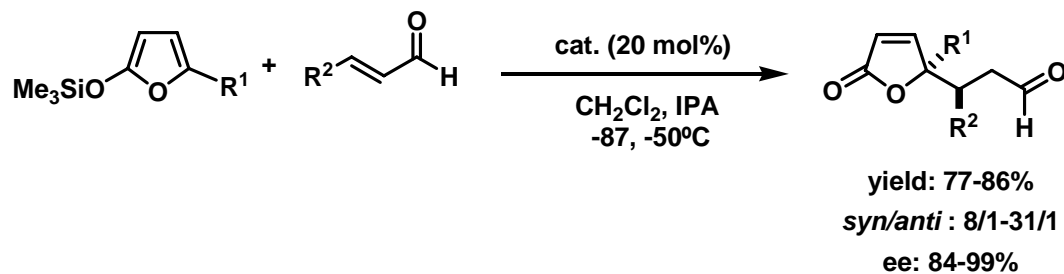
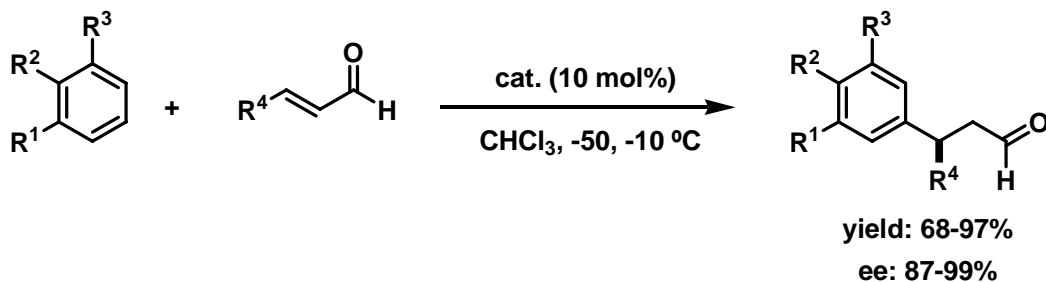


D. W. C. MacMillan et al., *J. Am. Chem. Soc.* **2001**, *123*, 4370; **2002**, *124*, 1172

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Michael acceptor activation



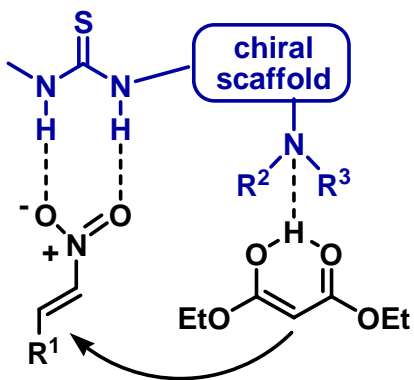
Catalyst

D. W. C. MacMillan et al., *J. Am. Chem. Soc.* **2003**, *125*, 1192

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

### Michael acceptor activation

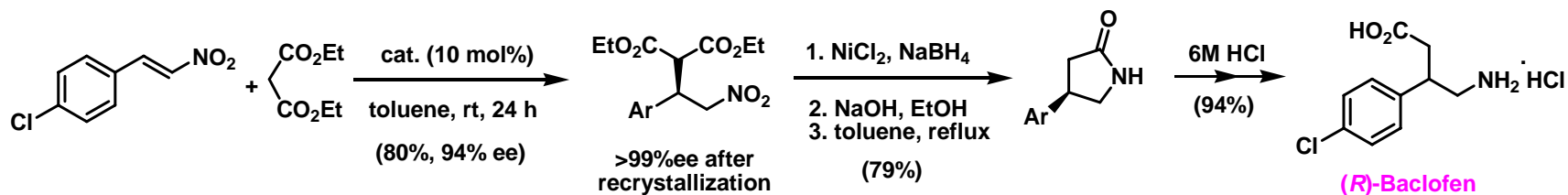
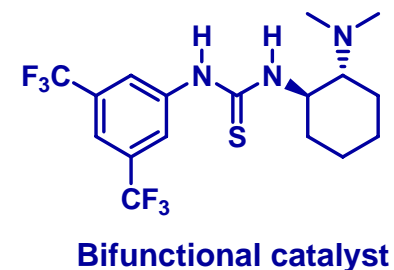
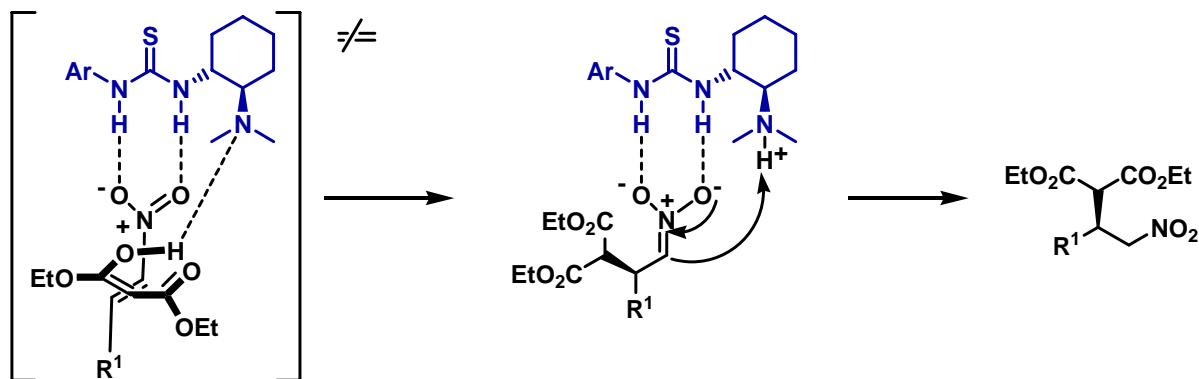
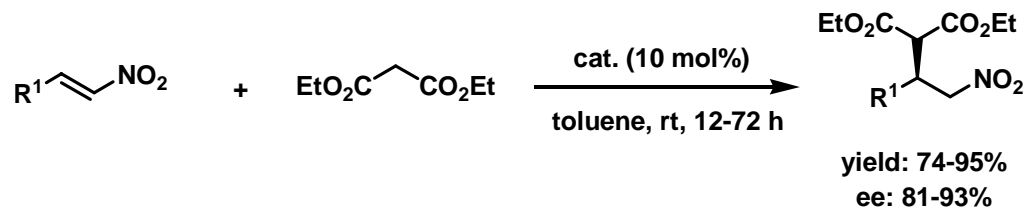


Y. Takemoto et al., *J. Am. Chem. Soc.* **2003**, *125*, 12672; **2005**, *127*, 119

# Enantioselective Organocatalysis (I): Organic Bases

## IVa. Additions to Alkenes: Michael addition

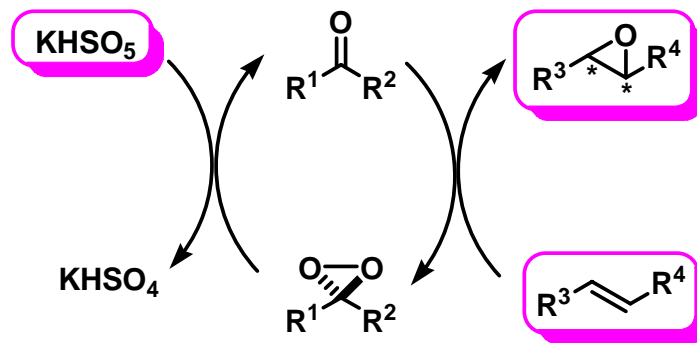
### Michael acceptor activation



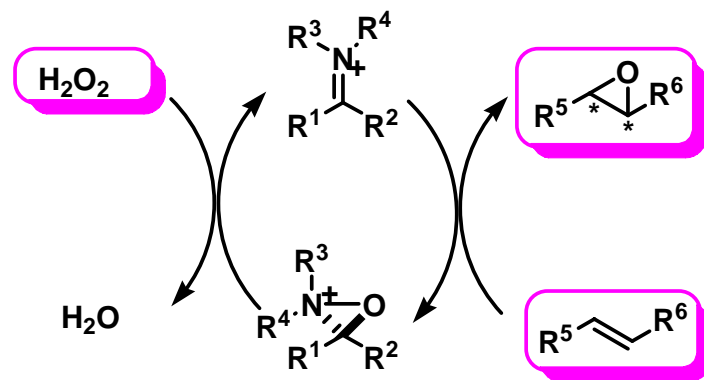
# Enantioselective Organocatalysis (I): Organic Bases

## IVb. Additions to Alkenes: epoxidation reactions

Catalysts: chiral ketones



Catalysts: chiral iminium salts

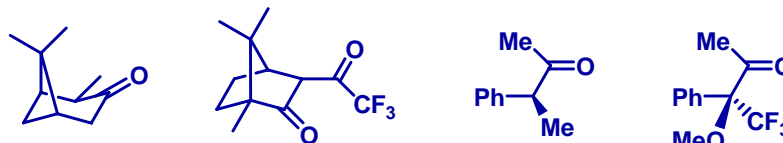


# Enantioselective Organocatalysis (I): Organic Bases

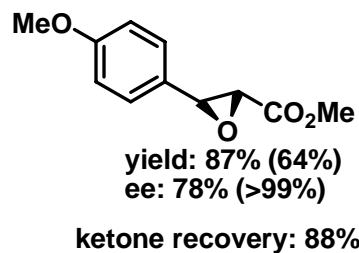
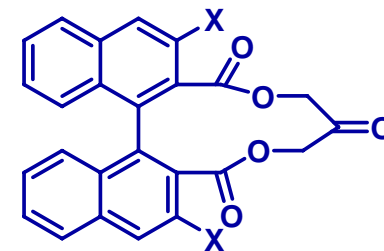
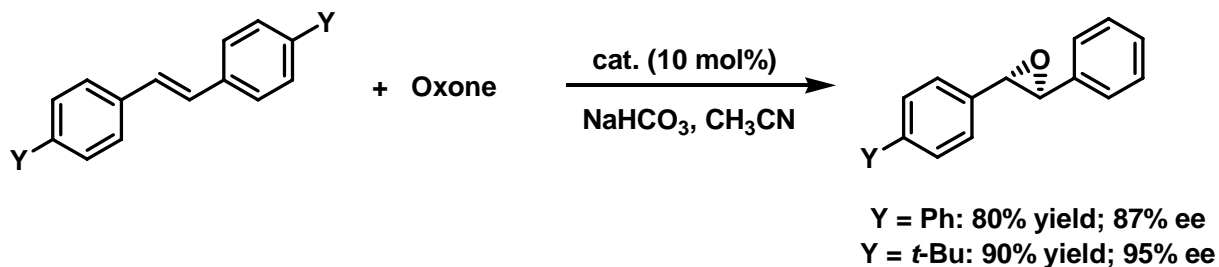
## IVb. Additions to Alkenes: epoxidation reactions

### Chiral ketones

Catalysts



R. Curci et al., *J. Chem. Soc., Chem Commun.* **1984**, 155; *Tetrahedron Lett.* **1995**, 36, 5831



Tanabe Seikayu Co. (Japan)

Diltiazem·HCl

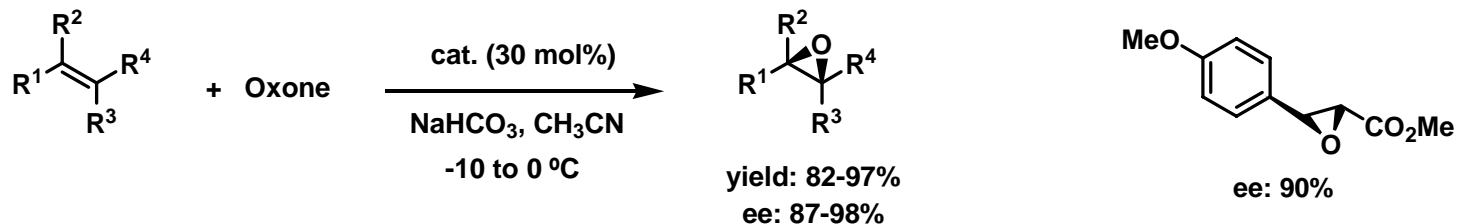
Catalyst

D. Yang et al., *J. Am. Chem. Soc.* **1996**, 118, 491 y 11311; **1998**, 120, 5943;  
*Acc. Chem. Res.* **2004**, 37, 497

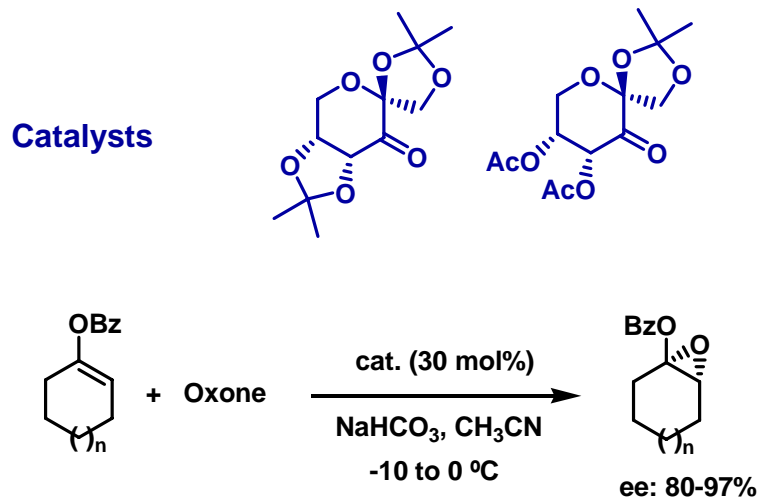
# Enantioselective Organocatalysis (I): Organic Bases

## IVb. Additions to Alkenes: epoxidation reactions

### Chiral ketones



Y. Shi et al., *J. Am. Chem. Soc.* **1996**, *118*, 9806; *Acc. Chem. Res.* **2004**, *37*, 488

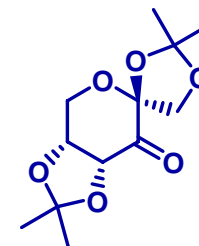
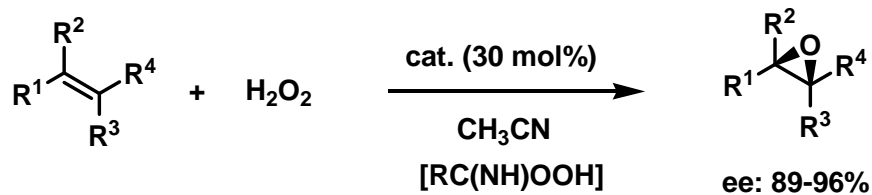


Y. Shi et al., *Tetrahedron Lett.* **1998**, *39*, 7819; *J. Org. Chem.* **2001**, *66*, 1818

# Enantioselective Organocatalysis (I): Organic Bases

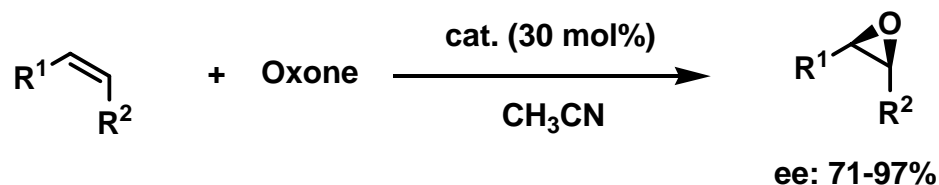
## IVb. Additions to Alkenes: epoxidation reactions

### Chiral ketones

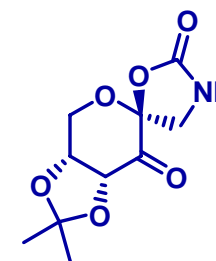
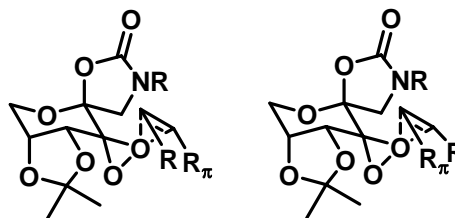


Catalyst

Y. Shi et al., *Tetrahedron Lett.* **1999**, 40, 8721; *Tetrahedron* **2001**, 57, 5213



*favoured*

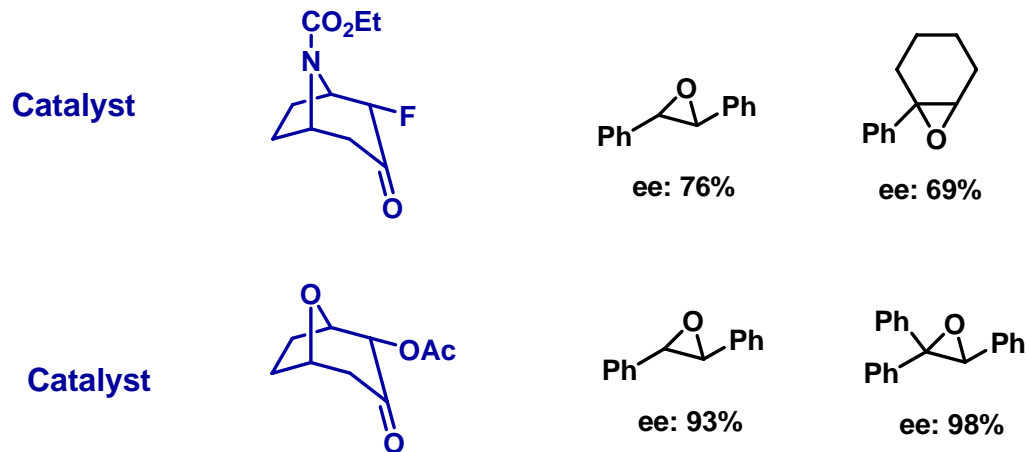


Catalyst

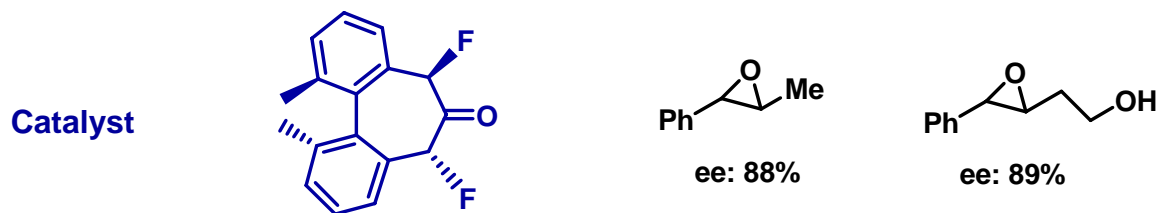
# Enantioselective Organocatalysis (I): Organic Bases

## IVb. Additions to Alkenes: epoxidation reactions

### Chiral ketones



A. Armstrong et al., *Chem. Commun.* **1998**, 621; *Tetrahedron: Asymmetry* **2001**, 12, 2779

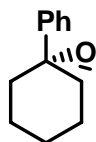
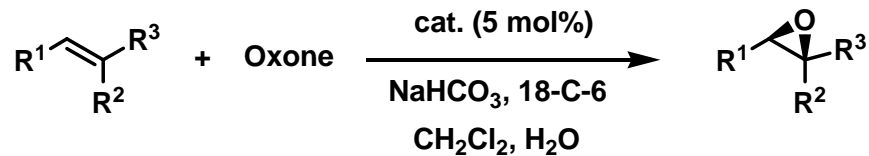


S. E. Denmark et al., *J. Org. Chem.* **1997**, 62, 8288; **2002**, 67, 3479

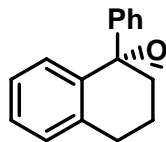
# Enantioselective Organocatalysis (I): Organic Bases

## IVb. Additions to Alkenes: epoxidation reactions

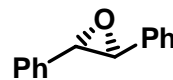
### Chiral iminium salts



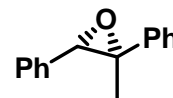
yield: 67%  
ee: 69%



yield: 85%  
ee: 76%

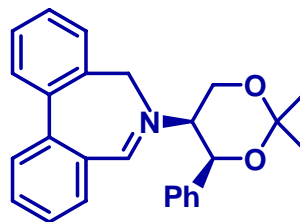


yield: 85%  
ee: 17%



yield: 64%  
ee: 42%

Catalyst

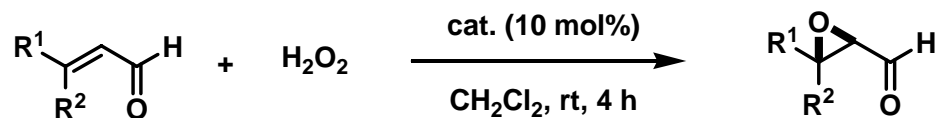


J. Lacour et al., *Tetrahedron Lett.* **2002**, *43*, 8257

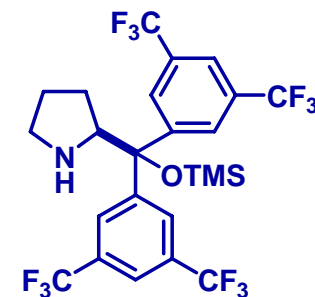
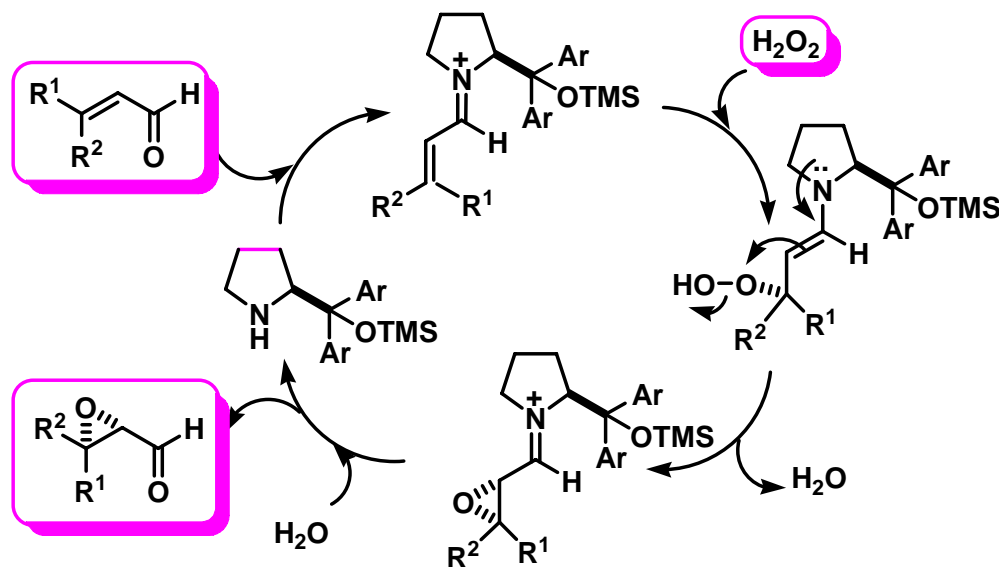
# Enantioselective Organocatalysis (I): Organic Bases

## IVb. Additions to Alkenes: epoxidation reactions

### Michael acceptor activation



yield: 63-90%  
de: 80-96%  
ee: 94-98%



Catalyst

## **Enantioselective Organocatalysis (I): Organic Bases**

### **V. Cycloaddition reactions**

**Va. Diels-Alder**

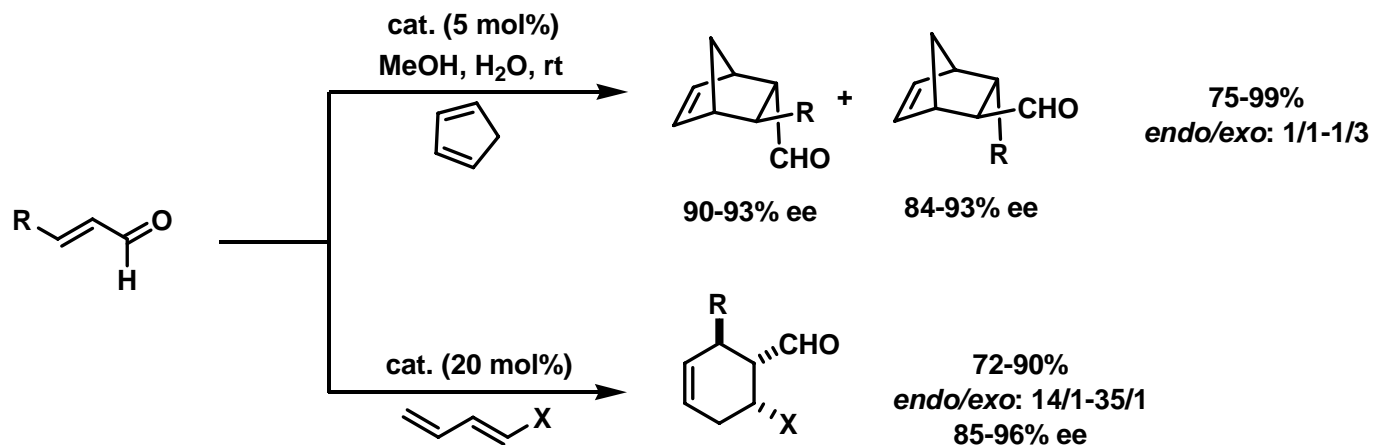
**Vb. Hetero Diels-Alder**

**Vc. 1,3-Dipolar cycloadditions**

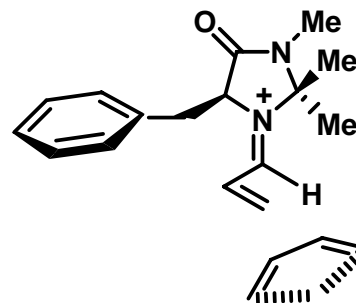
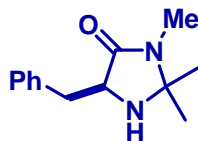
# Enantioselective Organocatalysis (I): Organic Bases

## Va. Cycloaddition reactions: Diels-Alder

### Dienophile (LUMO) activation



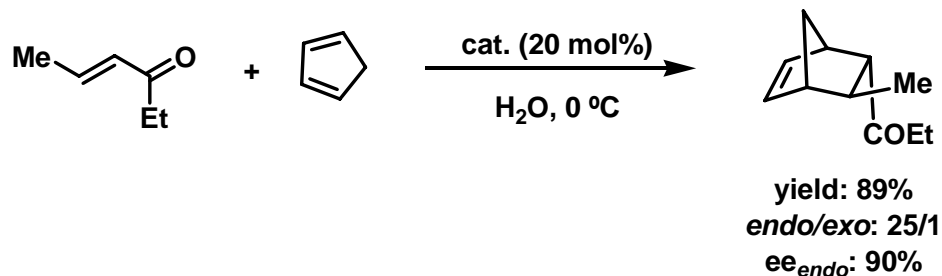
Catalyst



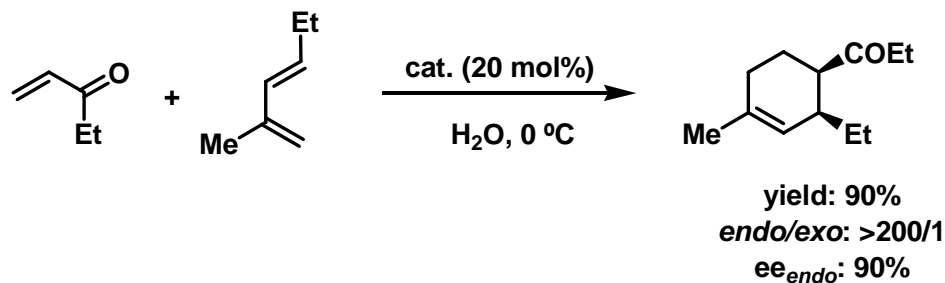
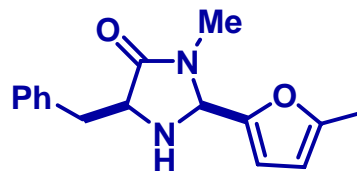
# Enantioselective Organocatalysis (I): Organic Bases

## Va. Cycloaddition reactions: Diels-Alder

### Dienophile (LUMO) activation



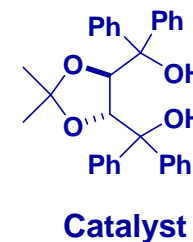
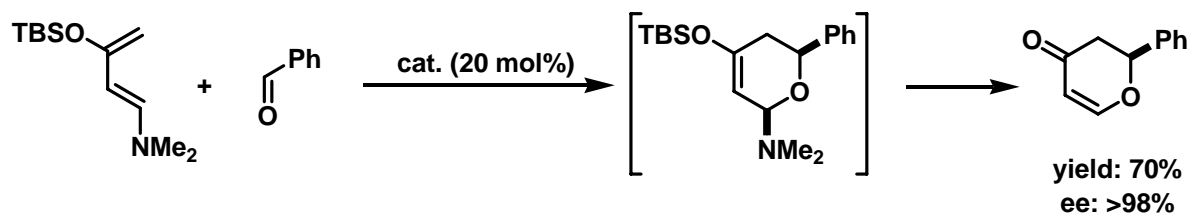
Catalyst



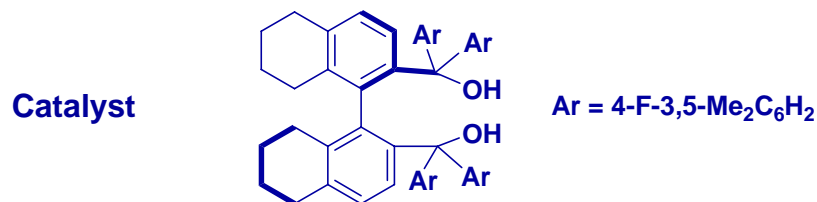
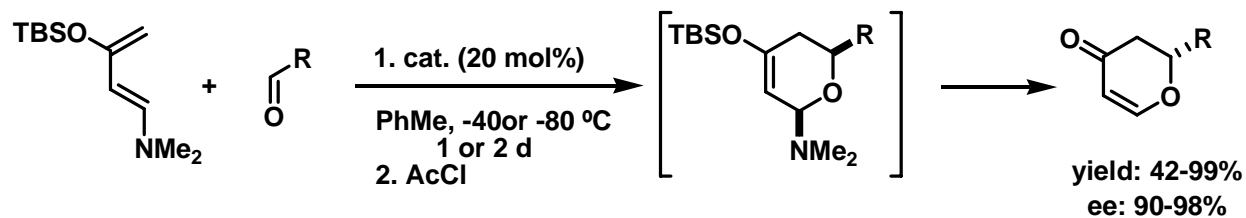
# Enantioselective Organocatalysis (I): Organic Bases

## Vb. Cycloaddition reactions: Hetero Diels-Alder

### Dienophile (LUMO) activation by hydrogen bonding



V. H. Rawal et al., *Nature* **2003**, 424, 140

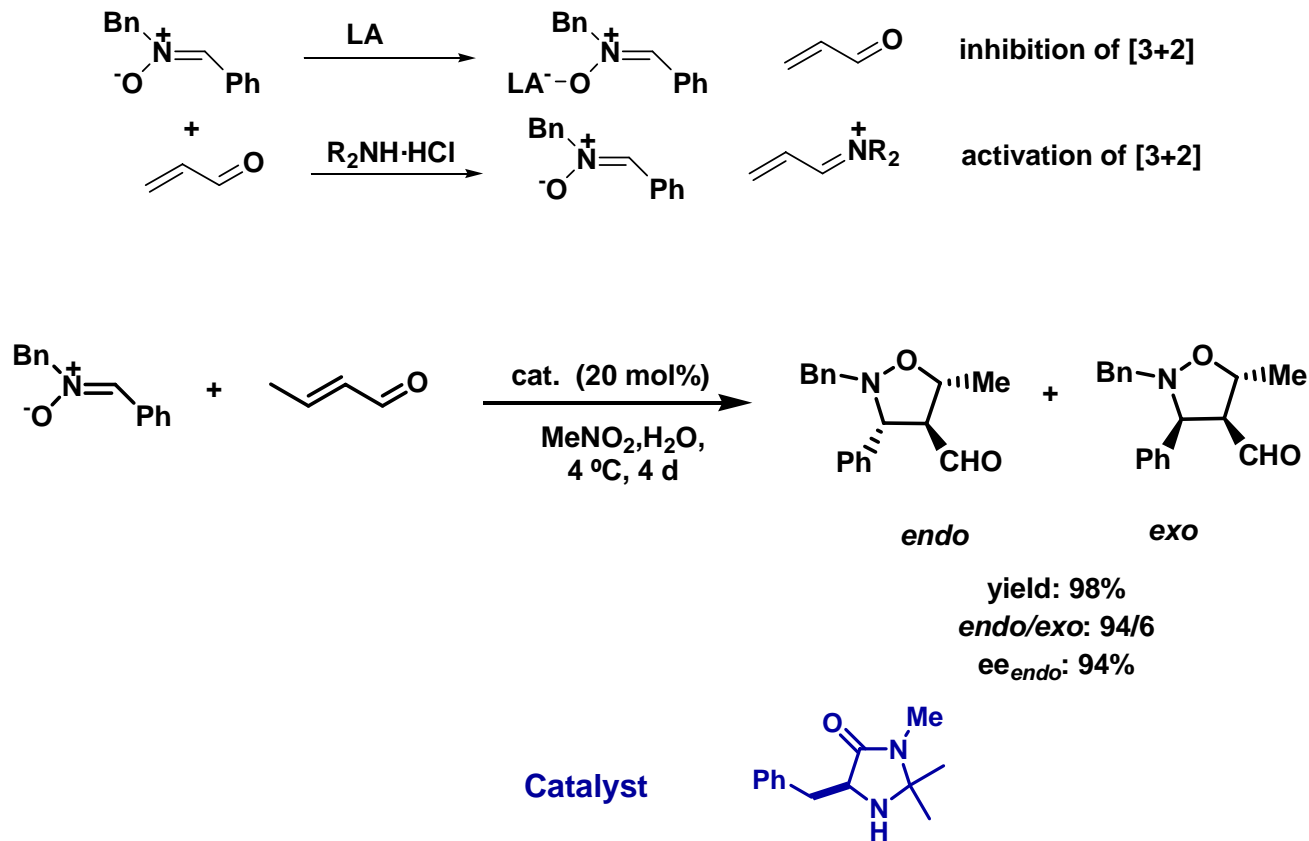


H. Yamamoto and V. H. Rawal et al., *J. Am. Chem. Soc.* **2005**, 127, 1336

# Enantioselective Organocatalysis (I): Organic Bases

## Vc. Cycloaddition reactions: 1,3-dipolar cycloadditions

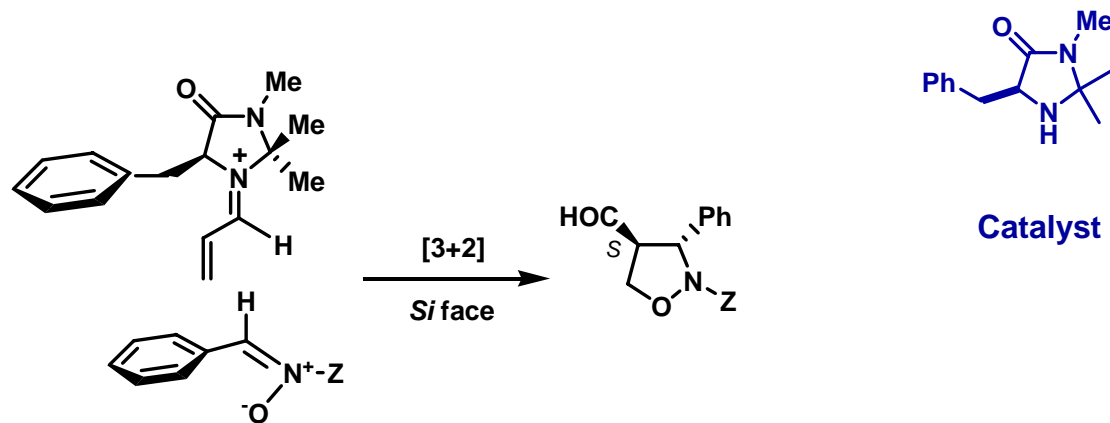
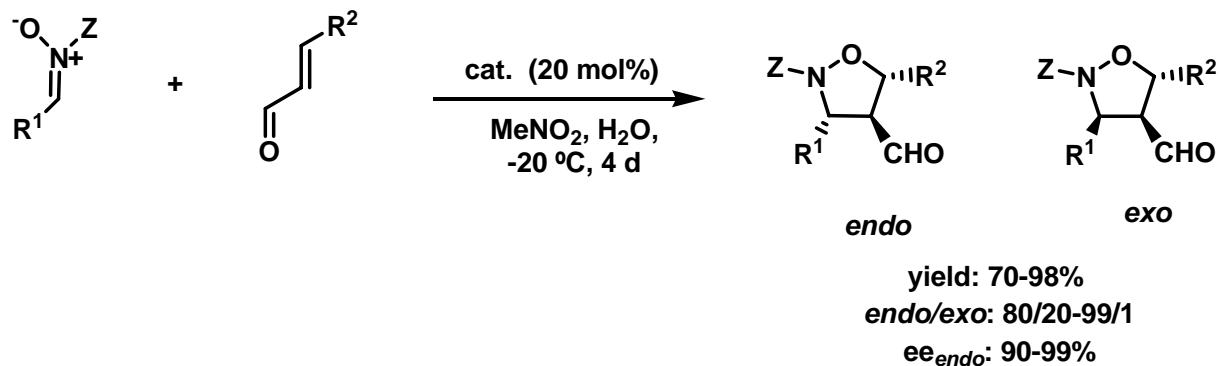
### Dipolarophile activation



# Enantioselective Organocatalysis (I): Organic Bases

## Vc. Cycloaddition reactions: 1,3-dipolar cycloadditions

### Dipolarophile activation



## **Enantioselective Organocatalysis (I): Organic Bases**

### **VI. $\alpha$ -Functionalization of Carbonyl Compounds**

**VIa. Oxygenation**

**VIb. Amination**

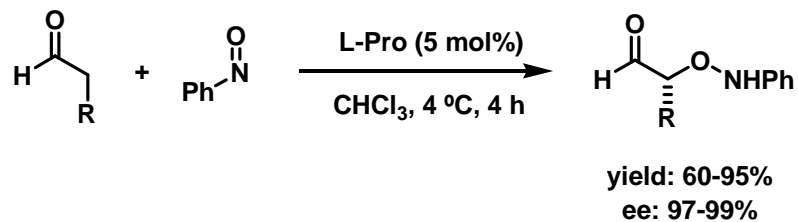
**VIc. Halogenation**

**VId. Sulfenylation**

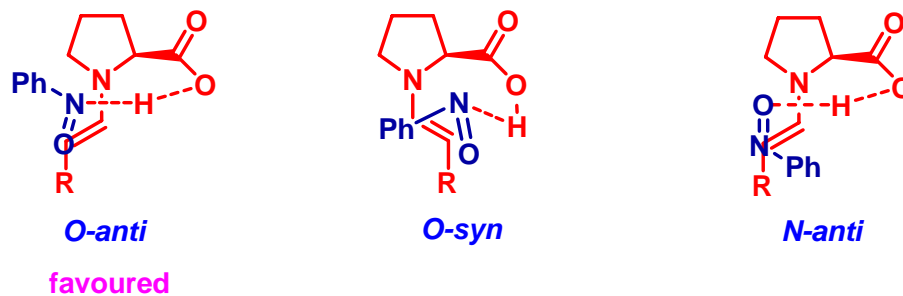
# Enantioselective Organocatalysis (I): Organic Bases

## Via. $\alpha$ -Functionalization of Carbonyl Compounds: Oxygenation

### Aminoxylation



D. W. C. MacMillan et al., *J. Am. Chem. Soc.* **2003**, *125*, 10808  
G. Zhong, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247  
Y. Hayashi et al., *Tetrahedron Lett.* **2003**, *44*, 8293

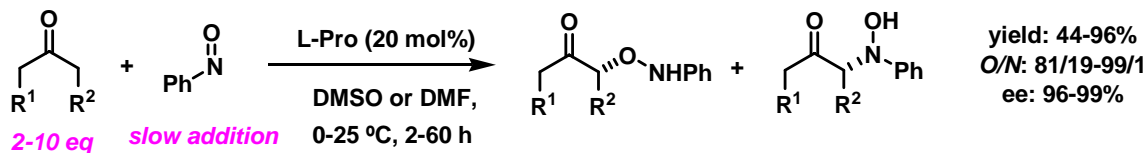


K. N. Houk et al., *J. Am. Chem. Soc.* **2004**, *126*, 13912

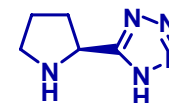
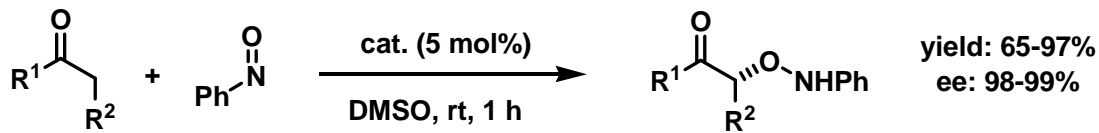
# Enantioselective Organocatalysis (I): Organic Bases

## Vla. $\alpha$ -Functionalization of Carbonyl Compounds: Oxygenation

### Aminoxylation

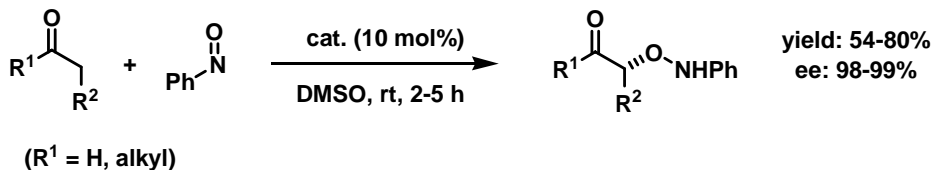


A. Córdova et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 1109  
Y. Hayashi et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 1112



Catalyst

H. Yamamoto et al., *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374



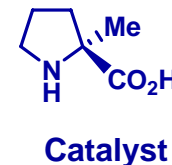
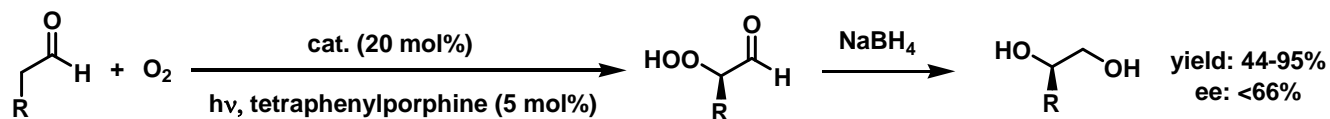
Catalyst

A. Córdova et al., *Tetrahedron Lett.* **2005**, *46*, 3385

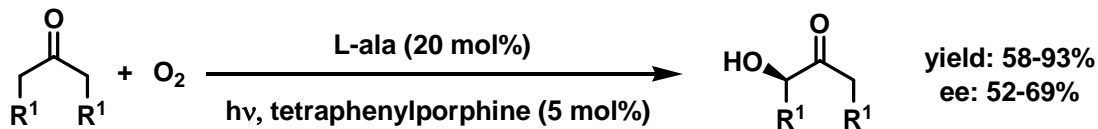
# Enantioselective Organocatalysis (I): Organic Bases

## Vla. $\alpha$ -Functionalization of Carbonyl Compounds: Oxygenation

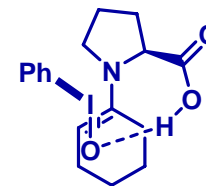
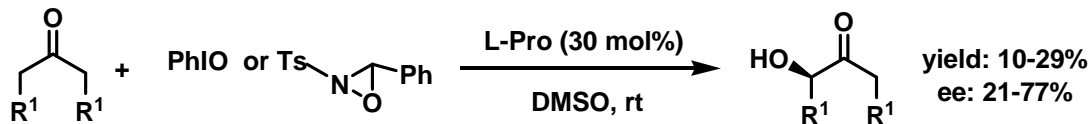
### Hydroxylation



A. Córdova et al., *J. Am. Chem. Soc.* **2004**, *126*, 8914



A. Córdova et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 6532

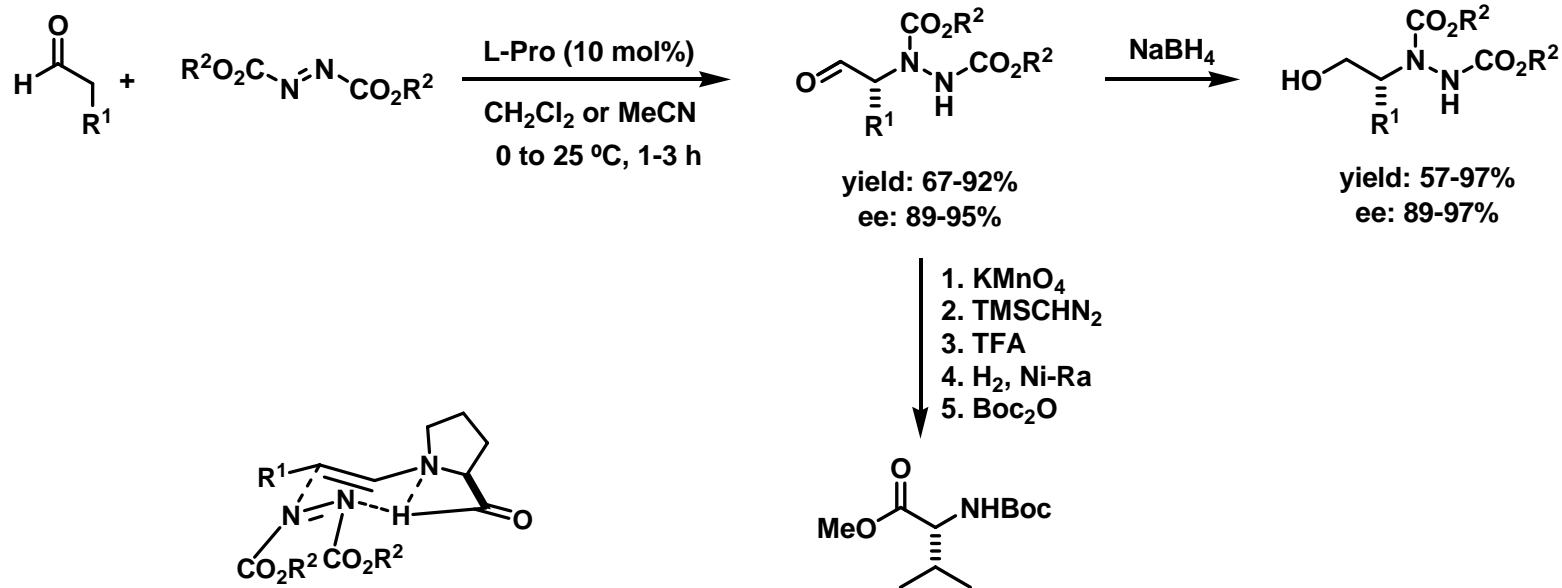


A. Córdova et al., *Tetrahedron Lett.* **2005**, *46*, 2053

# Enantioselective Organocatalysis (I): Organic Bases

## Vib. $\alpha$ -Functionalization of Carbonyl Compounds: Amination

### Azodicarboxylates

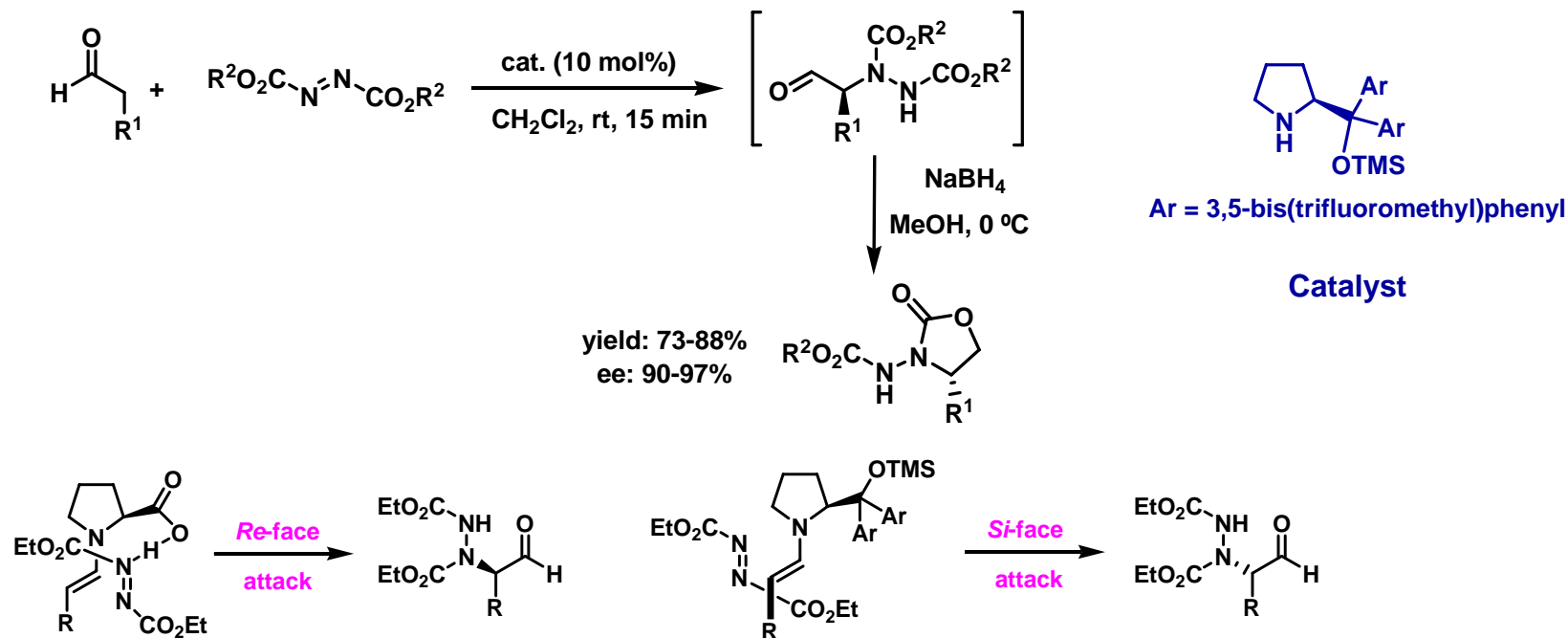


B. List et al., *J. Am. Chem. Soc.* **2002**, *124*, 5656  
K. A. Jorgensen et al., *Angew. Chem. Int. Ed.* **2002**, *41*, 1790

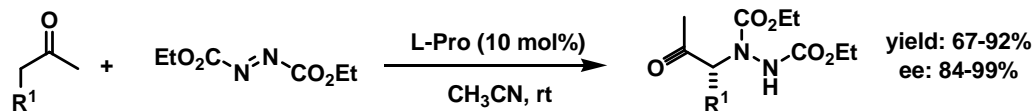
# Enantioselective Organocatalysis (I): Organic Bases

## Vlb. $\alpha$ -Functionalization of Carbonyl Compounds: Amination

### Azodicarboxylates



K. A. Jorgensen et al., *J. Am. Chem. Soc.* **2005**, *127*, 18296

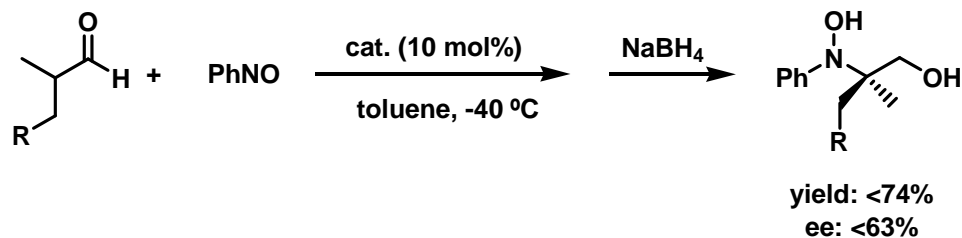


K. A. Jorgensen et al., *J. Am. Chem. Soc.* **2002**, *124*, 6254

# Enantioselective Organocatalysis (I): Organic Bases

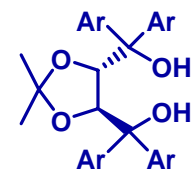
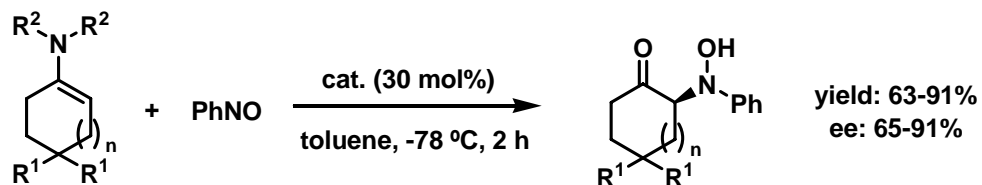
## Vib. $\alpha$ -Functionalization of Carbonyl Compounds: Amination

### Nitrosobenzene



Catalyst

H.-M. Guo et al., *Chem. Commun.* **2006**, 429



Ar = 1-naphthyl

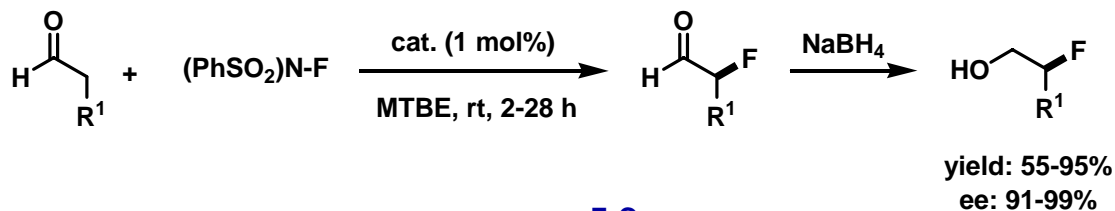
Catalyst

H. Yamamoto et al., *J. Am. Chem. Soc.* **2005**, 127, 1080

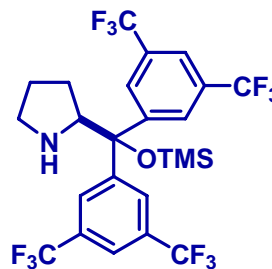
# Enantioselective Organocatalysis (I): Organic Bases

## Vlc. $\alpha$ -Functionalization of Carbonyl Compounds: Halogenation

### Fluorination

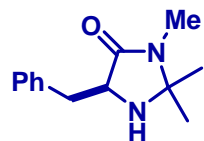


Catalyst



K. A. Jorgensen et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 3703

Catalyst



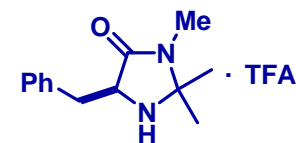
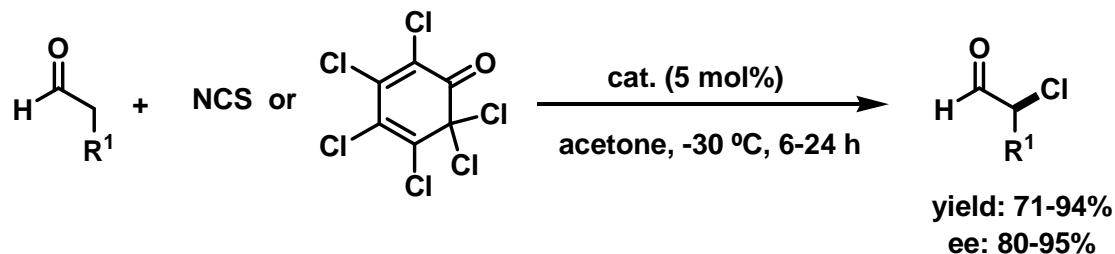
yield: 54-96%  
ee: 91-99%

C. F. Barbas III et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 3706  
D. W. C. Mac Millan et al., *J. Am. Chem. Soc.* **2005**, *127*, 8826

# Enantioselective Organocatalysis (I): Organic Bases

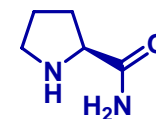
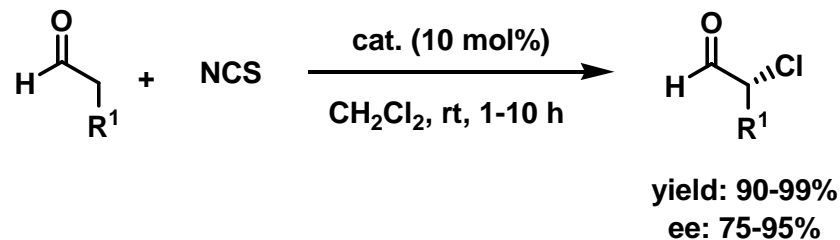
## Vlc. $\alpha$ -Functionalization of Carbonyl Compounds: Halogenation

### Chlorination of aldehydes



Catalyst

D. W. C. MacMillan et al., *J. Am. Chem. Soc.* **2004**, *126*, 4108



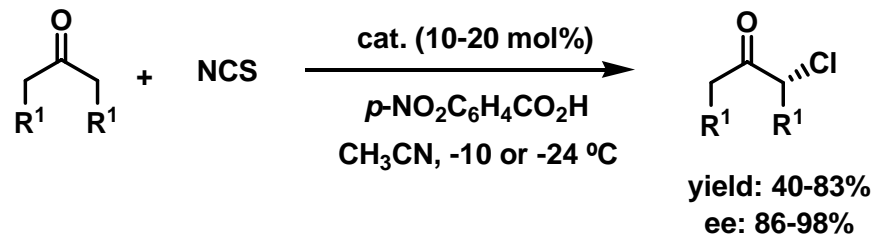
Catalyst

K. A. Jorgensen et al., *J. Am. Chem. Soc.* **2004**, *126*, 4790

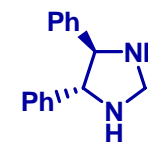
# Enantioselective Organocatalysis (I): Organic Bases

## Vlc. $\alpha$ -Functionalization of Carbonyl Compounds: Halogenation

### Chlorination of ketones

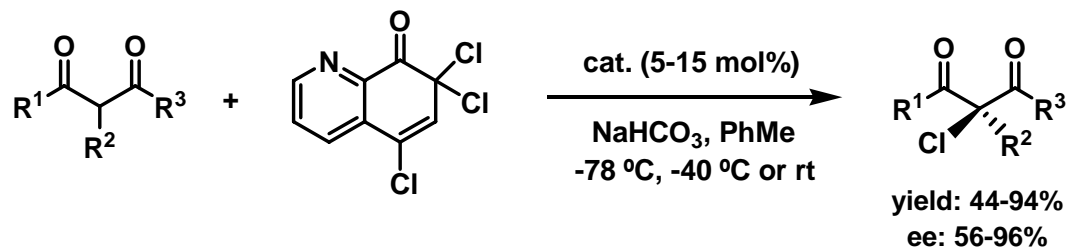


### Catalyst

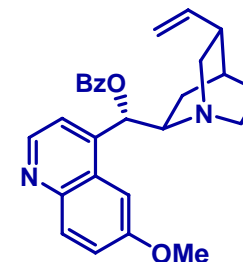


K. A. Jorgensen et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 5507

### Chlorination of 1,3-dicarbonyl compounds



### Catalyst

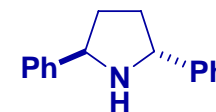
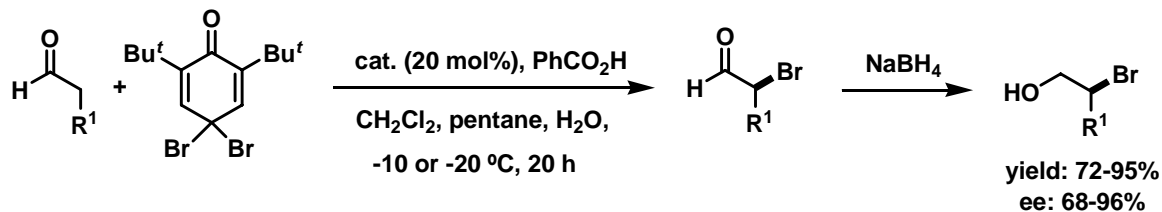


G. Bartoli et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 6219

# Enantioselective Organocatalysis (I): Organic Bases

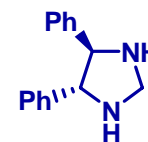
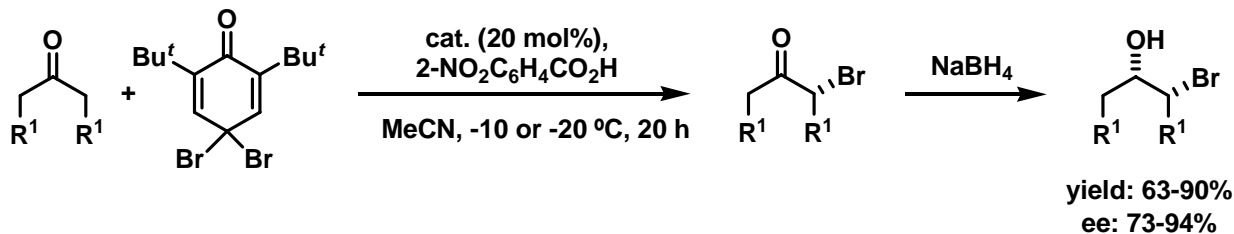
## Vlc. $\alpha$ -Functionalization of Carbonyl Compounds: Halogenation

### Bromination of aldehydes



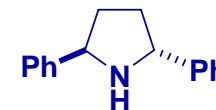
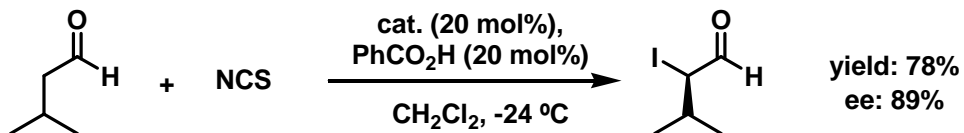
Catalyst

### Bromination of ketones



Catalyst

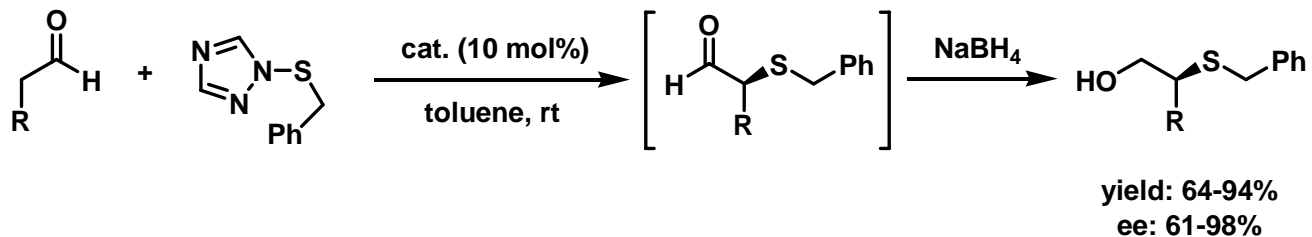
### Iodination of aldehydes



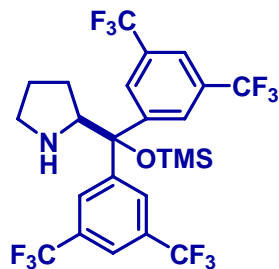
Catalyst

# Enantioselective Organocatalysis (I): Organic Bases

## Vld. $\alpha$ -Functionalization of Carbonyl Compounds: Sulfenylation



Catalyst



K. A. Jorgensen et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 794