

# Enantioselective Organocatalysis (II): PTC

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- III. Nucleophilic Addition to C=O
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- IV. Nucleophilic Addition to C=N
  - IVa. Imino esters
  - IVb. Nitromethane
- V. Additions to alkenes
  - Va. Michael additions
  - Vb. Epoxidation reactions

A. Nelson, *Angew. Chem. Int. Ed.*, **1999**, 38, 1583

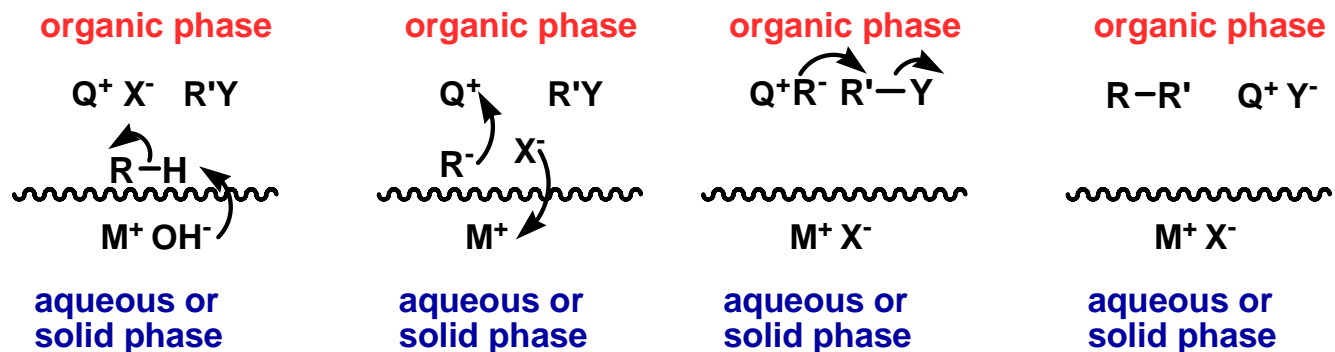
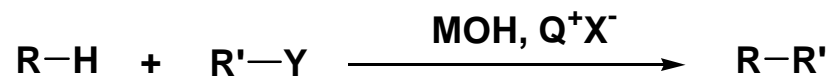
M. J. O'Donnell, *Catalytic Asymmetric Synthesis*, I. Ojima, Ed., 2<sup>nd</sup> Ed., Wiley-VCH:Weinheim, 2000

K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, 103, 3013

A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH: Weinheim, 2005

# Enantioselective Organocatalysis (II): PTC

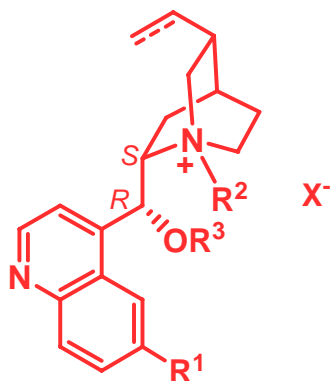
## I. Introduction: Phase-transfer Catalysis



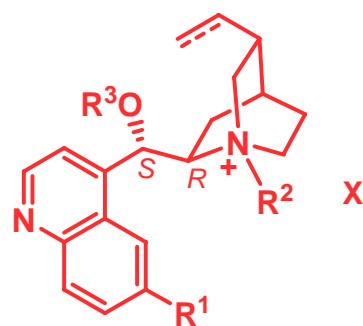
# Enantioselective Organocatalysis (II): PTC

## I. Introduction: Phase-transfer Catalysts

### *Cinchona quats*



- R<sup>1</sup> = H, cinchonidinium salts (CD)
- R<sup>1</sup> = OMe, quininium salts (QN)
- R<sup>1</sup> = H, dihydrocinchonidinium salts (DHCD)
- R<sup>1</sup> = OMe, dihydroquininium salts (DHQN)

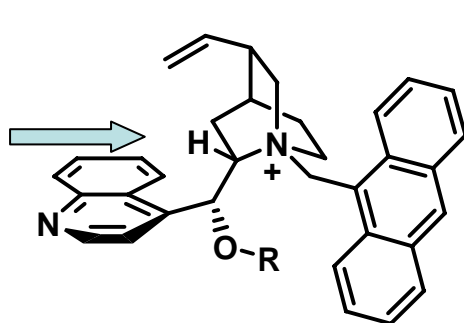


- R<sup>1</sup> = H, cinchoninium salts (CN)
- R<sup>1</sup> = OMe, quinidinium salts (QD)
- R<sup>1</sup> = H, dihydrocinchoninium salts (DHCN)
- R<sup>1</sup> = OMe, dihydroquinidinium salts (DHQD)

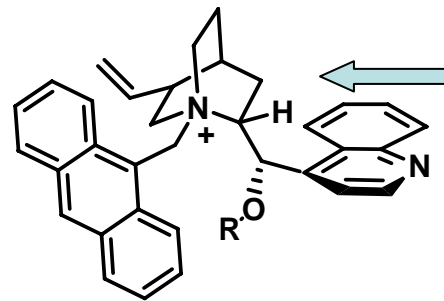
# Enantioselective Organocatalysis (II): PTC

## I. Introduction: Phase-transfer Catalysts

*Cinchona quats*



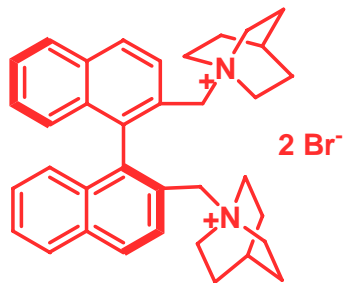
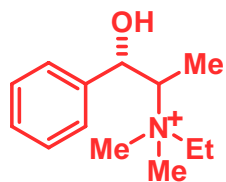
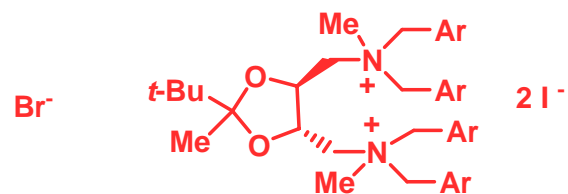
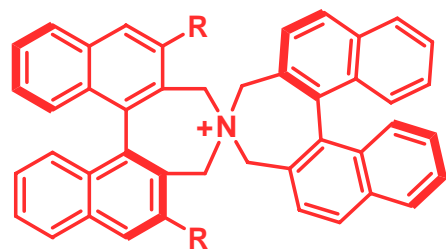
**CD<sup>+</sup>**



**CN<sup>+</sup>**

# Enantioselective Organocatalysis (II): PTC

## I. Introduction: Phase-transfer Catalysts



# Enantioselective Organocatalysis (II): PTC

## II. Electrophilic Substitution of Enolates

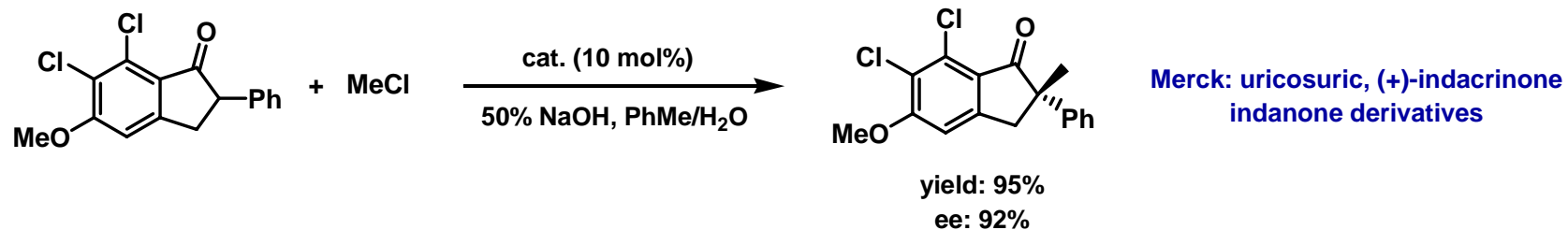
IIa. Alkylation

IIb. Halogenation

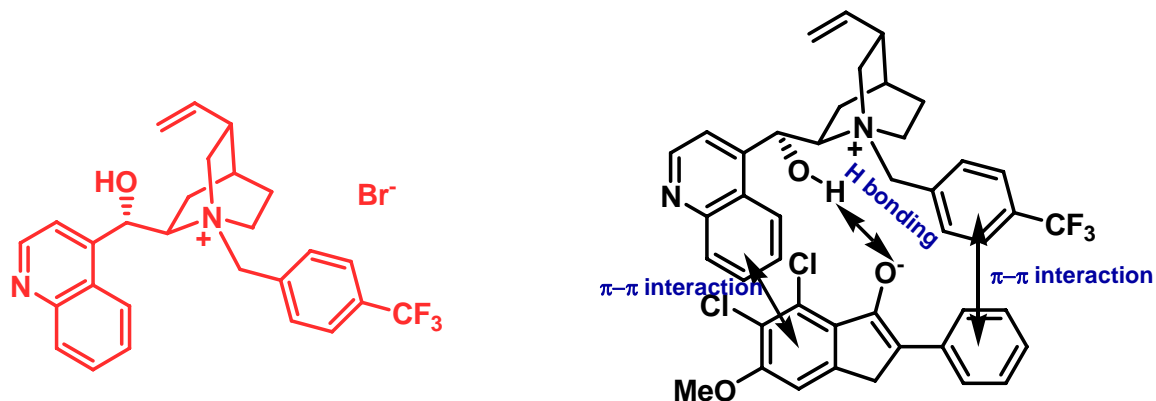
# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

### Indanones



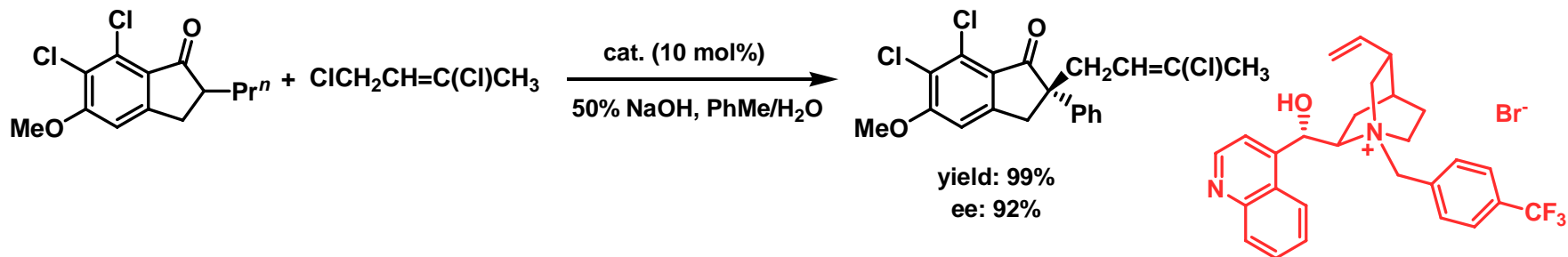
### Catalyst



# Enantioselective Organocatalysis (II): PTC

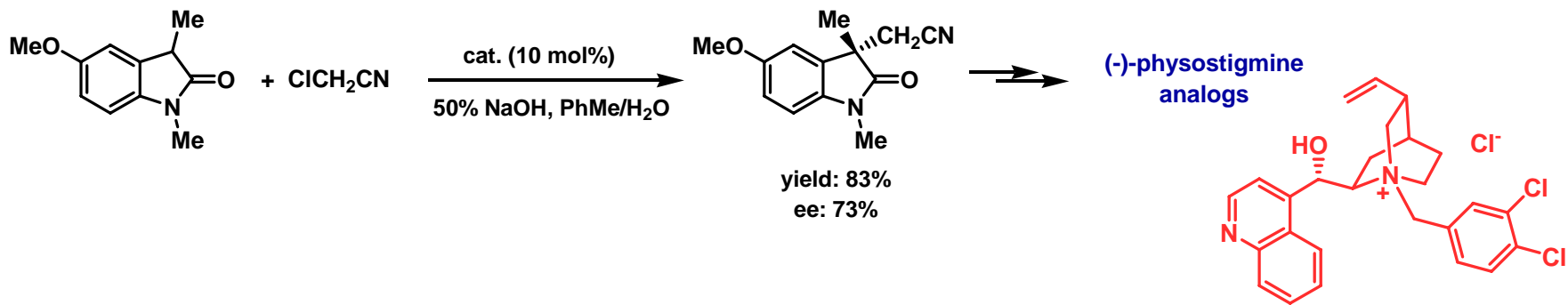
## Ila. Electrophilic Substitution of Enolates: Alkylation

### Indanones



U. H. Dolling et al., *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 476

### Oxindoles

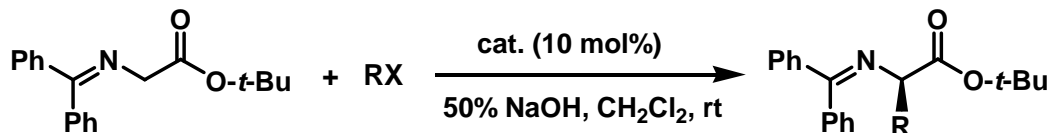


T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, 56, 872

# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

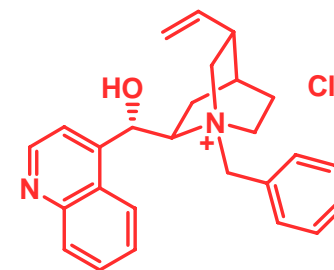
Iminic glycinates: 1<sup>st</sup> generation



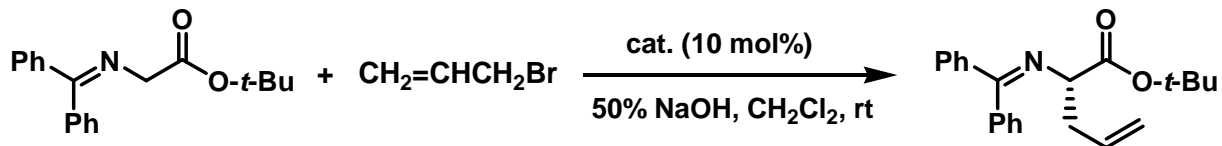
(R = Allyl, *n*-Bu, Bn, 4-ClBn)

yield: 61-81%  
ee: 52-62%

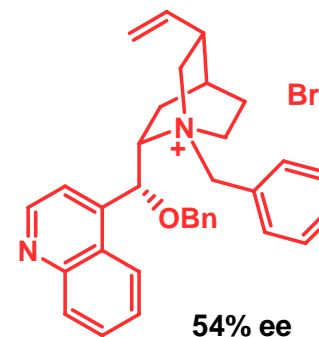
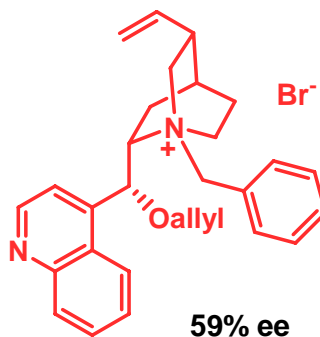
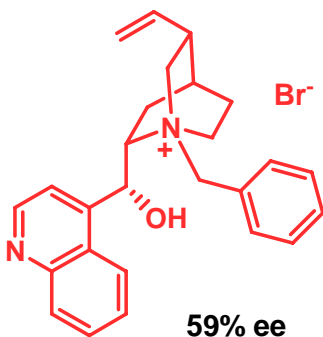
Catalyst



M. J. O'Donnell et al., *J. Am. Chem. Soc.* **1989**, *111*, 2353



Catalysts

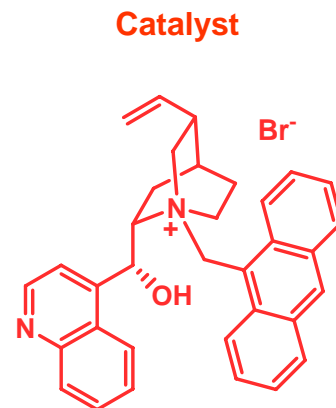
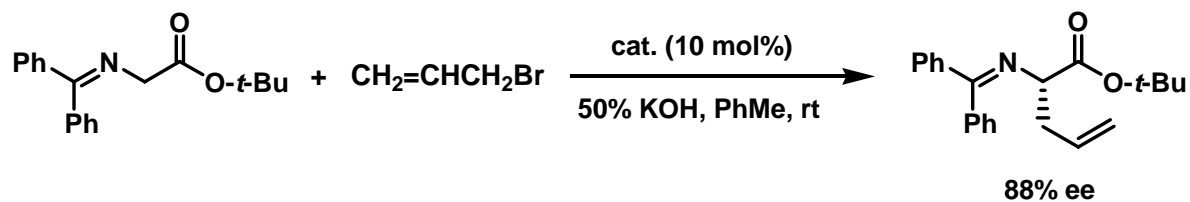


M. J. O'Donnell et al., *J. Org. Chem.* **1991**, *56*, 5181

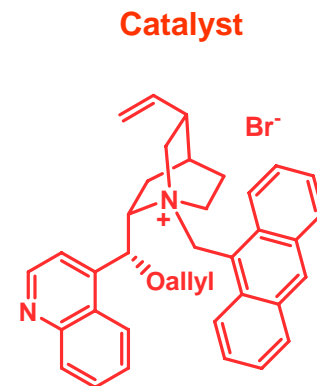
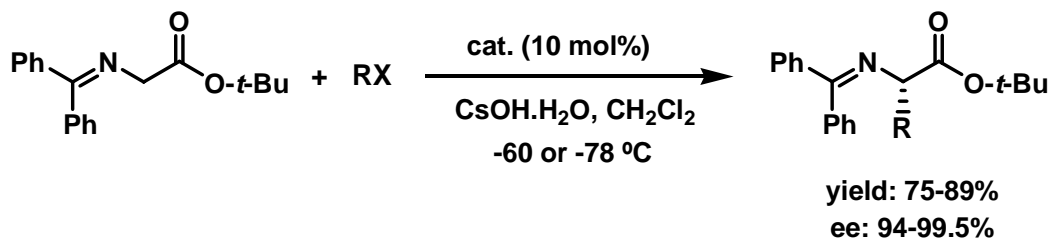
# Enantioselective Organocatalysis (II): PTC

## Ia. Electrophilic Substitution of Enolates: Alkylation

Iminic glycinates: 2<sup>nd</sup> generation



B. Lygo et al., *Tetrahedron Lett.* **1997**, 38, 2343; **2002**, 43, 8015; **2003**, 44, 5629

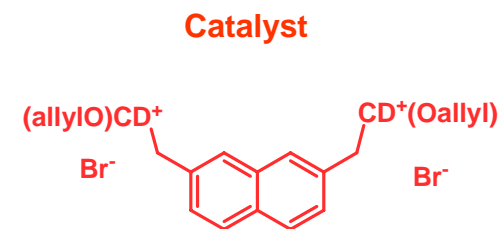
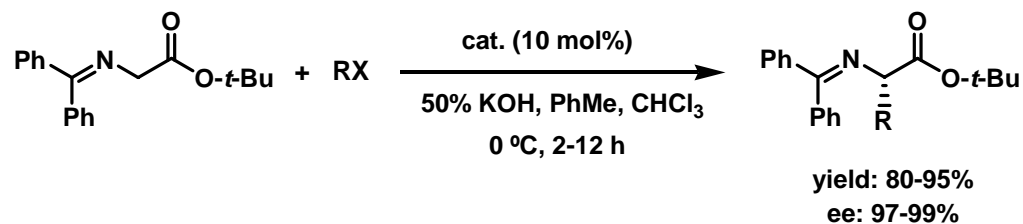


E. J. Corey et al., *J. Am. Chem. Soc.* **1997**, 119, 12414

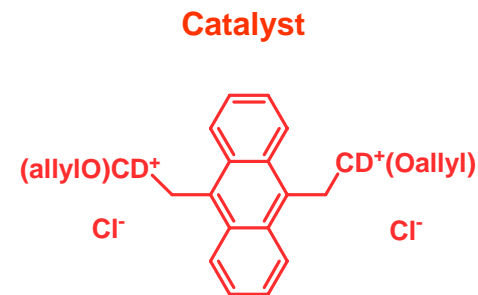
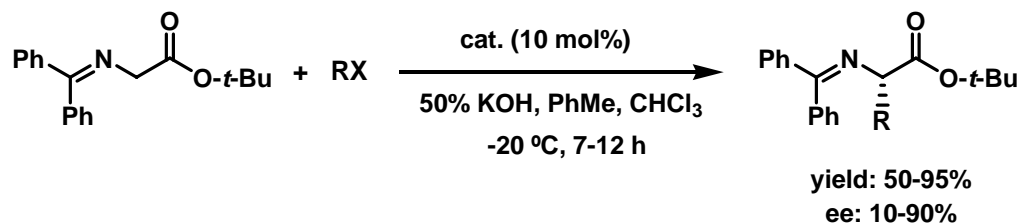
# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

### Iminic glycinates: 3<sup>rd</sup> generation



S.-s. Jew, H.-g. Park et al., *Angew. Chem. Int. Ed.* **2002**, 41, 3036

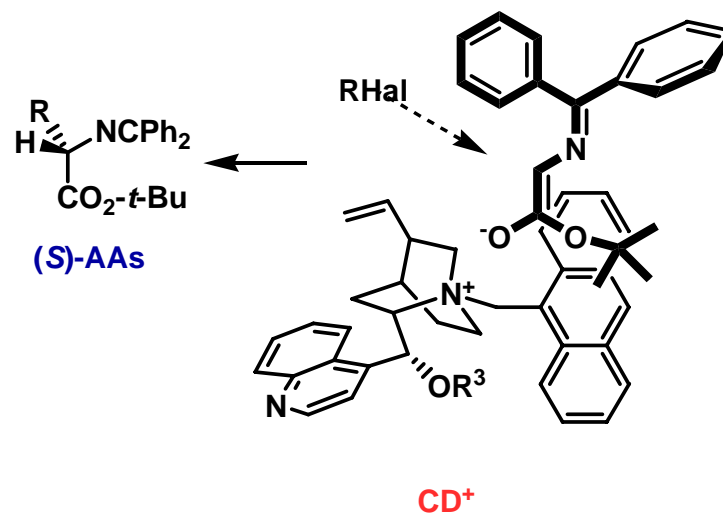


C. Nájera et al., *Tetrahedron: Asymmetry* **2002**, 13, 927

# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

Iminic glycinates

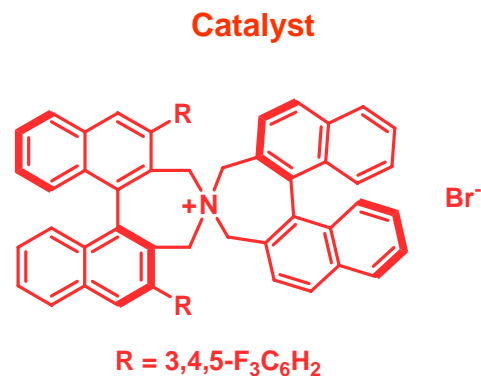
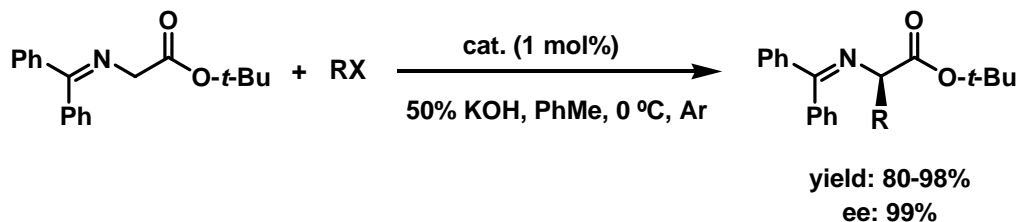


E. J. Corey et al., *J. Am. Chem. Soc.* **1997**, *119*, 12414

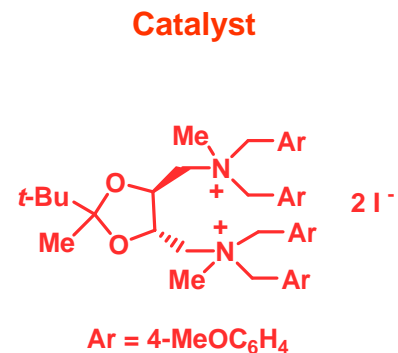
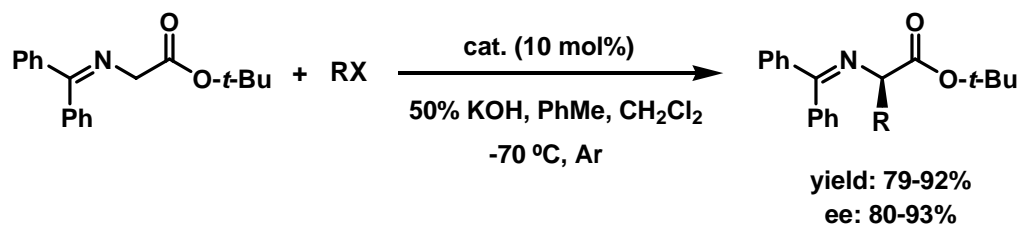
# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

### Iminic glycinates



K. Maruoka et al., *J. Am. Chem. Soc.* **1999**, 121, 6519

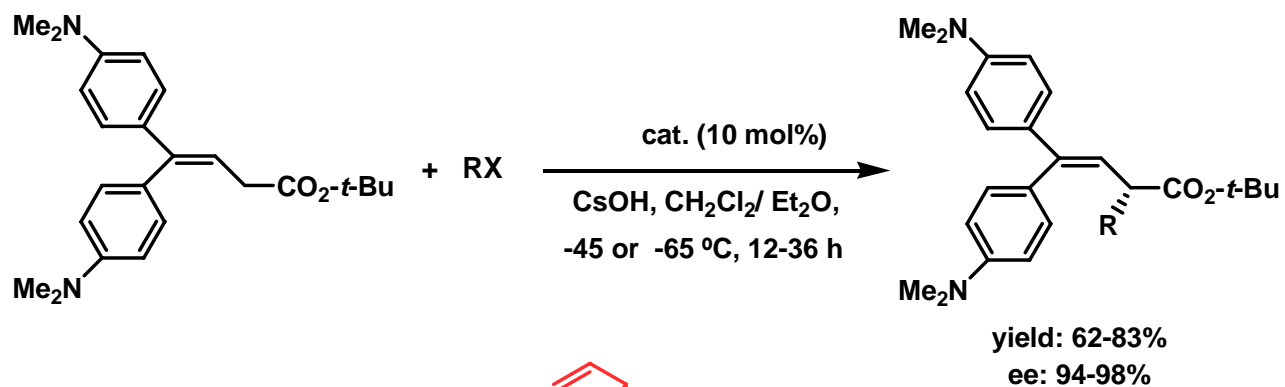


M. Shibasaki et al., *Tetrahedron Lett.* **2002**, 43, 9539

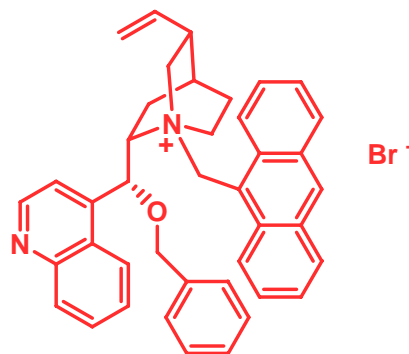
# Enantioselective Organocatalysis (II): PTC

## Ia. Electrophilic Substitution of Enolates: Alkylation

### Dienolates



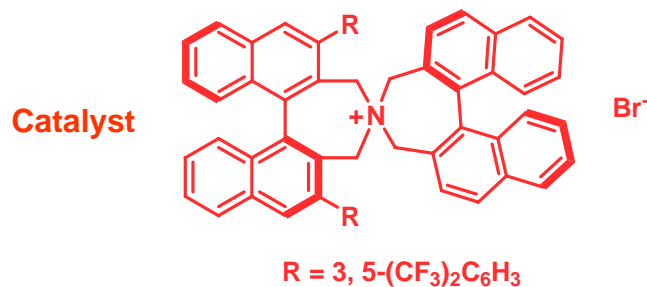
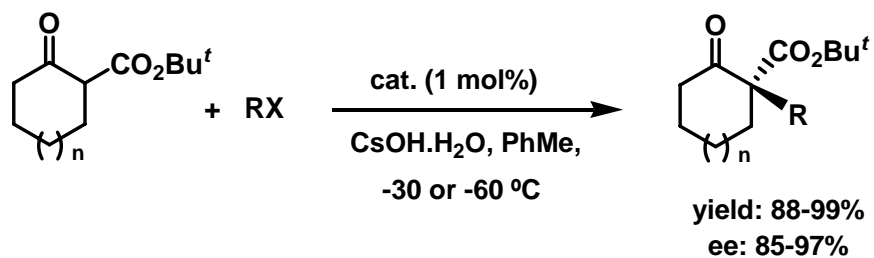
Catalyst



# Enantioselective Organocatalysis (II): PTC

## Ia. Electrophilic Substitution of Enolates: Alkylation

### $\beta$ -Keto Esters

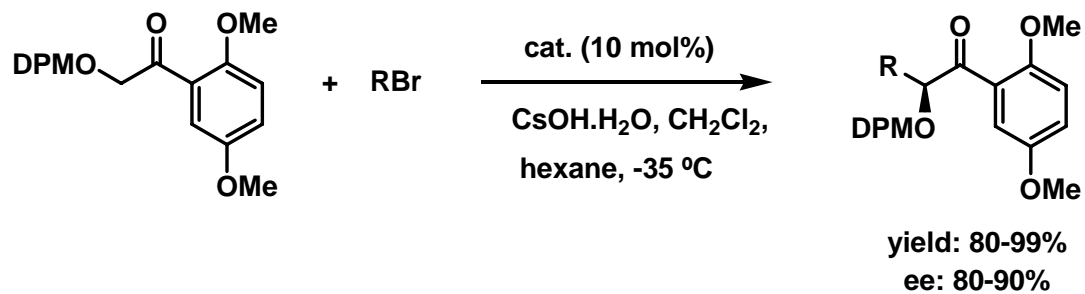


K. Maruoka et al., *Angew. Chem. Int. Ed.* **2003**, 42, 3796

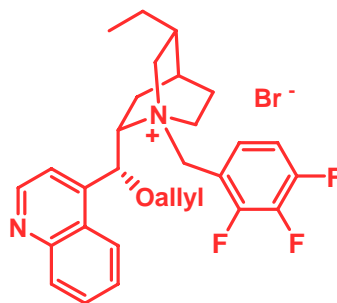
# Enantioselective Organocatalysis (II): PTC

## Ila. Electrophilic Substitution of Enolates: Alkylation

Ketones



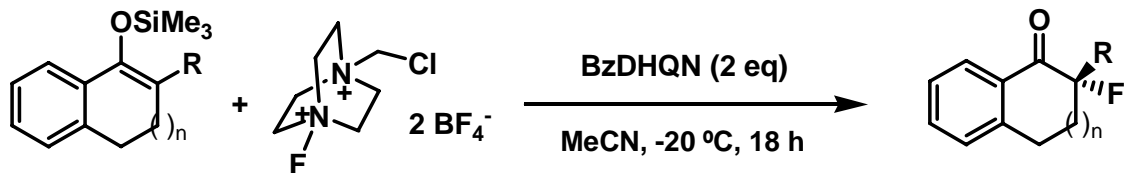
Catalyst



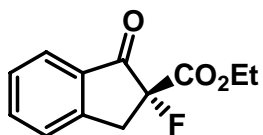
# Enantioselective Organocatalysis (II): PTC

## IIb. Electrophilic Substitution of Enolates: Halogenation

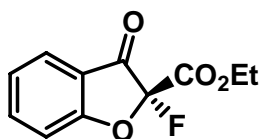
### Fluorination with Selectfluor



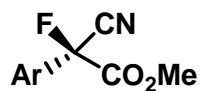
yield: 95-99%  
ee: 71-89%



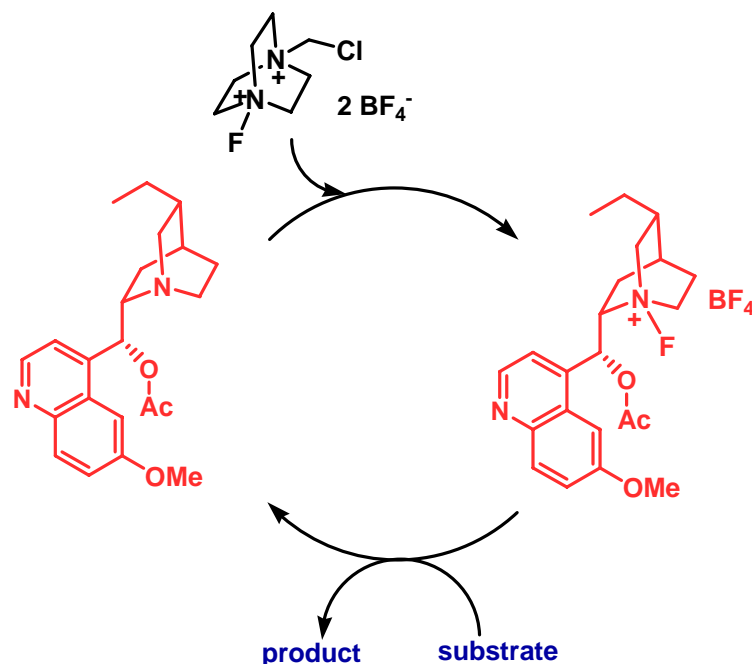
yield: 89%  
ee: 78%



yield: 92%  
ee: 80%



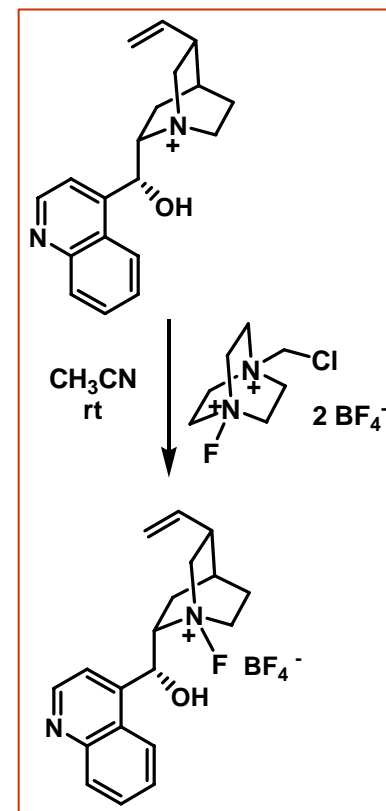
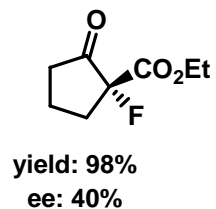
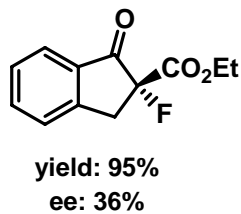
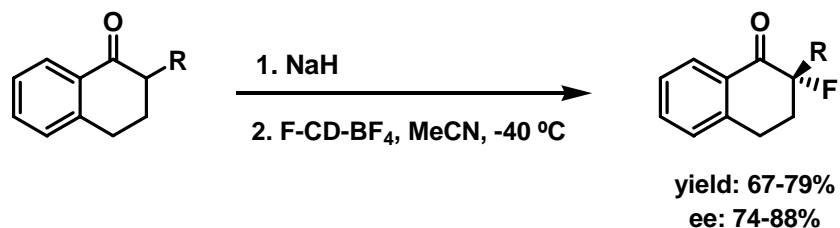
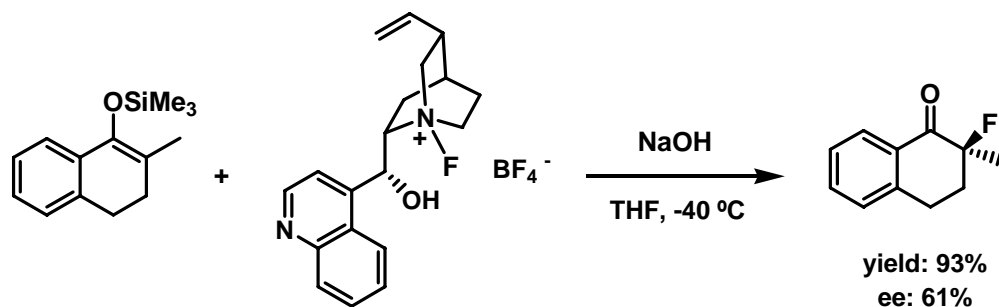
yield: 80-87%  
ee: 76-87%



# Enantioselective Organocatalysis (II): PTC

## IIb. Electrophilic Substitution of Enolates: Halogenation

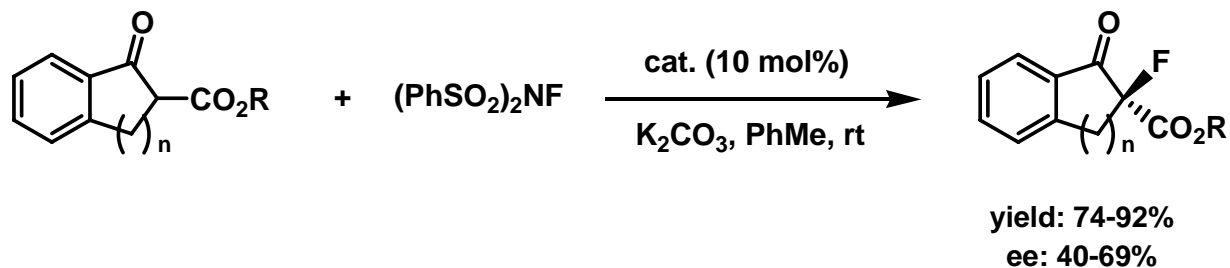
### Fluorination with Selectfluor



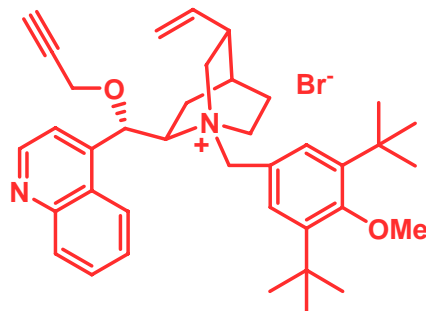
# Enantioselective Organocatalysis (II): PTC

## IIb. Electrophilic Substitution of Enolates: Halogenation

### Fluorination



Catalyst



# Enantioselective Organocatalysis (II): PTC

## III. Nucleophilic Addition to C=O

IIIa. Aldol reactions

IIIb. Nitroaldol reactions

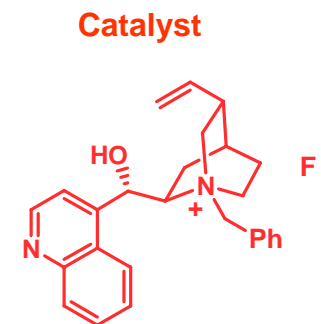
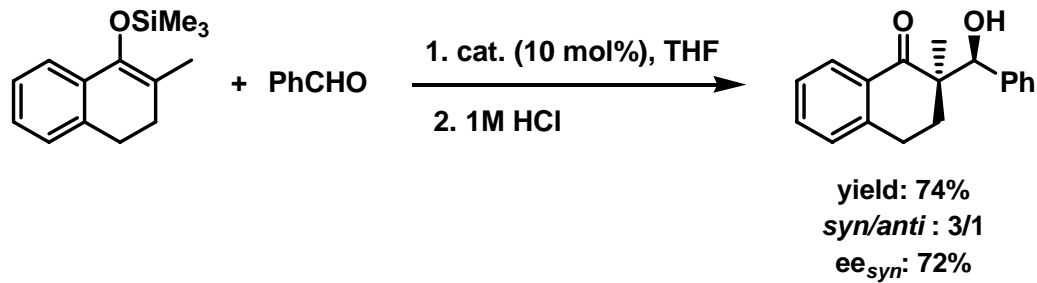
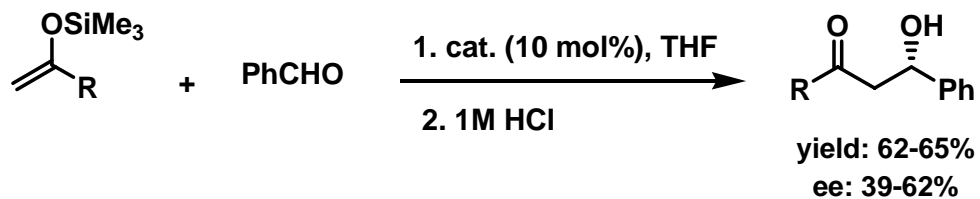
IIIc. Trifluoromethylation

IIId. Darzens reaction

# Enantioselective Organocatalysis (II): PTC

## IIIa. Nucleophilic Addition to C=O: Aldol reactions

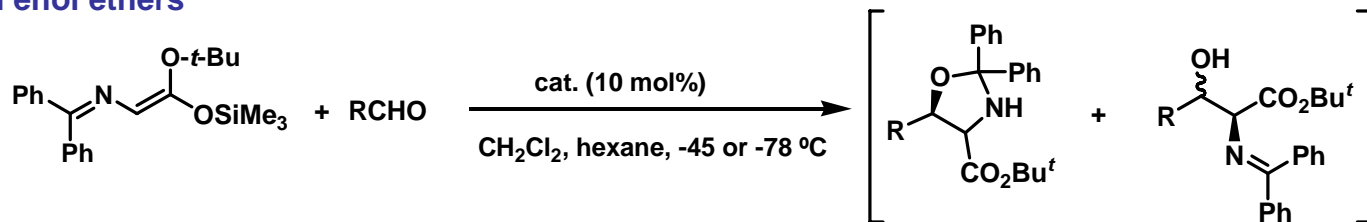
### Silyl enol ethers



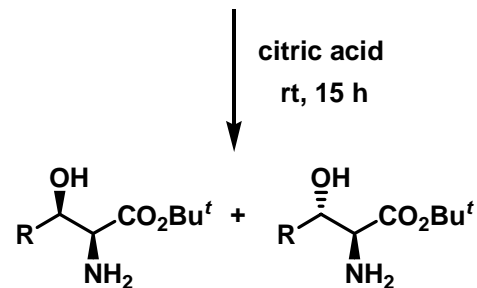
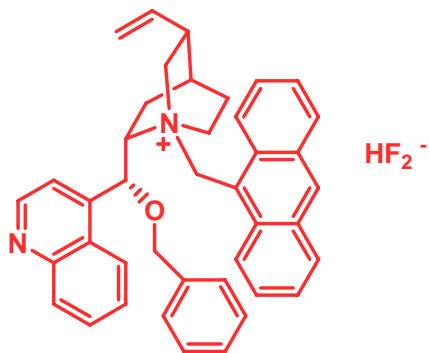
# Enantioselective Organocatalysis (II): PTC

## IIIa. Nucleophilic Addition to C=O: Aldol reactions

### Silyl enol ethers



### Catalyst

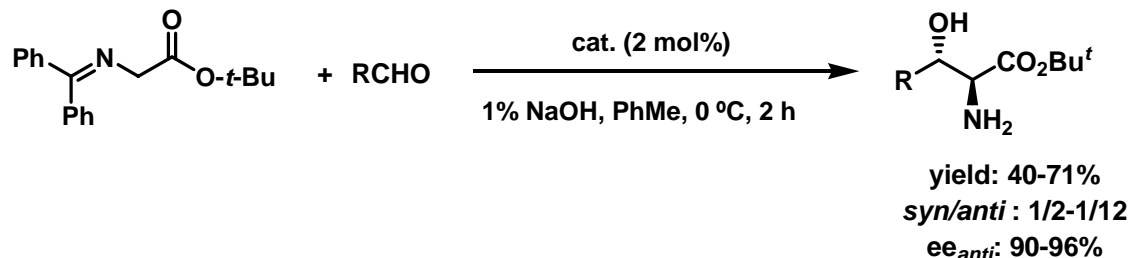


yield: 61-81%  
*syn/anti* : 1/1-13/1  
*ee<sub>syn</sub>*: 72-95%

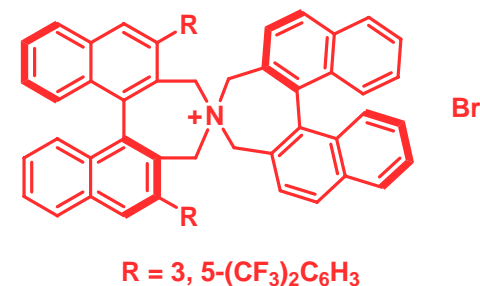
# Enantioselective Organocatalysis (II): PTC

## IIIa. Nucleophilic Addition to C=O: Aldol reactions

### Iminic glycinates

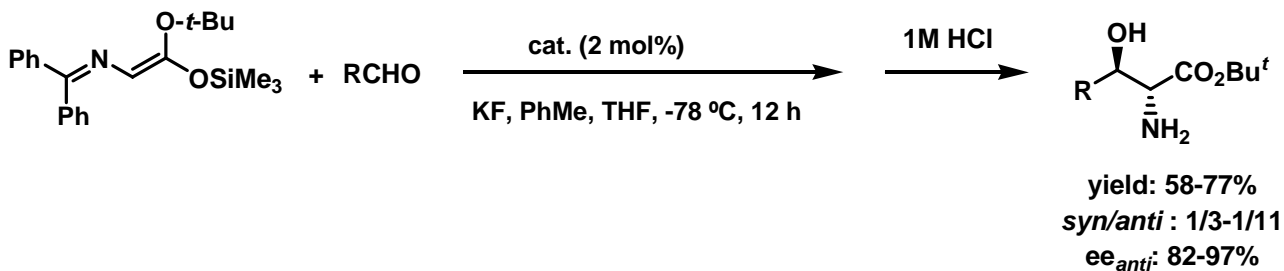


### Catalyst

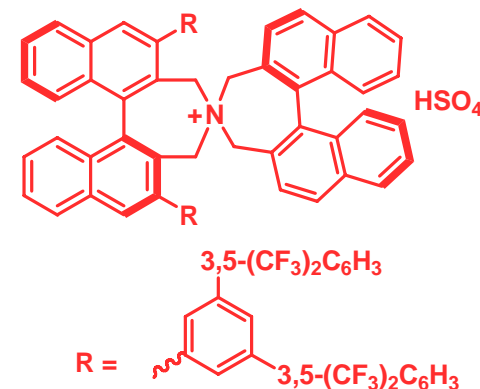


K. Maruoka et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4542

### Silyl enol ethers



### Catalyst

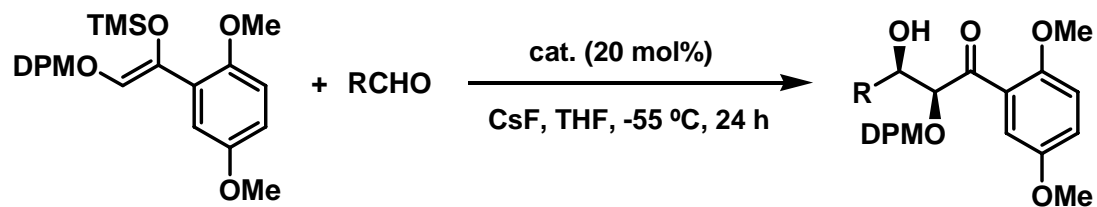


K. Maruoka et al., *Adv. Synth. Catal.* **2004**, 346, 1073

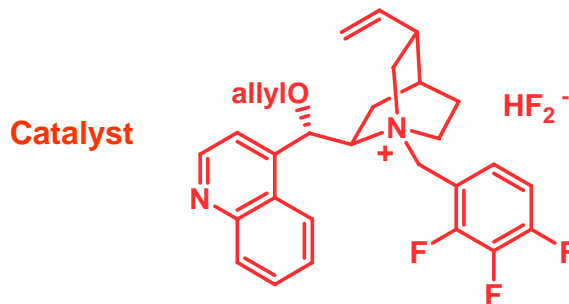
# Enantioselective Organocatalysis (II): PTC

## IIIa. Nucleophilic Addition to C=O: Aldol reactions

### Silyl enol ethers

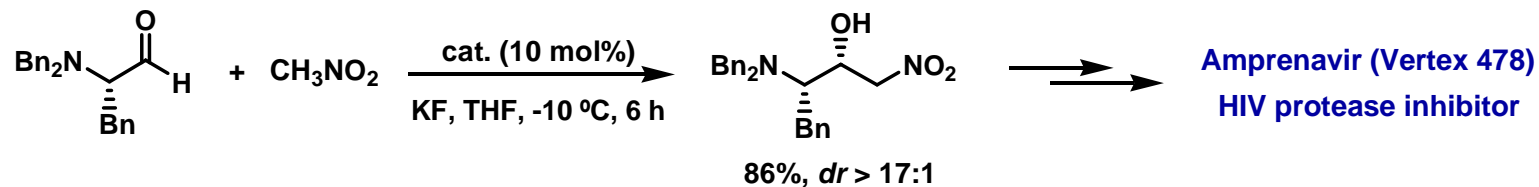


yield: 23-86%  
*syn/anti* : 10/1-99/1  
*ee<sub>syn</sub>*: 44-83%

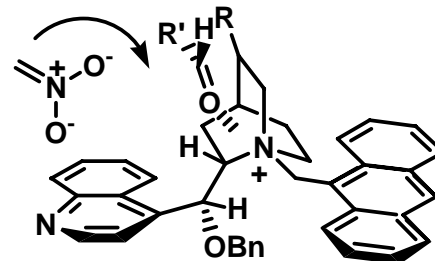
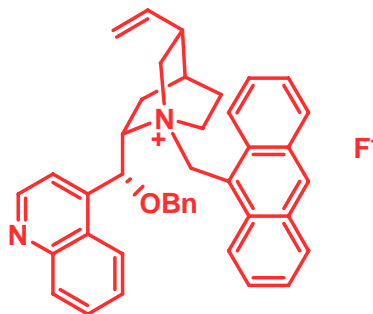


# Enantioselective Organocatalysis (II): PTC

## IIIb. Nucleophilic Addition to C=O: Nitroaldol reactions

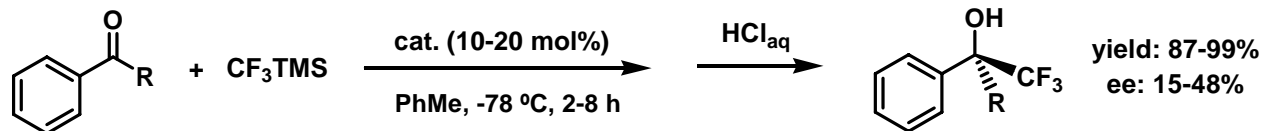


Catalyst

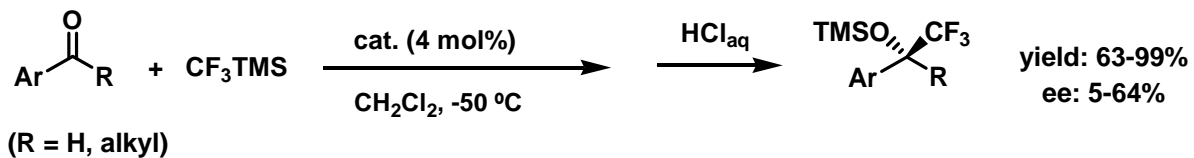


# Enantioselective Organocatalysis (II): PTC

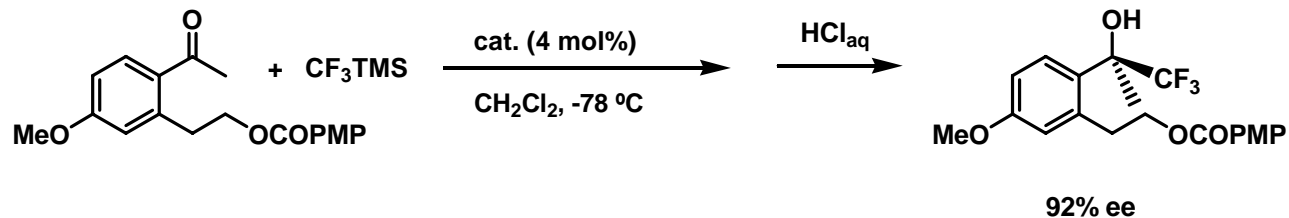
## IIIc. Nucleophilic Addition to C=O: Trifluoromethylation



K. Iseki et al., *Tetrahedron. Lett.* **2005**, 35, 3137

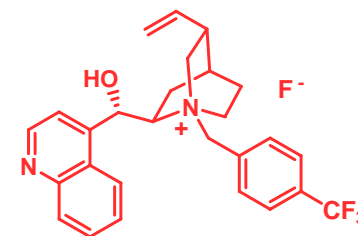


(R = H, alkyl)

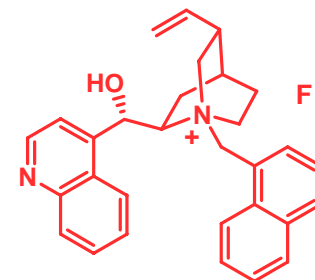


S. Caron et al., *Synthesis* **2003**, 1693

Catalyst

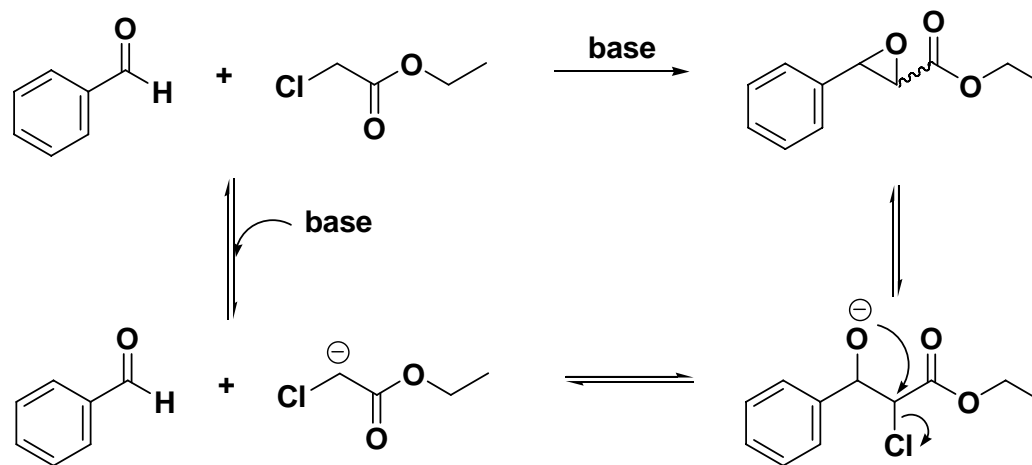


Catalyst



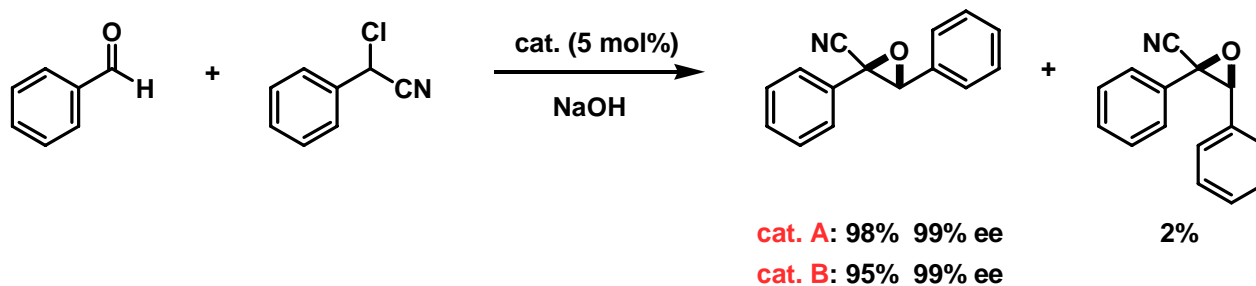
## Enantioselective Organocatalysis (II): PTC

### III d. Nucleophilic Addition to C=O: Darzens reaction

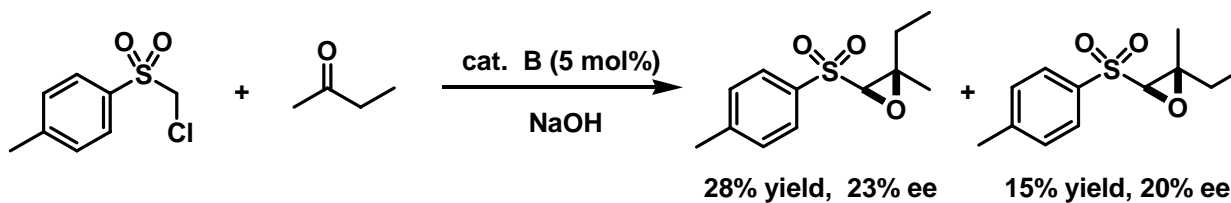
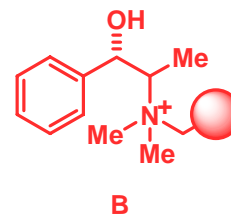
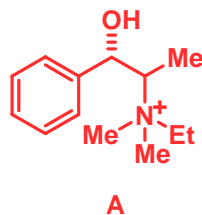


# Enantioselective Organocatalysis (II): PTC

## IIId. Nucleophilic Addition to C=O: Darzens reaction

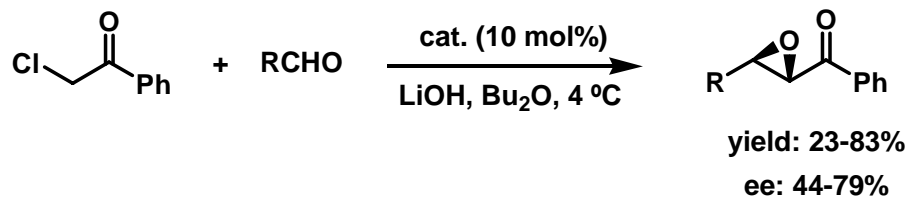


Catalysts

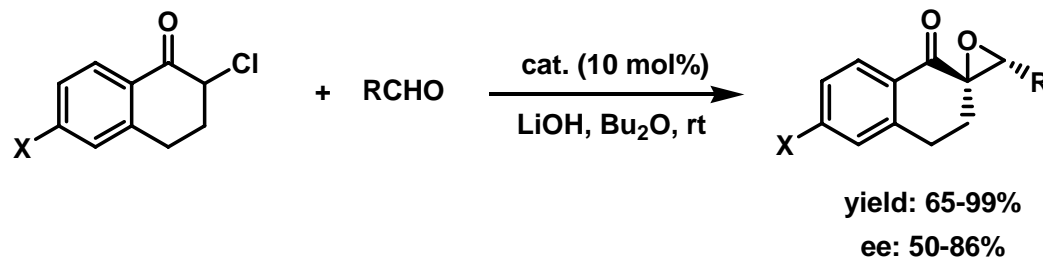
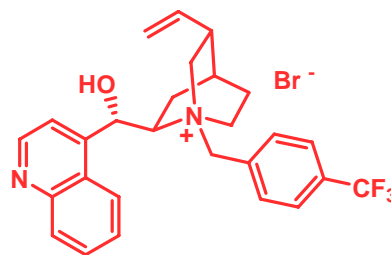


# Enantioselective Organocatalysis (II): PTC

## IIId. Nucleophilic Addition to C=O: Darzens reaction

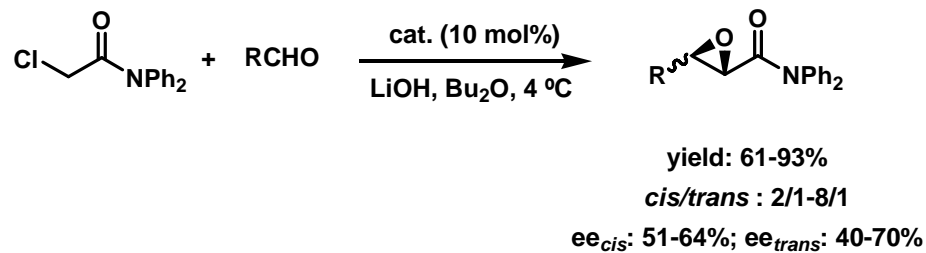


Catalyst

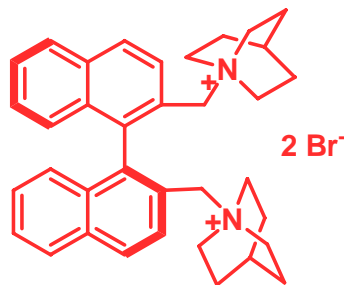


# Enantioselective Organocatalysis (II): PTC

## IIId. Nucleophilic Addition to C=O: Darzens reaction



Catalyst



## **Enantioselective Organocatalysis (II): PTC**

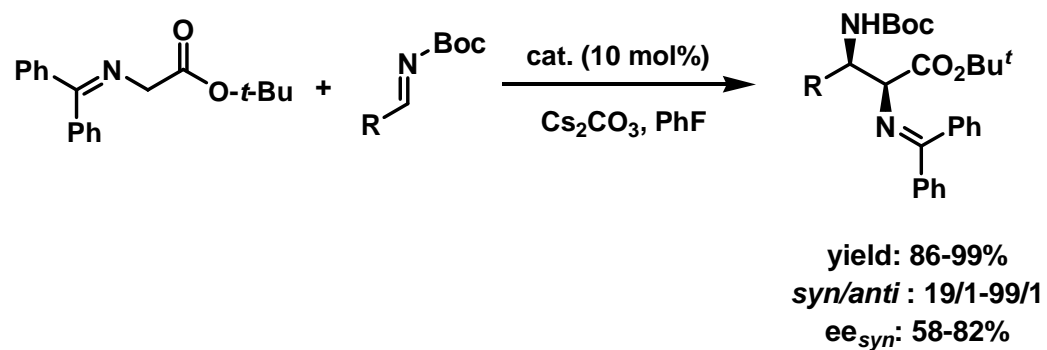
### **IV. Nucleophilic Addition to C=N**

**IVa. Imino esters**

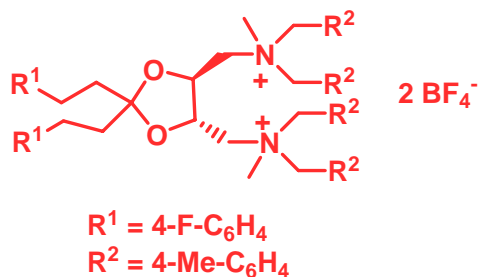
**IVb. Nitromethane**

# Enantioselective Organocatalysis (II): PTC

## IVa. Nucleophilic Addition to C=N: Imino esters

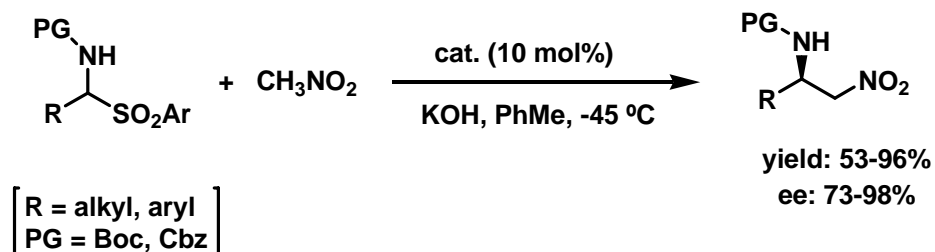


Catalysts

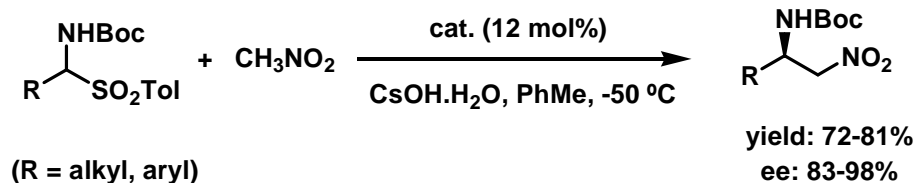


# Enantioselective Organocatalysis (II): PTC

## IVb. Nucleophilic Addition to C=N: Nitromethane

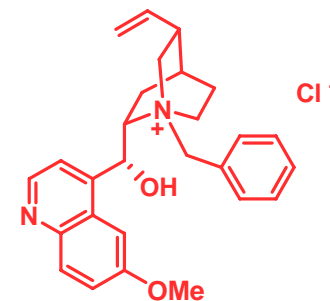


R. P. Herrera, L. Bernardi et al., *Angew. Chem. Int. Ed.* **2005**, *44*, 7975



C. Palomo et al., *J. Am. Chem. Soc.* **2005**, *127*, 17622

Catalyst



## **Enantioselective Organocatalysis (II): PTC**

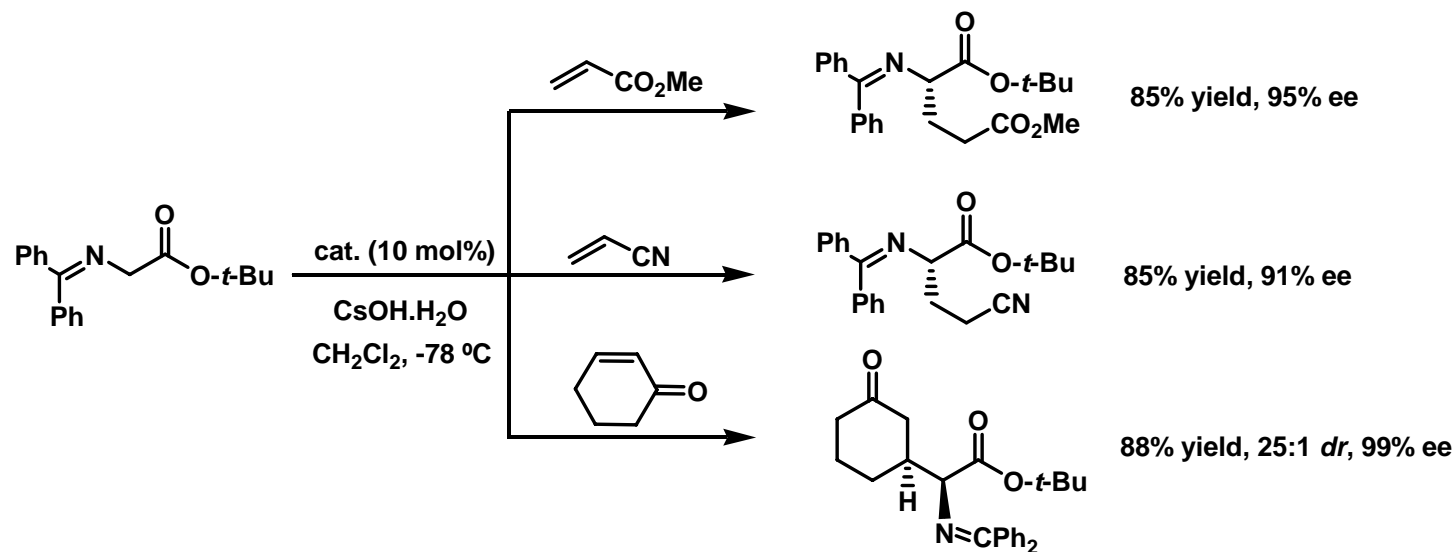
### **V. Additions to alkenes**

#### **Va. Michael additions**

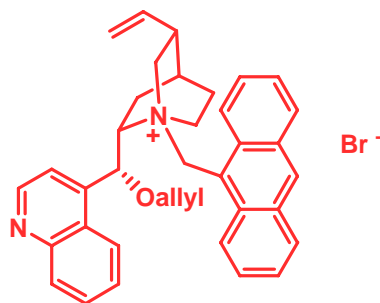
#### **Vb. Epoxidation reactions**

# Enantioselective Organocatalysis (II): PTC

## Va. Additions to alkenes: Michael additions

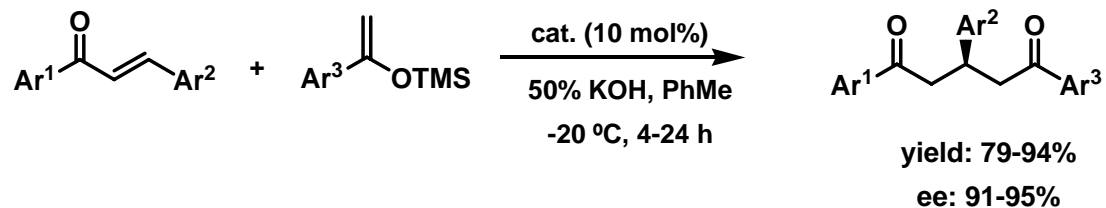


Catalyst

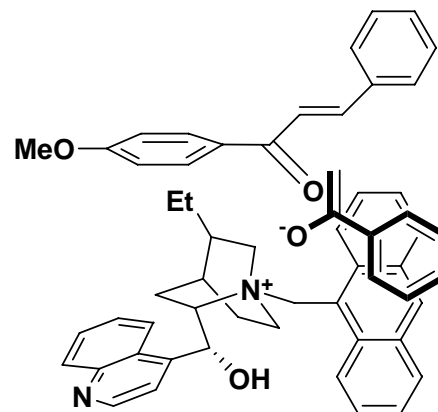
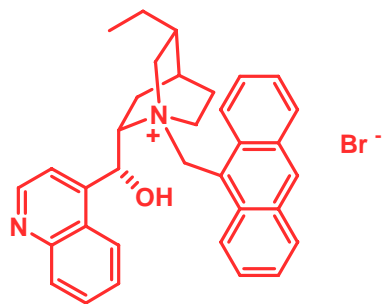


# Enantioselective Organocatalysis (II): PTC

## Va. Additions to alkenes: Michael additions

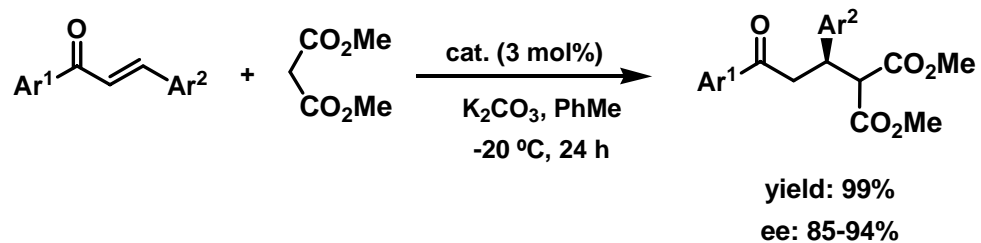


Catalyst

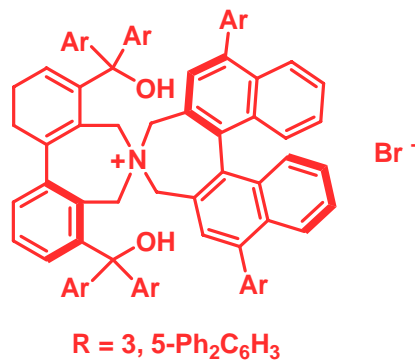


# Enantioselective Organocatalysis (II): PTC

## Va. Additions to alkenes: Michael additions

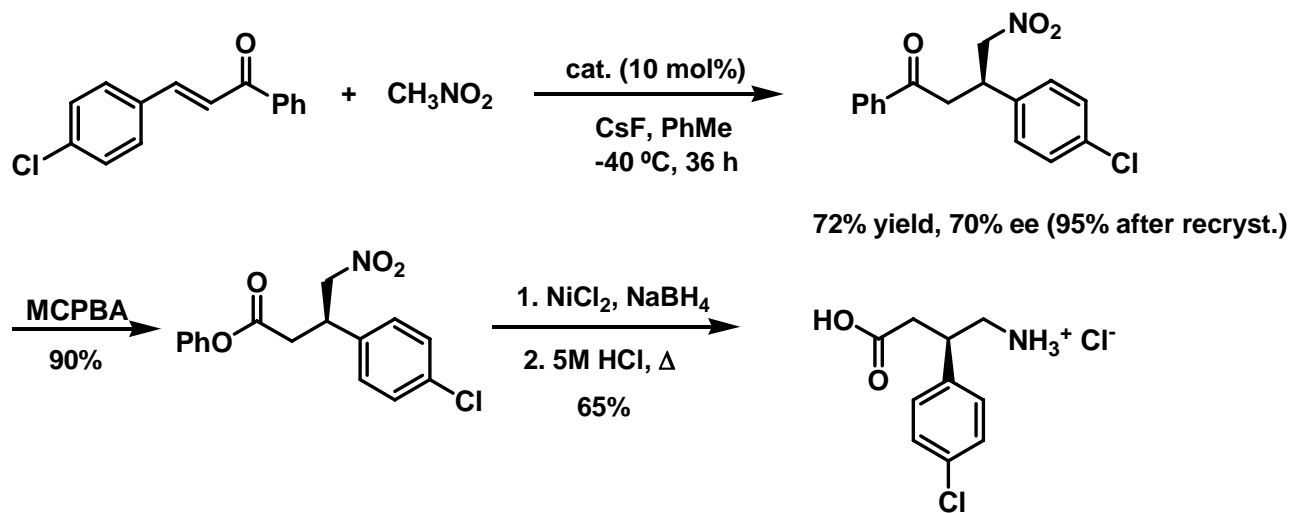


Catalyst



# Enantioselective Organocatalysis (II): PTC

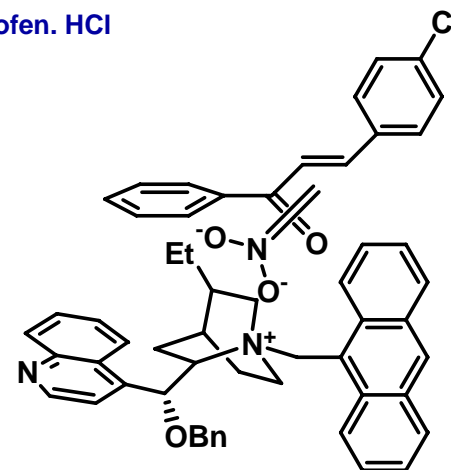
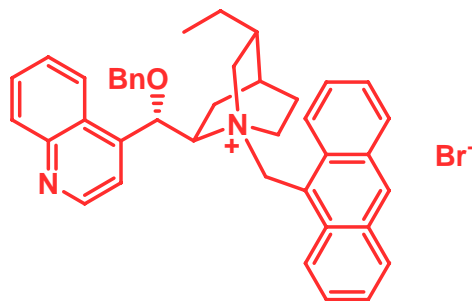
## Va. Additions to alkenes: Michael additions



72% yield, 70% ee (95% after recryst.)

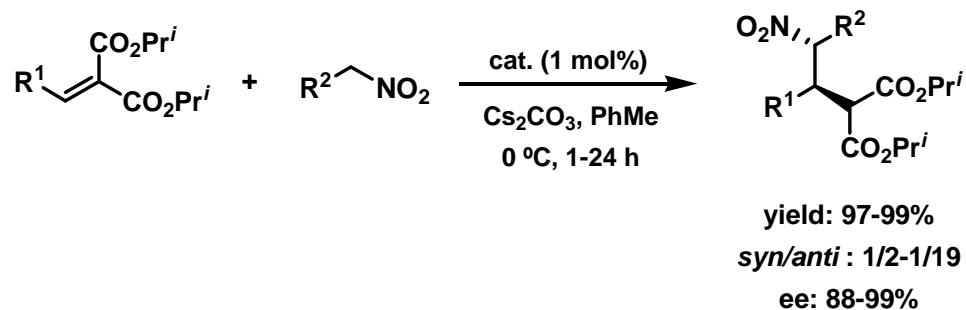
(R)-baclofen. HCl

Catalyst

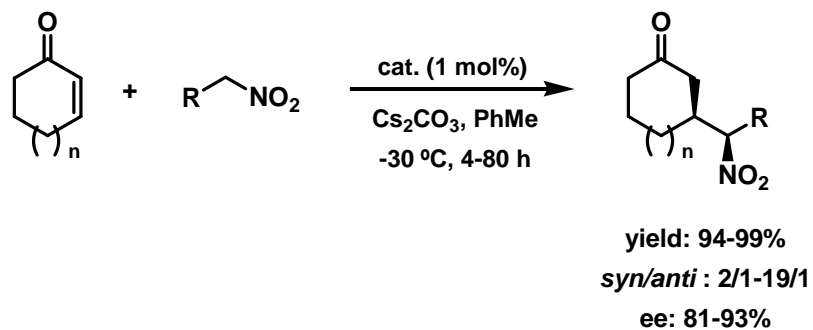


# Enantioselective Organocatalysis (II): PTC

## Va. Additions to alkenes: Michael additions

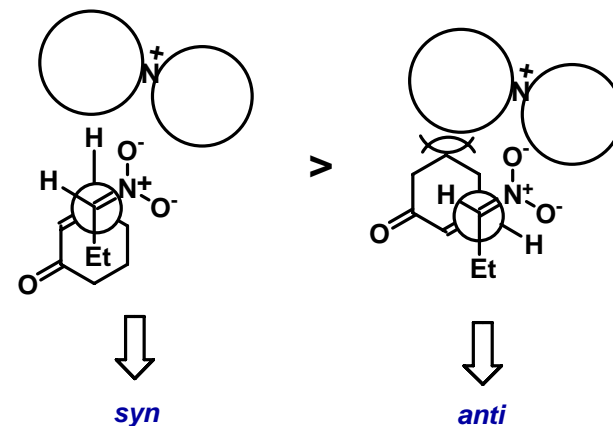
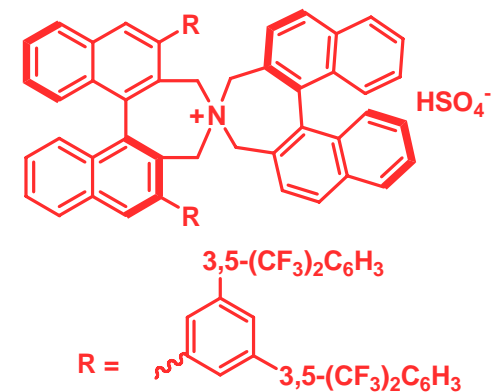


K. Maruoka et al., *J. Am. Chem. Soc.* **2004**, 126, 11790



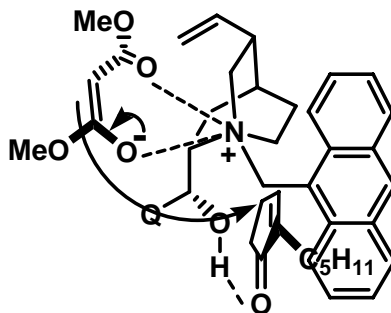
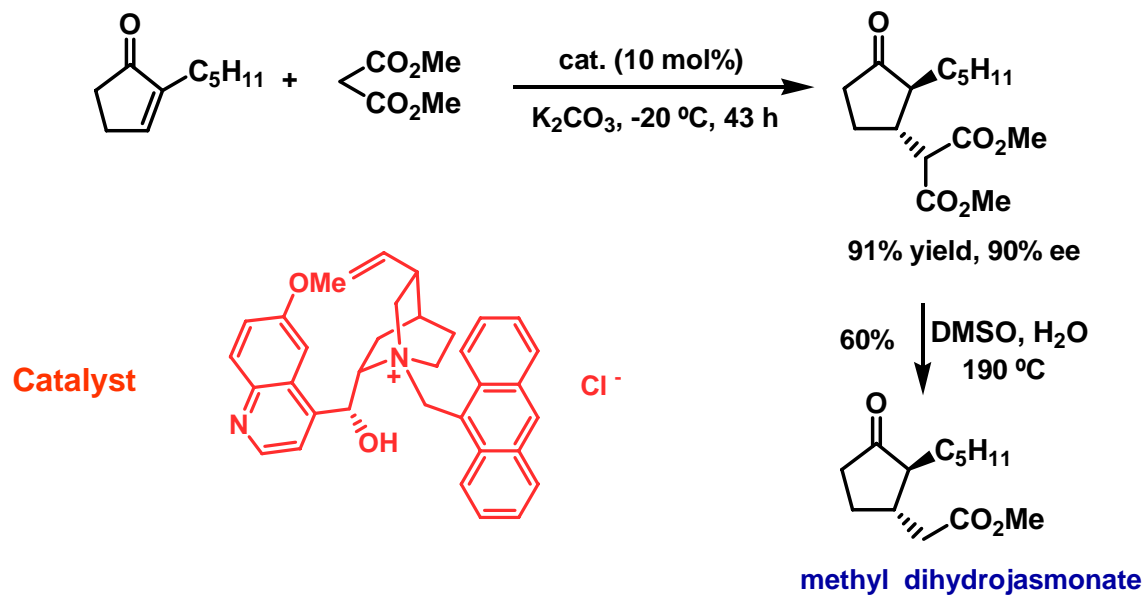
K. Maruoka et al., *Org. Lett.* **2005**, 7, 5143

## Catalyst



# Enantioselective Organocatalysis (II): PTC

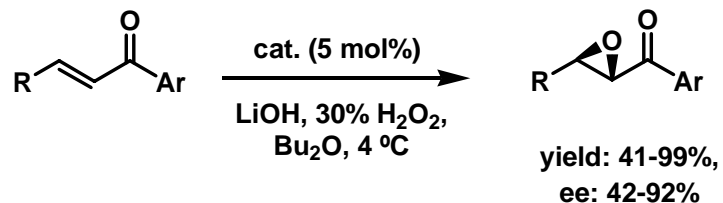
## Va. Additions to alkenes: Michael additions



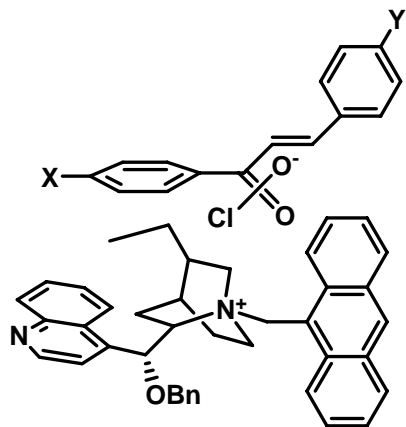
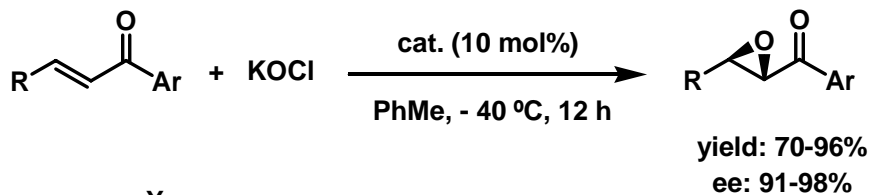
# Enantioselective Organocatalysis (II): PTC

## Vb. Additions to alkenes: Epoxidation reactions

### Enones

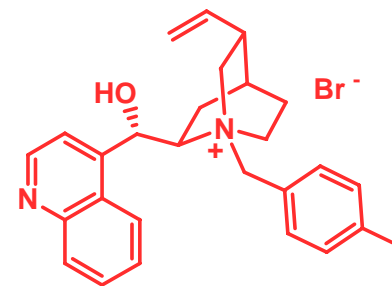


T. Shioiri et al., *Tetrahedron Lett.* **1998**, 39, 7563

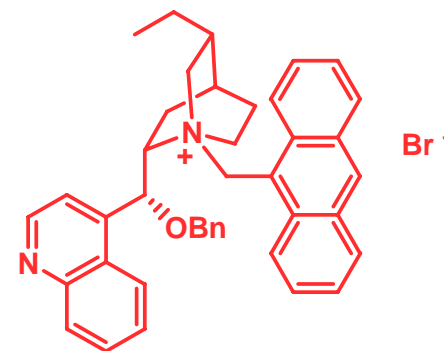


E. J. Corey et al., *Org. Lett.* **1999**, 1, 1287

### Catalyst



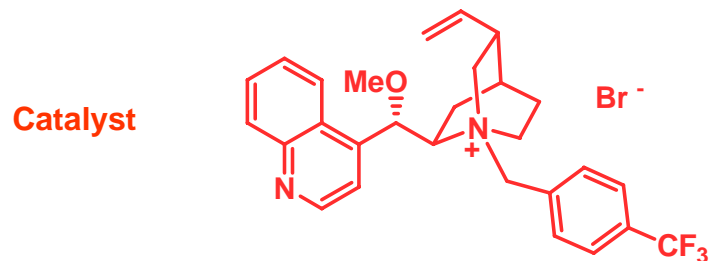
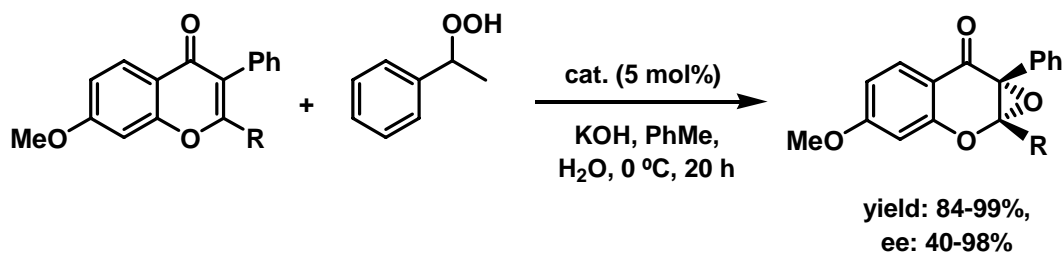
### Catalyst



# Enantioselective Organocatalysis (II): PTC

## Vb. Additions to alkenes: Epoxidation reactions

### Isoflavones: Weitz-Scheffer conditions



# Enantioselective Organocatalysis

## Conclusions

**Clean and efficient processes**

**High yield and enantioselectivity**

**Operational simplicity**

**Mild reaction conditions**

**Easy recoverability**

**Low cost**