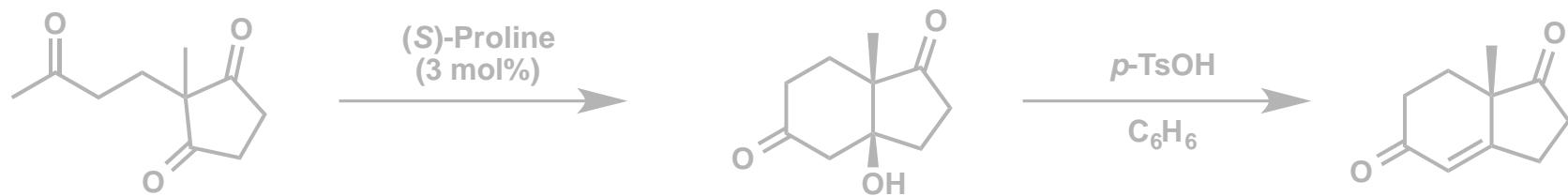


*Asymmetric Organocatalytic Transformations*  
*Lewis Base Organocatalysis*

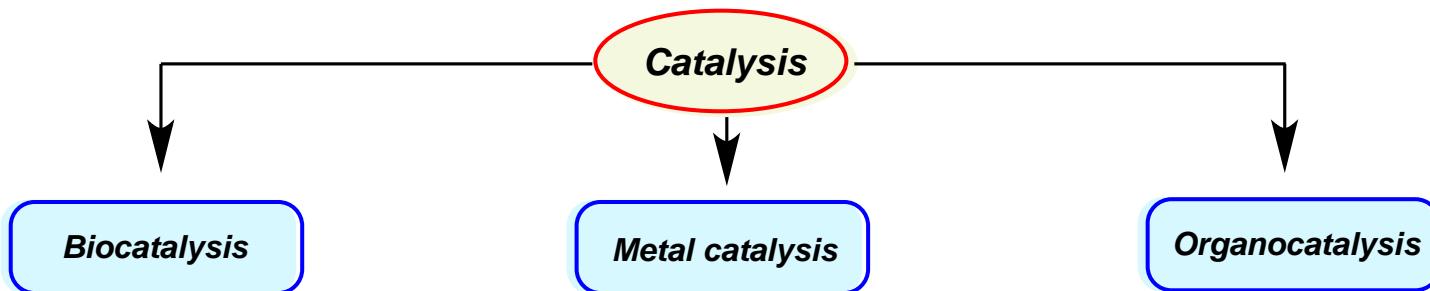


*Stoltz / Reisman Group Meeting*  
*January 09, 2015*

*Seojung Han*

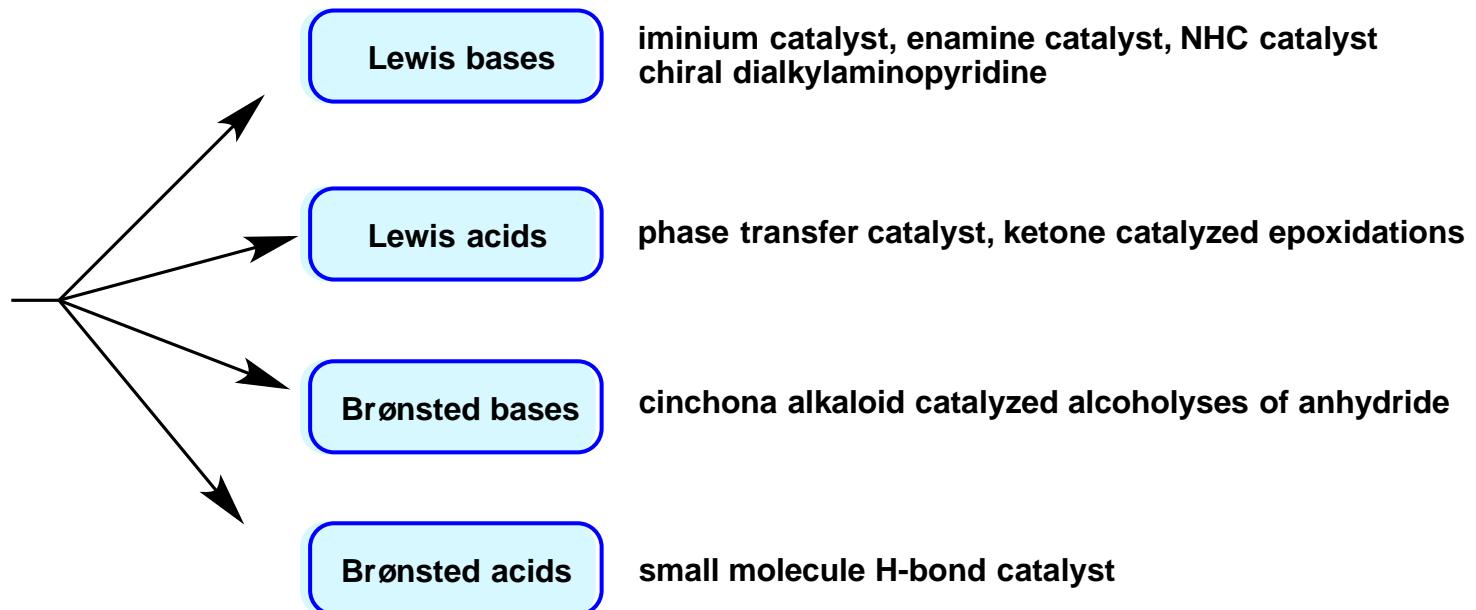


# *Organocatalysis*

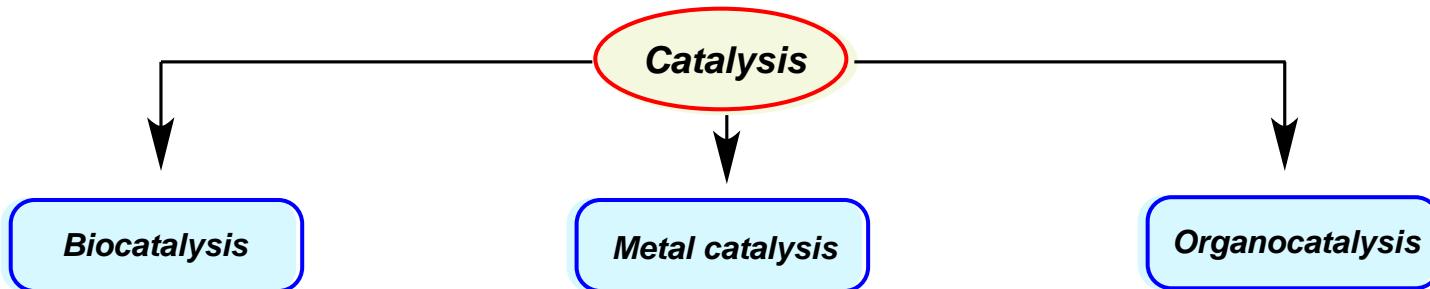


· **Organocatalysis:** The catalysis with small organic molecules, where an inorganic element is not part of the active principle.

## **Organocatalysis**



## *Organocatalysis*



· **Organocatalysis:** The catalysis with small organic molecules, where an inorganic element is not part of the active principle.

### **Organocatalysis**

#### Lewis bases

iminium catalyst, enamine catalyst, NHC catalyst  
chiral dialkylaminopyridine

#### Lewis acids

phase transfer catalyst, ketone catalyzed epoxidations

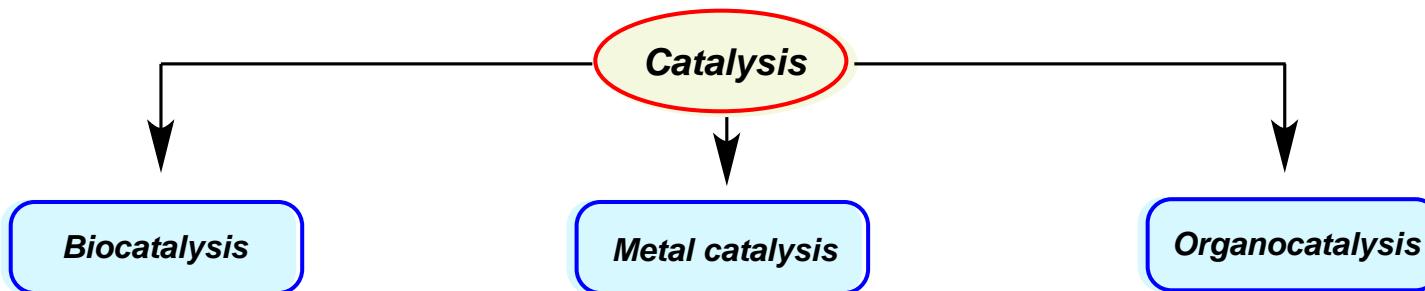
#### Brønsted bases

cinchona alkaloid catalyzed alcoholyses of anhydride

#### Brønsted acids

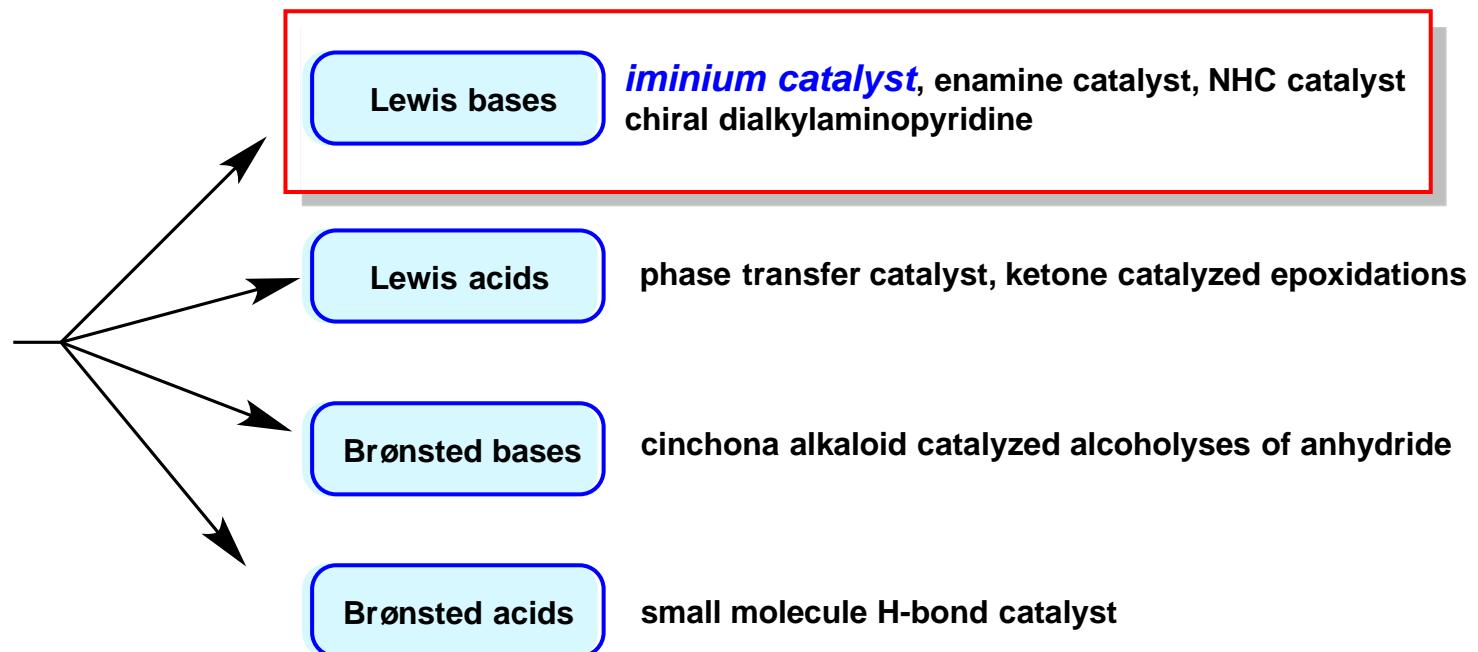
small molecule H-bond catalyst

# Organocatalysis

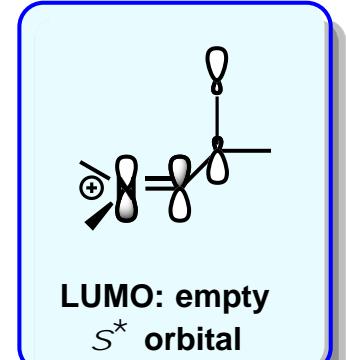
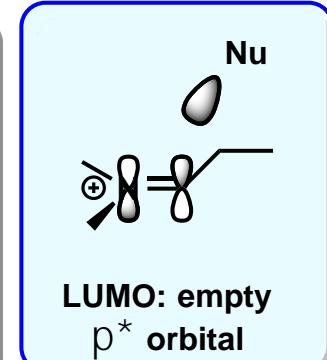
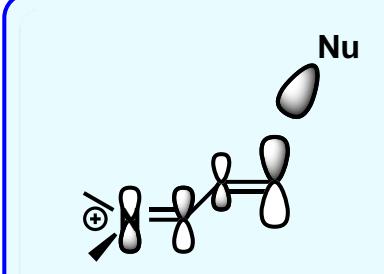
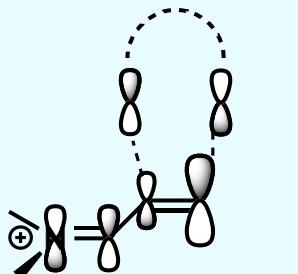
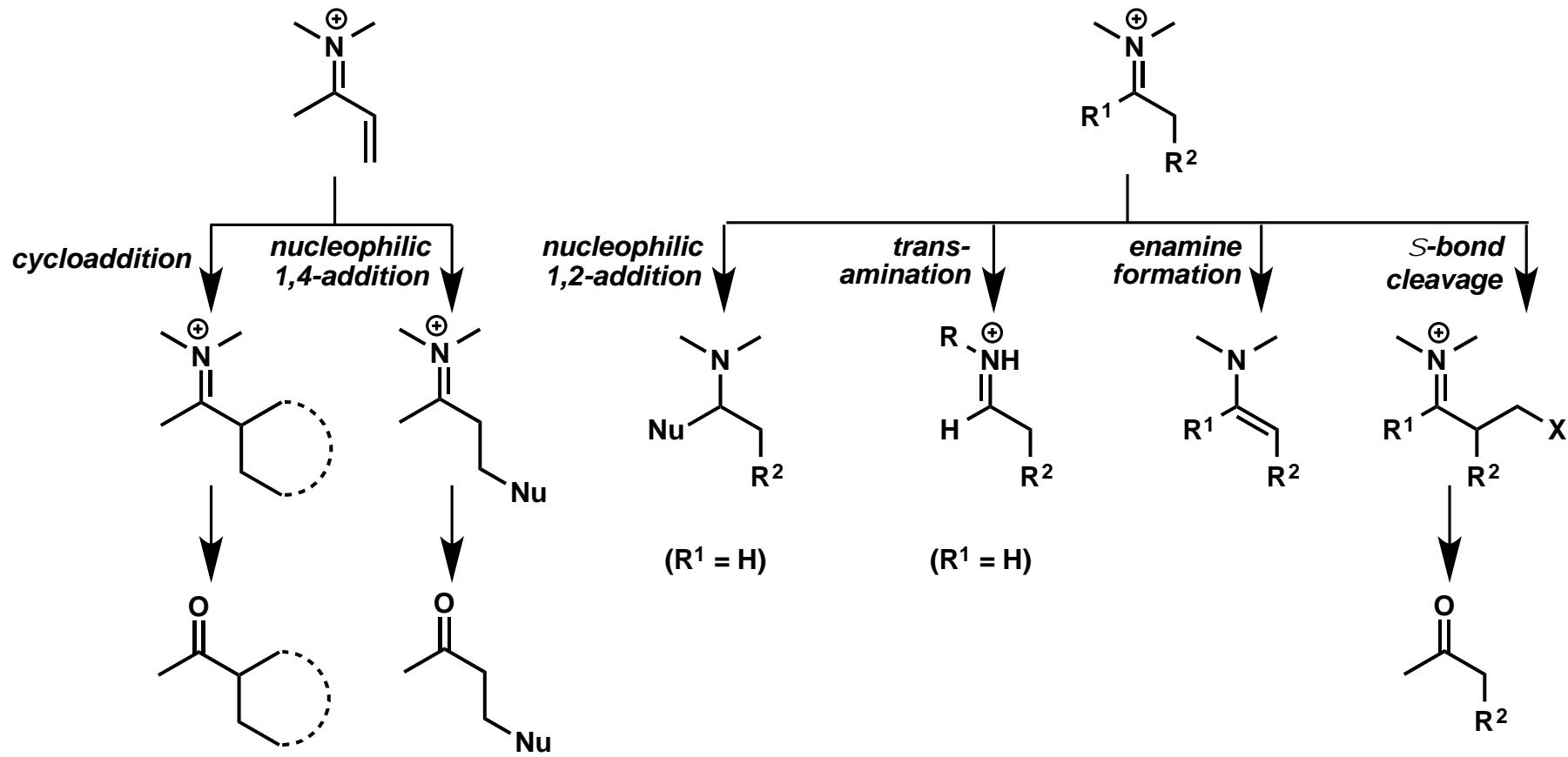


**Organocatalysis:** The catalysis with small organic molecules, where an inorganic element is not part of the active principle.

## Organocatalysis



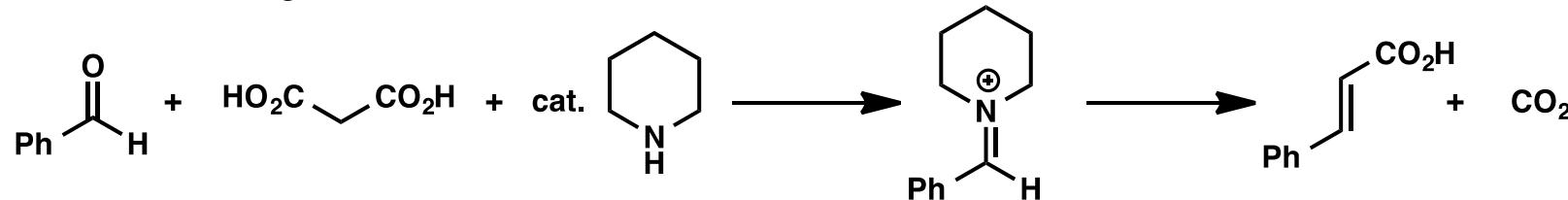
# Lewis Base Catalysis: Iminium Catalysis



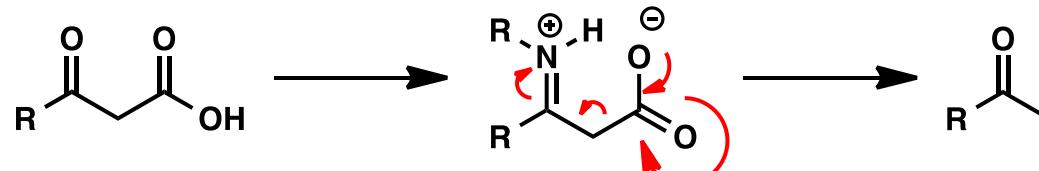
# Lewis Base Catalysis: Iminium Catalysis

## Historical Development of Iminium Catalysis

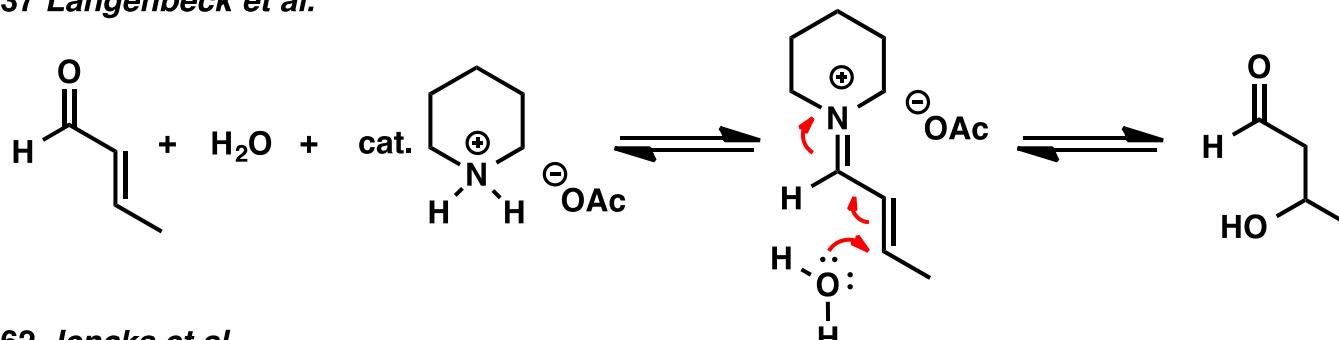
1894-1898 Knoevenagel condensation



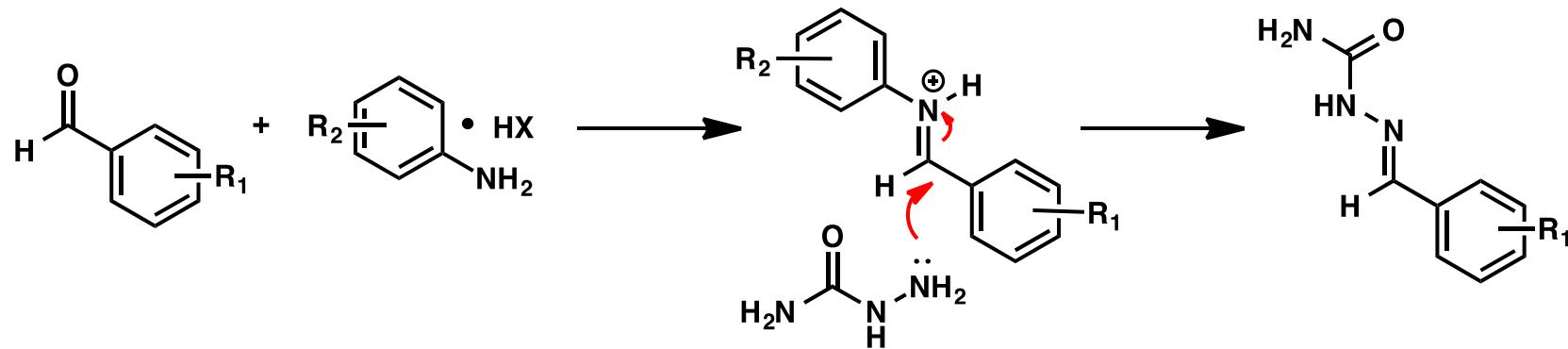
1907 Pollak et al.



1937 Langenbeck et al.



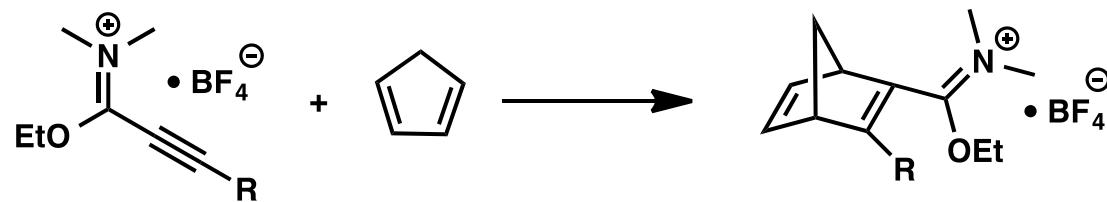
1962 Jencks et al.



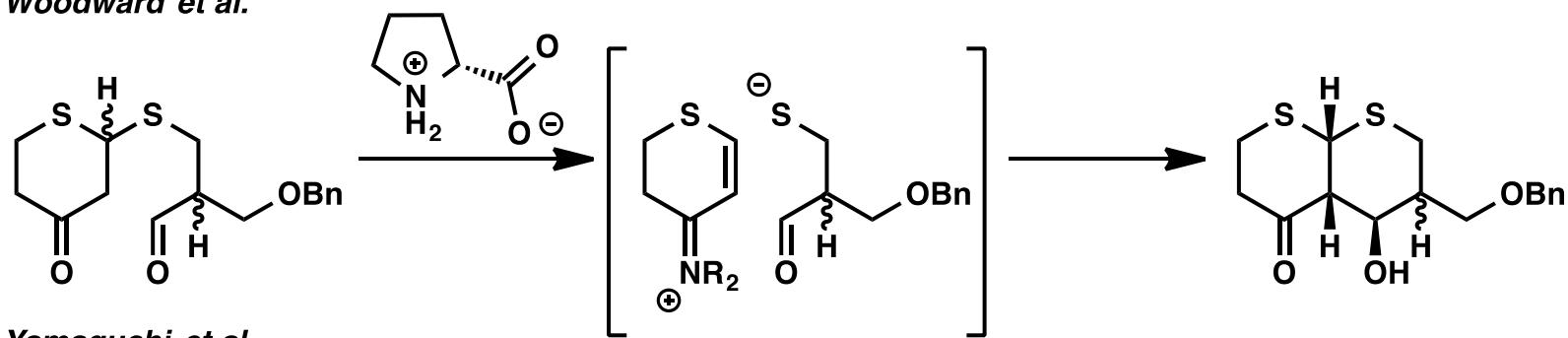
# Lewis Base Catalysis: Iminium Catalysis

## Historical Development of Iminium Catalysis

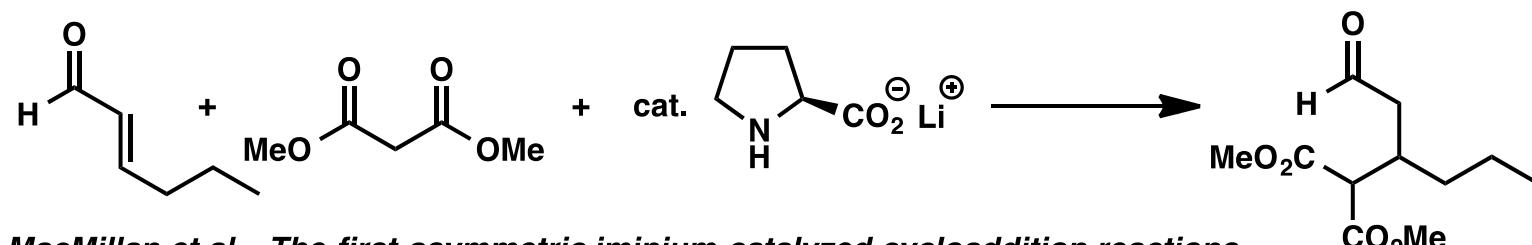
1976 Viehe and Baum *et al.*



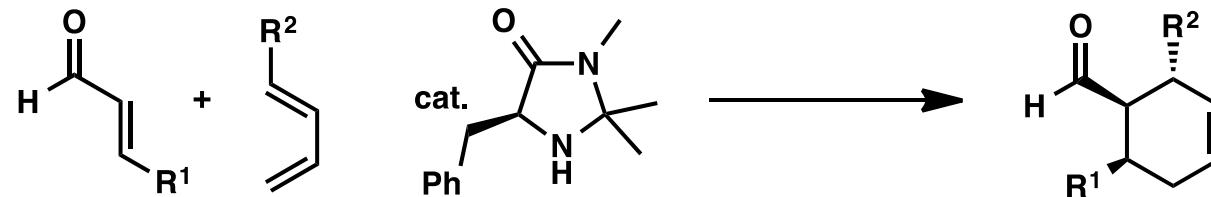
1981 Woodward *et al.*



1991 Yamaguchi *et al.*

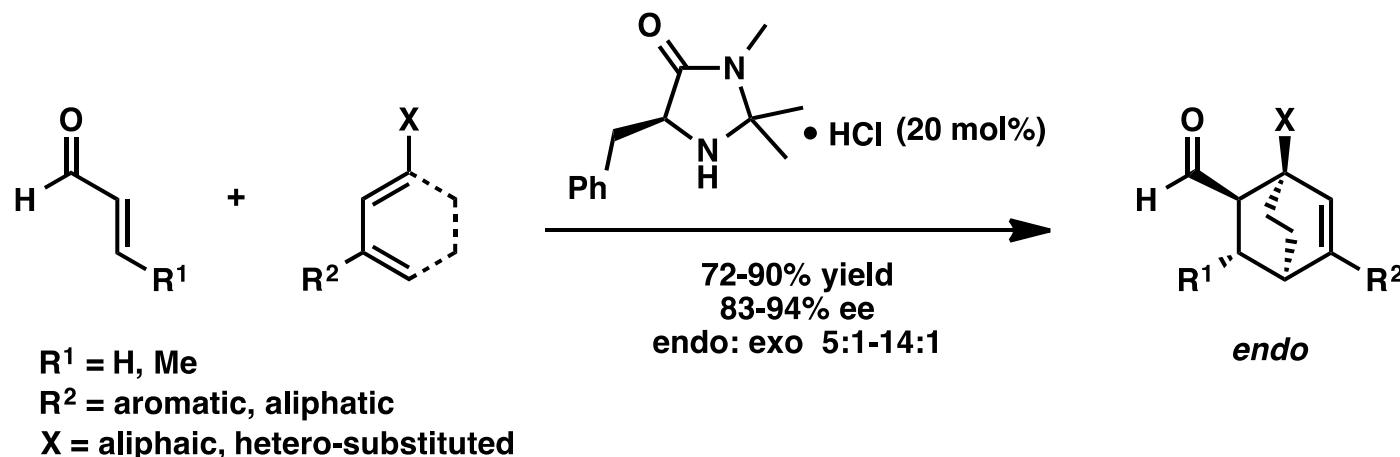
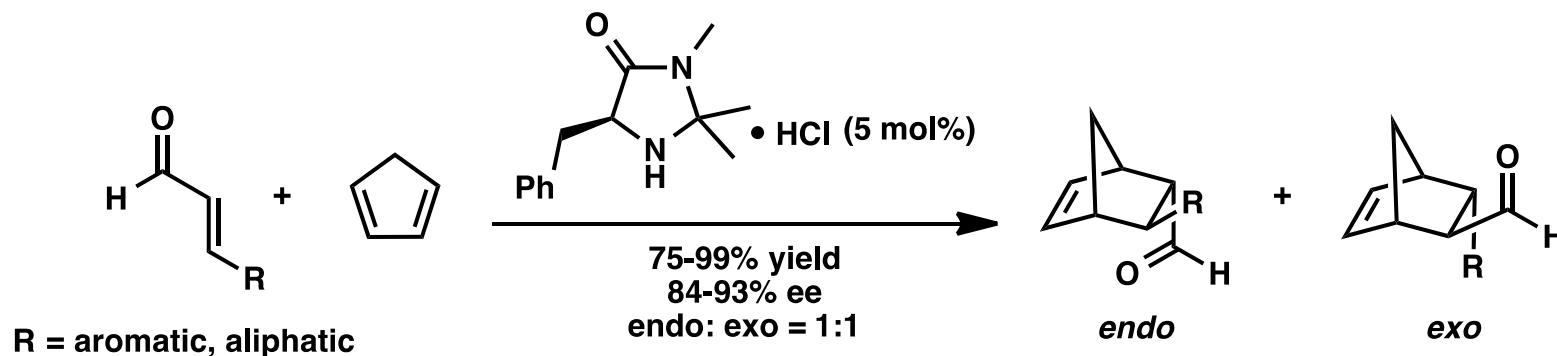


2000 MacMillan *et al.* - The first asymmetric iminium-catalyzed cycloaddition reactions

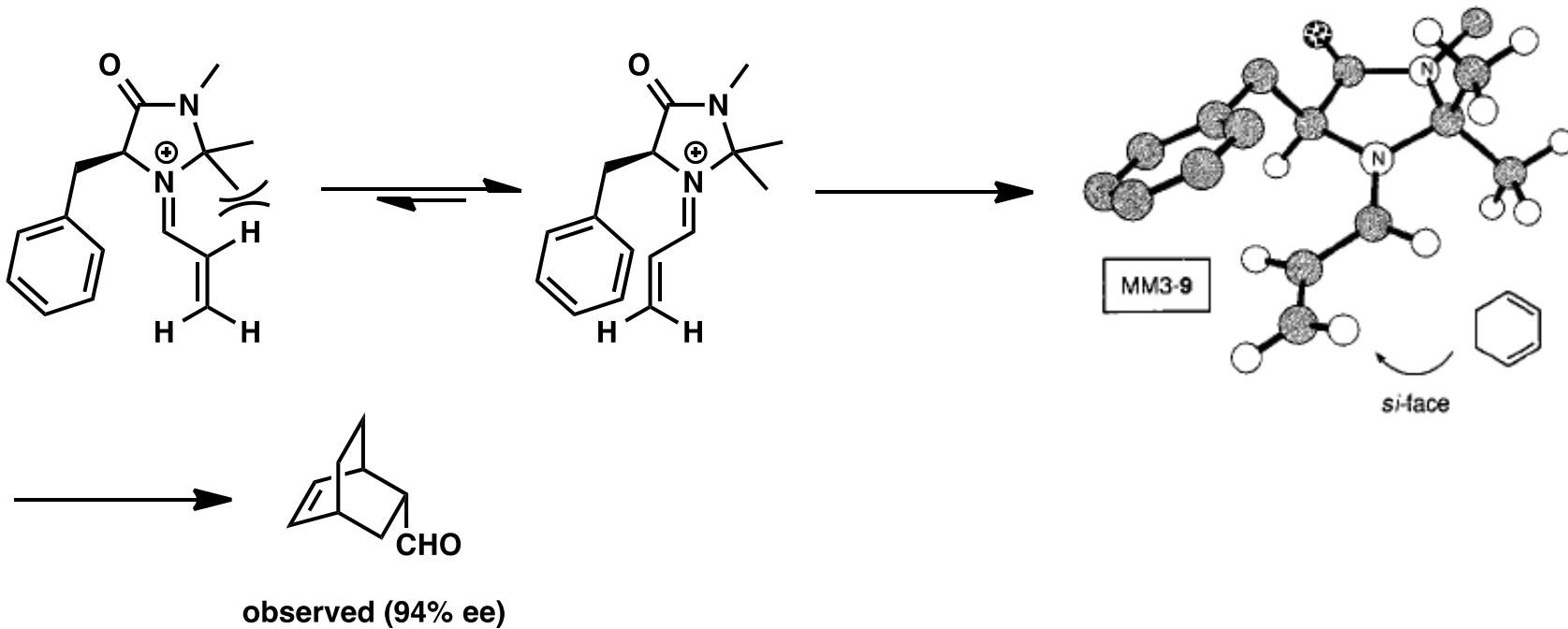


# Iminium Catalyzed cycloadditions

## Diels–Alder Reactions of Enals

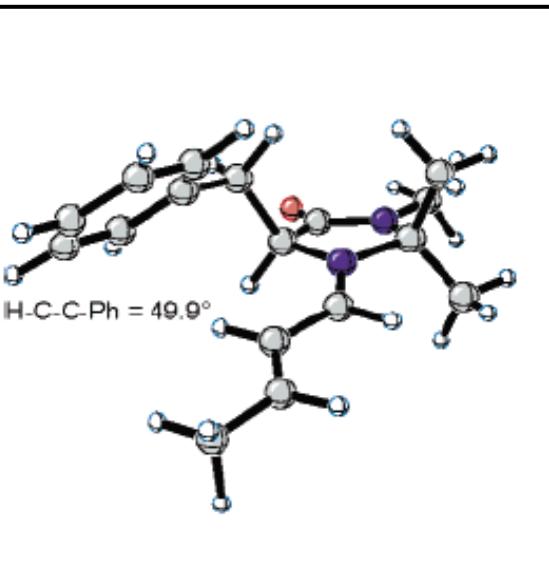
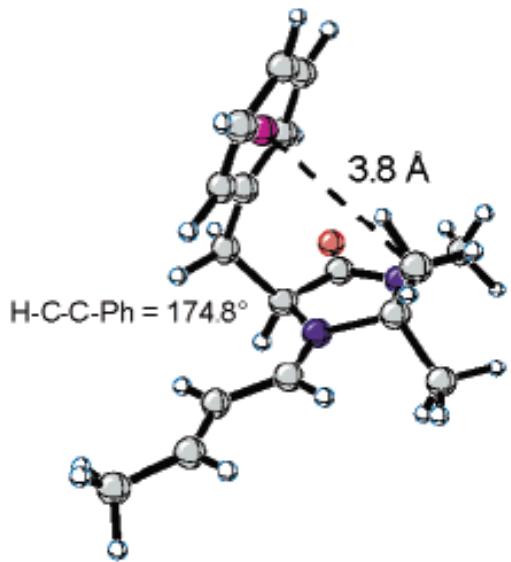


## *Iminium Catalyzed cycloadditions*



- Selective formation of the (E)-iminium isomer to avoid nonbonding interactions between the substrate olefin and the geminal methyl substituents.
- The benzyl group on the catalyst framework which effectively shields the *re* face of the dienophile, leaving the *si* face exposed to cycloaddition.
- The position of the benzyl group is presumably favored by  $\pi$ -stacking between the electron rich benzyl group and the electron poor iminium cation.

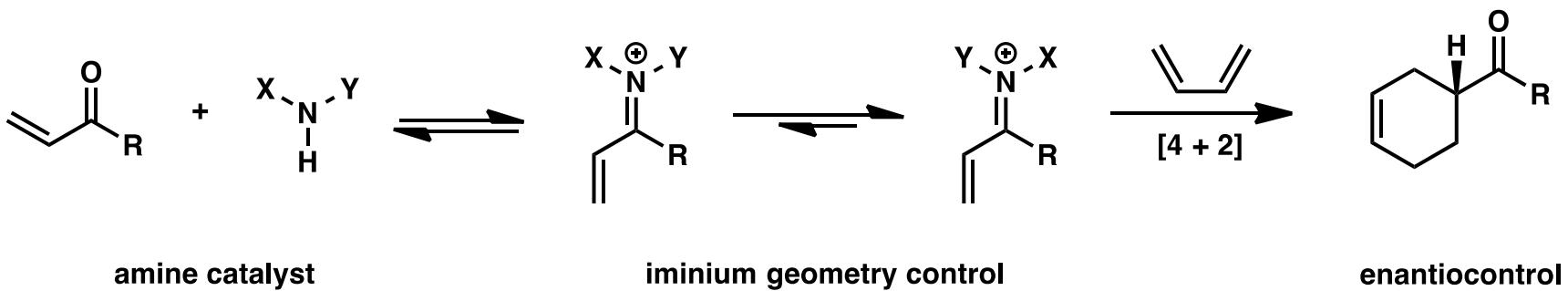
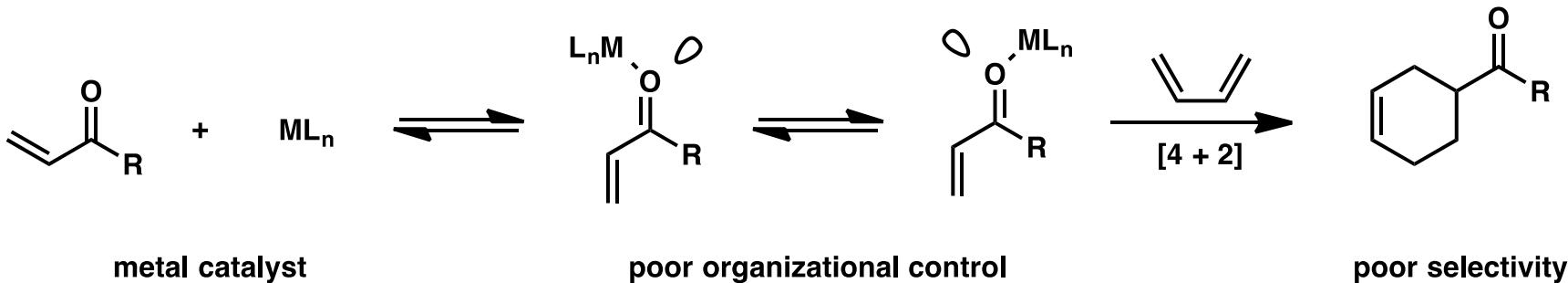
## *Iminium Catalyzed cycloadditions*



- The MacMillan's model has been criticized in light of more powerful density functional theory (DFT) ab initio calculations (B3LYP/6-31G(d)) by the Houk group.
- The most stable conformation of TS is the compound where the benzyl group is situated almost orthogonally against the double bond as a result of a  $C-H \cdots \pi$  interaction between a C2 methyl group and the phenyl ring of the benzyl group.

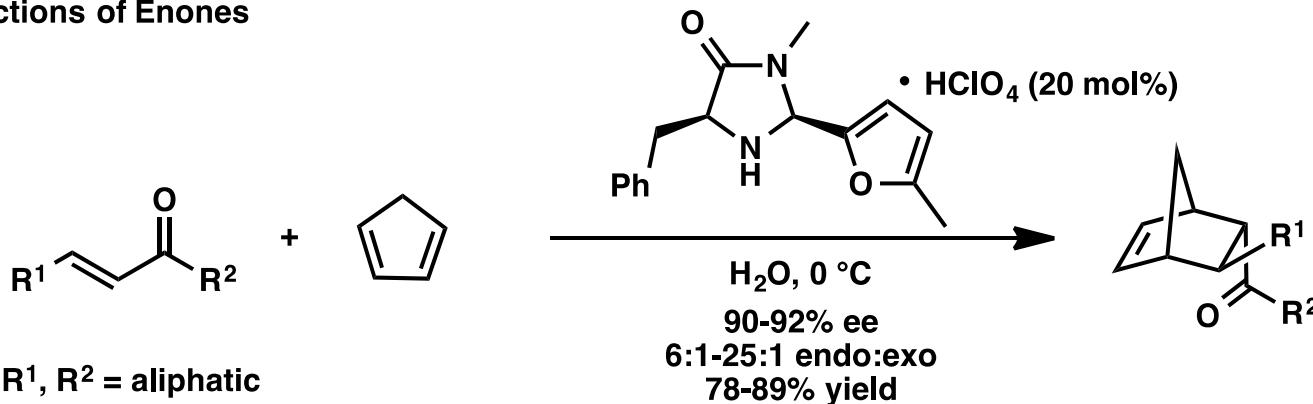
## *Iminium Catalyzed cycloadditions*

### Diels–Alder Reactions of Enones

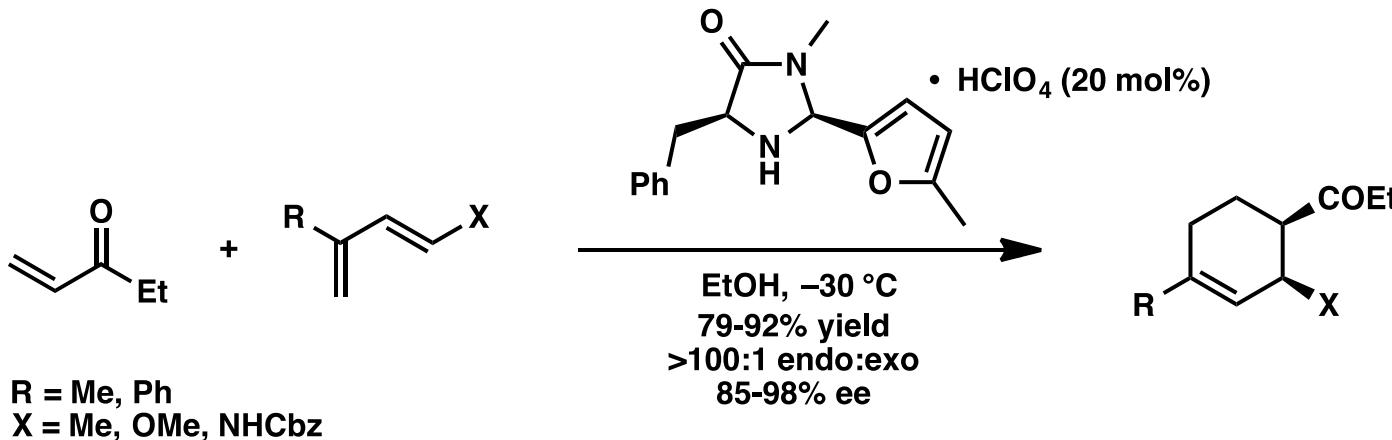


## Iminium Catalyzed cycloadditions

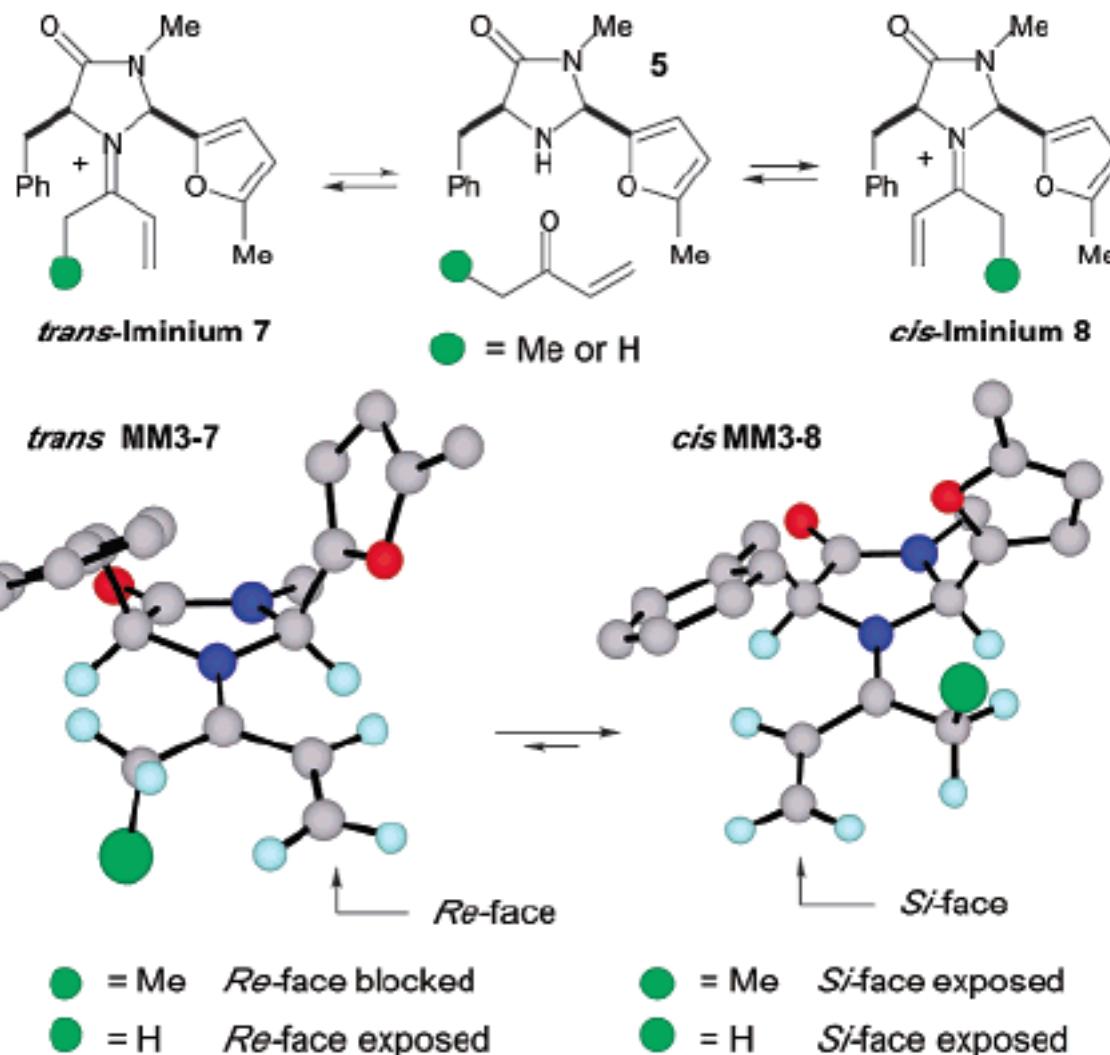
### Diels–Alder Reactions of Enones



- When  $\text{R}^2$  was Me, the ee of the product dropped to 61%.
- When  $\text{R}^2$  was isopropyl, no enantioselectivity was observed.
- With small cyclic ketones, a drop in ee was observed. (e.g., cyclopentenone; 48% ee, cyclohexenone; 63% ee)
- With larger rings, the enantioselectivities were good.



## *Iminium Catalyzed cycloadditions*



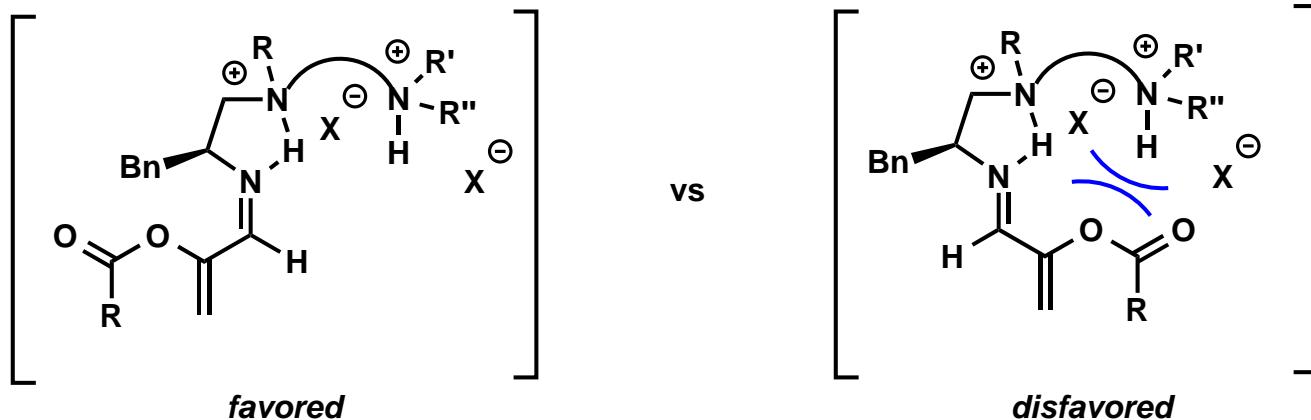
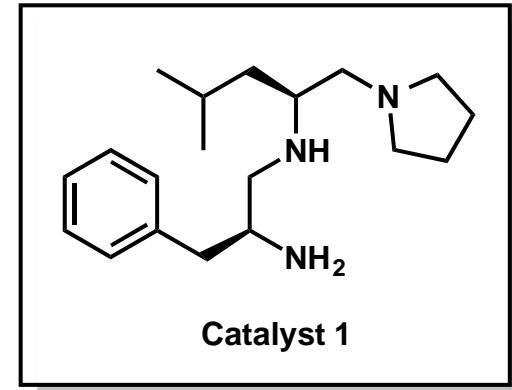
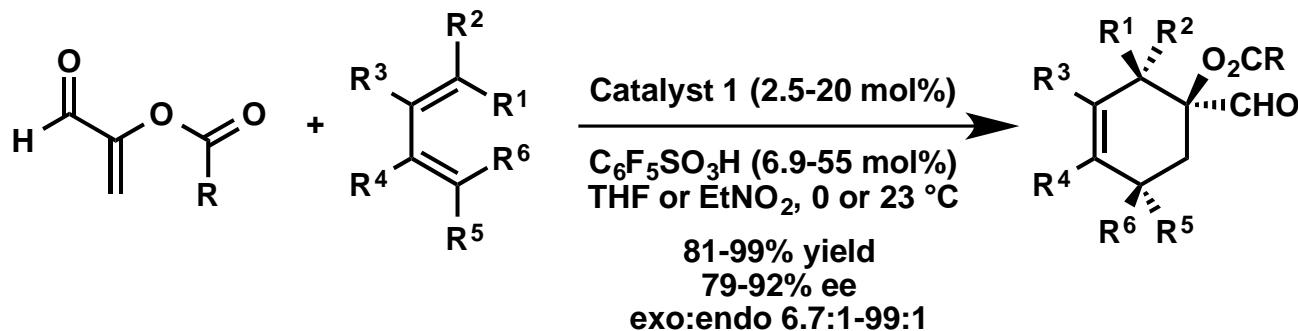
MacMillan, D. W. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543.

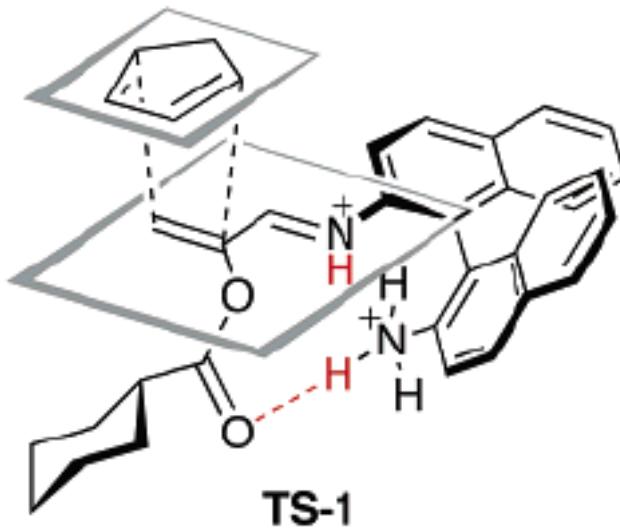
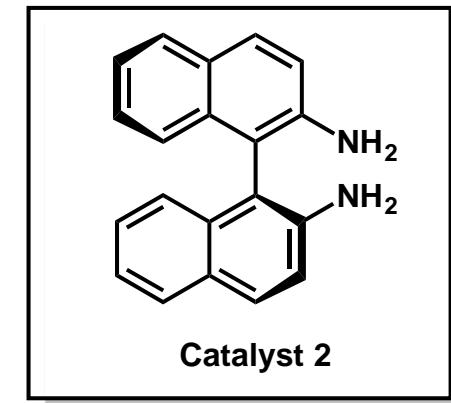
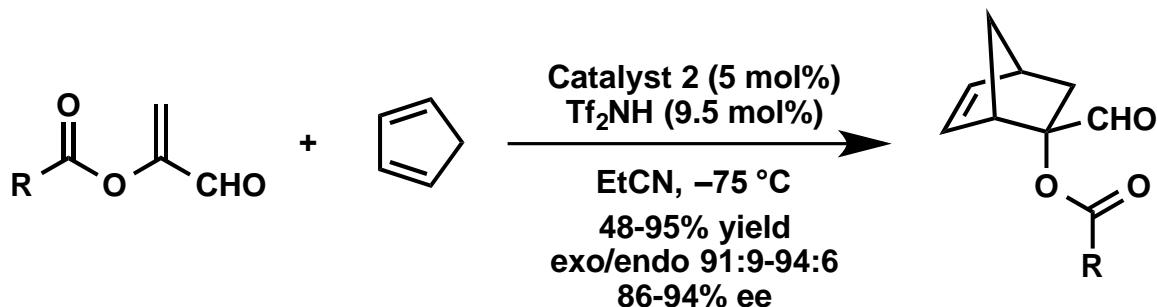
# Iminium Catalyzed cycloadditions

## Diels–Alder Reactions Catalyzed by Primary Amines

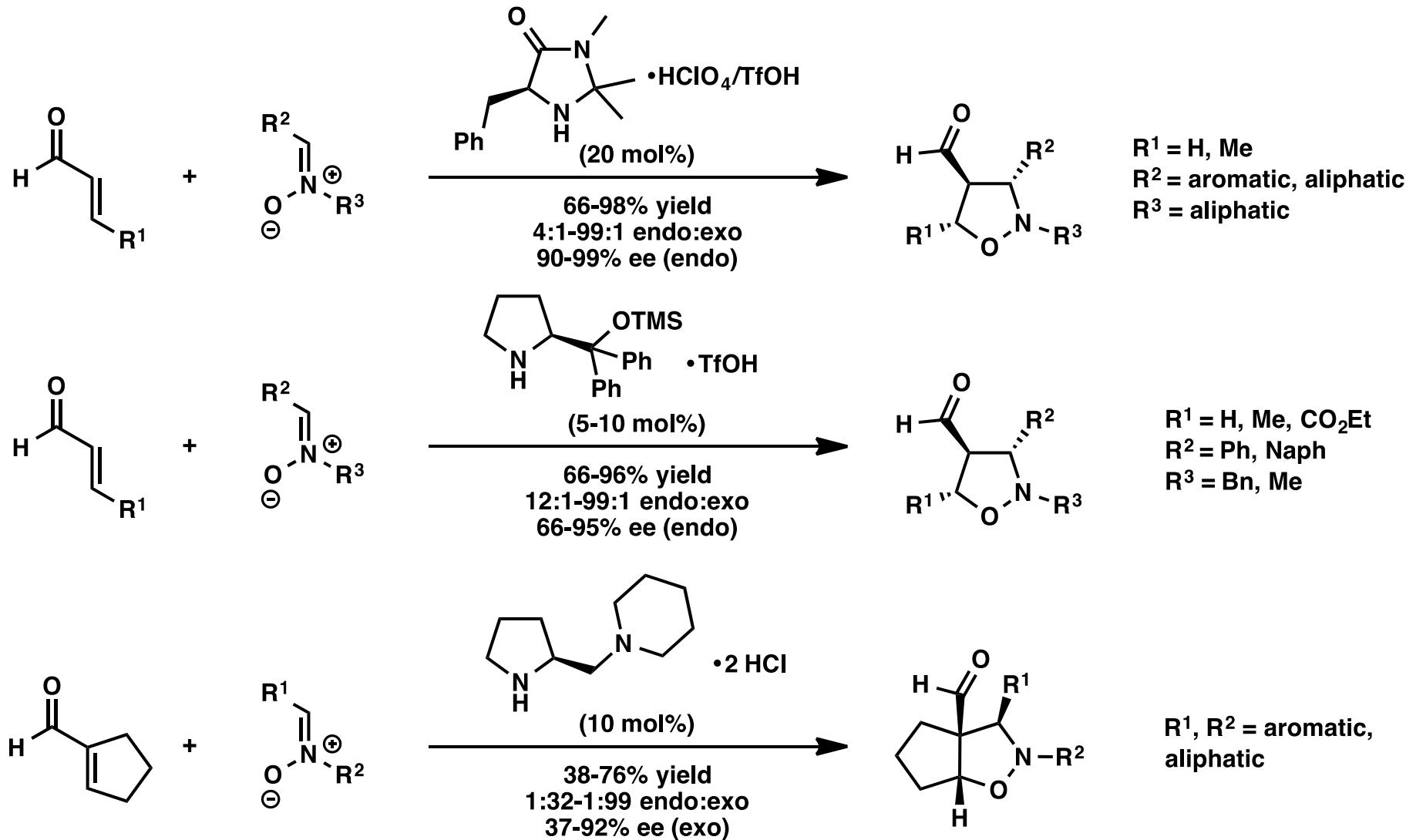
- The limitation of secondary amine catalysts: The catalytically active nitrogen atom is located in a sterically hindered environment, imposing strict demands on the structure of the substrate aldehyde or ketone. (e.g.,  $\alpha$ -substituted  $\alpha,b$ -unsaturated aldehydes and an isopropyl-substituted ketone as dienophiles)
- Novel primary amine organocatalyst has overcome this problem



## *Iminium Catalyzed cycloadditions*



# *Iminium Catalyzed [3+2] cycloadditions*



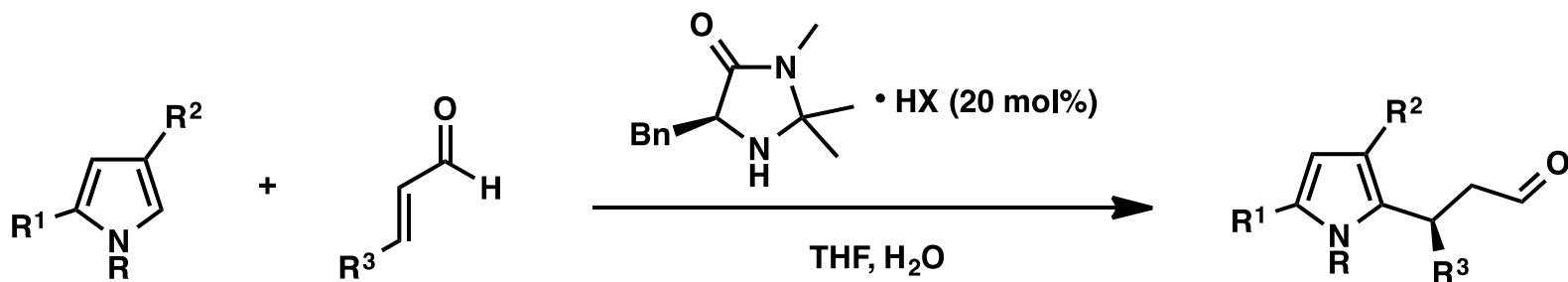
MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

Nevalainen, M. *Tetrahedron Lett.* **2007**, *48*, 277.

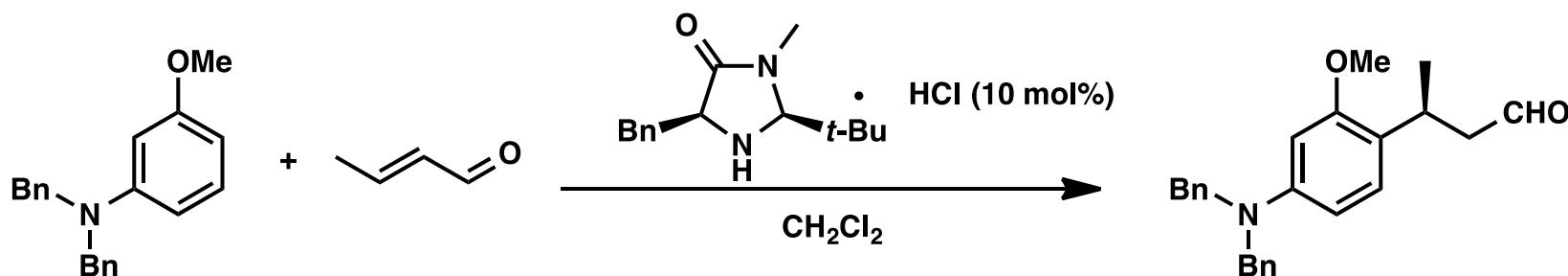
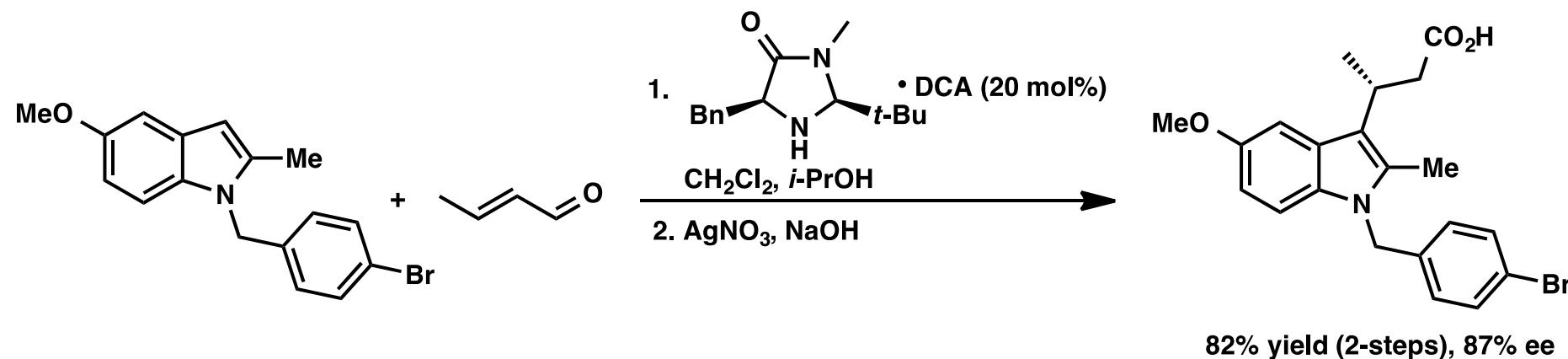
Karlsson, S. *Tetrahedron: Asymmetry* **2002**, *13*, 923.

Karlsson, S. *Eur. J. Org. Chem.* **2003**, 2782.

# Friedel-Crafts Alkylation



12 examples  
68-90% yield, 87-97% ee



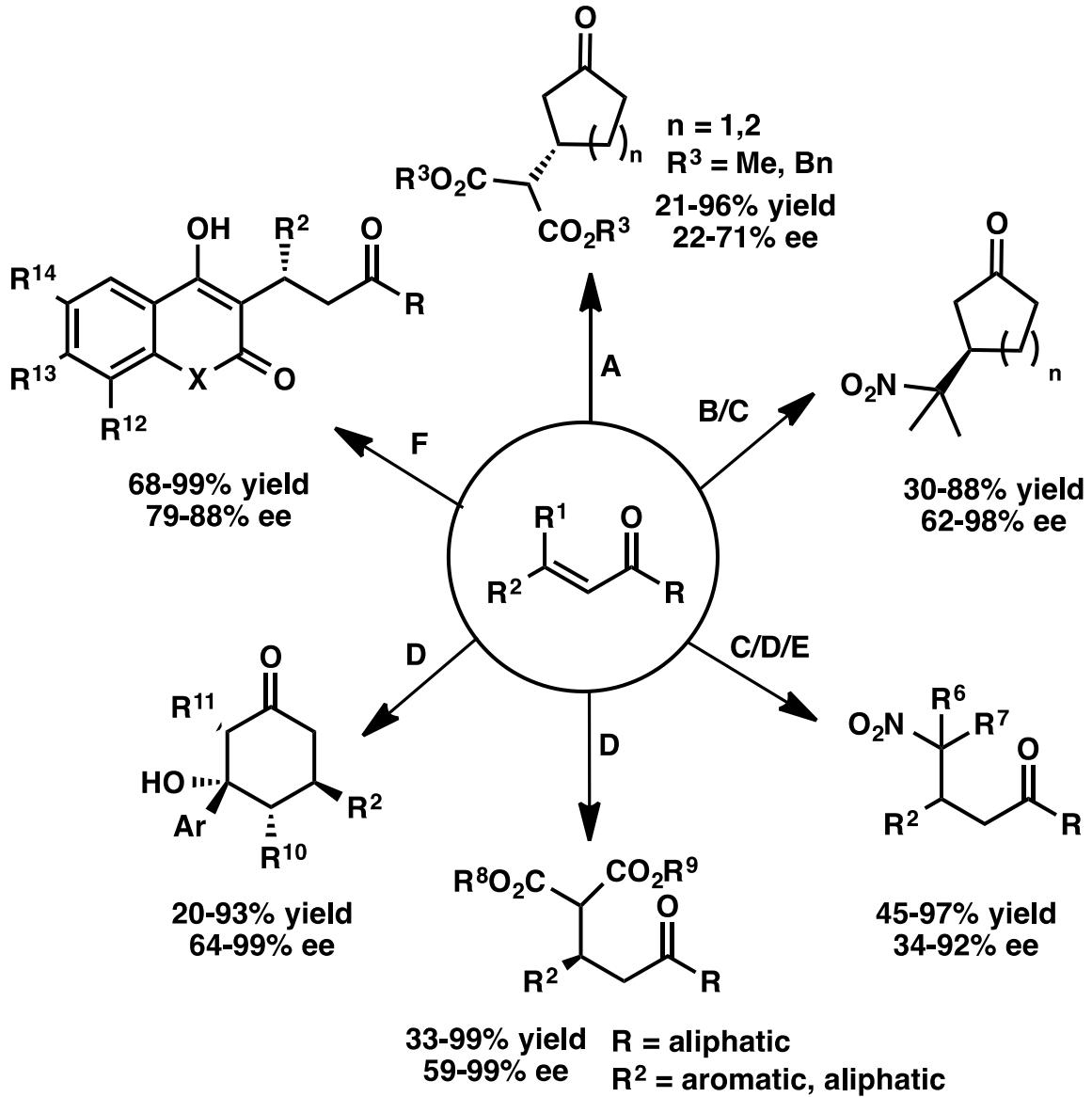
90% yield, 90% ee

MacMillan, D. W. C. *J. Am. Chem. Soc.* 2001, 123, 4370.

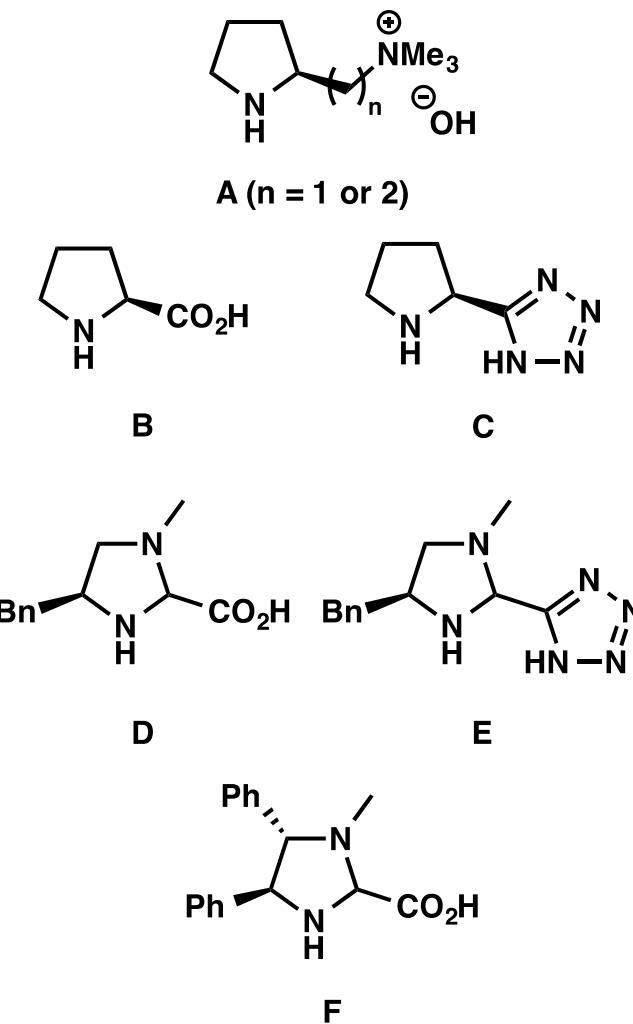
MacMillan, D. W. C. *J. Am. Chem. Soc.* 2002, 124, 1172.

MacMillan, D. W. C. *J. Am. Chem. Soc.* 2002, 124, 7894.

# Michael Reactions of $\alpha,\beta$ -Unsaturated Ketones



catalyst:



Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, 35, 8805.

Hanessian, S. *Org. Lett.* **2000**, 2, 2975

Jørgensen, K. A. *J. Org. Chem.* **2002**, 67, 8331.; Jørgensen, K. A. *Org. Lett.* **2005**, 7, 3897.; Ley, S. V. *Chem. Commun.* **2005**, 5346.

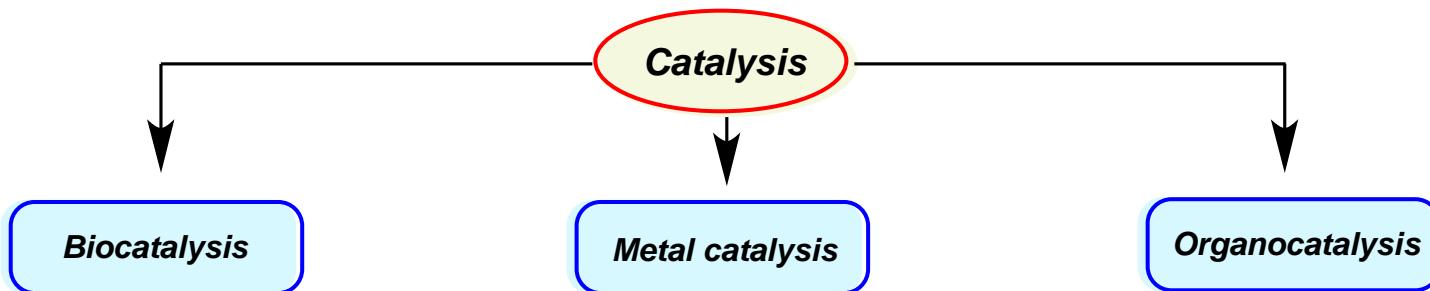
Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, 42, 661.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, 43, 1272.

Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, 42, 4955.

## *Conclusion*

- \* Since the introduction of the first highly enantioselective organocatalytic Diels–Alder reaction in 2000, there has been a large expansion in the iminium-catalyzed reactions.  
(e.g., cycloaddition, conjugate addition, domino reaction, etc.)
- \* Some iminium catalyzed reactions still require relatively high catalyst loadings (up to 20-30 mol%).
- \* Nearly all iminium-catalyzed processes are very user-friendly to operate: the reactions are not particularly sensitive to moisture or air, most reactions can be conducted at ambient temperatures, and catalysts are often readily available or easy to prepare.

# Organocatalysis



**Organocatalysis:** The catalysis with small organic molecules, where an inorganic element is not part of the active principle.

## Organocatalysis

### Lewis bases

iminium catalyst, **enamine catalyst**, NHC catalyst  
chiral dialkylaminopyridine

### Lewis acids

phase transfer catalyst, ketone catalyzed epoxidations

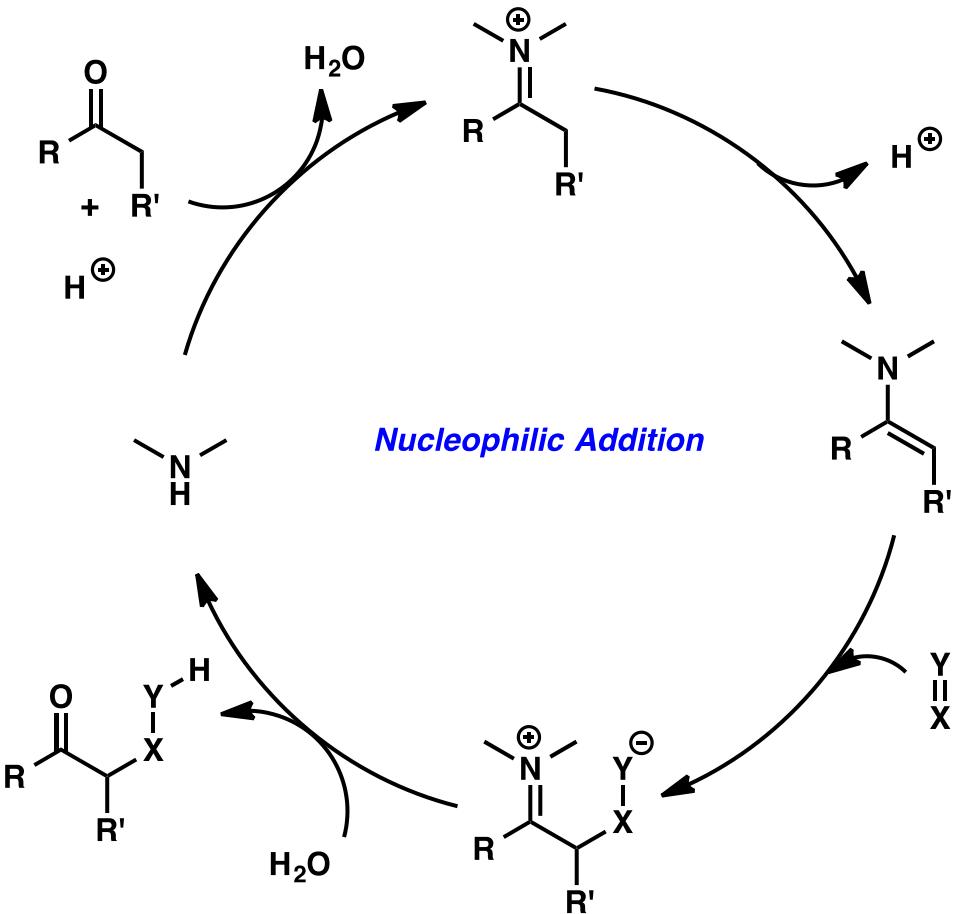
### Brønsted bases

cinchona alkaloid catalyzed alcoholyses of anhydride

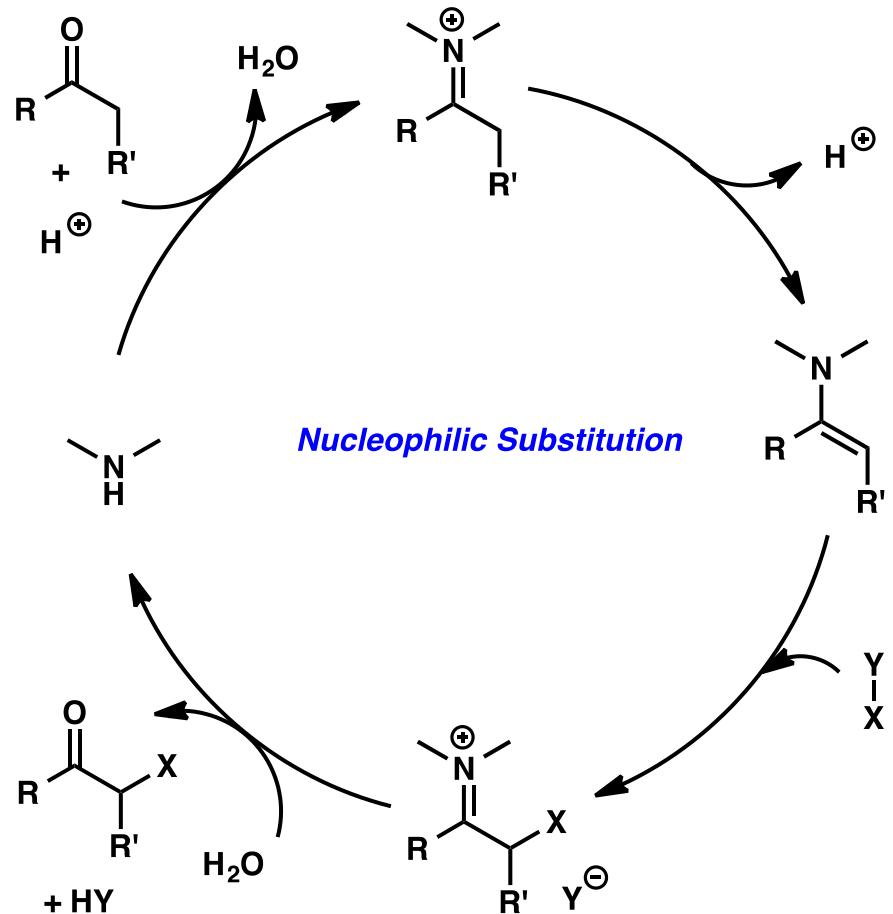
### Brønsted acids

small molecule H-bond catalyst

## Two Modes of Enamine Catalysis



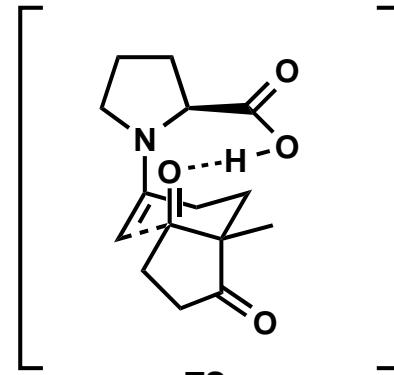
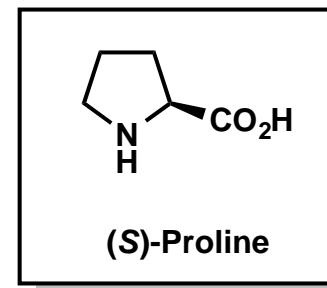
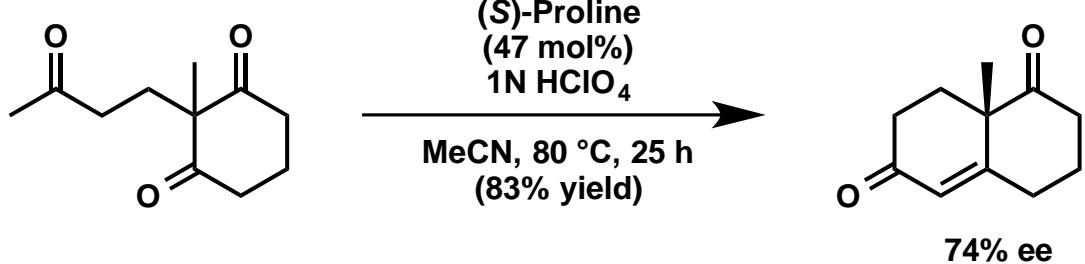
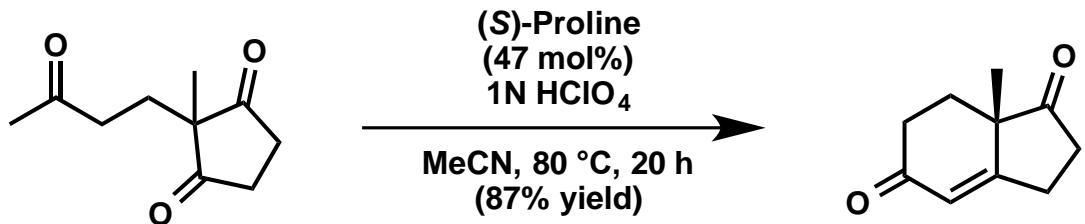
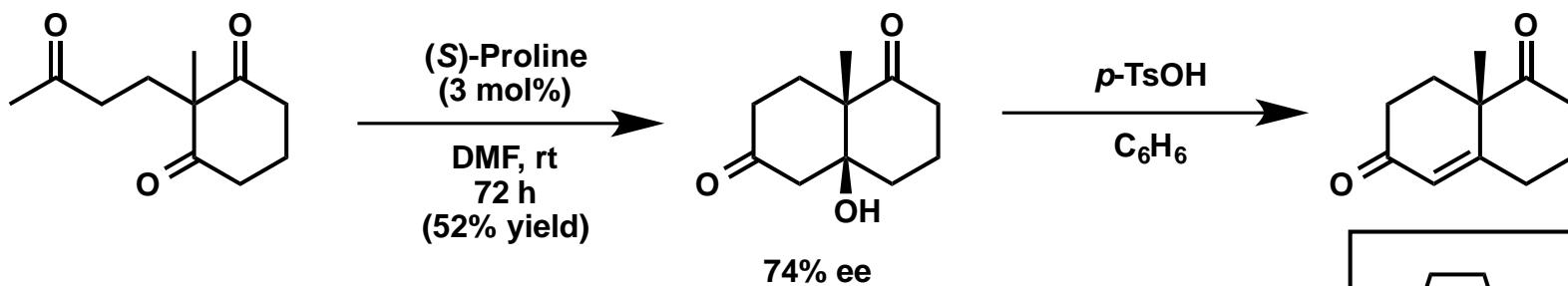
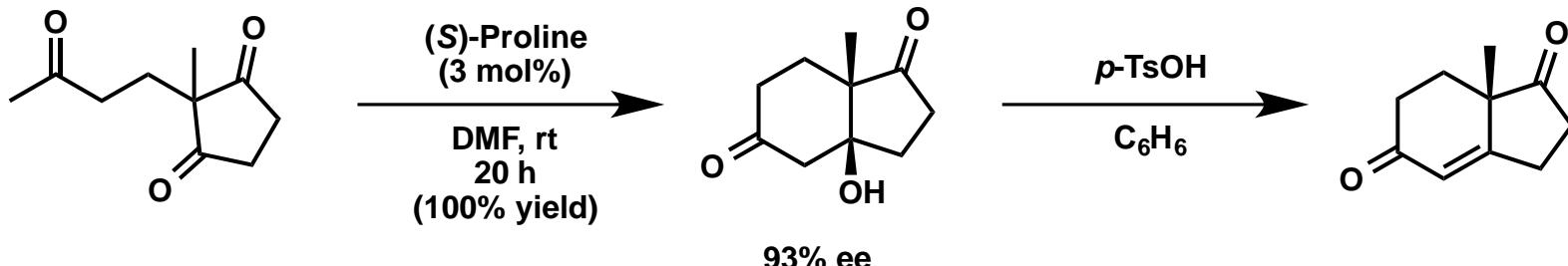
*Nucleophilic Addition*



*Nucleophilic Substitution*

# Enolendo Aldolizations

## Hajos-Parrish-Eder-Sauer-Wiechert Reactions



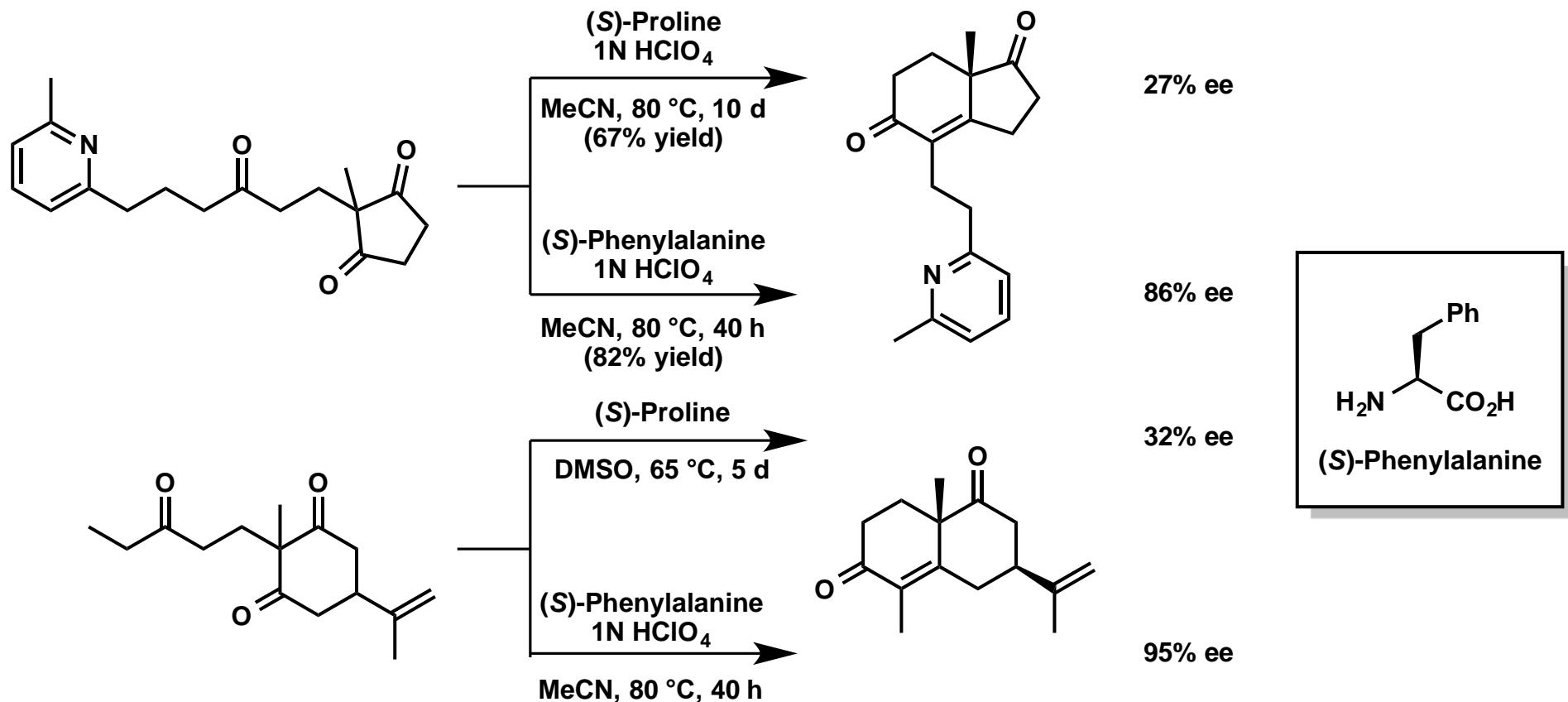
Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, 1971.

Eder, U.; Sauer, G. R.; Wiechert, R. German Patent DE 2014757, 1971.

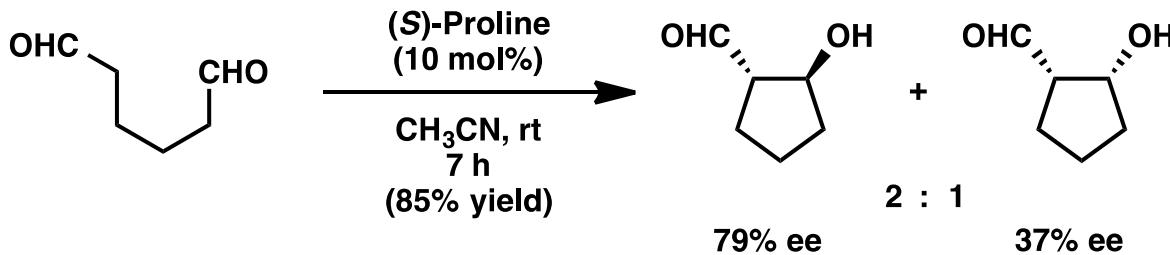
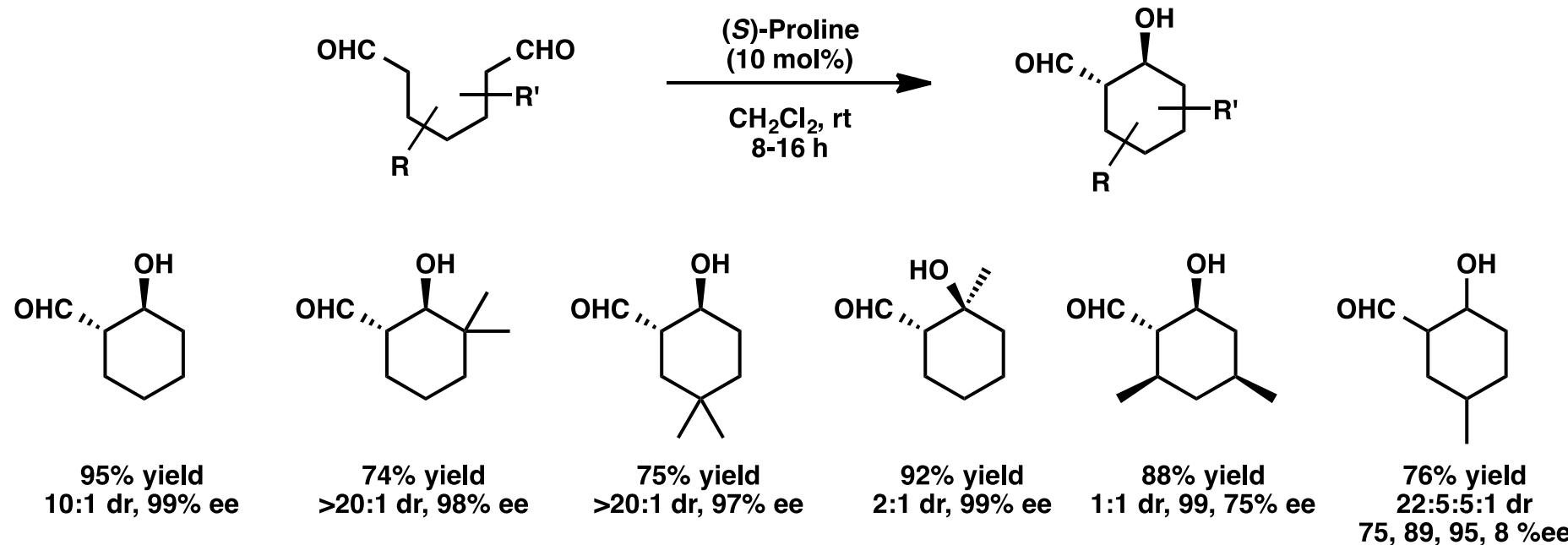
Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, 39, 1615.

Houk, K. N. *J. Am. Chem. Soc.* **2001**, 123, 12911.

# *Phenylalanine Catalyzed Intramolecular Aldolizations*



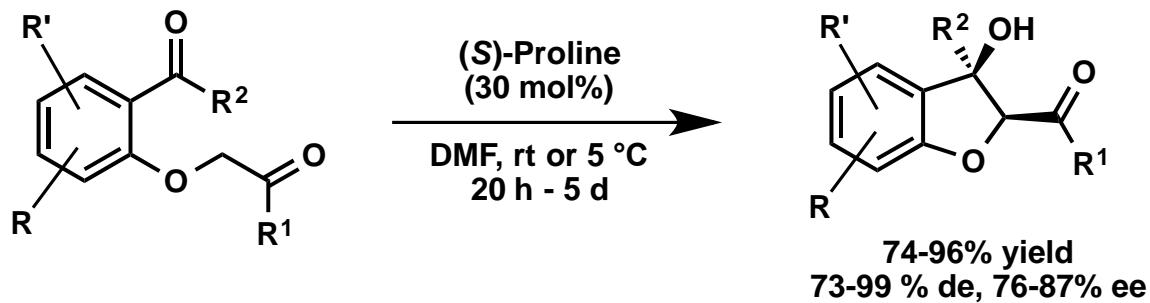
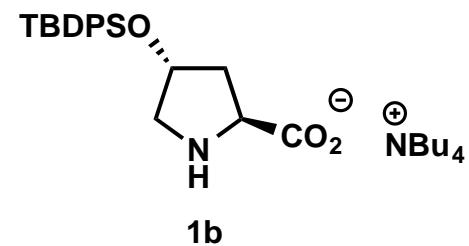
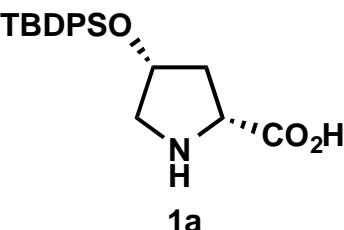
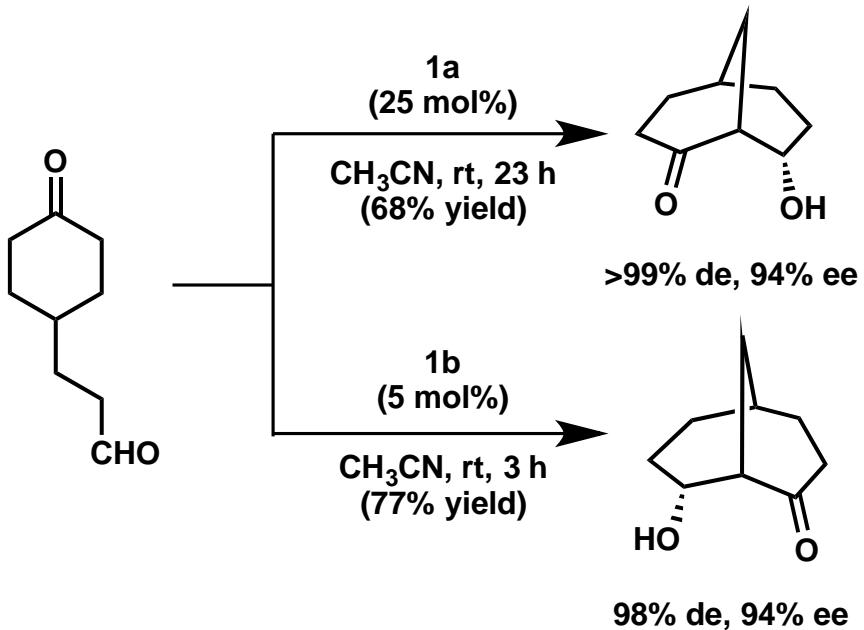
## Enolexo Aldolizations



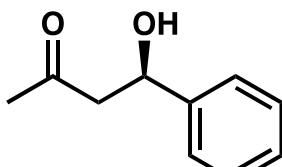
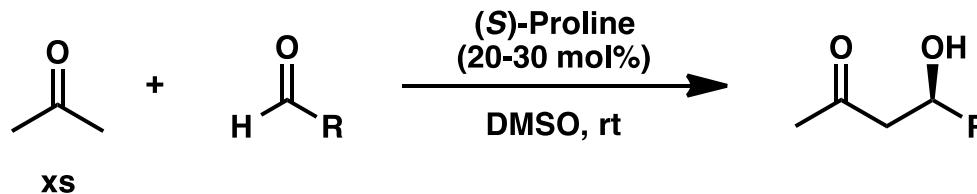
List, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 2785.

List, B. In *Modern Aldol Reactions*; Mahwald, R., Ed.; Wiley-VCH Verlag GmbH&Co. KGaAL Weinheim, 2004; Vol 1, p161.

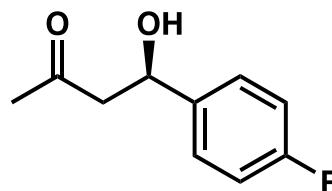
## Intramolecular Aldol Reactions



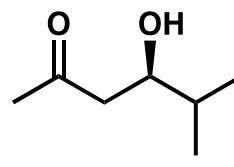
## Intermolecular Aldolizations



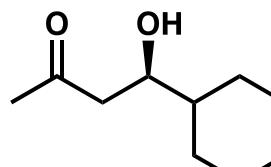
62%, 72% ee



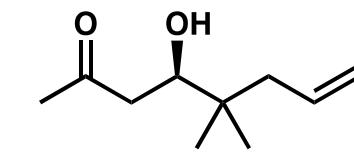
68-74%, 65-76% ee



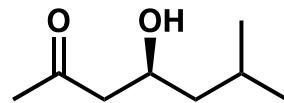
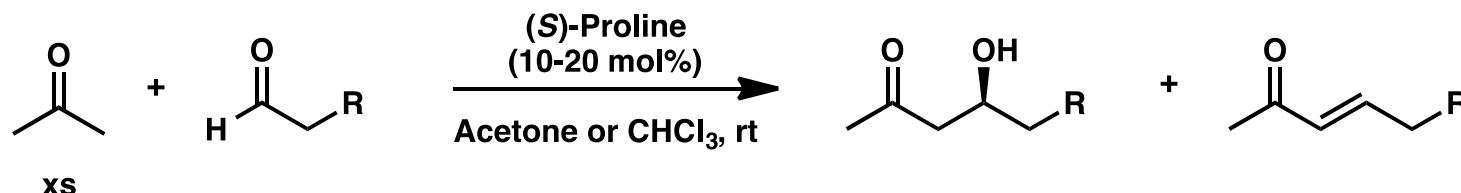
97%, 96% ee



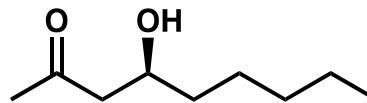
63%, 84% ee



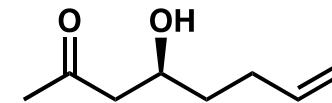
85%, >99% ee



34%, 73% ee



35%, 73% ee



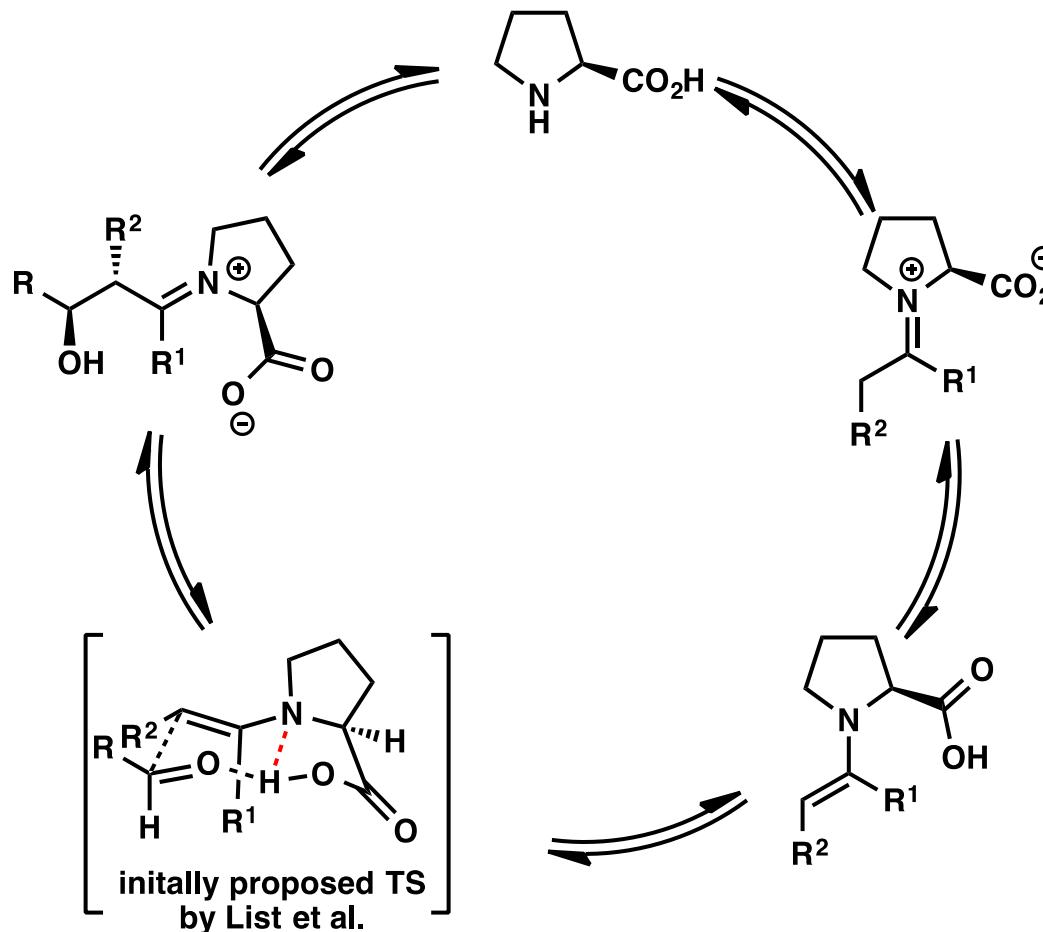
34%, 72% ee

List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

List, B. *Org. Lett.* **2001**, *3*, 573.

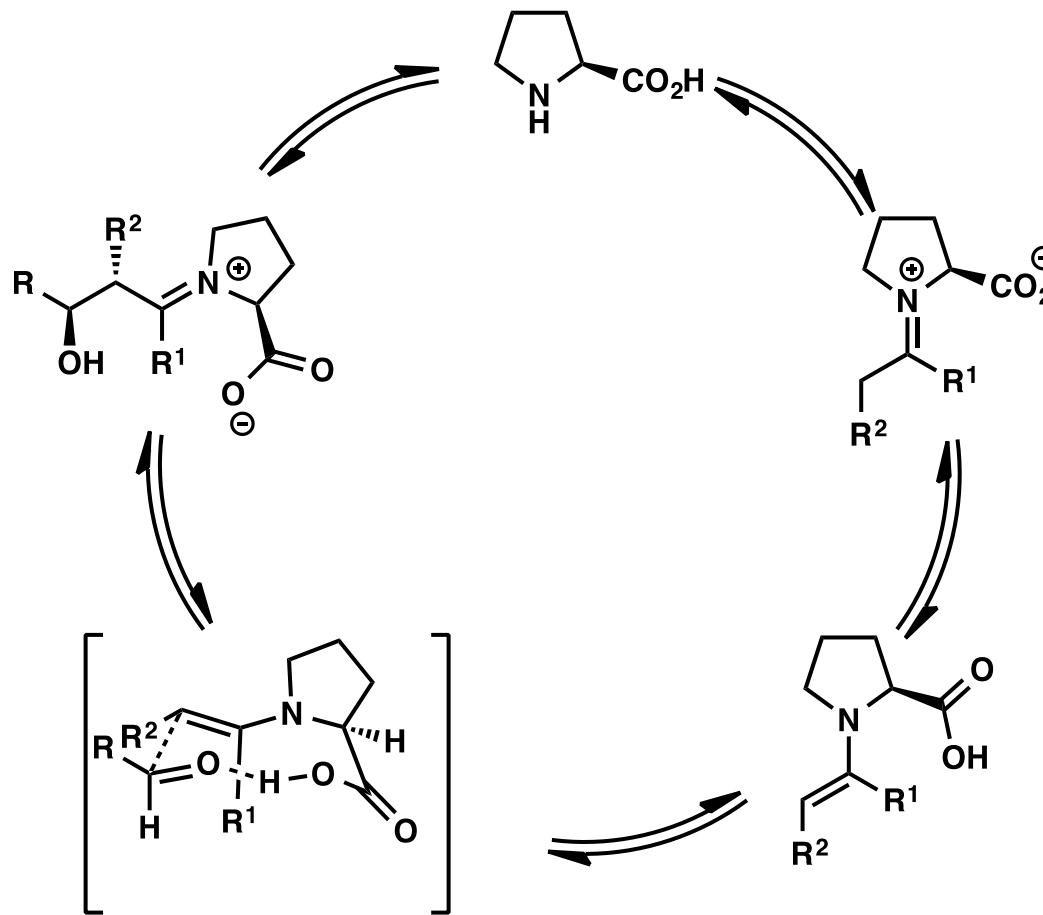
List, B. *Tetrahedron* **2002**, *58*, 5573.

# Proposed Mechanistic Cycle for the Proline-Catalyzed Intermolecular Aldol Reaction



- \* Proline not only acts as an enamine catalyst but also brings along its own Bronsted acid cocatalyst and therefore can be regarded as a "bifunctional catalyst".
- \* Houk and co-workers proposed that a simultaneous hydrogen bond to the enamine nitrogen does not contribute to lowering the energy of the TS.

*Proposed Mechanistic Cycle for the Proline-Catalyzed Intermolecular Aldol Reaction*



\* Proline not only acts as an enamine catalyst but also brings along its own Bronsted acid cocatalyst and therefore can be regarded as a "bifunctional catalyst".

\* Houk and co-workers proposed that a simultaneous hydrogen bond to the enamine nitrogen does not contribute to lowering the energy of the TS.

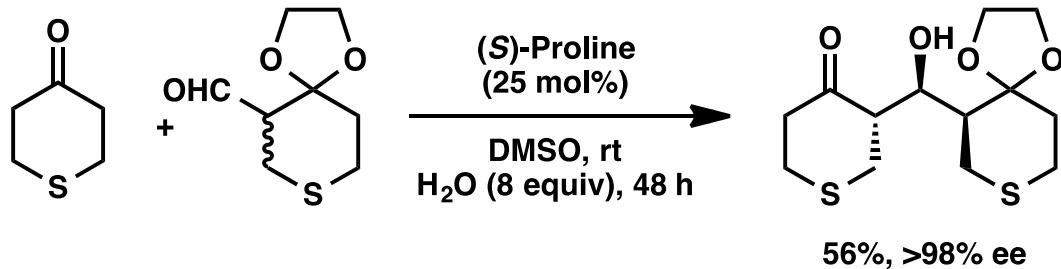
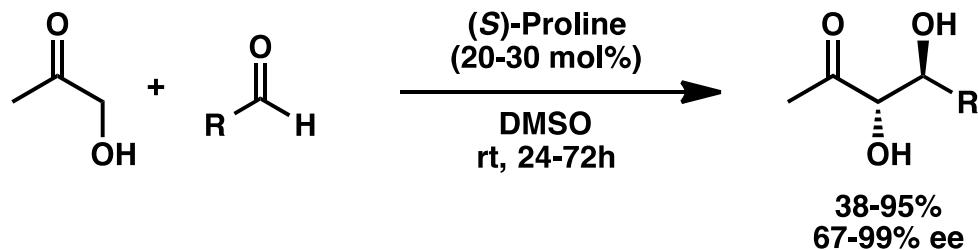
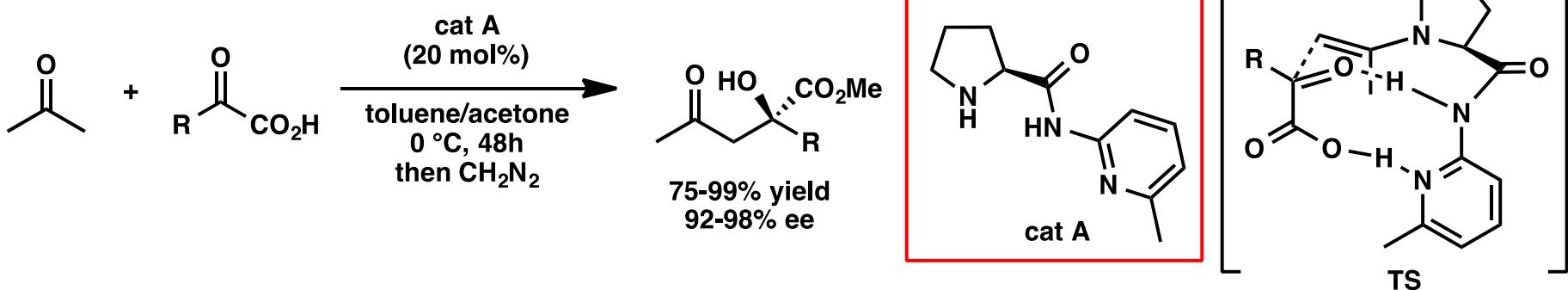
List, B.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, 122, 2395.

Houk, K. N. *J. Am. Chem. Soc.* **2001**, 123, 11273.

Houk, K. N. *J. Am. Chem. Soc.* **2001**, 123, 12911.

Houk, K. N. *Acc. Chem. Res.* **2004**, 37, 558.

## Prolinamide Organocatalyst



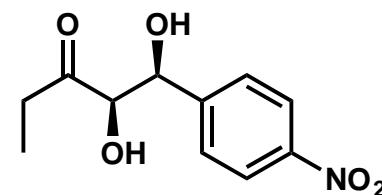
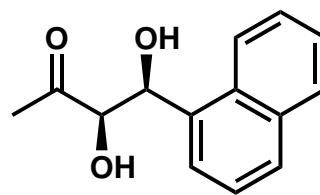
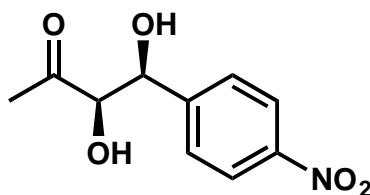
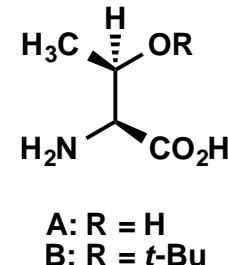
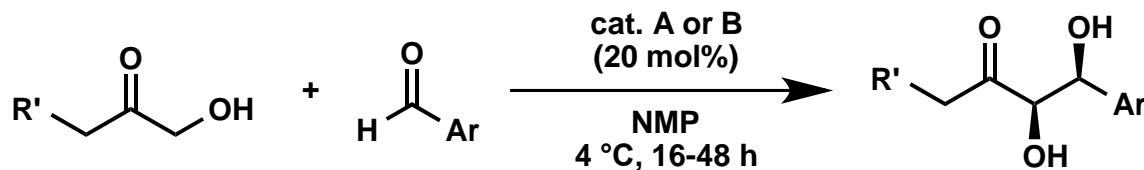
\* Proline catalyzes the isomerization of aldehydes and, since these isomerizations are faster than the aldol addition, the reaction proceeds with DKR

Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263.

List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

Ward, D. E. *Org. Lett.* **2005**, *7*, 1181.

## Direct Catalytic Asymmetric *syn*-Aldol Reactions

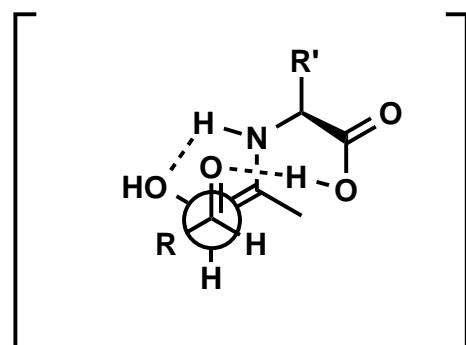


With cat. A  
With cat. B

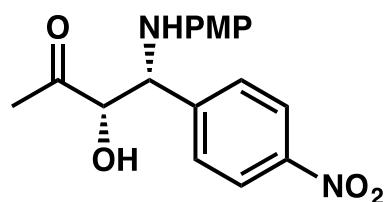
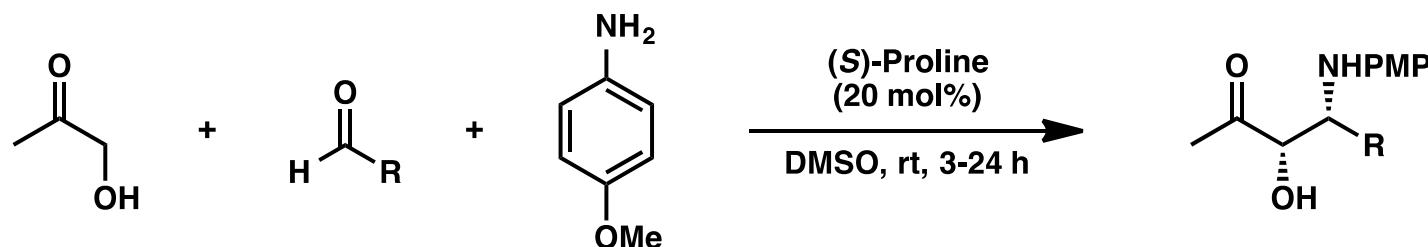
75%, 15:1 dr, 90% ee  
>95%, 18:1 dr, 98% ee

70%, 8:1 dr, 86% ee  
87%, 10:1 dr, 80% ee

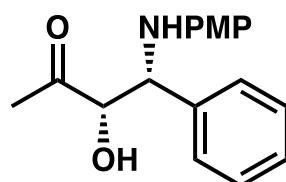
78%, 12:1 dr, 94% ee



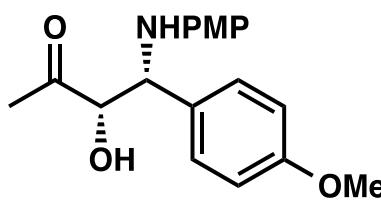
## Asymmetric Mannich Reactions of Ketones



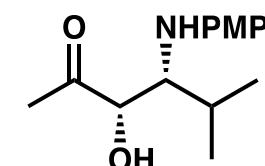
92%, 20:1 dr, >99% ee



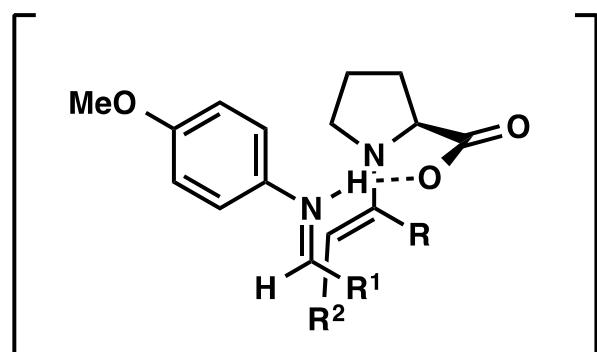
83%, 9:1 dr, 93% ee



88%, 3:1 dr, 61% ee

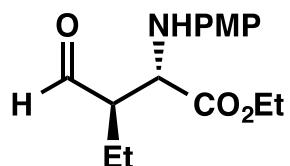
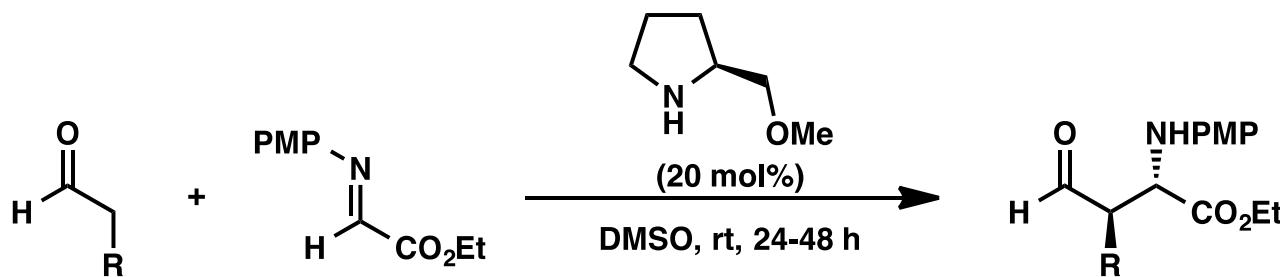


57%, 17:1 dr, 65% ee

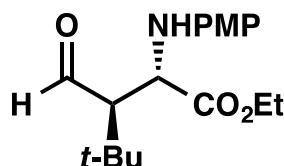


- \* (E)-Configurations are assumed for both the enamine and the imine.
- \* The two components react to avoid unfavorable steric interaction between the N-substituent of the imine and the proline ring.
- \* The transition state allow for a stabilizing hydrogen bond between the carboxylate and the protonated imine.
- \* Approach of the *si*-face of the imine to the *si*-face of the enamine results to the observed stereochemistry.

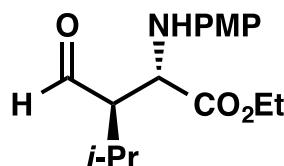
## Asymmetric anti-Mannich Reactions



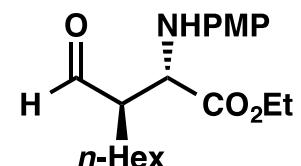
44%  
1:1 dr, 75% ee



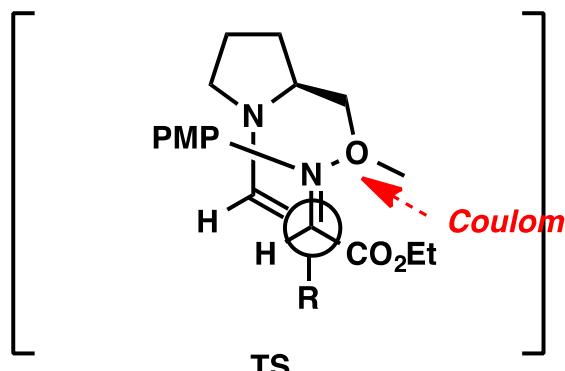
57%  
>10:1 dr, 92% ee



52%  
10:1 dr, 82% ee

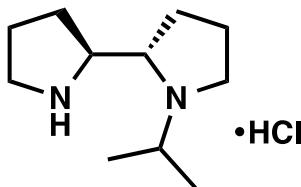
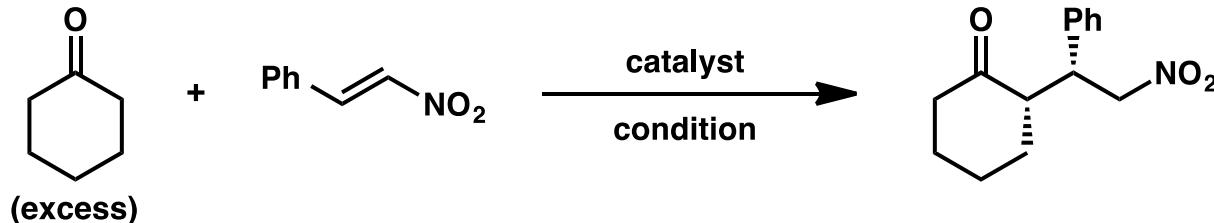


68%  
>19:1 dr, 76% ee

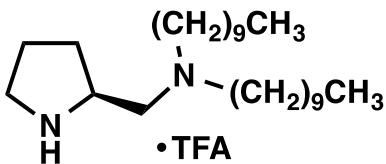


\* The *anti*-selectivity was achieved because the *s-cis*-(*E*)-enamine could attack to the *si*-face of imine by a favorable Coulombic interaction between the ethereal oxygen group of the catalyst and the nitrogen group of the imine.

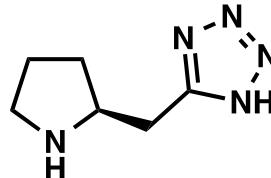
## Michael Addition



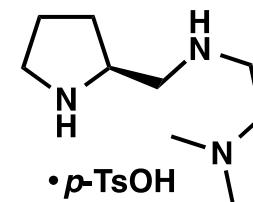
(15 mol%)  
 $\text{CHCl}_3$ , rt, 15h  
 74% yield, syn/anti = 95/5  
 ee = 74%  
 Alexakis



(20 mol%)  
 $\text{THF}$ , rt, 22h  
 92% yield, syn/anti = 98/2  
 ee = 90%  
 Barbas III



(15 mol%)  
 $i\text{-PrOH:EtOH}$  (1:1), rt  
 syn/anti = >19/1  
 ee = 91%  
 Ley

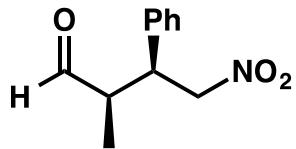
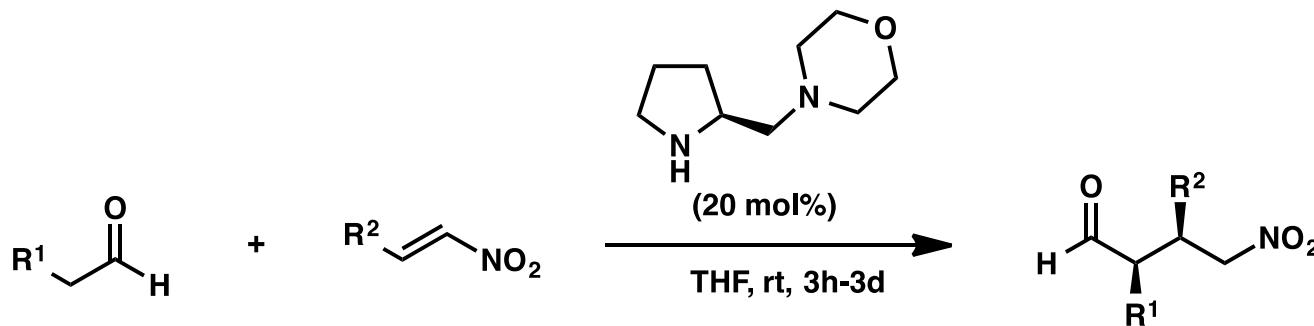


(15 mol%)  
 $\text{DMF}$ , rt  
 90% yield, syn/anti = 19/1  
 ee = >99%  
 Pansare

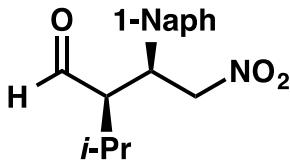
\* Various catalysts having an N-containing side chain or heterocycle were developed.

\* The match between the catalyst and co-catalyst is the determinant factor both for the selectivity and for the rate of transformation.

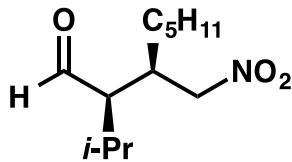
## Michael Reactions of Aldehydes



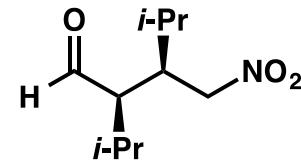
85%  
9:1 dr, 56% ee



67%  
24:1 dr, 75% ee



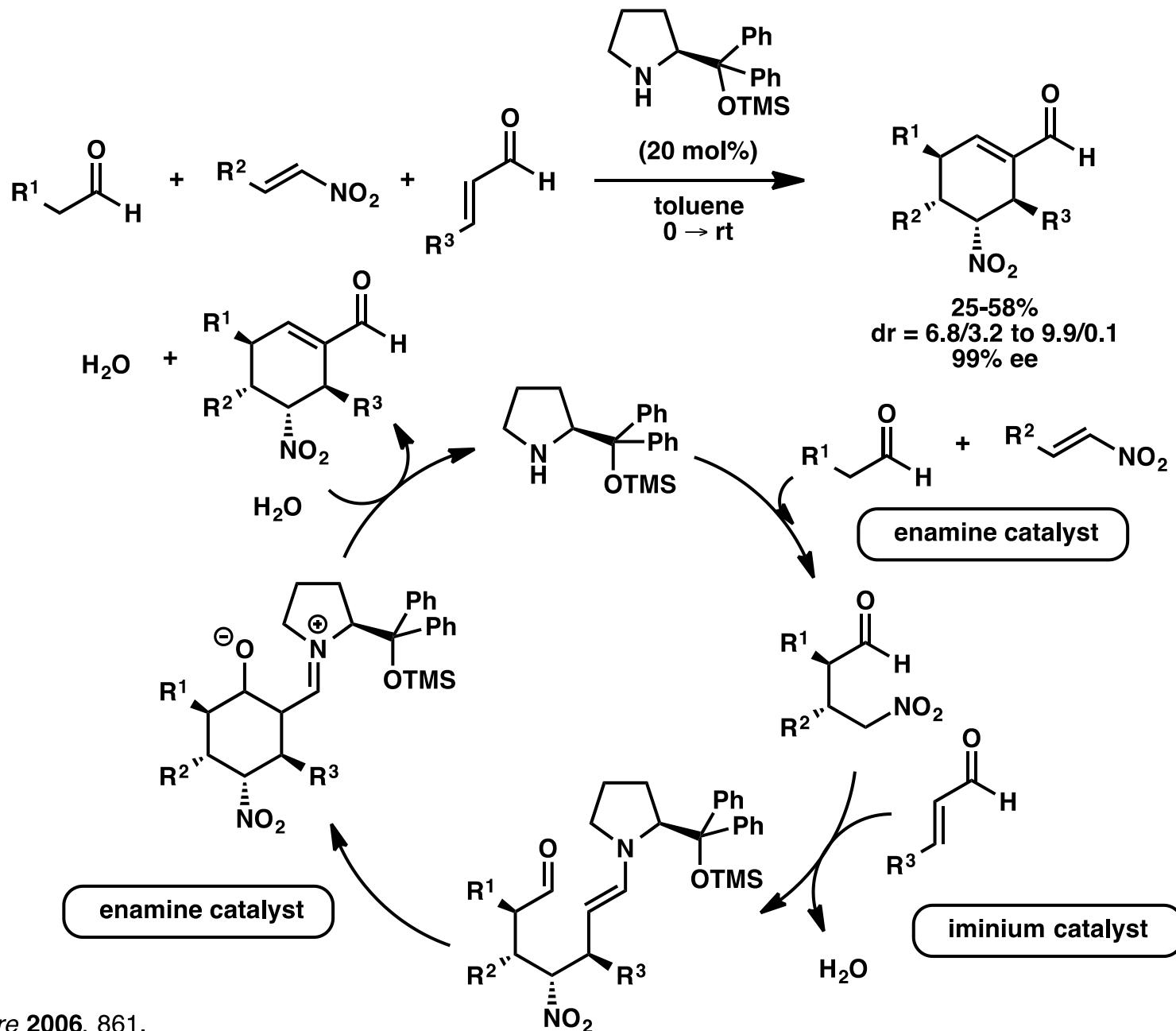
42%  
8:1 dr, ee n.d.



not observed

\* Higher ee were observed with increasing substituent bulk on the Michael donor in the order Me < Et < Bu < *i*-Pr.  
 \* Aliphatic nitroolefins provided Michael adducts in low yields.

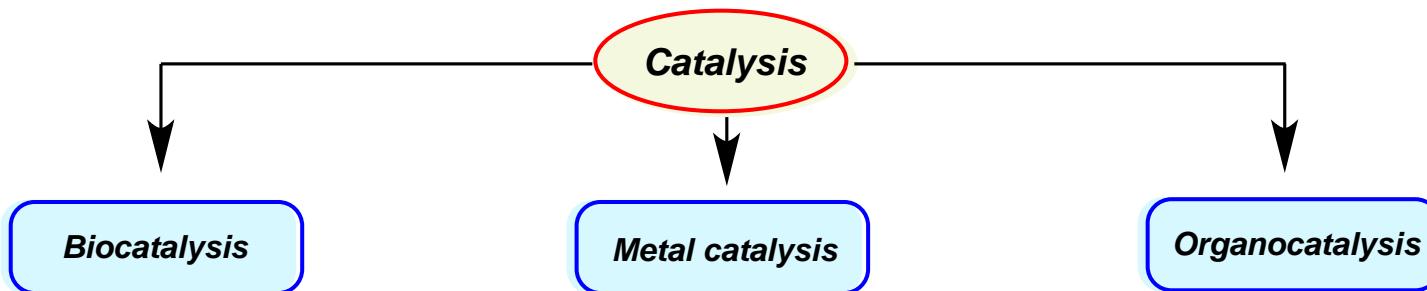
# Three-Component Catalytic Asymmetric Domino Reactions



## *Conclusion*

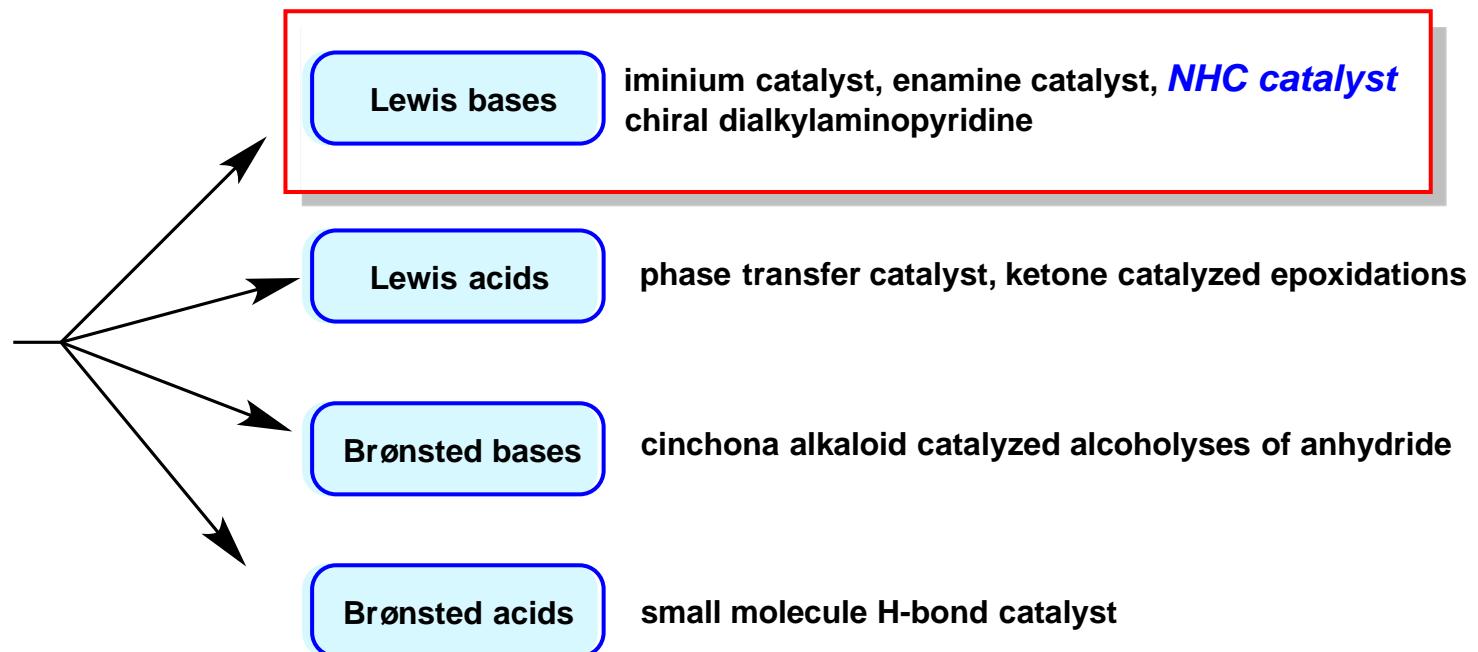
- \* Various asymmetric enamine catalyzed reactions have been developed. (e.g., aldol reactions, Mannich reactions, Michael reactions, and so on.)
- \* Despite the great advancements already made with regard to catalyst amounts, high catalyst loadings are required in some cases.
- \* A difficult challenge would be the development of a direct catalytic asymmetric intermolecular  $\alpha$ -alkylation of ketones and aldehydes.

# Organocatalysis



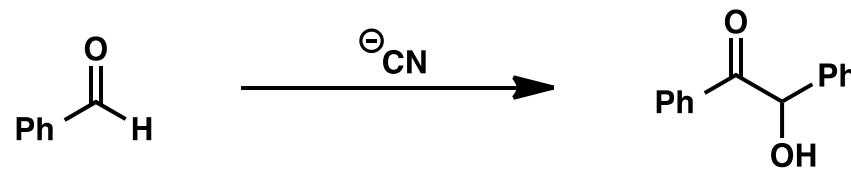
**Organocatalysis:** The catalysis with small organic molecules, where an inorganic element is not part of the active principle.

## Organocatalysis

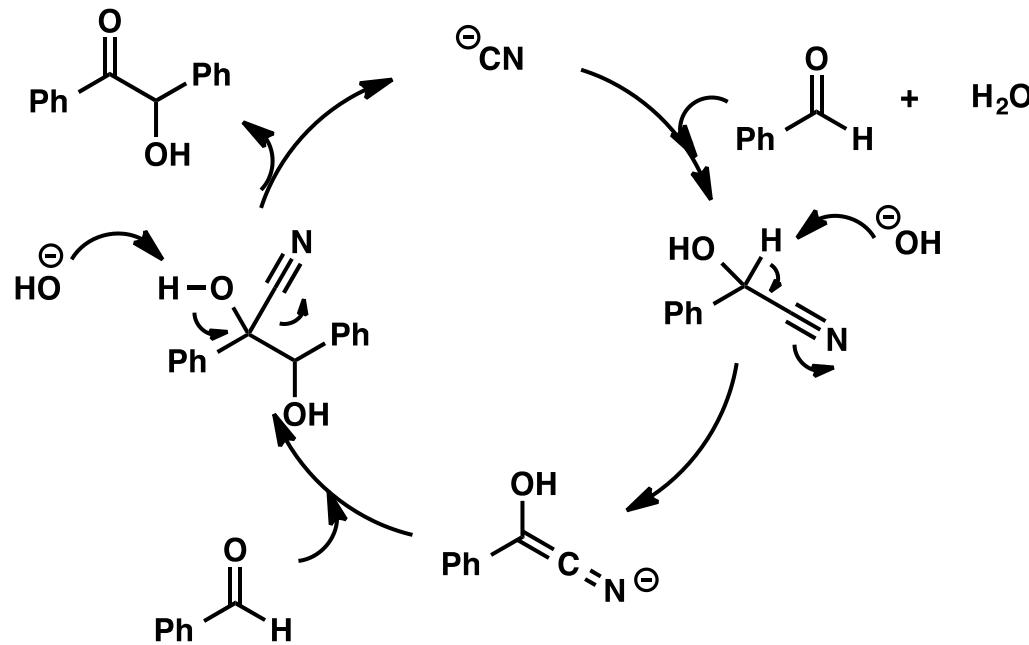


## *History*

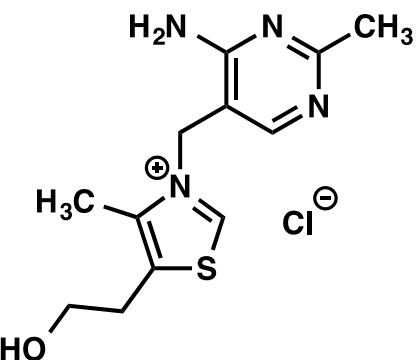
\* In 1832, Wöhler and Liebig



\* In 1903, Lapworth

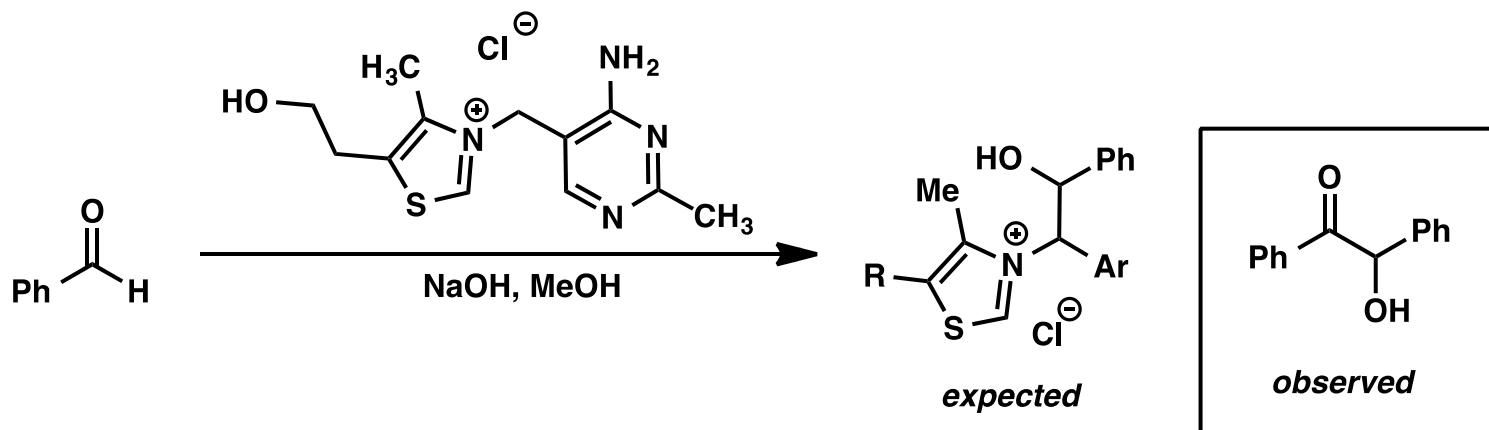


## History



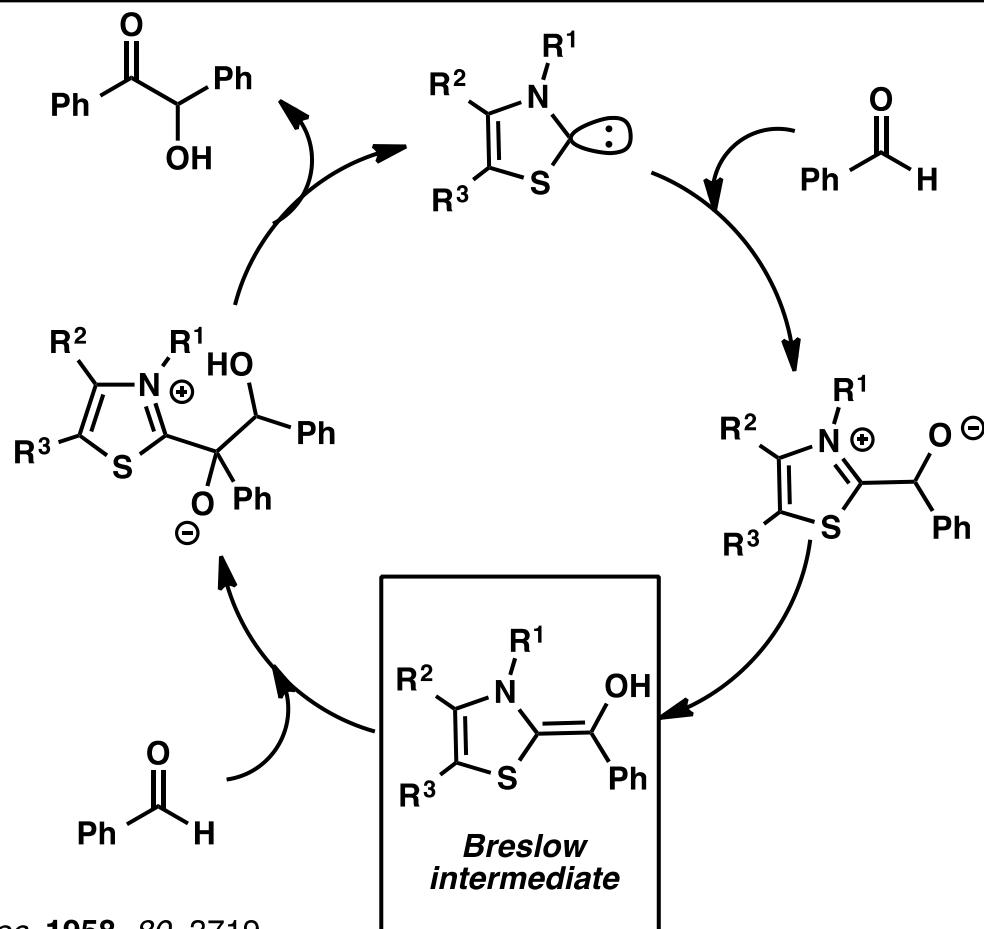
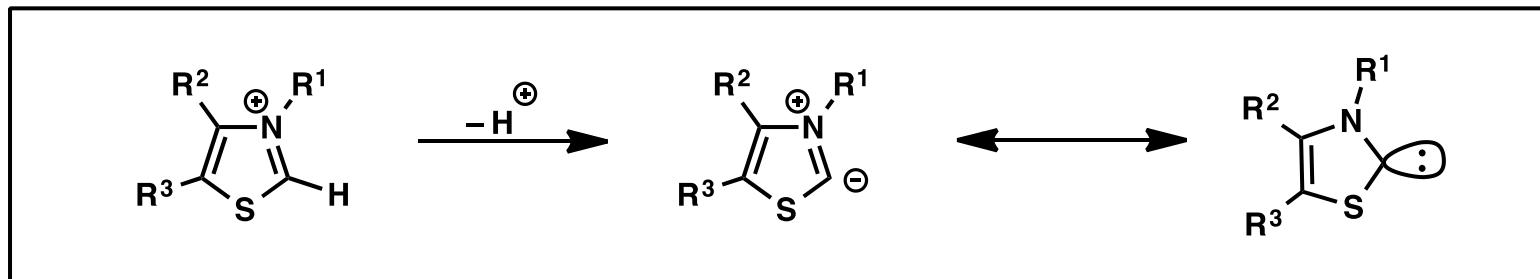
\* In nature, nucleophilic acylation reactions are catalyzed by transketolase enzymes in the presence of coenzyme thiamine (vitamin B<sub>1</sub>).  
\* In 1954, Mizuhara et al. found that the catalytic active species of the coenzyme thiamine is a nucleophilic carbene.

\*In 1943, Ugai

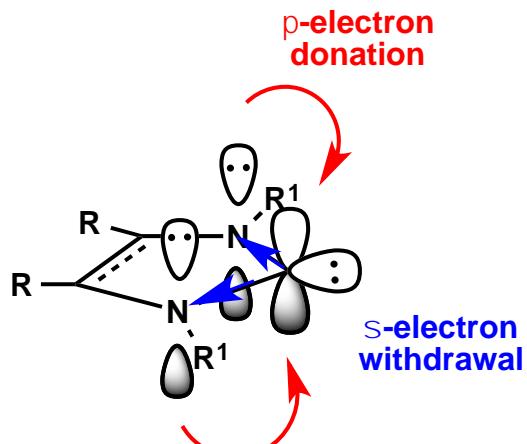


# History

\* In 1958, Breslow



## *Isolable NHCs*



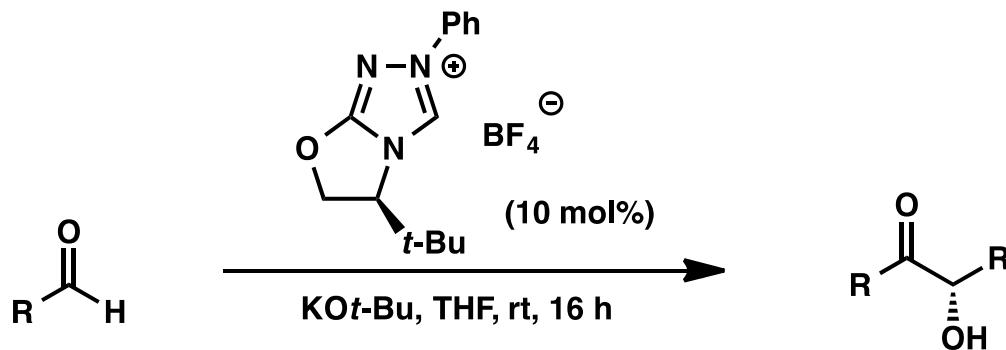
\*Electronic factors operating in both the p and s frameworks result in a "push-pull" synergistic effect to stabilize the carbene.

\*p donation into the carbene from the out-of-plane p orbital of heteroatoms stabilizes electrophilic reactivity of carbenes.

\*The electronegative heteroatoms adjacent to C-2 provide additional stability through the framework of s bonds.

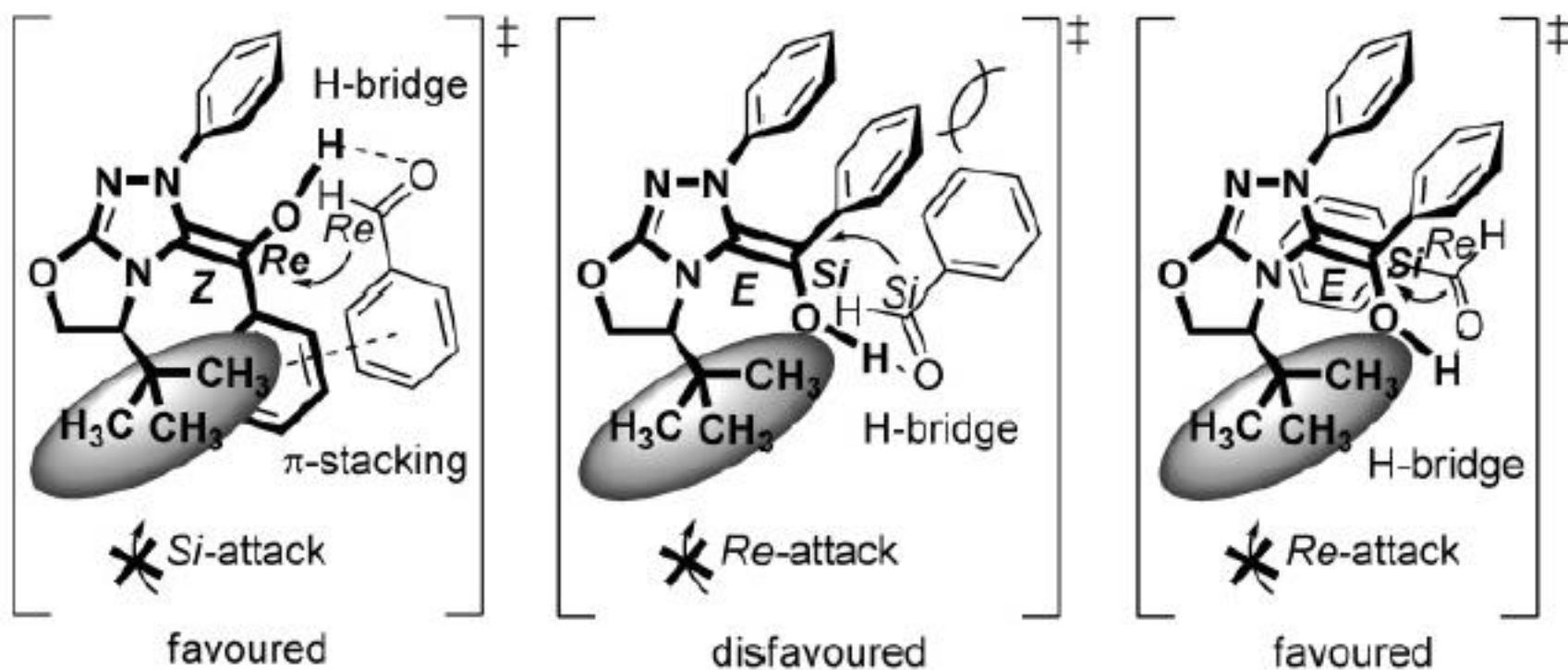
\* The combined effect is to increase the singlet-triplet gap and stabilize the singlet-state carbene over the more reactive triplet-state carbene.

## Asymmetric Benzoin Condensations

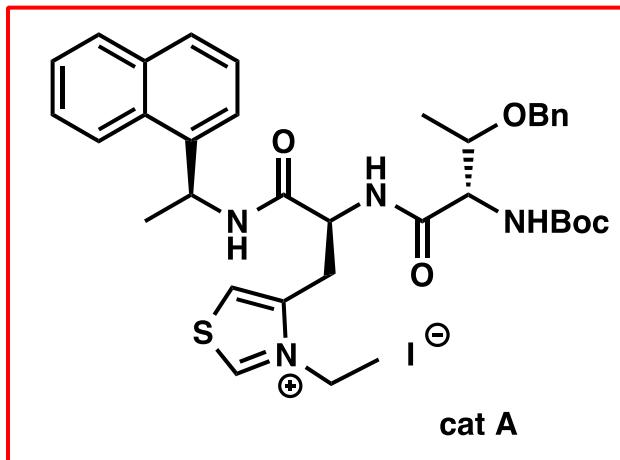
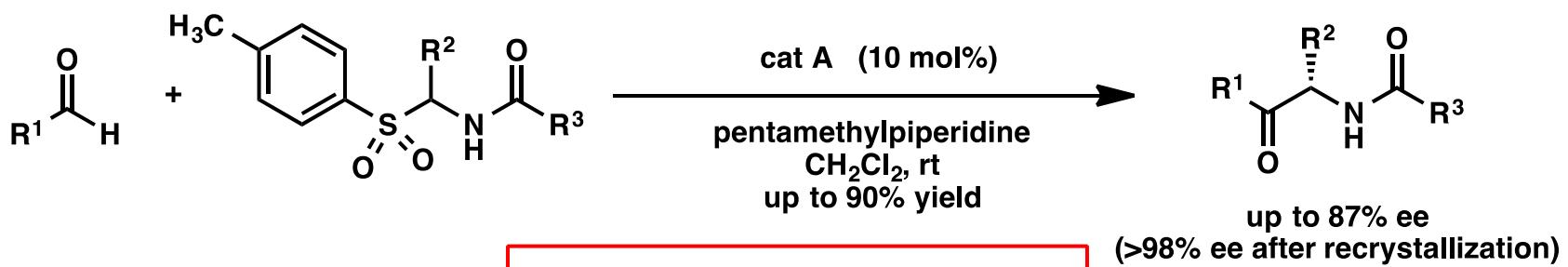
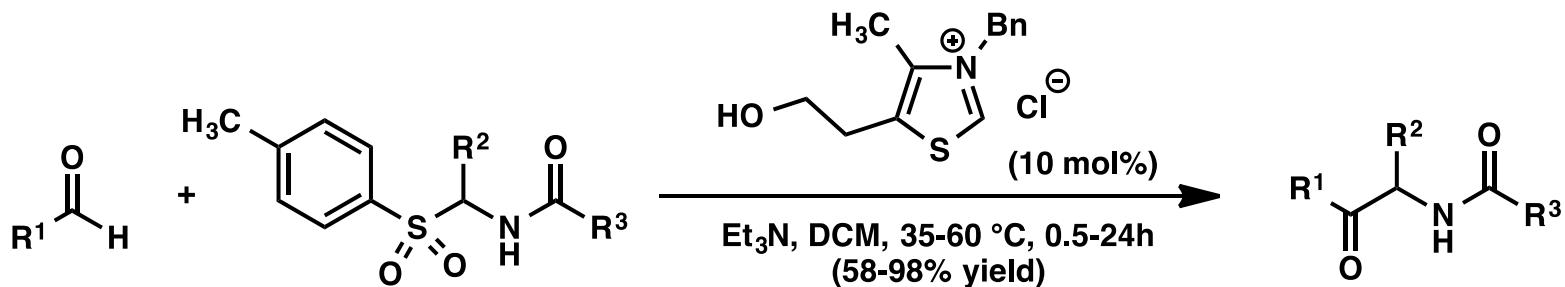


R	T (°C)	yield (%)	ee (%)	R	T (°C)	yield (%)	ee (%)
Ph	18	83	90	<i>m</i> -Cl-Ph	18	92	62
Ph	18	46	93	<i>m</i> -Cl-Ph	0	85	86
Ph	18	33	99	<i>p</i> -Me-Ph	18	16	93
<i>p</i> -F-Ph	18	81	83	<i>m</i> -Me-Ph	18	70	86
<i>p</i> -F-Ph	0	61	91	<i>m</i> -Me-Ph	0	36	91
<i>p</i> -Cl-Ph	18	80	64	<i>p</i> -OMe-Ph	18	8	95
<i>p</i> -Cl-Ph	0	44	89	<i>o</i> -furyl	0	100	64
<i>p</i> -Br-Ph	18	82	53	<i>o</i> -furyl	-78	41	88
<i>p</i> -Br-Ph	0	59	91	<i>o</i> -naphthyl	18	69	80

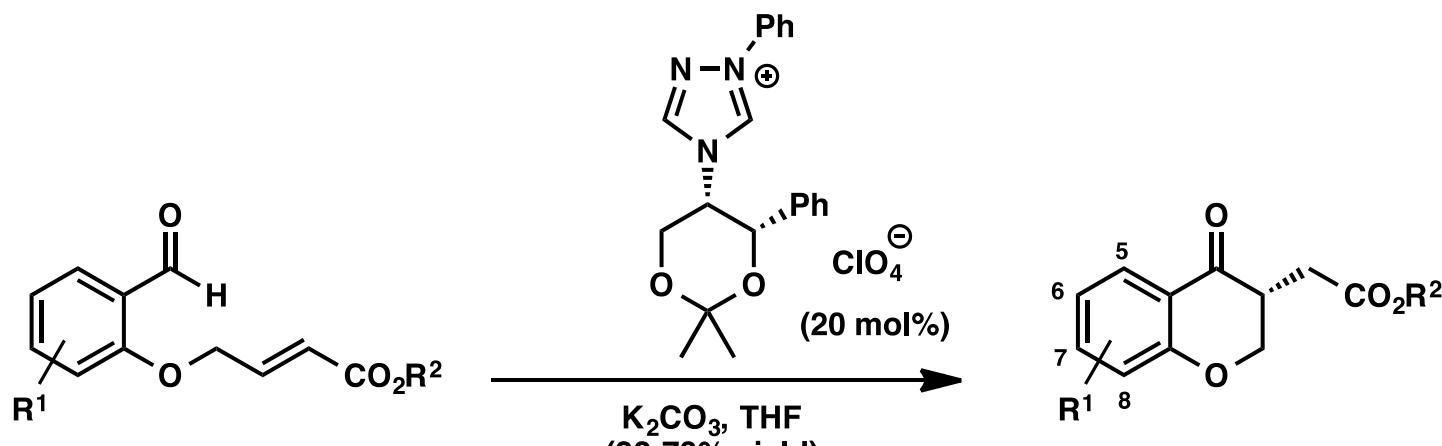
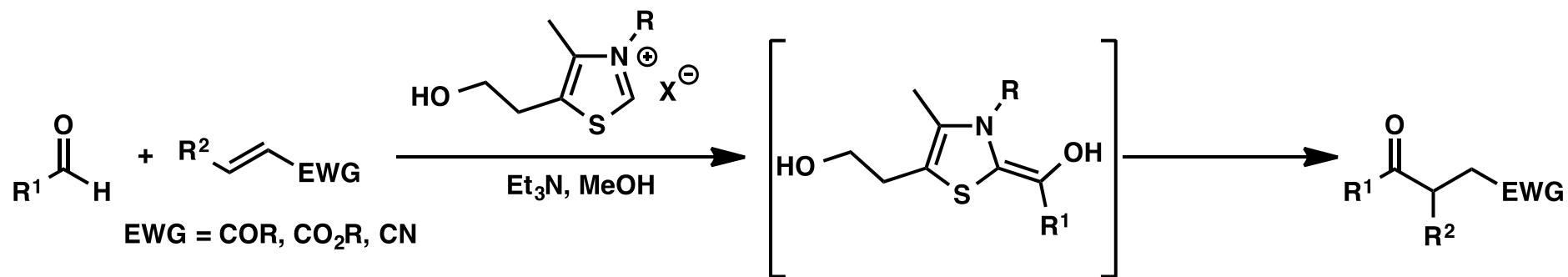
*Aymmetric Benzoin Condensations*



## Crossed Benzoin Condensations

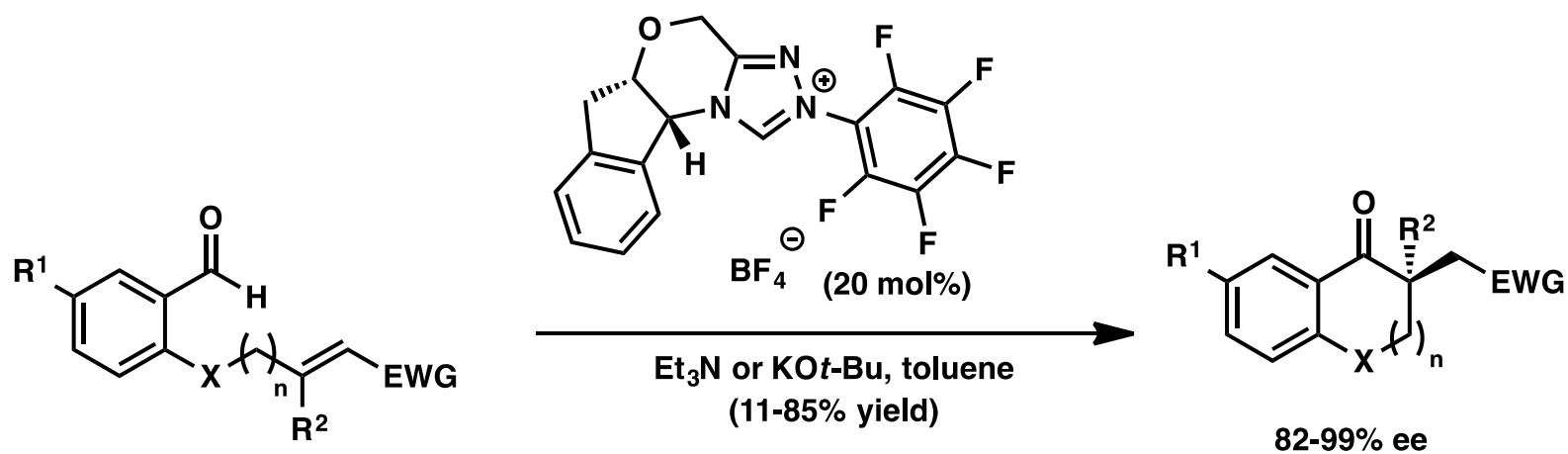
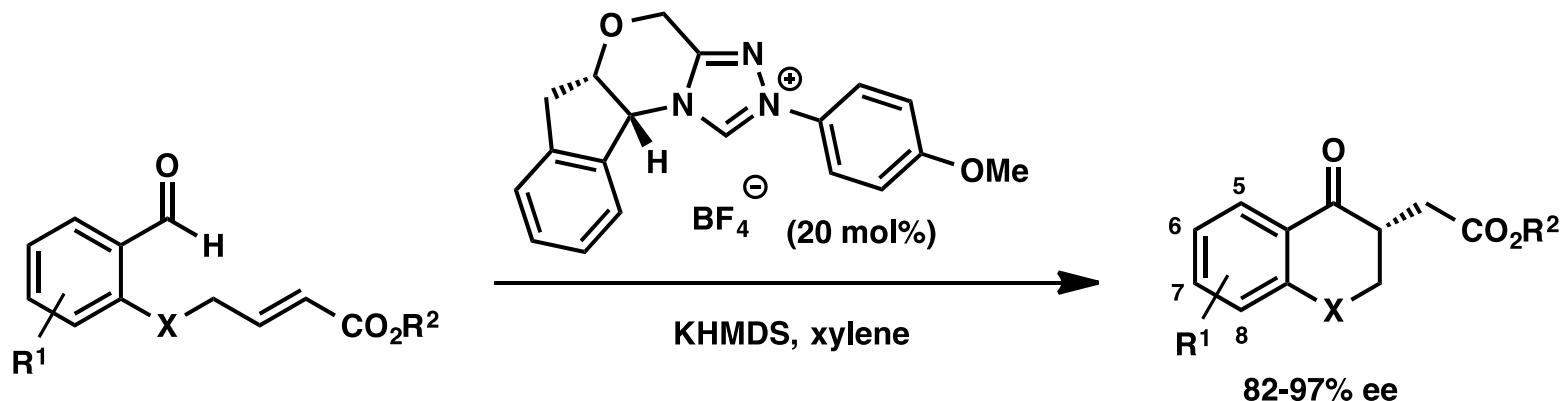


## Stetter Reaction

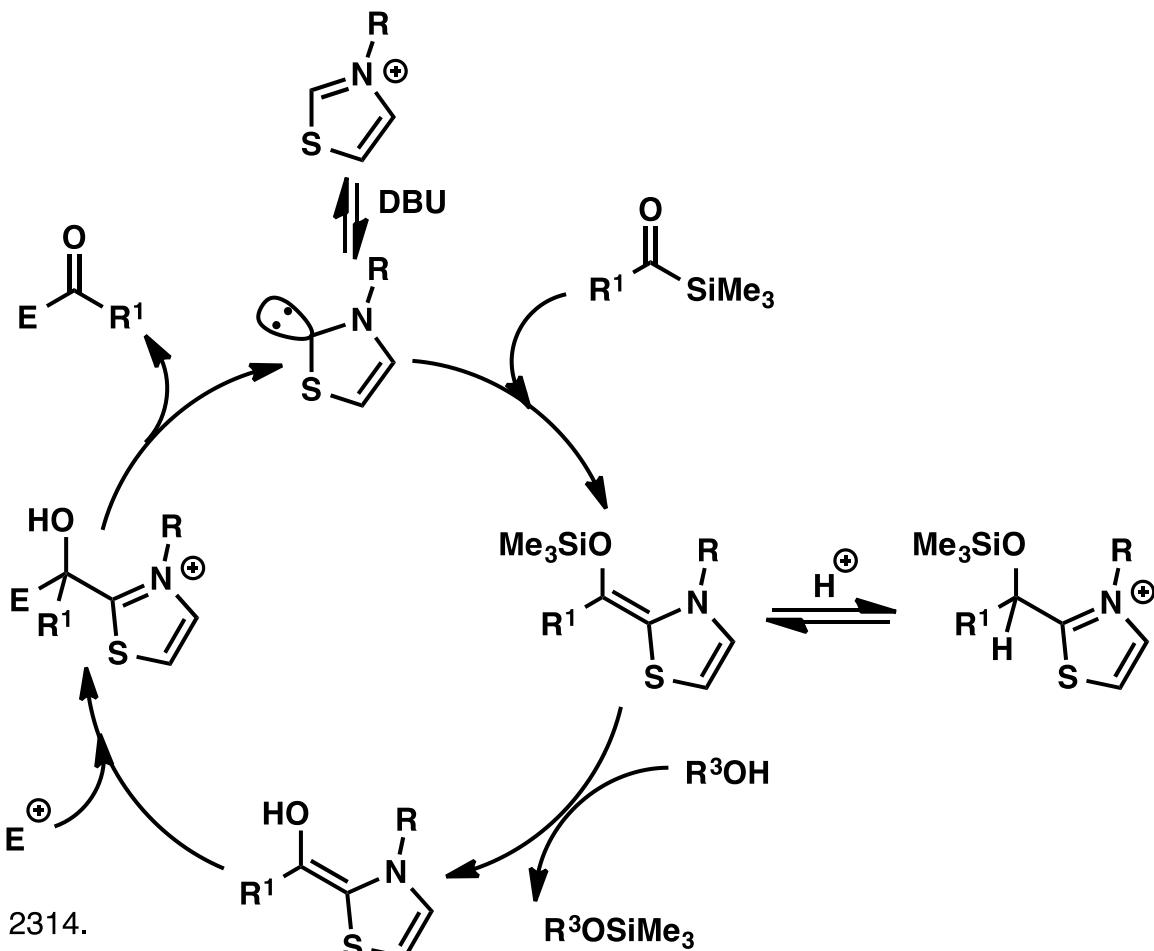
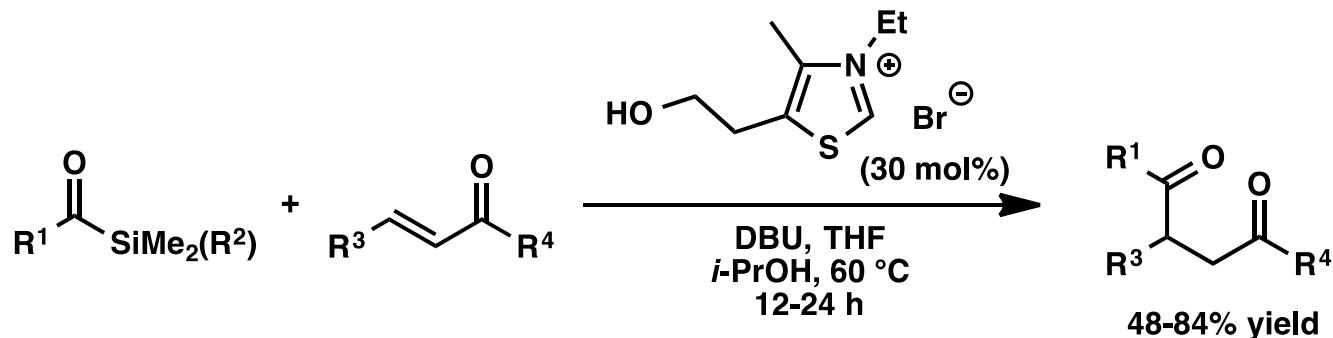


Stetter, H. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 539.  
 Enders, D. *Helv. Chim. Act.* **1996**, *79*, 1899.

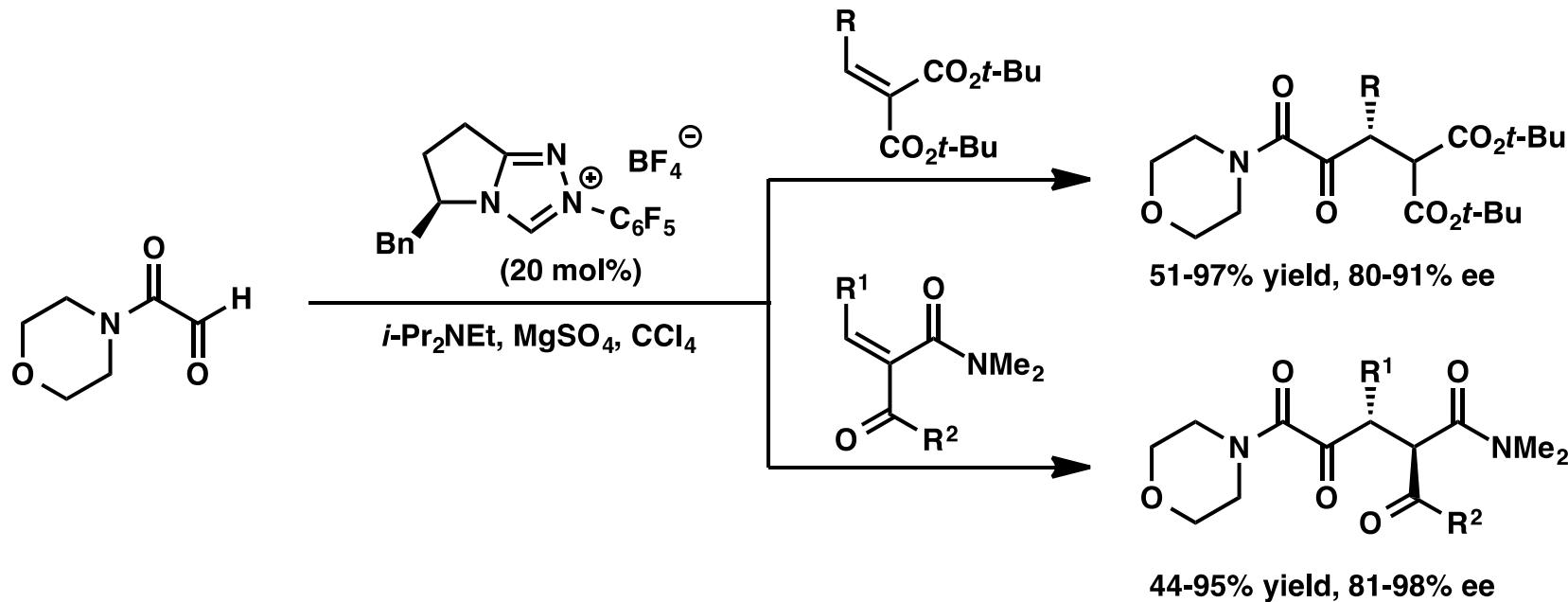
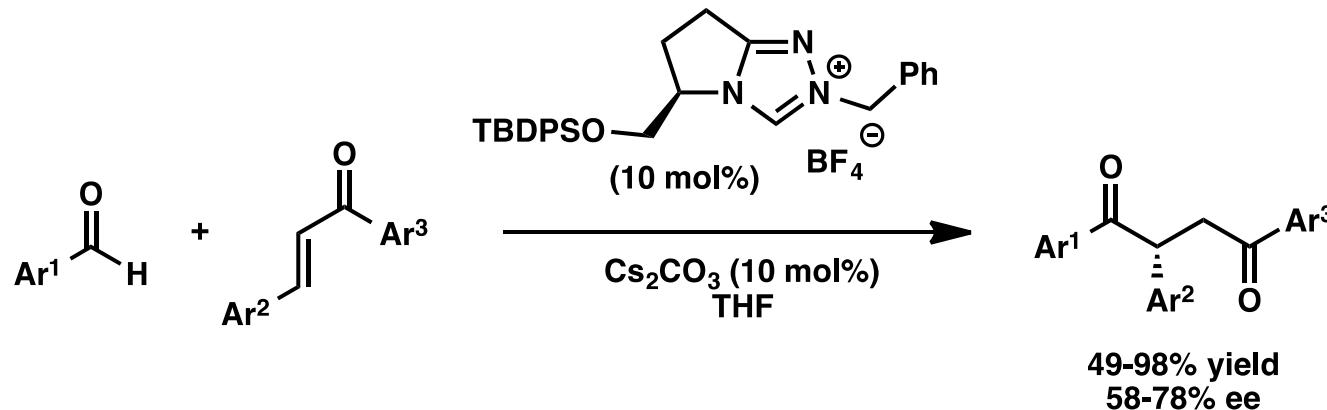
*Stetter Reaction*



## Sila-Stetter Reaction



## Intermolecular Stetter Reaction

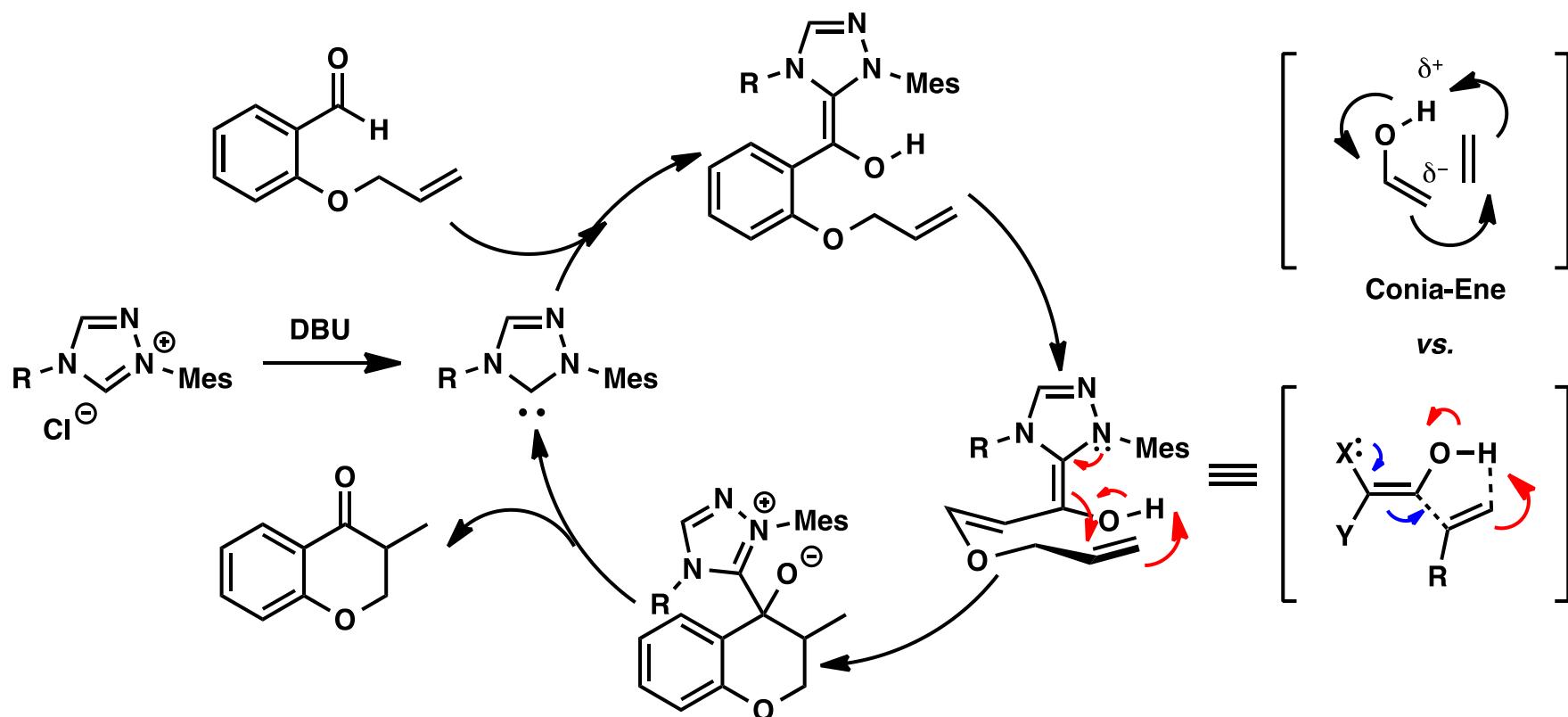
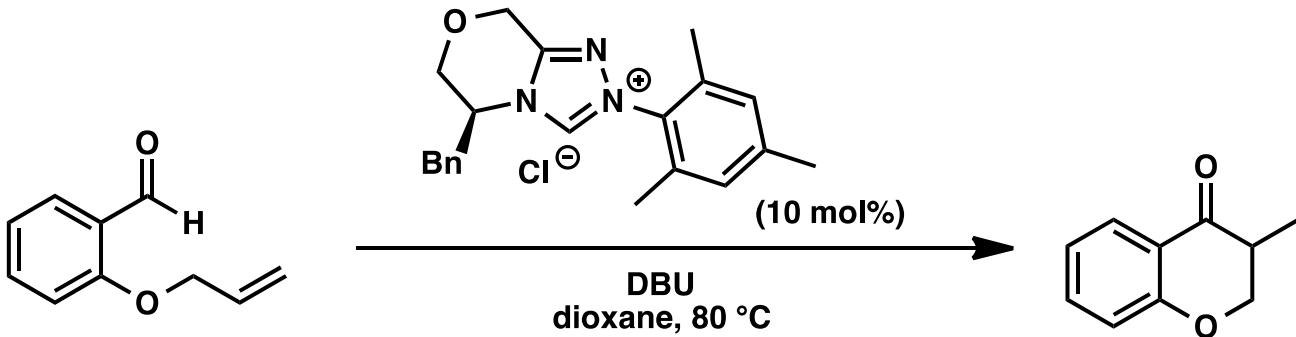


Enders, D. *Chem. Commun.* **2008**, 3989.

Rovis, T. *Org. Lett.* **2009**, 11, 2856.

Rovis, T. *J. Am. Chem. Soc.* **2008**, 130, 14066.

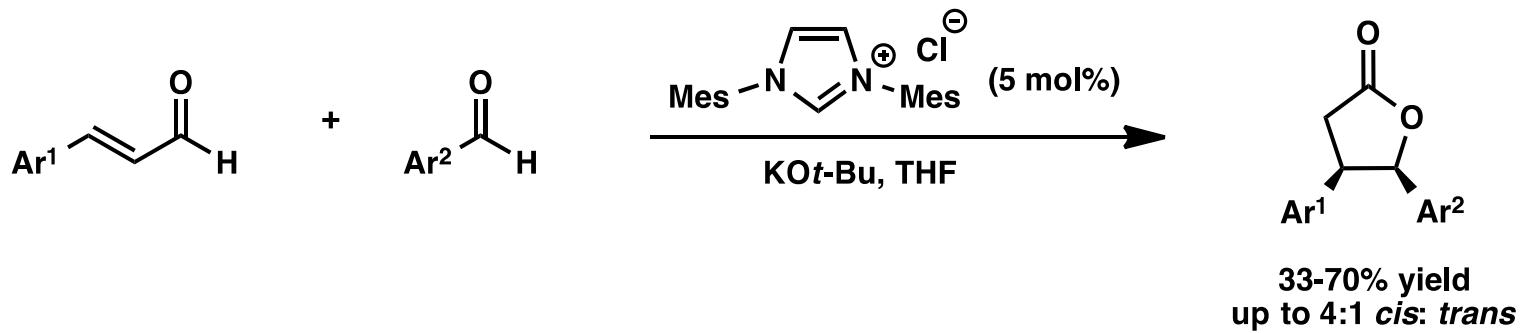
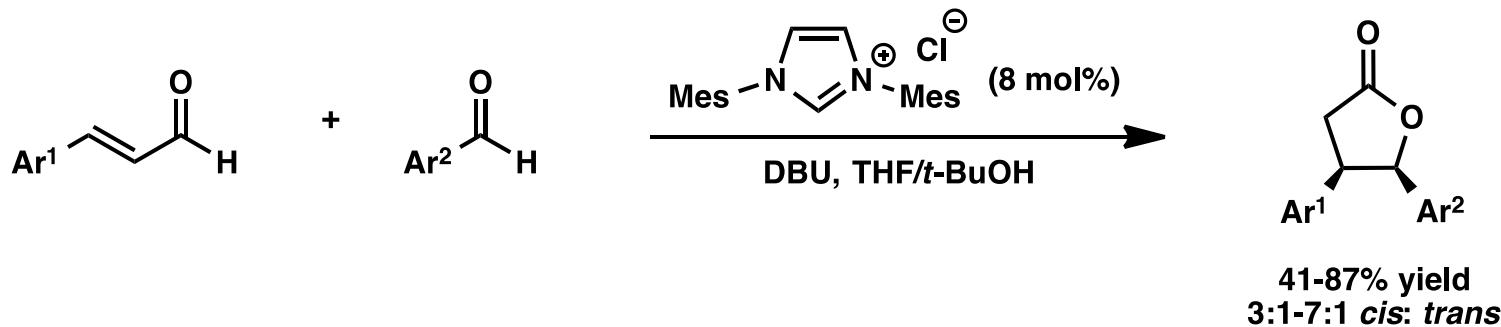
# Hydroacylation of Unactivated Double Bonds



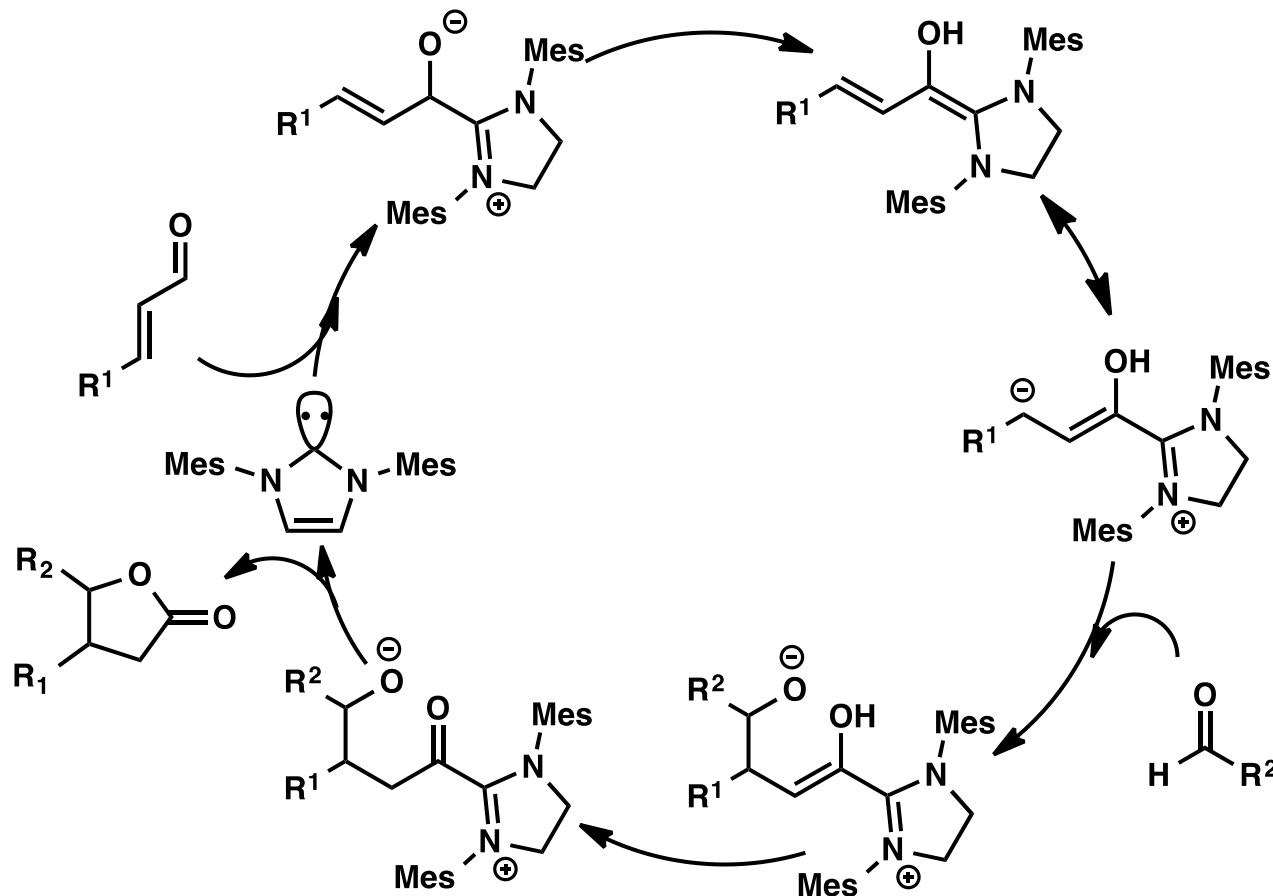
Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.

Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.

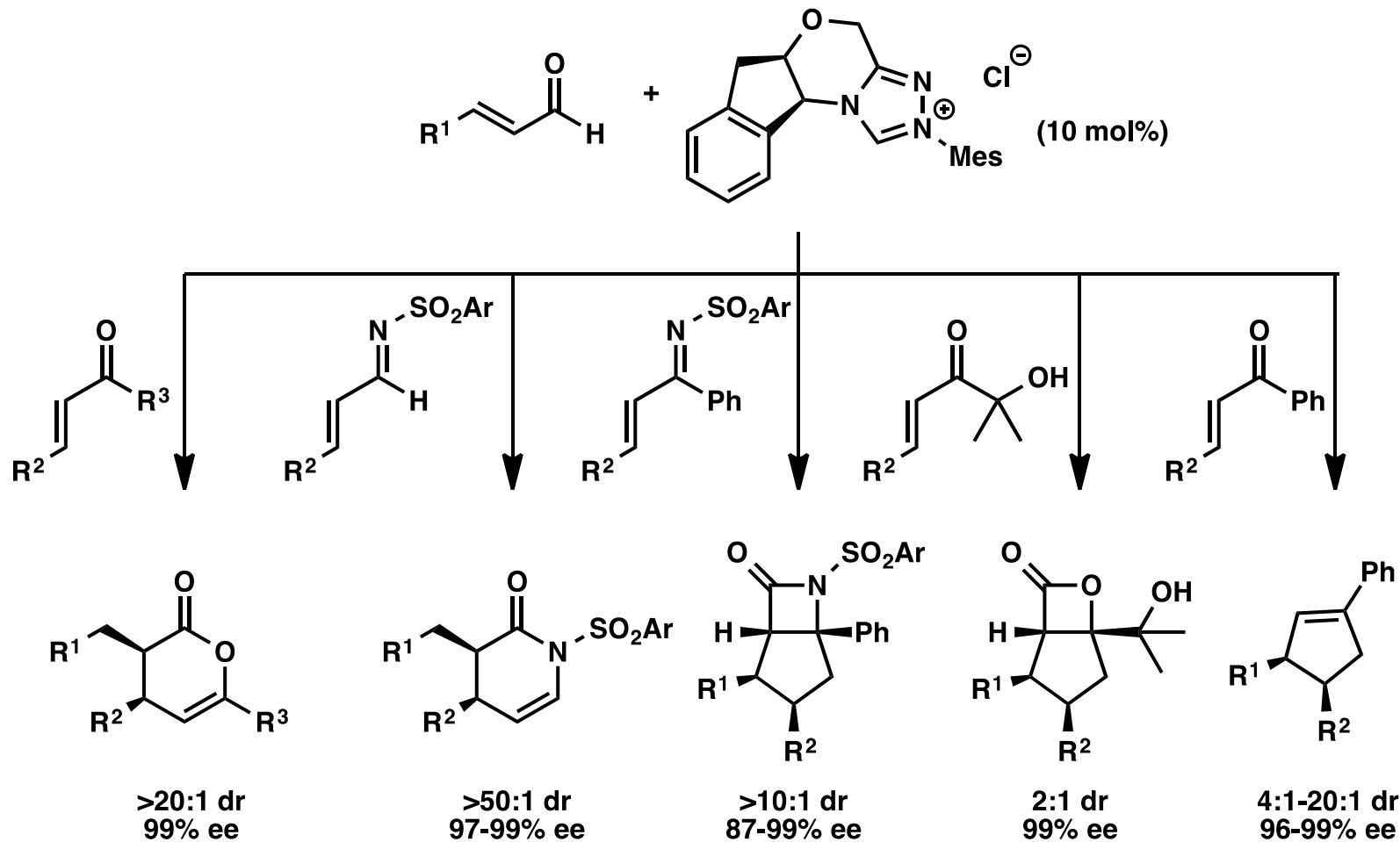
*a<sup>3</sup>-d<sup>3</sup> Umpolung*



*Postulated Catalytic Cycle*



*Enantioselective transformation of homoenolates*



Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418.

Bode, J. W. *Org. Lett.* **2009**, *11*, 677.

Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

Bode, J. W. *Proc. Nat. Acad. Sci.* **2010**, *107*, 20661.

## *Conclusion*

- \* A variety of NHC catalyst has enabled a lot of organic reactions, such as nucleophilic acylations, transesterifications, hydroacylations, sila-Stetter reactions, etc.
- \* It can be foreseen that new reaction partners for the NHCs and low catalyst loadings will broaden the remarkable potential of NHC-catalyzed reactions and will generate polyfunctionalized molecules of great synthetic importance.

## *Acknowledgement*

Prof. Brian Stoltz

Prof. Sarah Reisman

Stoltz Group  
Reisman Group

### **Reference:**

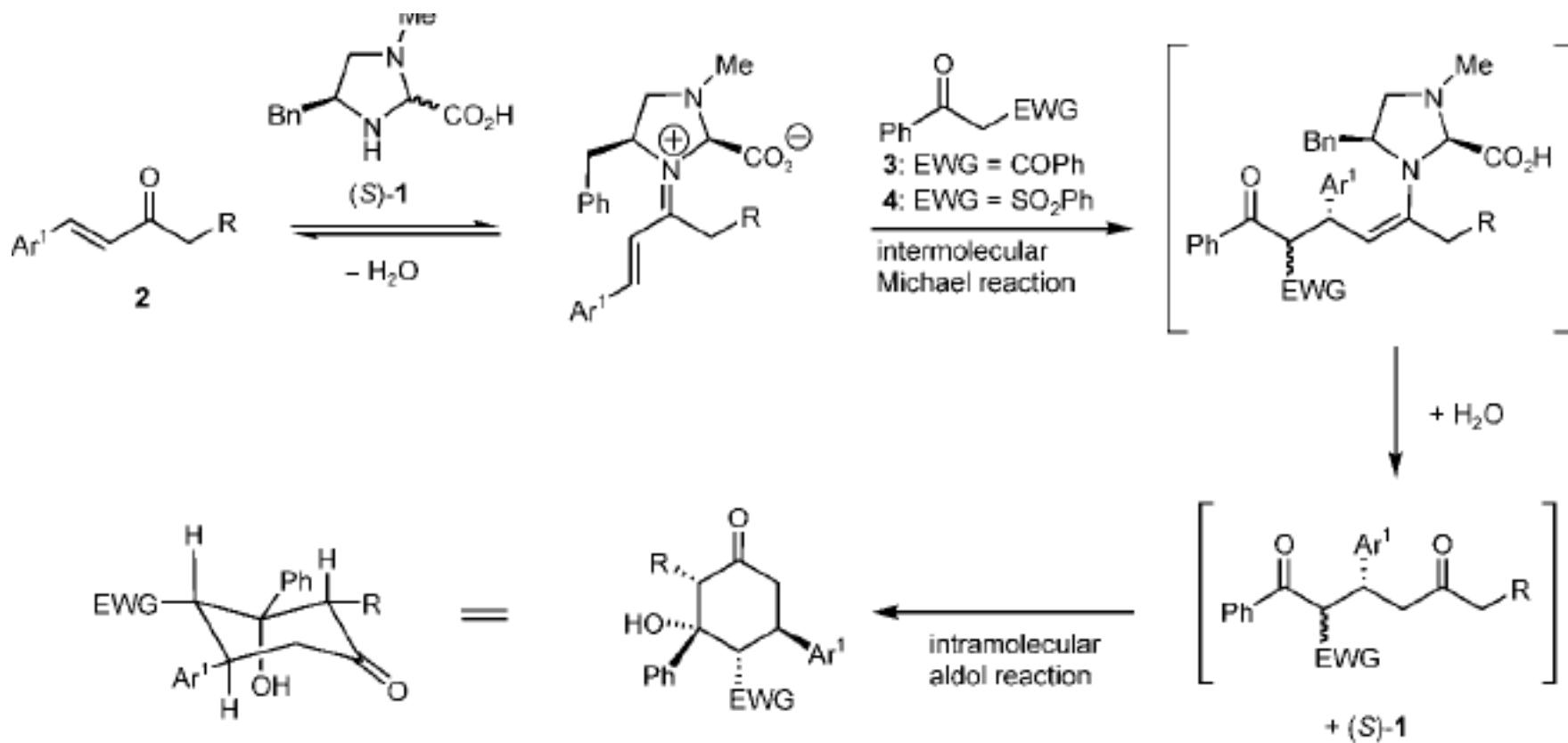
Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

List, B. *Chem. Rev.* **2007**, *107*, 5471.

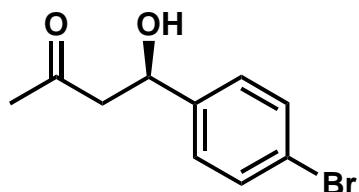
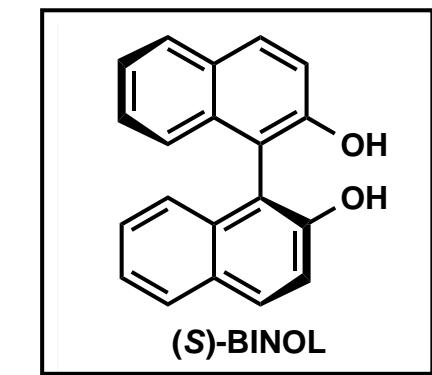
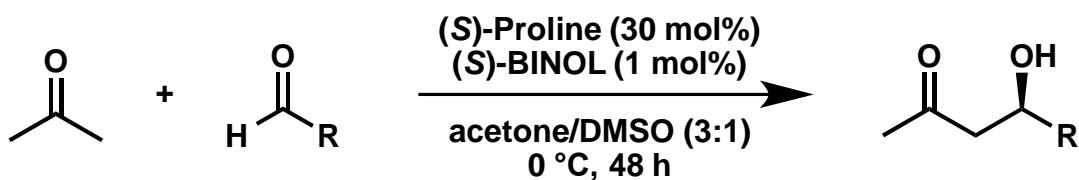
Enders, D. *Chem. Rev.* **2007**, *107*, 5606.

Dalko, P. I. *Enantioselective Organocatalysis*, 1st ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2007.

The MacMillan group's group meeting slide: Asymmetric Organocatalysis with N-Heterocyclic Carbenes (Adam Noble)

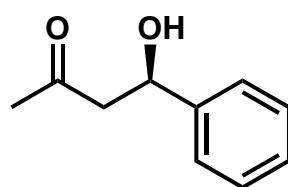


## Additive Effect

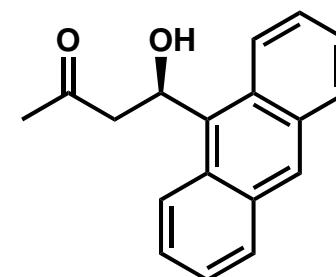


Without BINOL  
With BINOL

82%, 75% ee  
76%, 97% ee

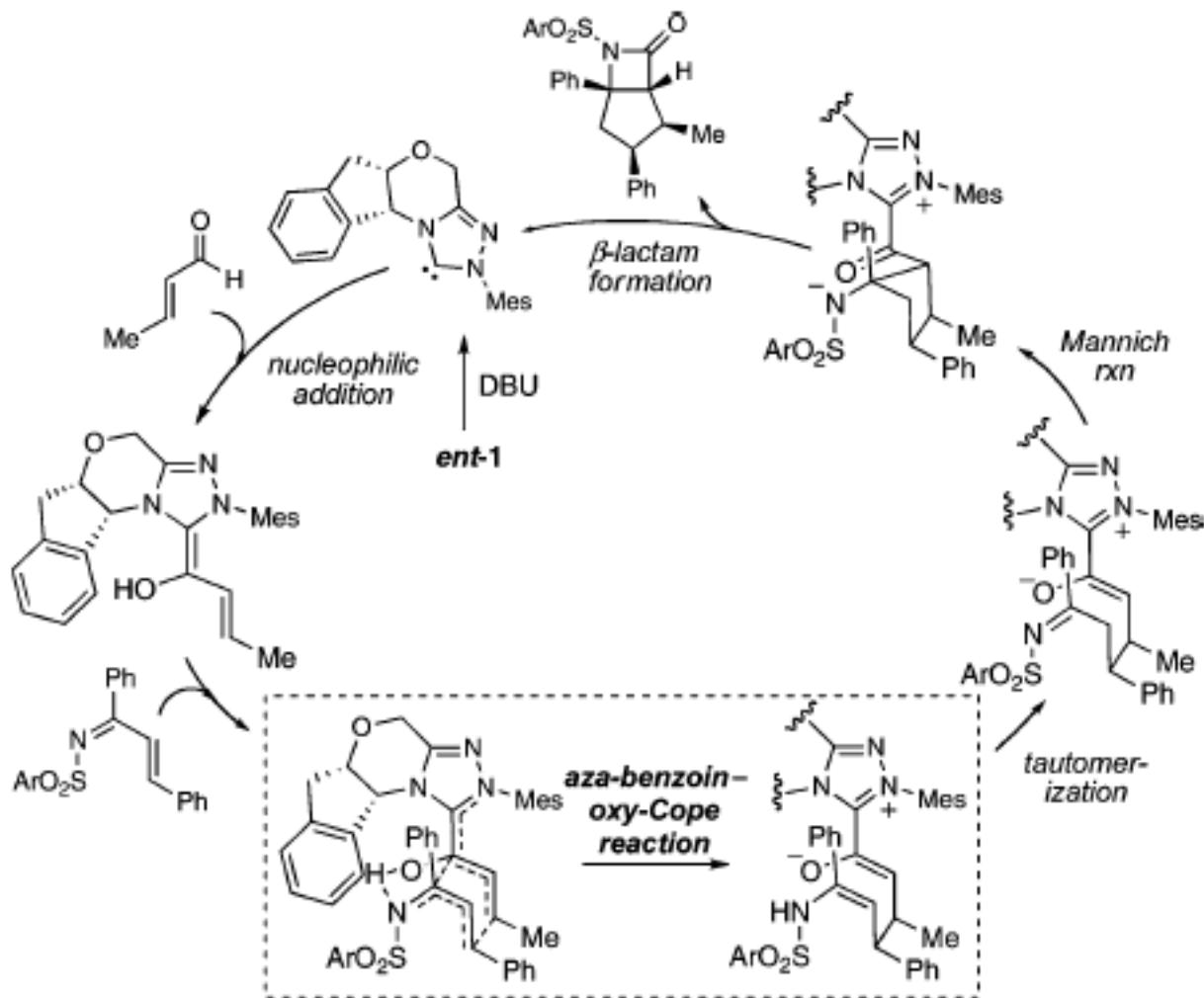


43%, 72% ee  
56%, 98% ee

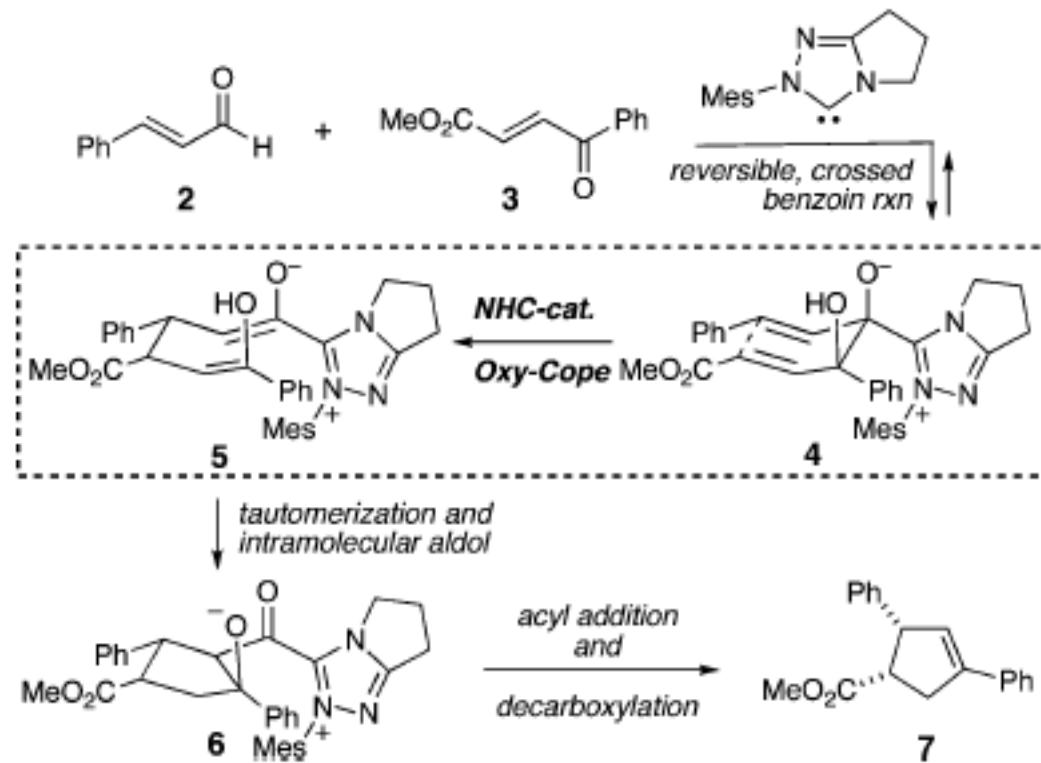


10%, 92% ee  
23%, 87% ee

**Scheme 2.** Postulated Catalytic Cycle (*ent*-1 is shown as the NHC)



**Scheme 1.** Cyclopentenes via NHC-Catalyzed Oxy-Cope RAR



**Scheme 2.** Postulated Catalytic Cycle

