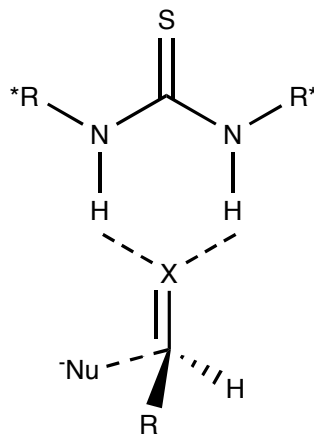


# *Asymmetric Hydrogen-Bond Catalysis*



Anthony Mastracchio  
MacMillan Group  
12/11/06

Lead Material:

M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543

T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999-1010

# Asymmetric Hydrogen-Bond Catalysis

*presentation outline*

## I. Introduction to hydrogen-bond (H-bond) catalysis

- Definitions and possible benefits of H-bond catalysis
- Early developments in the field

## II. Double H-bond catalysts

- Ureas and thioureas
- Chiral guanidinium and amidinium ions

## III. Single H-bond catalysts

- Diols and biphenols
- Chiral phosphoric acids

## IV. Bifunctional H-bond donor catalysts

- Proline and proline analogs
- Cinchona alkaloids and derivatives
- Bifunctional thioureas derivatives
- H-bonding phase transfer catalysts

## V. Summary

# Asymmetric Hydrogen-Bond Catalysis

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## I. Introduction to hydrogen-bond (H-bond) catalysis

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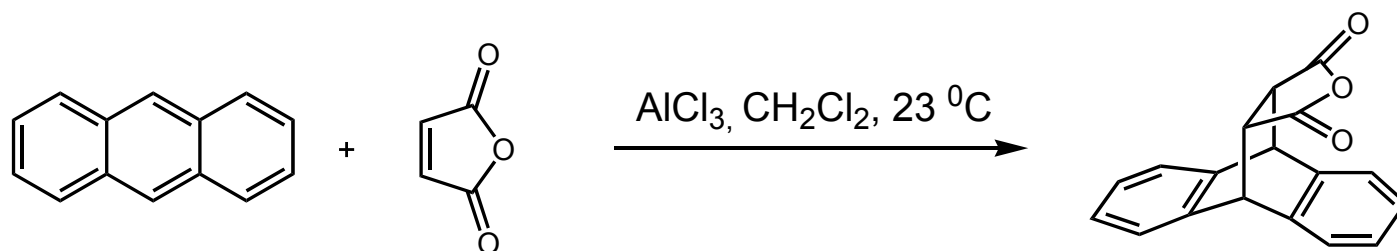
## V. Summary

**Not covered in this presentation: Hydrogen bonding in biological catalysis**

## Early H-Bond Catalyzed Transformation

*the beginning of H-bond catalysis*

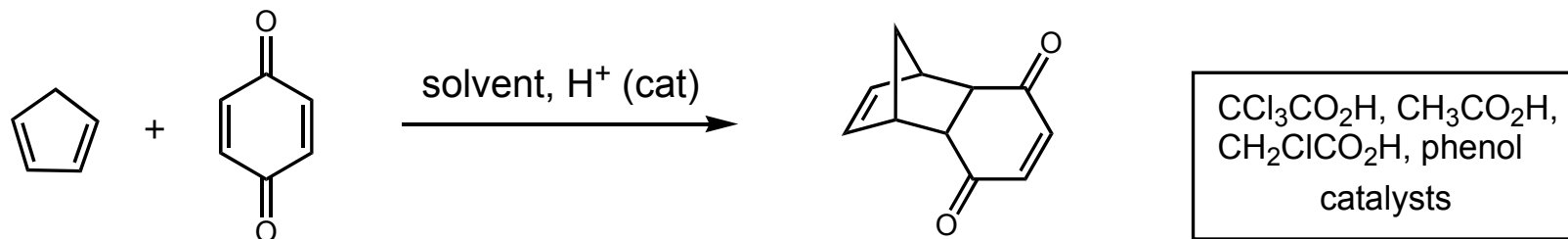
### ■ Acceleration of the Diels-Alder reaction by Aluminum Chloride



- IR spectroscopy showed completion of the reaction in 1.5 minutes. In the absence of aluminum chloride is estimated that 4800 hours would be required for 95% completion

P. Yates, P. Eaton, *J. Am. Chem. Soc.* **1960**, 82, 4436-4437

### ■ First example of catalytic Diels-Alder cycloaddition using protic additives

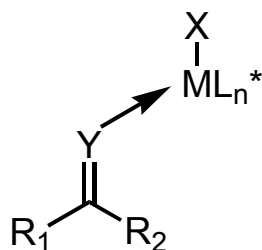


A. Wasserman, *J. Chem. Soc.* **1942**, 618-621

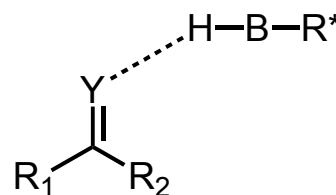
# Benefits of H-Bond Catalysis

*pros and cons of this concept*

## ■ Considerations in Lewis acid versus H-Bond activation of a generic electrophile



- Highly tunable (M, X, L<sup>\*</sup>)  
well defined interactions



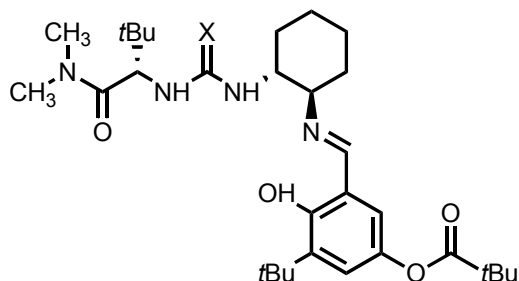
- Somewhat tunable (structure of R<sup>\*</sup>B, pK<sub>a</sub>)  
Dominant mechanism in biocatalysis  
Loosely defined interactions

## ■ Other considerations

- cost
- toxicity
- sensitivity & stability issues
- isolation
- etc.

## Double H-Bond Catalysts

*Jacobsen ureas and thioureas are the most efficient and broadly used scaffold today*



**1a:**  $R^1 = \text{Bn}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OCH}_3$ ,  $X = \text{S}$

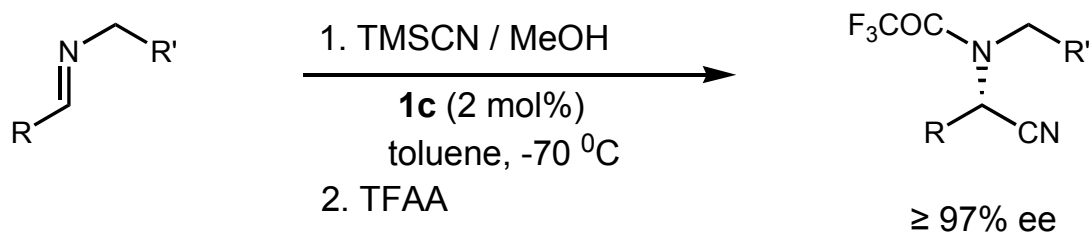
**1b:**  $R^1 = \text{Bn}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OCOtBu}$ ,  $X = \text{O}$

**1c:**  $R^1 = R^2 = \text{CH}_3$ ,  $R^3 = \text{OCOtBu}$ ,  $X = \text{S}$

**1d:**  $R^1 = \text{Bn}$ ,  $R^2 = \text{CH}_3$ ,  $R^3 = \text{OCH}_3$ ,  $X = \text{S}$

[Thioureas catalysts were originally designed as potential ligands for Lewis acidic metals](#)

### ■ Asymmetric Strecker Reactions



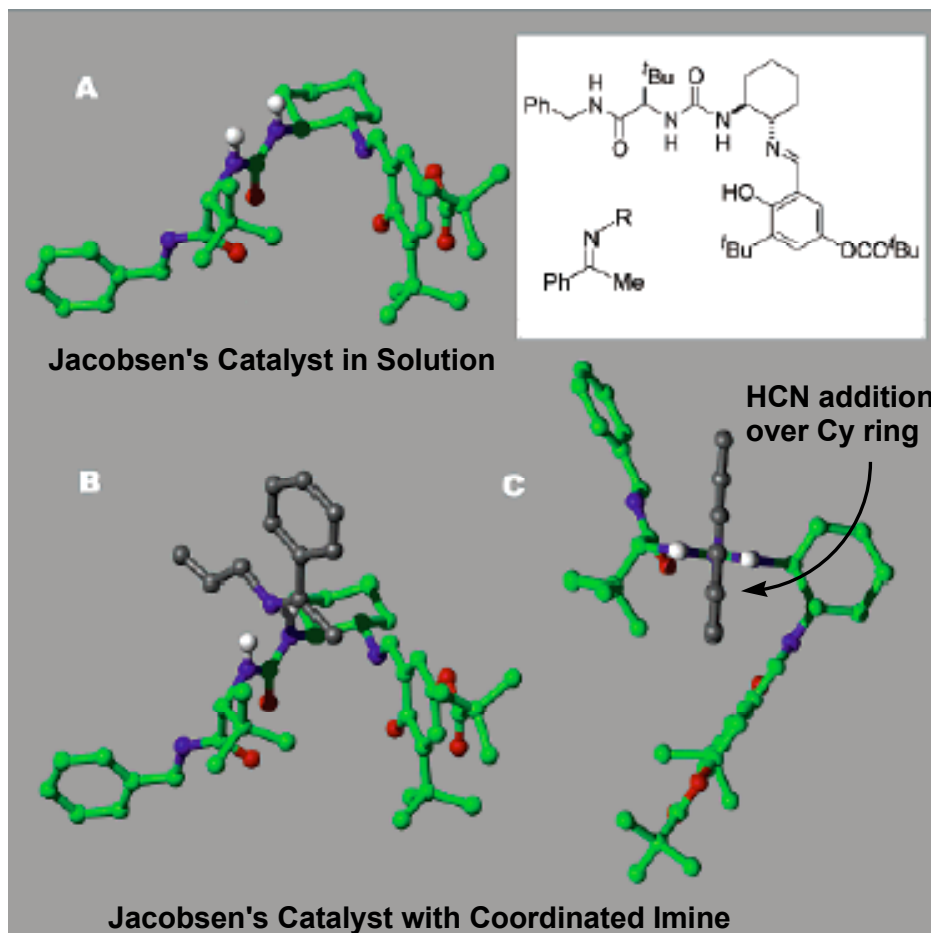
- Tolerates a wide range of aryl and aliphatic group
- Work well with methylketoimines but larger group are poor substrate

M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902  
P. Vachal, E. N. Jacobsen, *Org Lett.* **2000**, *2*, 867-870  
M. S. Sigman, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281

## Double H-Bond Catalysts

*Origins of the selectivity in the catalyzed Strecker reaction*

### ■ Structure of the catalyst and catalyst / imine Complex in solution using MOLMOL



- Reactive imine stereoisomer (Z-imine) was determined by NMR titration with the catalyst
- Urea/thiourea protons were identified as the only essential protons for catalysis
- Double H-bond: urea/imine: 8.5 kcal/mol, thiourea/imine: 10 kcal/mol; H-bond to ptd: 5.0 and 6.3 kcal/mol, respectively

M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902

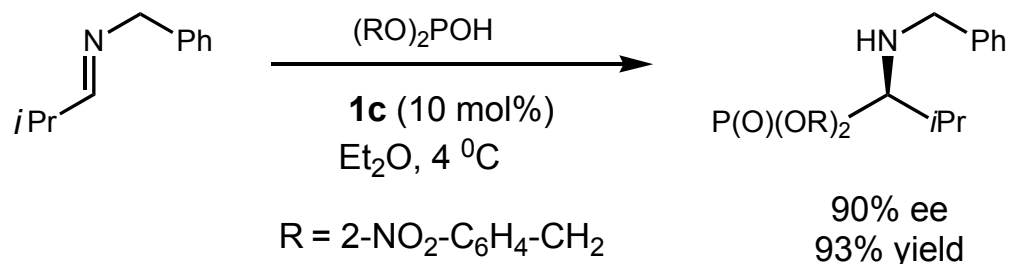
P. Vachal, E. N. Jacobsen, *Org Lett.* **2000**, *2*, 867-870

M. S. Sigman, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281

## Double H-Bond Catalysts

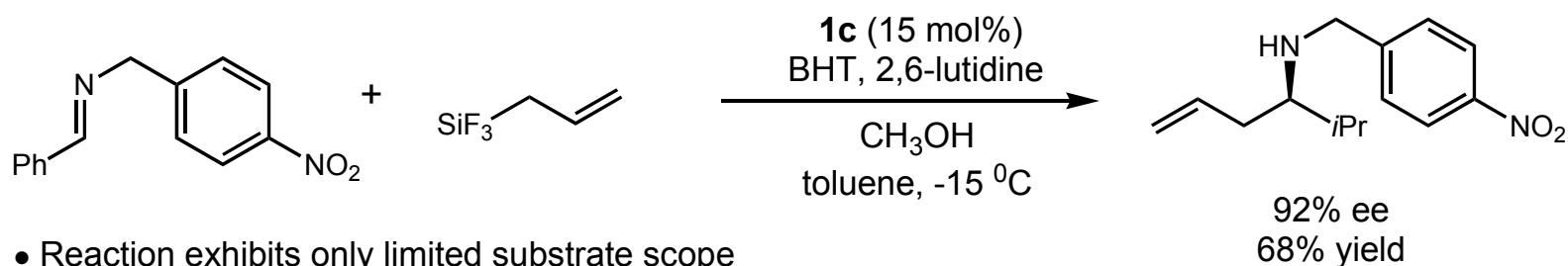
*Thiourea catalysts can also be applied to enantioselective additions of a number of nucleophiles*

### ■ Addition of di-(2-nitro-benzyl) phosphite to imines

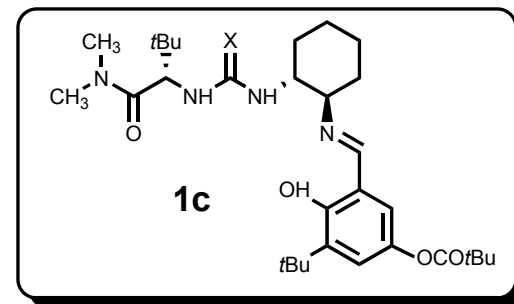


- Tolerates a wide range of aryl and aliphatic group
- Constitute an efficient asymmetric synthesis of aminophosphonic acids

### ■ Allylation of *N*-(4-nitrobenzyl) imines with allyltrifluorosilane



- Reaction exhibits only limited substrate scope

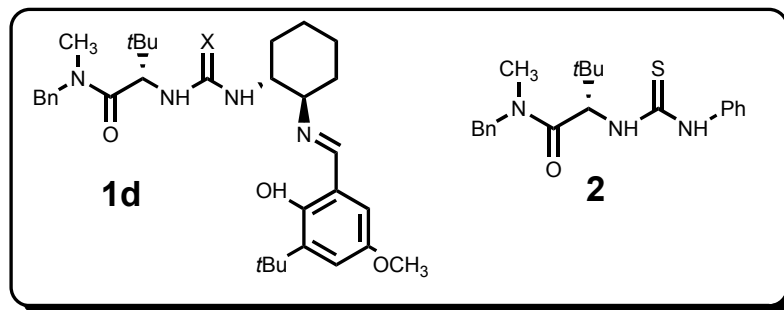


T. Kuribayashi, A. M. Lerchner, E. N. Jacobsen, *unpublished results*  
G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, 126, 4102-4103

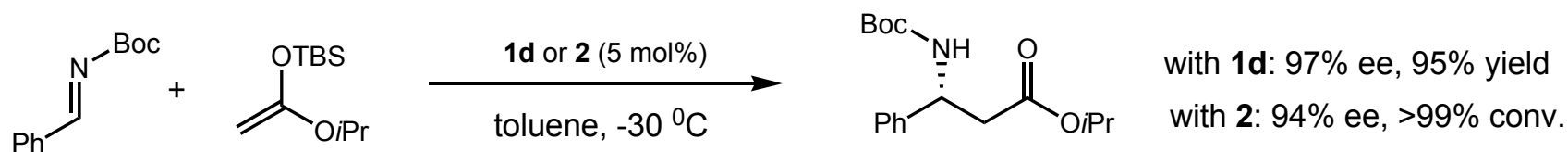


## Double H-Bond Catalysts

*Thiourea catalysts can also promote enantioselective additions to a range of functionally diverse electrophiles*

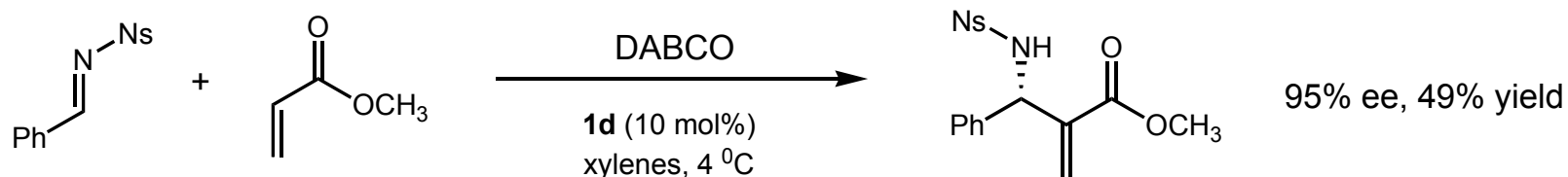


### ■ Asymmetric Mannich reactions



- Mechanism not well understood
- Structure-mechanism studies showed that Schiff base and diamine linker on original catalyst are unnecessary
- Tolerates a wide range of aryl groups, no aliphatic example

### ■ Asymmetric aza-Baylis-Hillman reactions



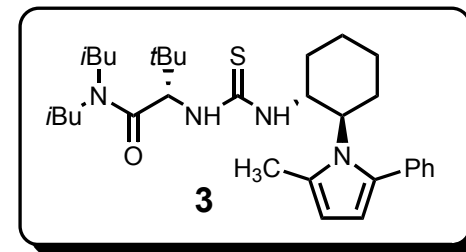
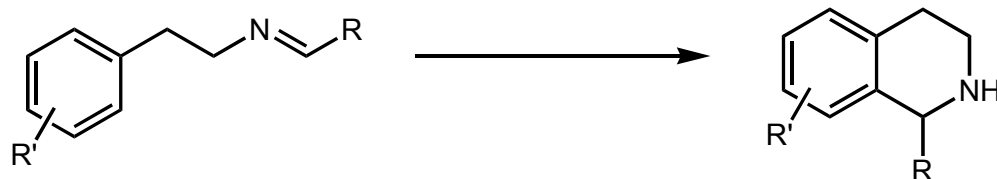
A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965

I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701-1708

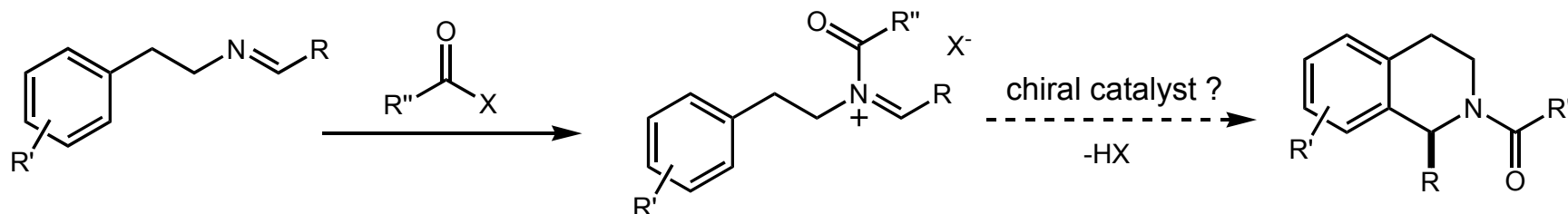
## Double H-Bond Catalysts

*Thiourea catalysts can also activate very reactive imine derivatives*

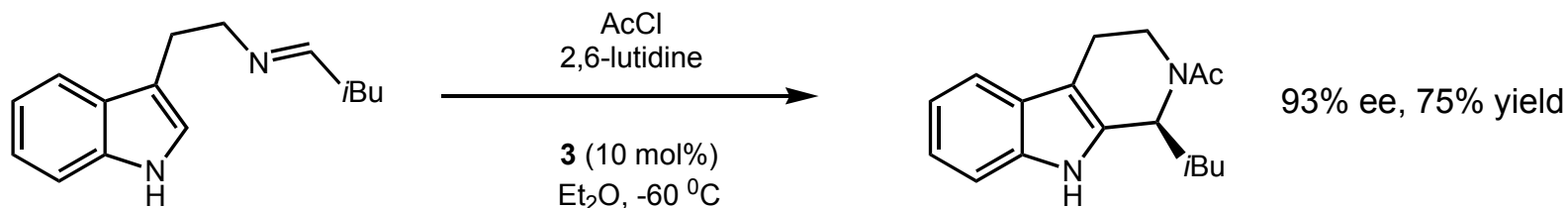
The Pictet-Spengler reaction:



The acyl-Pictet-Spengler reaction:



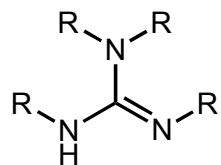
### ■ Asymmetric acyl-Pictet-Spengler Reactions



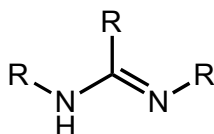
## Double H-Bond Catalysts

*Guanidinium and amidinium ions as H-bond catalyst*

**Guanidinium and amidinium ions are also capable of double H-bond interactions**



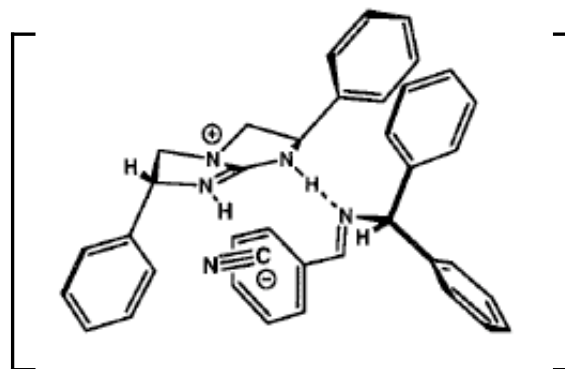
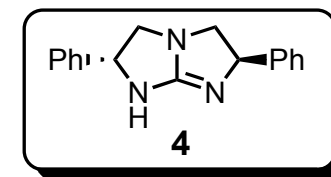
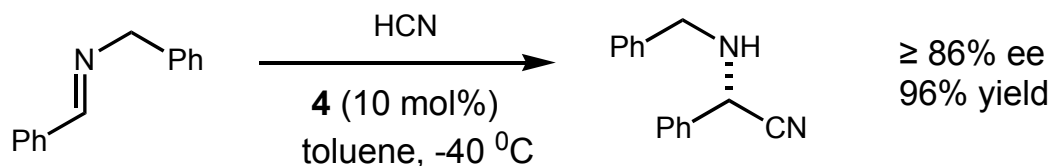
**Guanidine**



**Amidine**

- The positively charged nature of these species result in an increase H-bond donor ability
- However the positive charge can introduce problems like nonproductive binding with counteranions

### ■ Guanidine Mediated Assymmetric Strecker Reactions



E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157-160

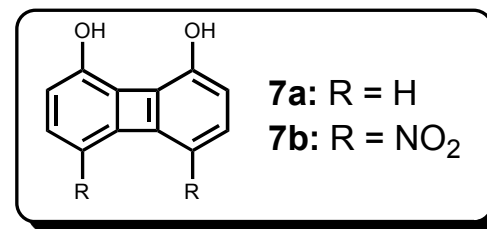
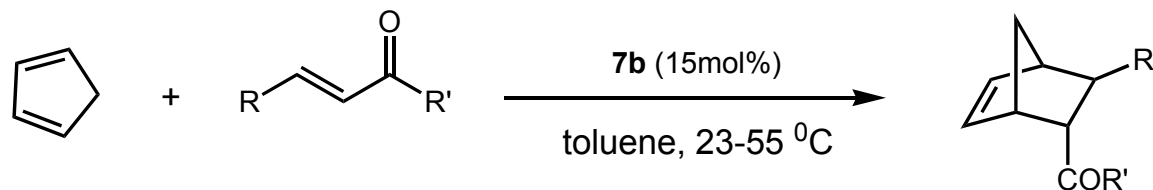
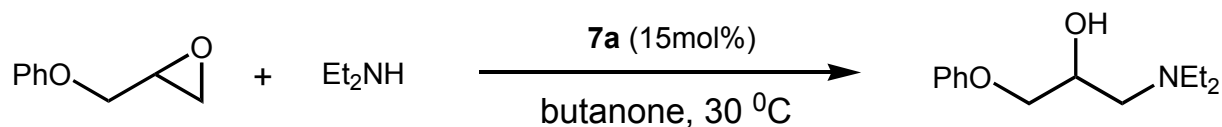
# Single H-Bond Catalysts

## Single H-bond activation challenges:

- Less strength than double H-bond
- Less directionality which reduces the ability to achieve suitably rigid catalyst substrate complex

*Hine and co-workers provided one of the first examples of catalysis by well-defined H-bond donors*

## ■ Biphenylenediol-accelerated aminolysis and Diels-Alder Cycloaddition

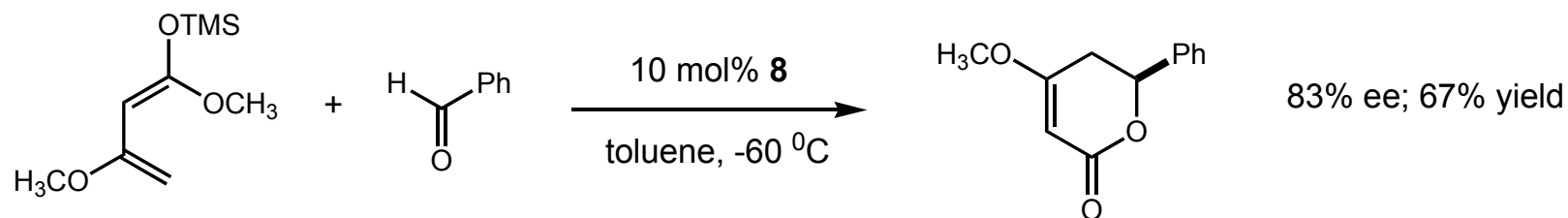
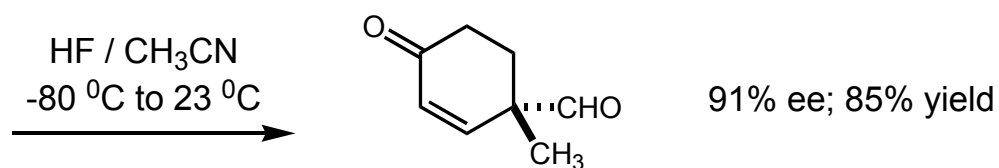
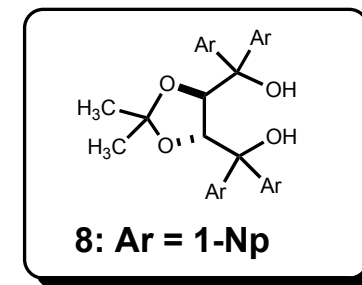
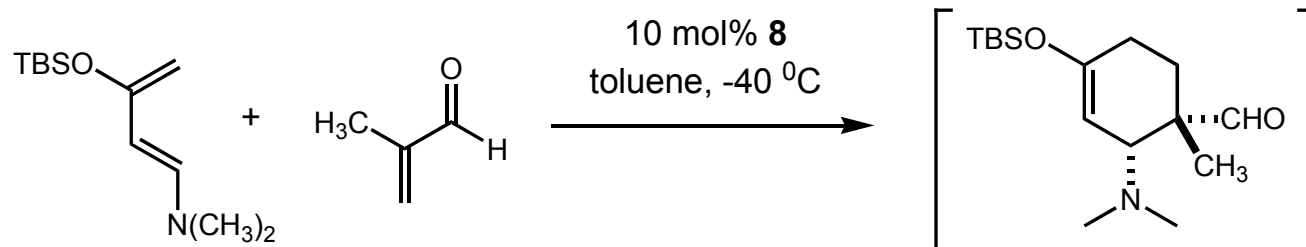


J. Hine, S.-M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082-1083;  
J. Hine, S.-M. Linden, V. M. Kanagasabapathy, *J. Org. Chem.* **1985**, *50*, 5096-5099

## Single H-Bond Catalysts

Rawal's TADDOL catalyzed Diels-Alder cycloaddition is the first successful application of chiral diols as enantioselective H-bond catalysts

### ■ Enantioselective Cycloadditions Mediated by TADDOL derivatives



### ● First highly enantioselective H-bond catalyzed cycloaddition

A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846-5850  
H. Du, D. Zhao, K. Ding, *Chem. Eur. J.* **2004**, *10*, 5964-5970

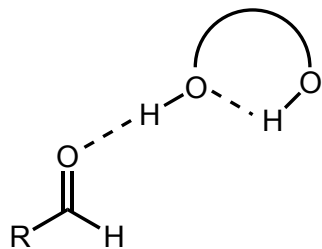
**"Hydrogen bonding by a simple chiral alcohol to a carbonyl group can accomplish what has previously been considered to be the domain of enzymes, catalytic antibodies and metal-based Lewis acids. These studies indicate the broad potential for hydrogen-bond catalysis in asymmetric synthesis"**

**V. H. Rawal**

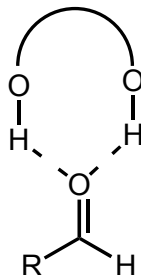
## Single H-Bond Catalysts

### *Proposed working model for the TADDOL-catalyzed Diels-Alder reactions:*

The carbonyl is expected to complex with the diol through a single point activation:

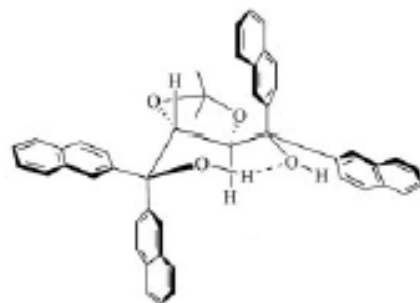


single point activation

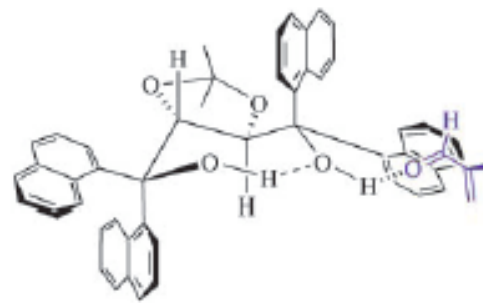


two-points activation

- As a result of the intramolecular H-bond, the proton not engaged in H-bonding is acidified and orientally defined



Solid-state structure of TADDOL



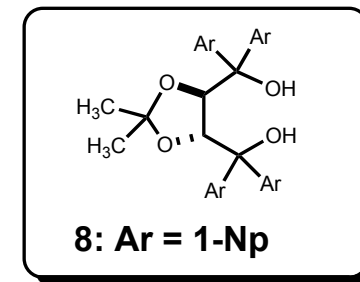
TADDOL-acrolein complex

- The free hydroxyl group on TADDOL is expected to form a strong intermolecular hydrogen bond to the carbonyl
- The electron deficient carbonyl double bond is expected to be stabilized through a  $\pi$ - $\pi$  donor acceptor interaction with the electron-rich system of the proximal naphthyl group

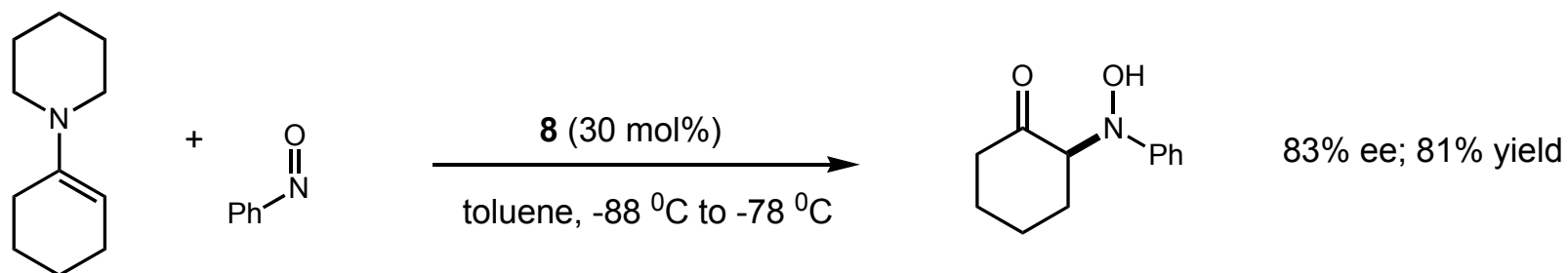
A. N. Thadani, A. R. Stankovic, V. H. Rawal, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5846-5850  
H. Du, D. Zhao, K. Ding, *Chem. Eur. J.* **2004**, *10*, 5964-5970

## Single H-Bond Catalysts

*Electrophiles other than aldehydes may be activated towards enantioselective transformations by TADDOL*



### ■ Asymmetric *N*-Aldol reactions of enamines

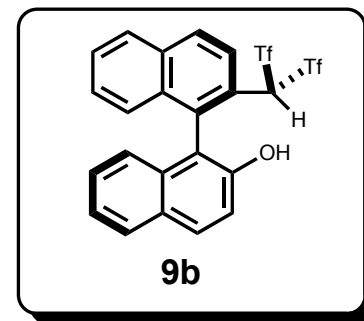
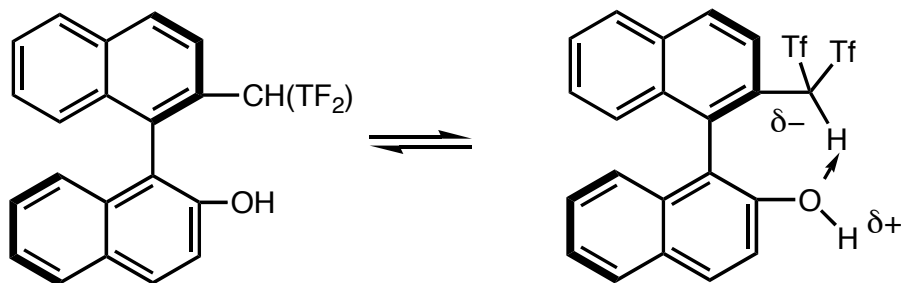




## Single H-Bond Catalysts

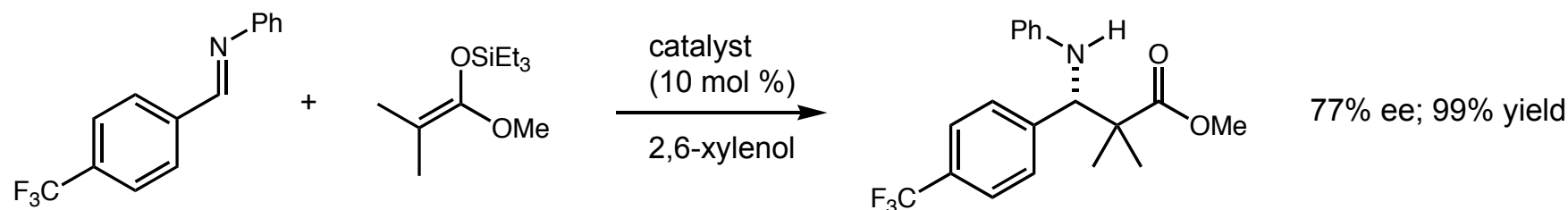
*BINOL as H-bond catalyst*

**Yamamoto bis(triflyl)methylbinaphthyl catalyst is also capable of intramolecular hydrogen bonding**



**Possible intramolecular hydrogen bonding in Yamamoto catalyst**

### ■ Asymmetric Mannich reaction using Yamamoto catalyst

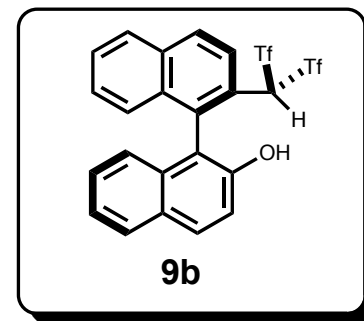
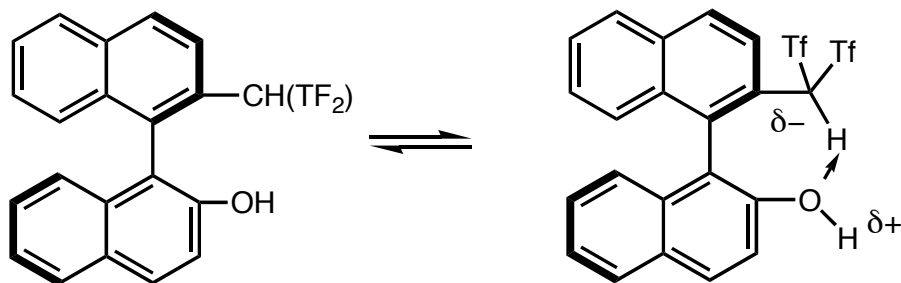


A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175-3178

## Single H-Bond Catalysts

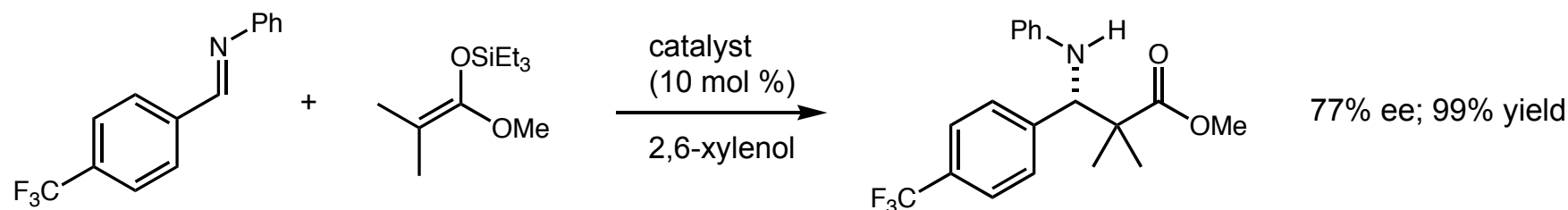
*BINOL as H-bond catalyst*

*Yamamoto bis(triflyl)methylbinaphthyl catalyst is also capable of intramolecular hydrogen bonding*



Possible intramolecular hydrogen bonding in Yamamoto catalyst

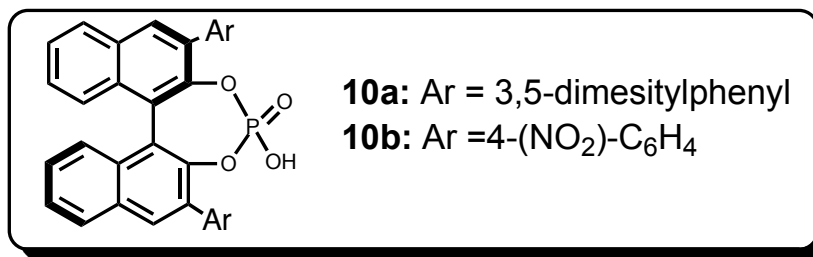
### ■ Asymmetric Mannich reaction using Yamamoto catalyst



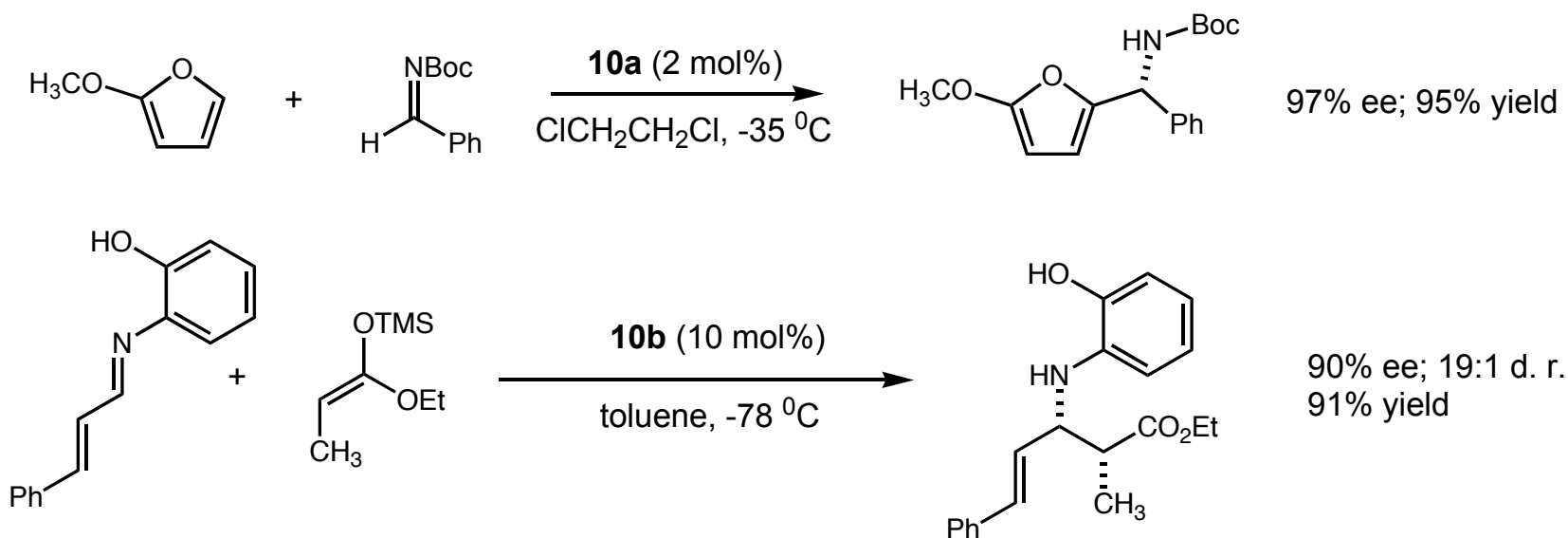
A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175-3178

## Single H-Bond Catalysts

Chiral phosphoric acid derivatives



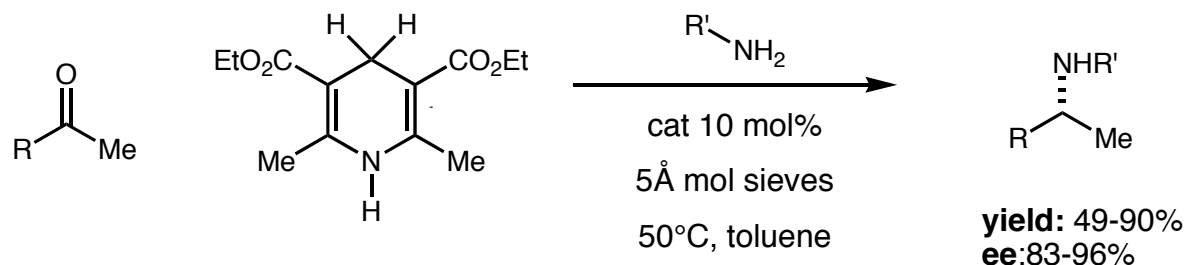
### Applications of BINOL-based chiral phosphoric acids



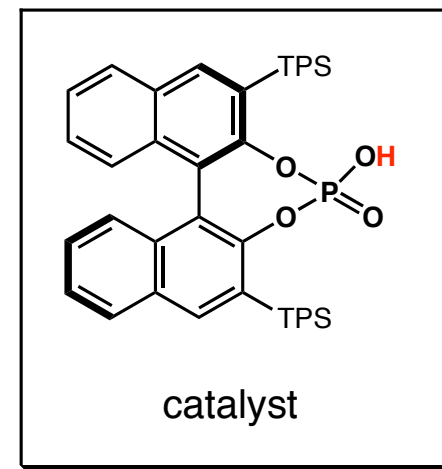
T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568;  
D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804-11805;  
T. Akiyama, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583-2585;

## Single H-Bond Catalysts

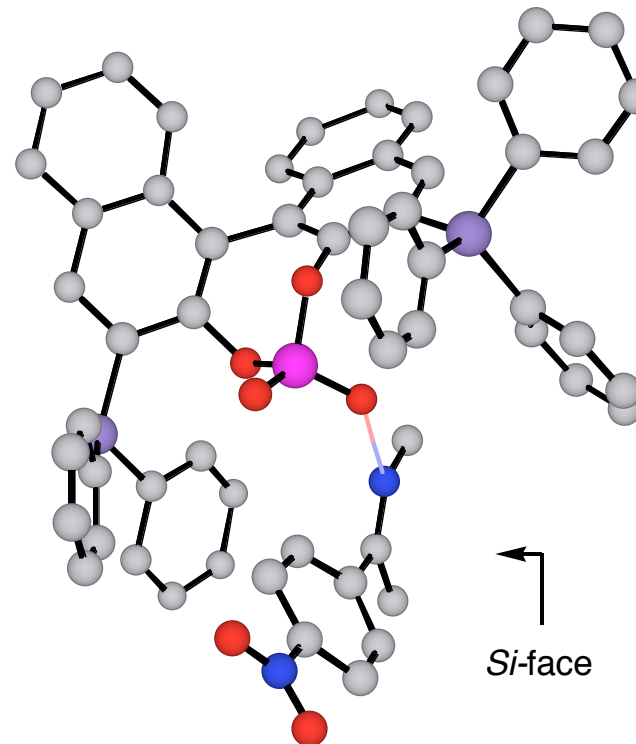
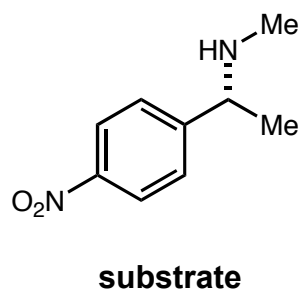
### Chiral phosphoric acid catalyzed reductive amination



Tolerates a wide variety of substrate: alkyl or aryl ketone



### X-ray crystal structure of catalyst-imine complex



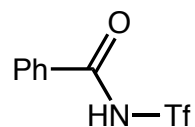
X-ray structure

R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. Macmillan, *J. Am. Chem. Soc.* **2006**, *128*, 84-86

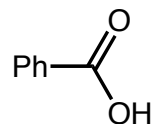
# Single H-Bond Catalysts

*Chiral phosphoramidate*

**Yamamoto discovered enhancement of the acidity of Bronsted acid by using phosphoramidate with strong Lewis acceptor**

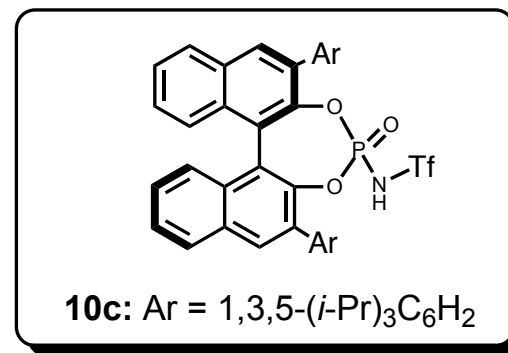


$PK_a = 11.06$

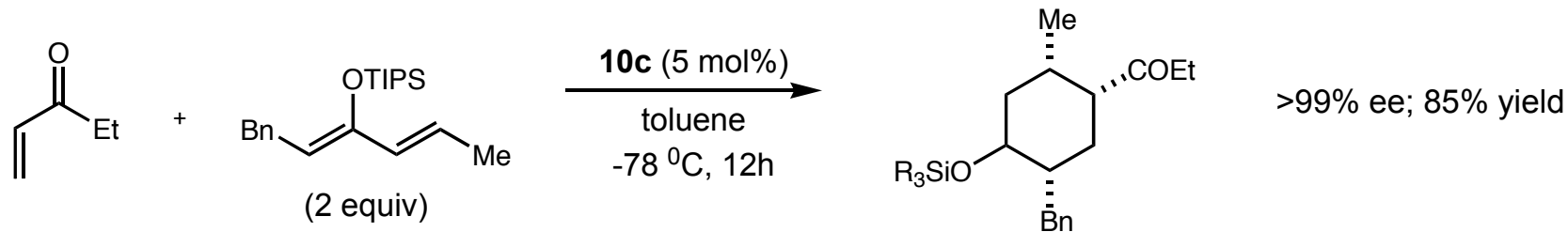


$PK_a = 20.7$

**Introduction of a strong electron acceptor group such as NTf into an acid system increases the stability of the counteranions and increases the acidity of the system**



## ■ Applications of *N*-triflyl phosphoramidate catalysts in asymmetric Diels-Alder reactions

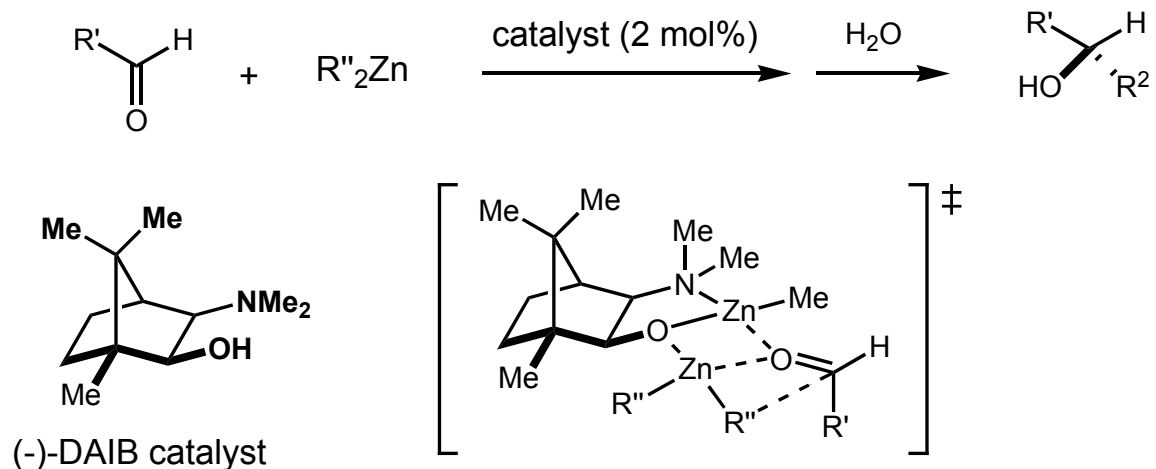


D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626-9627

## Bifunctional H-Bond Donor Catalysts

*Metal catalysts capable of bifunctional activation have shown useful applications in asymmetric transformations*

- Noyori's DAIB catalyst: the first example of highly enantioselective alkylation of aldehydes

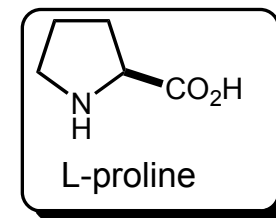


- Both zinc atoms activates and directs the addition

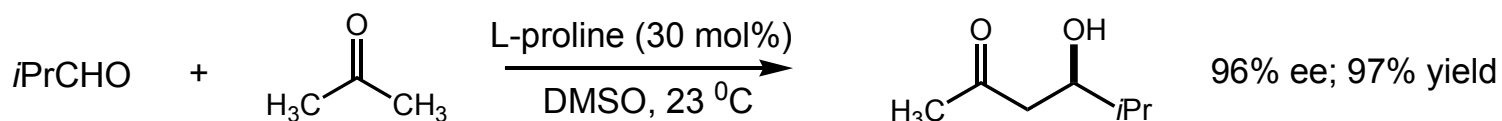
***Catalysts capable of simultaneous activation of nucleophiles and electrophiles can be a powerful tool for enantioselective transformations***

## Bifunctional H-Bond Donor Catalysts

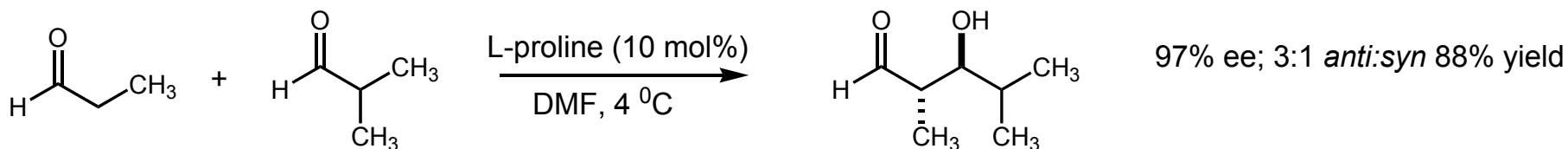
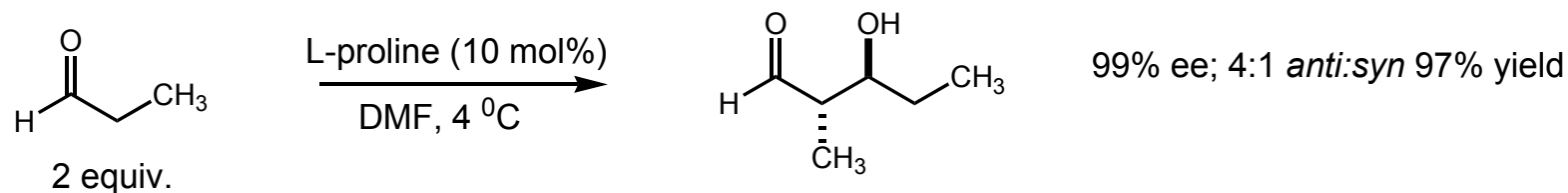
*Proline: a very accessible bifunctional catalysts*



### ■ Proline-catalyzed, intermolecular aldol addition



### ■ Proline-Catalyzed, cross-aldol reactions of aldehydes



- A number of research groups have demonstrated the generality of proline catalysis for the formation of carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-halogens

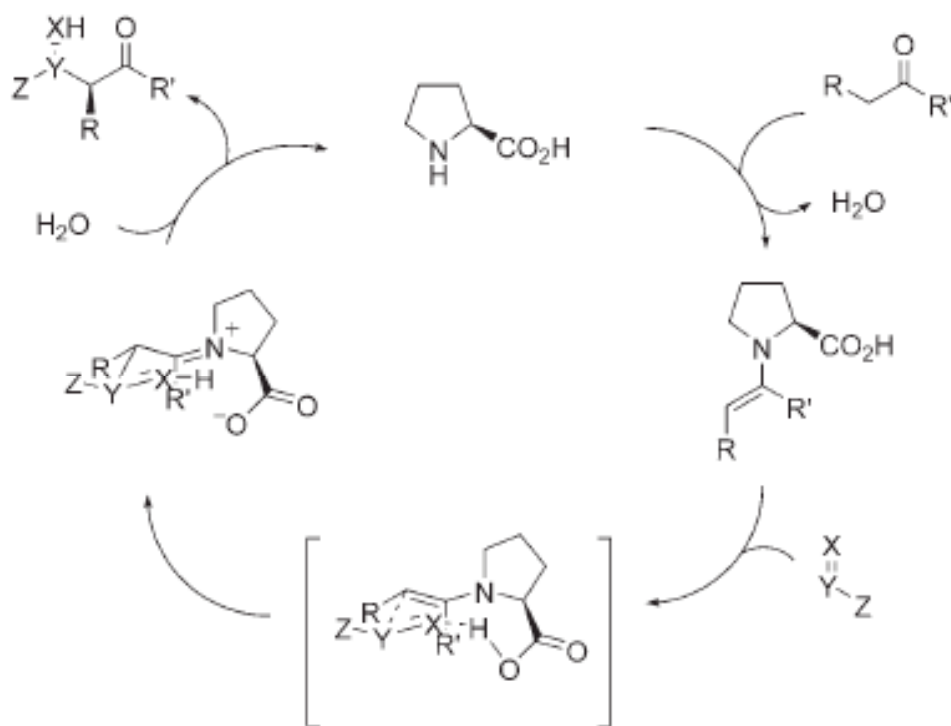
B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, 122, 2395-2396

A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 6798-6799

## Bifunctional H-Bond Donor Catalysts

*Proline and proline analogs are among the simplest and most accessible bifunctional catalysts*

### ■ Proposed mechanism for proline catalyzed transformations

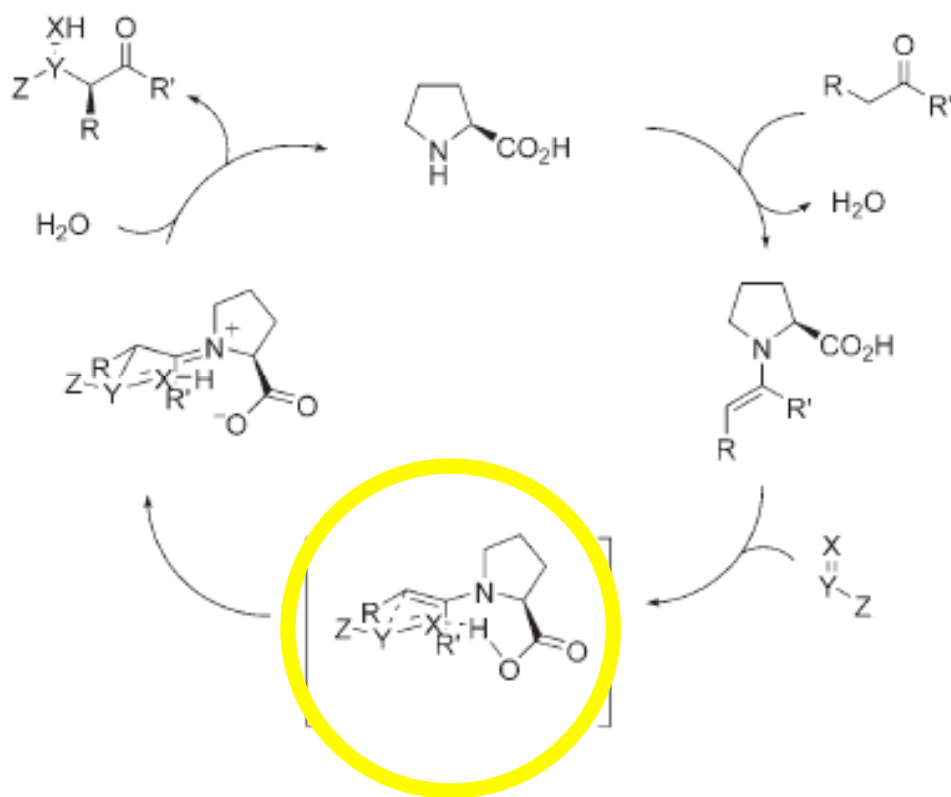




## Bifunctional H-Bond Donor Catalysts

*Proline and proline analogs are among the simplest and most accessible bifunctional catalysts*

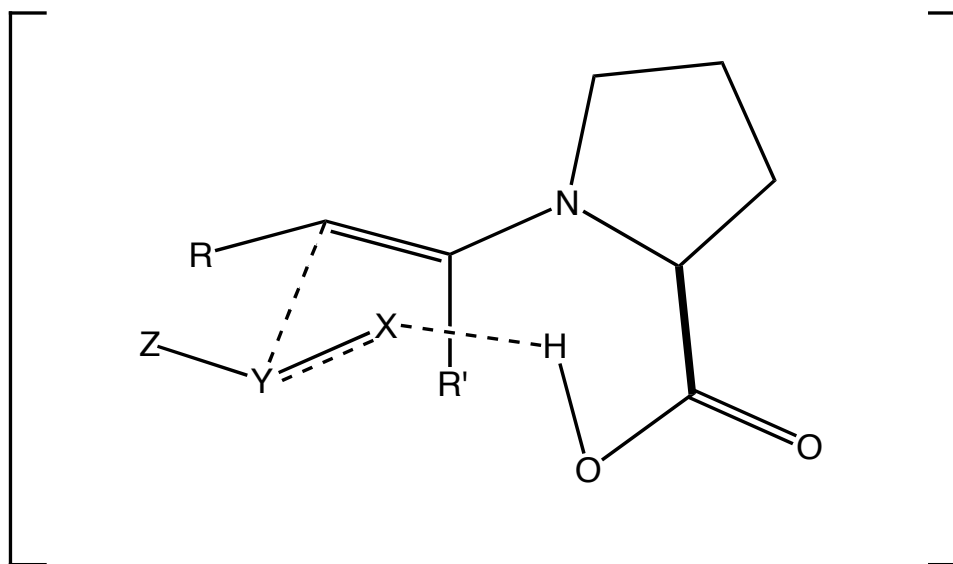
### ■ Proposed mechanism for proline catalyzed transformations



## Bifunctional H-Bond Donor Catalysts

*Proline and proline analogs are among the simplest and most accessible bifunctional catalysts*

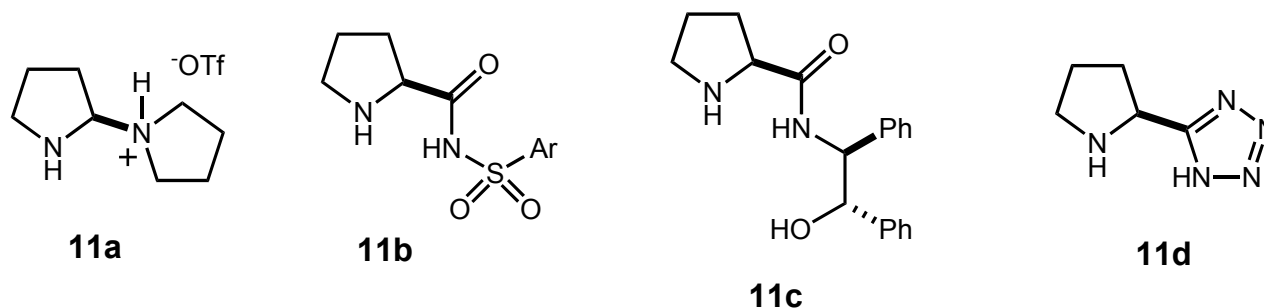
### ■ Proposed mechanism for proline catalyzed transformations



## Bifunctional H-Bond Donor Catalysts

*Proline and proline analogs are among the simplest and most accessible bifunctional catalysts*

### ■ Proline analogs developed for asymmetric catalysis



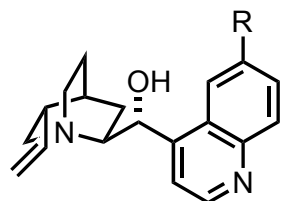
**Tuning of the H-bond donating ability of the catalyst by variation of the acidic moiety has proven particularly fruitful in several reactions:**

- **11a** mediate enantioselective aldol and Mannich reactions
- **11c** provides higher yields and selectivities for direct aldol of acetone with aldehydes than proline
- **11d** offers improved activity in *O*-nitroso aldol reactions of ketones and Mannich reactions of imino esters

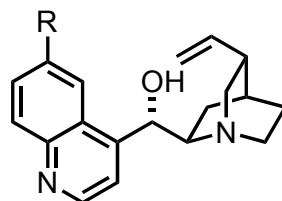
See references 87-91 in M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543

## Bifunctional H-Bond Donor Catalysts

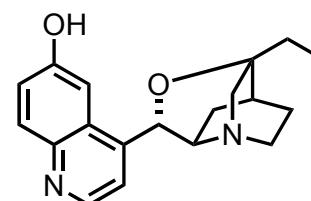
*Natural products have also been utilized in asymmetric H-bond catalysis*



R = OCH<sub>3</sub>: quinine  
R = H: cinchonidine



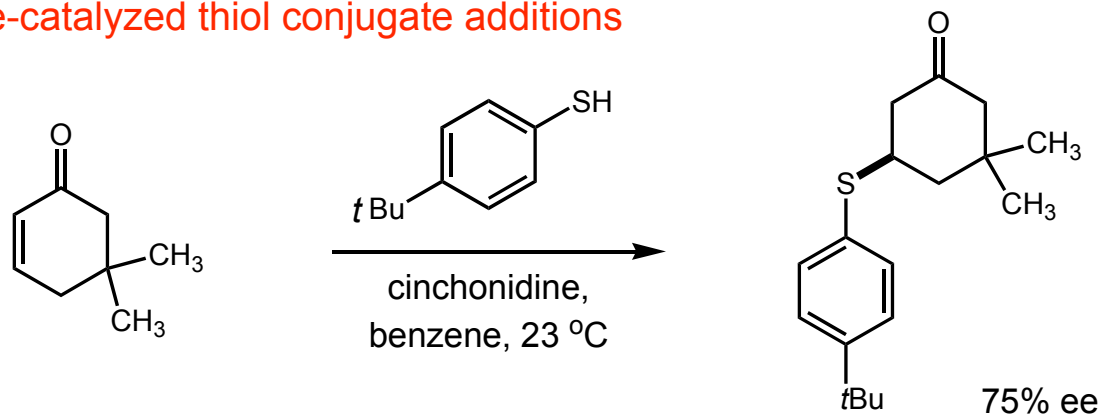
R = OCH<sub>3</sub>: quinine  
R = H: cinchonidine



$\beta$ -isocupreidine

### *Natural alkaloids utilized in asymmetric synthesis*

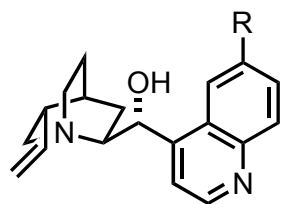
#### ■ Cinchonidine-catalyzed thiol conjugate additions



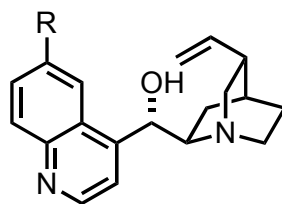
- Mechanism is still not clear

## Bifunctional H-Bond Donor Catalysts

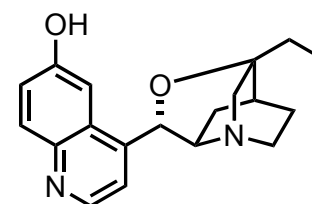
*Natural products have also been utilized in asymmetric H-bond catalysis*



R = OCH<sub>3</sub>: quinine  
R = H: cinchonidine



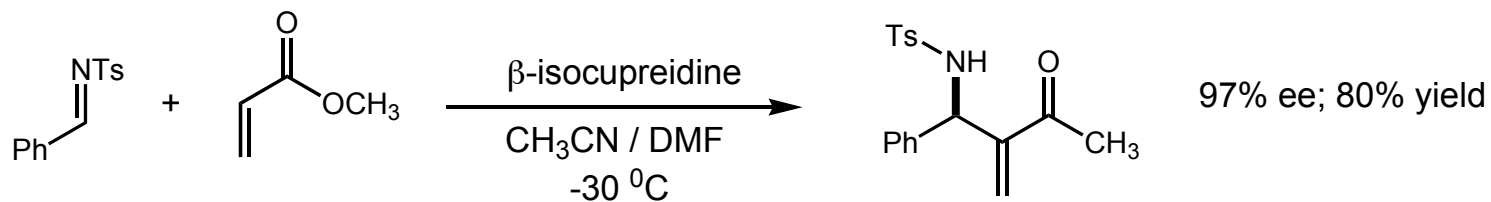
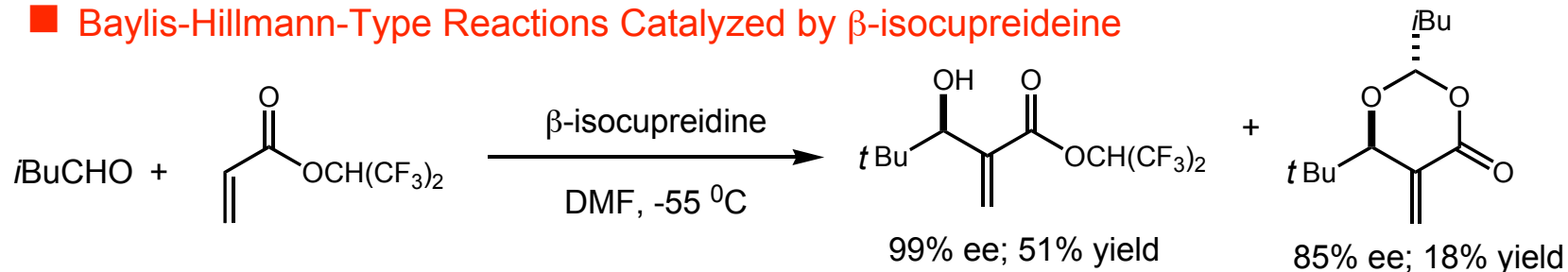
R = OCH<sub>3</sub>: quinine  
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$\beta$ -isocupreidine

### *Natural alkaloids utilized in asymmetric synthesis*

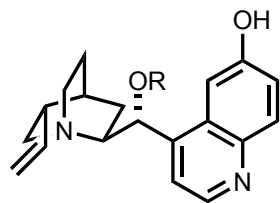
#### ■ Baylis-Hillmann-Type Reactions Catalyzed by $\beta$ -isocupreidine



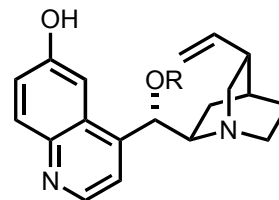
M. Shi, Y.-M. Xu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4507-4510  
H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907

## Bifunctional H-Bond Donor Catalysts

*Natural products have also been utilized in asymmetric H-bond catalysis*



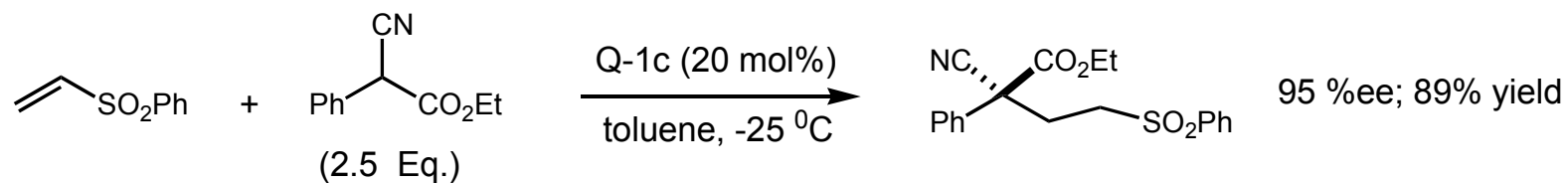
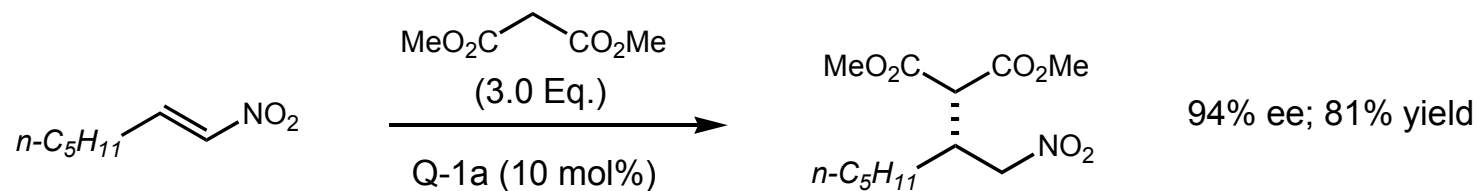
Q-1a: R = H  
Q-1b: R = Bn  
Q-1c: R = 9-phenantryl



QD-1a: R = H  
QD-1b: R = Bn  
QD-1c: R = 9-phenantryl

### **Cinchona alkaloid based bifunctional catalysts**

#### ■ Some Applications of the Cinchona Based Bifunctional Catalysts

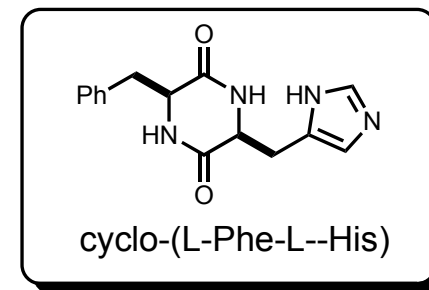
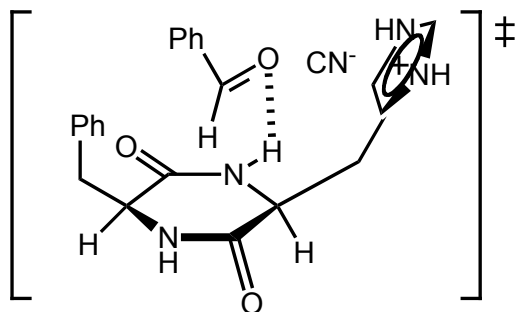
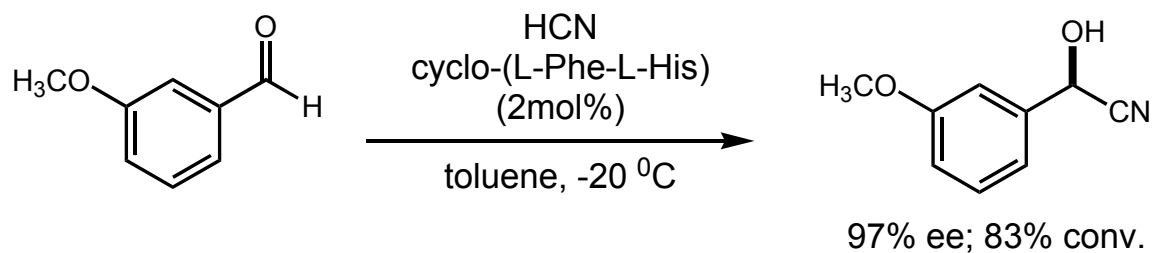


H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105-108  
H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948-8949

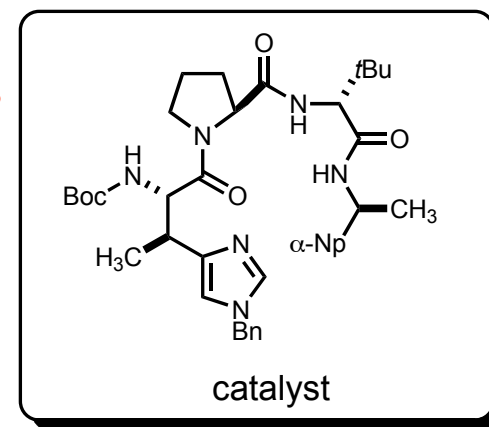
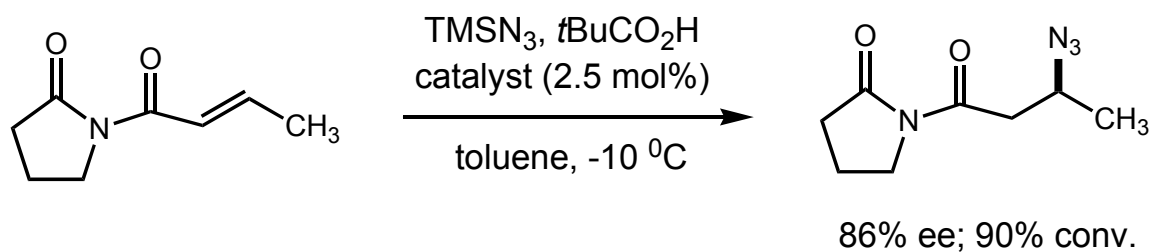
# Bifunctional H-Bond Donor Catalysts

Oligopeptides an attractive platform for catalyst development

## ■ Cyclo (L-phenylalanine-L-histidine)-catalyzed aldehyde hydrocyanation

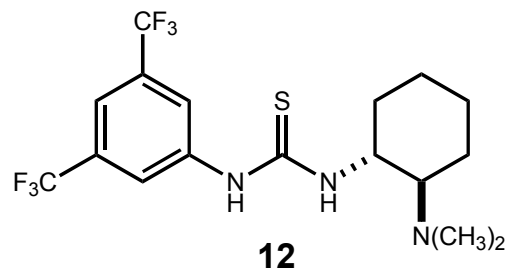


## ■ Peptide catalyzed asymmetric conjugate addition of hydrazoic acids



S. Inoue, J.-I. Oku, *J. Chem. Soc. Chem. Comm.* **1981**, 229-230  
D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134-2136

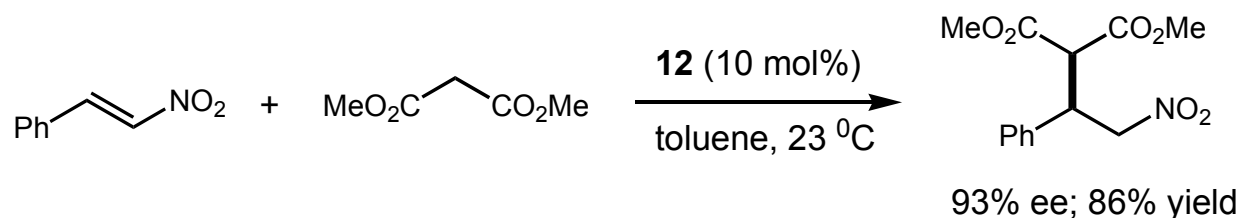
## Bifunctional H-Bond Donor Catalysts



**Thiourea bifunctional catalyst  
Takemoto catalyst**

- Reaction kinetic and catalyst modification confirms the bifunctional nature of the catalyst
- Catalyst activates both nucleophile, by general base catalysis, and electrophile, by H-bonding to the nitro group.

### Michael addition reactions mediated by bifunctional thiourea



- This methodology has also been applied to enantioselective additions of substituted ketoester, and double Michael additions of  $\gamma,\delta$ -unsaturated  $\beta$ -ketoesters

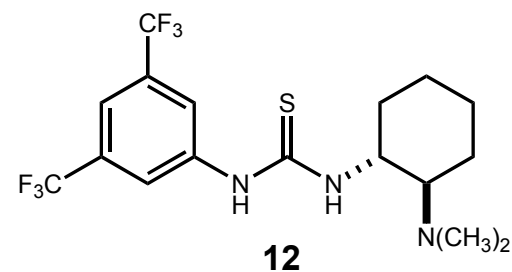
T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673  
T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625-627  
B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, *4*, 603-606



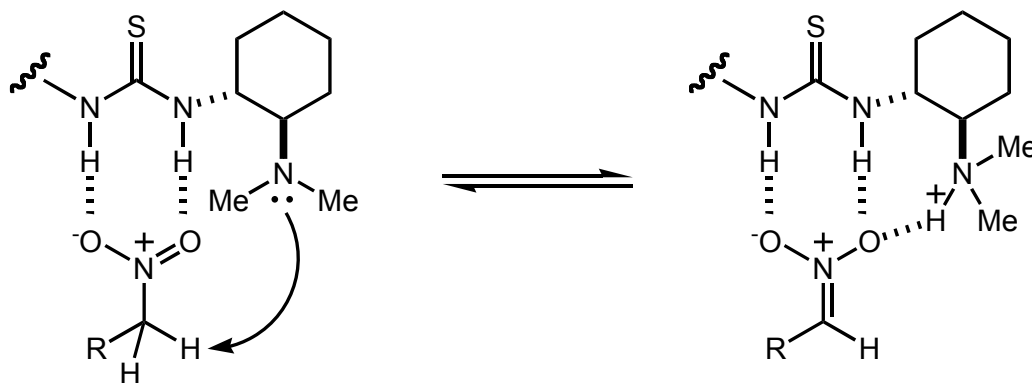
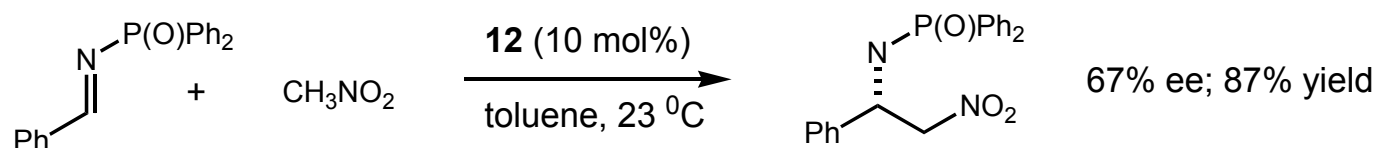
## Bifunctional H-Bond Donor Catalysts

*Scope of Takemoto catalyst has also been expanded to transformations using substantially different electrophiles and nucleophiles*

### ■ Nitro-Mannich reactions mediated by bifunctional thiourea

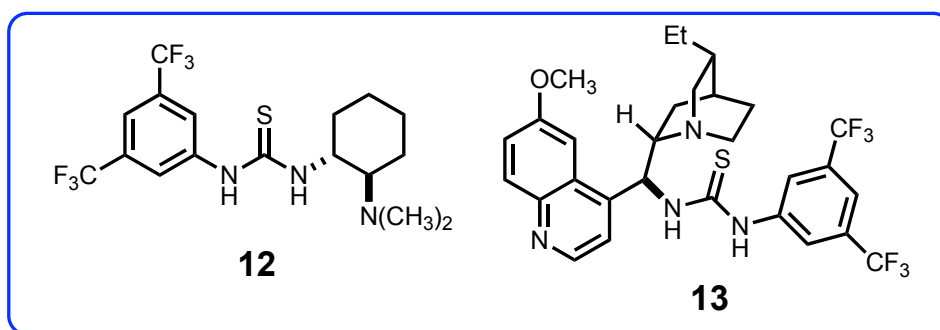
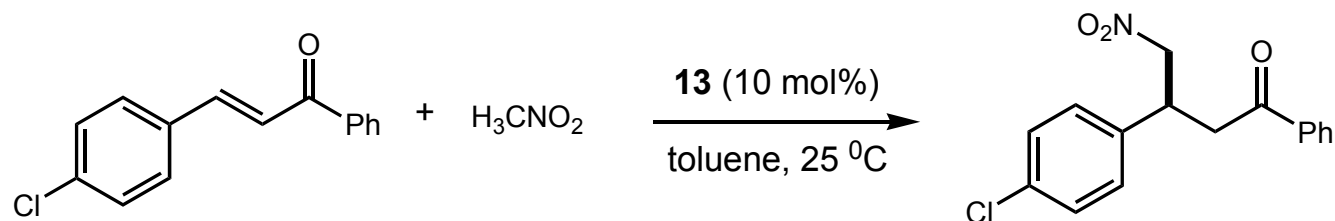
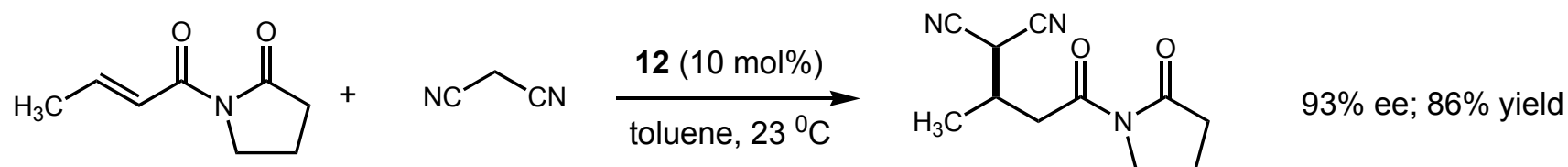
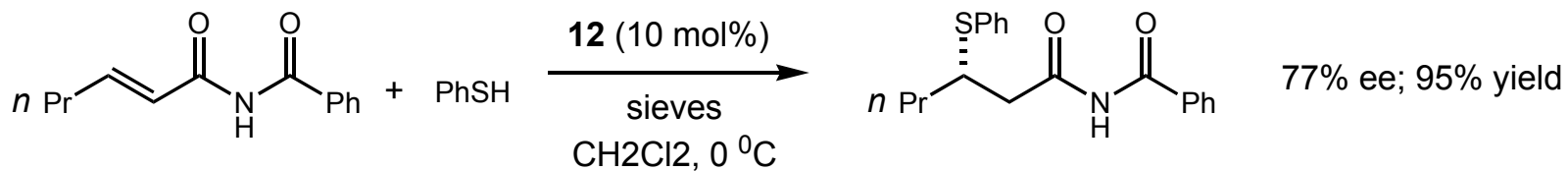


**Takemoto catalyst**



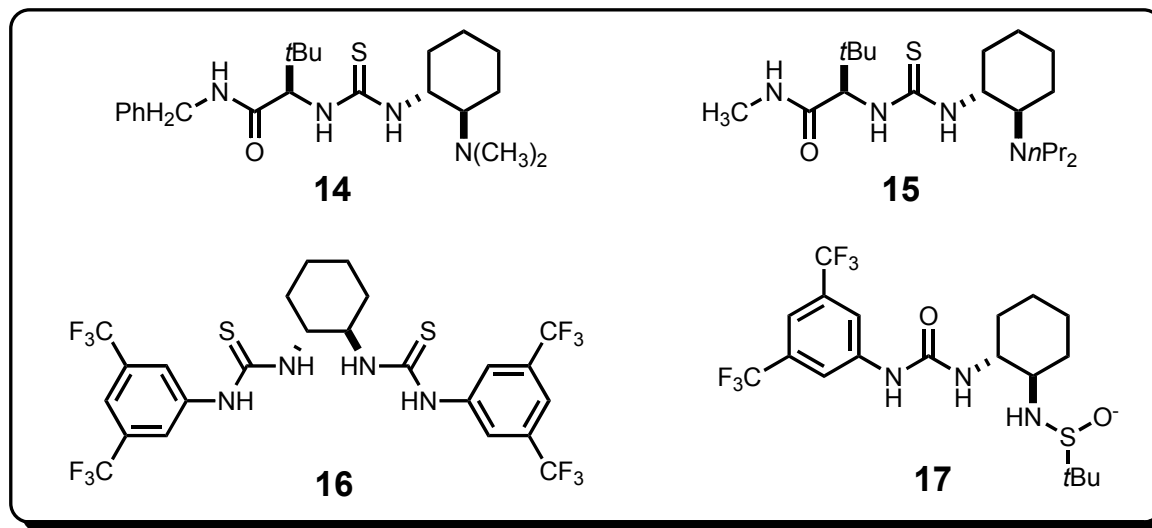
## Bifunctional H-Bond Donor Catalysts

### ■ Applications of bifunctional thiourea catalysis in various conjugate additions



## Bifunctional H-Bond Donor Catalysts

### ■ Bifunctional thiourea developed for asymmetric catalysis



- **14** mediate enantioselective kinetic resolution of azlactone
- **15** promote enantioselective cyanosilation of ketones
- **17** is an efficient catalyst for enantioselective Baylis-Hillman reaction
- **16** promotes enantioselective addition of allylindium to *N*-benzoylhydrazones

Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589-5592

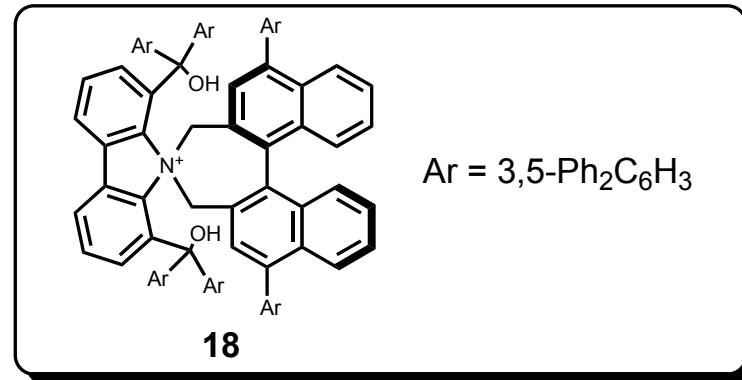
K. L. Tian, E. N. Jacobsen, *unpublished results*

A. Berkessel, F. Cleeman, S. Mukherjee, T. N. Muller, J. Lex, *Angew. Chem. Int. Ed.* **2005**, *44*, 817-821

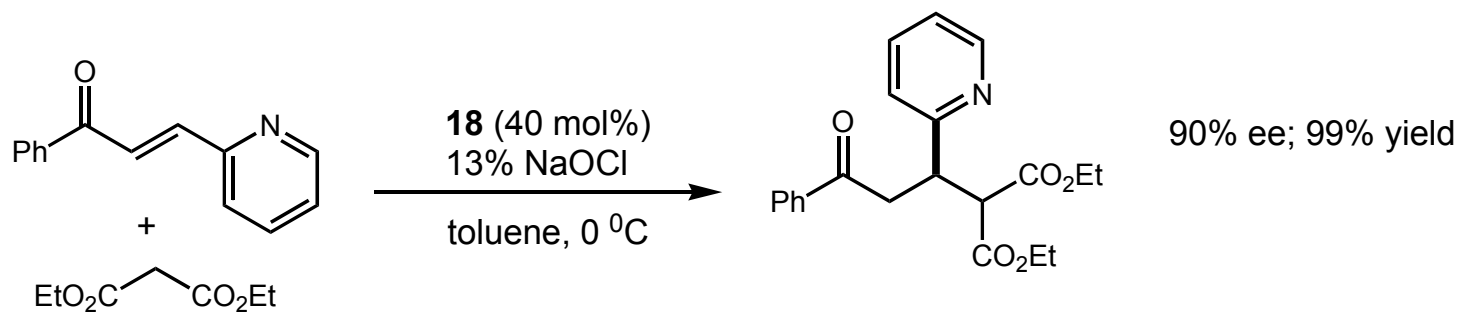
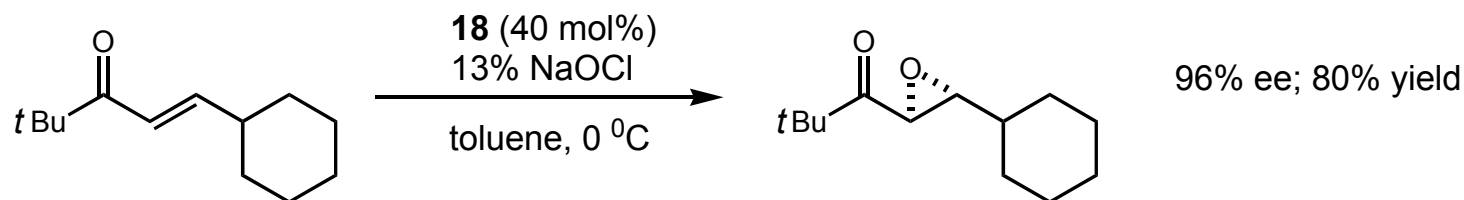
D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964-8965

## Bifunctional H-Bond Donor Catalysts

*Spiro ammonium derived phase-transfer catalyst is believed to act as H-bond donors to the enone carbonyl group*



### ■ Asymmetric H-Bond Assisted phase-transfer catalysis



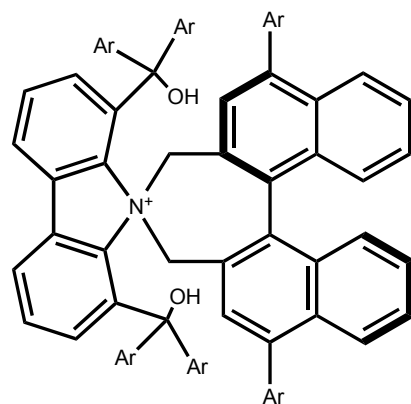
T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, 126, 6844-6845

T. Ooi, D. Ohara, M. K. Fukumoto, K. Maruoka, *Org. Lett.* **2005**, 7, 3195-3197

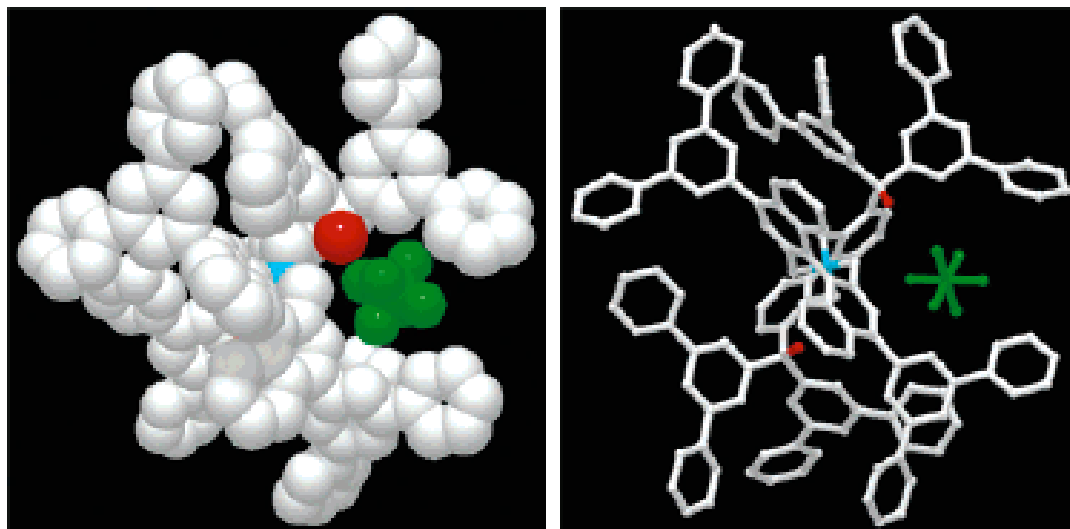
## Bifunctional H-Bond Donor Catalysts

*Single-crystal X-ray diffraction analysis gives insight to the mechanism*

### ■ X-ray structure of the catalyst-PF6



Ar = 3,5-Ph<sub>2</sub>C<sub>6</sub>H<sub>3</sub>



- Biphenyl and binaphthyl subunits of the core *N*-spiro structure are nearly perpendicular which creates an attractive chiral reaction cavity around the central nitrogen.
- Hypochlorite ions would be correctly position before the reaction bringing the enone inside the cavity resulting in efficient bond formation with rigorous enantiofacial differentiation

## Summary

- H-bond catalysis is unique because of the ability of the catalyst to readily dissociate from the product allowing superior turnover
- Research in asymmetric H-bond donor catalysis is progressing at a rapid pace and its scope is expanding
- To realize the full potential of H-bond donor catalysis a more detailed mechanistic understanding of this chemistry is needed