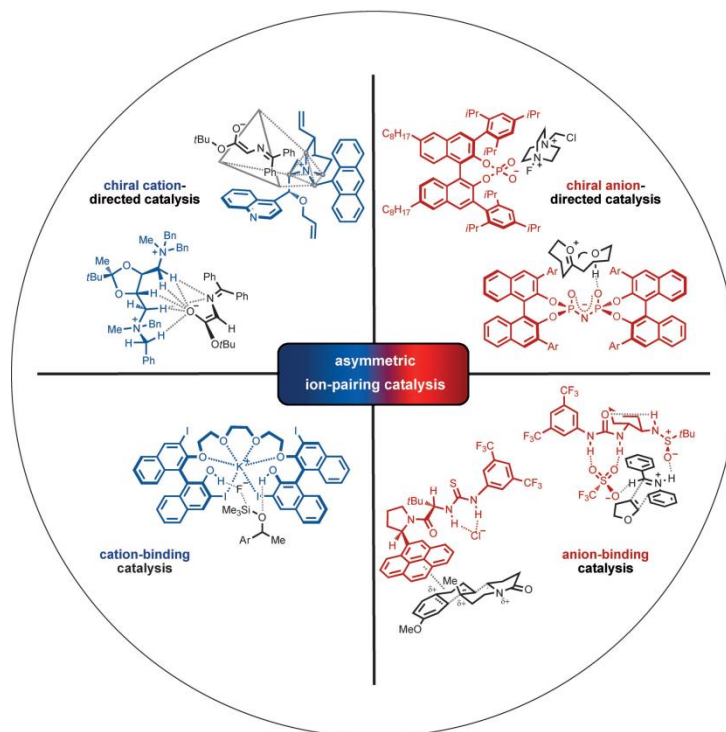


Asymmetric Ion-Pairing Catalysis

Katrien Brak and Eric N. Jacobsen*



*Dedicated to the memory and
legacy of W. S. Knowles*

Reporter: Yan Fang

Superior: Prof. Yong Huang

Apr. 21st 2014

Eric N. Jacobsen



Eric N. Jacobsen was born and raised in New York City. He earned his B.S. degree from New York University in 1982 and his Ph.D. degree at the UC Berkeley in 1986, working under the direction of Robert Bergman. He carried out postdoctoral studies with Barry Sharpless at MIT. In 1988, he began his independent career at the University of Illinois at Urbana-Champaign. He moved to Harvard University in 1993, where he is currently the Sheldon Emory Professor of Organic Chemistry and Department Chair. His research interests lie in the discovery, mechanistic elucidation, and application of new catalytic processes.

Introduction:

with charged catalysts:

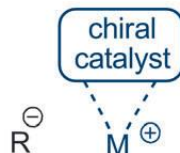


chiral cation-directed catalysis (Section 2)

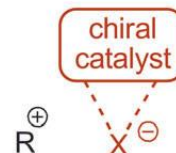


chiral anion-directed catalysis (Section 4)

with neutral catalysts:

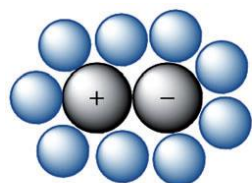


cation-binding catalysis (Section 3)



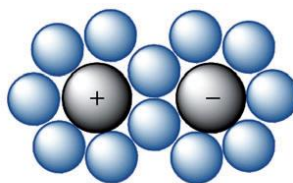
anion-binding catalysis (Section 5)

Coulomb's law :
$$E = \frac{q_1 q_2}{4\pi\epsilon\epsilon_0 r}$$



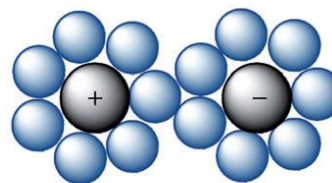
contact

low dielectric solvents



solvent-shared

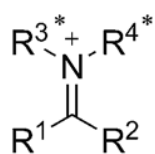
higher dielectric solvents



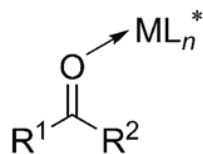
solvent-separated

Introduction:

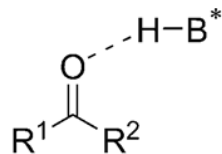
◆ Comparative Directionality of Catalyst–Substrate Interactions of Common Asymmetric Catalysis Strategies



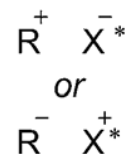
iminium



Lewis acid



Brønsted acid



ion-pairing

inherent directionality of interaction

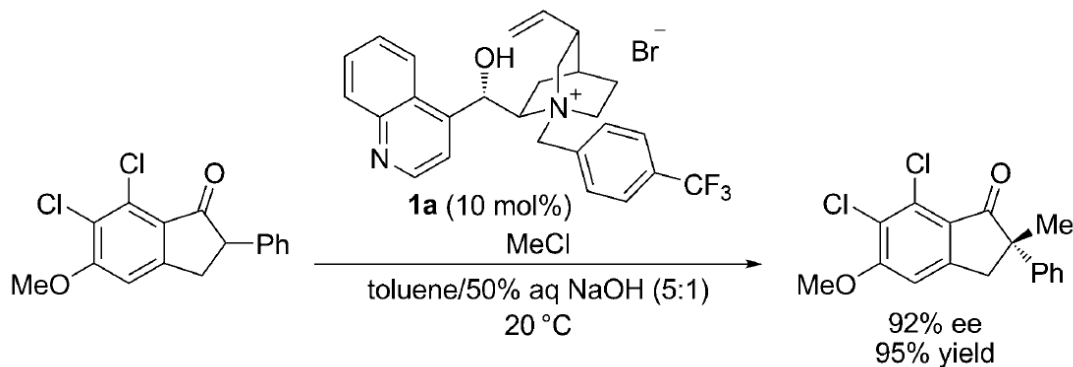
(L_n^* = chiral ligand; B^*H = chiral Brønsted acid; X^* = chiral counterion)

Contents

- *Chiral Cation-Directed Catalysis*
- *Cation-Binding Catalysis*
- *Chiral Anion-Directed Catalysis*
- *Anion-Binding Catalysis*
- *Summary & Outlook*

Chiral Cation-Directed Catalysis

◆ History

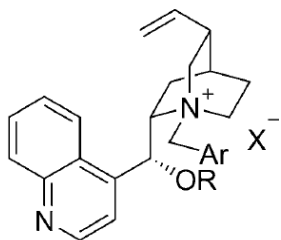


*First reported
enantioselective phase-transfer-catalyzed alkylation of indanone derivatives*

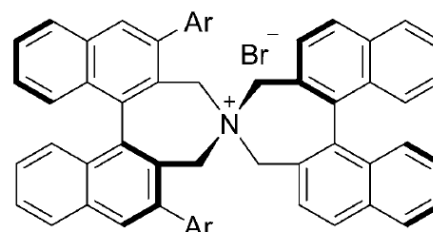
*induce high levels of enantioselectivity in a wide range of reactions,
including enolate alkylation, Michael, Aldol, Mannich, and
Darzens reactions, as well as epoxidations and aziridinations.*

Chiral Cation-Directed Catalysis(I)

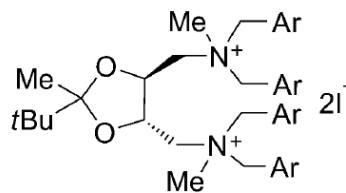
◆ Quaternary Ammonium Cations



- 1b**, R = H, Ar = Ph, X = Cl
1c, R = H, Ar = 9-anthracenyl, X = Cl
1d, R = CH₂CH=CH₂,
Ar = 9-anthracenyl, X = Br



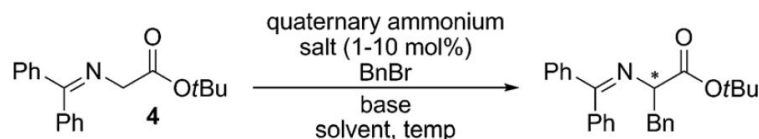
2, Ar = 3,4,5-F₃-C₆H₂



3, Ar = 4-MeO-C₆H₄

Chiral Cation-Directed Catalysis(I) Quaternary Ammonium Cations

Enantioselective Alkylation Catalyzed by Various Quaternary Ammonium Ions



1b, 64% ee (S), 85% yield

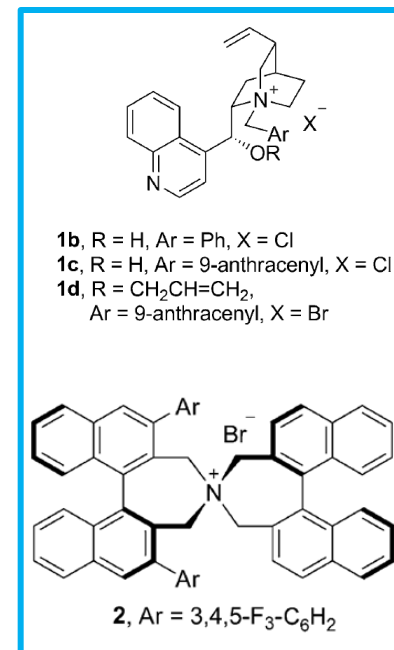
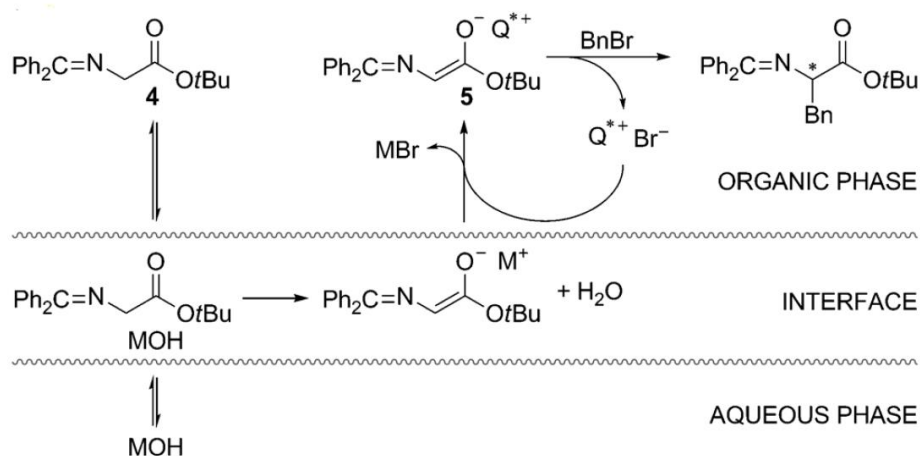
1c, 91% ee (S), 68% yield

1d, 94% ee (S), 87% yield

2, 99% ee (R), 90% yield

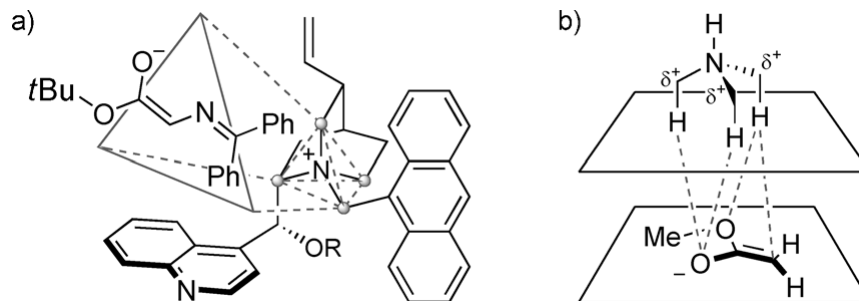
3, 93% ee (R), 87% yield

Interfacial Mechanism for Phase-Transfer Catalysis



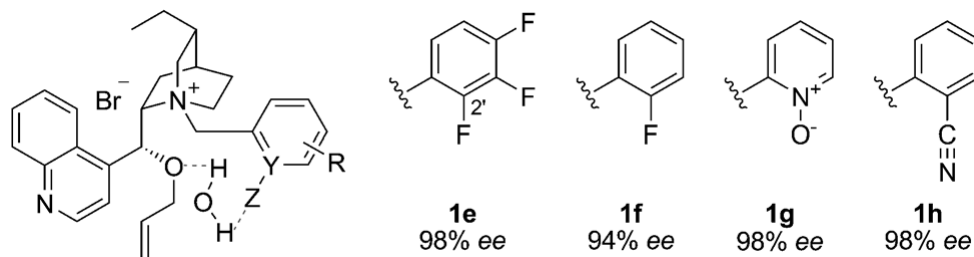
2. Chiral Cation-Directed Catalysis(I) Quaternary Ammonium Cations

Tetrahedron Stereoselectivity Model for Cinchona Alkaloidderived Catalysts



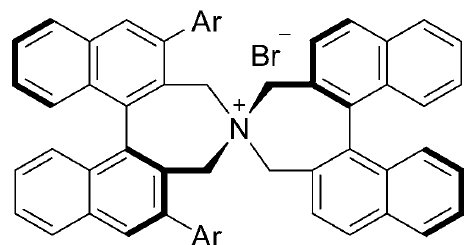
Corey, E. J. *JACS* **1997**, *119*, 12414; Houk, K. N. *JACS* **2002**, *124*, 7163.

Proposed Internal Hydrogen-Bonding via a Water Molecule

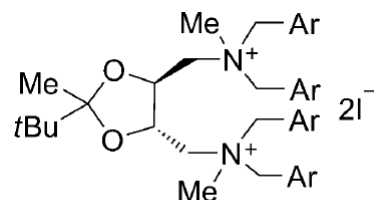


Park, H.-g. *OL* **2002**, *4*, 4245.

2. Chiral Cation-Directed Catalysis(I) Quaternary Ammonium Cations

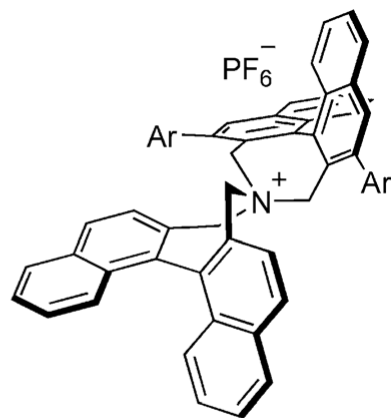
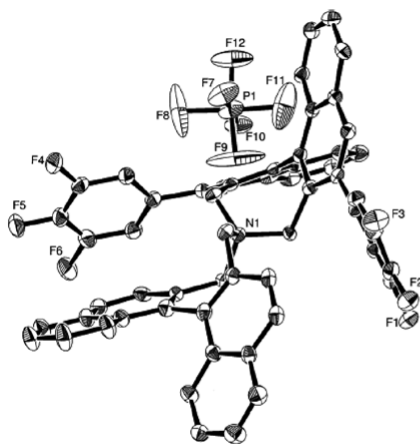


2, Ar = 3,4,5-F₃-C₆H₂

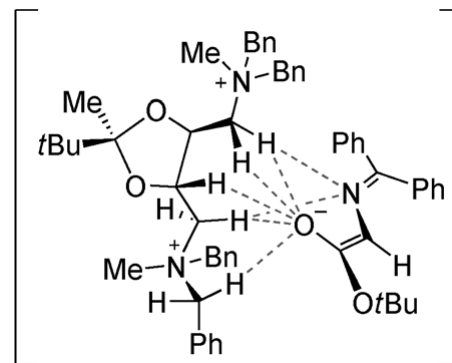


3, Ar = 4-MeO-C₆H₄

a well-defined pocket by blocking two sides of the central ammonium cation

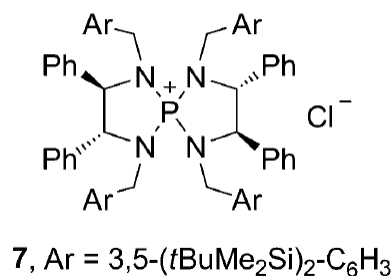
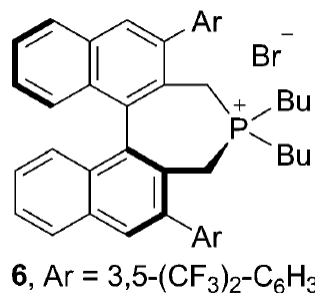


Ar = 3,4,5-F₃-C₆H₂

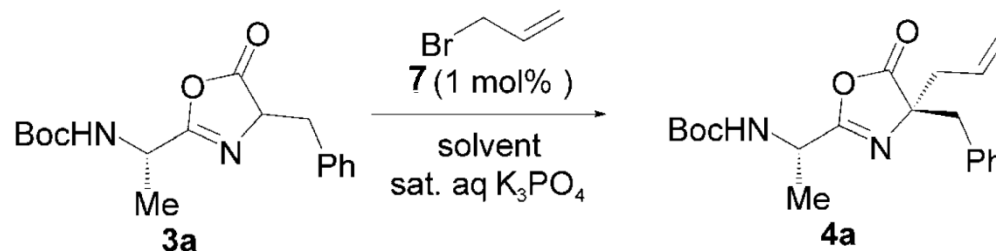


2. Chiral Cation-Directed Catalysis(II)

◆ Quaternary Phosphonium Cations

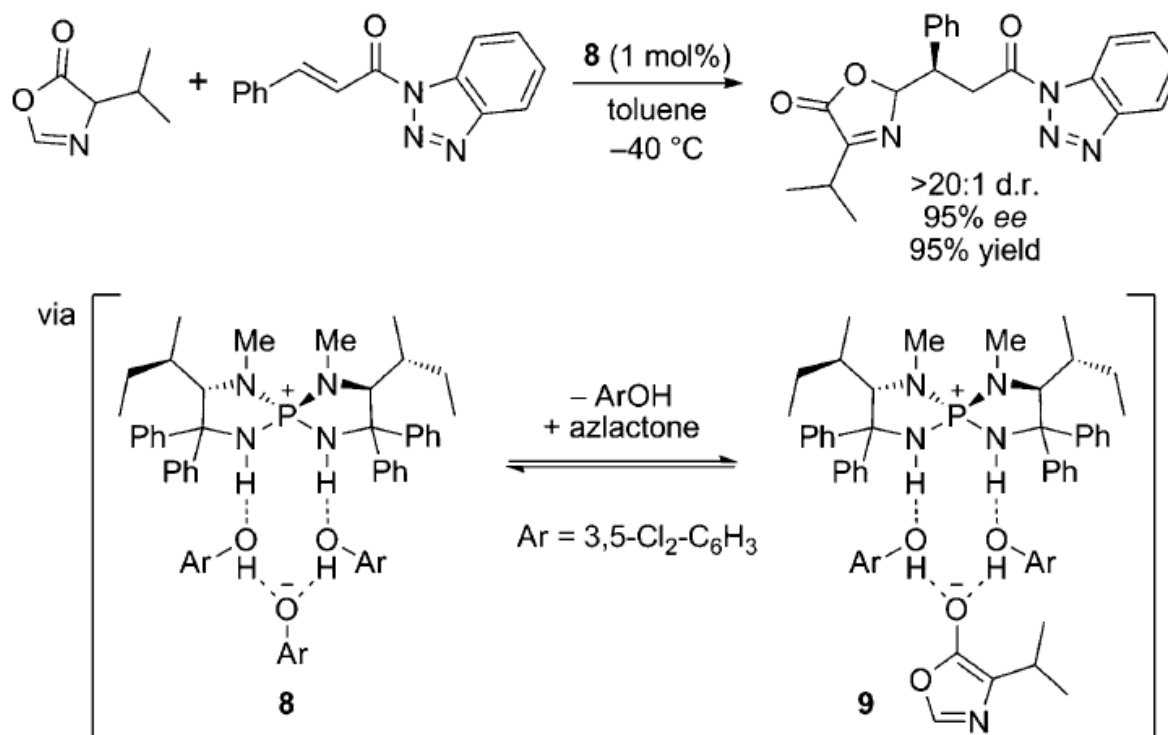


catalytic enantioselective amination, Michael, and Mannich reactions



2. Chiral Cation-Directed Catalysis(II) Quaternary Phosphonium Cations

As a Supramolecular Chiral Organic Base Catalyst

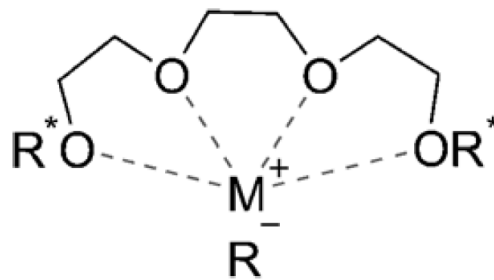


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- *Chiral Cation-Directed Catalysis*
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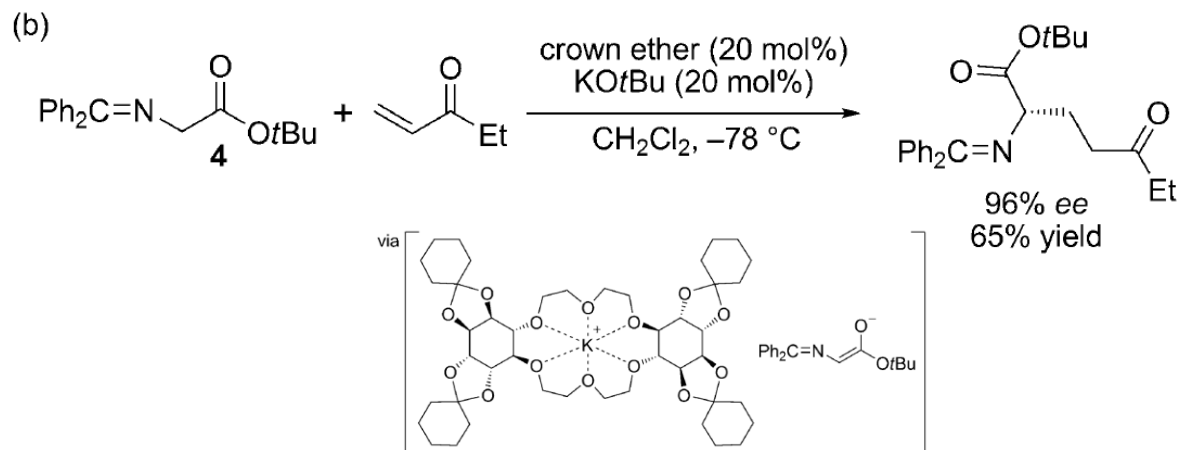
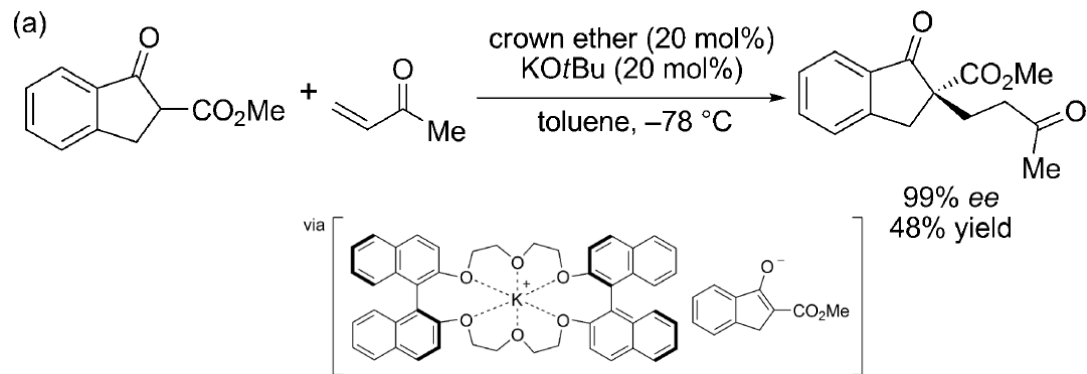
3. Cation-Binding Catalysis

◆ Polyether Catalysts



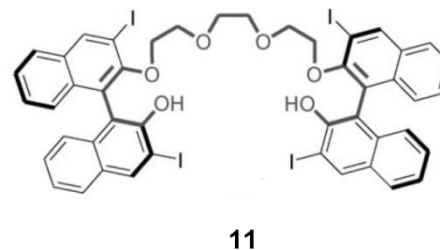
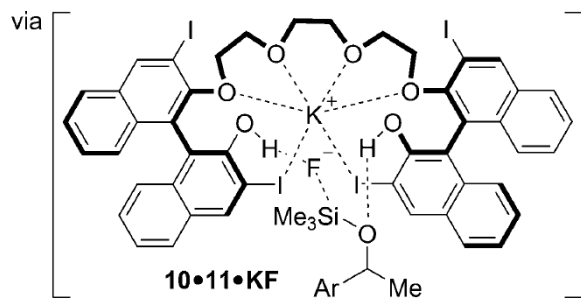
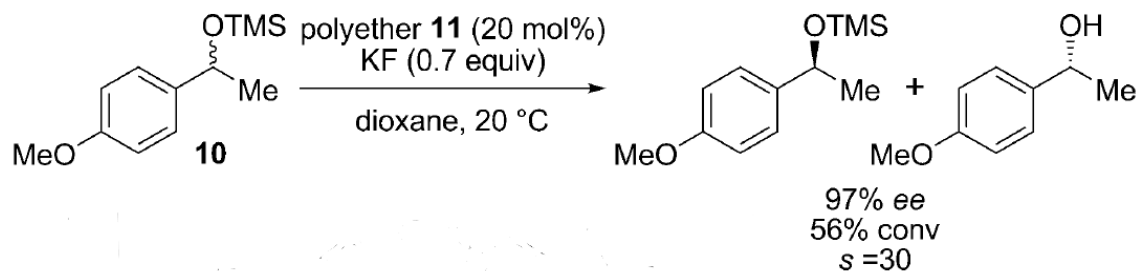
3. Cation-Binding Catalysis

Enantioselective Michael Addition Reactions



3. Cation-Binding Catalysis

Desilylative Kinetic Resolution of Silyl-protected Secondary Alcohols

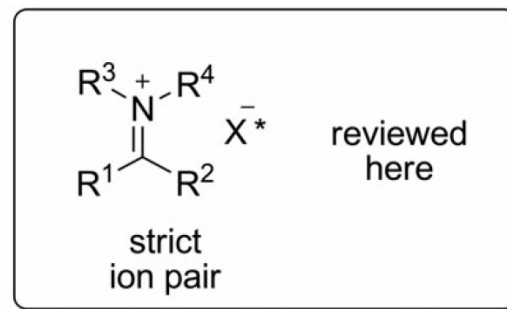
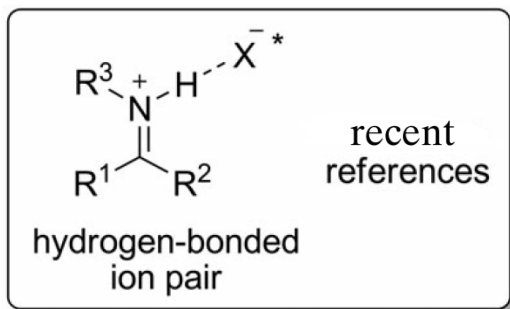


Contents

- *Chiral Cation-Directed Catalysis*
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4. Chiral Anion-Directed Catalysis

◆ Types of ion-pairing interactions.



4.1. *Borate Anions*

4.2. *Phosphate Anions*

4.3. *N-Triflylphosphoramidate Anions*

4.4. *Noncovalent Interactions between Cationic Intermediates and BINOL-derived Phosphates and Phosphoramidates*

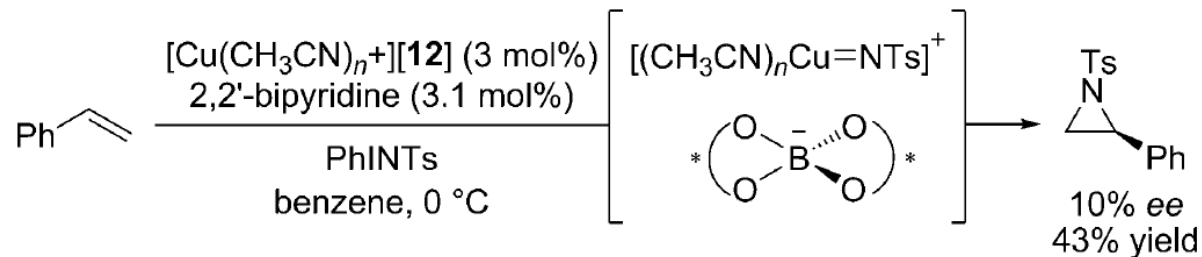
4.5. *Disulfonimide Anion*

4.6. *Imidodiphosphate Anion*

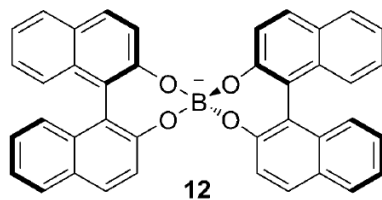
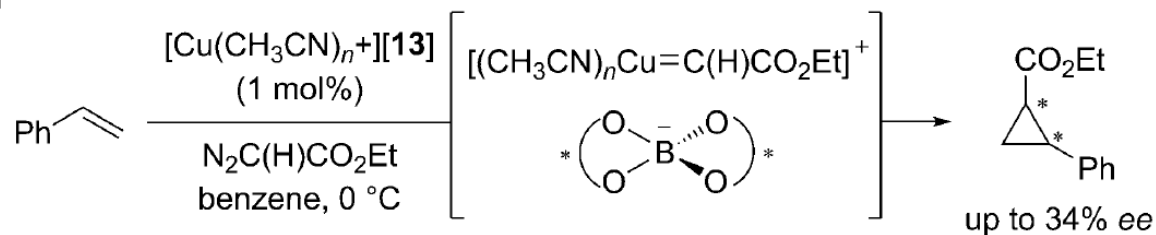
4. Chiral Anion-Directed Catalysis(I)

◆ Borate Anions

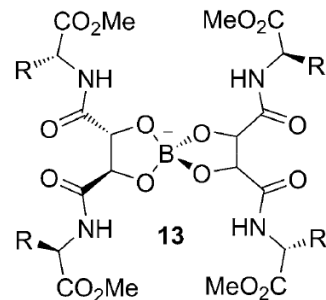
(a)



(b)



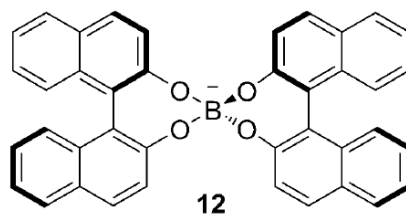
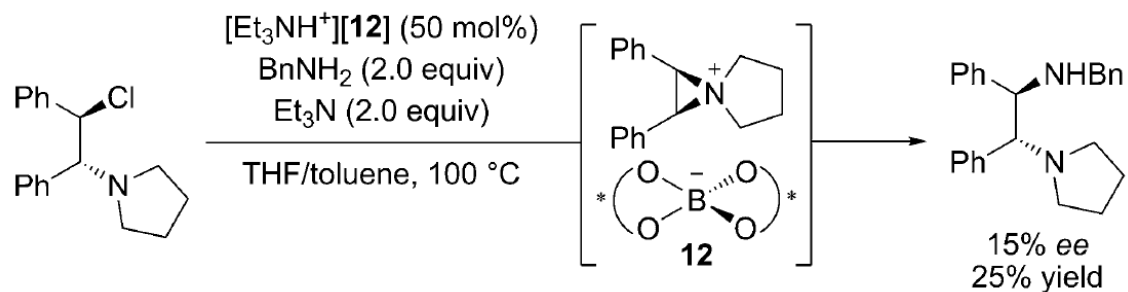
12



13

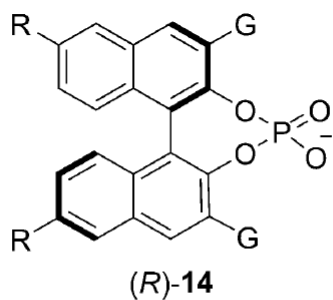
4. Chiral Anion-Directed Catalysis(I) Borate Anions

Chiral borate anion-directed aziridinium opening reaction

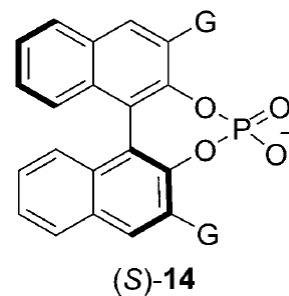


4. Chiral Anion-Directed Catalysis(II)

◆ Phosphate Anions



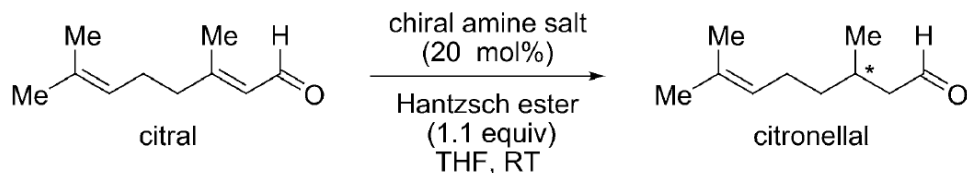
- 14a**, R = H, G = 2,4,6-(*i*Pr)₃-C₆H₂
14b, R = H, G = SiPh₃
14c, R = H, G = 3,5-(CF₃)-C₆H₃
14d, R = C₈H₁₇, G = 2,4,6-(*i*Pr)₃-C₆H₂



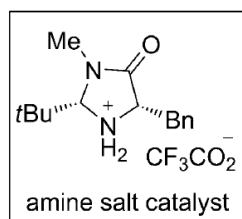
- 14d**, G = 4-NO₂-C₆H₄

4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

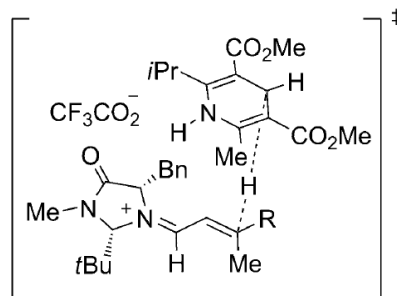
◆ 1、 Reactions of Iminium Ions-- Enantioselective Transfer Hydrogenations of Enals



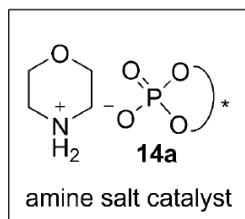
(a) covalent asymmetric catalysis



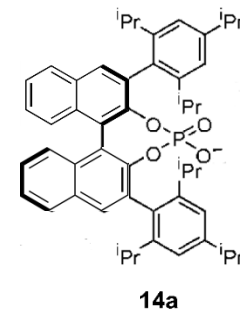
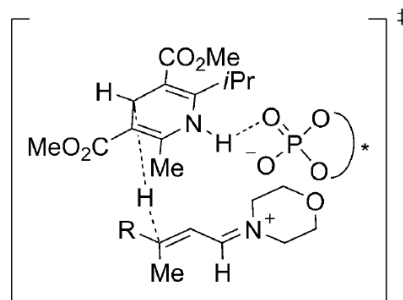
(*S*)-citronellal
40% ee
58% yield



(b) ion-pairing asymmetric catalysis



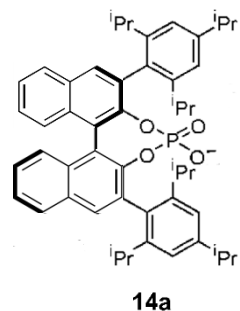
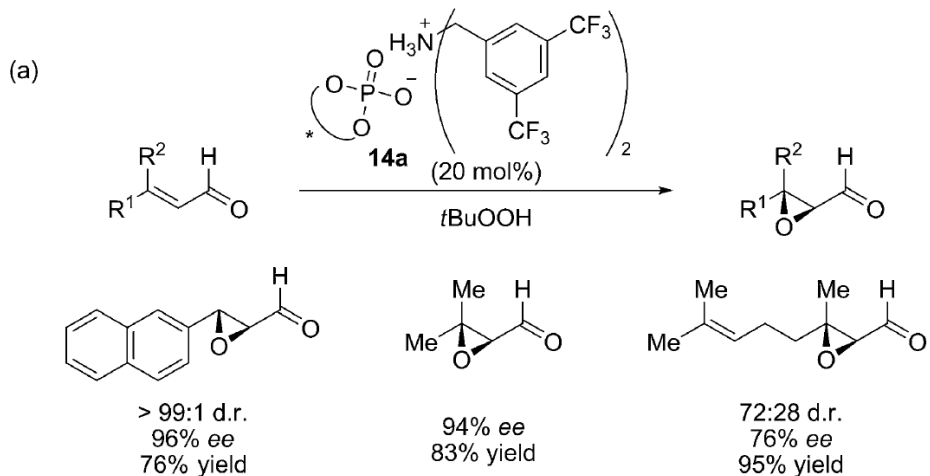
(*R*)-citronellal
90% ee
71% yield



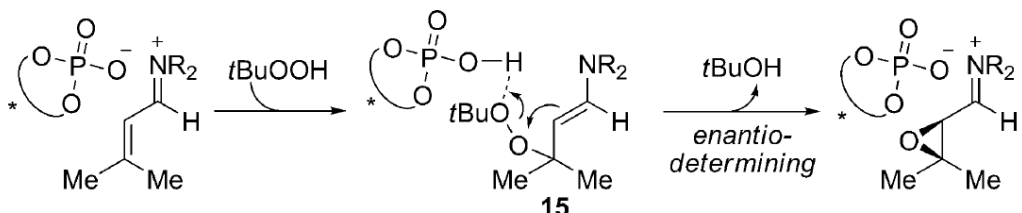
4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

----Reactions of Iminium Ions

Epoxidation of Enals



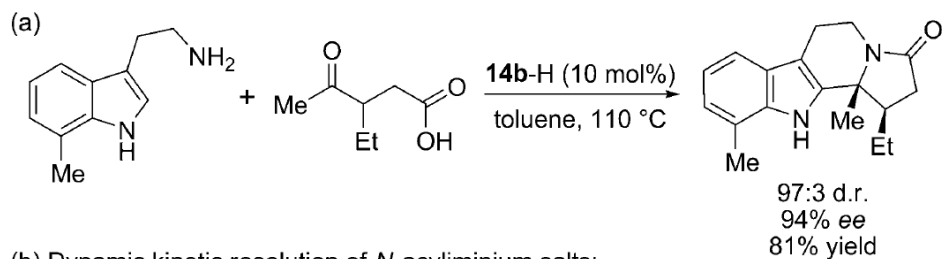
(b) Proposed mechanism for $R^1 = R^2 = \text{Me}$:



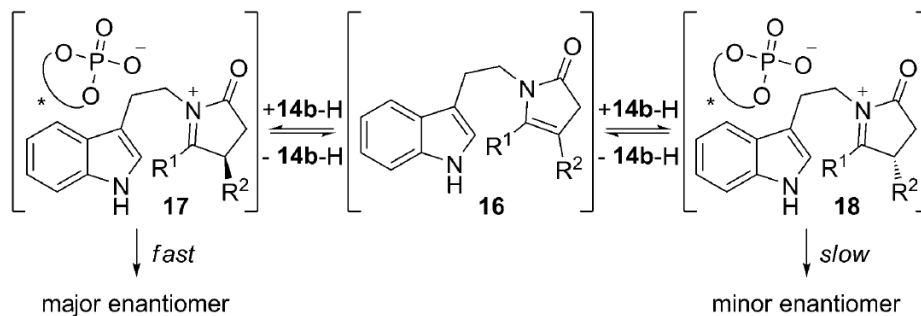
4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

----Reactions of Iminium Ions

N-acyliminium Ion Cyclization Cascade



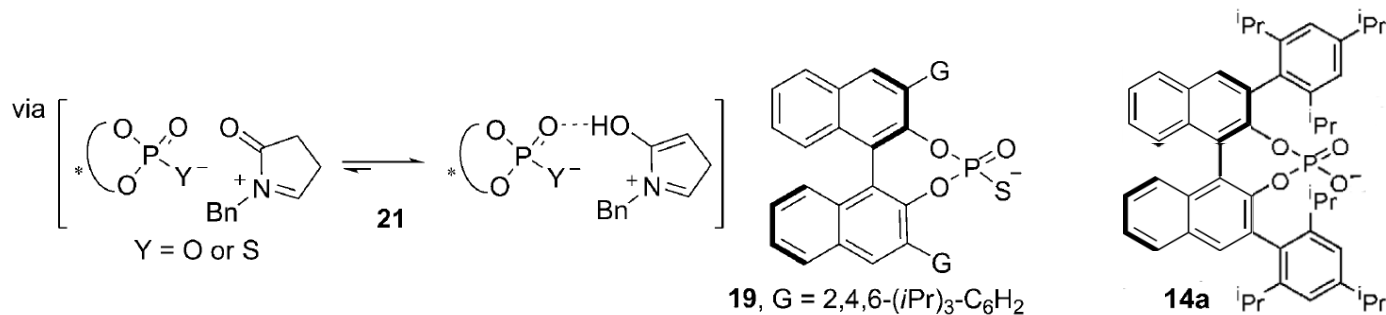
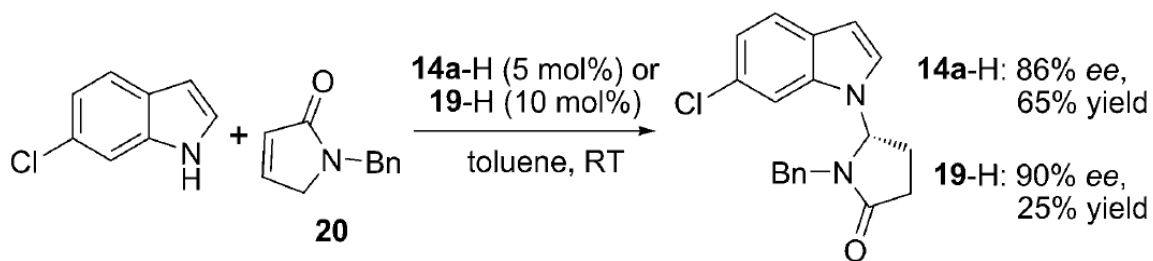
(b) Dynamic kinetic resolution of *N*-acyliminium salts:



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

----Reactions of Iminium Ions

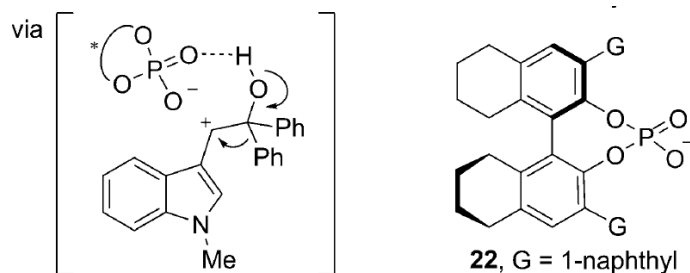
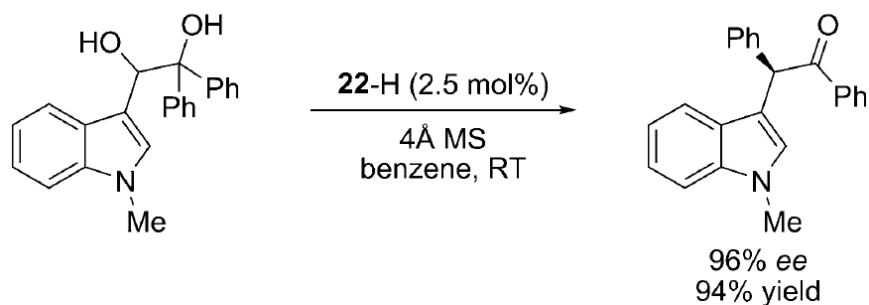
Enantioselective N-alkylation with Cyclic N-acyliminium Ion Intermediates



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

◆ 2、 Reactions of Carbocations-----

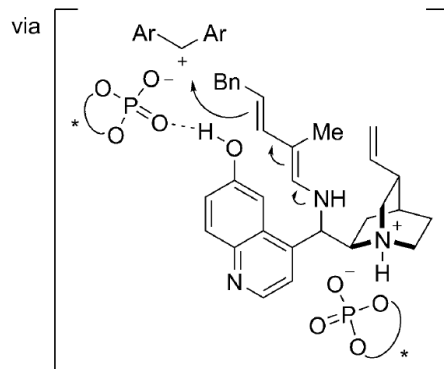
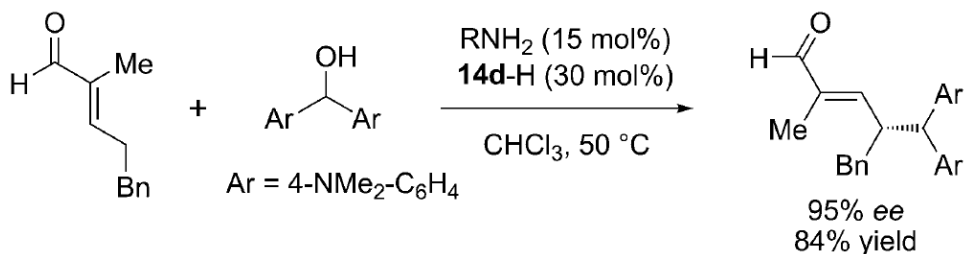
Pinacol Rearrangement



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

----Reactions of Carbocations

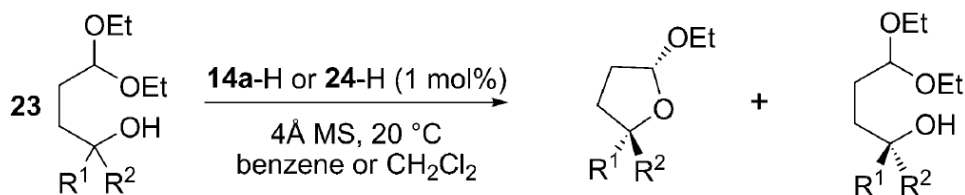
δ -Alkylation of α -Branched Enals



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

◆ 3、 Oxocarbenium Ions----

Enantioselective Transacetalization Reactions



$R^1 = R^2 = \text{Ph}$

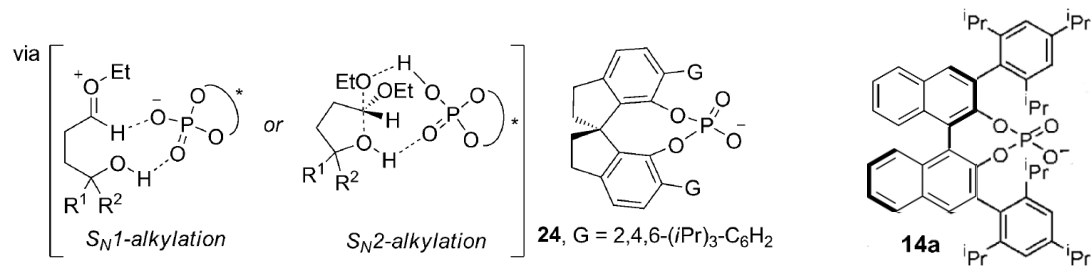
$R^1 = \text{H, } R^2 = \text{Ph}$ (racemic)

$R^1 = \text{Et, } R^2 = \text{Ph}$ (racemic)

95% yield, 89% ee

55% conv, 94% ee, 13:1 d.r. 97% ee

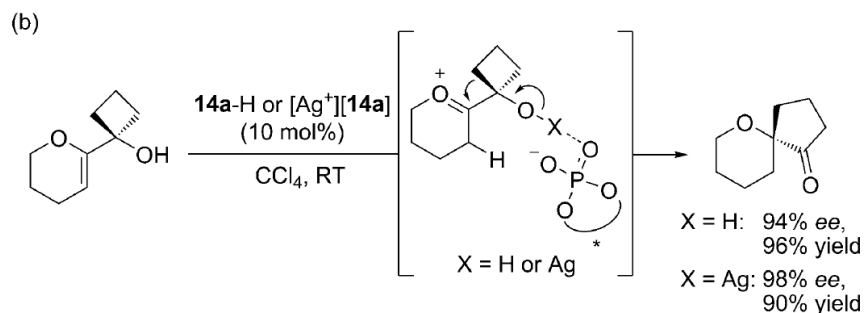
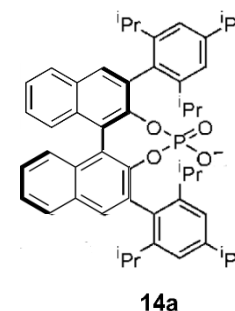
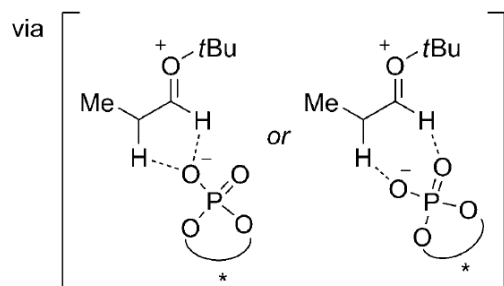
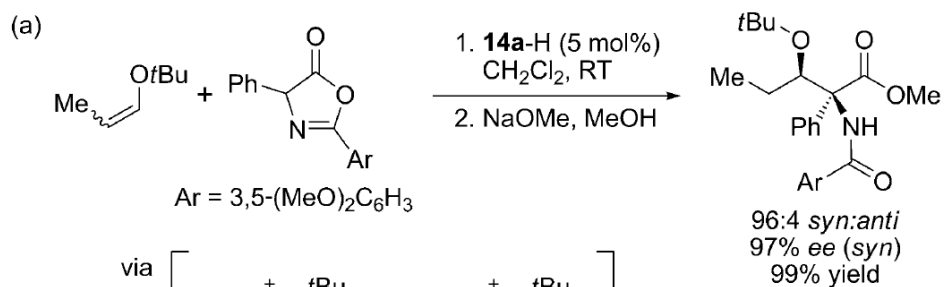
55% conv, 97% ee, 9:1 d.r. 92% ee



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

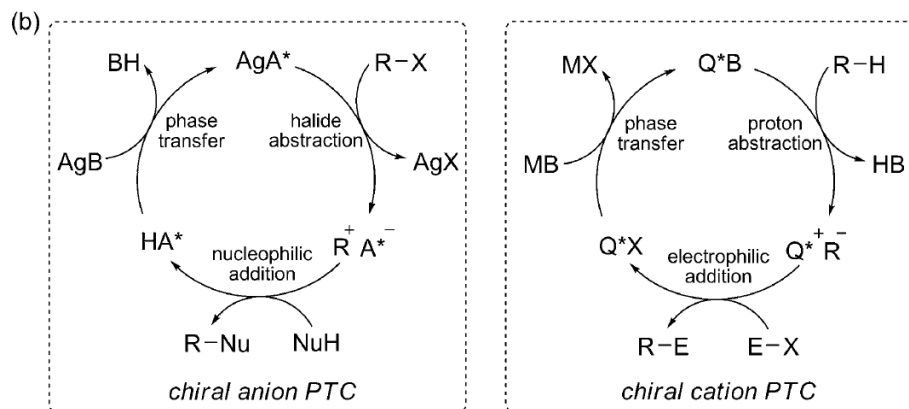
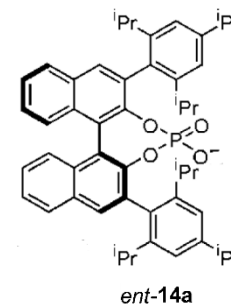
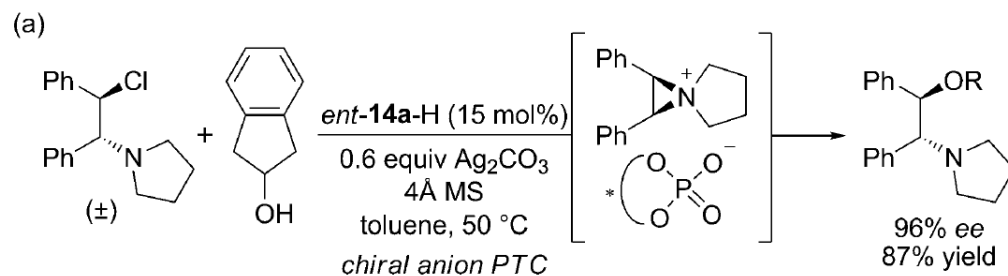
----Oxocarbenium Ions

Aldol-type Reaction and Semipinacol Rearrangement



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

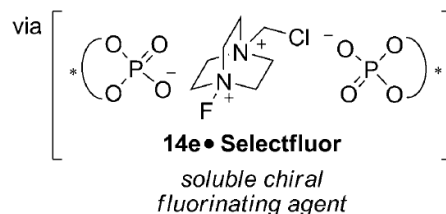
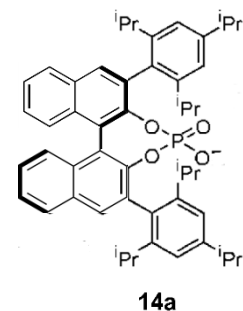
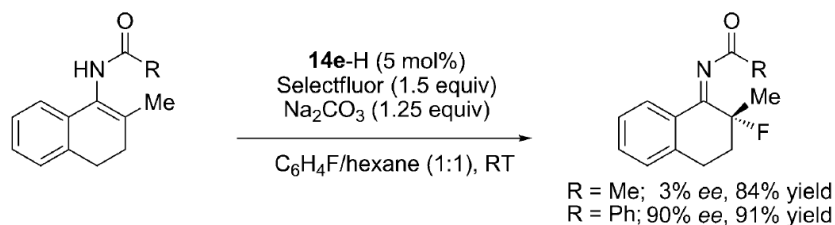
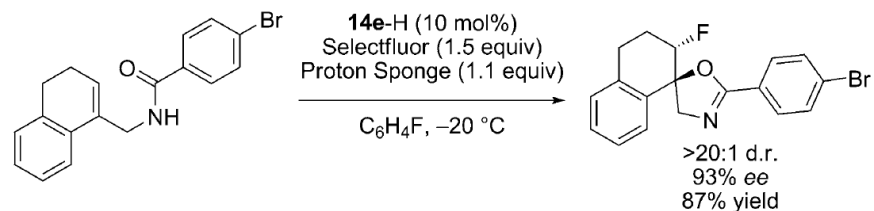
◆ 4、 Chiral Anion Phase-Transfer Catalysis



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

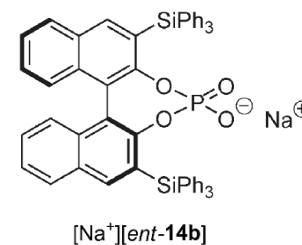
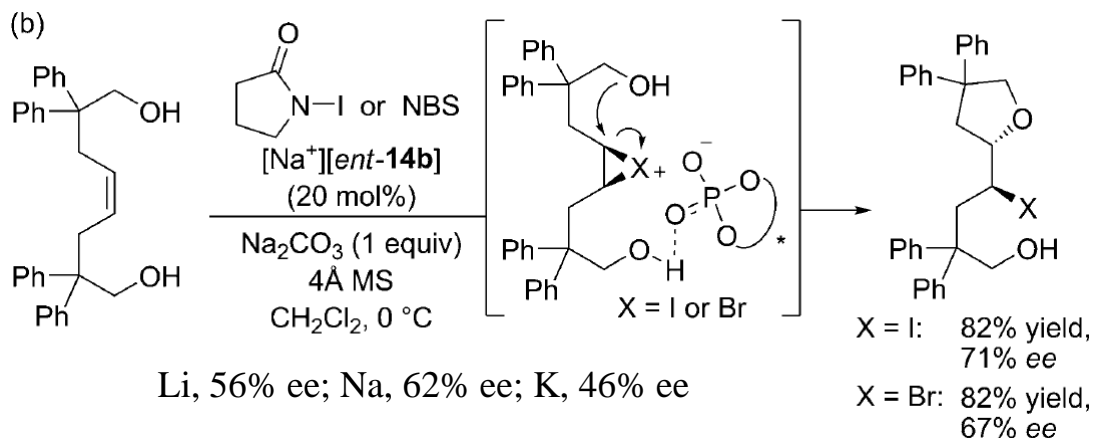
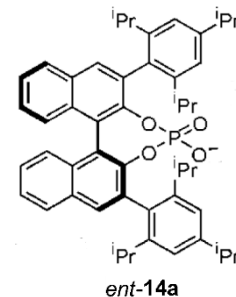
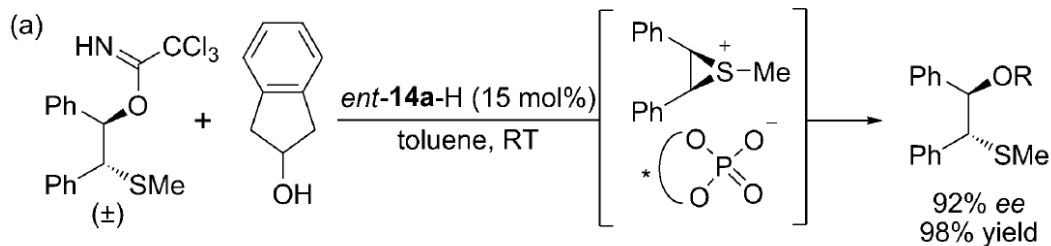
----Chiral Anion Phase-Transfer Catalysis

Enantioselective Fluorocyclization of Olefins and Fluorination of Enamides



4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

◆ 5. Desymmetrization Reactions of Episulfonium and Halonium Ions

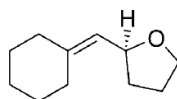
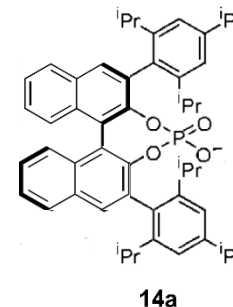
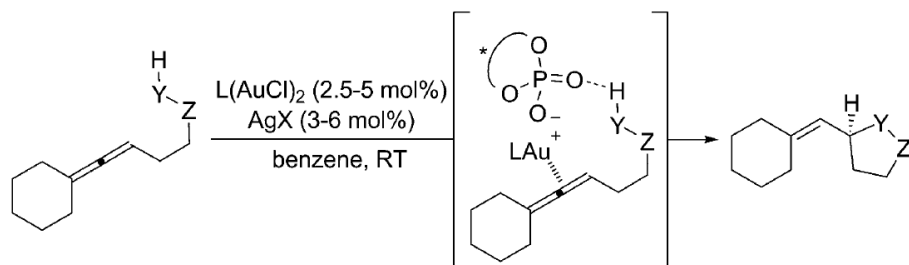


Li, 56% ee; Na, 62% ee; K, 46% ee

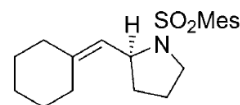
not readily accomplished by traditional Lewis acid catalysis

4. Chiral Anion-Directed Catalysis(II) Phosphate Anions

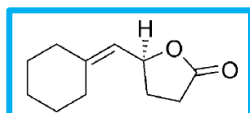
◆ 6、 Transition-Metal Catalyzed Reactions



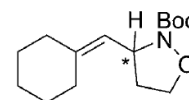
L = (*R*)-binap, X = BF₄⁻ 52% yield, 6% ee
L = dppe, X = **14a** 90% yield, 97% ee



L = Ph(Me)₂P, X = **14a**
97% yield, 96% ee



L = (*R*)-binap, X = **14a** 91% yield, 3% ee
L = (*S*)-binap, X = **14a** 88% yield, 82% ee

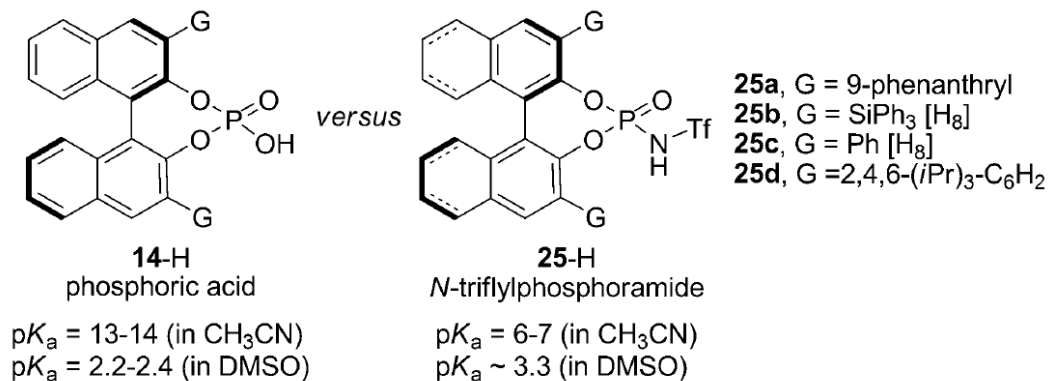


L = dppe, X = **14a**
75% yield, 99% ee

an important breakthrough

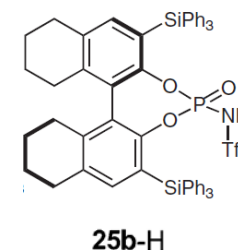
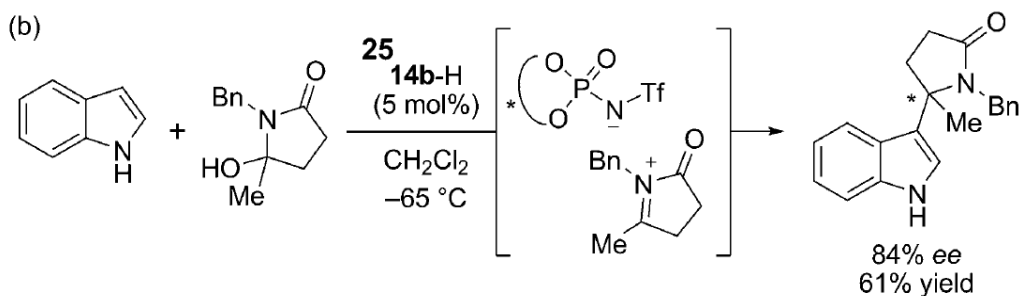
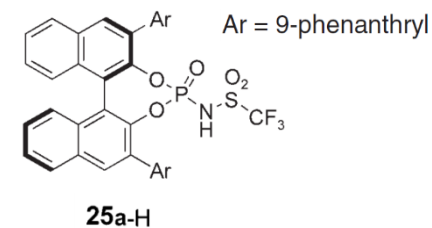
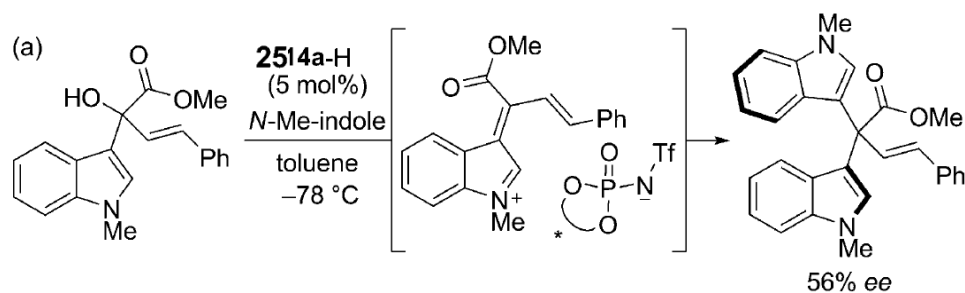
4. Chiral Anion-Directed Catalysis(III) N-Triflylphosphoramidate Anions

◆ Acidity of Phosphoric Acid versus N-triflylphosphoramide Catalysts



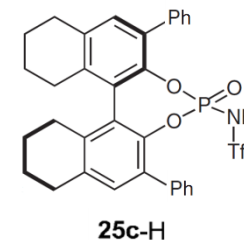
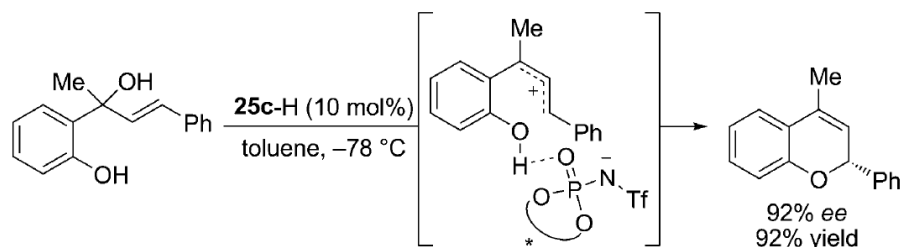
4. Chiral Anion-Directed Catalysis(III) N-Triflylphosphoramidate Anions

Nucleophilic Addition to N-alkylindolium and N-acyliminium Ions

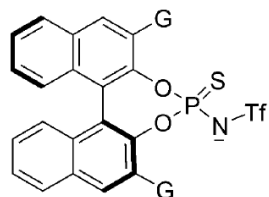
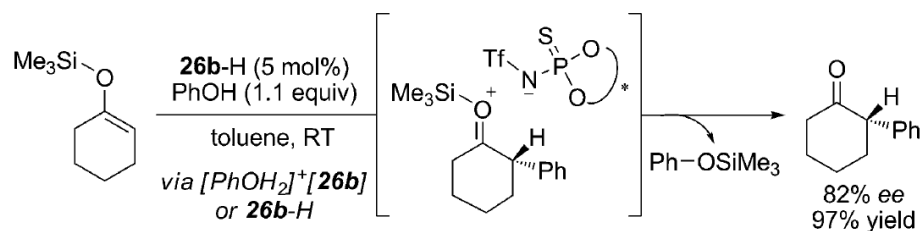


4. Chiral Anion-Directed Catalysis(III) N-Triflylphosphoramidate Anions

Enantioselective Allylic Alkylation Reaction



Enantioselective Protonation of Silyl enol Ethers

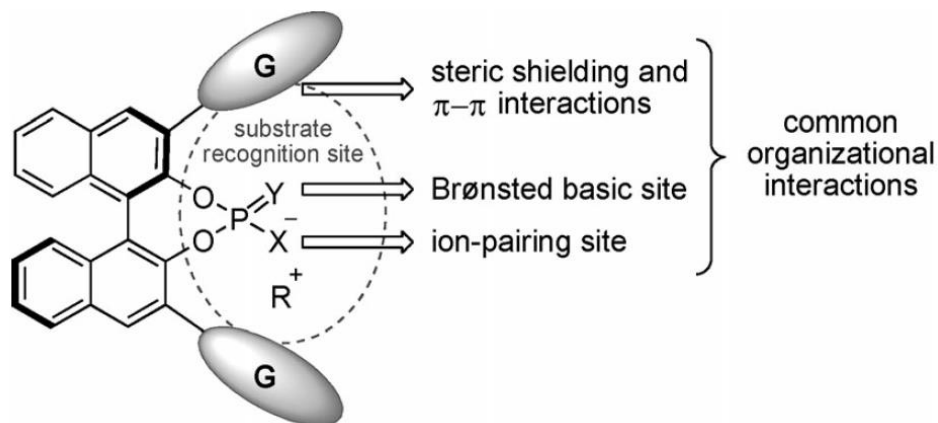


26a, G = 2,4,6-(*i*Pr)₃-C₆H₂
26b, G = 4-*t*Bu-2,6-(*i*Pr)₂-C₆H₂

Using 2,4,6-(Me)₃C₆H₂CO₂H (1.1 equiv),
phosphoramidate **25d-H**: 54% ee, 98% yield
thiophosphoramidate **26a-H**: 78% ee, 97% yield

4. Chiral Anion-Directed Catalysis(IV)

◆ Noncovalent Interactions between Cationic Intermediates and BINOL-derived Phosphates and Phosphoramidates

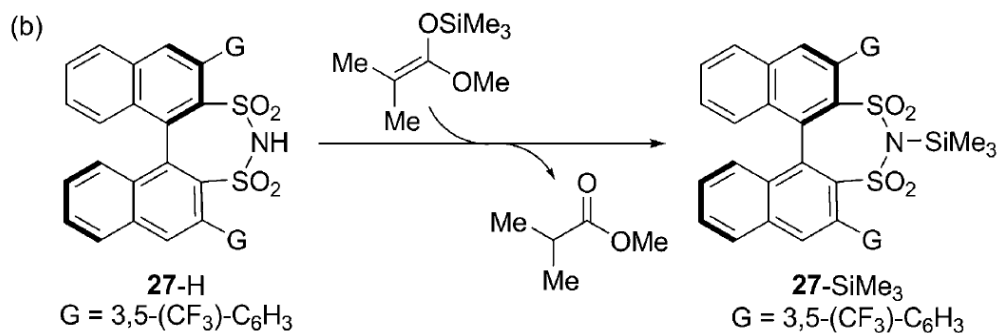
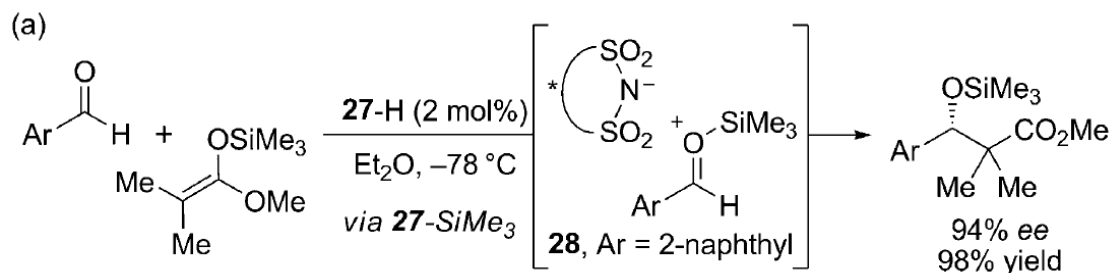


Substrate recognition site created by the 3,3'-substituents (G) of chiral BINOL-derived anions (Y=O, S; X=O, NTf).

4. Chiral Anion-Directed Catalysis(V)

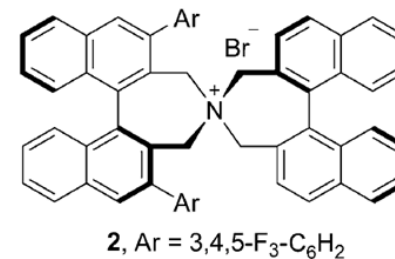
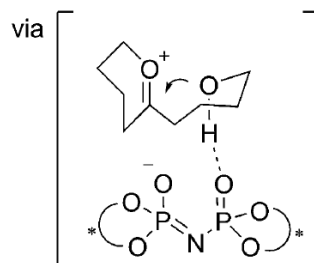
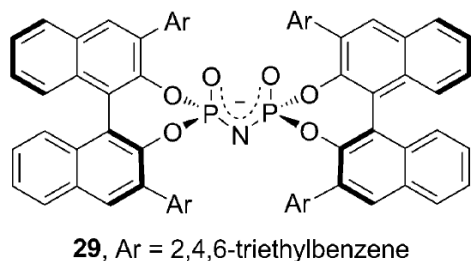
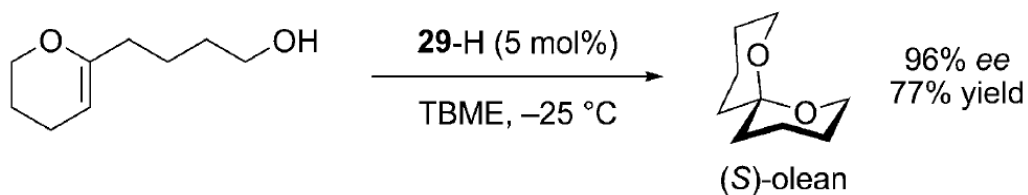
◆ Disulfonimide Anion----

Mukaiyama aldol reaction



4. Chiral Anion-Directed Catalysis(VI) Imidodiphosphate Anion

Enantioselective Spiroacetalization

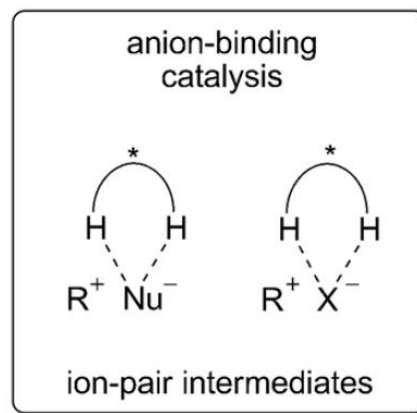
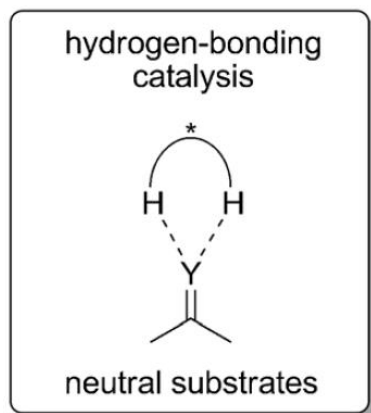


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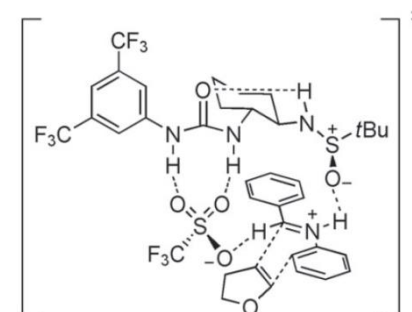
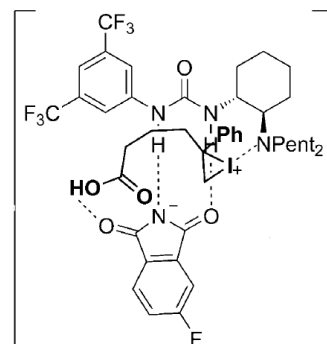
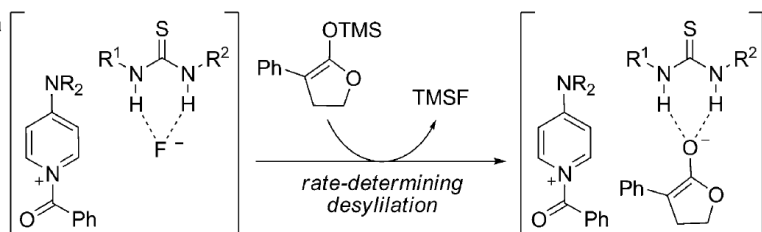
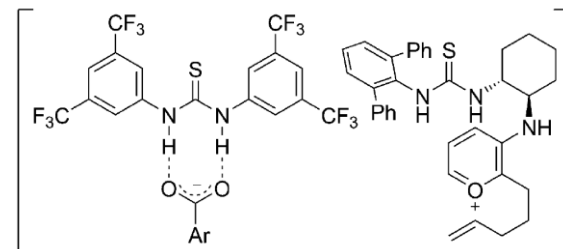
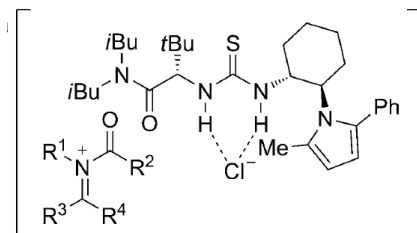
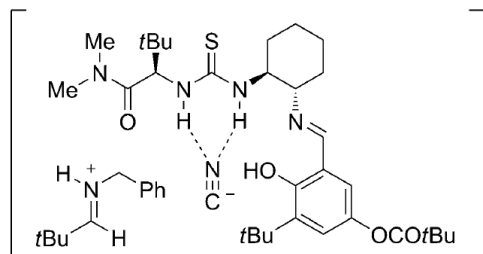
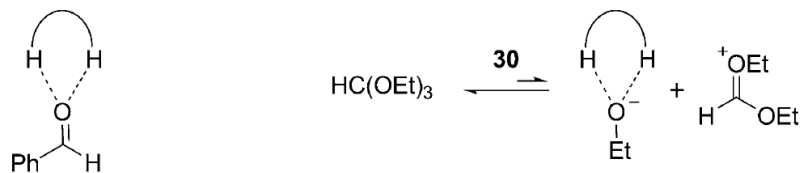
- *Chiral Cation-Directed Catalysis*
- *Cation-Binding Catalysis*
- *Chiral Anion-Directed Catalysis*
- ***Anion-Binding Catalysis***
- *Summary & Outlook*

5. Anion-Binding Catalysis

◆ Modes of electrophile activation by dual hydrogen-bond donors.



5. Anion-Binding Catalysis



Schreiner, P. R. *T* **2006**, *62*, 434; List, B *Chem. Asian J.* **2008**, *3*, 430;

Jacobson, E. N. *ACIE* **2005**, *44*, 6700; Jacobsen, E. N. *JACS* **2011**, *133*, 14578;

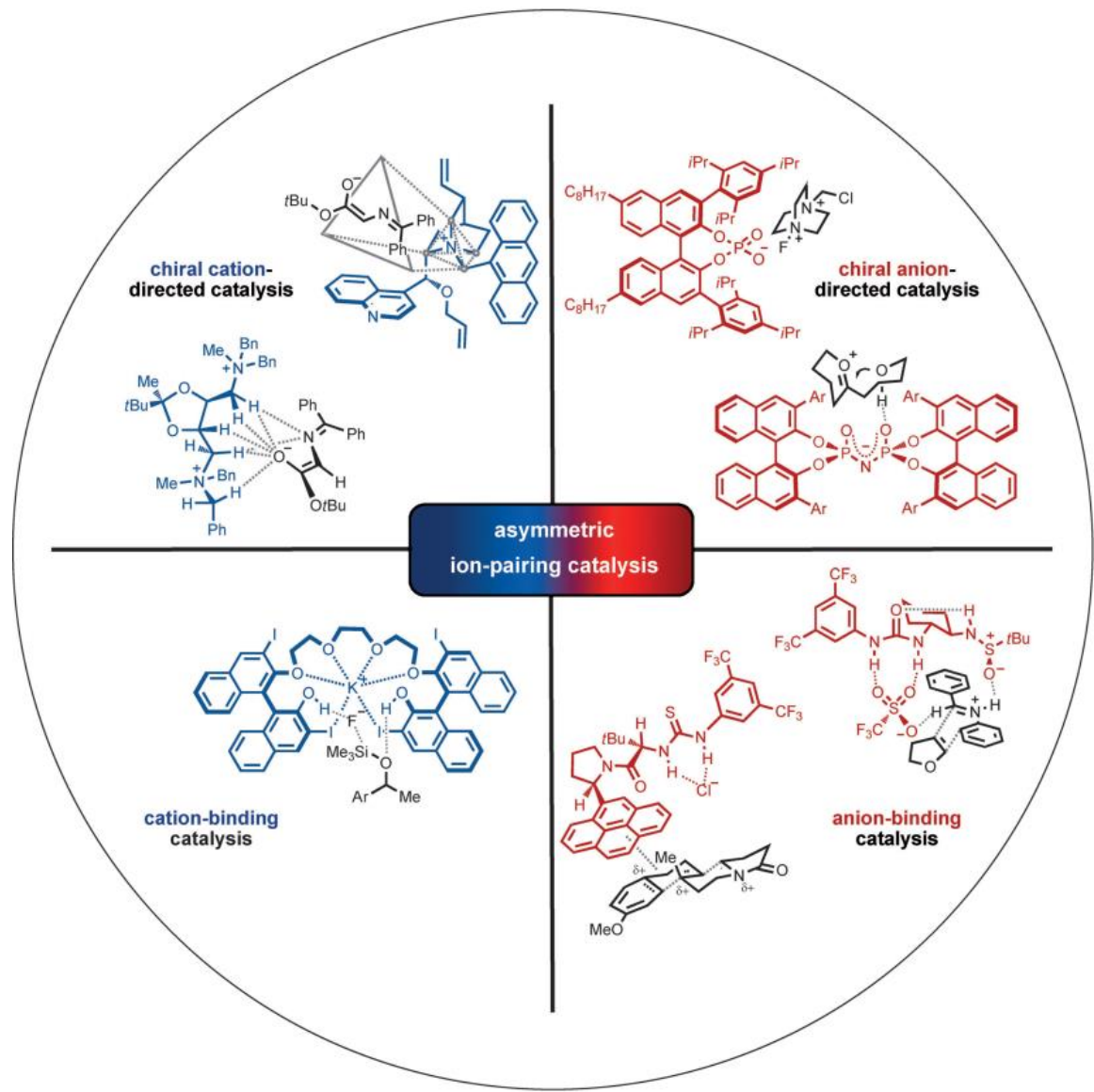
Jacobsen, E. N. *JACS* **2011**, *133*, 13872; Jacobsen, E. N. *ACIE* **2010**, *49*, 7332;

Jacobsen, E. N. *Science* **2010**, *327*, 986.

Contents

- *Chiral Cation-Directed Catalysis*
- *Cation-Binding Catalysis*
- *Chiral Anion-Directed Catalysis*
- *Anion-Binding Catalysis*
- *Summary & Outlook*

Summary:



Summary:

- **Noncovalent interactions, weakly directional**
 - **Secondary interactions:
hydrogen-bonding, π - π , and cation- π interactions
Others?**
- **Discovery of interesting and useful new transformations**
- **Design and Identify novel catalyst structures**
- **Deeply understanding of mechanisms**

Thank you for your attention !