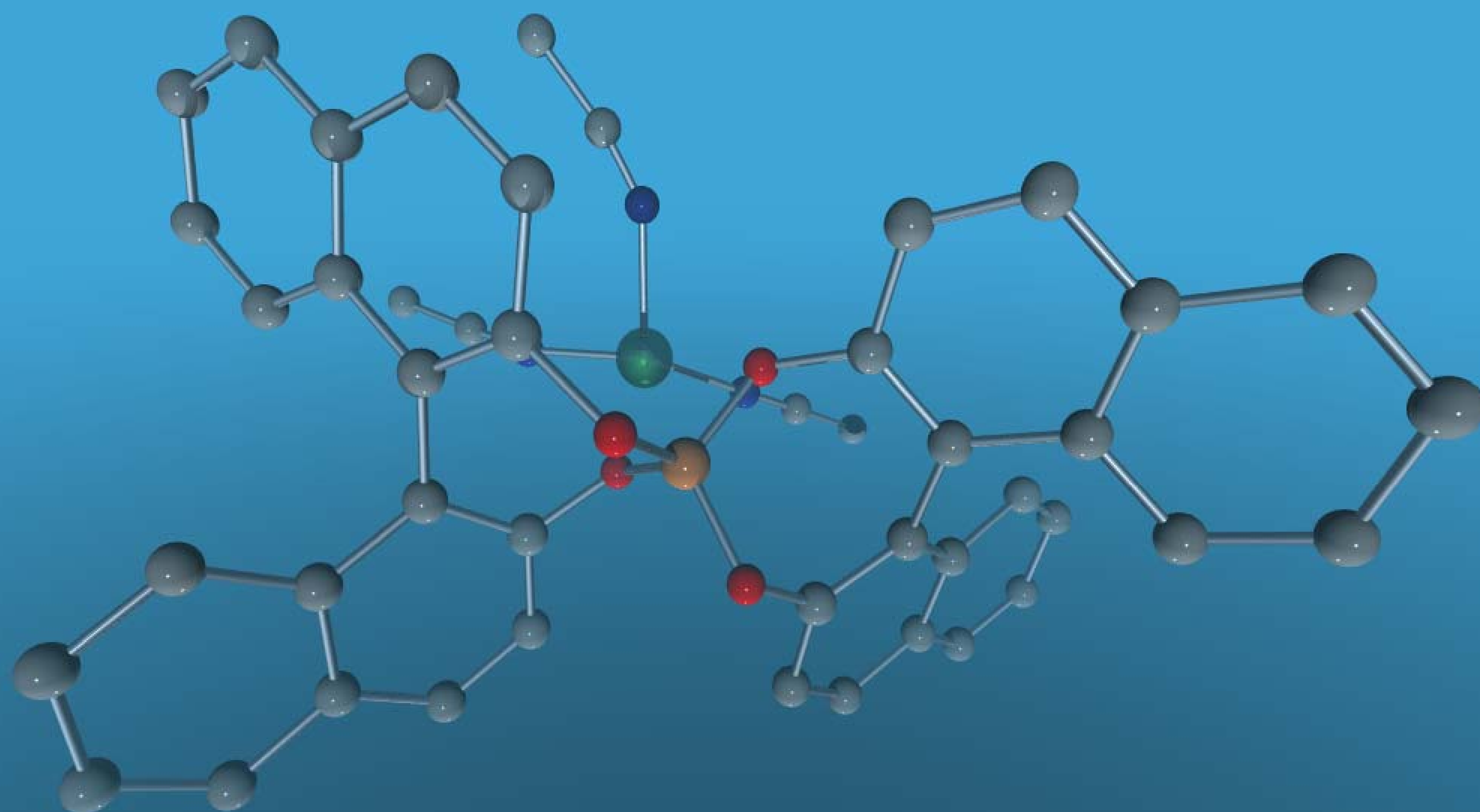
Chiral Counterions in Asymmetric Catalysis

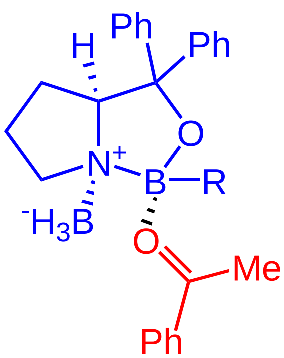


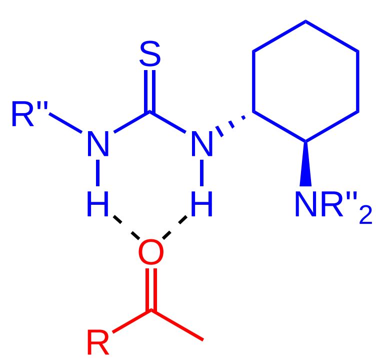
Peter Dornan • Dong Group

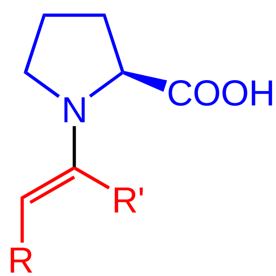
Monday Night Seminar • April 13, 2009

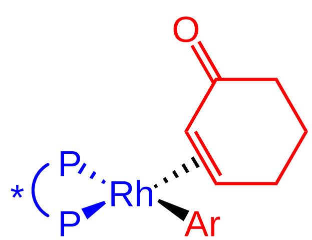
Asymmetric Catalysis

Chiral induction is typically achieved through strongly directional chiral catalyst – substrate interactions

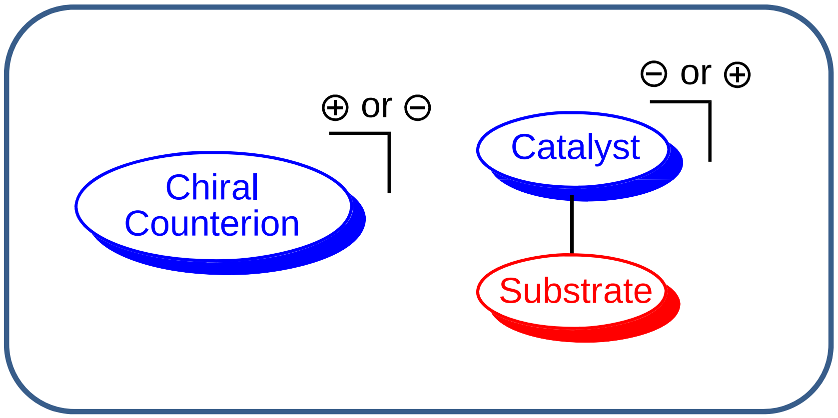




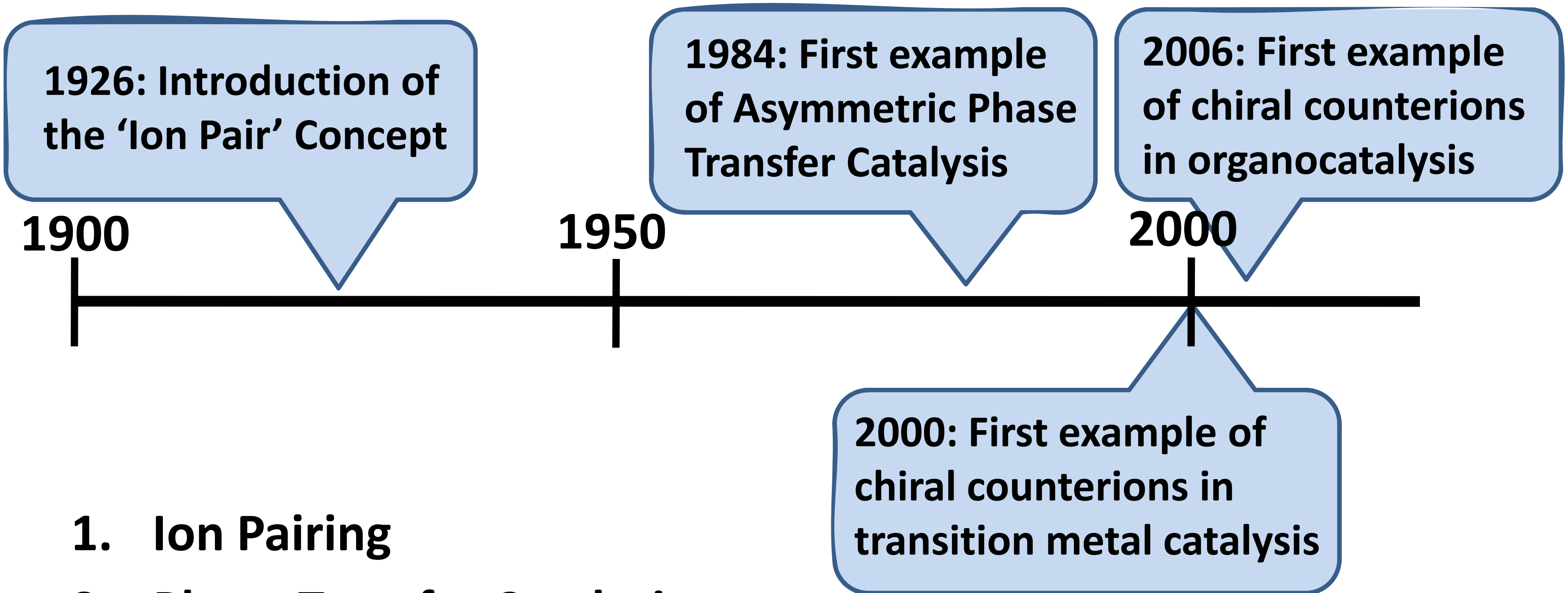




- **Lewis Acid/Base Interactions**
- **Hydrogen Bonds**
- **Covalent Bonds**
- **Coordination Bonds**
- **Ion Pairing ?**



Outline



1. Ion Pairing
2. Phase Transfer Catalysis
3. Transition Metal Catalysis
4. Organocatalysis (Single Phase)
   - Iminium Ion Catalysis
   - Anion Binding

Ion Pairing

Coulombic Interaction Energy:

$$E = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_o r}$$

Inversely proportional to the permittivity of the medium and the separation of charge

E = Energy
q = Charge of the ion
r = Separation of ions

ε_o = Permittivity of a vacuum
ε = Dielectric constant of the medium

Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039

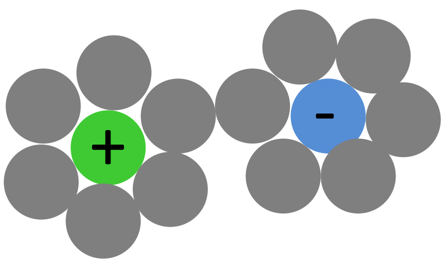
Ion Pairing

Coulombic Interaction Energy:

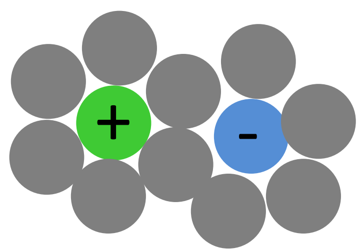
$$E = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_o r}$$

Inversely proportional to the permittivity of the medium and the separation of charge

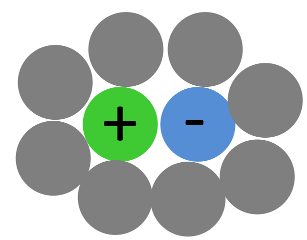
Solvent separated ion pair:



Solvent shared ion pair:



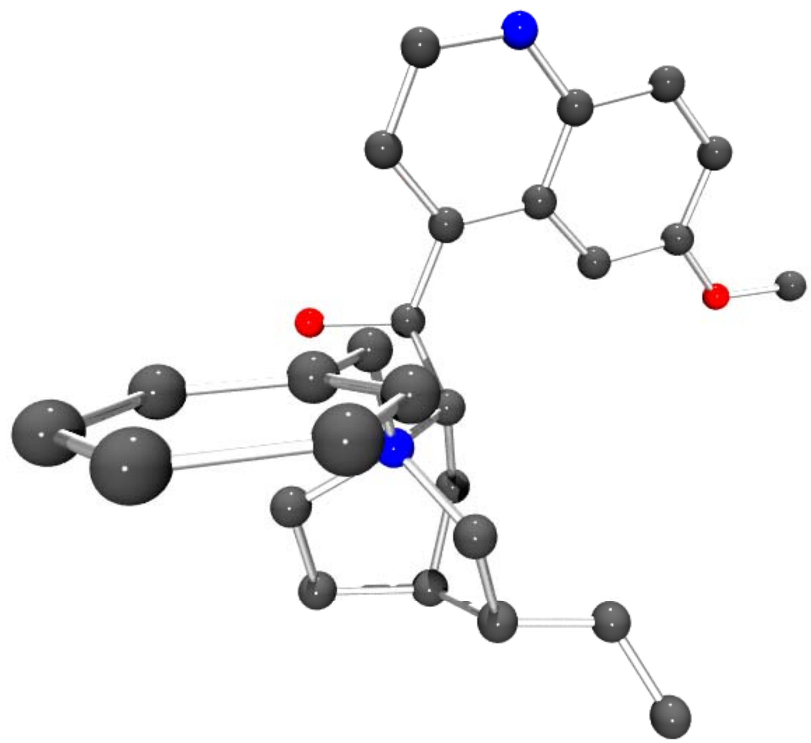
Contact Ion Pair:



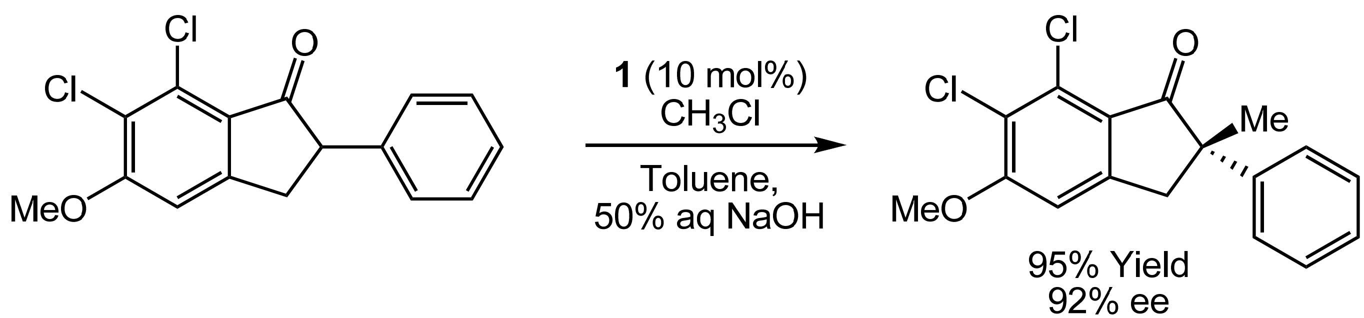
Decreasing Ion Separation

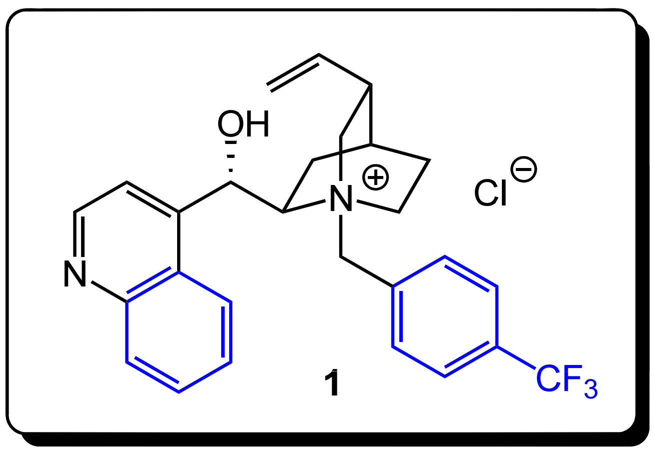
Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039

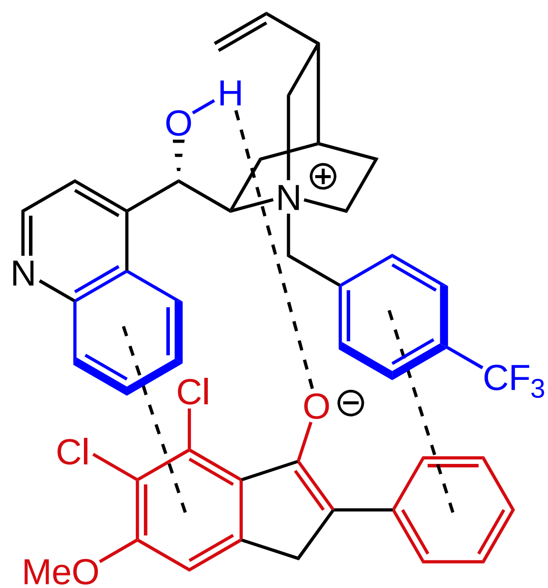
Phase Transfer Catalysis



Enolate Alkylation – Pioneering Report



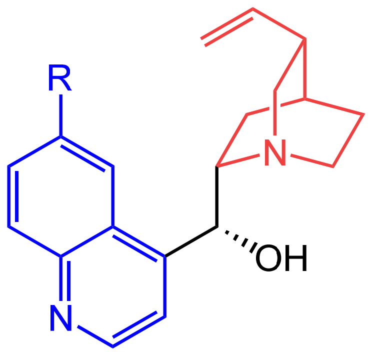




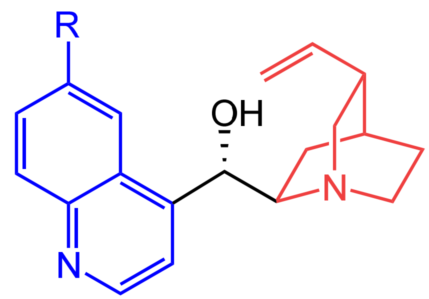
- **Electron withdrawing groups at the para-position of the benzyl ring improved the ee**

Dolling, U.-H. *et al. J. Am. Chem. Soc.* **1984**, *106*, 446

Cinchona Alkaloids



R = OMe Quinine
R = H Cinchonidine



R = OMe Quinidine
R = H Cinchonine

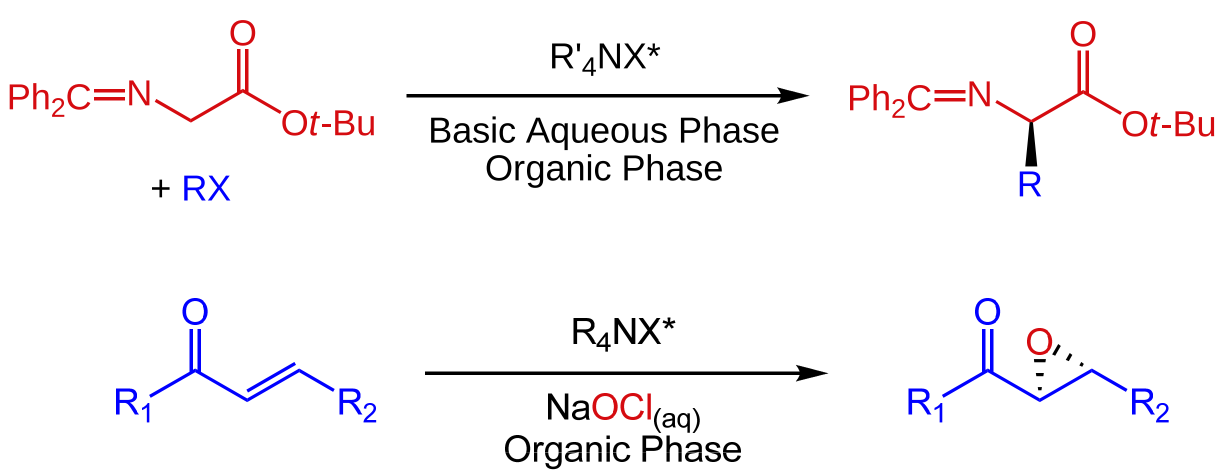
- **Isolated from the bark of the Cinchona trees**
- **Quinine is a potent antimalarial (found in tonic water)**
- **Privileged scaffold for asymmetric catalysis**

Hoffmann, H.M.R. *et al. Eur. J. Org. Chem.* **2004**, 4293

Dewick, P.M. *Medicinal Natural Products Second Edition*, John Wiley & Sons, **2001**

Asymmetric Phase Transfer Catalysis

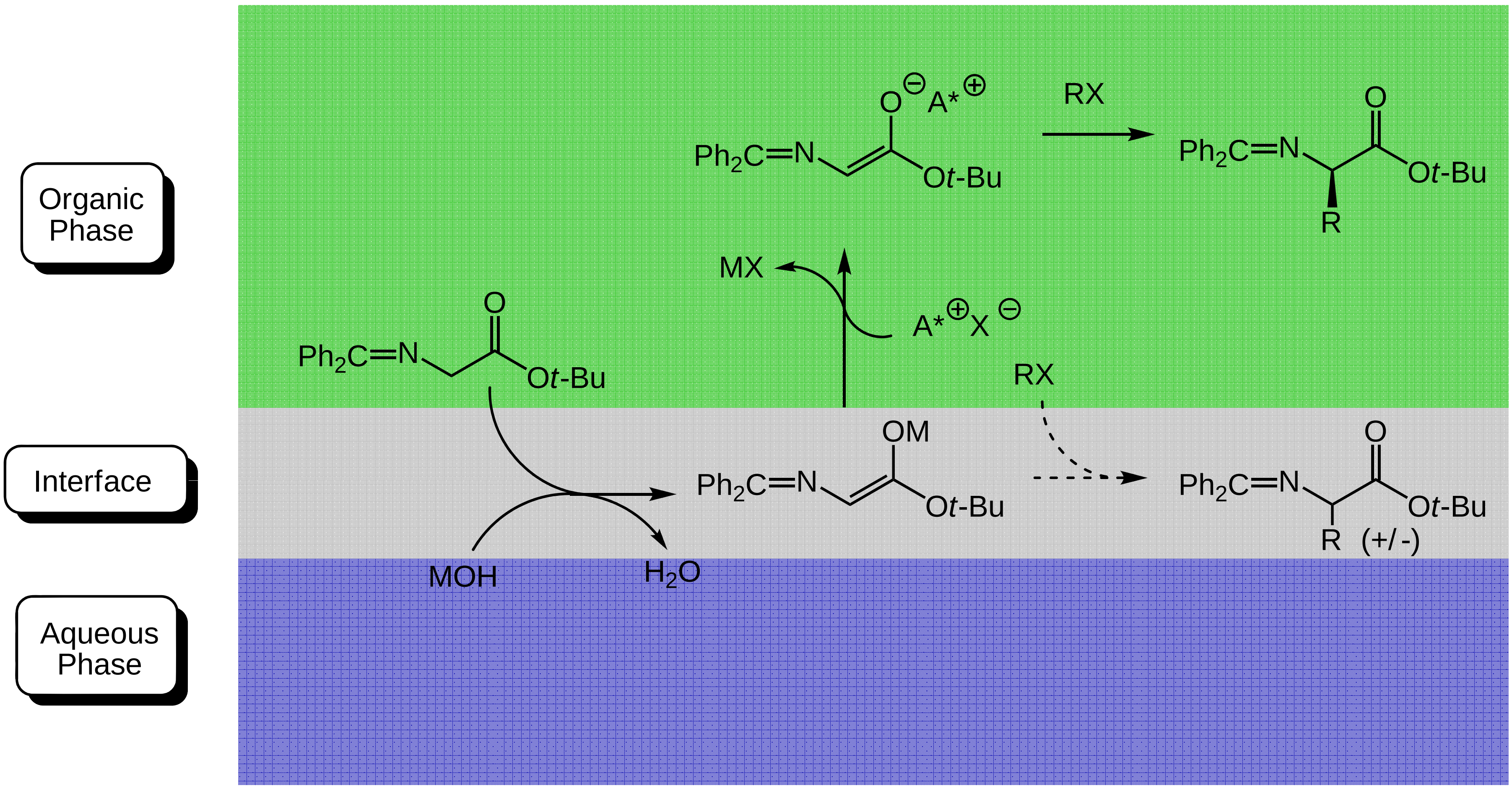
Asymmetric Phase Transfer Catalysis involves a chiral ion which facilitates migration of a charged species into the organic phase.



Two possible mechanisms: Interfacial and Extraction

Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 4222

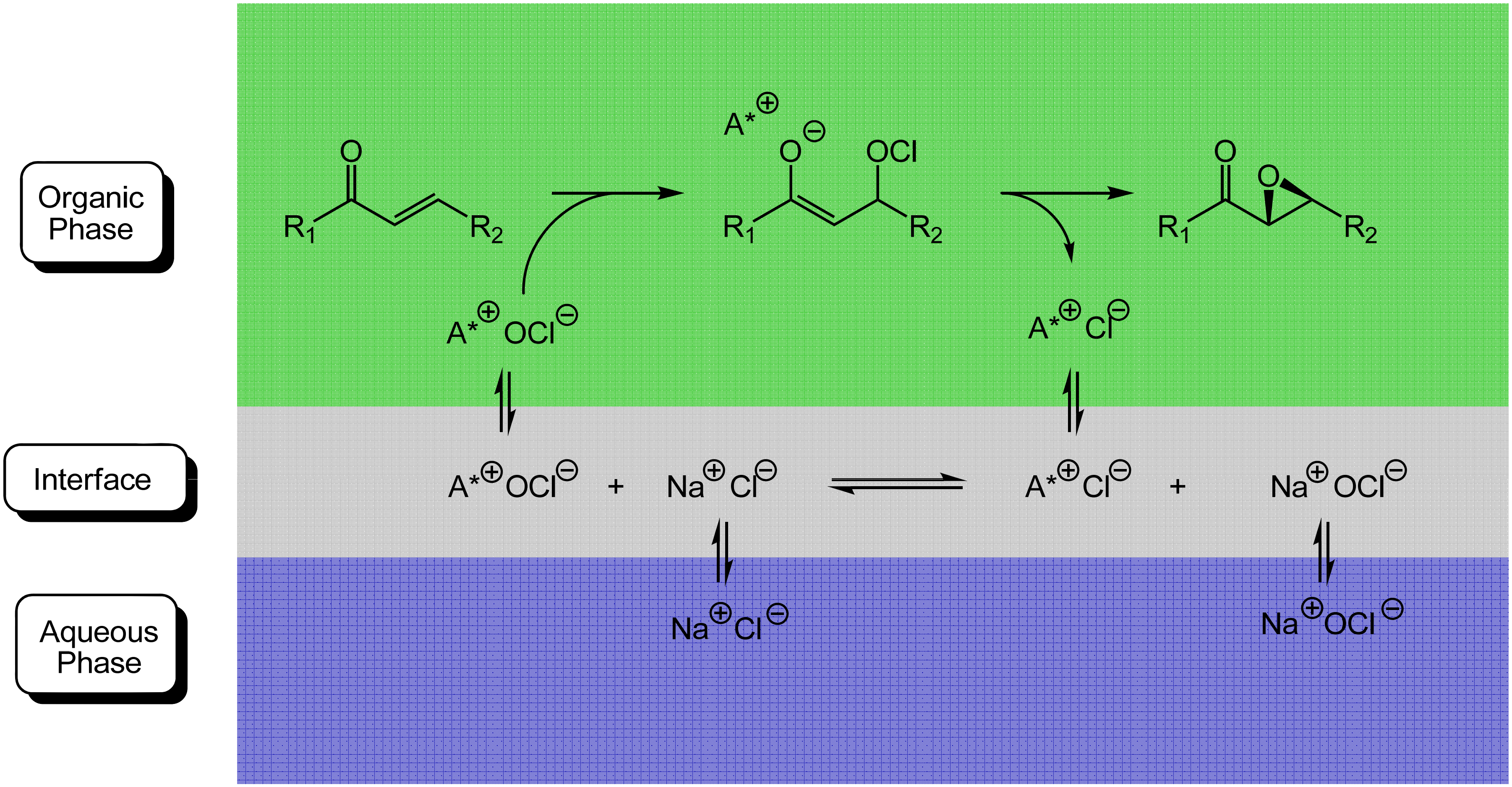
Interfacial Mechanism



The substrate is deprotonated at the interface

Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 4222

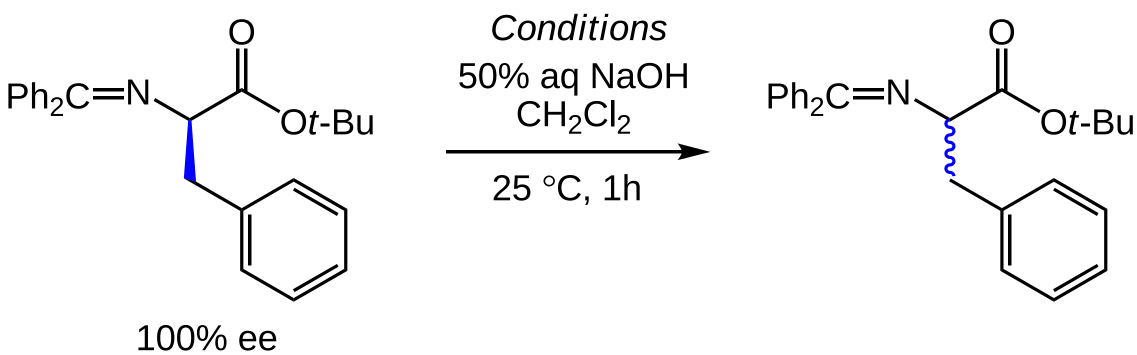
Extraction Mechanism

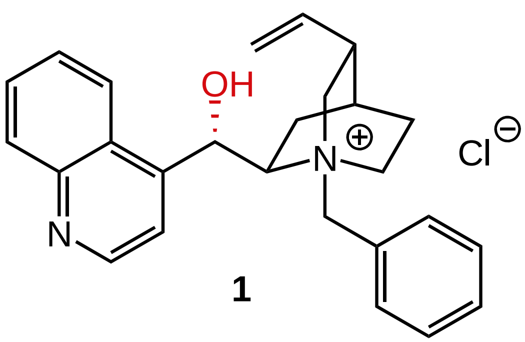


The substrate need not come to the interface

Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 4222

Enolate Alkylation – Racemization Studies





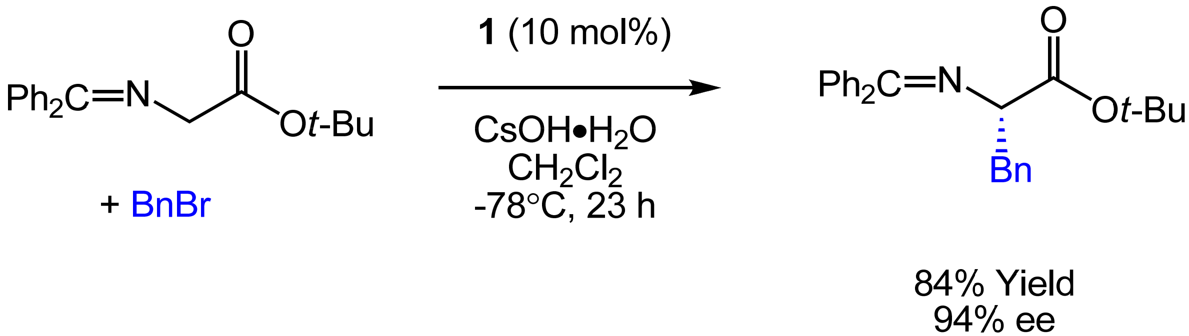
1

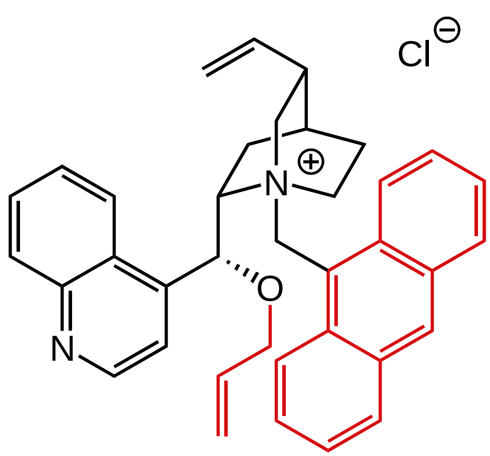
Conditions	ee (%)
No additives	100
1 (10 mol%)	30
1 (10 mol%) + BnBr (1.2 eq)	100

- **Racemization was catalyzed by the free alkoxide**
- ***In situ* benzylation likely yields the active catalyst**

O'Donnell, M.J. *et al. Tetrahedron.* **1994**, *50*, 4507

Enolate Alkylation – Catalyst Modifications

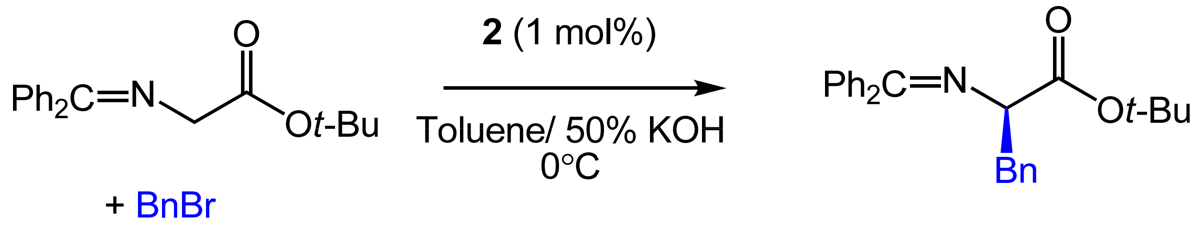




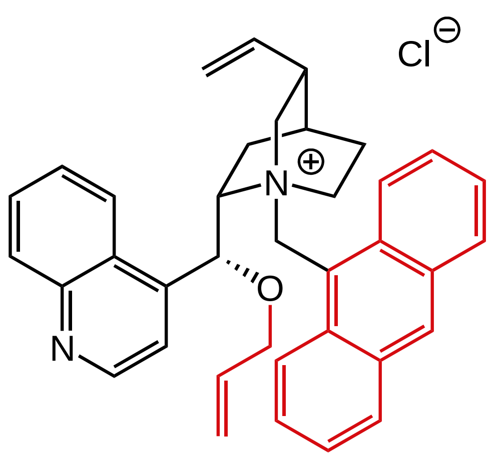
1

Corey, E.J. *et al. J. Am. Chem. Soc.* **1997**, *119*, 12414
Maruoka, K. *et al. J. Am. Chem. Soc.* **1999**, *121*, 6519

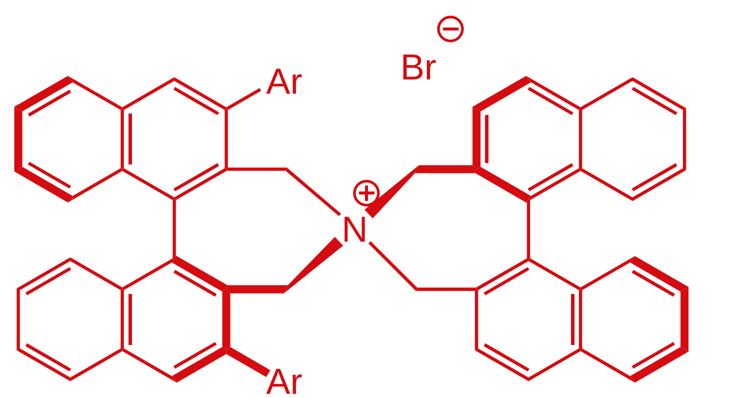
Enolate Alkylation – Catalyst Modifications



90% Yield
99% ee



1

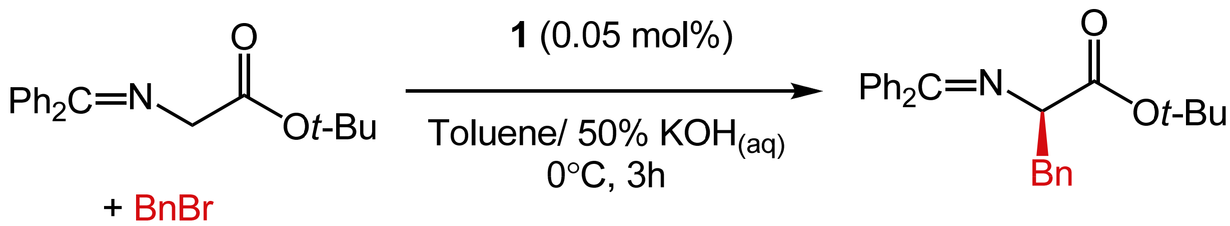


2

Ar = 3,4,5-$F_3C_6H_2$

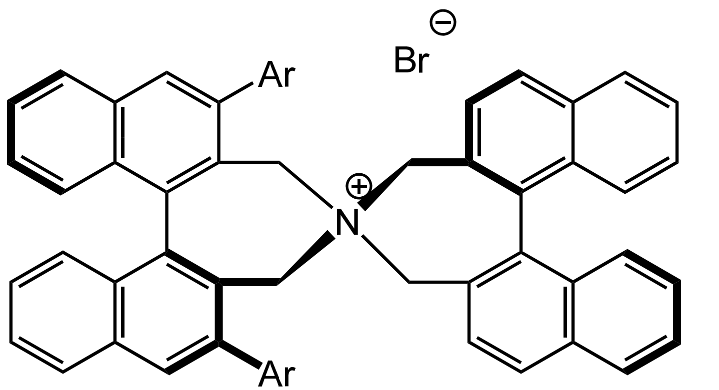
Corey, E.J. *et al. J. Am. Chem. Soc.* **1997**, *119*, 12414
Maruoka, K. *et al. J. Am. Chem. Soc.* **1999**, *121*, 6519

Enolate Alkylation – Crown Ethers

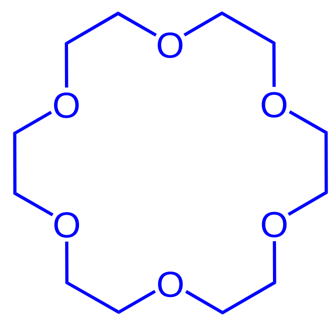


No co-catalyst: 4% Yield 92% ee

With 0.5 mol% [18]crown-6: 90% Yield 98% ee



1 Ar = 3,5-Ph$_2$C$_6$H$_3$

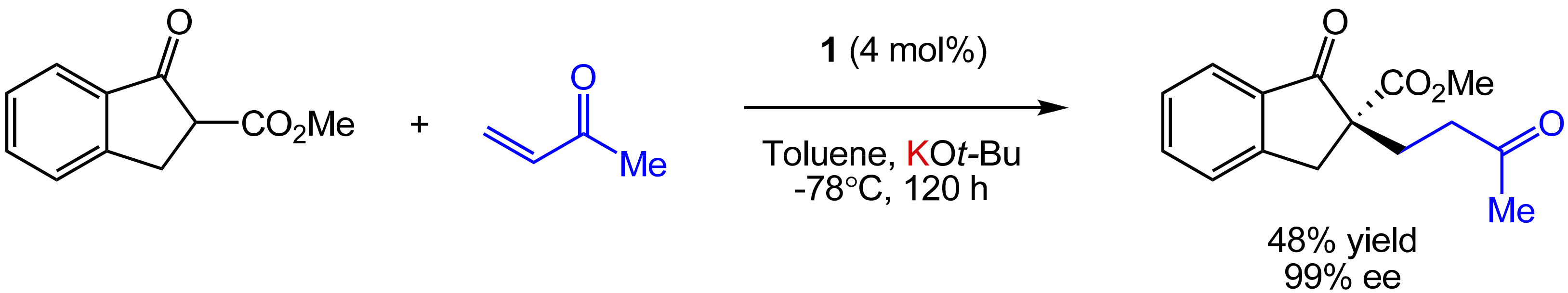


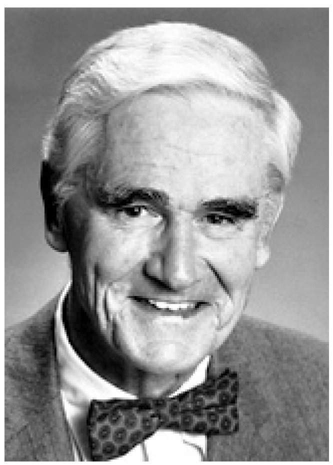
[18]crown-6

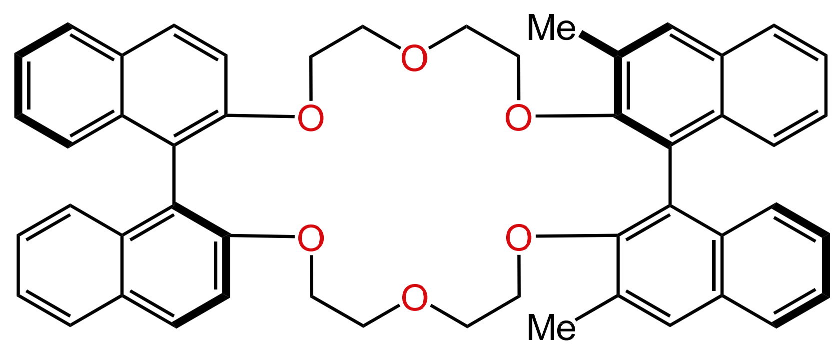
Crown ether is proposed to extract KOH into the organic phase

Maruoka, K. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 625

Michael Additions – Chiral Crown Ethers





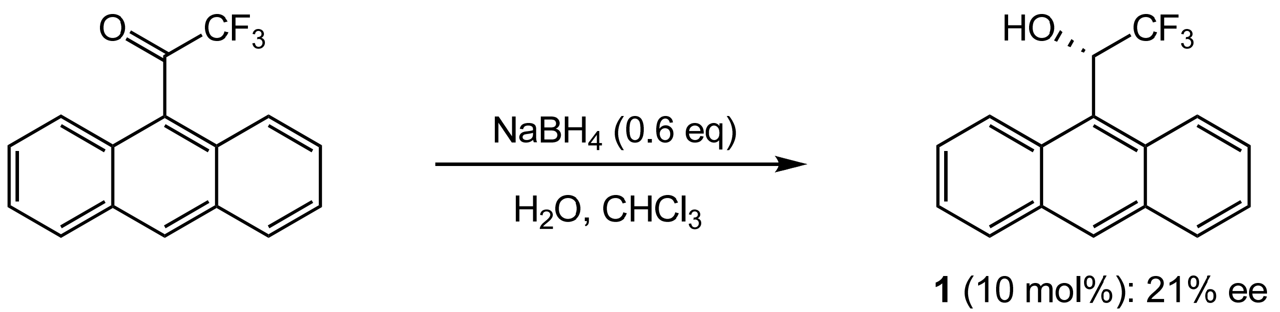


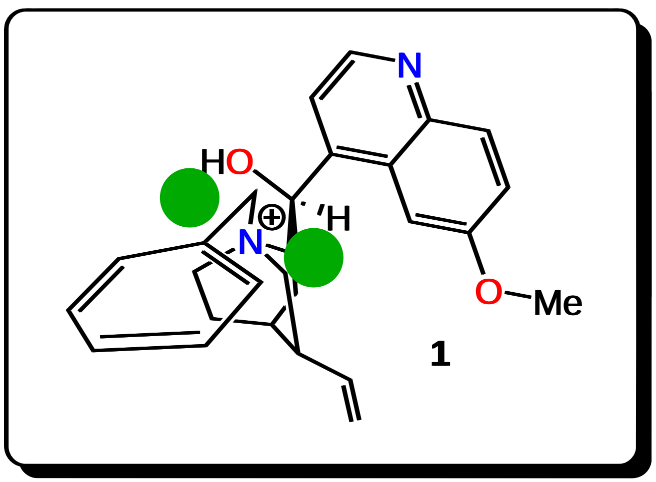
1

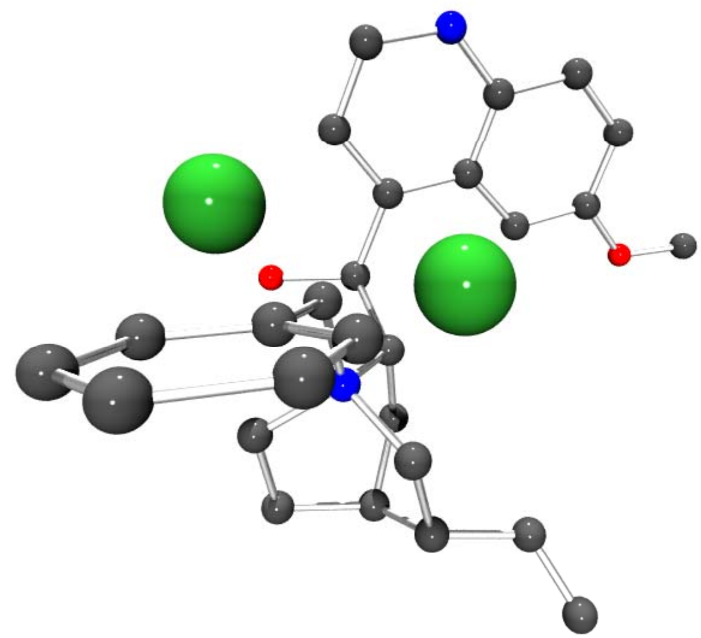
Chiral crown ether complexes K^+

Cram, D.J. *et al. J. Chem. Soc. Chem. Commun.* **1981**, 625

NOE Studies of Ion Pairing

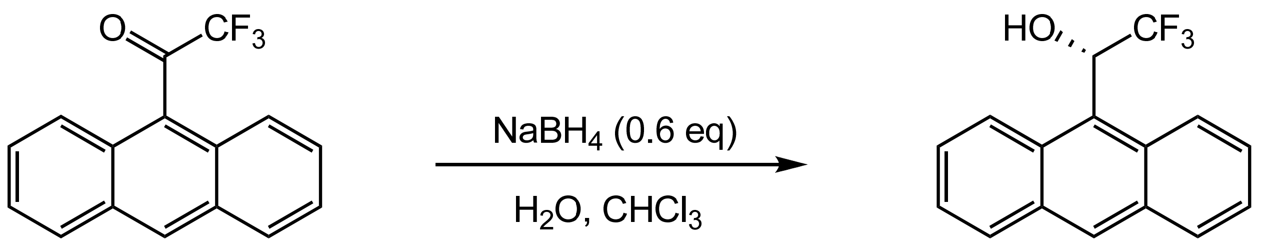




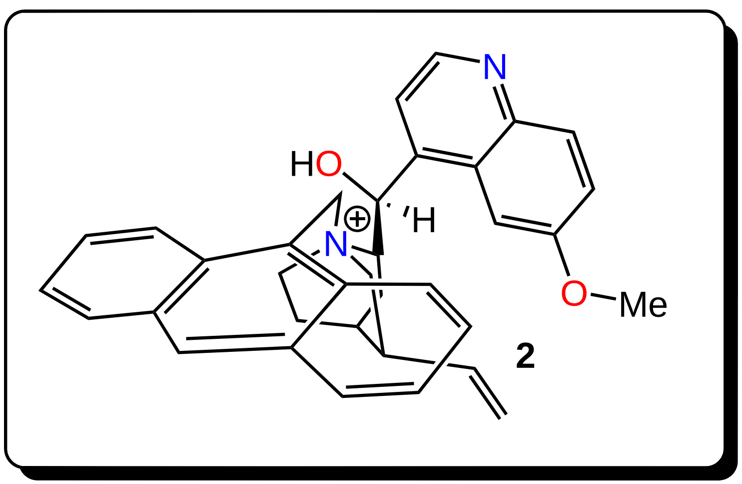


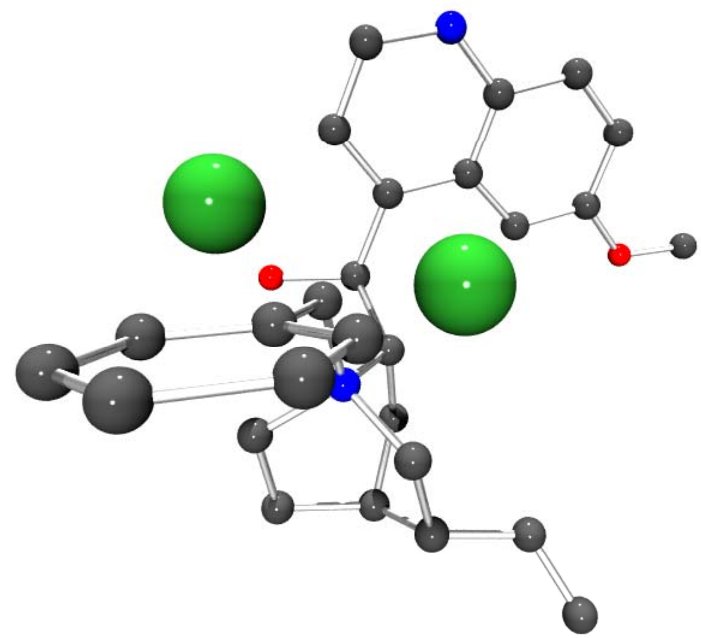
Pochapsky, T.C. *et al. J. Org. Chem.* **1999**, *64,* 8794

NOE Studies of Ion Pairing



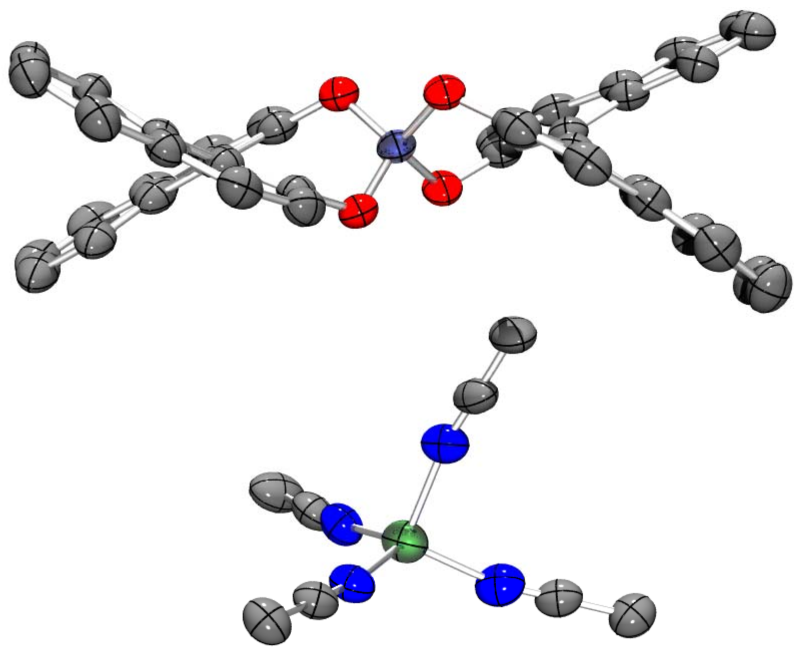
1 (10 mol%): 21% ee
2 (10 mol%): 30% ee





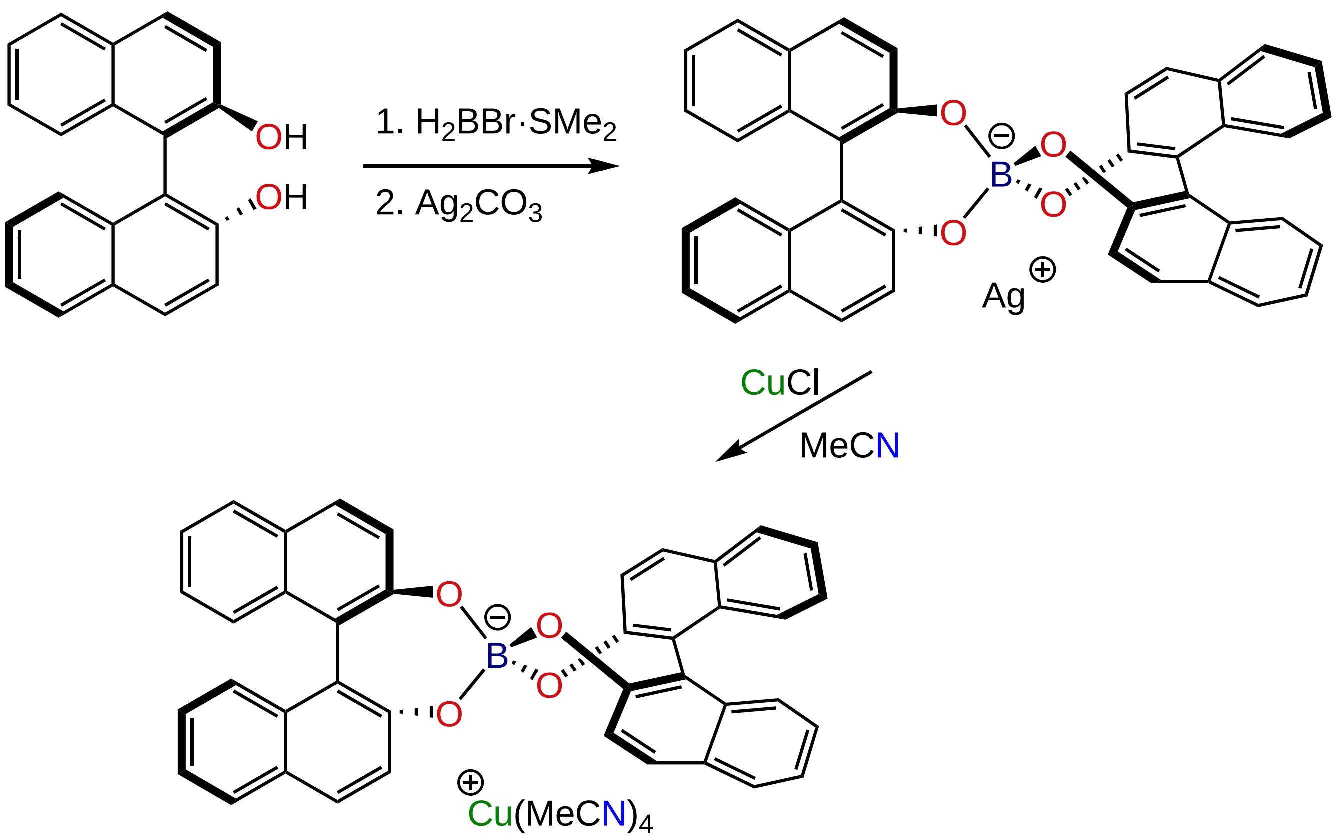
Pochapsky, T.C. *et al. J. Org. Chem.* **1999**, *64,* 8794

Transition Metal Catalysis



Chiral Borate Counterions

Design of a chiral counteranion for transition metal catalysts



Arndtsen, B. A. *et al. Org. Lett.* **2000**, *2*, 4165

Chiral Borate Counterions

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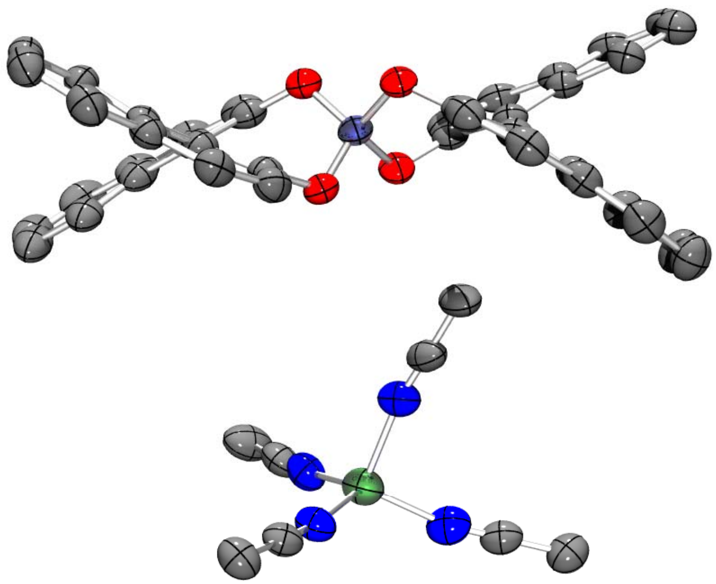
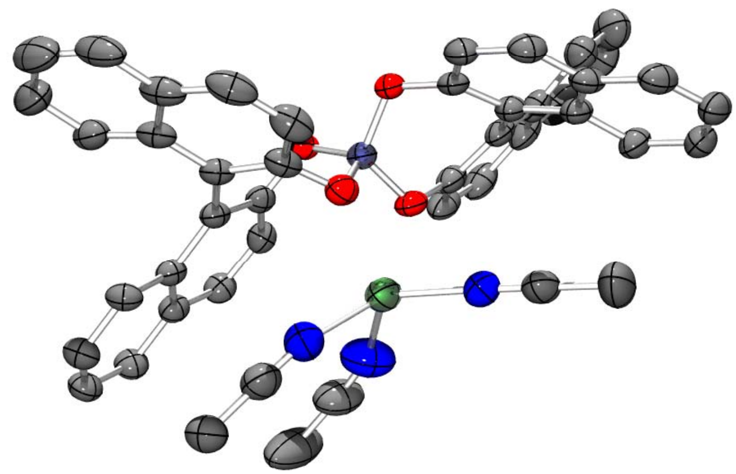
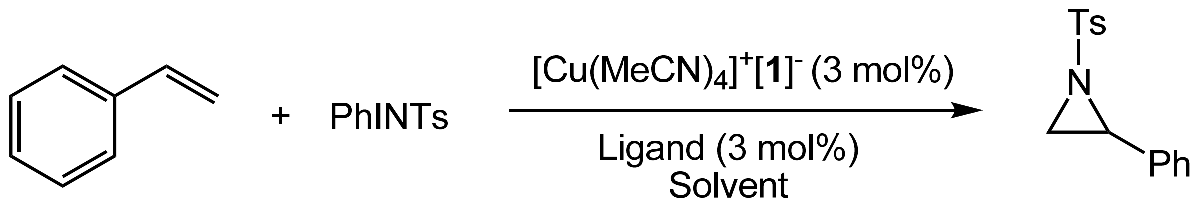


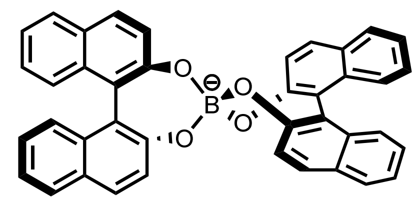


Arndtsen, B. A. *et al. Org. Lett.* **2000**, *2*, 4165

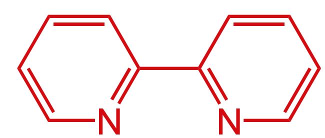
Chiral Borate Counterions



Ligand	Solvent	Yield (%)	ee (%)
MeCN	C_6H_6	86	7
2	C_6H_6	43	10
3	C_6H_6	90	2
MeCN	CH_2Cl_2	97	4
MeCN	MeCN	87	<1



1



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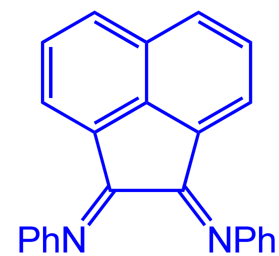
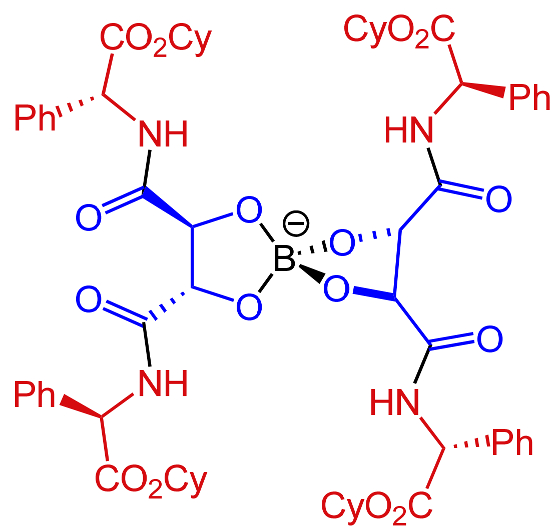


3

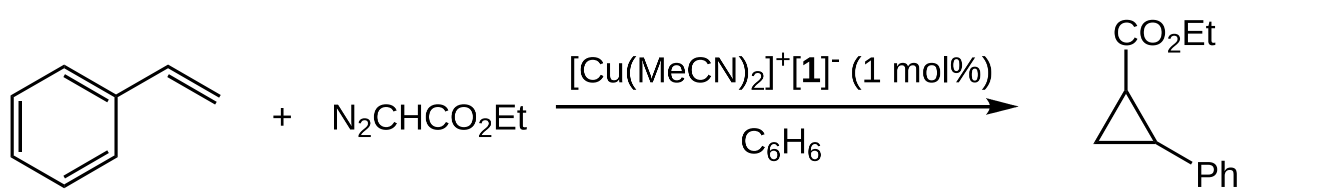
Modest enantioinduction was observed in aziridinations of olefins

Arndtsen, B. A. *et al. Org. Lett.* **2000**, *2*, 4165

Amino Acid Based Borate Counterions



1



trans: 20% (23% ee)
cis: 16% (19% ee)

- **A library of chiral counterions could be synthesized**
- **The amino acid fragments had a greater effect on enantioinduction than the tartrate fragments**

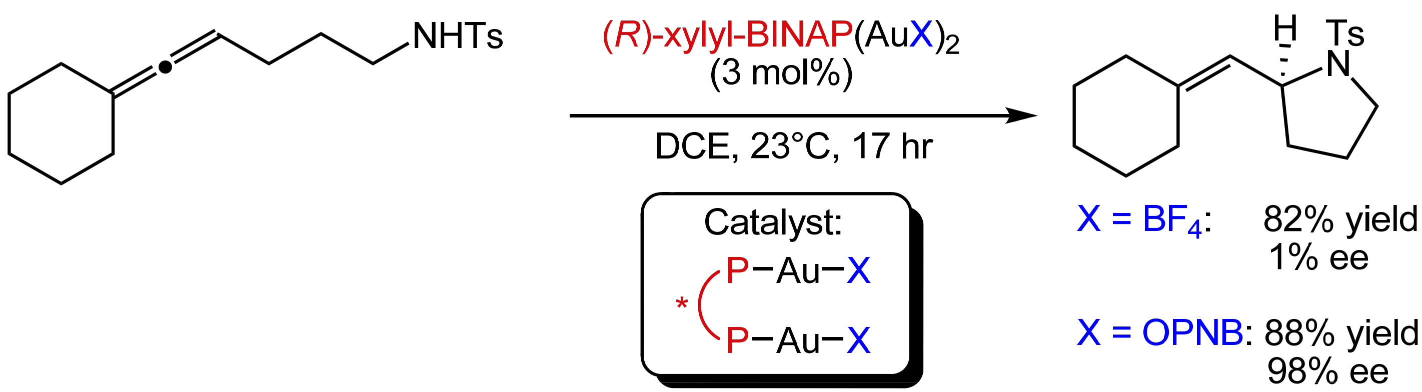
Arndtsen, B. A. *et al. Tetrahedron. Asymm.* **2005**, *16*, 1789

Asymmetric Gold Catalysis

Au(I) and Au(III) tend to adopt linear geometries

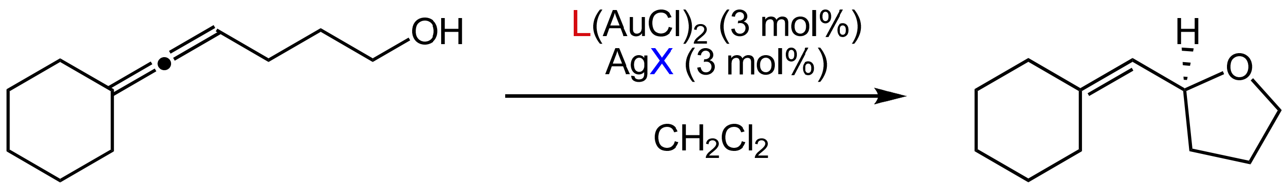
L*—Au—Substrate

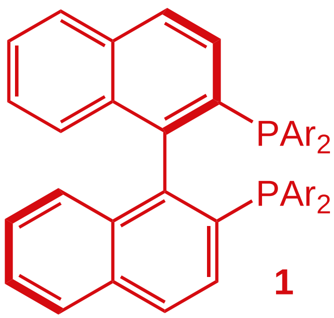
Asymmetric Induction is difficult when the chiral ligand is 180° from the substrate, however some examples are known:



Toste, F.D. *et al. J. Am. Chem. Soc.* **2005**, *129*, 2452

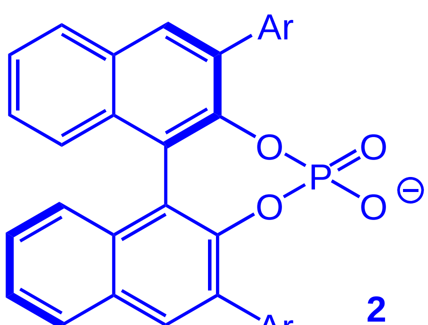
Phosphoric Acid Counterions





1

Ar = 3,5-Me-C_6H_3



2

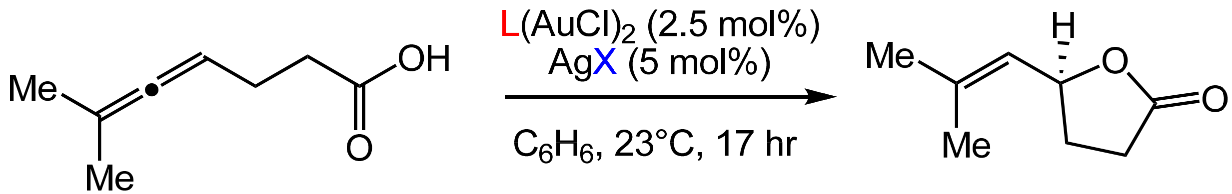
Ar = 2,4,6-(*i*-Pr)$_3$-C_6H_2

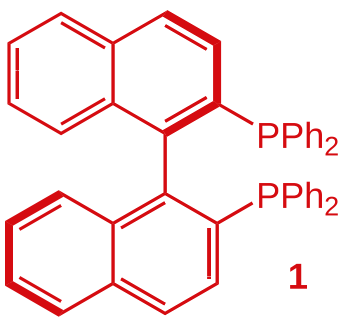
L	X	Solvent	Yield (%)	ee (%)
1	⊖OPNB (6 mol% AgX)	CH_2Cl_2	89	8
dppm	2	CH_2Cl_2	76	65
dppm	2	CH_3NO_2	60	18
dppm	2	C_6H_6	90	97

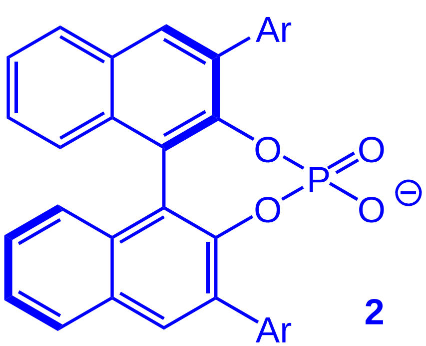
- **Traditional chiral ligands failed**
- **A chiral phosphoric acid counterion was successful in inducing chirality (97% ee)**

Toste, F.D. *et al. Science* **2007**, *317*, 497

Chiral Counterions with Chiral Ligands







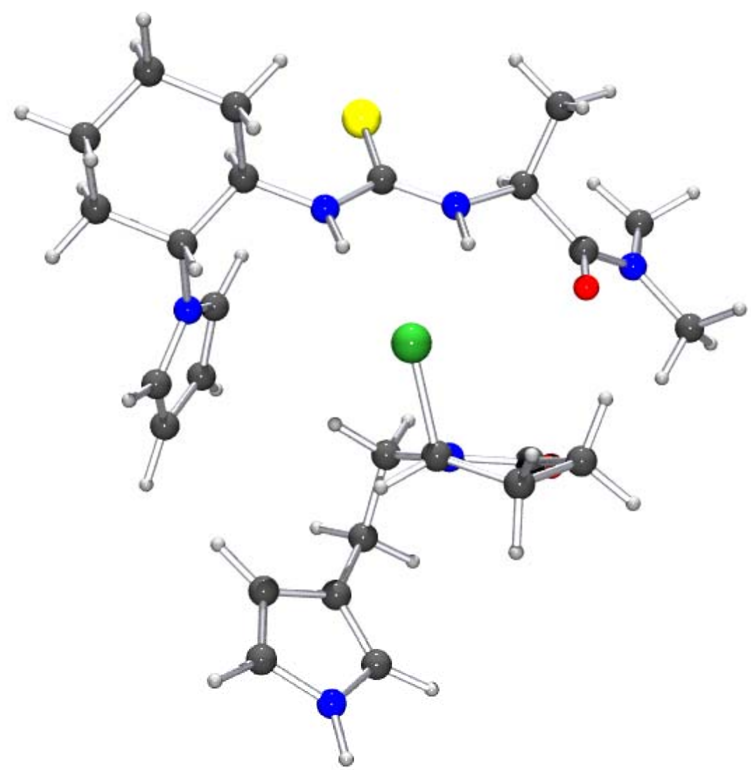
Ar = 2,4,6-(i-Pr)$_3$-C_6H_2

L	X	Yield (%)	ee (%)
1	$^{-}$OPNB	80	38
dppm	**2**	89	12
1	**2**	88	82

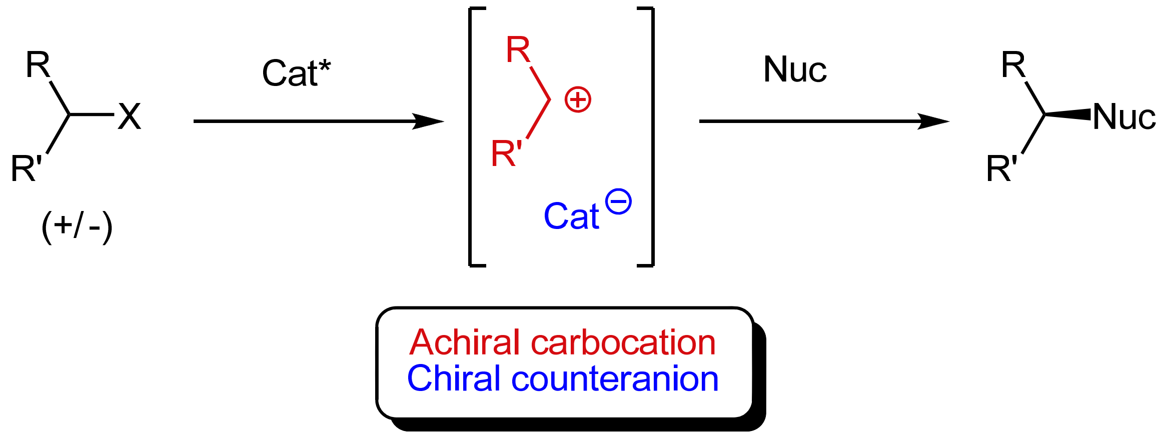
Together these two sources of chirality worked synergistically to give 82% ee.

Toste, F.D. *et al. Science* **2007**, *317*, 497

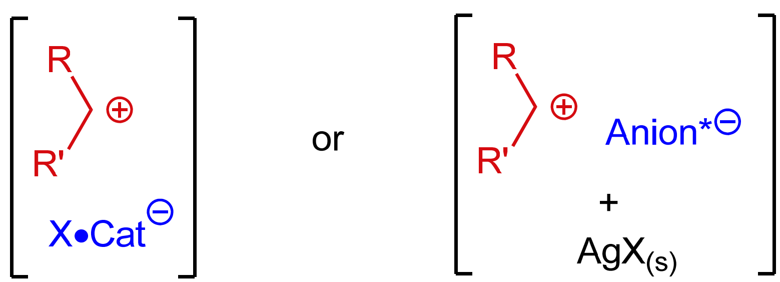
Organocatalysis



Anion Binding Catalysis

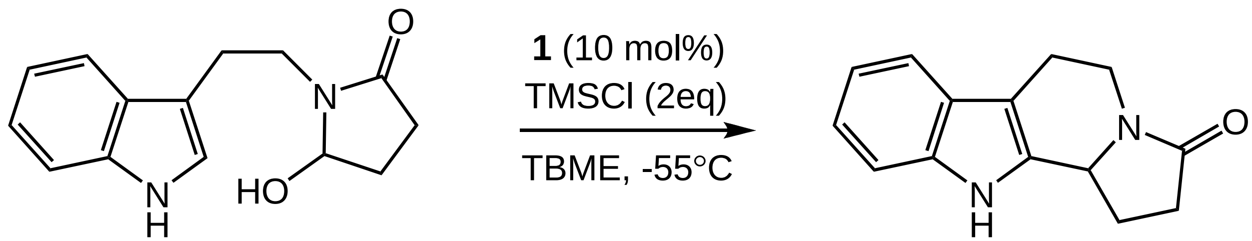


- Effectively an asymmetric S_N1 reaction
- The term 'Anion Binding Catalysis' coined by Eric Jacobsen
- Two possibilities:

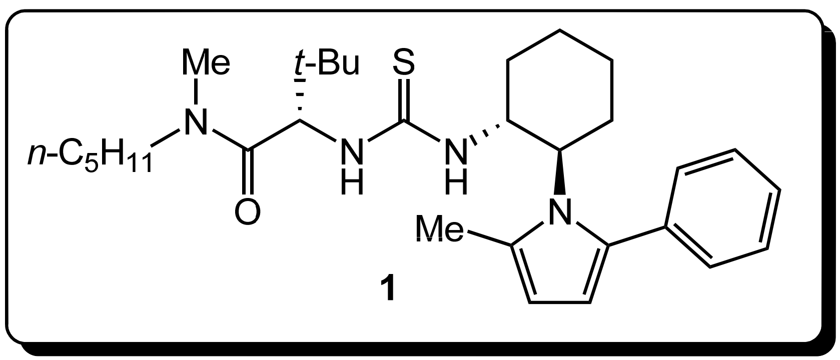


Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404

Thiourea Catalyzed Anion Binding

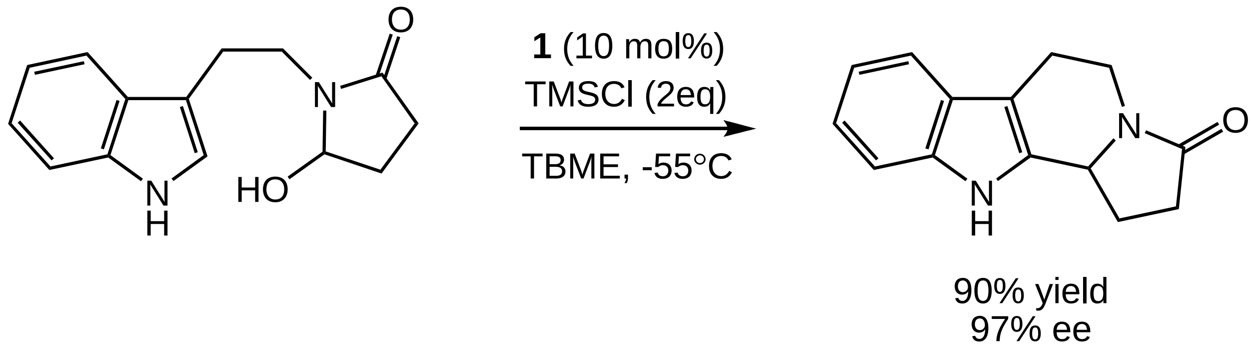


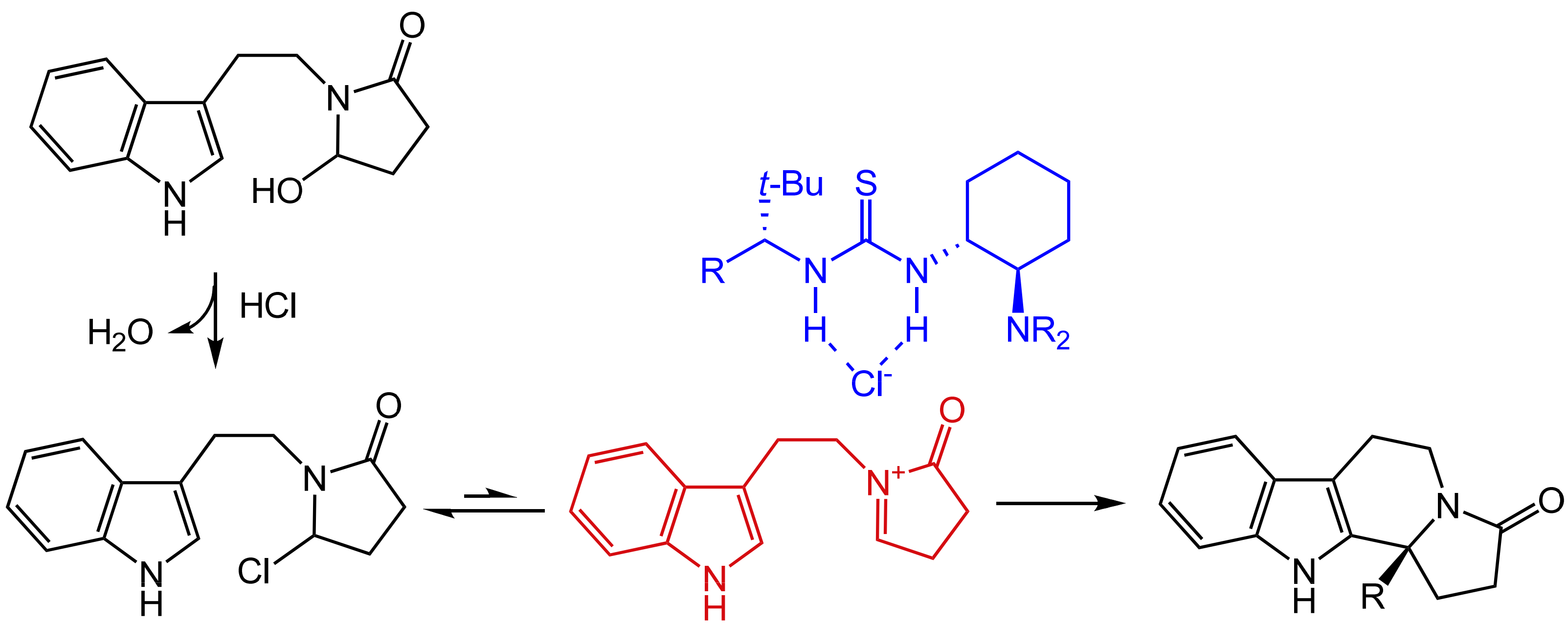
90% yield
97% ee



Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404

Thiourea Catalyzed Anion Binding

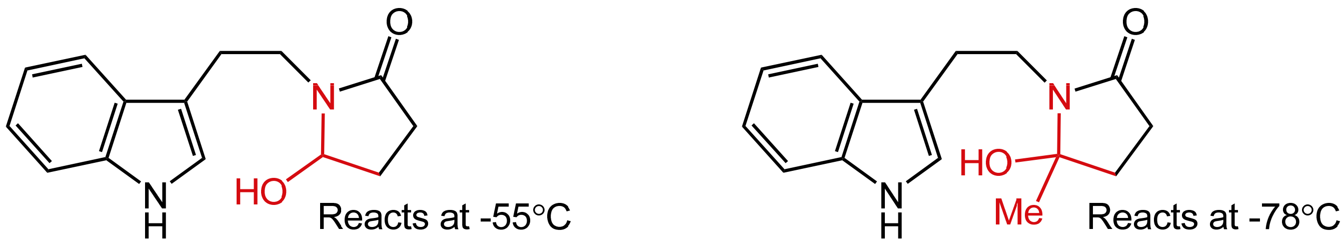




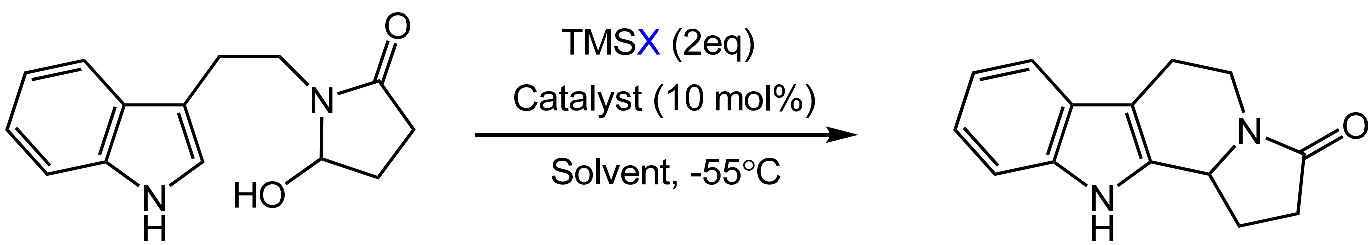
Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404

Thiourea Anion Binding - Mechanism

- **Reaction more effective for tertiary alcohol – supports an S_N1 mechanism**



- **A significant solvent and halide effect was observed**

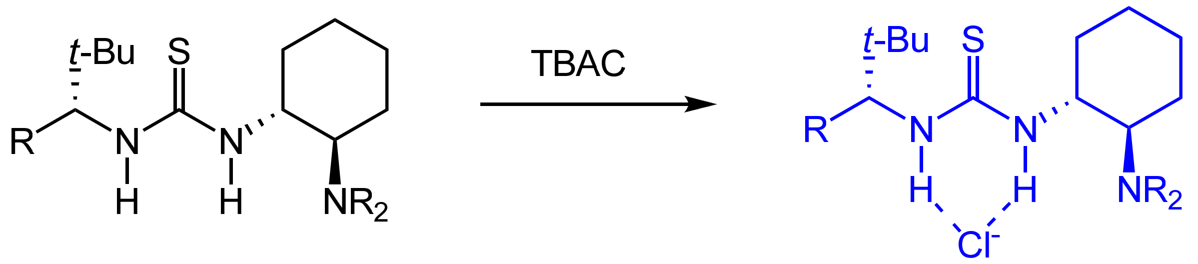


Solvent	Halide	Conversion (%)	ee (%)
TBME	Cl	80	97
TBME	Br	82	68
TBME	I	75	<5
CH_2Cl_2	Cl	>95	<5

Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404

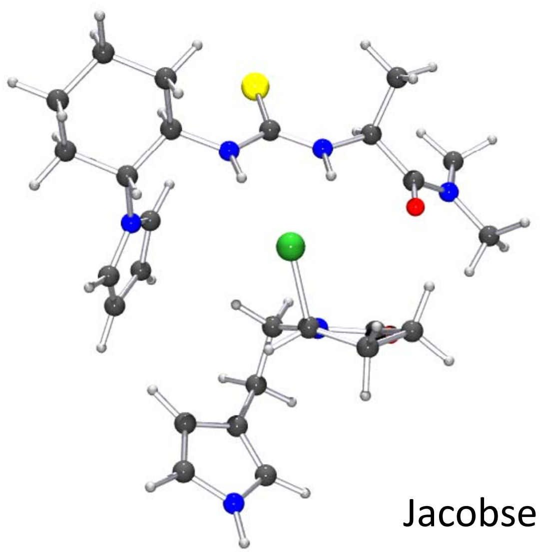
Thiourea Anion Binding - Mechanism

- **Treatment of thiourea with a chloride source causes a 0.56 ppm shift of N-H protons of the thiourea (Δppm : $Cl^- > Br^- > I^-$)**



(Assignment by ^{1}H NMR)

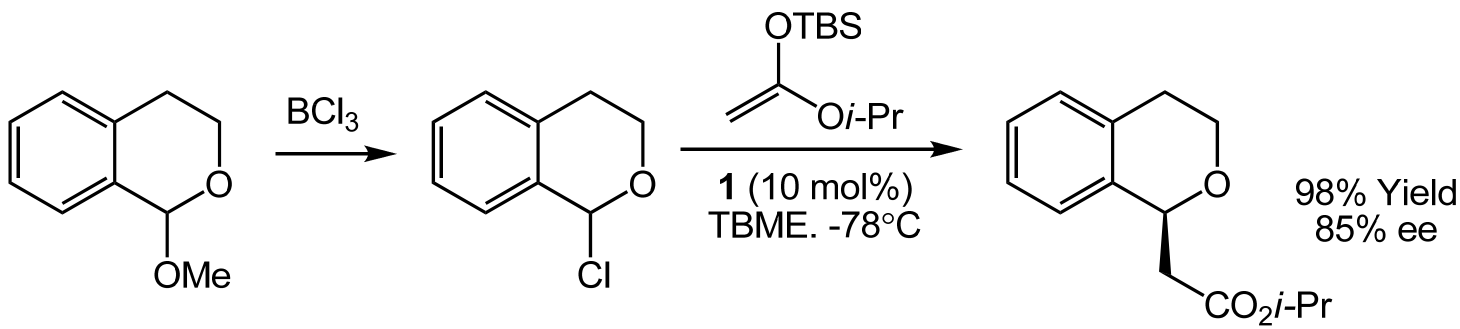
- **DFT calculations (B3LYP/6-31G(d)) indicate interactions between the thiourea and the chloride.**

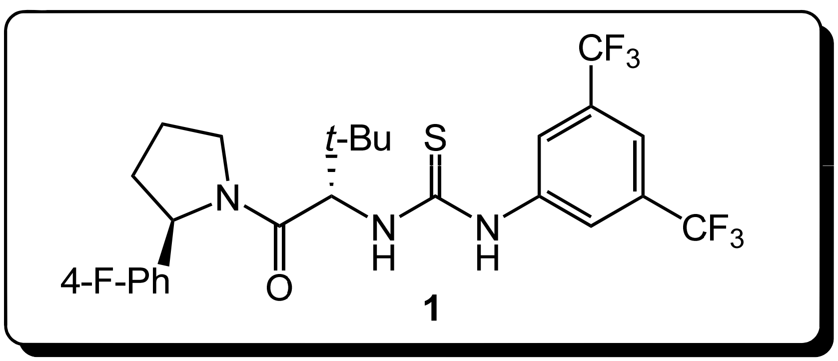


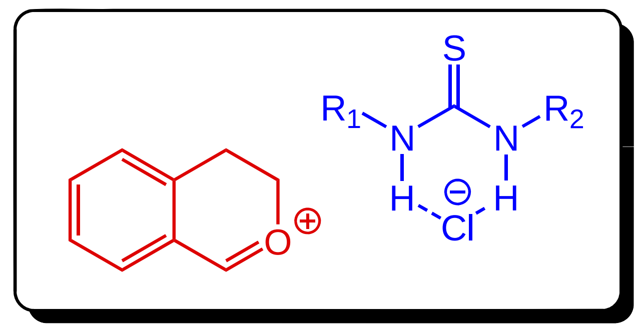
- **No minimum could be optimized with the thiourea bound to the N-acyliminium ion**

Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404

Thiourea Anion Binding - Oxocarbeniums



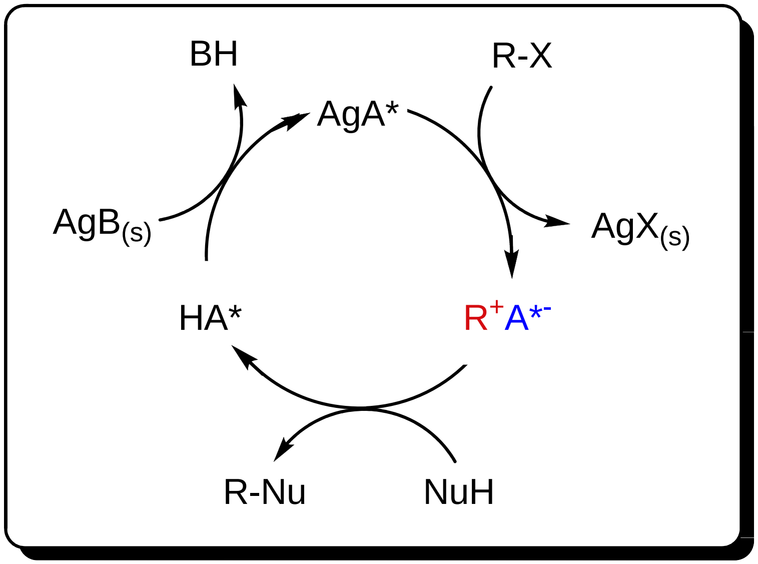


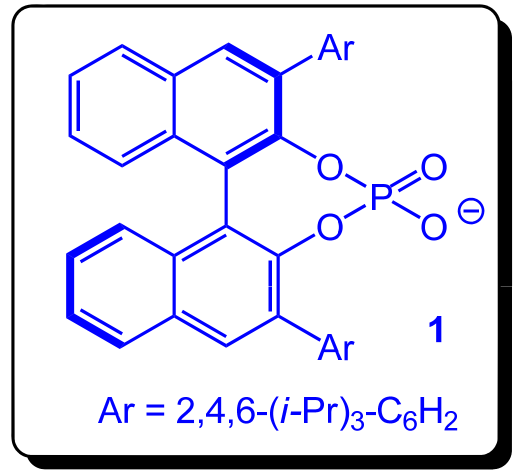


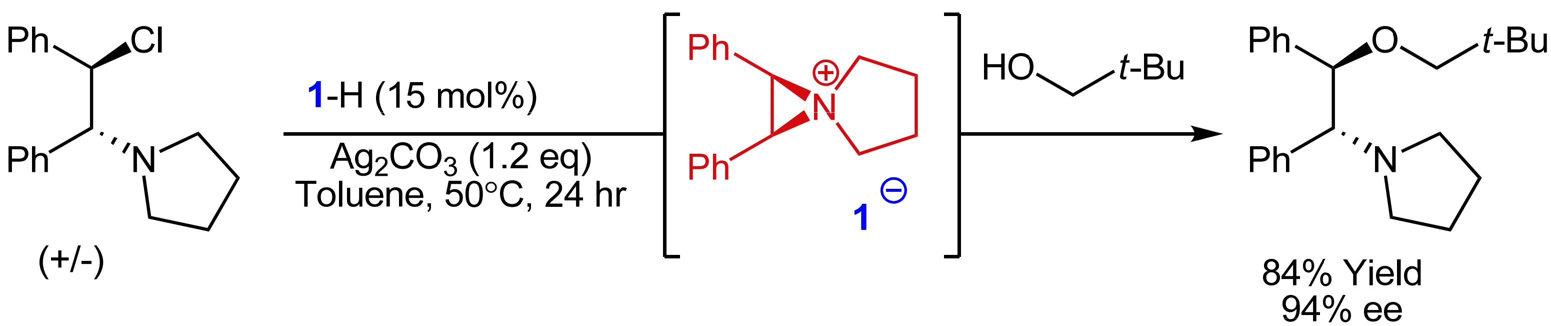
- An efficient DYKAT process involving oxocarbenium ions
- 10 mol% *n*-BuN_4Cl was found to shut down the reaction

Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2008**, *130*, 7198

Silver Mediated Halide Abstraction Catalysis



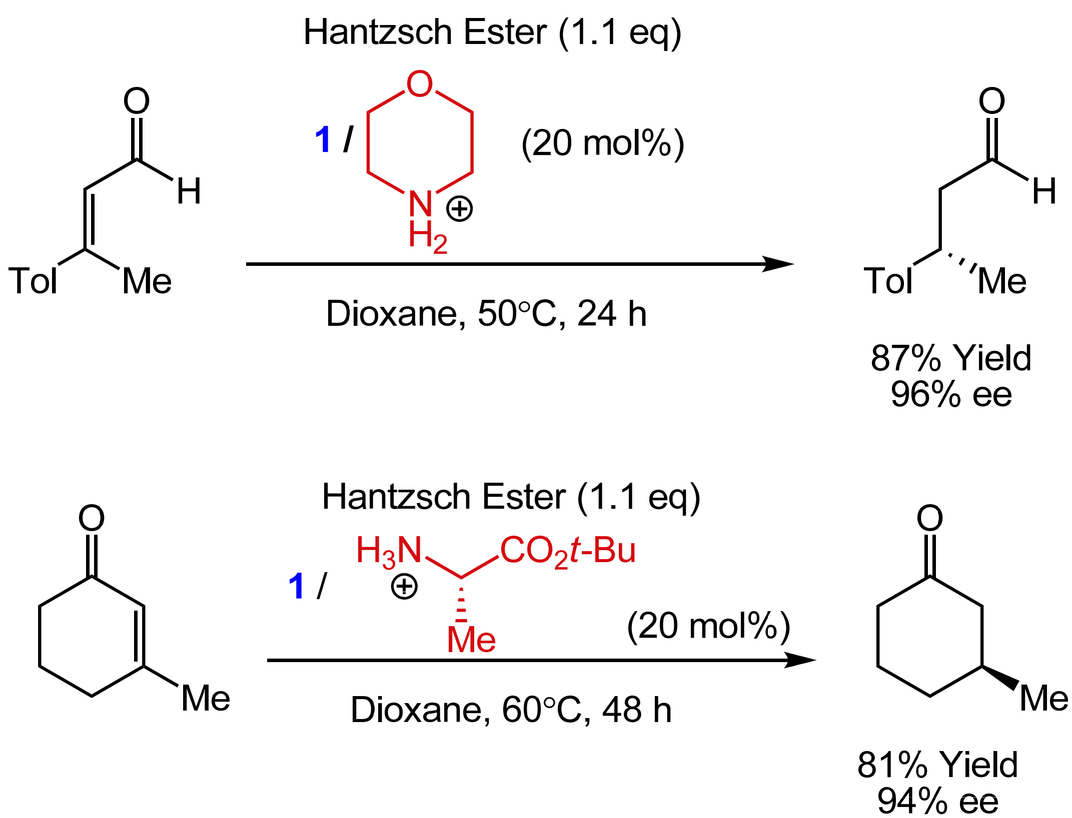


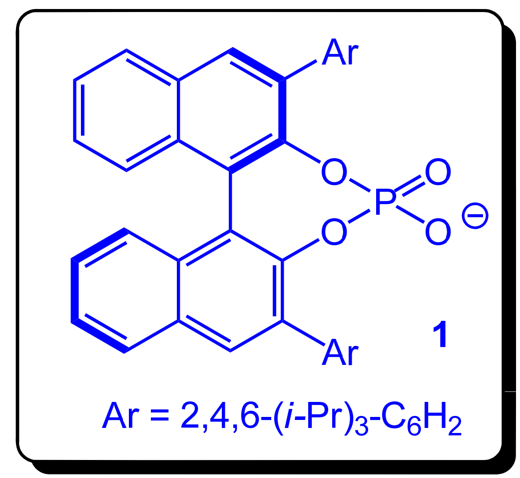


Effective chiral discrimination of a meso aziridinium ion

Toste, F.D. *et al. J. Am. Chem. Soc.* **2008**, *130*, 14984

Transfer Hydrogenation



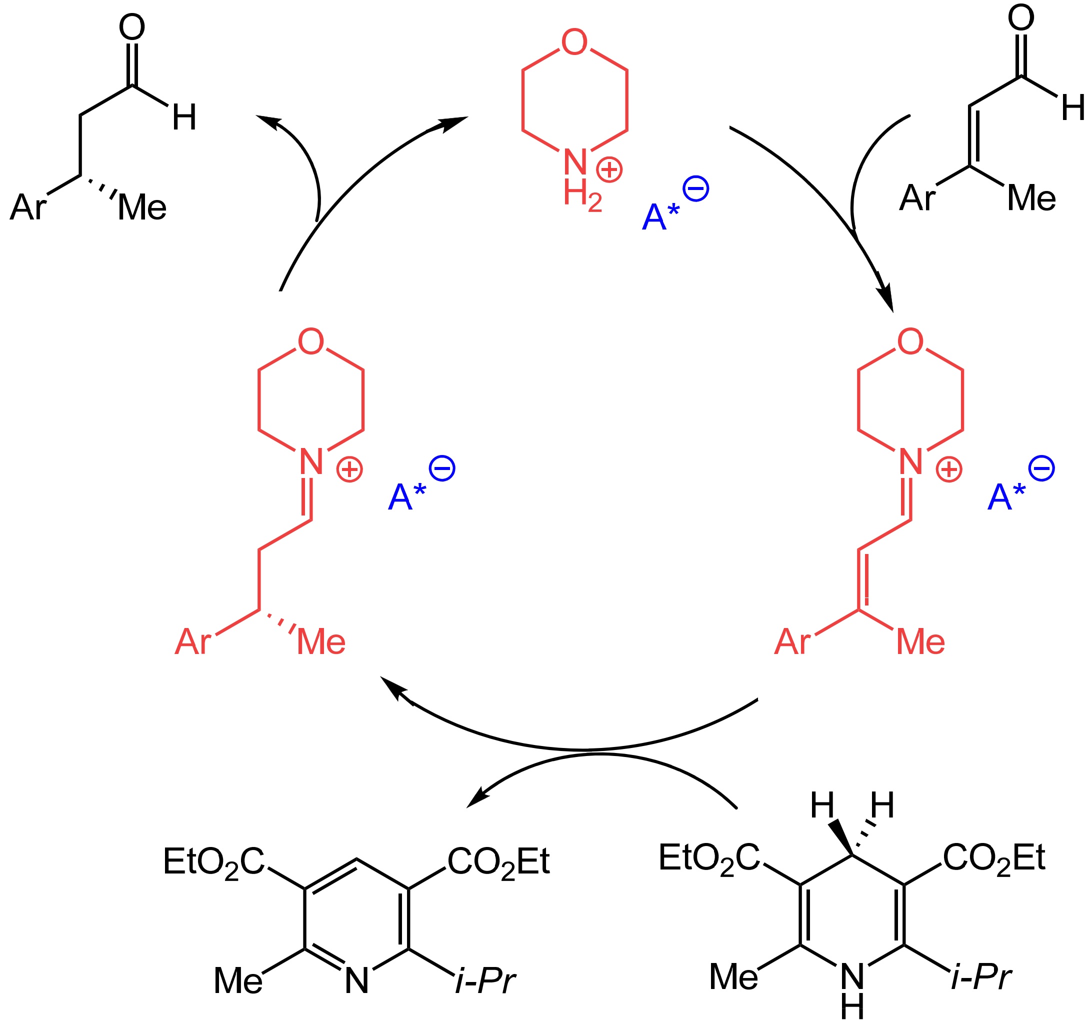


- **List coined the term 'Asymmetric Counteranion-Directed Catalysis' (ACDC)**

List, B. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 4193

List, B. *et al. J. Am. Chem. Soc.* **2006**, *128*, 13368

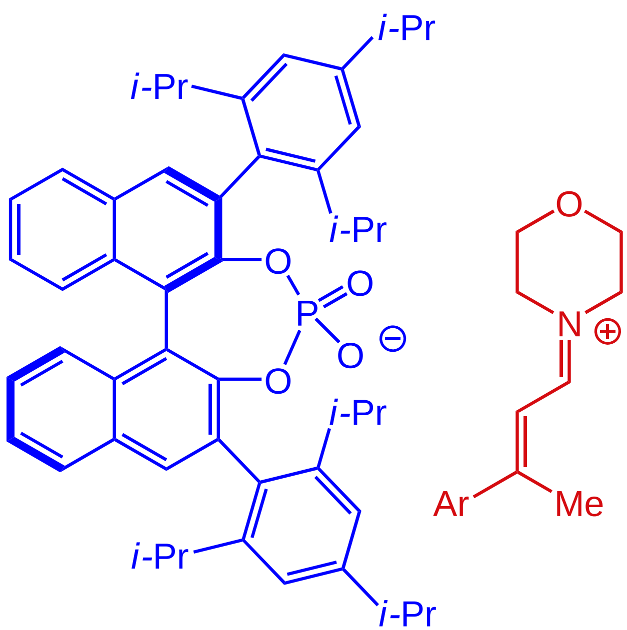
Transfer Hydrogenation Mechanism



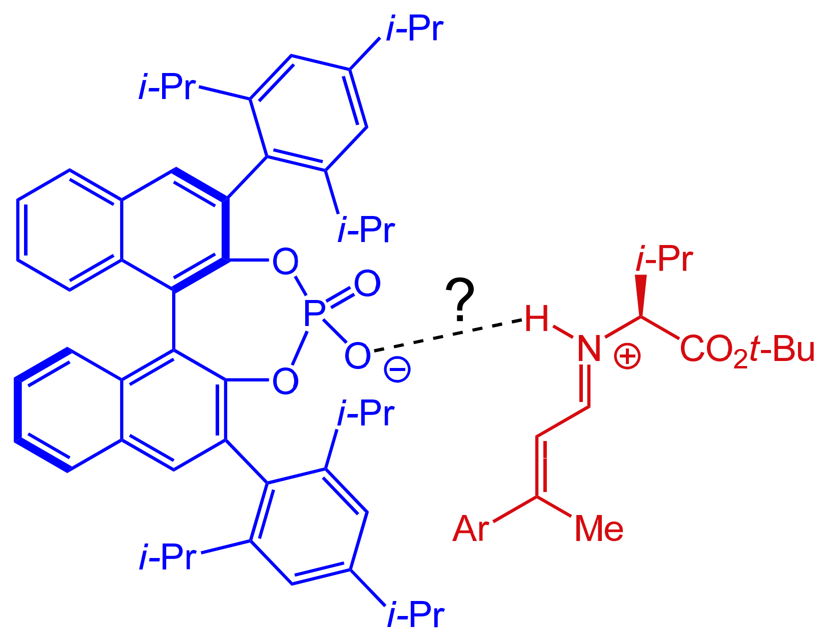
Complementary to traditional iminium ion catalysis

List, B. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 4193

Brønsted Acid versus Chiral Counterion



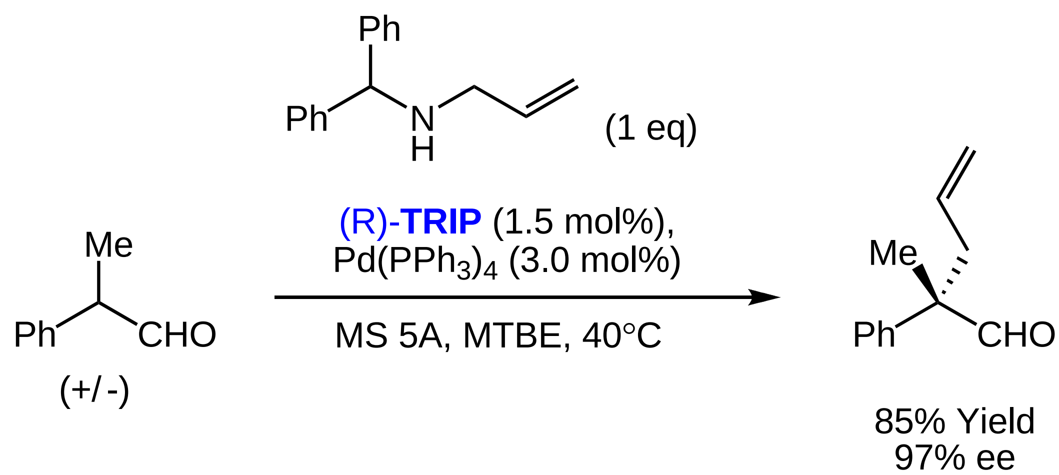
Ion Pair

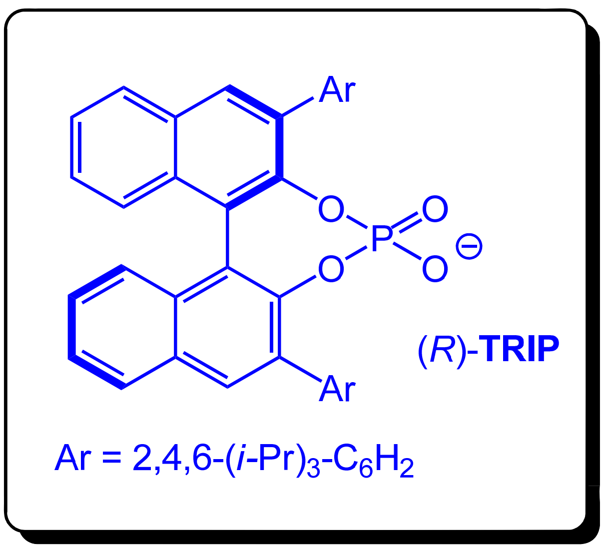


Ion Pair or H-bond?

In some cases, the distinction between Brønsted Acid and Chiral Counterion Catalysis can be difficult to distinguish.

Organo- and Transition Metal Catalysis

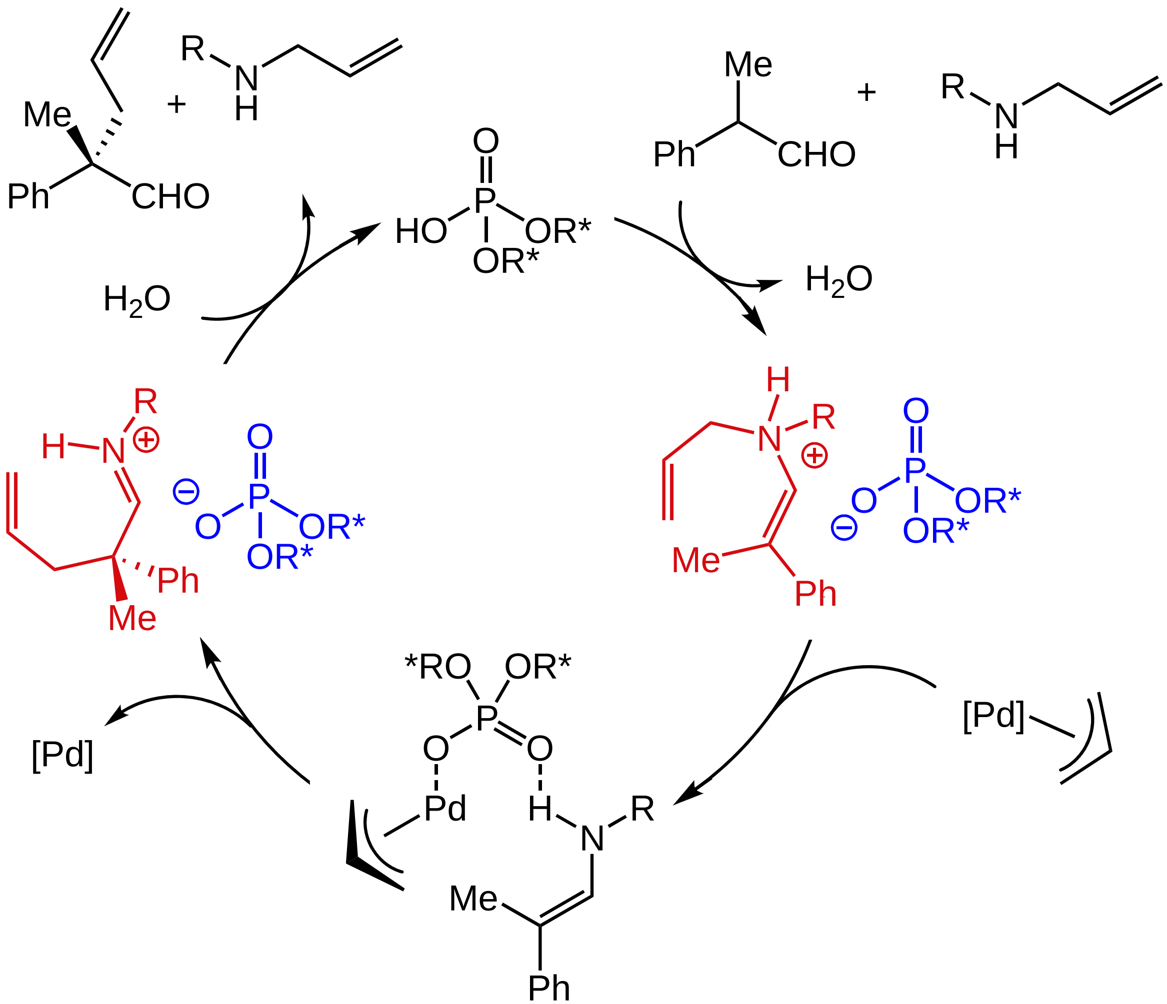




- **A novel combination of different modes of catalysis**
- **Secondary amine acts as a reagent and a catalyst**
- **Role of the counterion?**

List, B. *et al. J. Am. Chem. Soc.* **2007**, *129*, 11336

Organo- and Transition Metal Catalysis



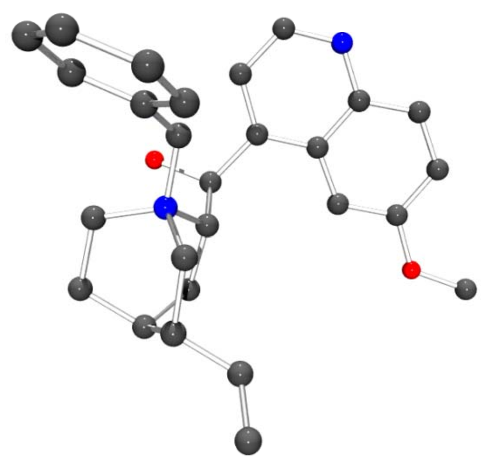
Phosphoric acid acts as both a counterion and an anionic ligand

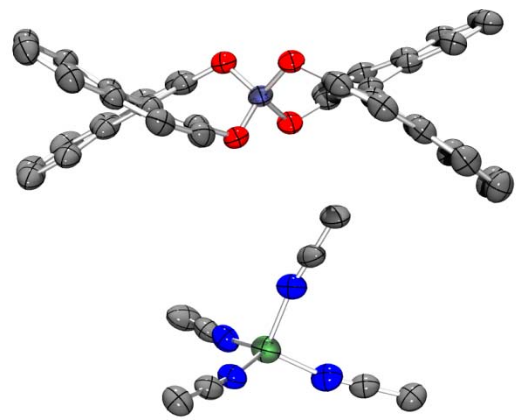
List, B. *et al. J. Am. Chem. Soc.* **2007**, *129*, 11336

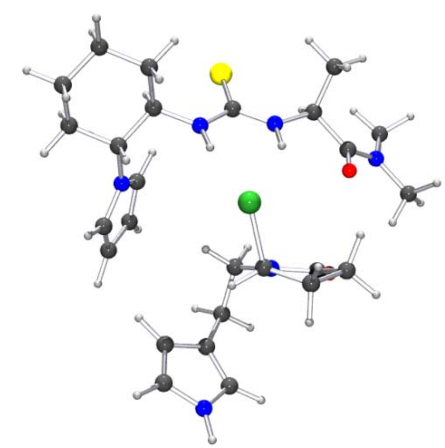
Conclusion

• **Many examples of efficient chiral induction using chiral counterions:**

Phase Transfer Catalysis **Transition Metal Catalysis** **Organocatalysis**







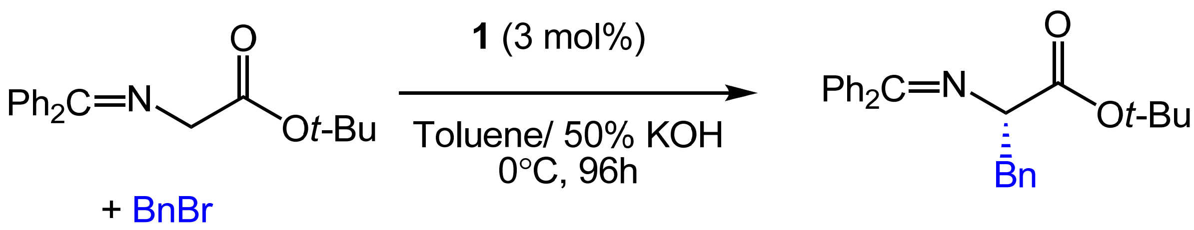
• **We can expect more chemistry using chiral counterions in the future**

• **More mechanistic information will be required for rational design**

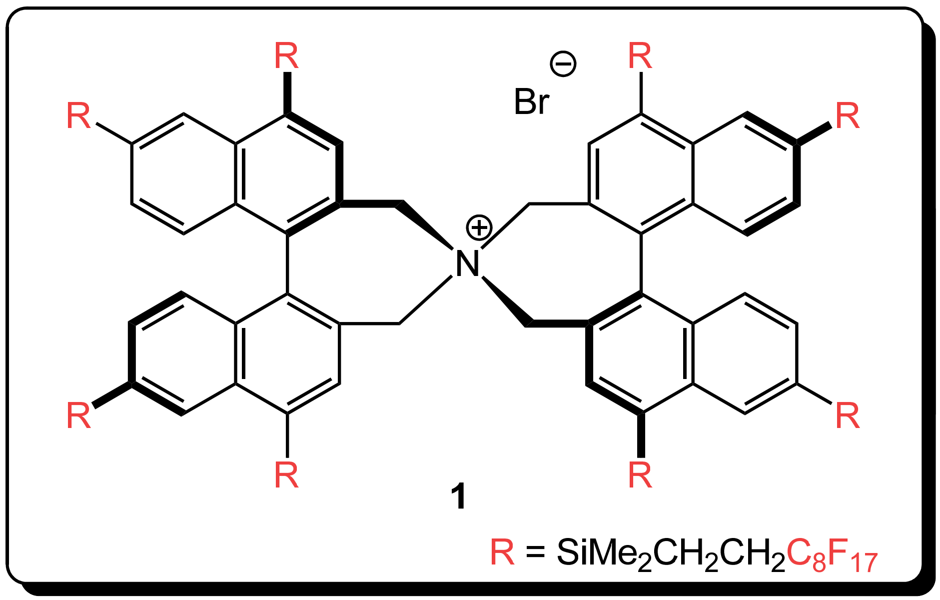
Acknowledgements

Prof. Vy Dong
The Dong Group

Recyclable Phase Transfer Catalysts

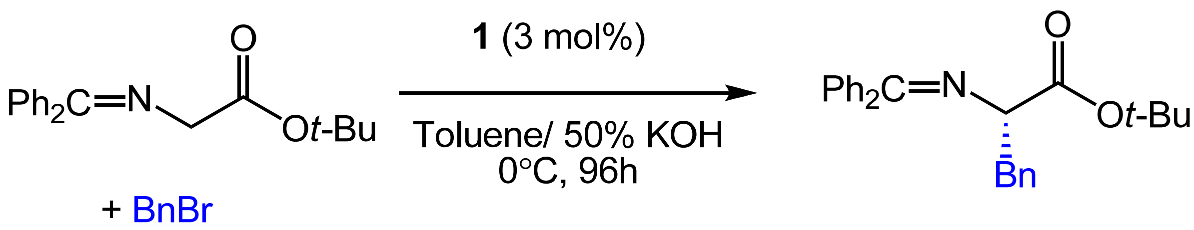


First reaction: 82%, 90% ee
Second reaction: 79%, 92% ee
Third reaction: 81%, 92% ee



Maruoka, K. *et al. Org. Lett.* **2004**, *6*, 1429

Recyclable Phase Transfer Catalysts



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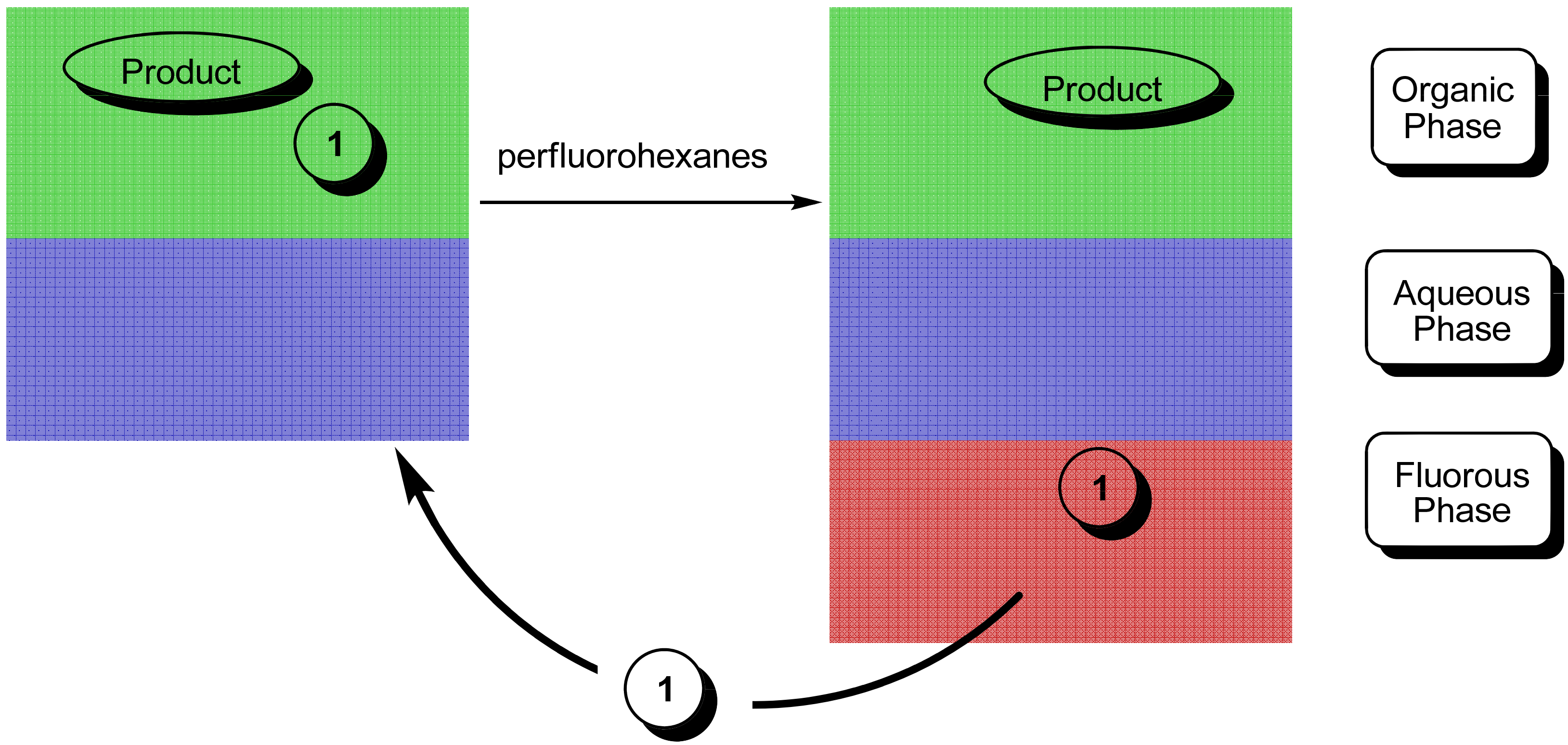
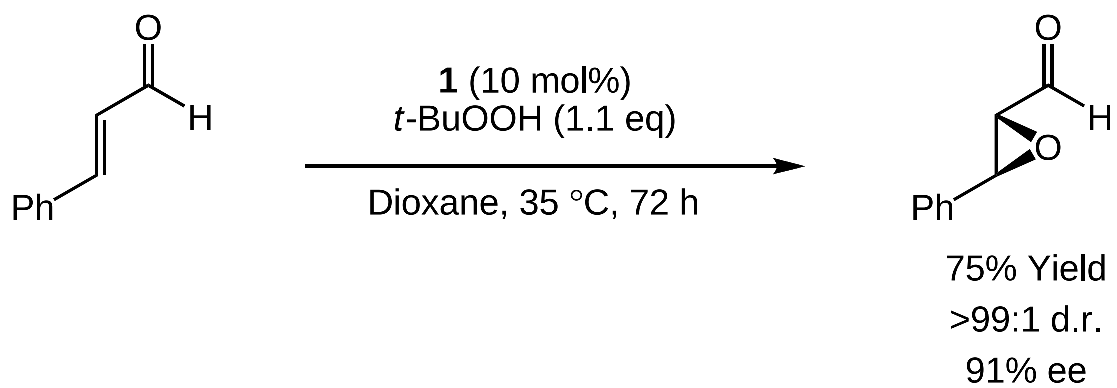
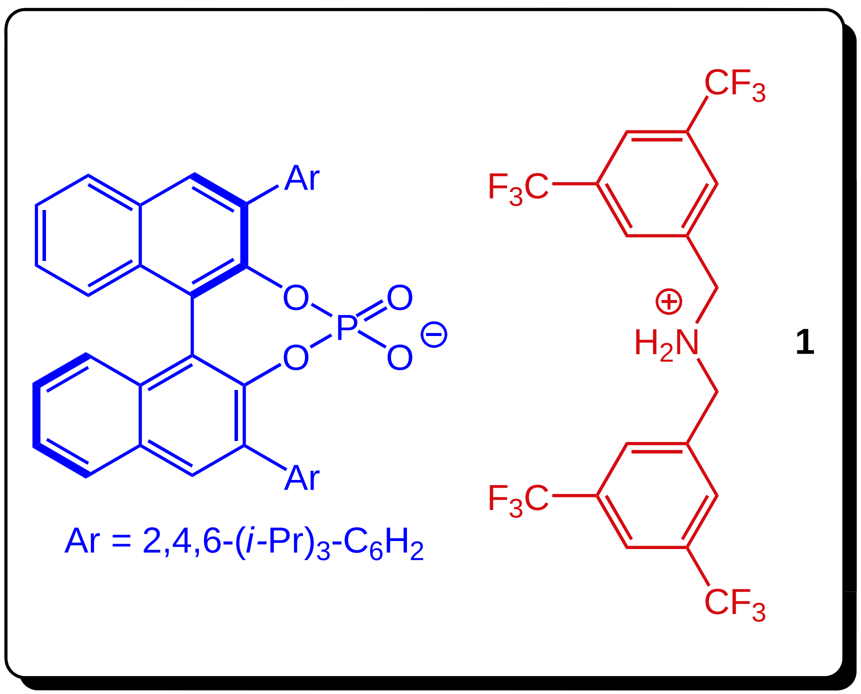


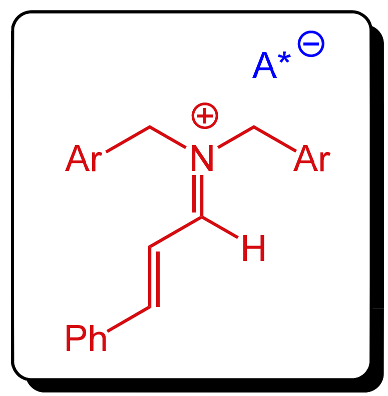
Maruoka, K. *et al. Org. Lett.* **2004**, *6*, 1429

Epoxidation with Chiral Anions



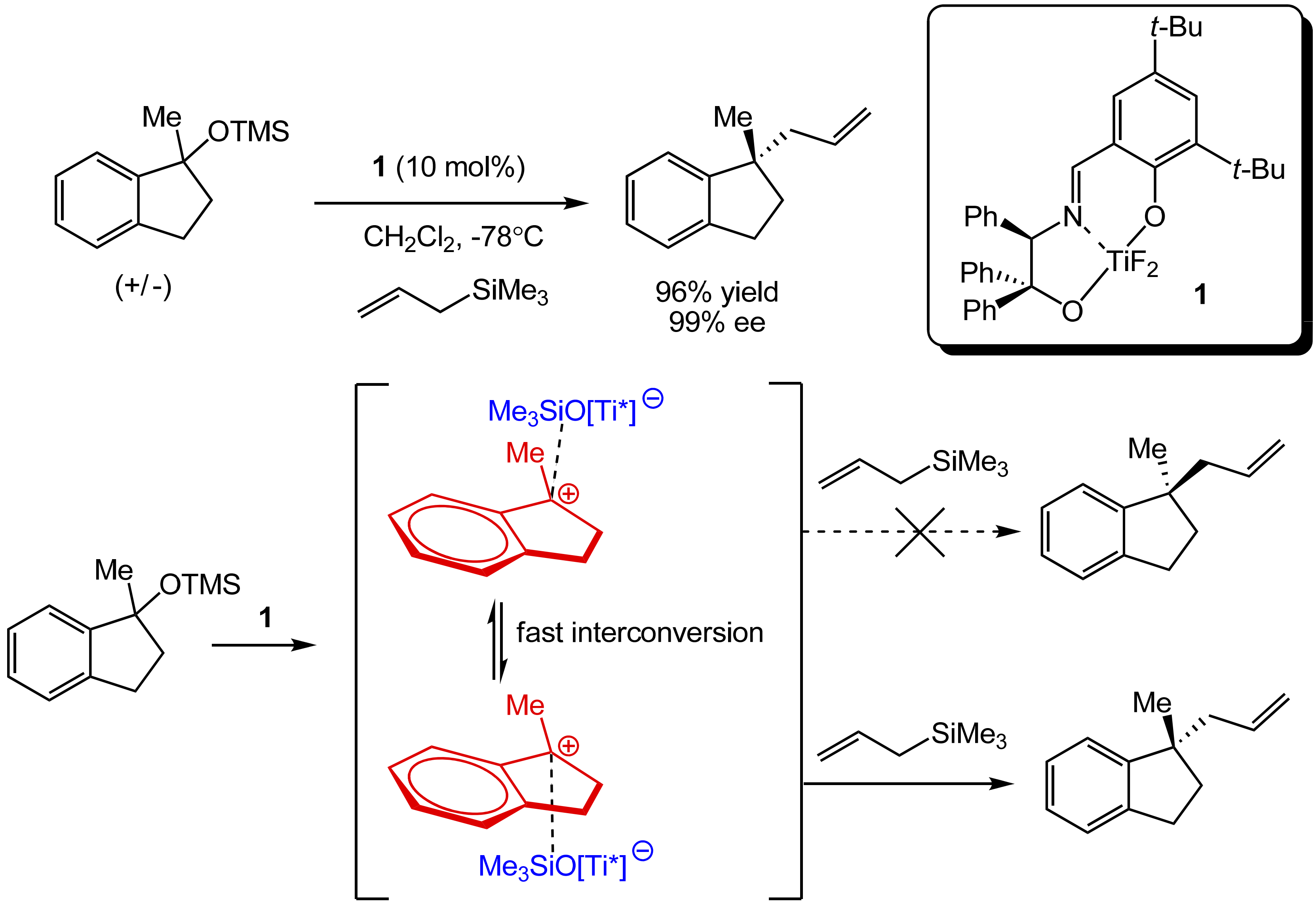


- **This strategy has been extended to epoxidation of α,β-unsaturated aldehydes, involving an iminium ion with a chiral counterion**



List, B. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 1119

Lewis Acid Catalyzed DYKAT



Braun, M. *et al. Angew. Chem. Int. Ed.* **2004,** *43*, 514