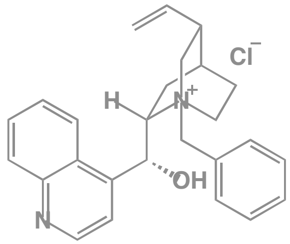
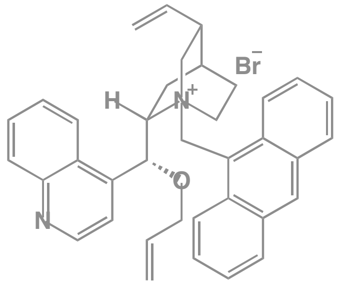
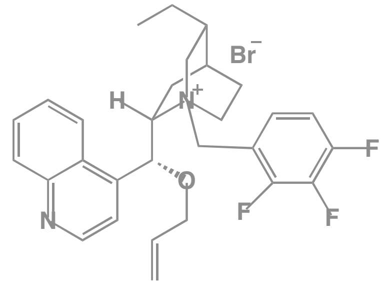
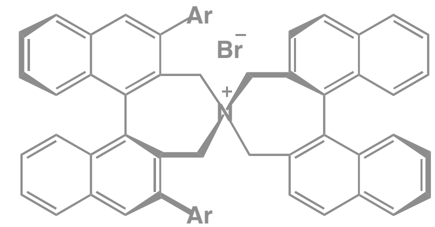
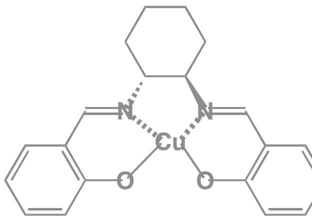


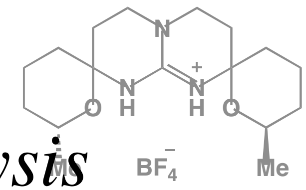








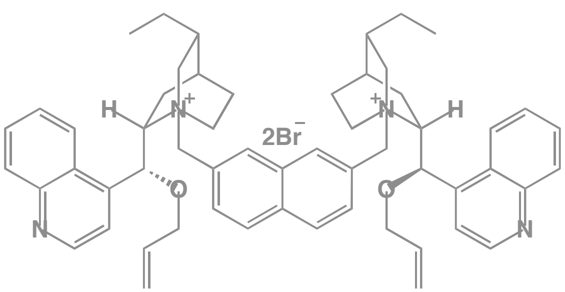
Recent Advances in Asymmetric Phase-Transfer Catalysis

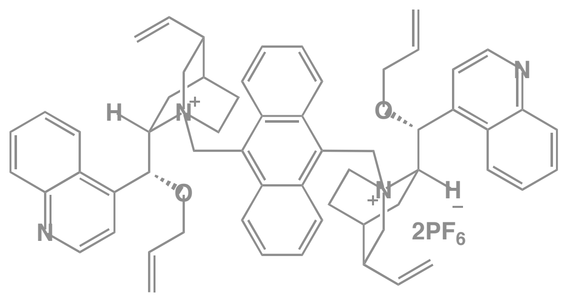


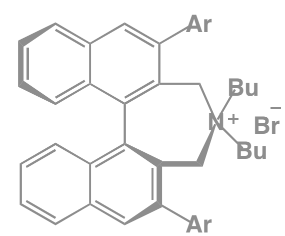
9 May 2011

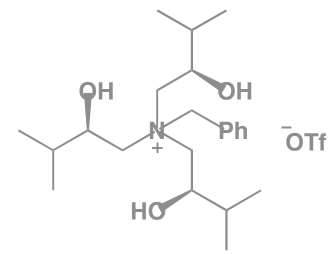
Stoltz/Reisman Literature Group Meeting

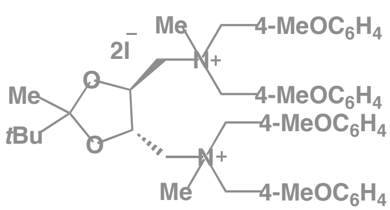
Jimin Kim

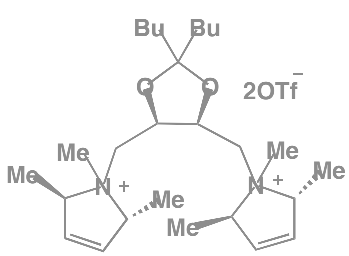


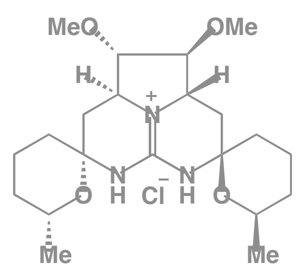


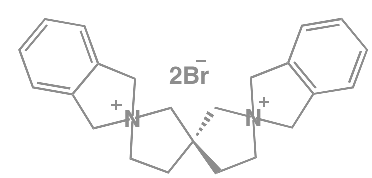








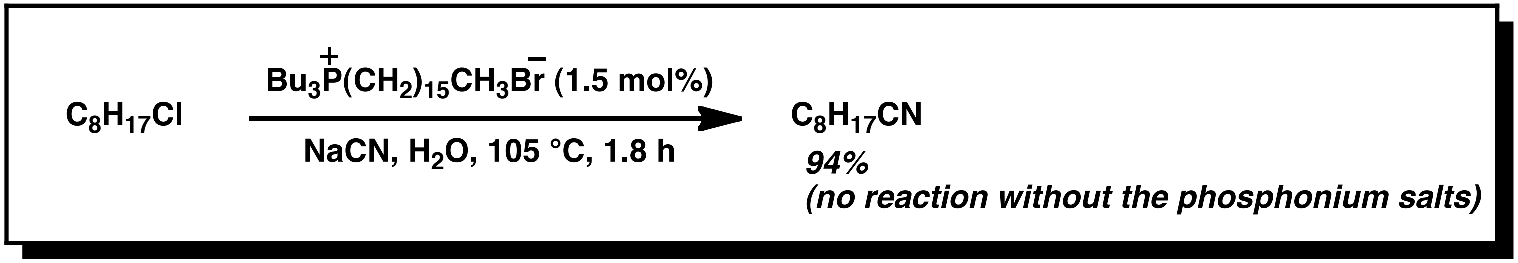


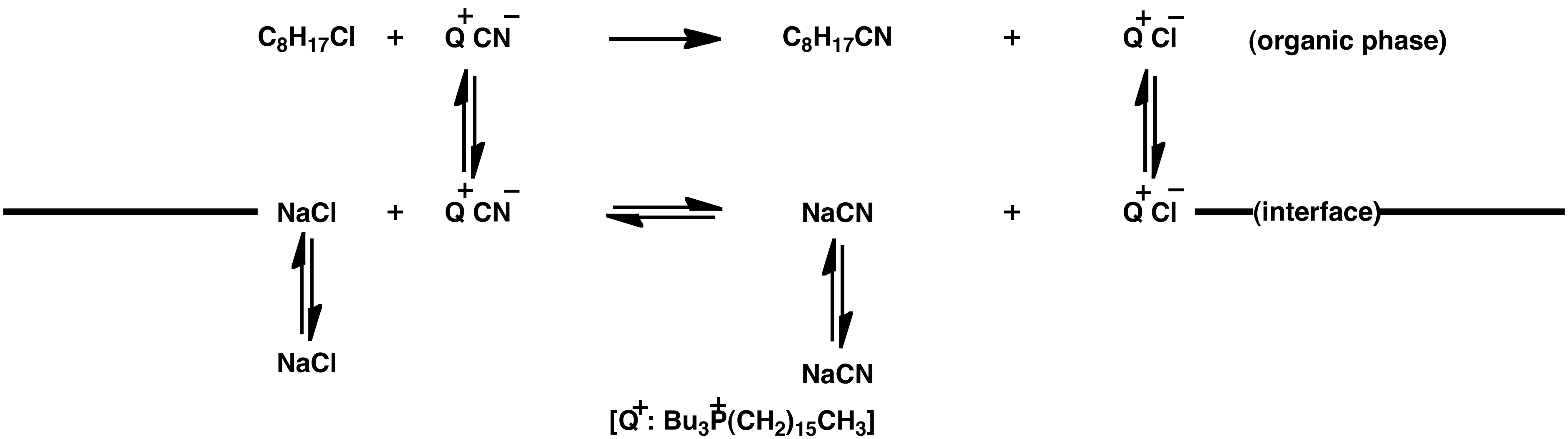


Outline

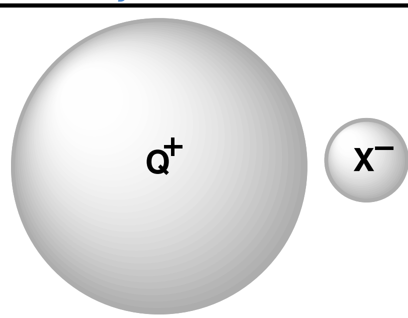
- Introduction of Phase-Transfer Catalysis
  : General Mechanism of Asymmetric PTC
- Asymmetric Alkylation
- Michael Addition
- Aldol Reaction
- Mannich Reaction
- Epoxidation
- Fluorination and Strecker Reaction

Introduction of Phase-Transfer Catalysis





quaternary onium salt



$Q^+ \equiv R_4N^+, R_4P^+$

organic soluble

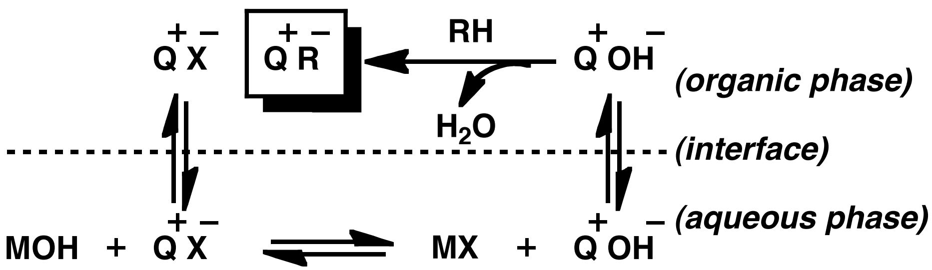
large ionic radius

ready structural modification

Starks, *J. Am. Chem. Soc.* **1971**, *93*, 195–199.

Generation of Reactive Onium Carbanion Species

Starks Extraction Mechanism



Distribution of the PTC between the organic and aqueous phases

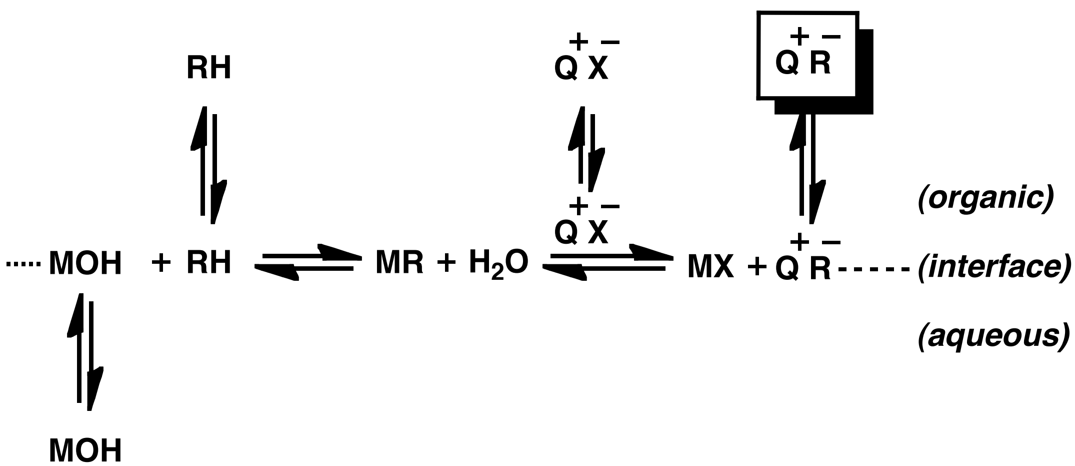
Equilibration of the PTC with the inorganic base in the aqueous phase

Extraction of hydroxide into the organic phase

Abstraction of hydrogen from the acidic organic compound by the onium hydroxide

ex) asymmetric epoxidation

Makosza Interfacial Mechanism



Formation of metal carbanion at the interface without the PTC

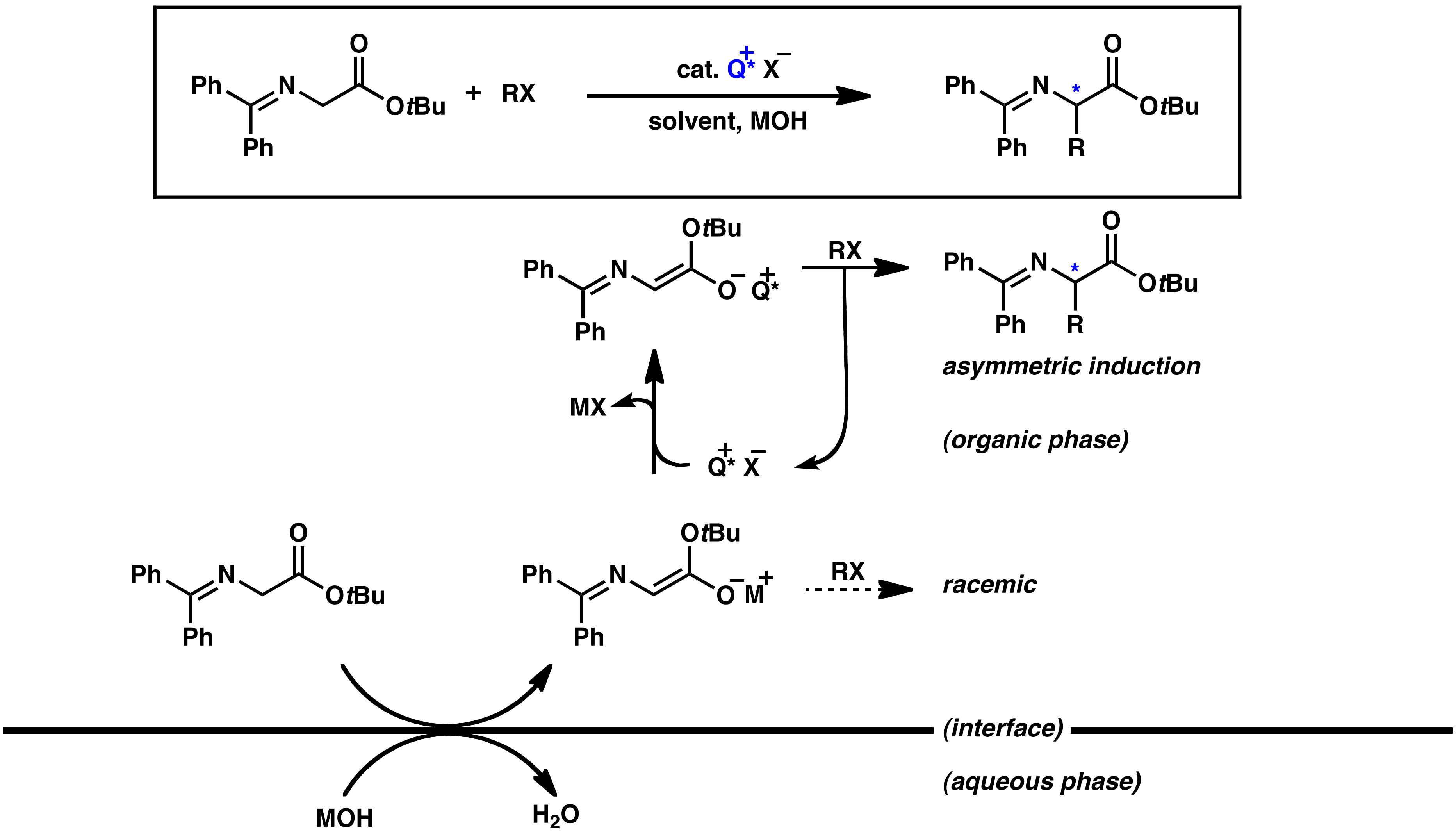
Extraction of the formed carbanion species from the interface into the organic phase by the action of PTC

ex) asymmetric alkylation

Review: Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

General Mechanism for the Asymmetric Alkylation

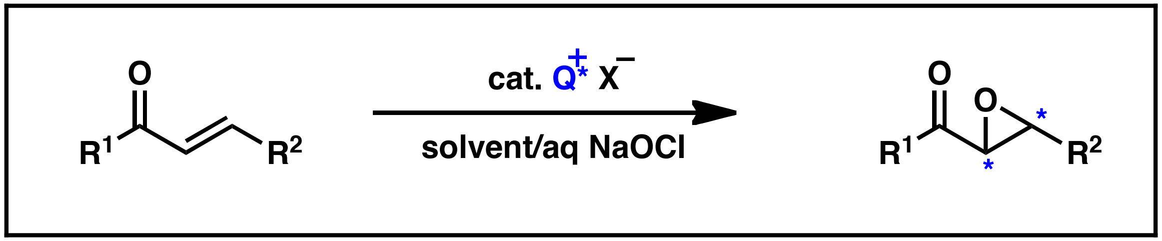
Interfacial Mechanism

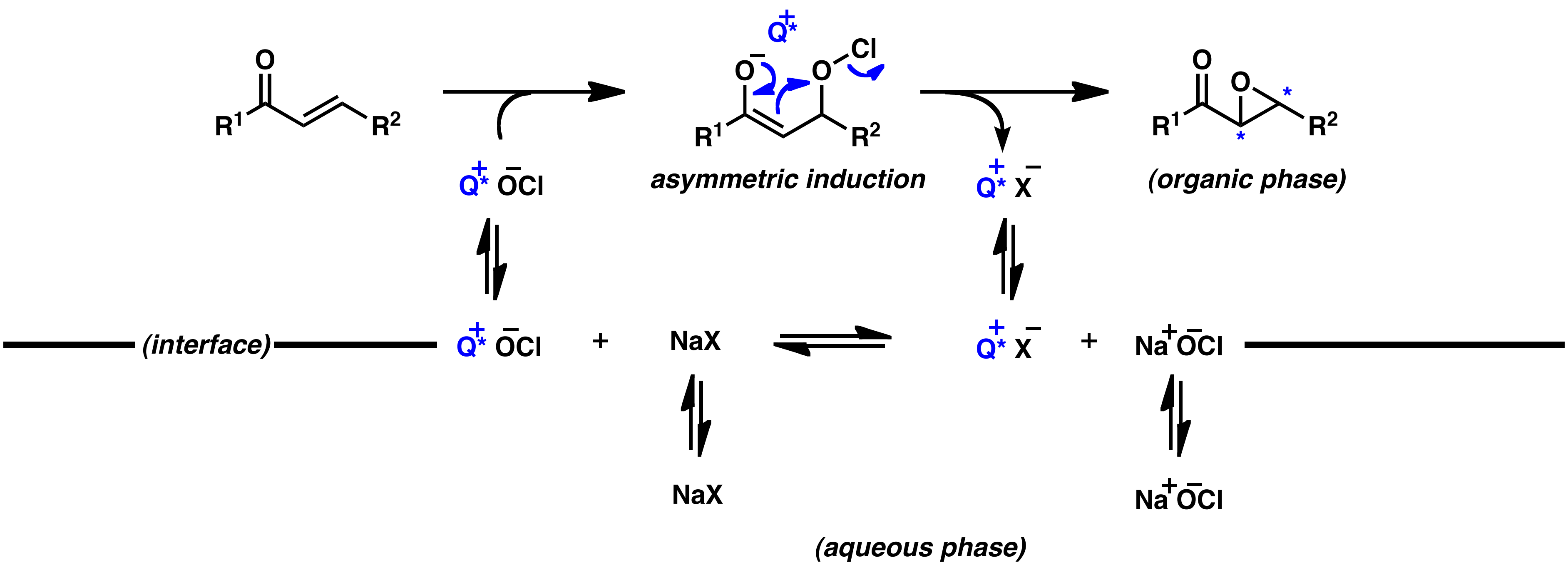


O'Donnell, *Catalytic Asymmetric Syntheses*, 2nd ed., Wiley-VCH, New York, **2000**, chap. 10

Mechanism for the Asymmetric Epoxidation

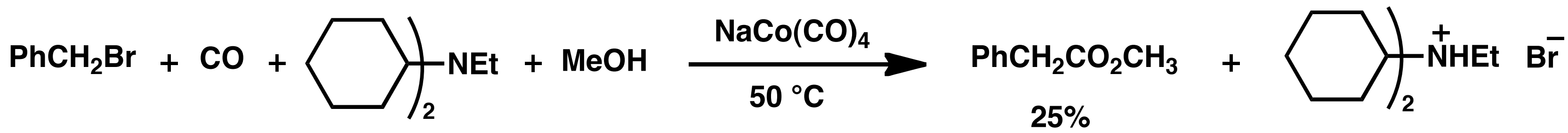
Extraction Mechanism



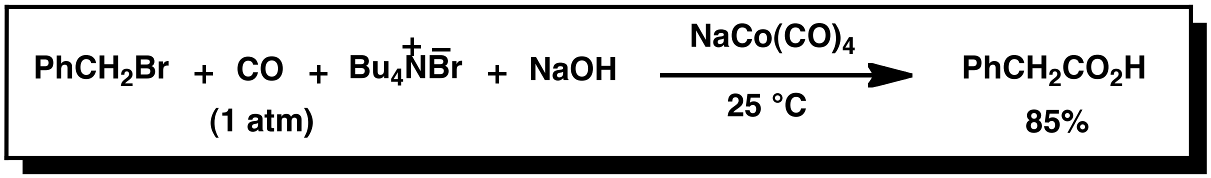


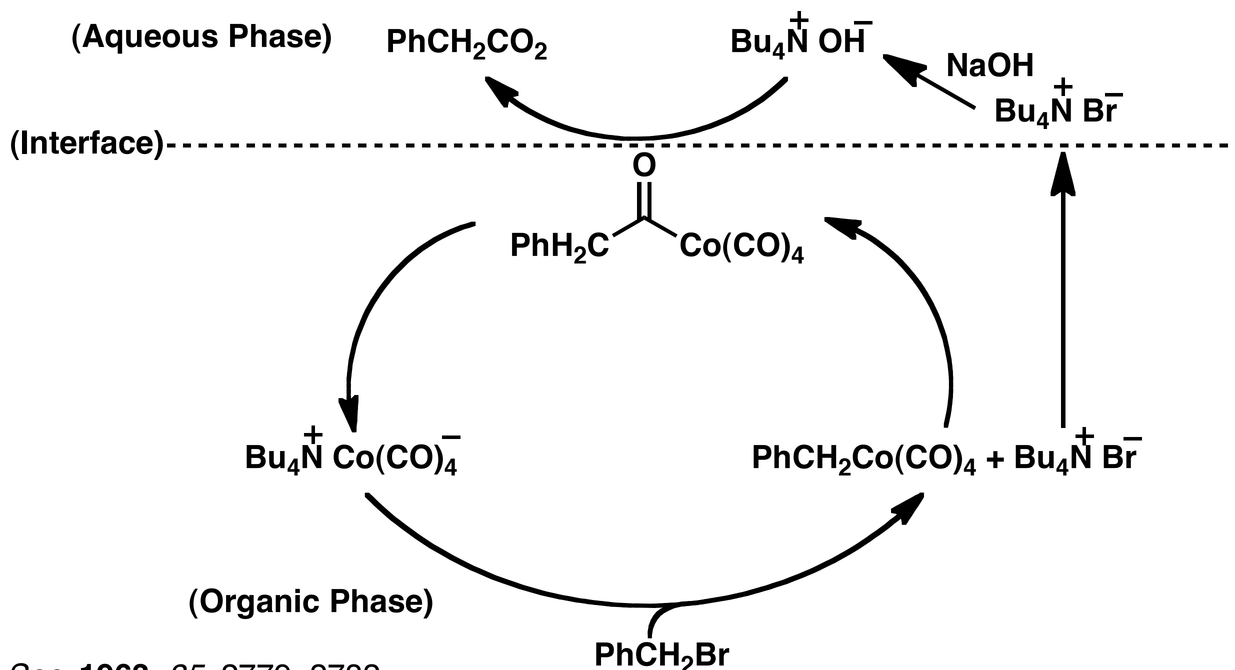
Starks, *J. Am. Chem. Soc.* **1971**, 93, 195–199.

The Application of PTCs in Organometallic Chemistry



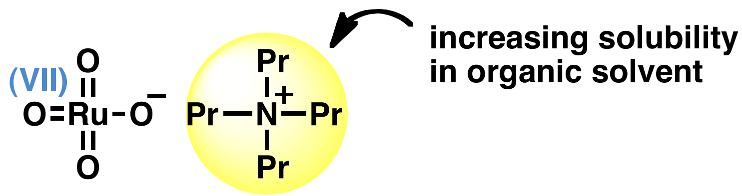
Phase-Tansfer-Catalyzed Carbonylation of Benzyl Bromide by Cobalt Tetracarbonyl Anion



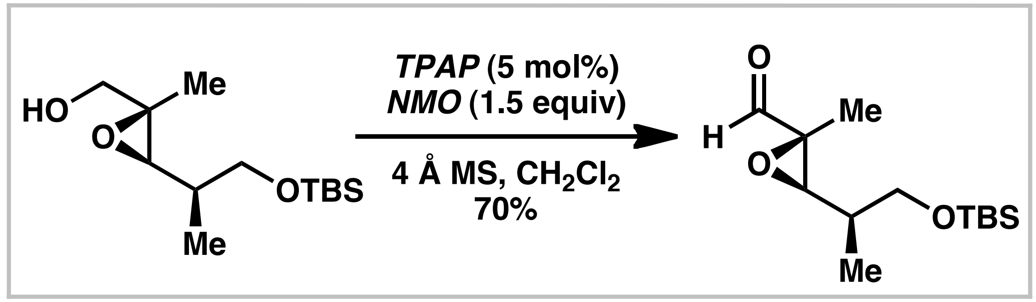


Heck, *J. Am. Chem. Soc.* **1963**, *85*, 2779–2782.
Abbayes, *Organometallics* **1983**, *2*, 1730–1736.

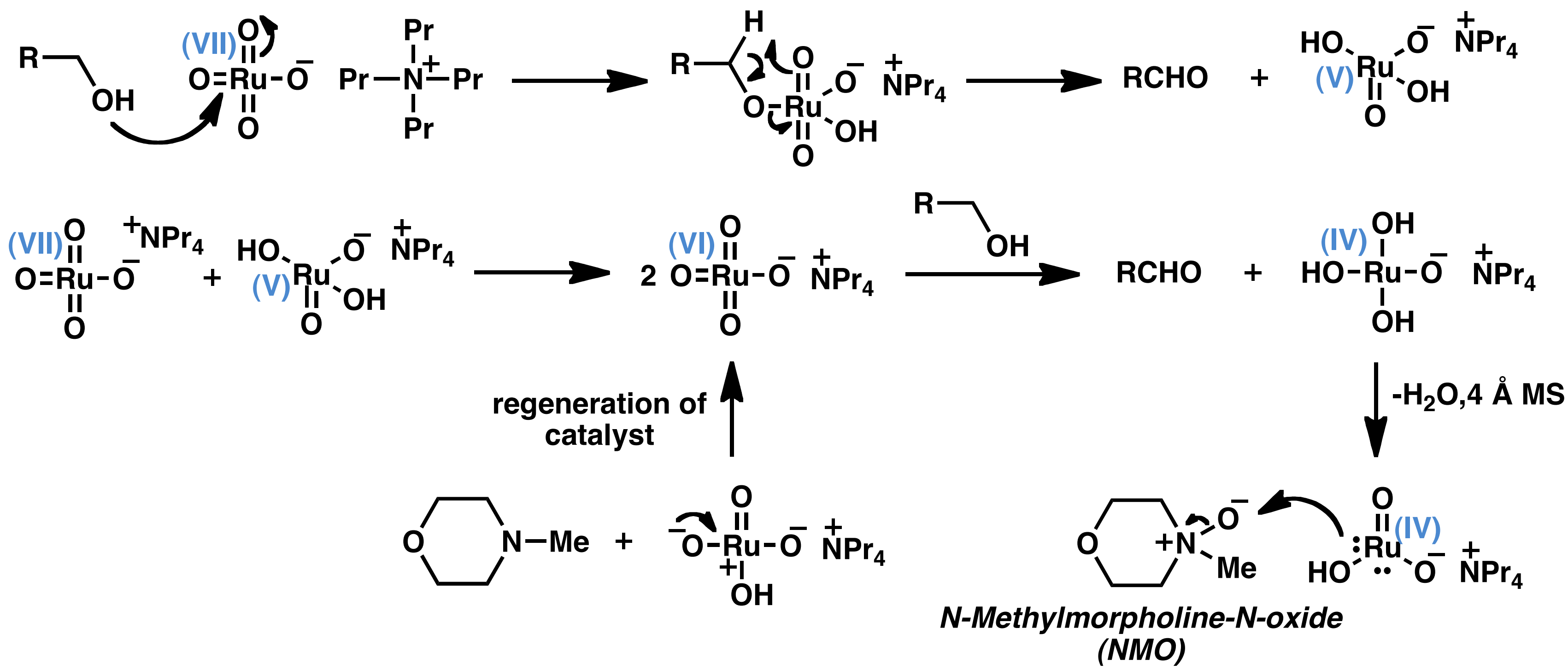
Catalytic Oxidation: Ley Oxidation



Tetrapropylammonium Perruthenate (TPAP)



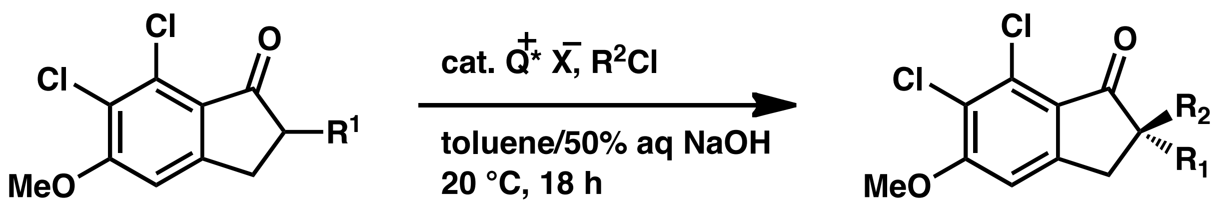
Mechanism



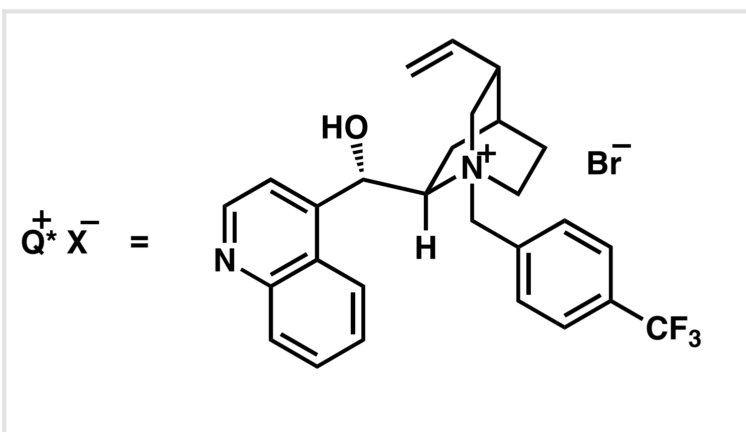
Ley, *J.Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
Griffith, *Chem. Soc. Rev.* **1992**, *21*, 179–185.

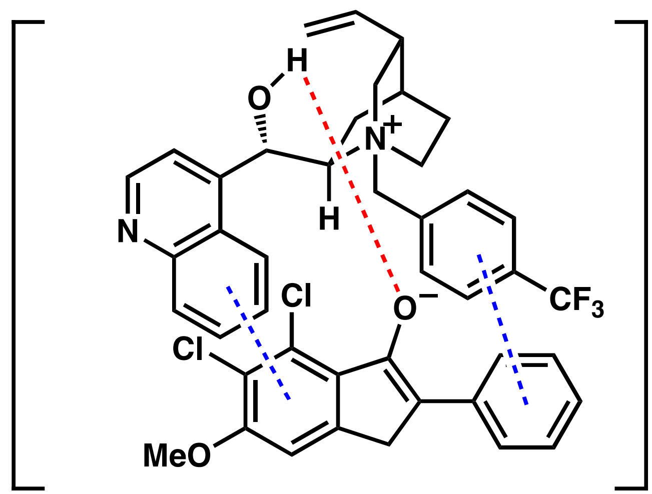
Asymmetric Alkylation

Pioneering Studies by a Merk Research Group



R^1 = Ph, R^2 = Me	*95%, 92% ee*
R^1 = Pr, R^2 = MeC(Cl)=CHCH$_2$	*99%, 92% ee*

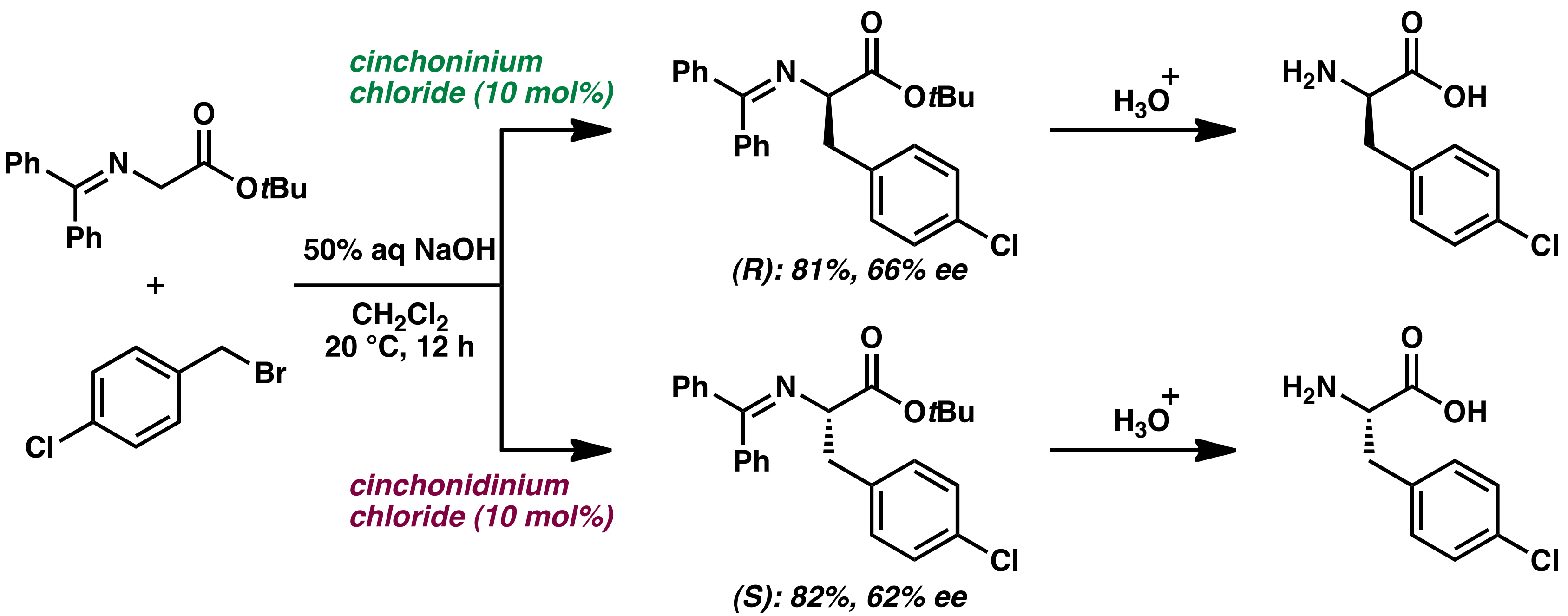


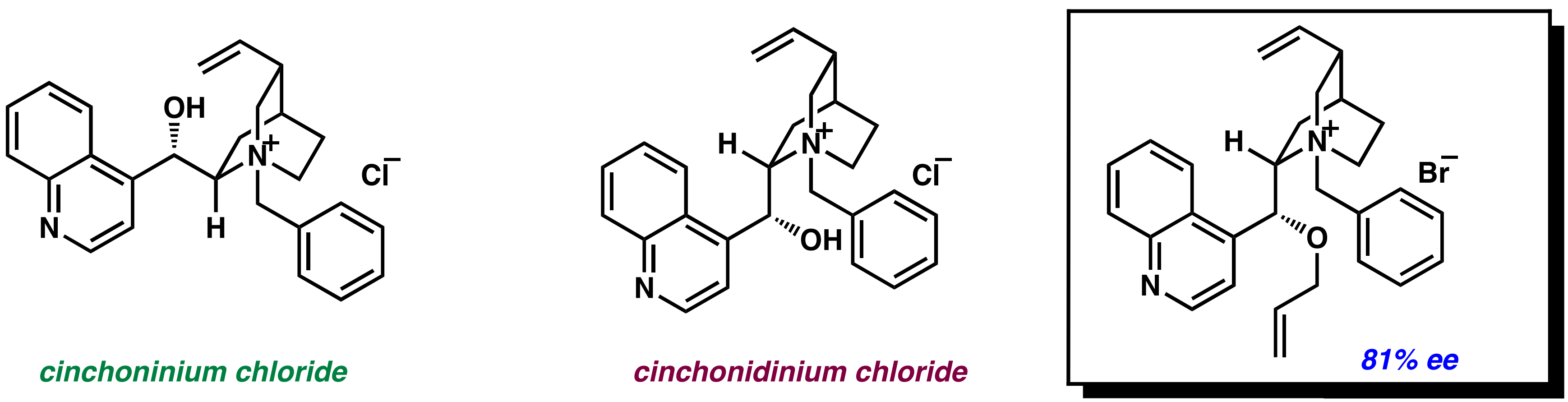


Dolling, *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

Asymmetric Synthesis of α-Amino Acids

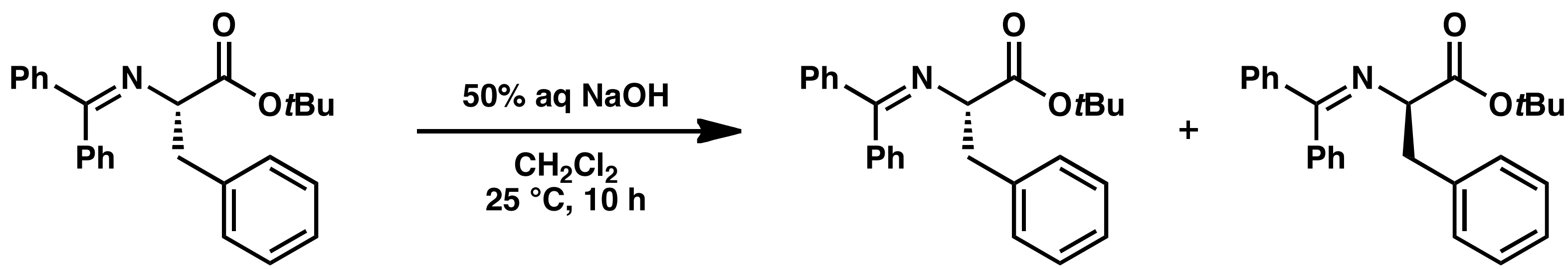
Monoalkylation of Schiff Bases Derived from Glycine





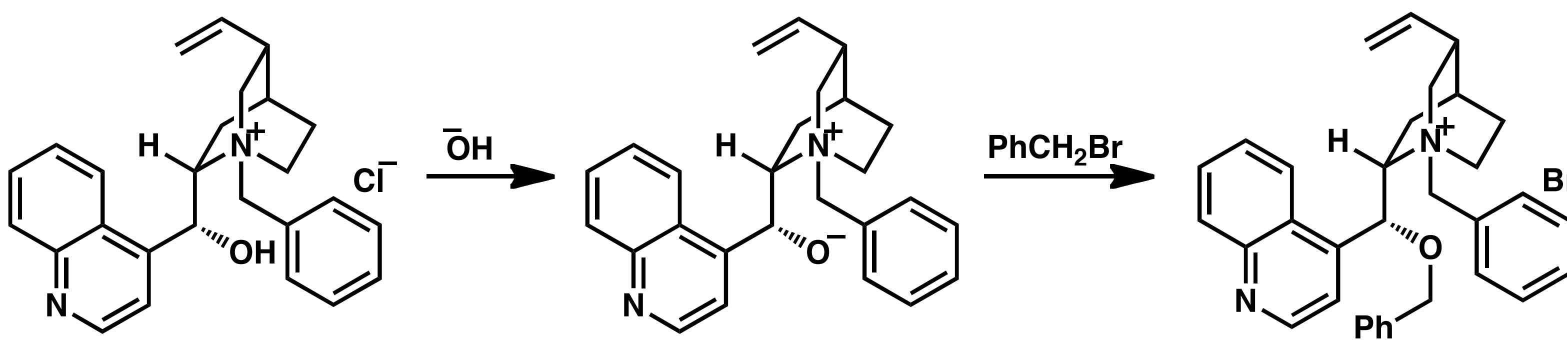
O'Donnell, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.
O'Donnell, *Tetrahedron* **1994**, *50*, 4507–4518.

Racemization Experiments on Monoalkylated Product



(S) *(S)* *(R)*

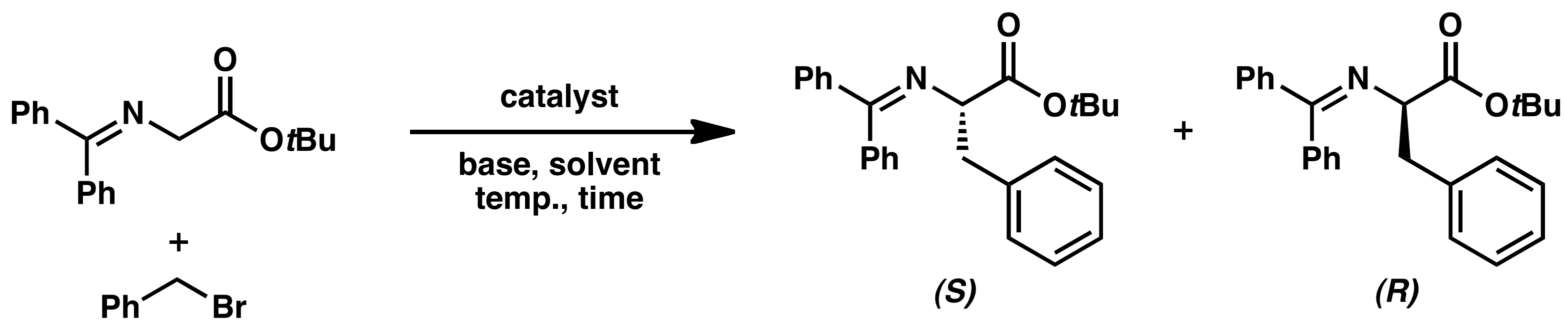
	(S)	(R)
no catalyst and alkyl halide	100%	0%
with Bu_4NBr (10 mol%)	100%	0%
with cinchonidinium chloride	65%	35%
with cinchonidinium chloride and $PhCH_2Br$ (1.2 equiv)	100%	0%
with benzylated ammonium salt	100%	0%

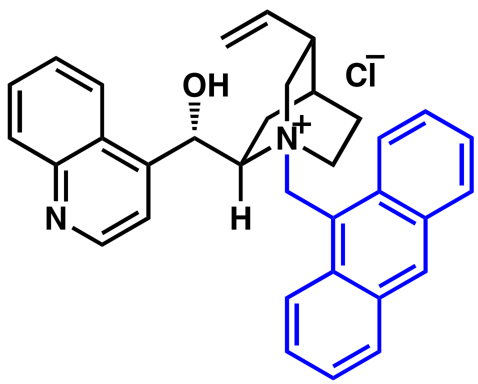


cinchonidinium chloride organic soluble base *benzylated ammonium salt*

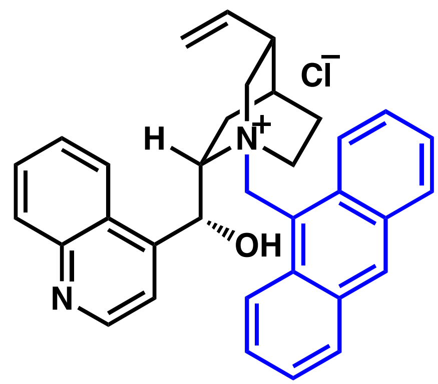
O'Donnell, *Tetrahedron* **1994**, *50*, 4507–4518.
O'Donnell, *J. Am. Chem. Soc.* **1988**, *110*, 8520–8525.

New Class of Cinchona Alkaloid Derived Catalysts

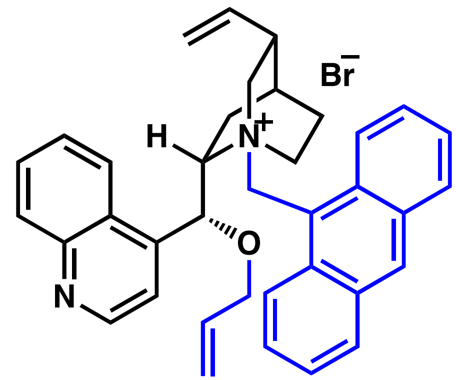




63%, 89% ee (R)
50% aq KOH
toluene
20 °C, 18 h
Lygo



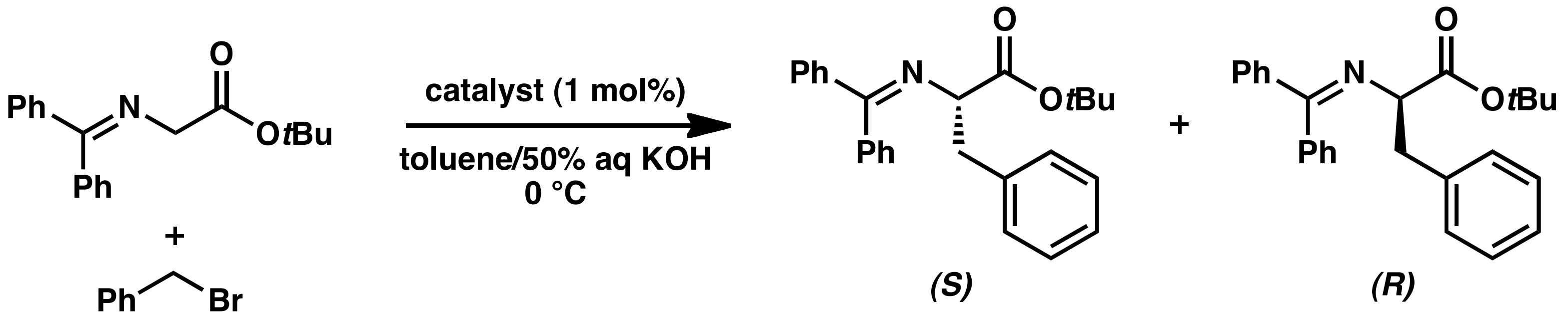
68%, 91% ee (S)
50% aq KOH
toluene
20 °C, 18 h
Lygo



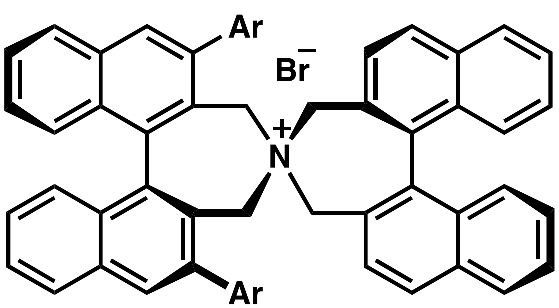
84%, 94% ee (S)
$CsOH•H_2O$
CH_2Cl_2
–78 C, 23 h
Corey

Lygo, *Tetrahedron Lett.* **1997**, *38*, 8595–8598.
Corey, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

Chiral Spiroammonium Salts

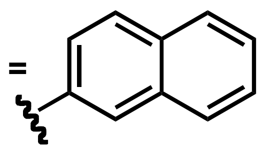


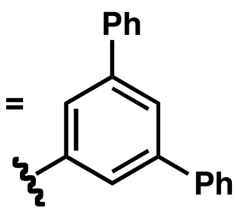
Effect of Aromatic Substituents (Ar)



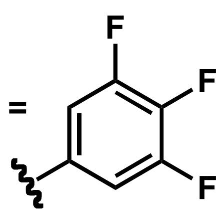
Ar = H — ***73%, 79% ee (R)***

Ar = Ph — ***81%, 89% ee (R)***

Ar =  ***95%, 96% ee (R)***

Ar = 

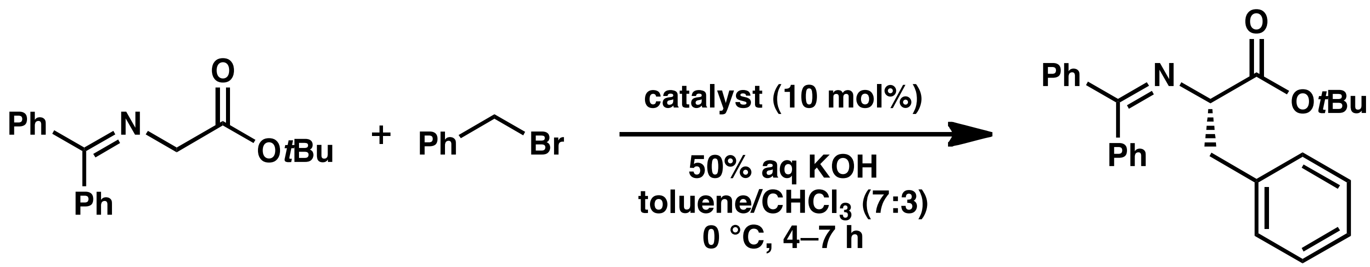
91%, 98% ee (R)

Ar = 

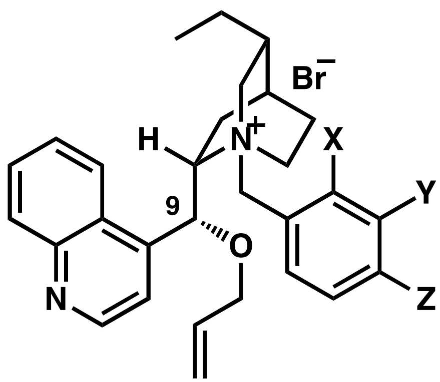
90%, 99% ee (R): 1 mol% catalyst
72%, 99% ee (R): 0.2 mol% catalyst

Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

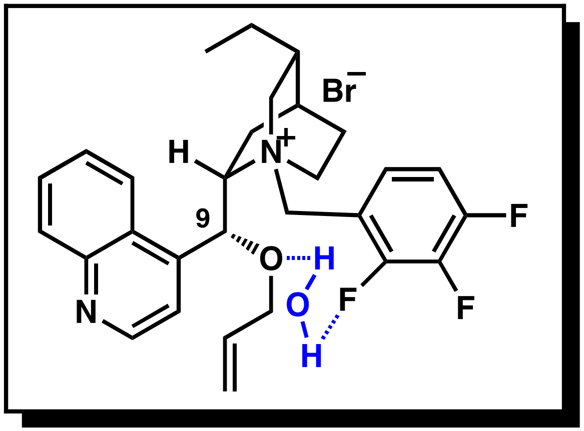
Fluoroaromatic Substituents on Catalysts



Effect of Aromatic Substituents (Ar)

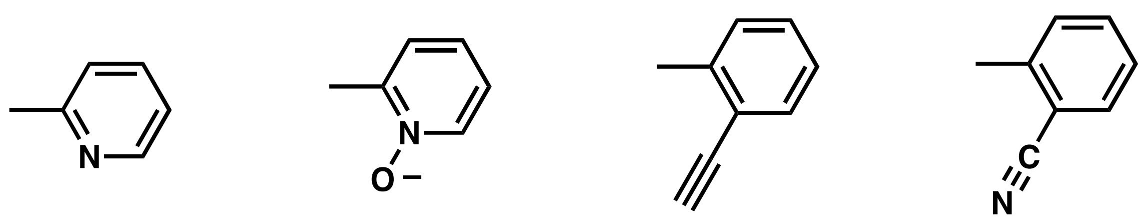


X = Y = Z = H	: 92%, 74% ee
X = F, Y = Z = H	: 93%, 89% ee
X = Z = H, Y = F	: 90%, 74% ee
X = Y = H, Z = F	: 92%, 75% ee
X = Y = Z = F	: 90%, 96% ee



Influence of Hydrogen Bonding in Catalysts

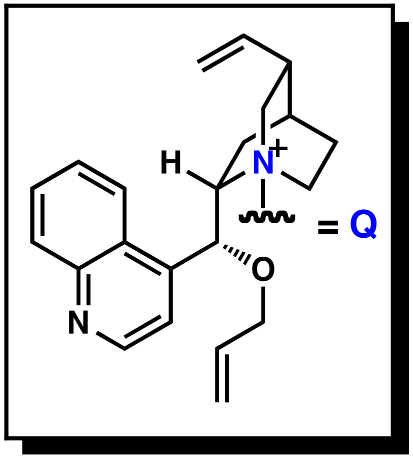
Ar =

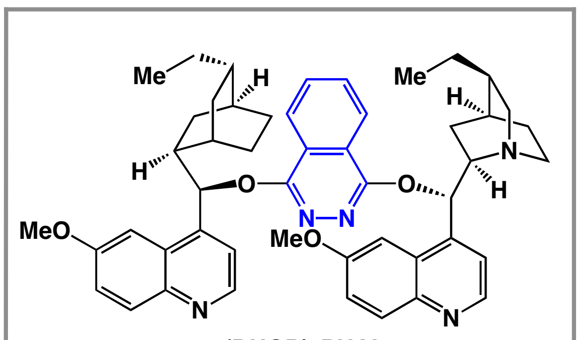


95%, 61% ee	94%, 96% ee	90%, 75% ee	95%, 92% ee

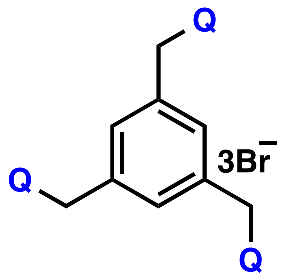
Jew, Park, *Org. Lett.* **2005**, *7*, 1129–1131.

Cinchona Derived Bis and Tris Ammonium Salts

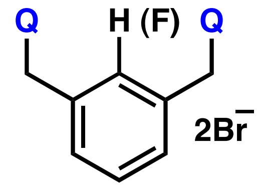




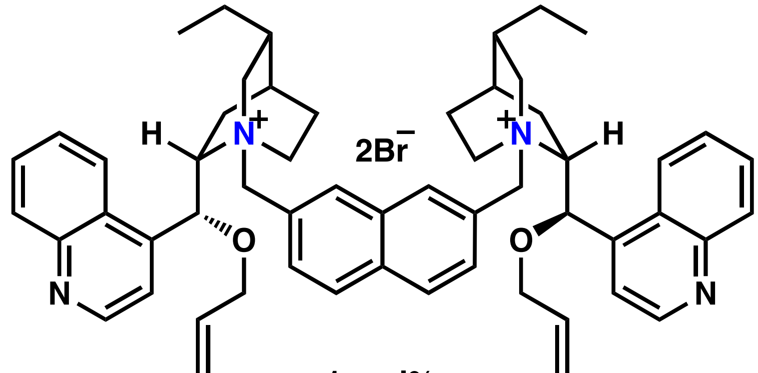
(DHQD)$_2$PHAL



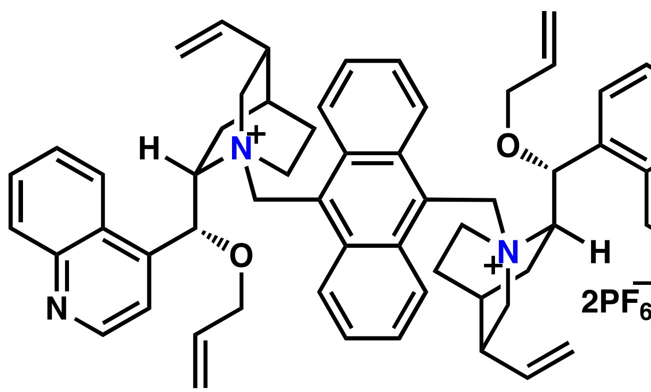
91%, 94% ee



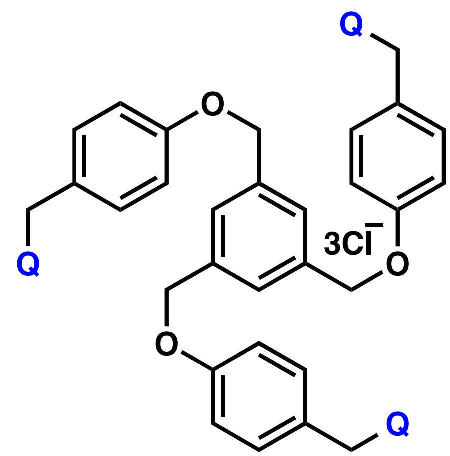
3–5 mol%
50% aq KOH
toluene/$CHCl_3$ (7:3)
0 °C
RX = $PhCH_2Br$
93%, 94% ee



1 mol%
50% aq KOH
toluene/$CHCl_3$ (7:3)
0 °C
95%, 97% ee



5 mol%
50% aq KOH
toluene/$CHCl_3$ (7:3)
0 °C
RX = $BrCH_2CO_2$*t*Bu
67%, 86% ee

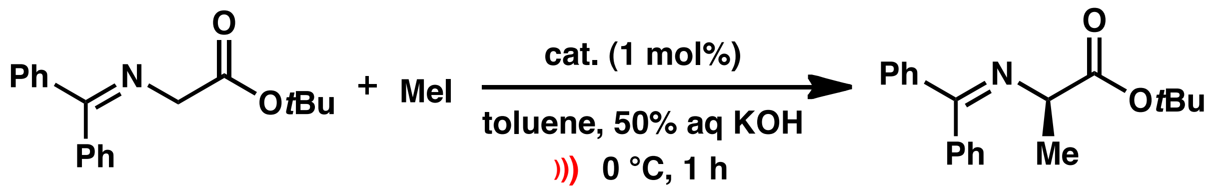


1.5–5 mol%
20% aq NaOH
toluene/CH_2Cl_2 (8:2)
–10 °C
RX = *p*-*t*-Bu-$PhCH_2Br$
93%, 95% ee

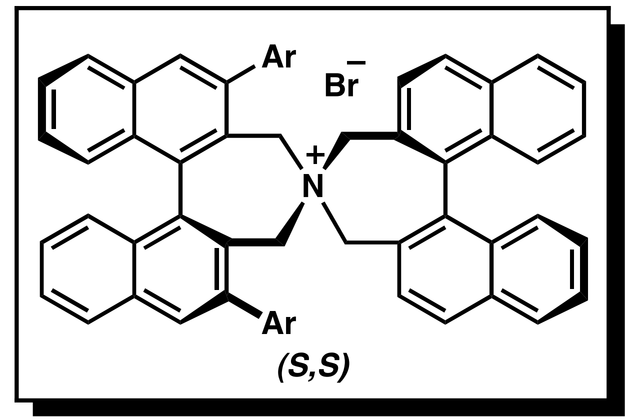
Jew, Park, *Chem. Commun.* **2001**, *14*, 1244–1245.
Nájera, *Tetrahedron: Asymmetry* **2004**, *15*, 2603–2607.
Siva, *Synthesis* **2005**, 2927–2933.

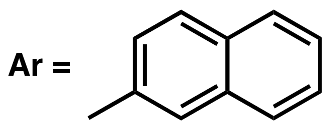
Acceleration of Reaction Rate in PTC Alkylations

Sonication



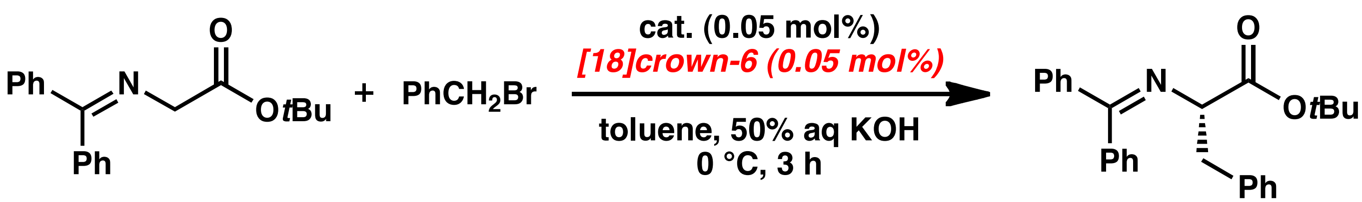
63%, 88% ee





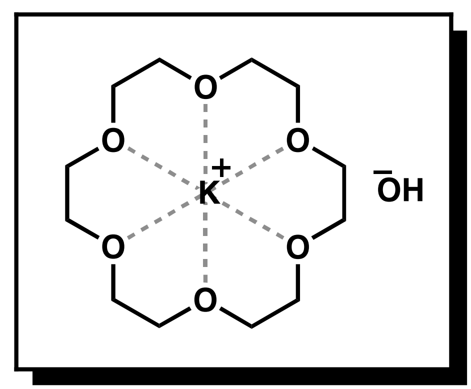
simple stirring at 0°C
: 8 h, 64%, 90% ee

Achiral co-catalyst



(R,R)-Ar = 3,5-$Ph_2C_6H_3$

90%, 98% ee

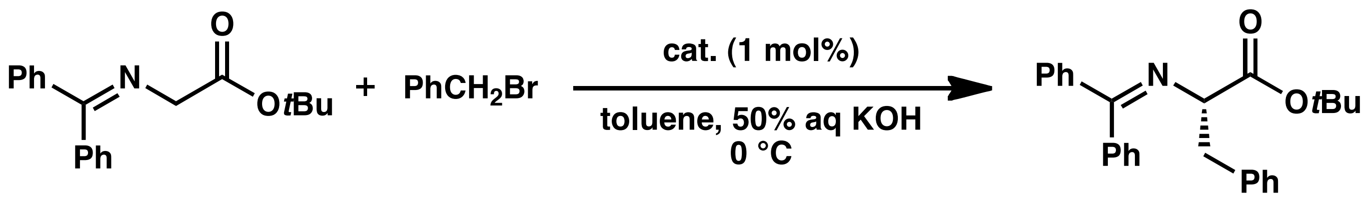


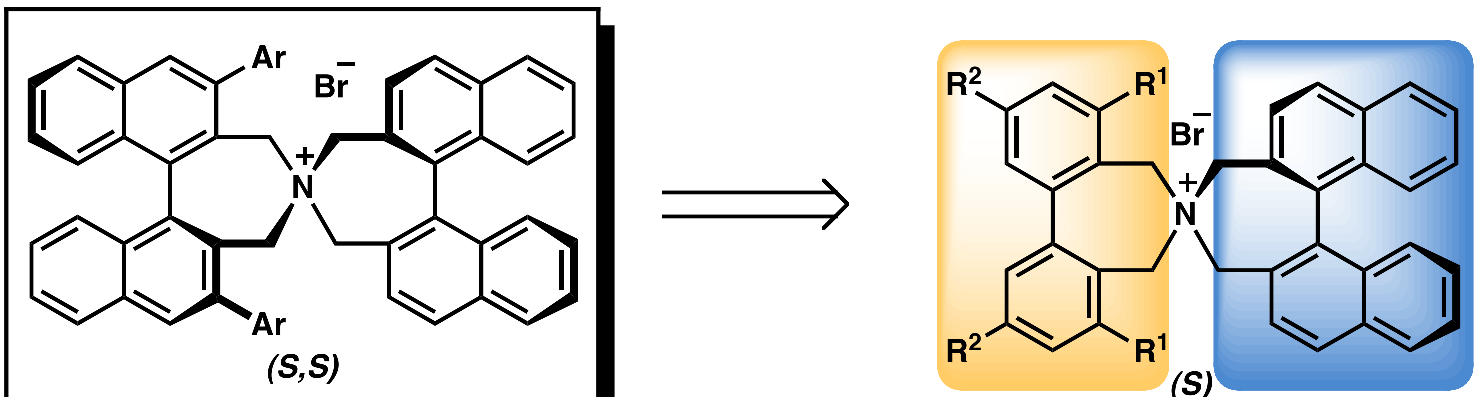
4%, 92% ee without the co-catalyst

with [15]crown-5: 29%, 96% ee
with [12]crown-4: 16%, 96% ee

Maruoka, *Synlett* **2000**, *10*, 1500–1502.
Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 625–628.

New C_2-Symmetric Chiral Ammonium Salts





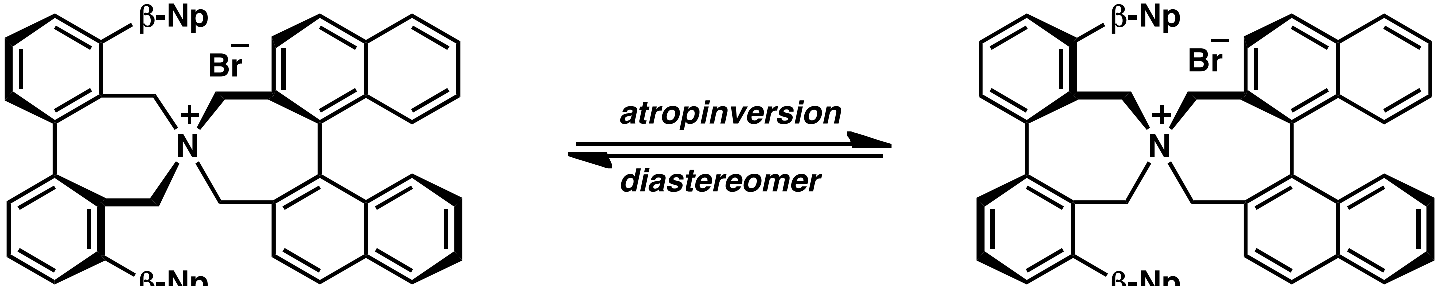
Limitations: two different chiral binaphtyl moieties

- ***Easy modification of achiral and flexible biphenyl unit***
- ***Simple chiral source***

R^1 = β-naphthyl (Np), R^2 = H: 85%, 87% ee [18 h]
R^1 = 3,5-$Ph_2C_6H_3$, R^2 = H
R^1 = 3,5-$Ph_2C_6H_3$, R^2 = Ph

Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 1551–1554.

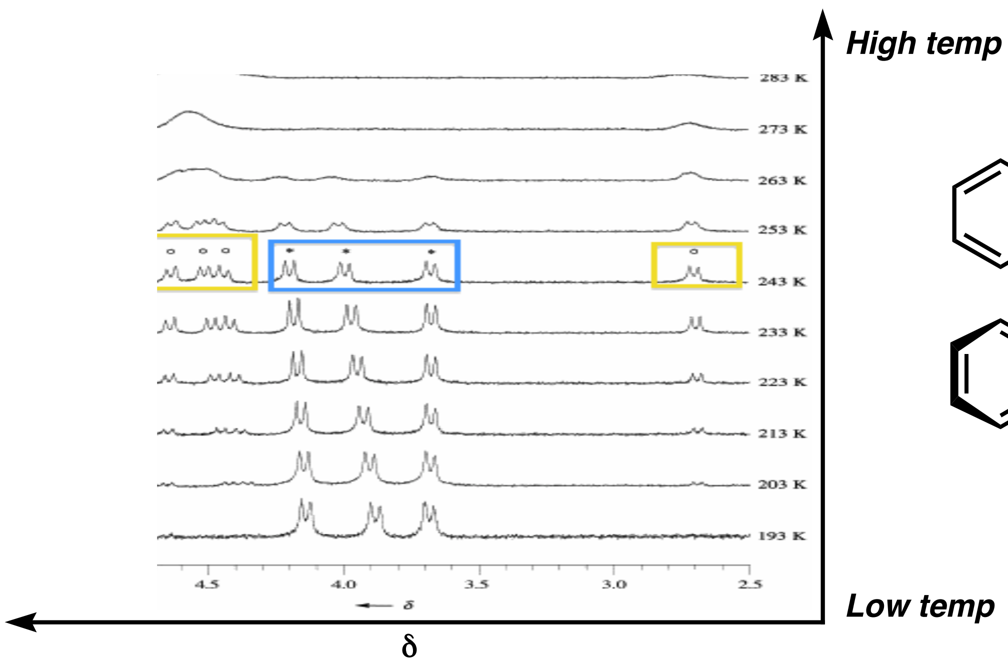
Expected Conformational Interconversion

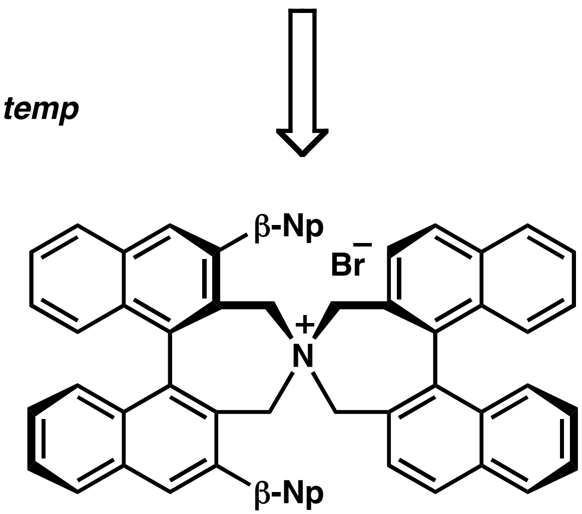


homochiral (S,S)
high activity and ee

heterochiral (R,S)
low activity and ee

Temperature Dependence
of Homochiral and Heterochiral conformers

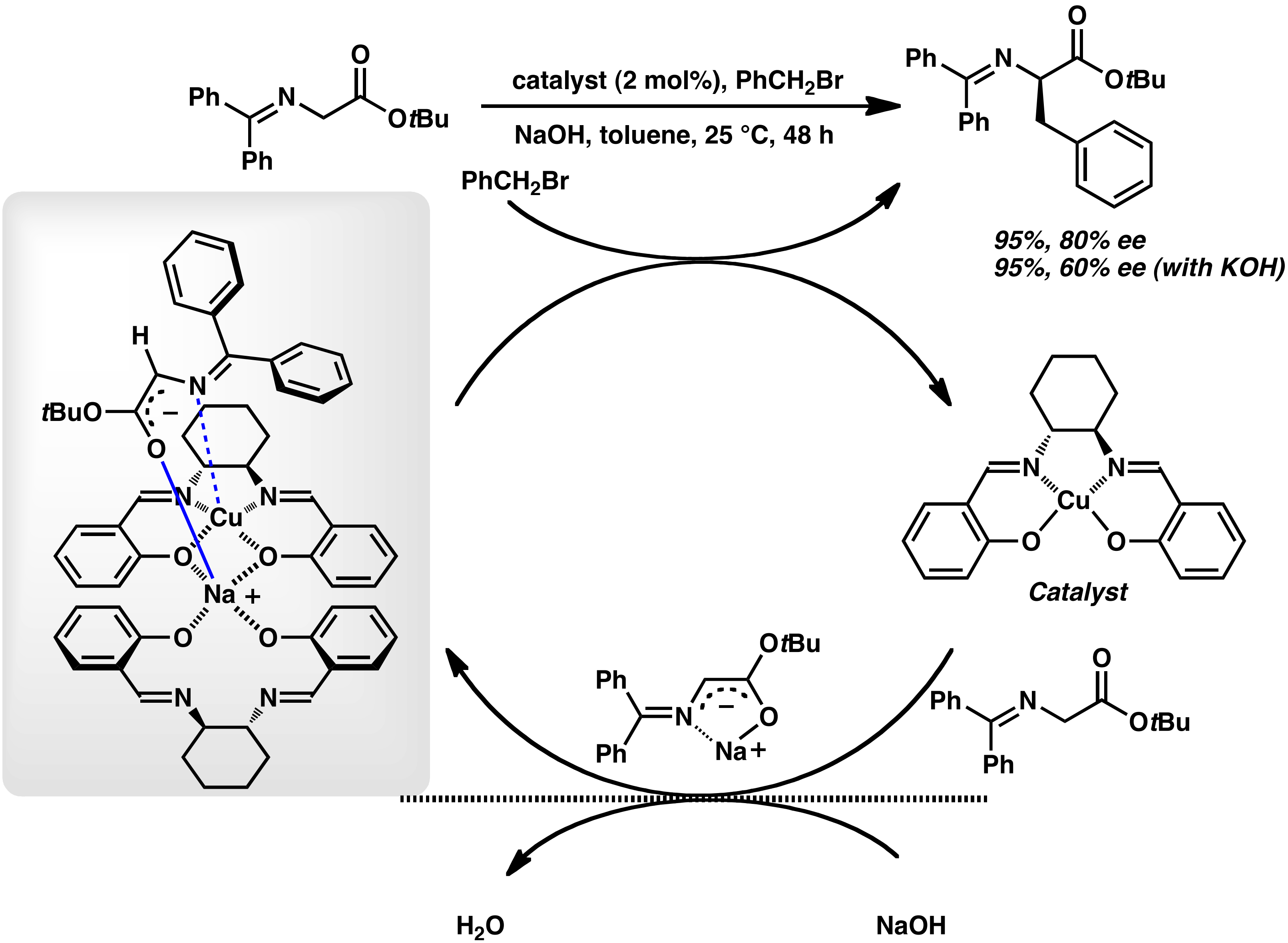




heterochiral (R,S)
47%, 11% ee (60 h)

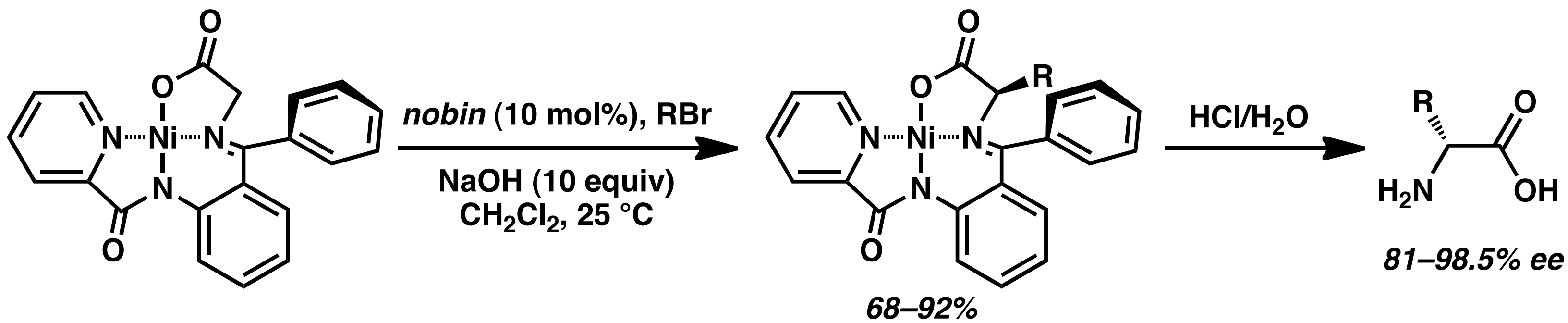
Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 1551–1554.

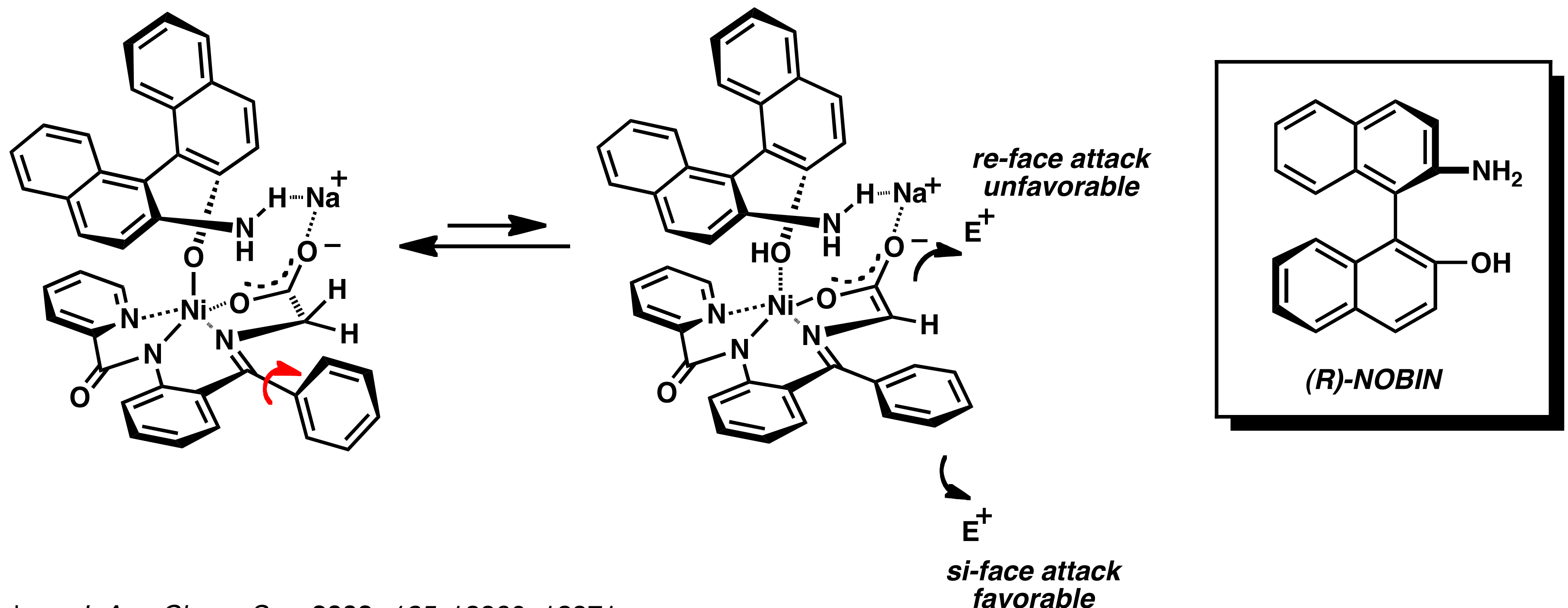
Chiral Copper-Salen Complex



Belokon, *Tetrahedron* **2001**, *57*, 2491–2498.

Achiral Nickel Complex with Nobin as a PTC

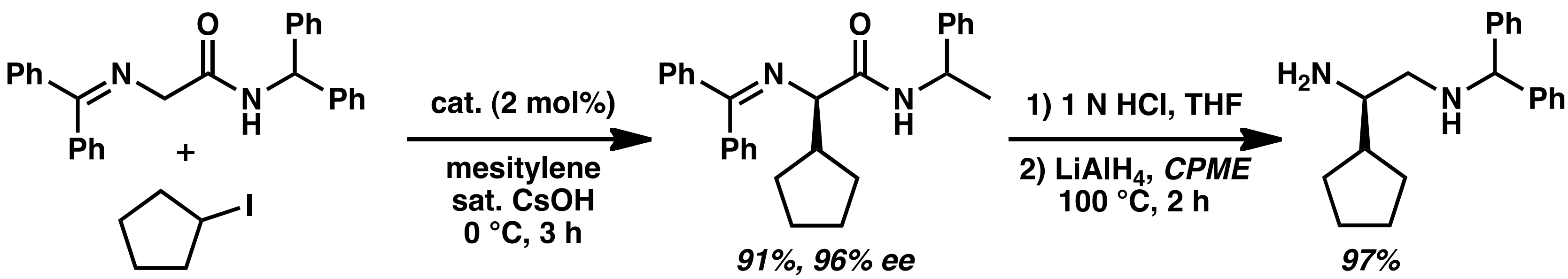




Belokon, *J. Am. Chem. Soc.* **2003**, *125*, 12860–12871.

Glycine Diphenylmethyl Amide Derived Schiff Base

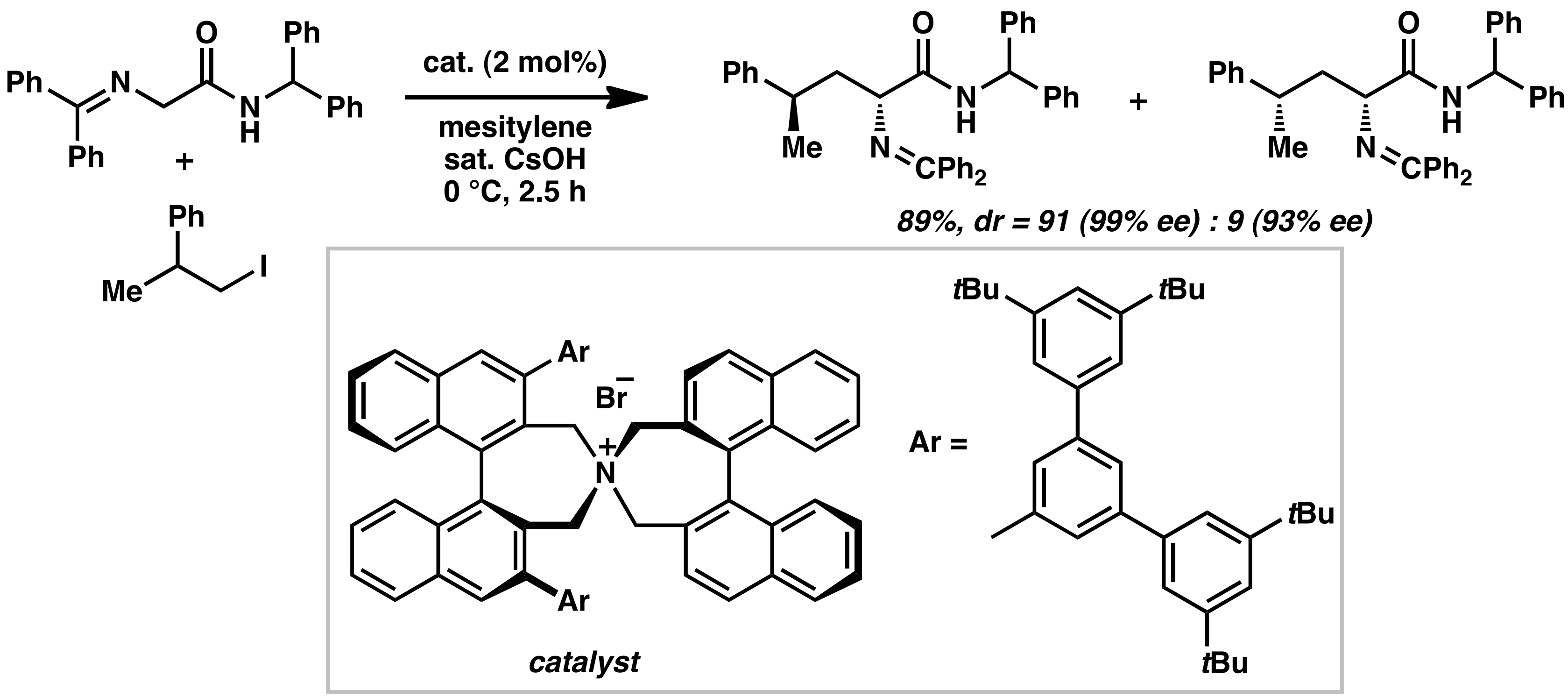
Secondary Alkyl Halides



Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 5868–5870.

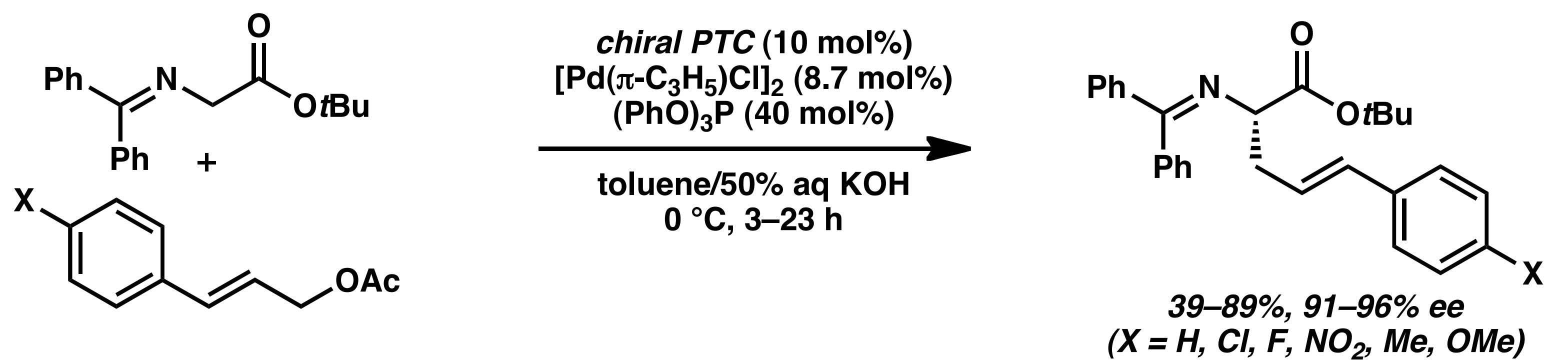
CPME = cyclopentyl methyl ether

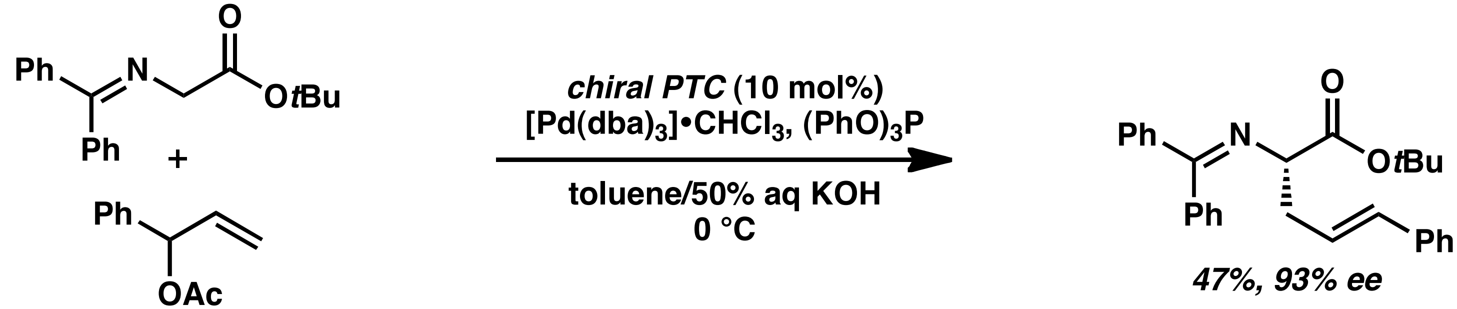
Kinetic Resolution

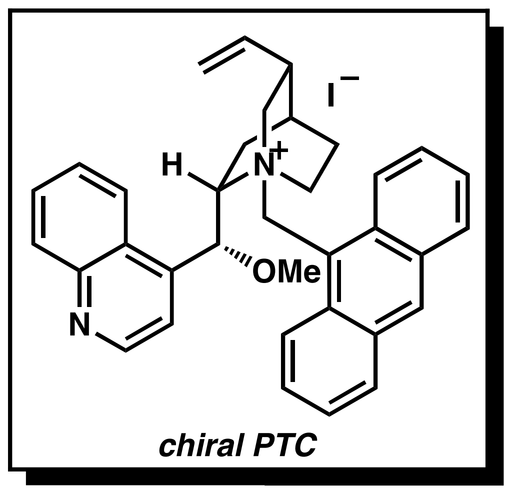


Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 5073–5083.

Pd-Catalyzed Allylation with the Chiral PTC

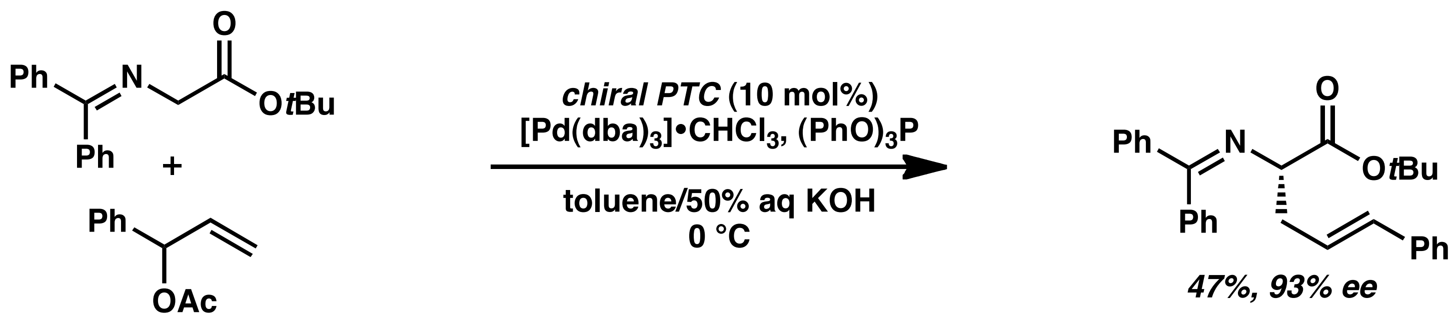


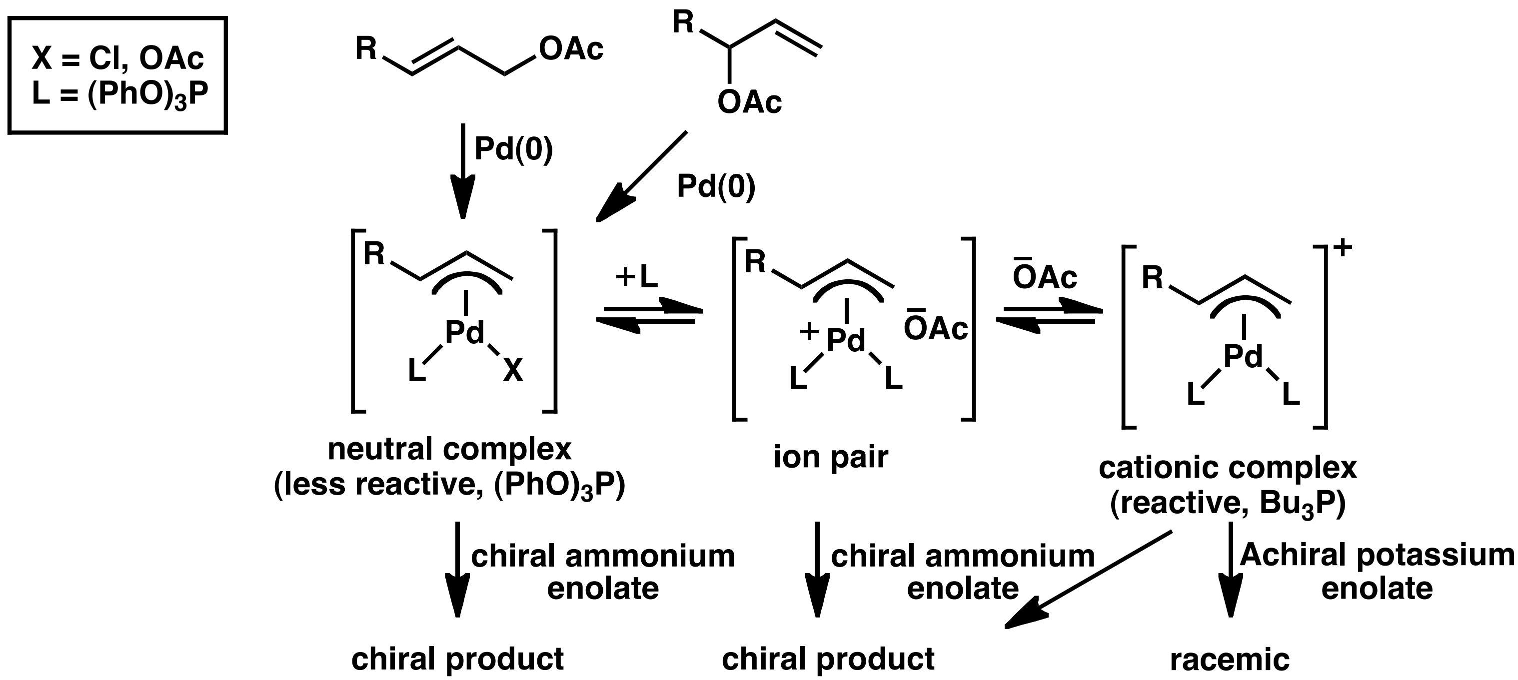




Takemoto, *Org. Lett.* **2001**, *3*, 3329–3331.
Takemoto, *J. Org. Chem.* **2002**, *67*, 7418–7423.

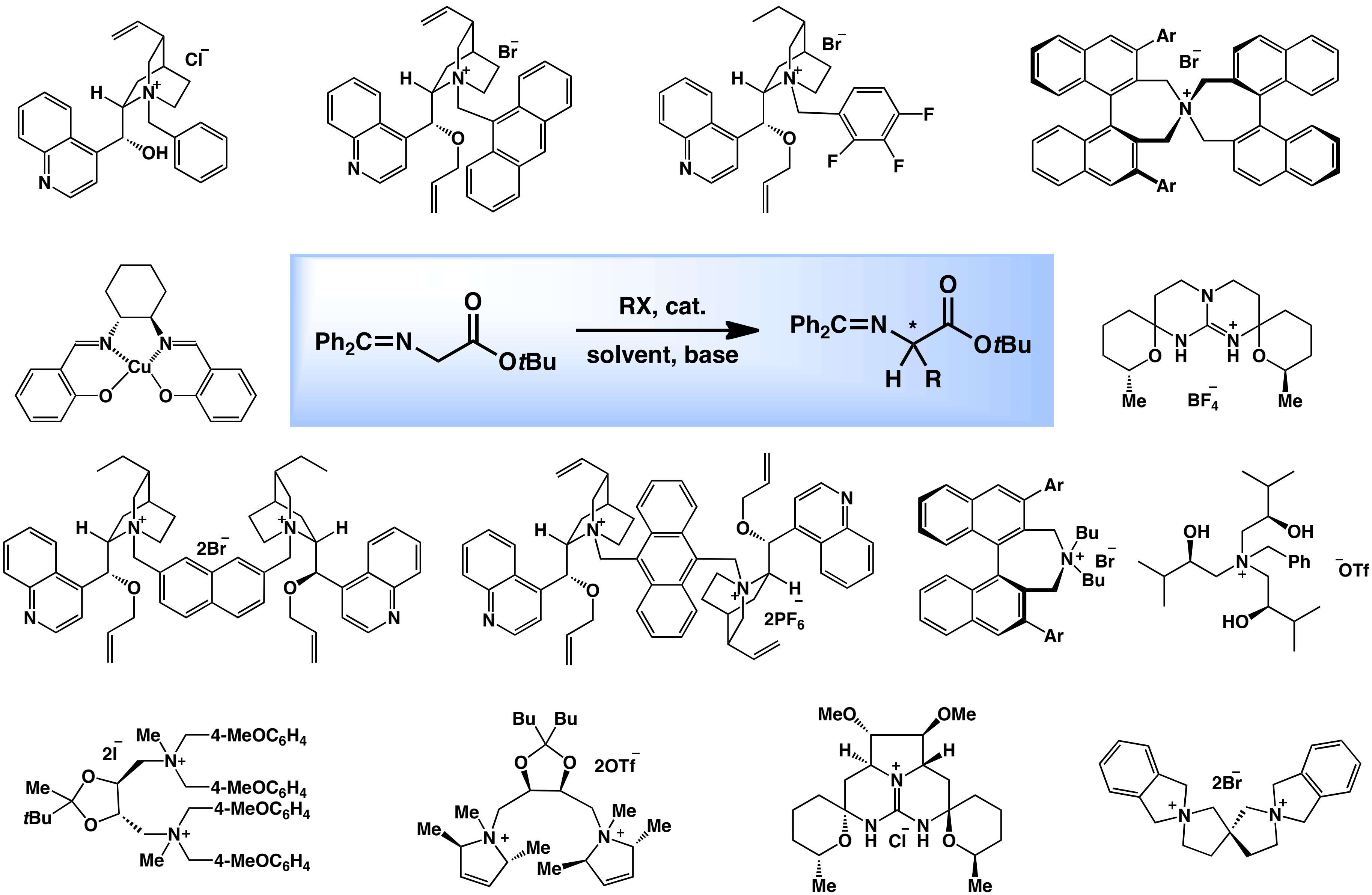
Pd-Catalyzed Allylation with the Chiral PTC





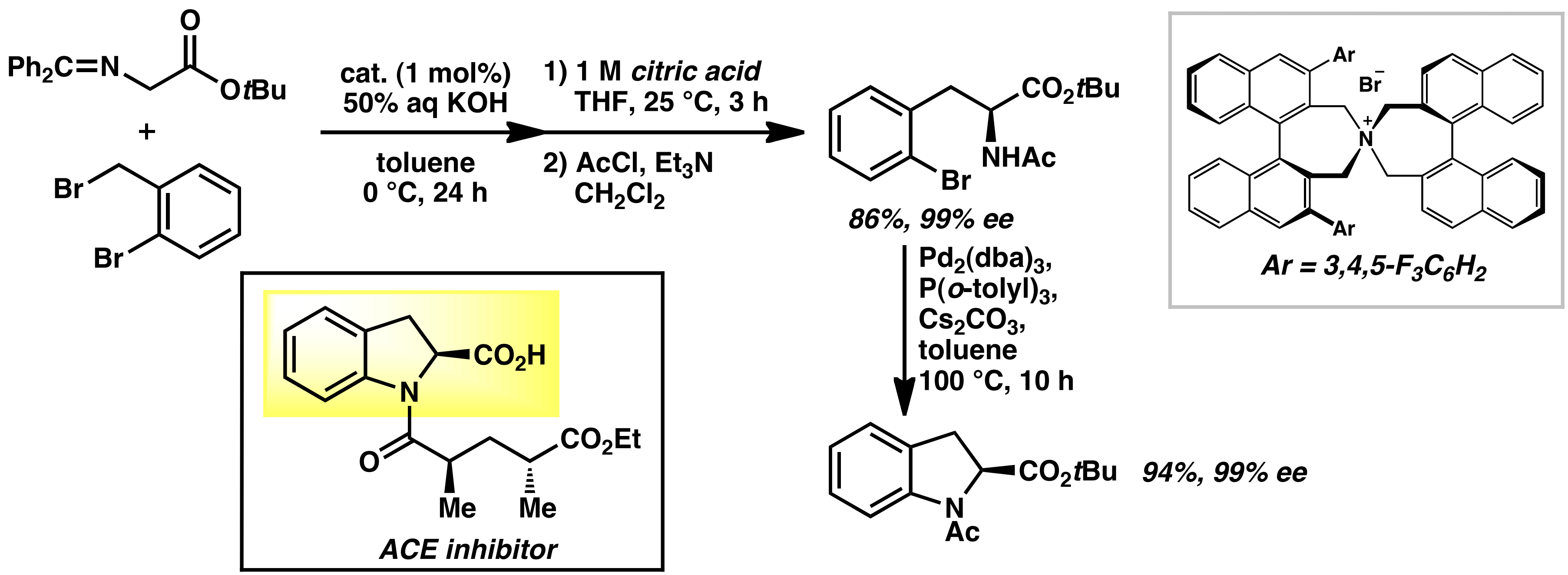
Takemoto, *Org. Lett.* **2001**, *3*, 3329–3331.
Takemoto, *J. Org. Chem.* **2002**, *67*, 7418–7423.

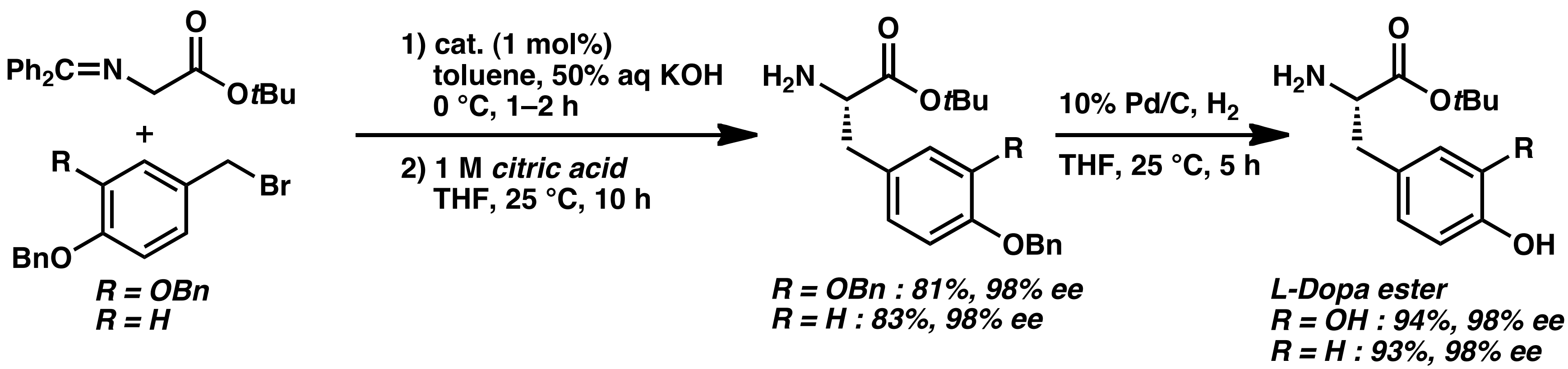
Representative Catalysts in the Alkylation



Review: Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

Asymmetric Syntheses of Biologically Active Compounds

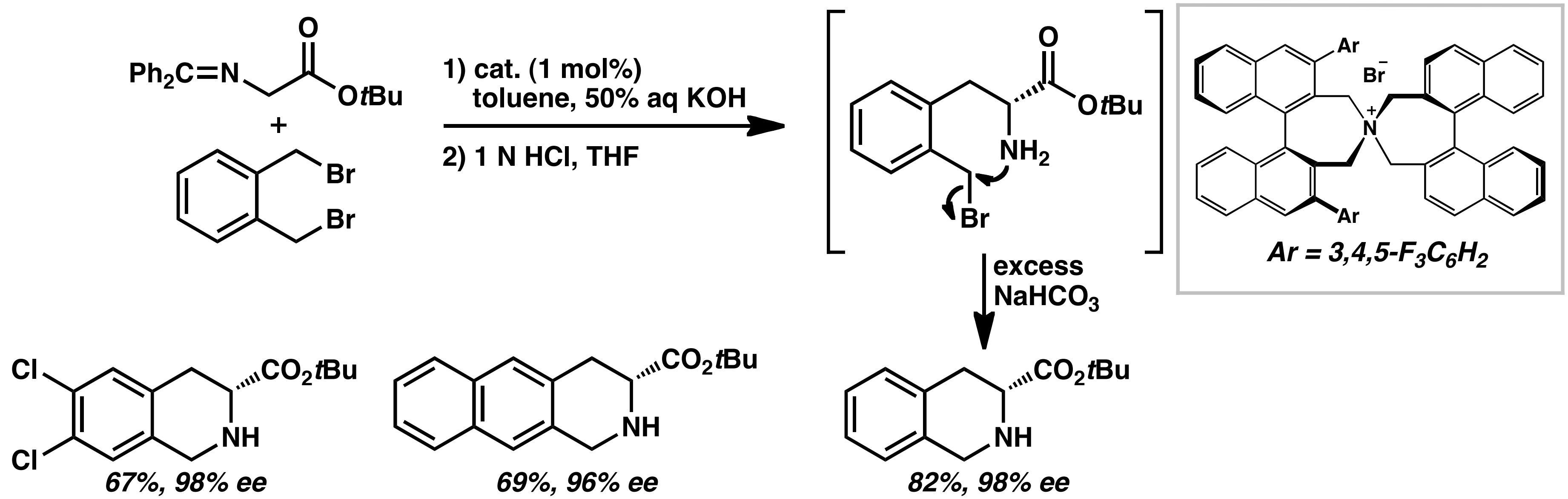




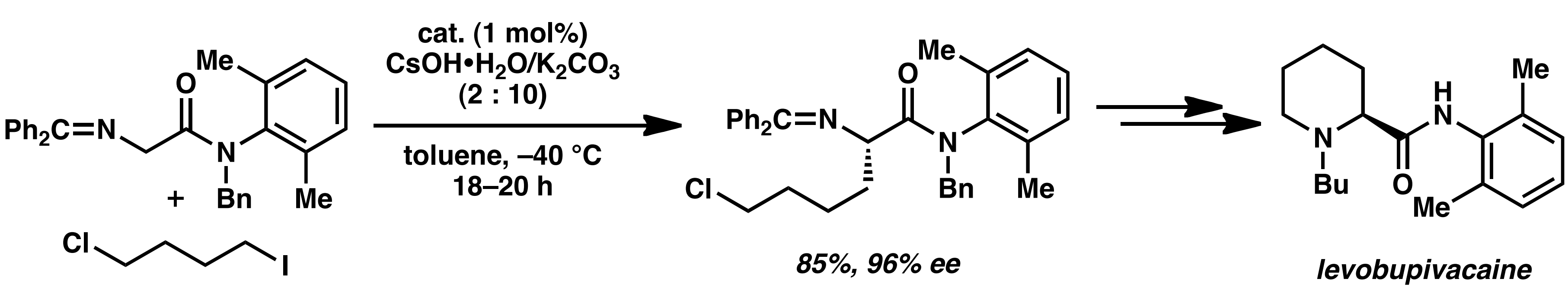
Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.

Asymmetric Syntheses of Biologically Active Compounds

Asymmetric Synthesis of Isoquinoline Derivatives



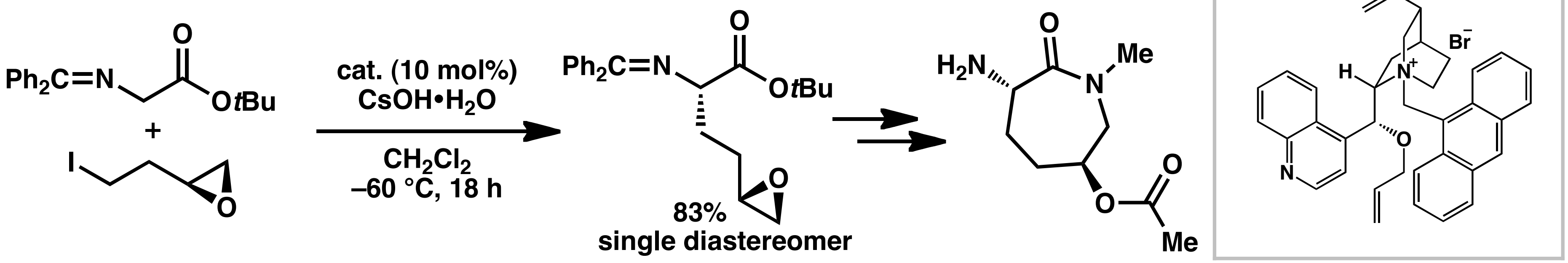
Asymmetric Synthesis of levobupivacaine

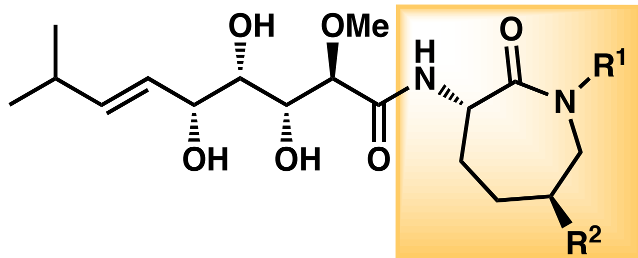


Maruoka, *Synthesis* **2001**, 1716–1718.
Ramachandran, *Tetrahedron Lett.* **2005**, *46*, 19–21.

Asymmetric Syntheses of Bengamides and Antofine

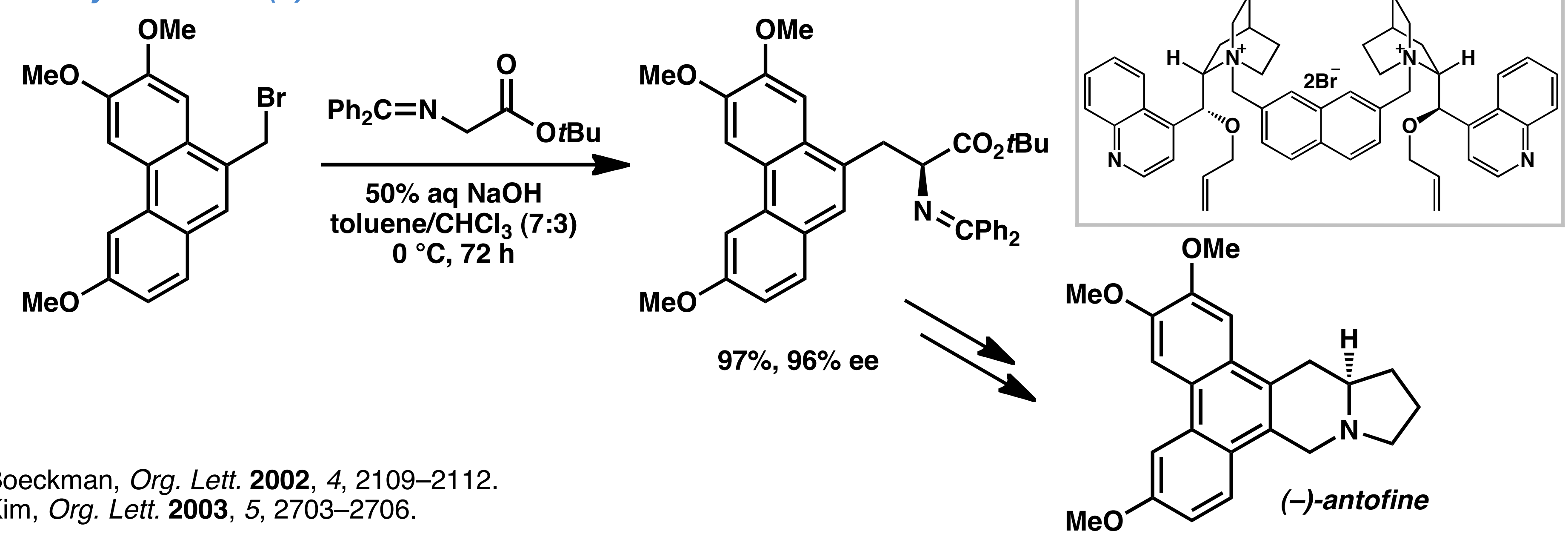
Asymmetric Synthesis of Bengamides B, E, and Z





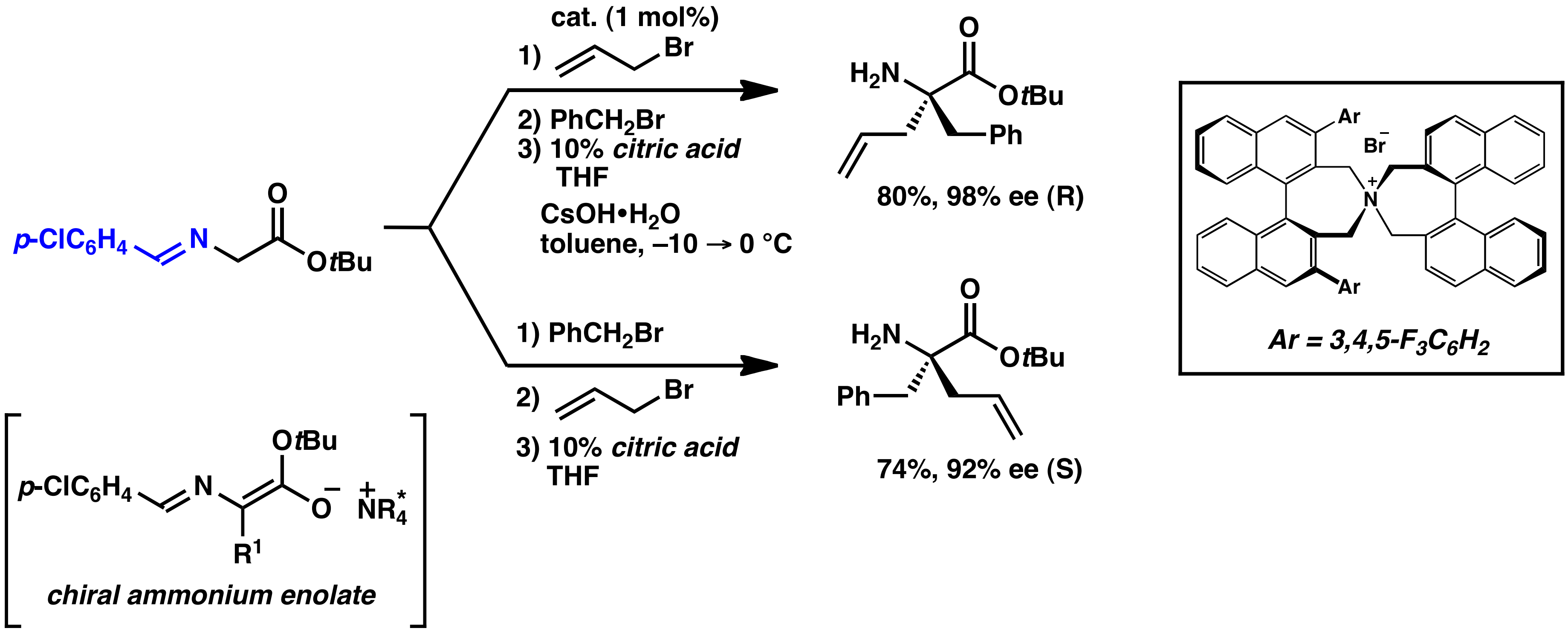
bengamides Z : R^1 = Me, R^2 = OH
B : R^1 = Me, R^2 = $O_2C(CH_2)_{12}Me$
E : R^1 = R^2 = H

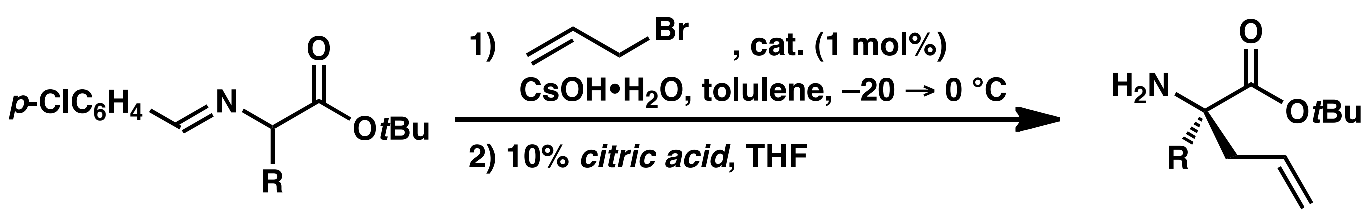
Total Synthesis of (–)-Antofine



Boeckman, *Org. Lett.* **2002**, *4*, 2109–2112.
Kim, *Org. Lett.* **2003**, *5*, 2703–2706.

One-Pot, Double Alkylation of the Aldimine Schiff Base

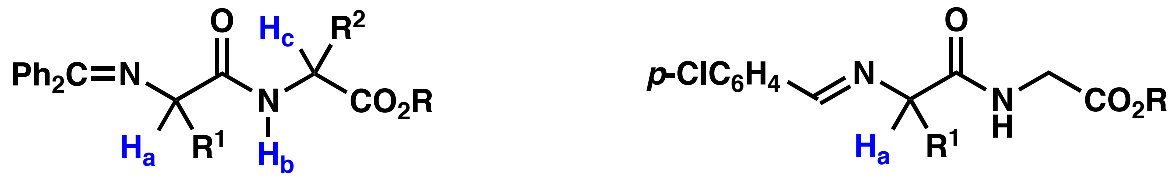




R = Me : 73%, 98% ee
R = iBu : 70%, 93% ee
R = $PhCH_2$: 71%, 97% ee

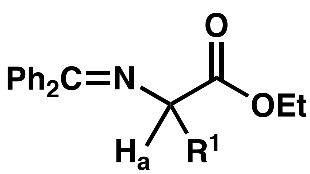
Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229.

Alkylation of Peptides Activated as Schiff Bases



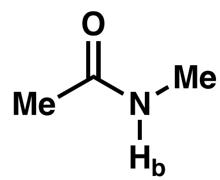
(in DMSO)

pK_a (H_a)

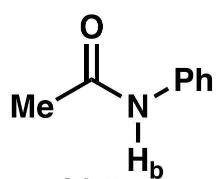


R^1 = H	18.7
= Me	22.8
= CH_2Ph	23.2
= Ph	21.2

pK_a (H_b)

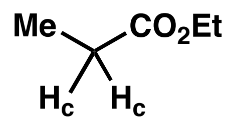


25.9

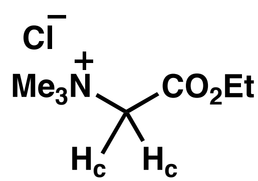


21.5

pK_a (H_c)

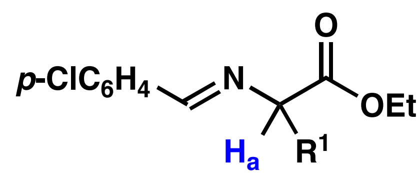


30–31

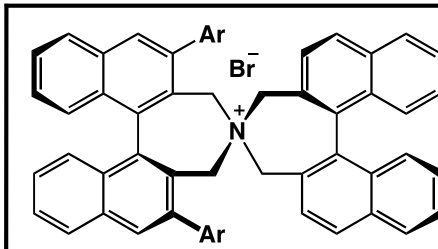


20.0

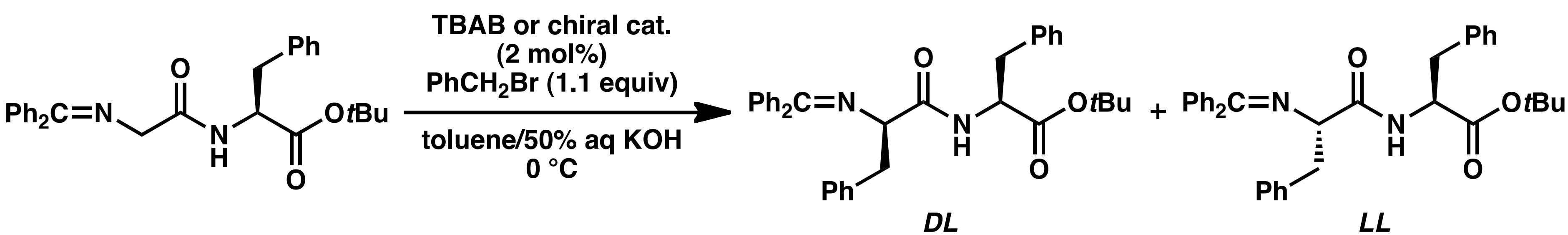
pK_a (H_a)



R^1 = H	18.8
= Me	19.2
= CH_2Ph	19.0
= Ph	17.2



Ar = 3,5-(3,5-$tBu_2C_6H_3$)$_2C_6H_3$

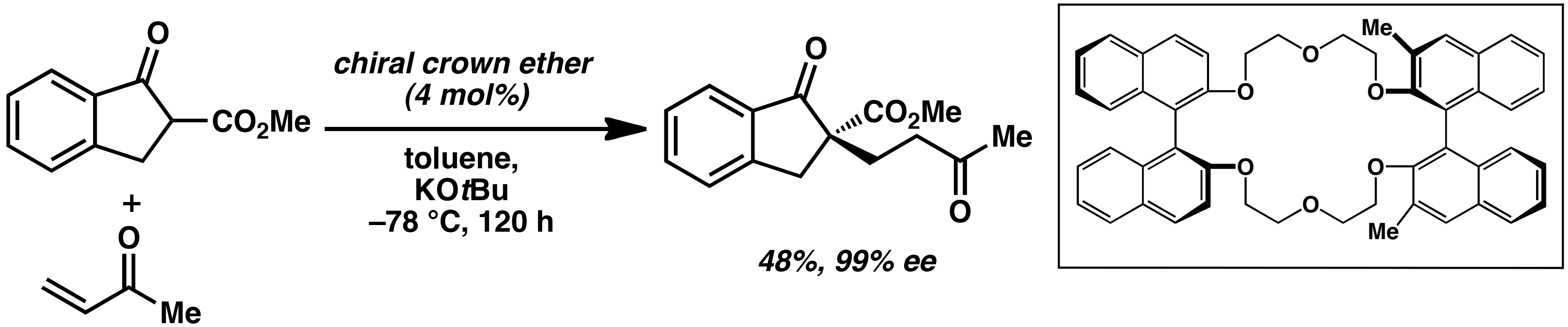


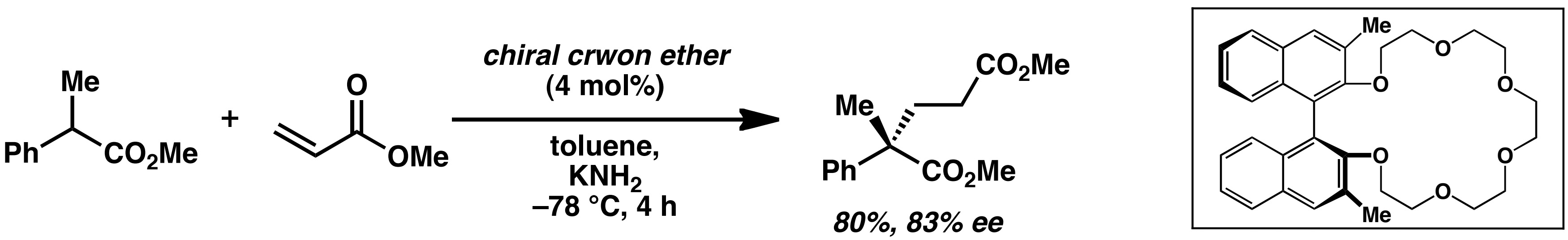
Catalyst	*t [h]*	*Yield [%]*	*de [%]*
TBAB	4	85	8
chiral ammonium salt	6	97	97

O'Donnell, *Pol. J. Chem.* **1994**, *68*, 2477–2488.
Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 579–582.

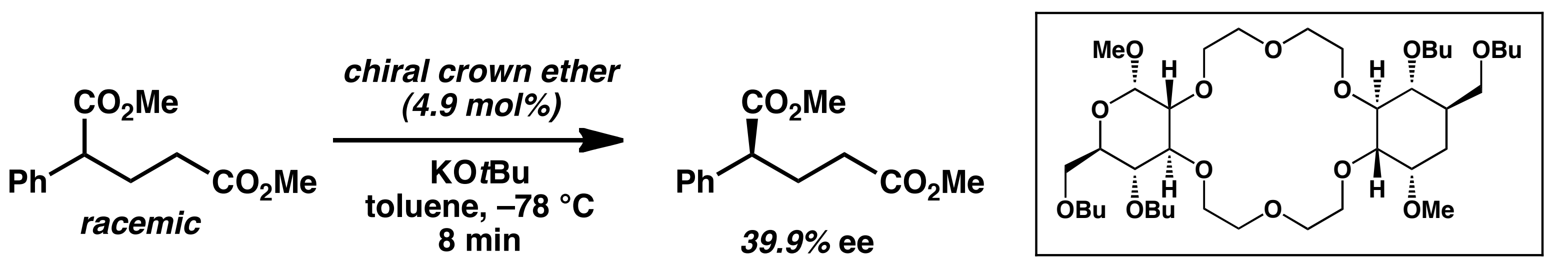
The First Successful Michael Addition

Chiral Crown Ethers



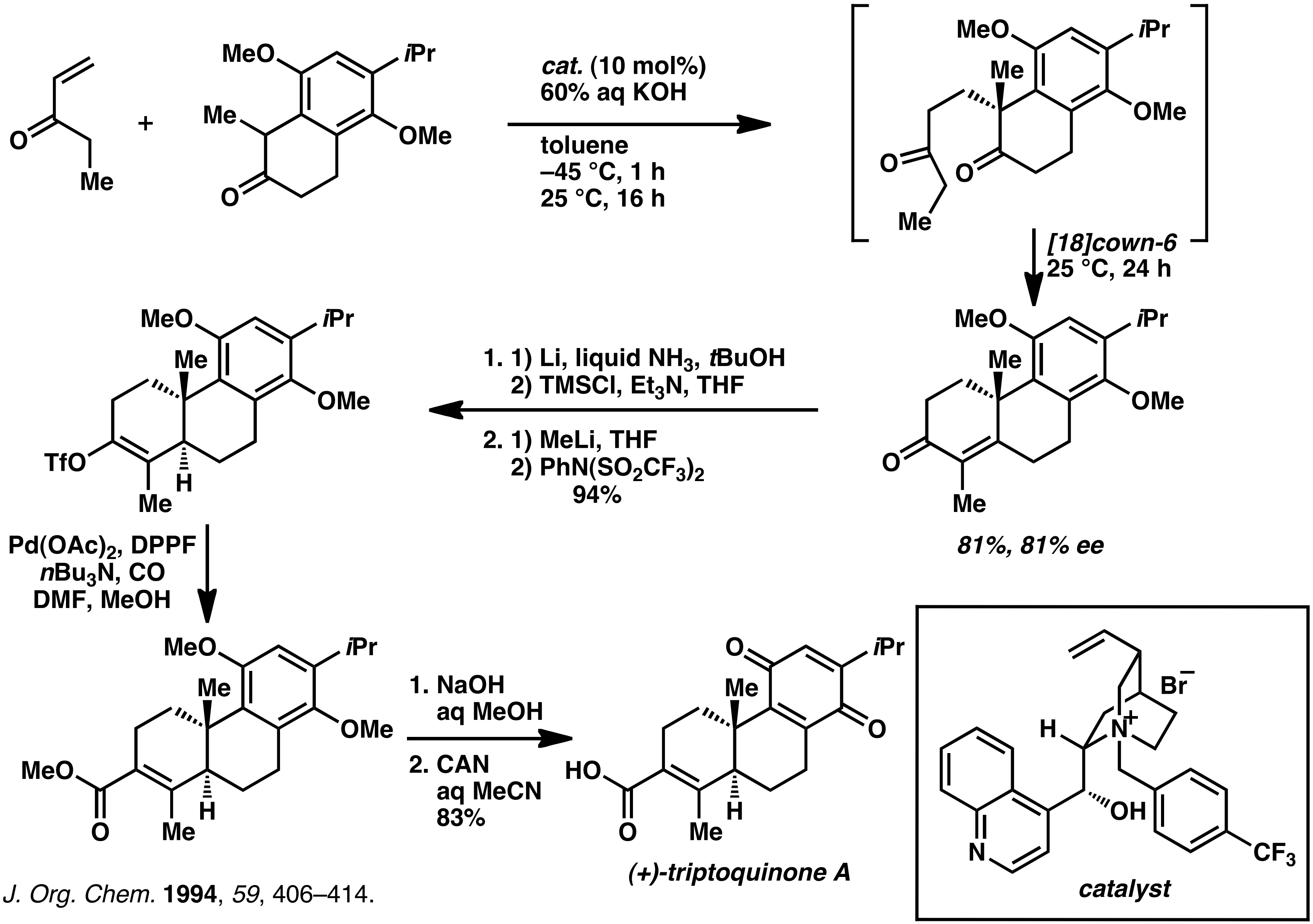


Deracemization



Cram, *J. Chem. Soc. Chem. Commun.* **1981**, 625–628.
Tõke, *Tetrahedron* **1998**, *54*, 213–222.

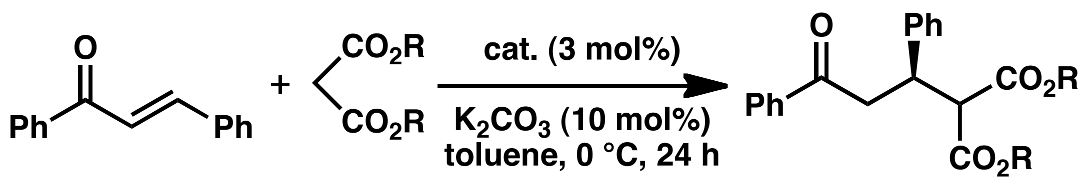
Michael Addition of Tetralone and Total Synthesis of (+)-Triptoquinone A

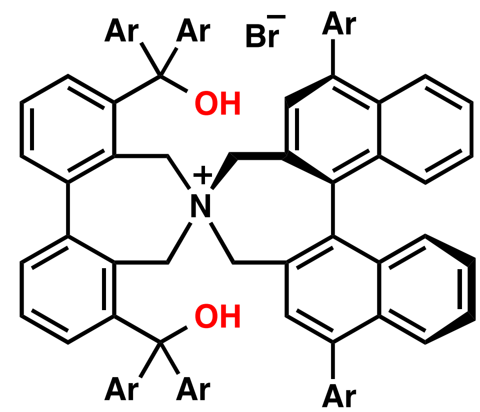


Shishido, *J. Org. Chem.* **1994**, *59*, 406–414.

Asymmetric Michael Addition of Diethyl Malonate and Malononitrile to Chalcone

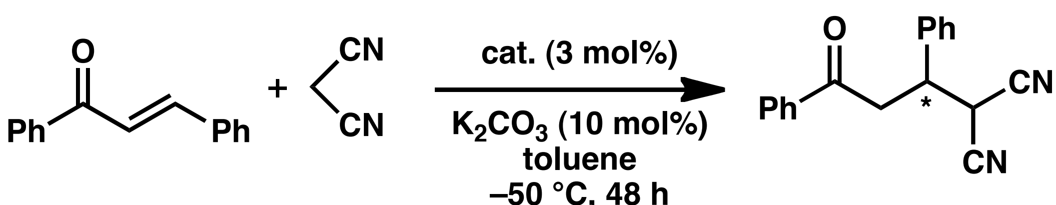
Dual-Functioning Chiral Phase-Transfer Catalyst



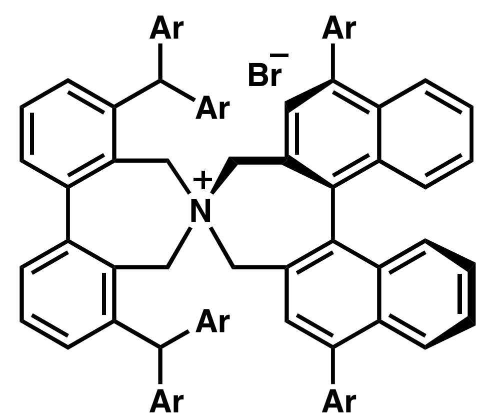


Ar = 3,5-Ph_2-C_6H_3

catalyst	*R*	*% yield*	*% ee*
OH-ammonium bromide	Me	99	84
	Et	99	90
	Bn	99	61
	i-Pr	99	74
	t-Bu	NR	
ammonium bromide	Et	98	15

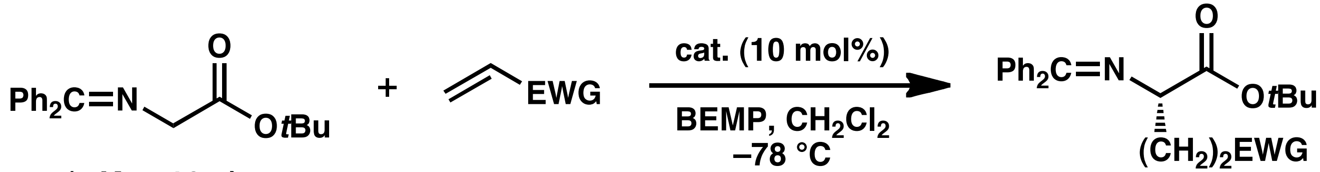


98%, 81% ee

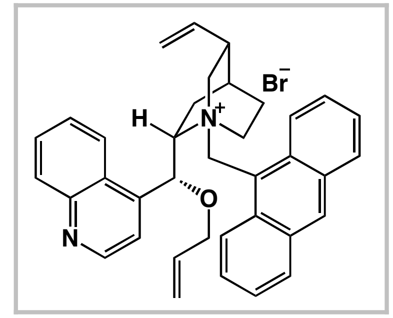


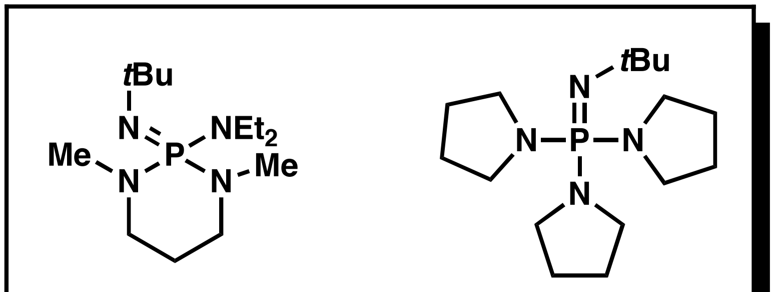
Maruoka, *Org. Lett.* **2005**, *7*, 3195–3197.

Use of Organic-Soluble Base BEMP



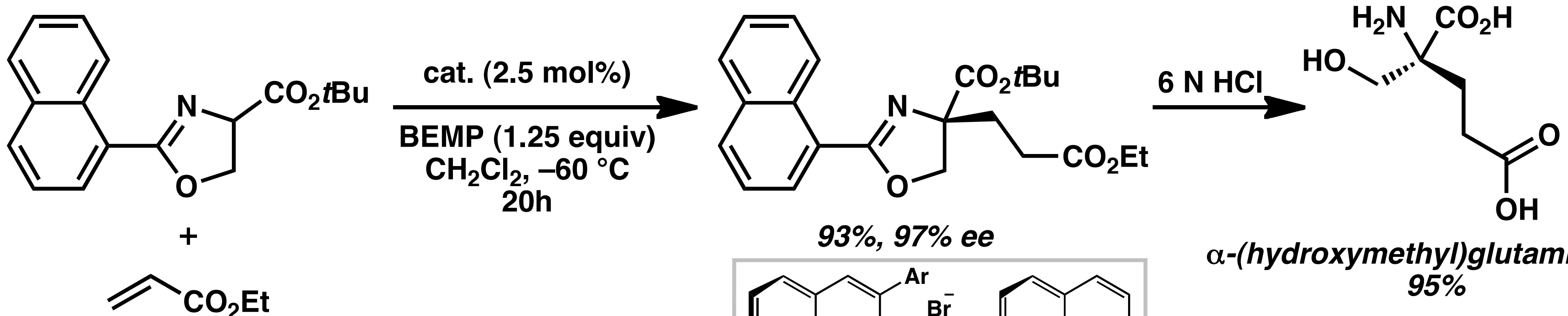
(pK_a = 19.7)





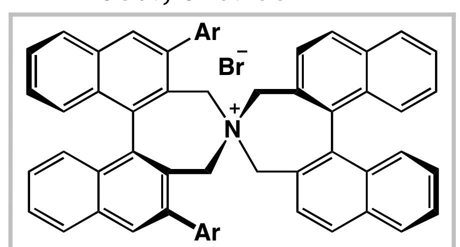
BEMP **(pK_a = 16.2)** ***BTPP*** **(pK_a = 17.0)**

EWG = CO_2Me	**:**	**93%, 89% ee**
[with *BTPP*	**:**	**92%, 86% ee]**
CN	**:**	**83%, 84% ee**
COMe	**:**	**82%, 89% ee**
COEt	**:**	**87%, 87% ee**
SO_2Ph	**:**	**91%, 76% ee**



93%, 97% ee

α-(hydroxymethyl)glutamic acid
95%

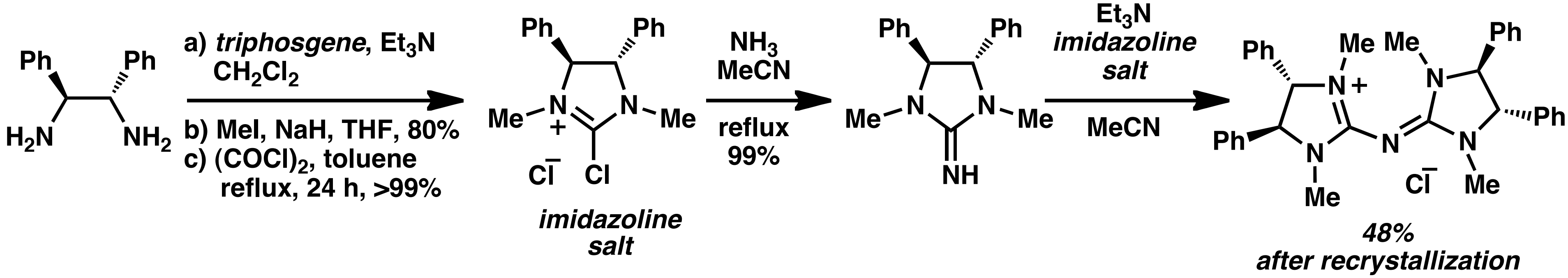


Ar = 3,4,5-$F_3C_6H_2$

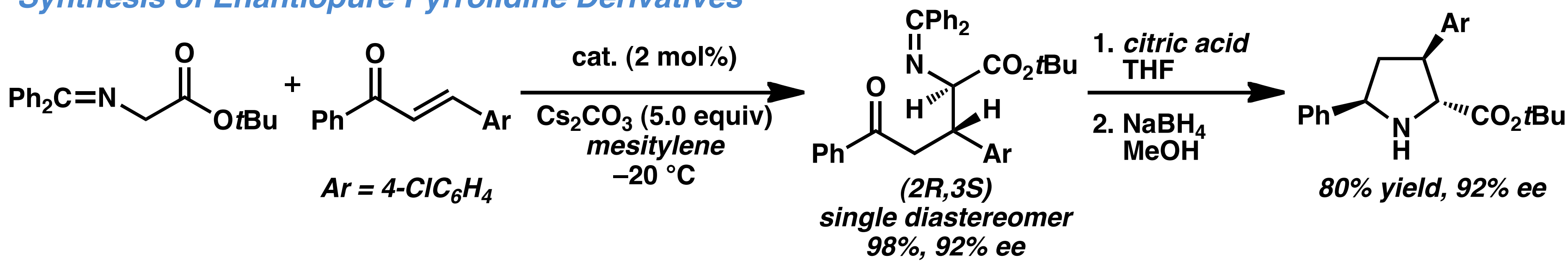
O'Donnell, *Tetrahedron: Asymmetry* **2001**, *12*, 821–828.
Jew, Park, *Org. Lett.* **2005**, *7*, 3207–3209.

New Phase-Transfer Catalysts

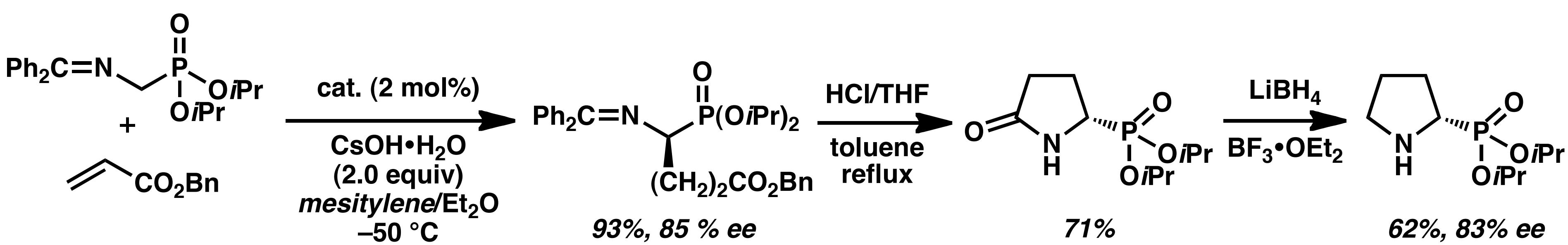
Preparation of Pentanidium Chloride: New Catalyst



Synthesis of Enantiopure Pyrrolidine Derivatives

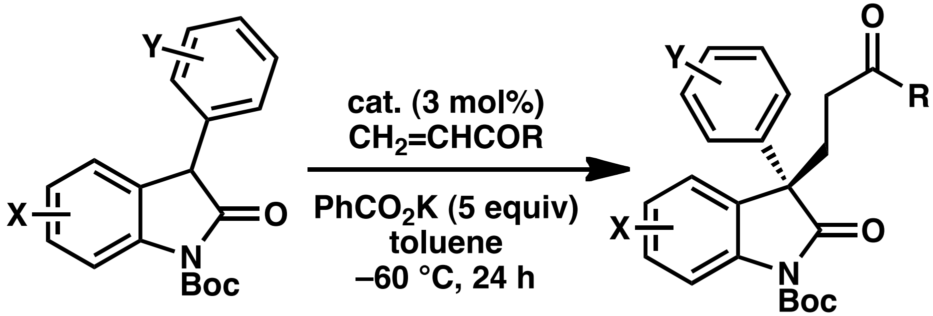


Synthesis of Enantiopure Phosphonic Analogues of (S)-Proline

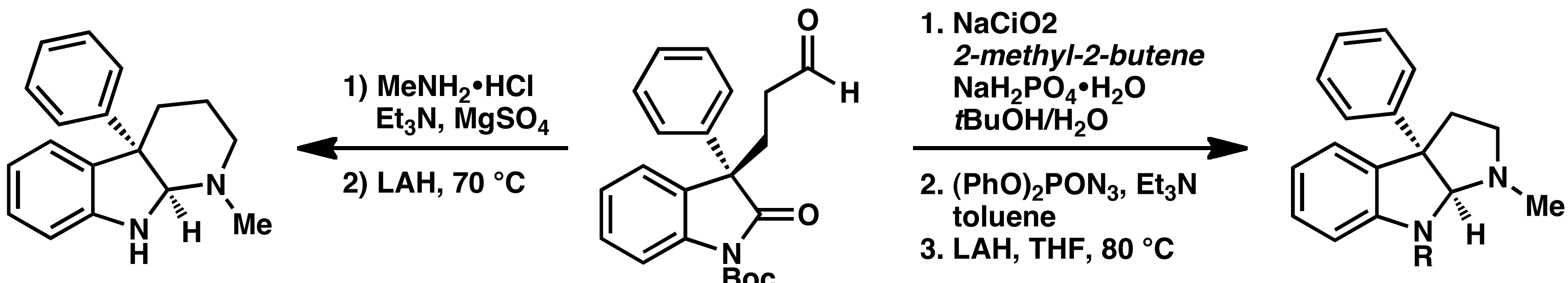


Tan, *J. Am. Chem. Soc.* **2011**, *133*, 2828–2831.

Chiral Phosphonium Salts as Chiral PTCs

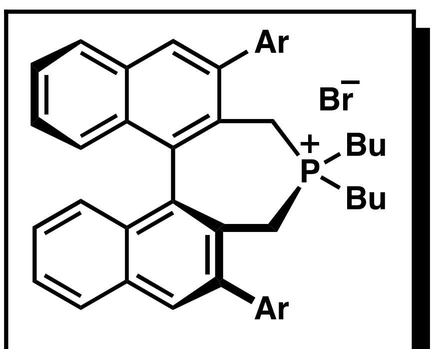


3-aryloxindole (X, Y)	*acceptor (R)*	*% yield*	*% ee*
(H, H)	Me	97	99
(H, 4-F)	Me	99	99
(H,4-OMe)	Me	96	94
(H, H)	Et	97	96
(H, 3-Cl)	Et	98	96
(H, H)	H	93	90
(5-F, H)	H	99	90

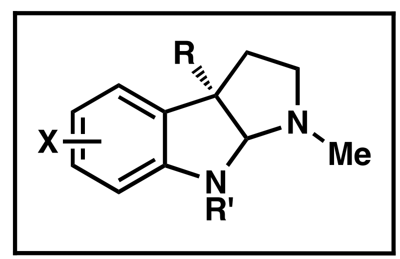


89% ee

R = H, 35%, 90% ee
R = Me, 40%



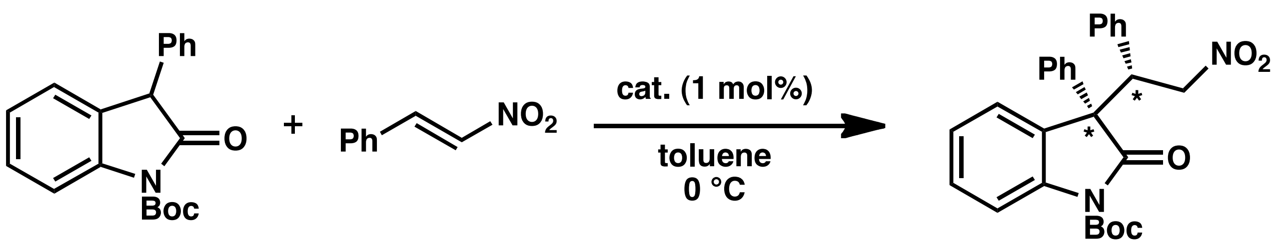
Ar = 3,5-$(CF_3)_2$-C_6H_3

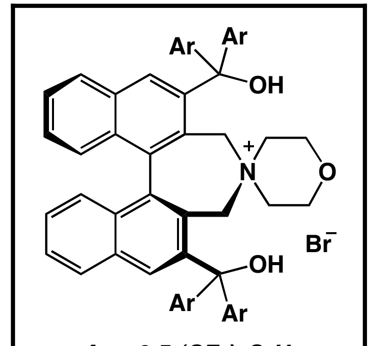


core structure of natural alkaloids

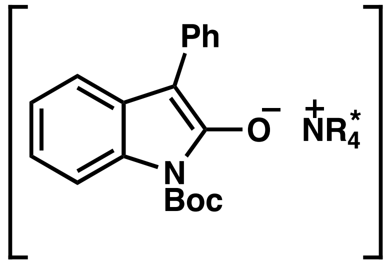
Maruoka, *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561.

Enantioselective Base-Free Phase-Transfer Reaction



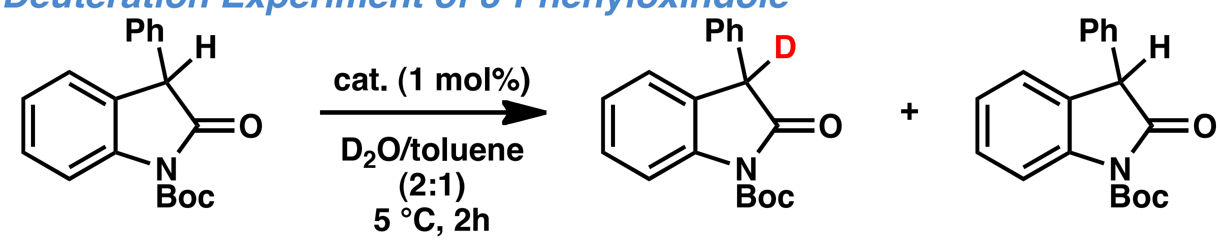


Ar = 3,5-$(CF_3)_2C_6H_3$



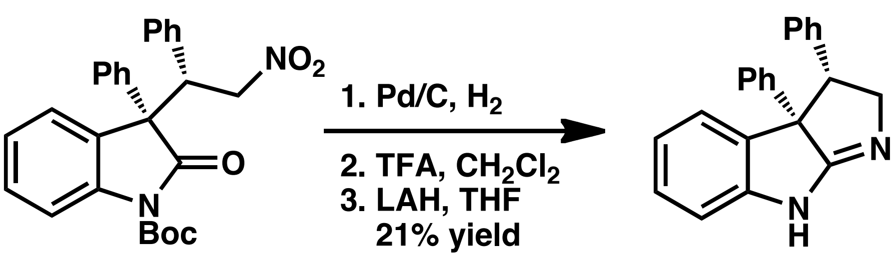
33% aq K_2CO_3 (10 min): 96%, 84:16 dr, 82% ee
10% aq $PhCO_2K$ (1 h): 95%, 88:12 dr, 83% ee
H_2O (2 h): 96%, 91:9 dr, 90% ee
Without H_2O & base: No reaction
H_2O buffer (pH 6.8) (1 h): 98%, 92:8 dr, 91% ee
H_2O buffer (pH 7.0) (1 h): 96%, 92:8 dr, 91% ee
H_2O buffer (pH 7.2) (1 h): 97%, 92:8 dr, 91% ee

Deuteration Experiment of 3-Phenyloxindole

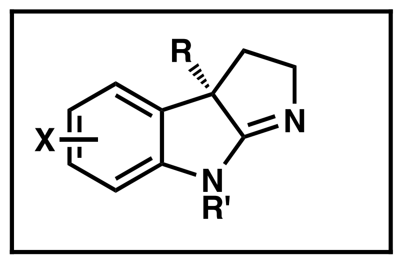


88% *11%*

Without the chiral catalyst
or With Bu_4NBr:
No deuterated product formed



90% ee

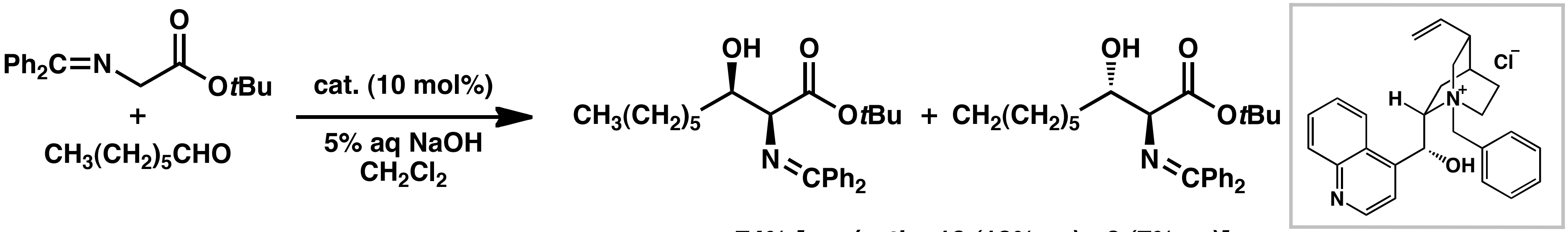


core structure of natural alkaloids

Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620–16621.

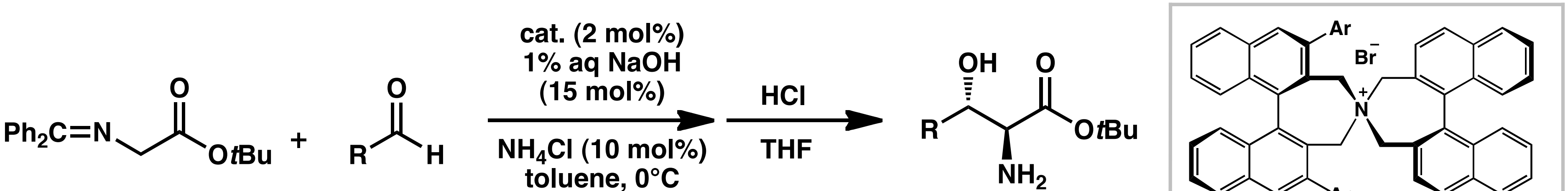
Aldol Reactions

First Example of a Phase-Transfer-Catalyzed Direct Asymmetric Aldol Reaction

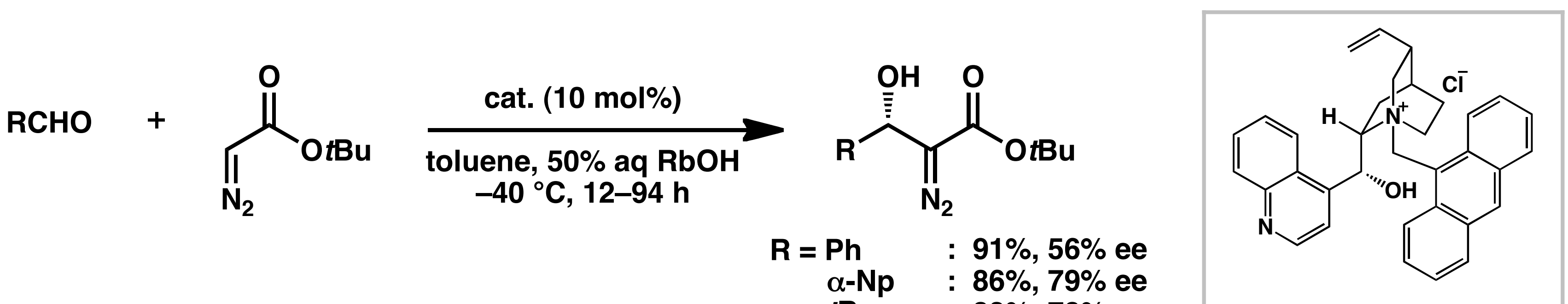


74% [syn/anti = 10 (12% ee) : 3 (7% ee)]

Highly Selective Aldol Reaction



Asymmetric Aldol Reactions of Diazoesters

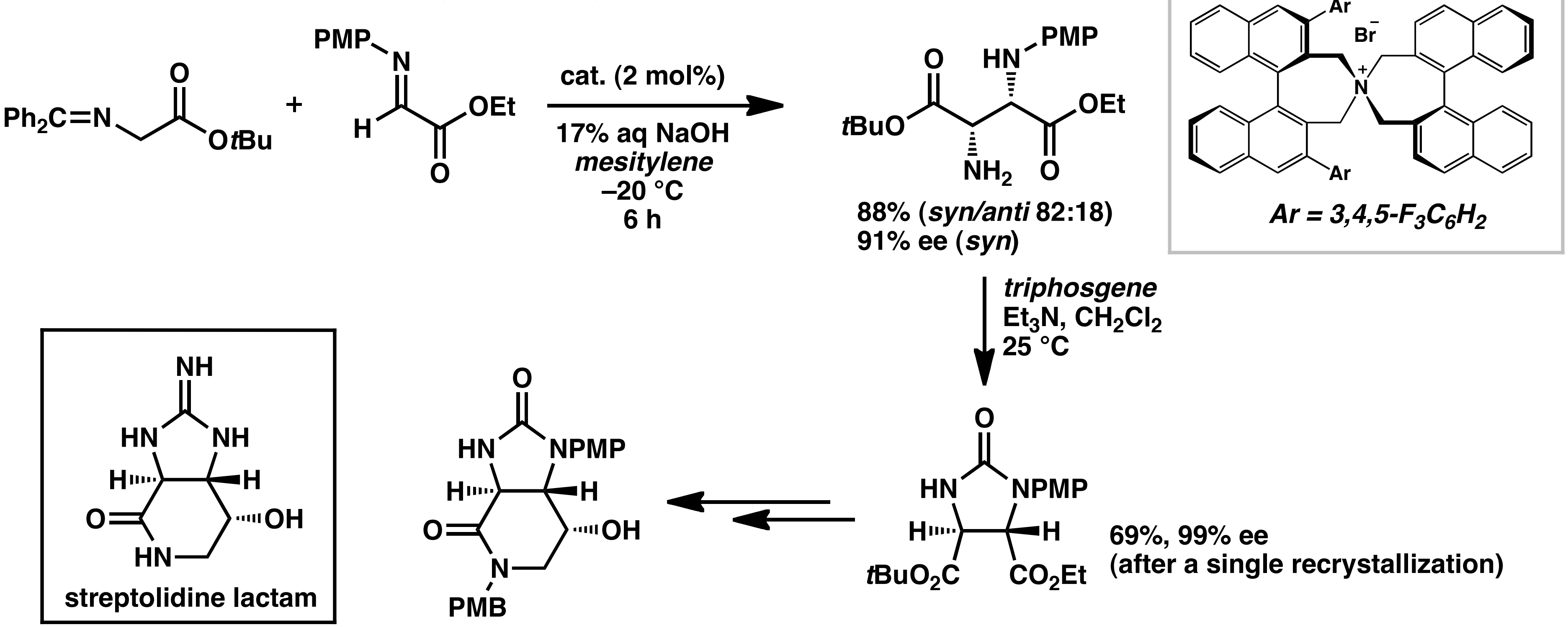


R = Ph : 91%, 56% ee
α-Np : 86%, 79% ee
*t*Bu : 83%, 78% ee

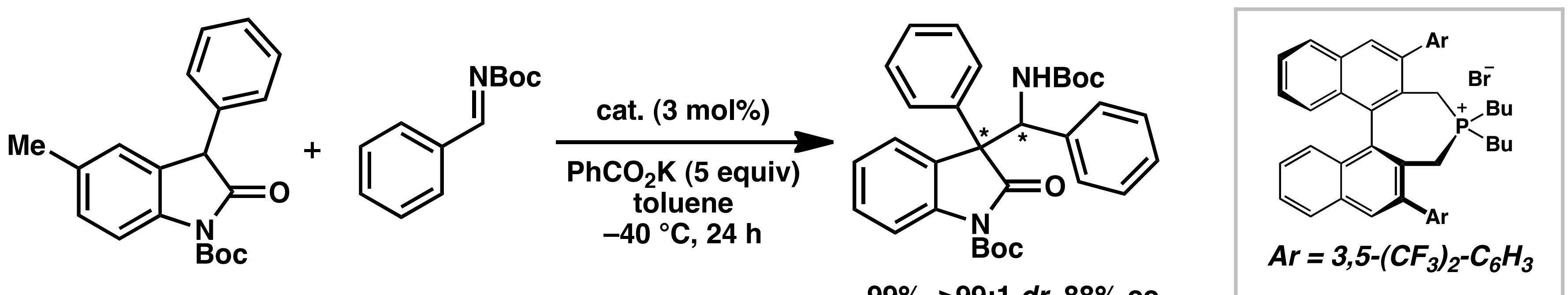
Miller, *Tetrahedron* **1991**, *47*, 5367–5378.
Maruoka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4542–4544.
Arai, Nishida, *Tetrahedron Lett.* **2004**, *45*, 1023–1026.

Asymmetric Mannich Reactions

Mannich Approach to a Nitrogen Analogue of Dialkyl Tartrate

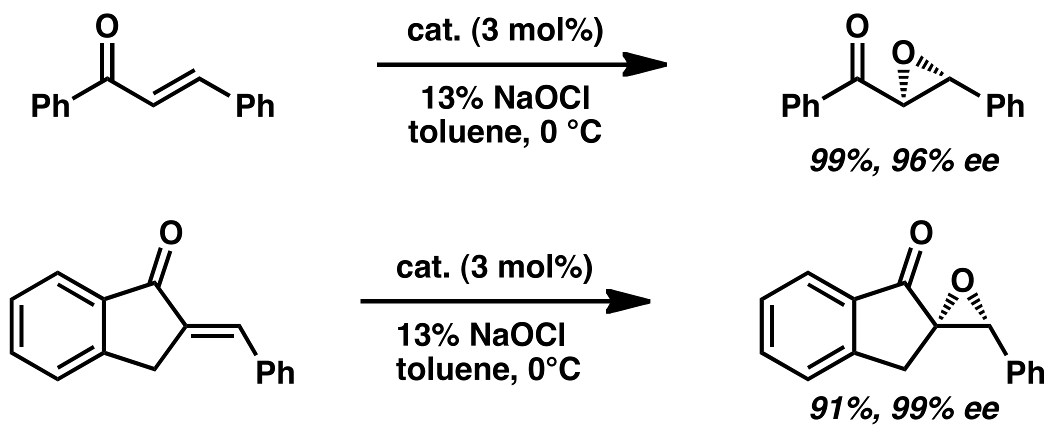


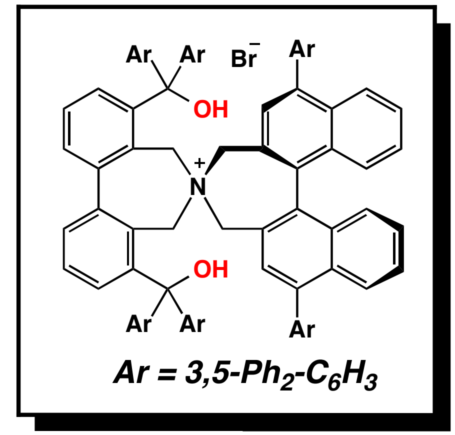
Asymmetric Mannich Addition of 3-Aryloxindole



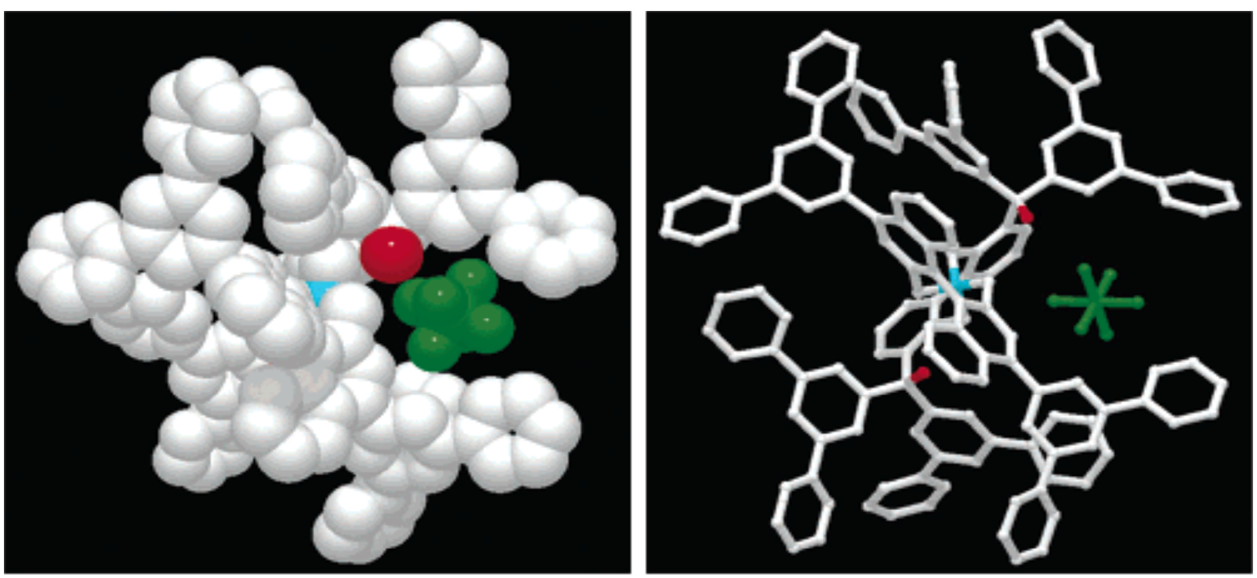
Maruoka, *Org. Lett.* **2004**, *6*, 2397–2399.
Maruoka, *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561.

Chiral Phase-Transfer Catalyst with Dual Functions





X-Ray Structure of the Ammonium-PF_6



(a) CPK (b) Stick

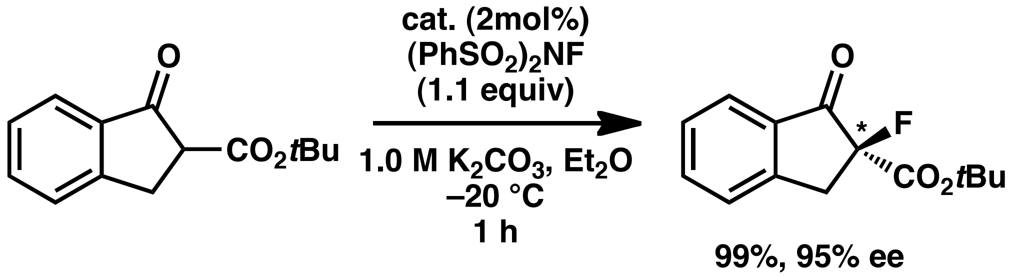
- ***The biphenyl and binaphthyl subunits are nearly perpendicular.***
  → Creating a chiral reaction cavity
- ***PF_6 ion is located inside the cavity being surrounded by diphenylphenyl groups.***
  → Properly positioning hypochlorite ion in the cavity
- ***OH is situated right above N and sticks to PF_6 ion.***
  → Bringing enones inside the cavity resulting an ideal proximity to hypochlorite

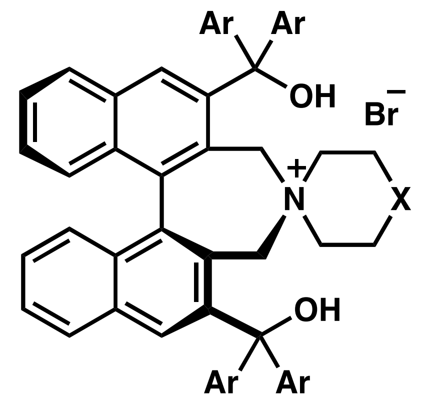
N: blue, PF_6: green, O: red

Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845.

Fluorination and Strecker Reaction

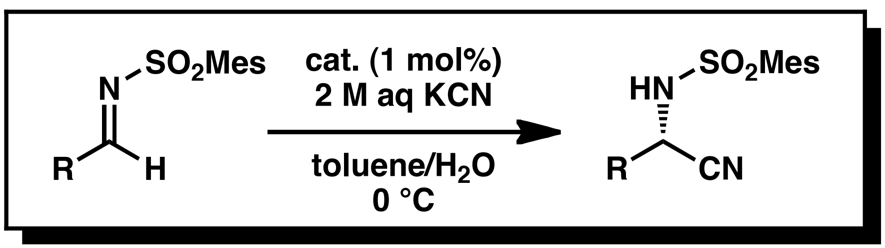
Catalytic Asymmetric Fluorination of β-Keto ester



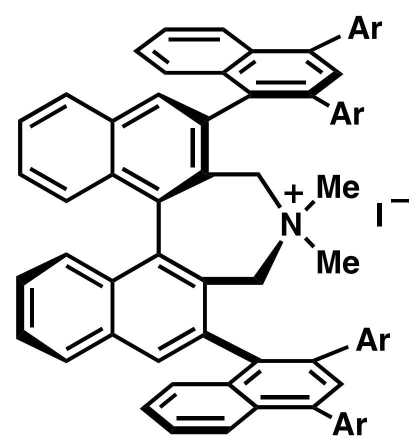


Ar = 3,5-$(CF_3)_2$-C_6H_3
X = O or S

First Phase-Transfer-Catalyzed Enantioselective Strecker Reaction



Mes = mesityl

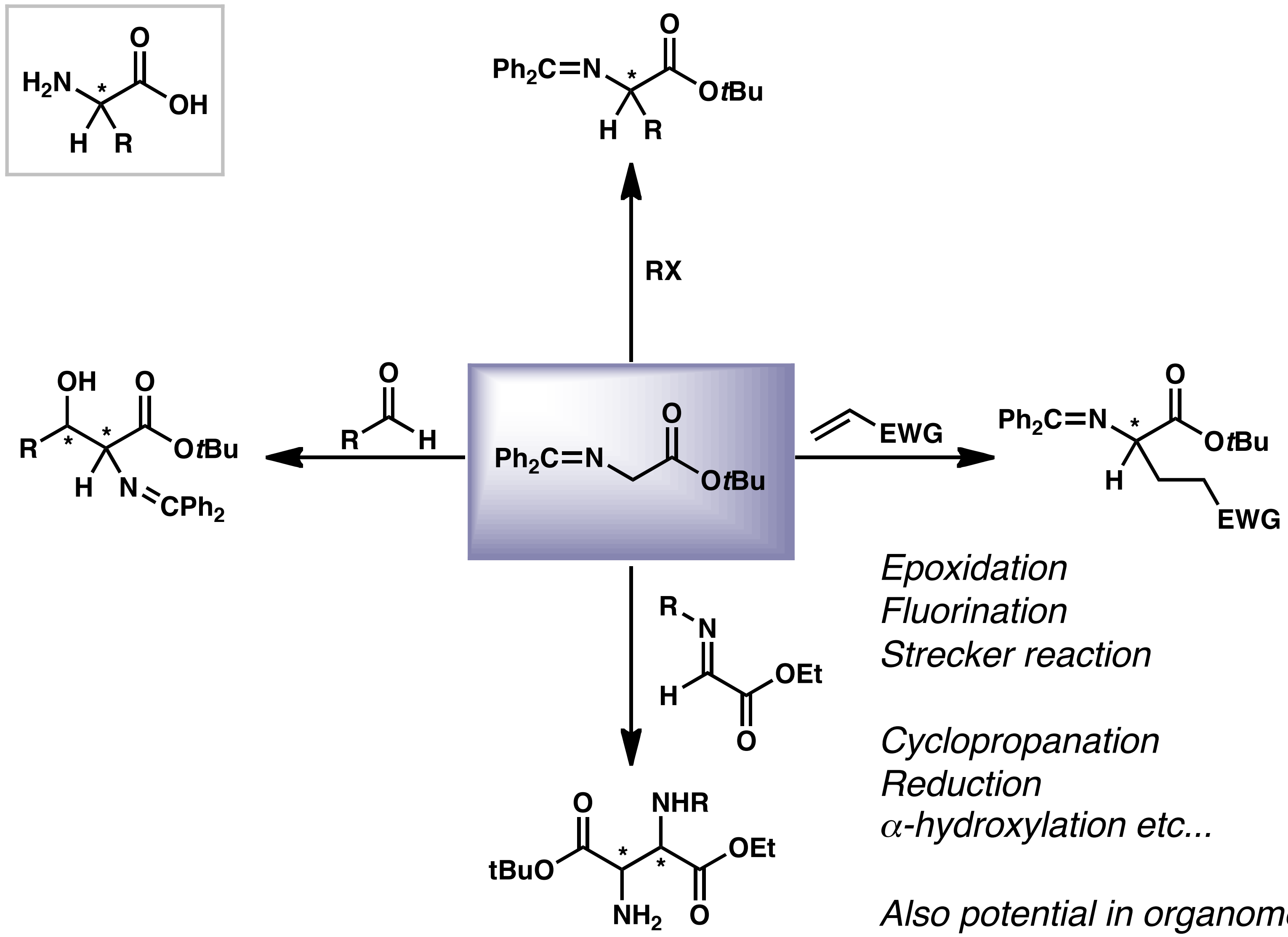


Ar = *p*-CF_3-C_6H_4

R =		
	c-Oct	88%, 97% ee
	i-Pr	85%, 93% ee
	$Ph(CH_2)_2$	81%, 90% ee
	$(CH_3)_2CHCH_2$	82%, 88% ee
	t-Bu	94%, 94% ee
	$Ph(CH_3)_2C$	95%, 98% ee

Maruoka, *Chem. Commun.* **2010**, *46*, 321–323.
Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548–2549.

Summary



Epoxidation
Fluorination
Strecker reaction

Cyclopropanation
Reduction
α-hydroxylation etc...

Also potential in organometallics

Acknowledgement

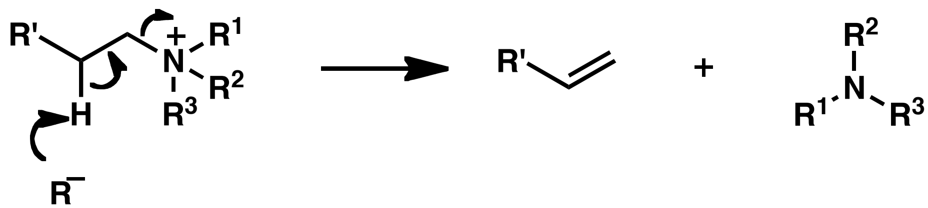
Prof. Brian Stoltz

Prof. Sarah Reisman

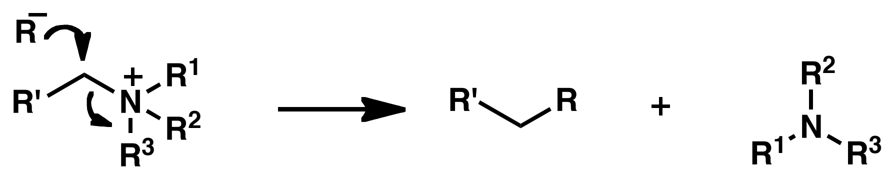
Stoltz Group
Reisman Group

Stability of the Onium Carbanion

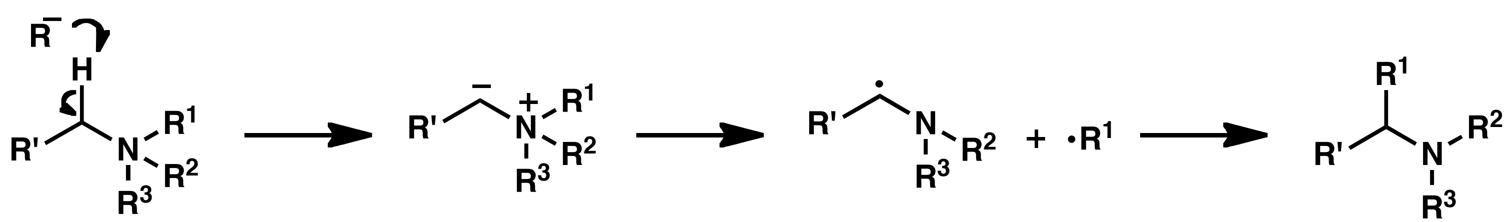
Hoffman Elimination



Nucleophilic Substitution

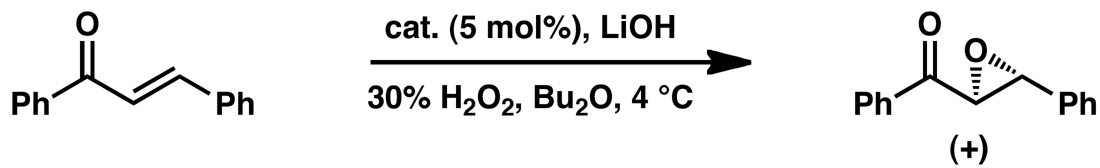


Stevens Rearrangement

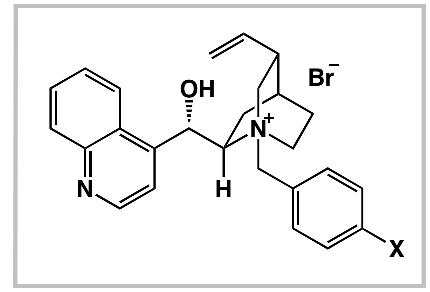


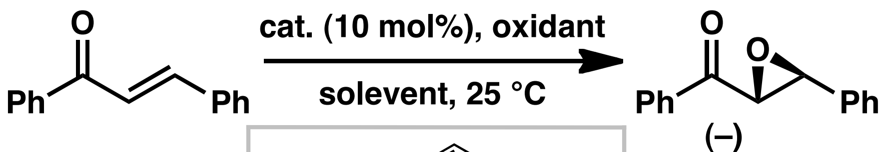
Asymmetric Epoxidation

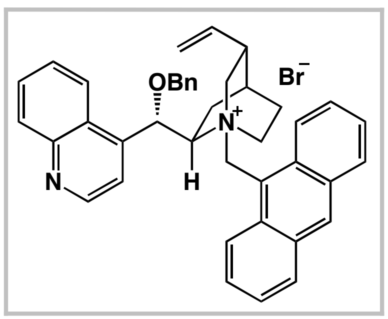
Influence of O- and N-Substituents in Catalyst, Oxidant, and Solvent



X = H : 72%, 1% ee
X = Cl : 68%, 65% ee
X = I : 97%, 84% ee



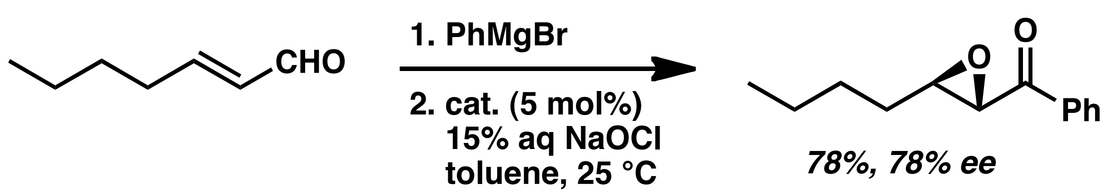


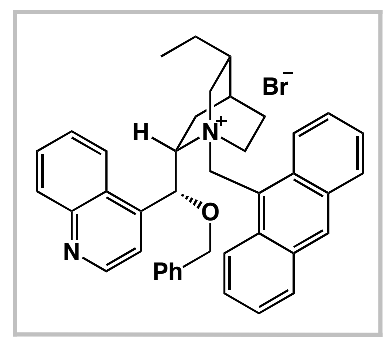


Solvent	*Oxidant*	*Time*	*% ee*	*% Yield*
toluene	**11% aq NaOCl**	**48**	**81**	**90**
toluene	30% aq H_2O_2*	48	10	69
CH_2Cl_2	11% aq NaOCl	48	66	60
CH_2Cl_2	30% aq H_2O_2*	48	2	<10

** 1 drop of 50% aq KOH also added.*

Transformation of an α,β-Unsaturated Aldehyde to an α,β-Epoxy Ketone





Arai, Shioiri, *Tetrahedron* **2002**, *58*, 1623–1630.
Lygo, *Tetrahedron.* **1999**, *55*, 6289–6300.
Lygo, *Chem. Commun.* **2002**, 2360–2361.