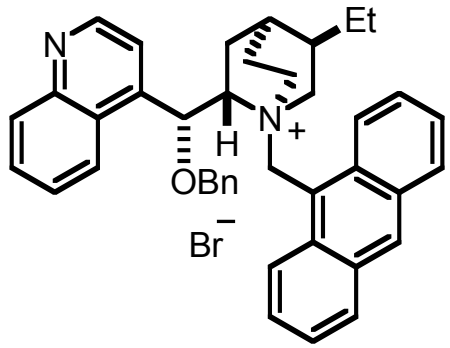
Asymmetric Transformations with Chiral Phase Transfer Catalyst



Group meeting

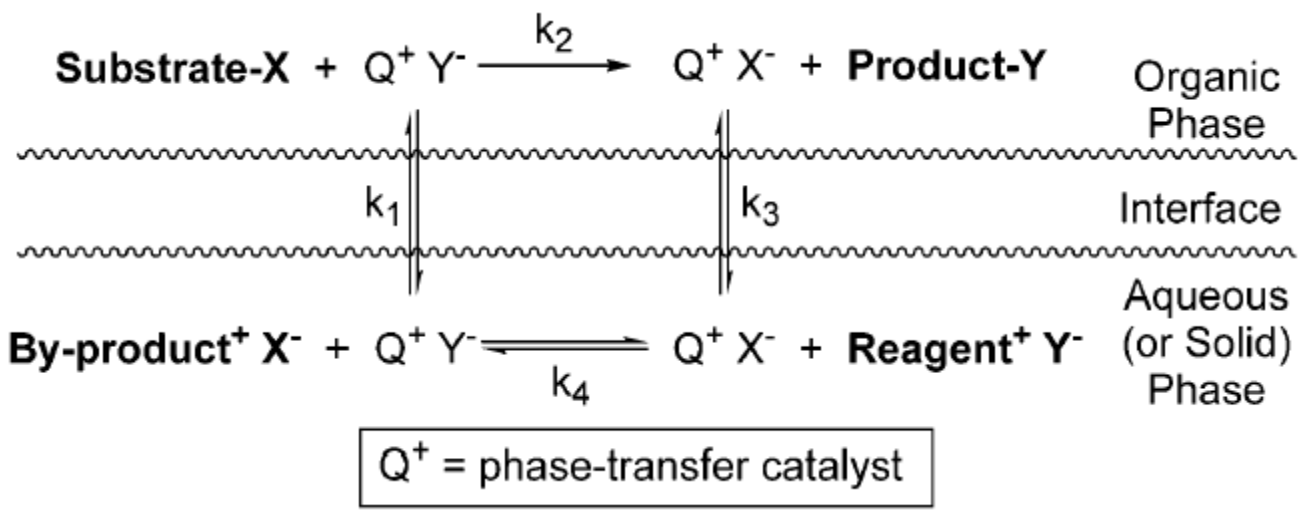
Nov. 16th, 2004

Won-jin Chung

Phase-Transfer Catalyst

Definition : Phase-Transfer Catalysis

The phenomenon of rate enhancement of a reaction between *chemical species* located in different phases by addition of a small quantity of an agent that extracts one of the reactants, most commonly an anion, across the interface into the other phase so that reaction can proceed.



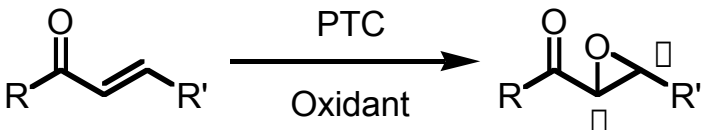
Advantages

- The reactivity of anion in the organic phase is usually enhanced due to the greater charge separation and reduced hydration.
- The reaction conditions are compatible with many organic solvent.
- The substrate itself can be used as the organic phase.
- The biphasic nature of these processes simplifies the separation.
- The catalysts are usually inexpensive and biodegradable.

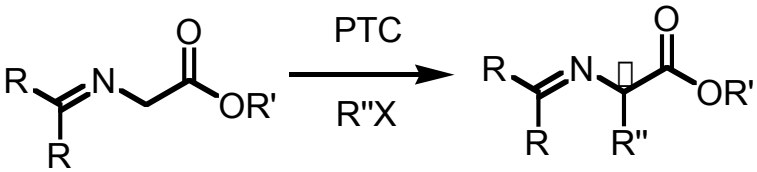
Lygo, B. *et. al. Acc. Chem. Res.* **2004**, *37*, 518.

Asymmetric Phase Transfer Catalysis

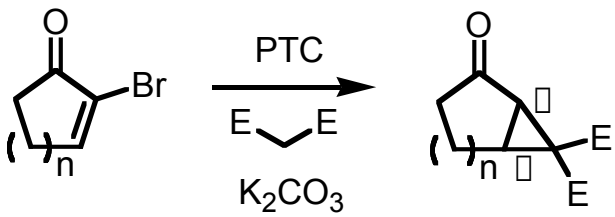
1. Epoxidation



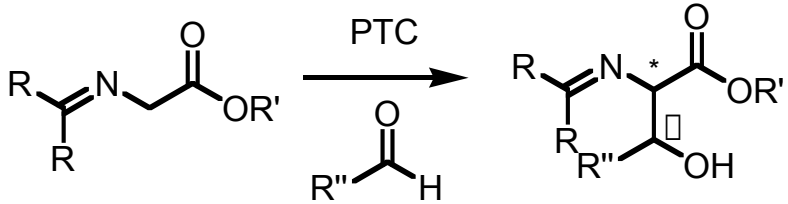
2. Alkylation



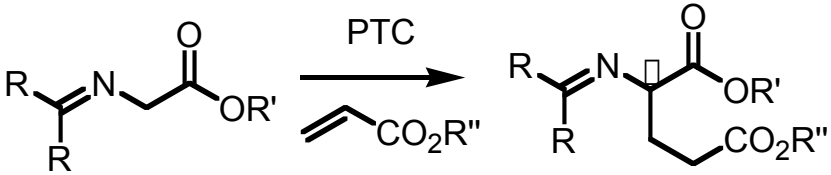
3. Cyclopropanation



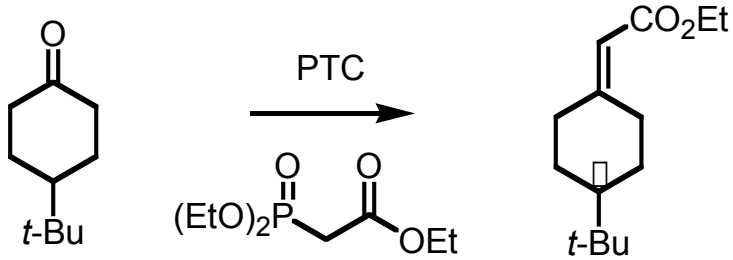
4. Aldol type reaction



5. Michael reaction

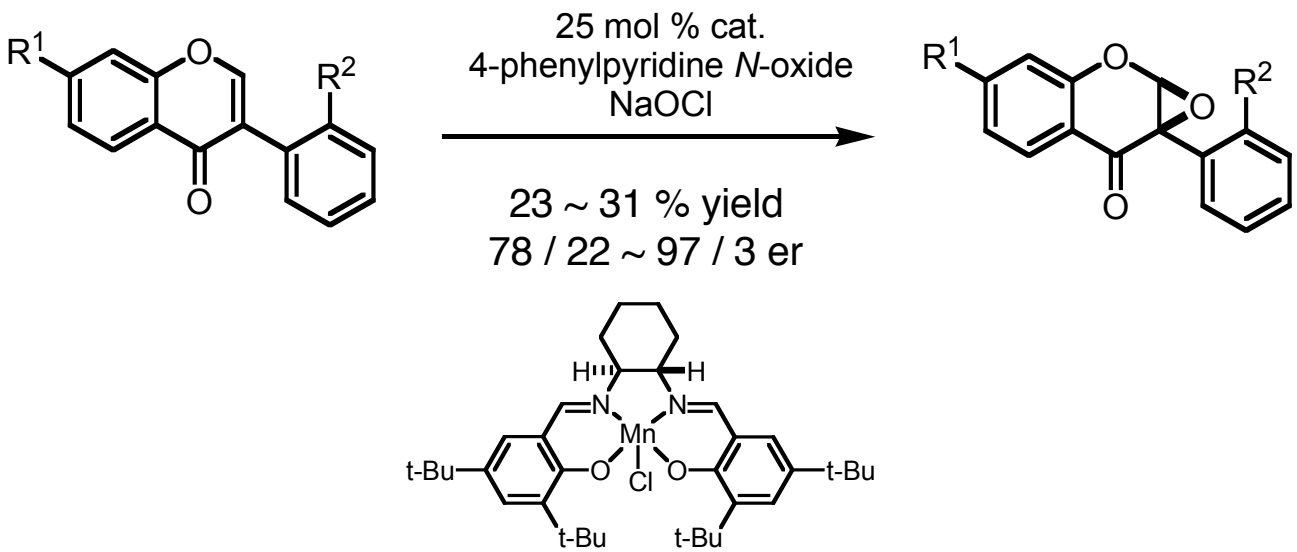


6. HWE reaction

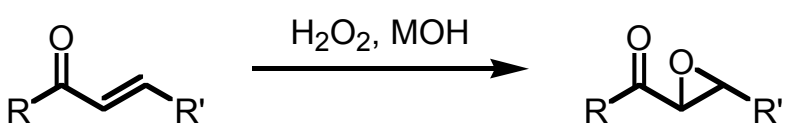


Asymmetric Epoxidation of e^- Deficient Olefin

- Electron deficient olefins suffer from low reactivity.



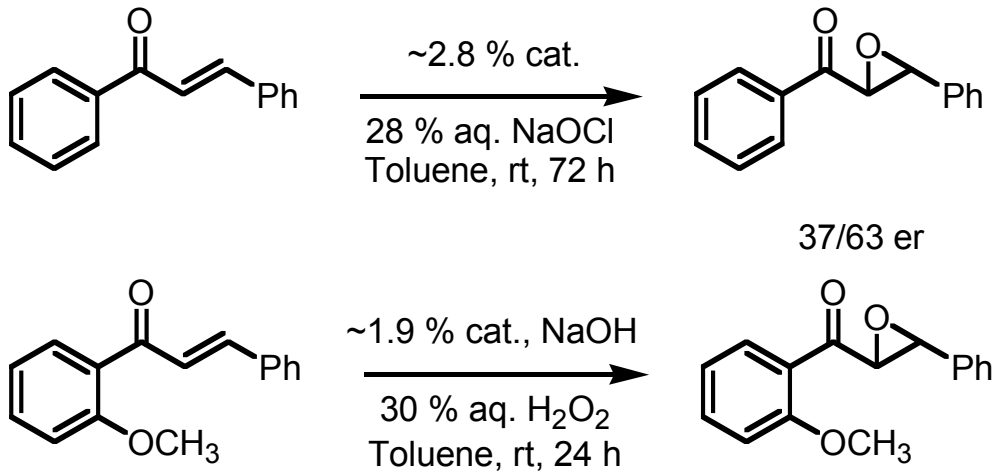
- Weitz-Scheffer epoxidation

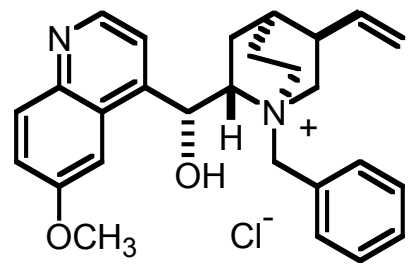


Alkaline H_2O_2
Selective for electron deficient alkene

Levai, A. *et. al. Tetrahedron* **1998**, *54*, 13105.
Weitz, E. and Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327.

Asymmetric Epoxidation with Chiral PTC





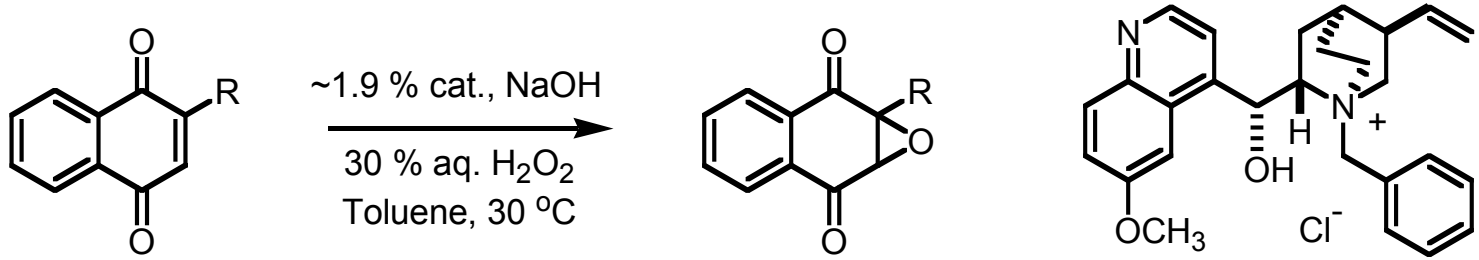
Solvent	*D*	1/*D*	er
$PhNO_2$	34.8	0.03	55 : 45
CH_2Cl_2	9.1	0.11	64 : 36
PhCl	5.71	0.18	67 : 33
o-$Me_2C_6H_4$	2.6	0.39	69 : 31
PhMe	2.44	0.41	74 : 26
C_6H_6	2.28	0.44	78 : 22

Wynberg, H. *et. al. Tetrahedron Lett.* **1976**, *17*, 1831.

Wynberg, H. *et. al. Tetrahedron Lett.* **1978**, *19*, 1089.

Wynberg, H. *et. al. JCS. Chem. Comm.* **1978**, 42

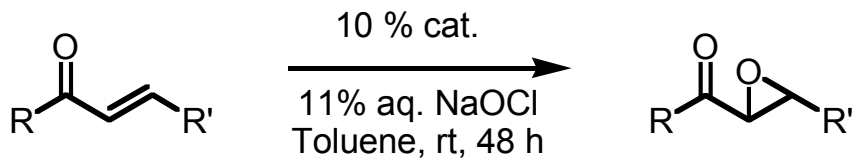
Asymmetric Epoxidation – *Z* alkene



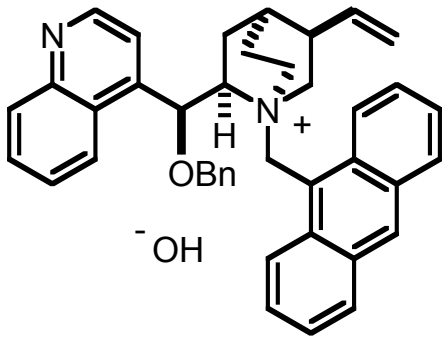
R	yield (%)	er
1° Alkyl groups	50 ~ 76	52.5/47.5 ~ 59/41
2° and 3° alkyl groups	60 ~ 100	58/42 ~ 69.5/30.5
Ph	92	72.5/28.5

Wynberg, H. *et. al. J. Org. Chem.* **1980**, *45*, 249

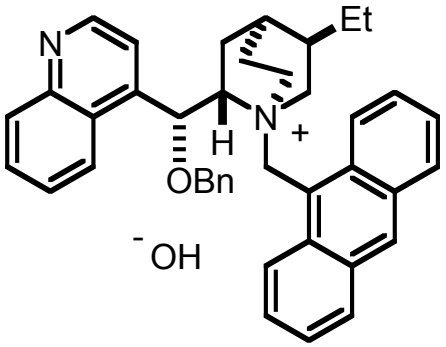
Asymmetric Epoxidation with Chiral PTC



When R and R' are aryl groups, the best results were obtained.



75 ~ 93 % yield
81 / 15 ~ 93 / 7 er



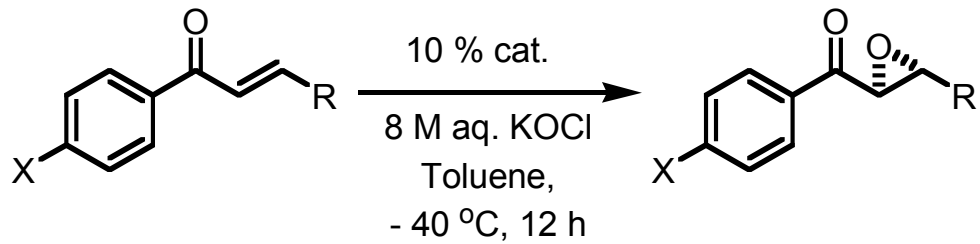
77 ~ 97 % yield
14 / 86 ~ 5 / 95 er

Enantioselectivity was improved by
- protecting alcohol
- introducing large N protection group.

Lygo B. *et. al. Tetrahedron Lett.* **1998**, *39*, 1599.
Lygo B. *et. al. Tetrahedron* **1999**, *55*, 6189.

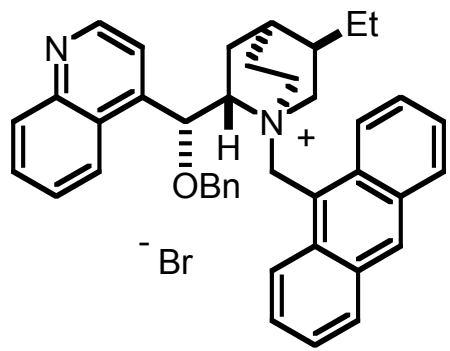
Asymmetric Epoxidation with Chiral PTC

- KOCl as oxidant

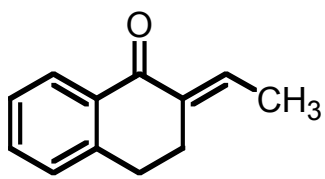


R = n-Pent, c-Hex, aryl
X = H, F, Br, RO

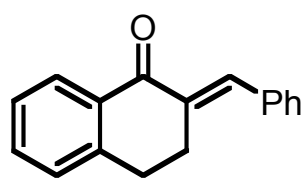
70 ~ 97 % yield
95.5/4.5 ~ 99/1 er



- Constrained enones



88/12 er

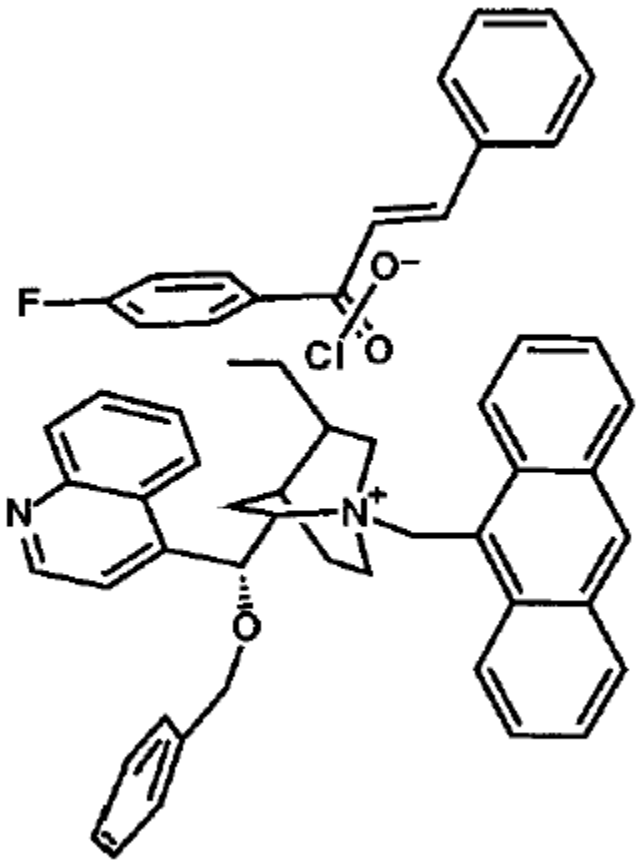


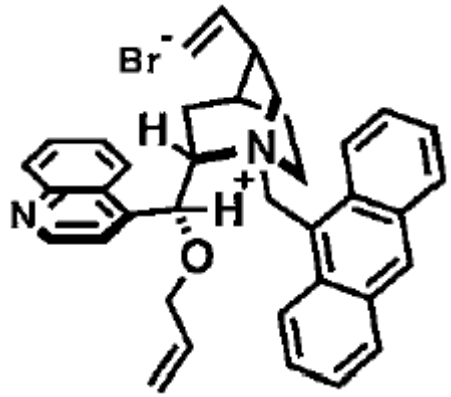
81/19 er

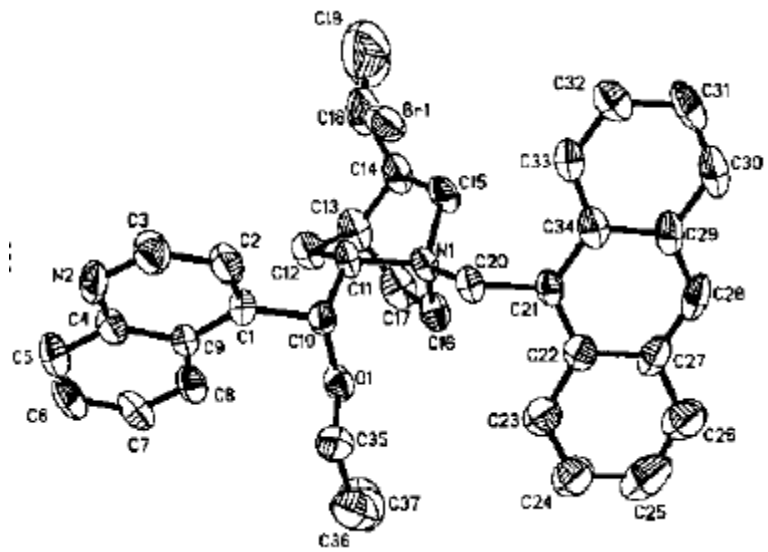
Phenyl substituent and the carbonyl π plane are nonplanar in TS.

Corey, E. J. *et. al. Org. Lett.* **1999**, *1*, 1287.

Asymmetric Epoxidation - TS

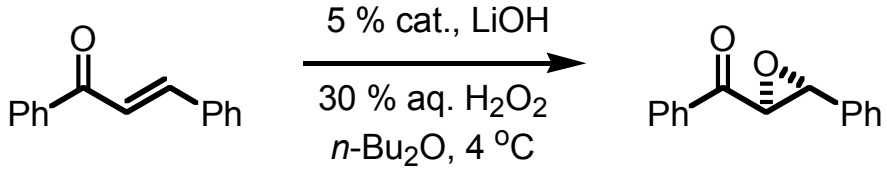




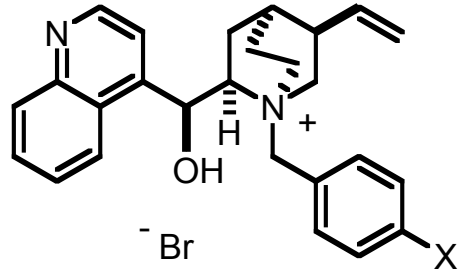


Corey, E. J. *et. al. Org. Lett.* **1999**, *1*, 1287.
Corey, E. J. *et. al. J. Am. Chem. Soc.* **1997**, *119*, 12414.

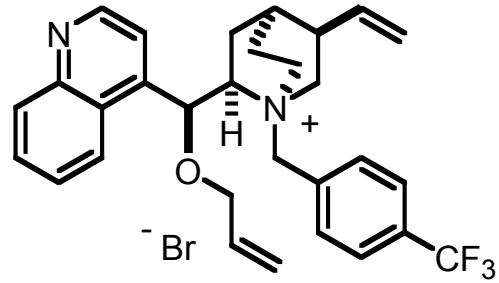
Asymmetric Epoxidation – H_2O_2



A



B

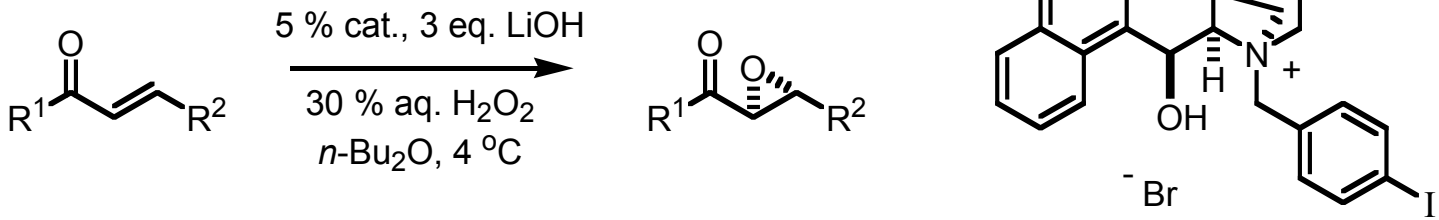


Entry	PTC	X	Yield (%)	er
1	A1	H	72	50.5/49.5
2	A2	CF_3	72	86.5/13.5
3	A3	NO_2	61	86/14
4	A4	I	97	92/ 8
5	A5	Br	56	88.5/11.5
6	A6	Cl	68	82.5/17.5
7	A7	F	24	51.5/48.5
8	A8	OCH_3	70	52/48
9	B		61	50/50

Arai S. *et. al. Tetrahedron* **2002**, *58*, 1623.

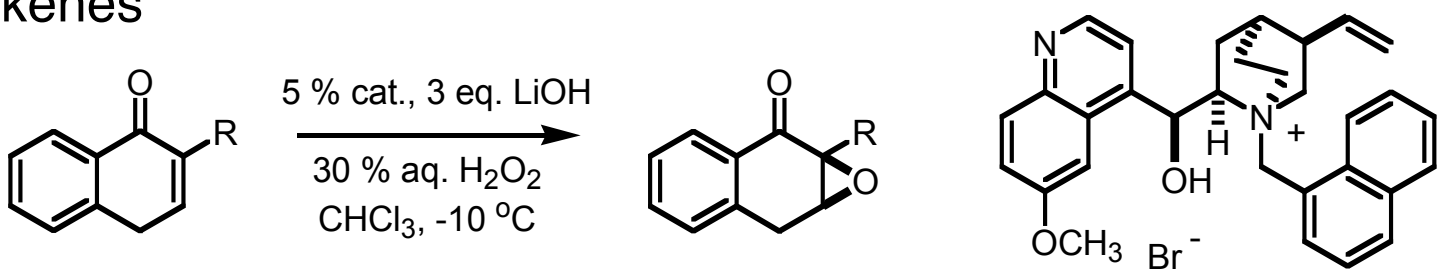
Asymmetric Epoxidation – H_2O_2

- *E*-alkenes



When R^1 and R^2 are aryl groups : 88 ~ 100 % yield, 82.5/17.5 ~ 96/4 er
When R^1 is phenyl and R^2 is alkyl : 41 ~ 82 % yield, 71/29 ~ 76.1/21.5 er

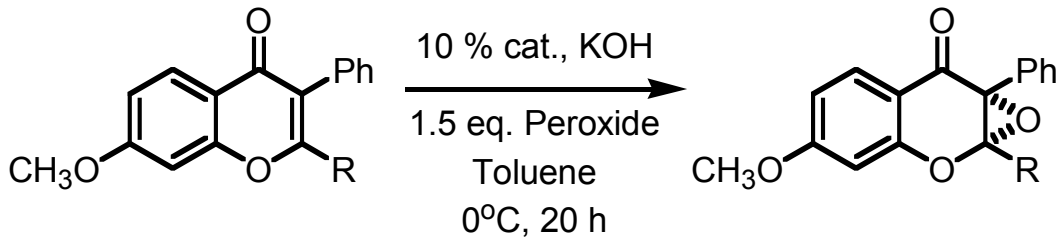
- *Z*-alkenes

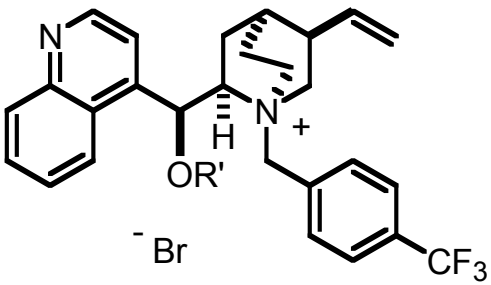


When R is 1° alkyl or acetylenyl : 87 ~ 99 % yield, 70/30 ~ 72/28 er
When R is 2° alkyl or Ph : 47 ~ 93 % yield, 82/18 ~ 88/12 er

Arai S. *et. al. Tetrahedron* **2002**, *58*, 1623.

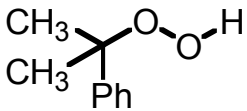
Asymmetric Epoxidation – Hydroperoxide





A : R' = H
B : R' = CH_3

Peroxide

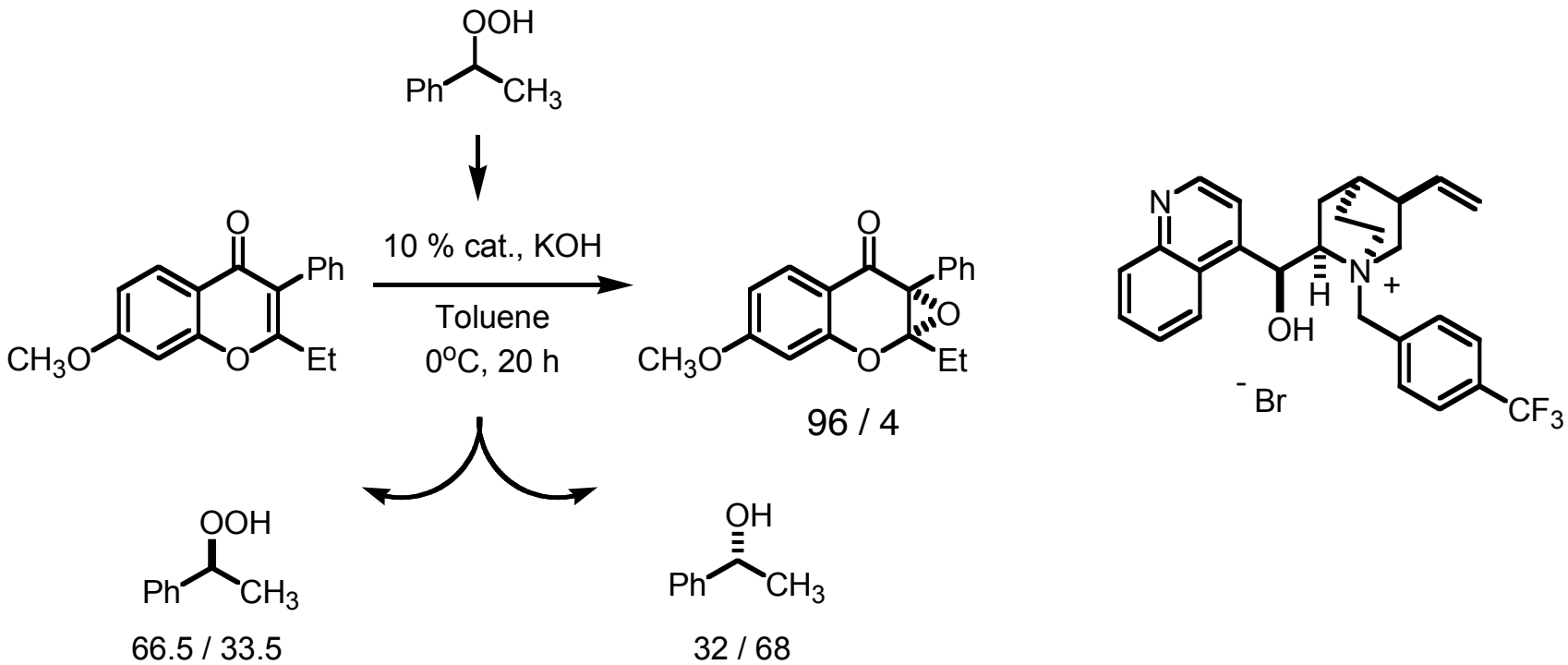


Entry	PTC	R	yield (%)	er
1	A	H	97	99 / 1
2	A	Me	97	94.5 / 5.5
3	A	Et	91	95 / 5
4	A	*i*-Pr	95	76.5 / 23.5
5	B	Et	95	70 / 30

OH is essencial for the high enantioselectivity.
Large R diminishes enantioselectivity.

Adam, W. *et. al. J. Org. Chem.* **2002**, *67*, 259.

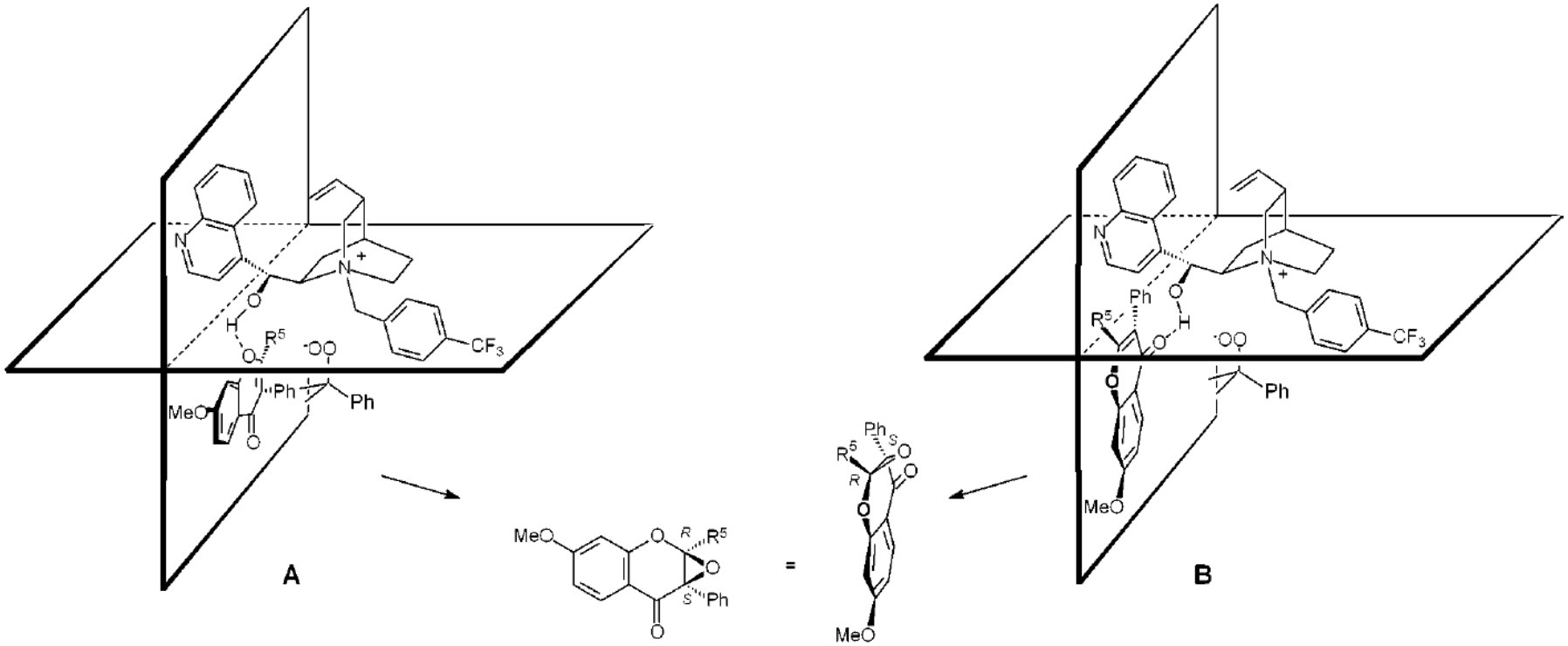
Asymmetric Epoxidation – Kinetic Resolution



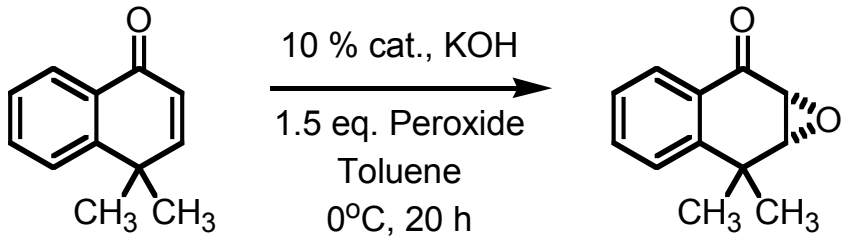
The moderate kinetic resolution
- Interaction between PTC and peroxide are not strong.

Adam, W. *et. al. J. Org. Chem.* **2002**, *67*, 259.

Asymmetric Epoxidation – TS

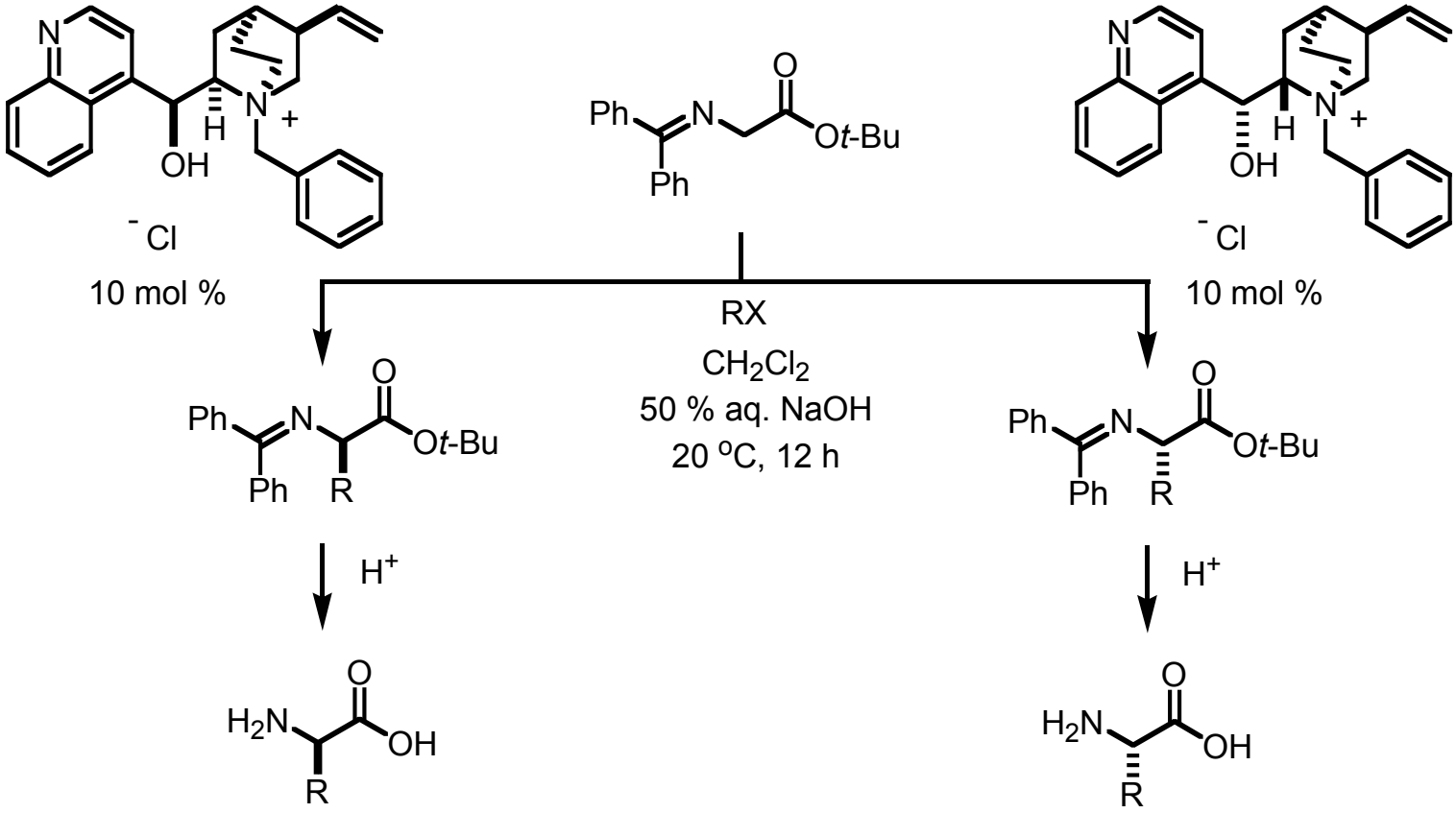


Aggregate A accounts best the observed enantioselectivity.



Adam, W. *et. al. J. Org. Chem.* **2002**, *67*, 259.

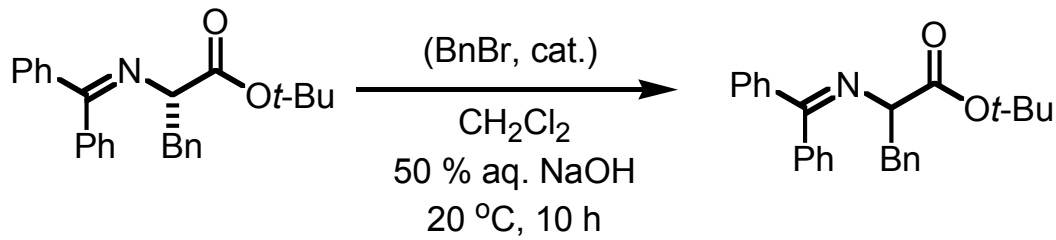
Asymmetric Alkylation – Amino Acid Synthesis

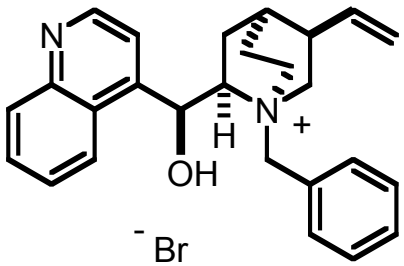


R = allyl, benzyl, 1° alkyl
60 ~ 85 % yield
71 / 29 ~ 83 / 17

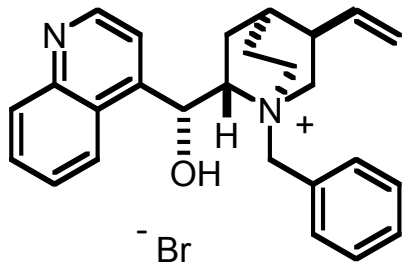
O'Donnell, M. J. *et. al. J. Am. Chem. Soc.* **1989**, *111*, 2353.

Asymmetric Alkylation – Racemization Study

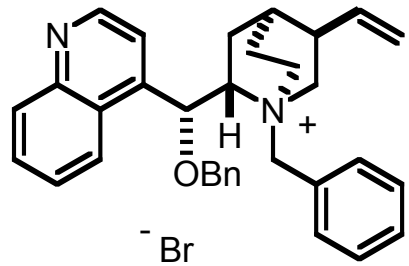




A



B

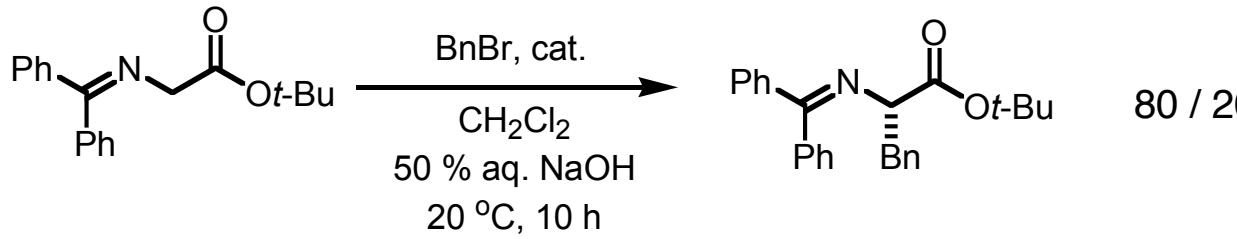


C

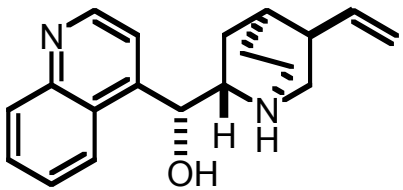
Entry	Cat.	BnBr	Product (%*S*)
1	None	No	100
2	*n*-Bu_4NBr	No	100
3	A	No	64
4	B	No	65
5	B	Yes	100
6	C	No	100

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

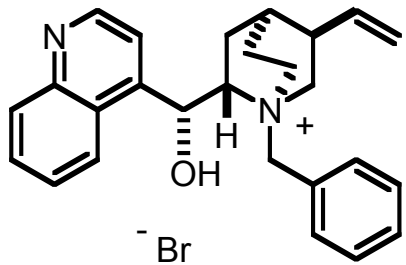
Asymmetric Alkylation – Active Catalyst



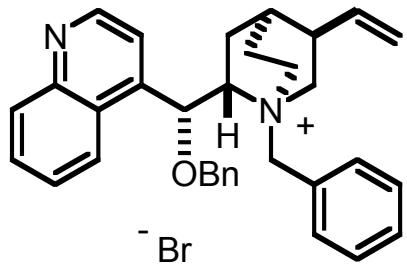
80 / 20 er



A



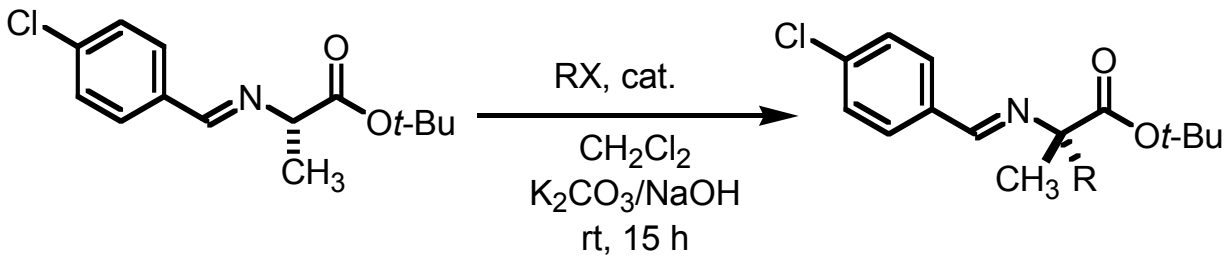
B

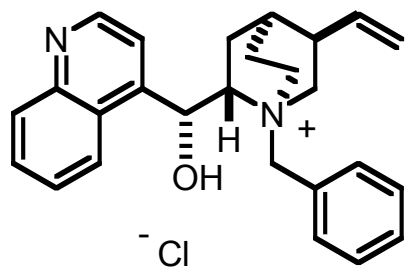


C

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

Asymmetric Alkylation – Second Alkylation

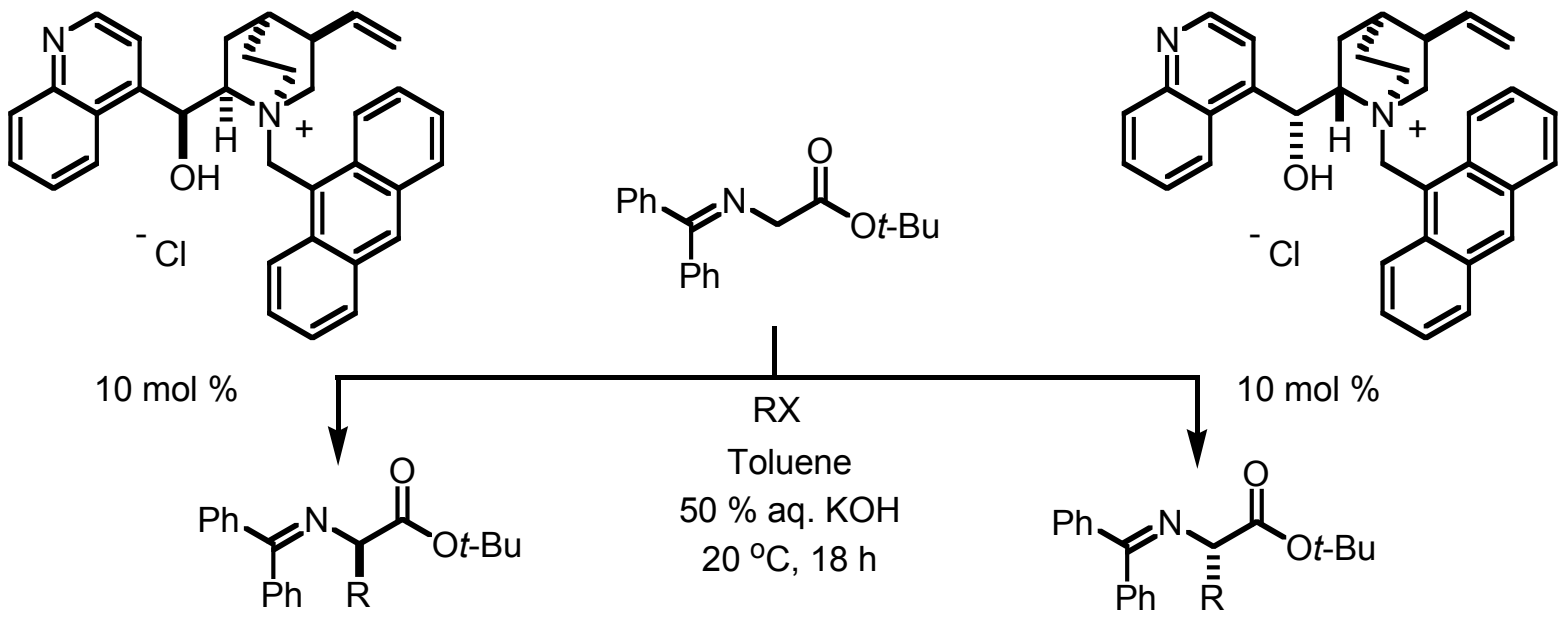




R	Yield (%)	er
Benzylic	80 ~ 87	71 / 29 ~ 75 / 25
Allyl	78	68 / 32

O'Donnell, M. J. *et. al. Tetrahedron: Asymmetry* **1992**, *3*, 591.

Asymmetric Alkylation – Variation of PTC

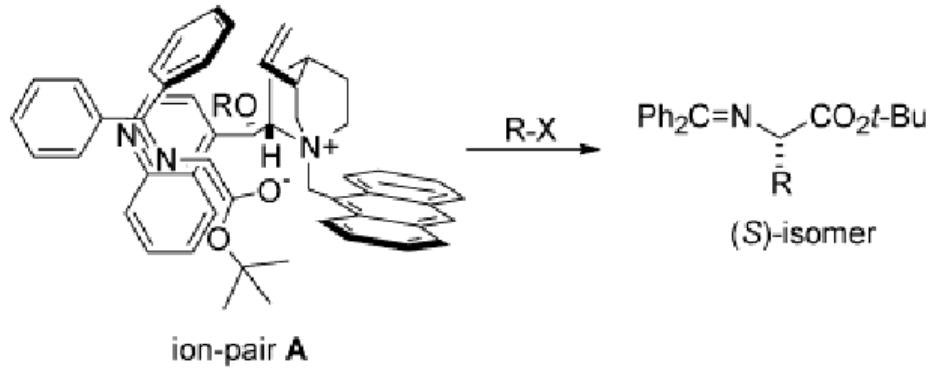


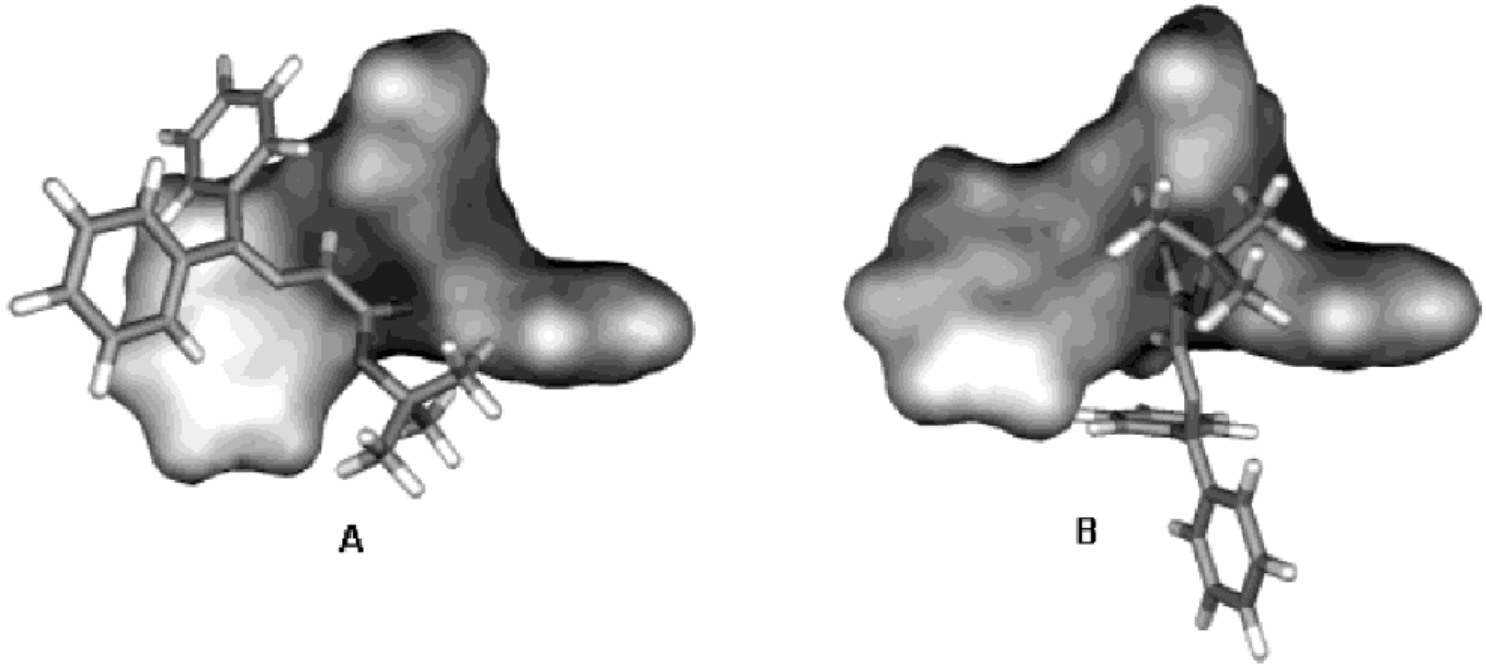
RX : benzyl bromide, allyl bromide, 1° alkyl iodide
40 ~ 86 % yield
83.5 / 16.5 ~ 95.5 / 4.5 er

N-anthracenylmethyl derivatives give higher enantioselectivity.

Lygo B. *et. al. Tetrahedron Lett.* **1997**, *38*, 8595.

Asymmetric Alkylation – Variation of PTC

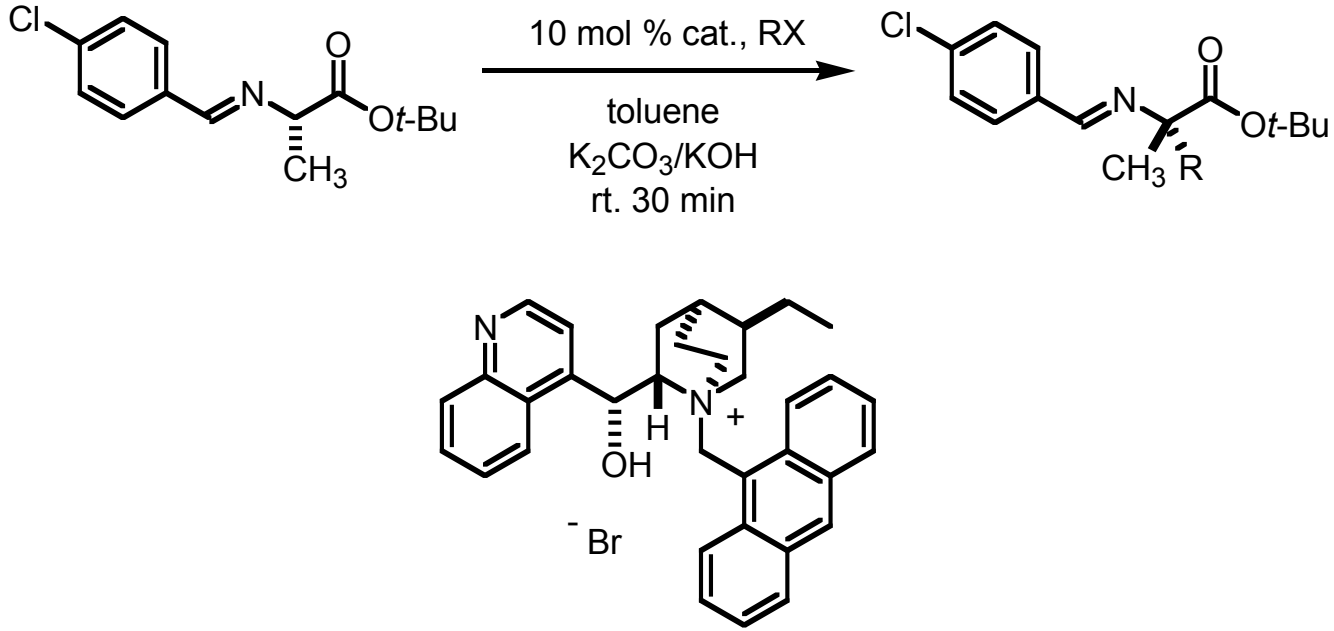




N-anthracenylmethyl derivatives give higher enantioselectivity.

Lygo B. *et. al. Acc. Chem. Res.* **2004**, *37*, 518.

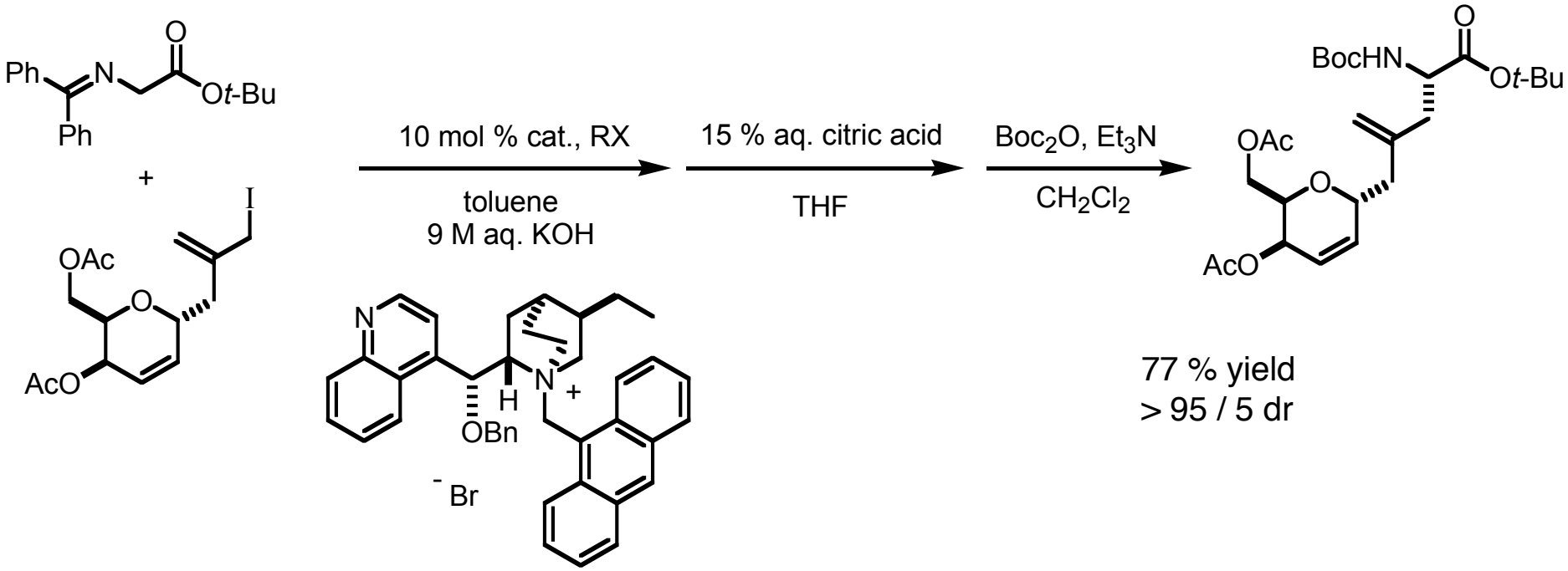
Asymmetric Alkylation – Second Alkylation



R	Yield (%)	er
Benzylic	72 ~ 95	88.5 / 11.5 ~ 93.5 / 6.5

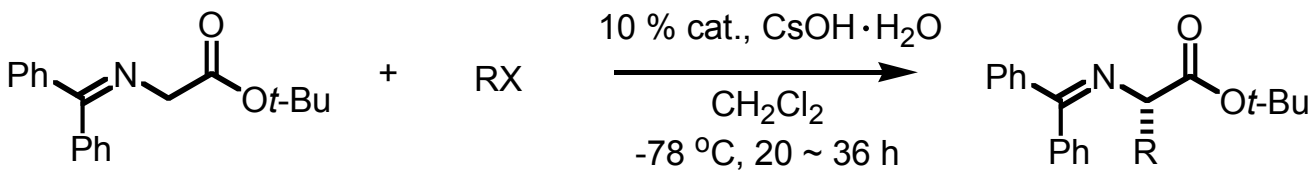
Lygo B. *et. al. Tetrahedron Lett.* **1999**, *40*, 8671.

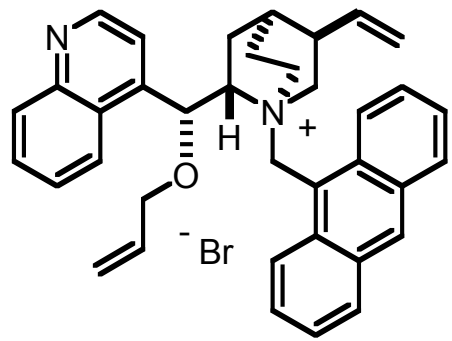
Asymmetric Alkylation – Mildness



Lygo B. *et. al. Tetrahedron Lett.* **2003**, *44*, 9039.

Asymmetric Alkylation – Improved system



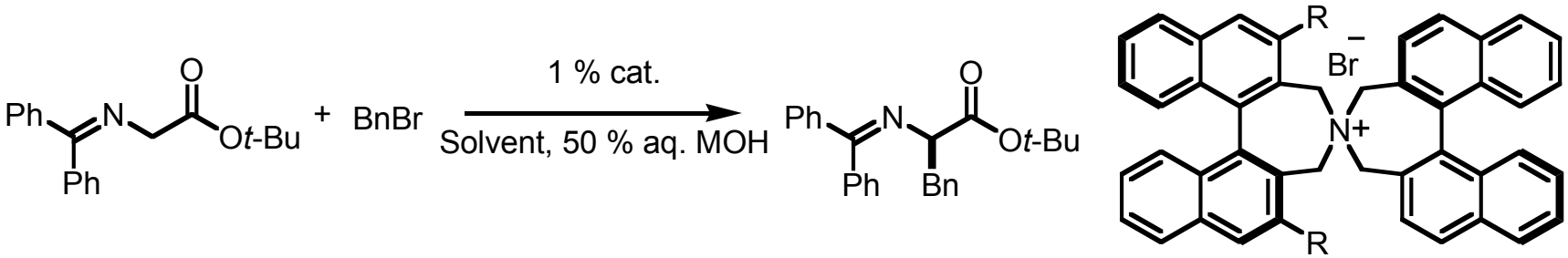


RX : benzyl bromide, allyl bromide, 1° alkyl iodide
68 ~ 91 % yield
96 / 4 ~ 99.75 / 0.25 er

The reaction can be carried out at low temp. by using CsOH.

Corey, E. J. *et. al. J. Am. Chem. Soc.* **1997**, *119*, 12414.

Asymmetric Alkylation – New Catalyst

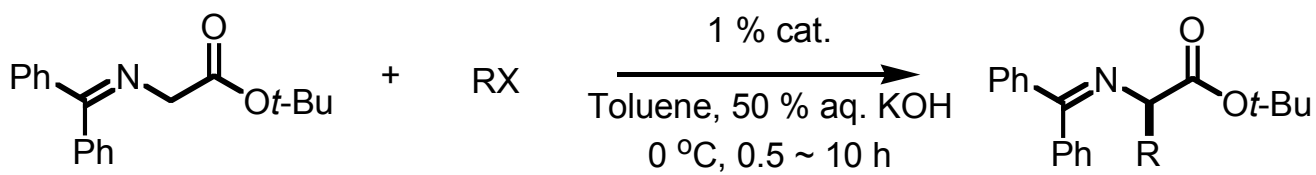


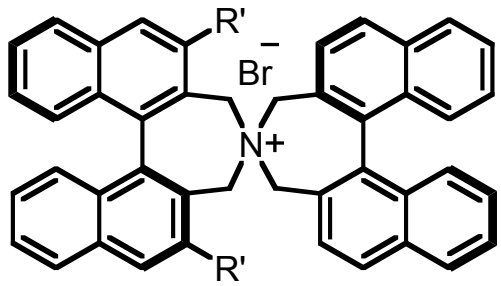
Entry	R	Solvent	base	Yield (%)	er
1	H	benzene	NaOH	76	86.5 / 13.5
2	Ph	benzene	NaOH	43	90.5 / 9.5
3	Ph	toluene	NaOH	62	94 / 6
4	Ph	toluene	KOH	82	94.5 / 5.5
5	-Np	toluene	KOH	95	98 / 2
6	3,5-Ph_2-Ph	toluene	KOH	91	99 / 1
7	3,4,5-F_3-Ph	toluene	KOH	90	99.5 / 0.5

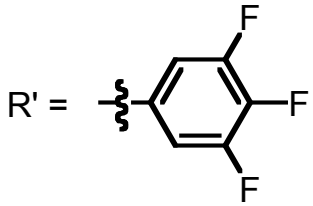
C_2 symmetric chiral PTC allows fine tuning.

Maruoka K. *et. al. J. Am. Chem. Soc.* **1999**, *121*, 6519.
Maruoka K. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 5139.

Asymmetric Alkylation – New Catalyst





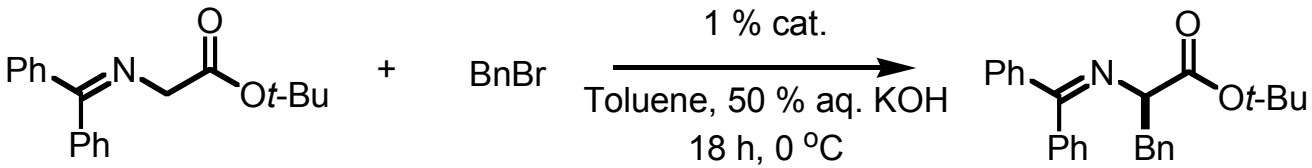


R	Yield (%)	er
Benzylic	81 ~ 98	98 / 2 ~ 99.5 / 0.5
Allylic	80 ~ 89	99.5 / 0.5
Propagyl	80	99.5 / 0.5
1° Alkyl	89 ~ 92	98 / 2 ~ 99 / 1

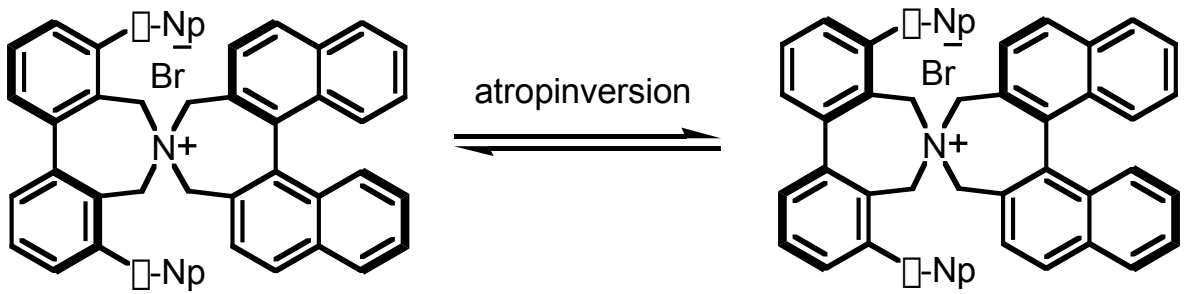
C_2 symmetric chiral PTC was successfully applied.

Maruoka K. *et. al. J. Am. Chem. Soc.* **1999**, *121*, 6519.

Asymmetric Alkylation – Catalyst Modification

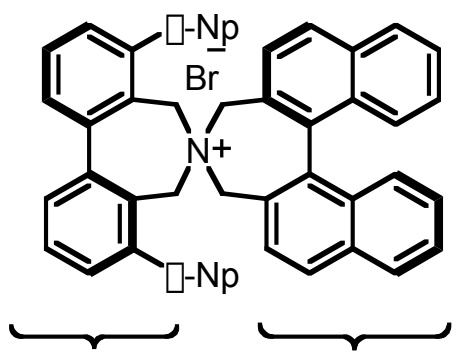


85 % yield
93.5 / 6.5 er



Homochiral
High activity

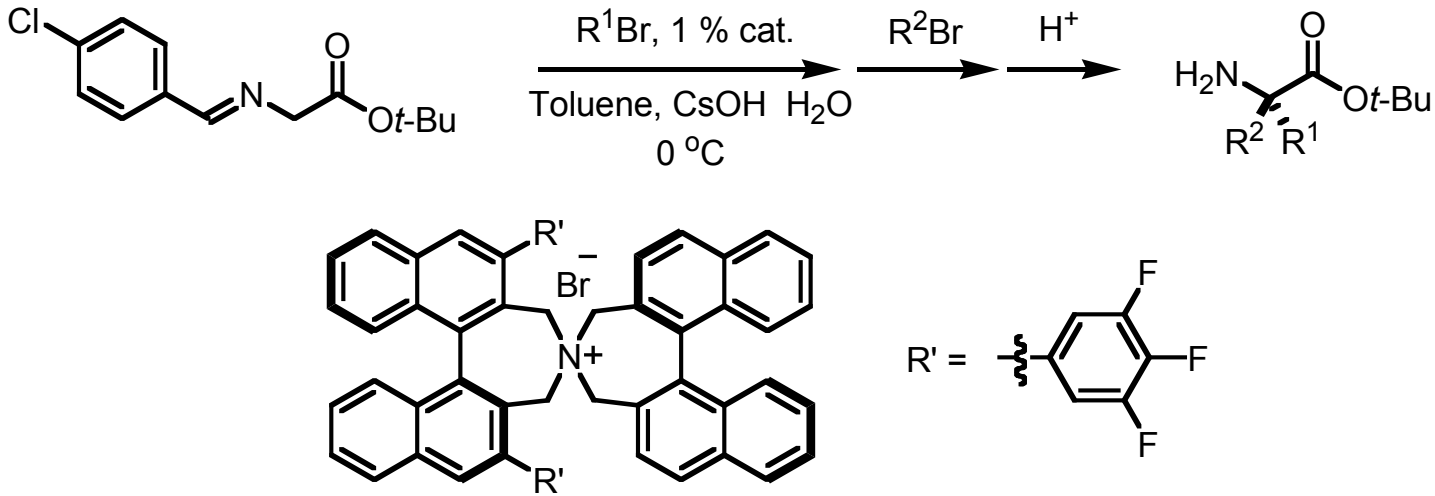
Heterochiral
Low activity



Easily modifiable achiral subunit Simple chiral source

Maruoka K. *et. al. Angew. Chem. Int. Ed.* **2002**, *41*, 1551.

Asymmetric Alkylation – Sequencial Alkylation

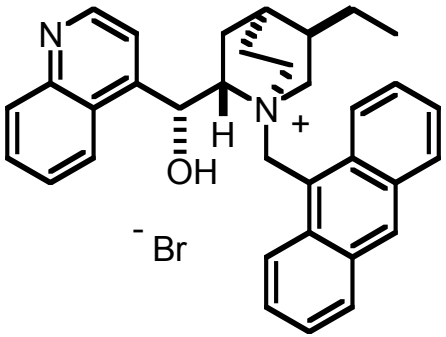


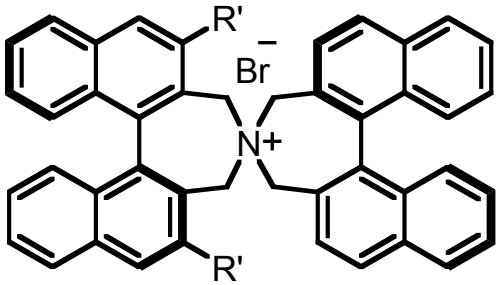
Entry	R^1	time (h)	R^2	time (h)	Yield (%)	er
1	Allyl	3.5	Bn	0.5	80	99 / 1
2	Allyl	3.5	$CH{=}C(CH_3)CH_2$	0.7	60	98.5 / 1.5
3	Allyl	3.5	Propargyl	0.5	58	98 / 2
4	Bn	2	Allyl	0.3	74	96 / 4

Maruoka K. *et. al. J. Am. Chem. Soc.* **2000**, *122*, 5228.

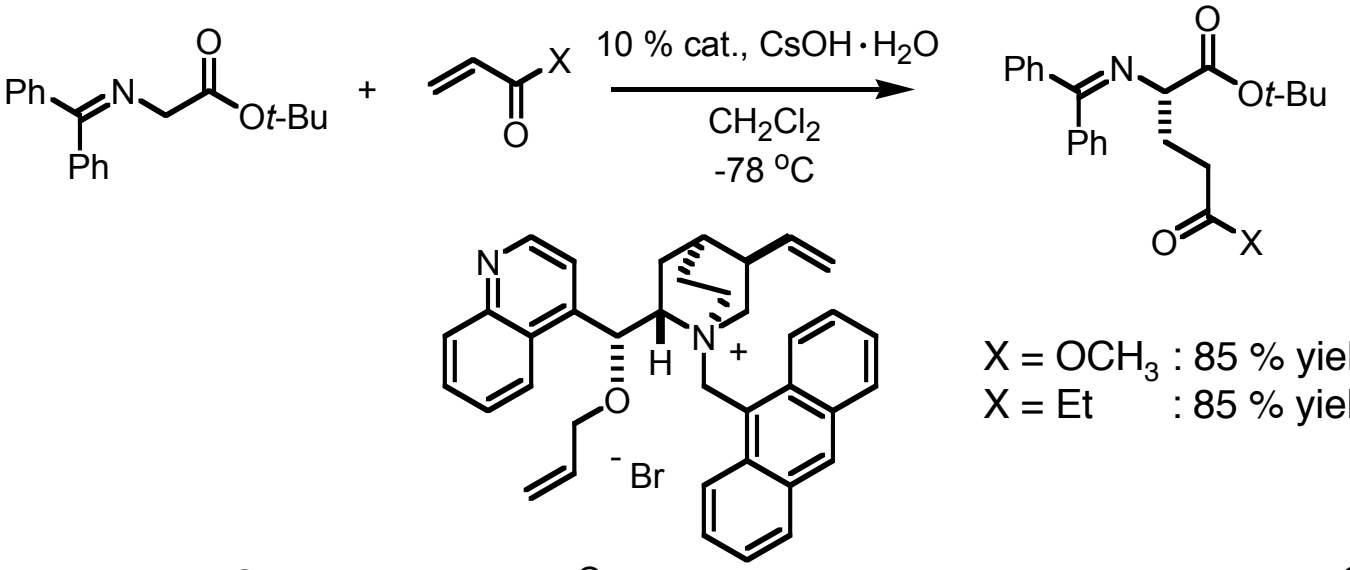
Summary

- Phase transfer catalysis is highly selective and mild.
- Chiral phase transfer catalyst allows the asymmetric epoxidation of enones.
- X-ray structure of catalyst gives insight for the enantioselectivity.
- Asymmetric alkylation of glycines imines with chiral phase transfer catalyst affords amino acids with high enantioselectivity.
- Maruoka's catalyst allows fine tuning of the structure.

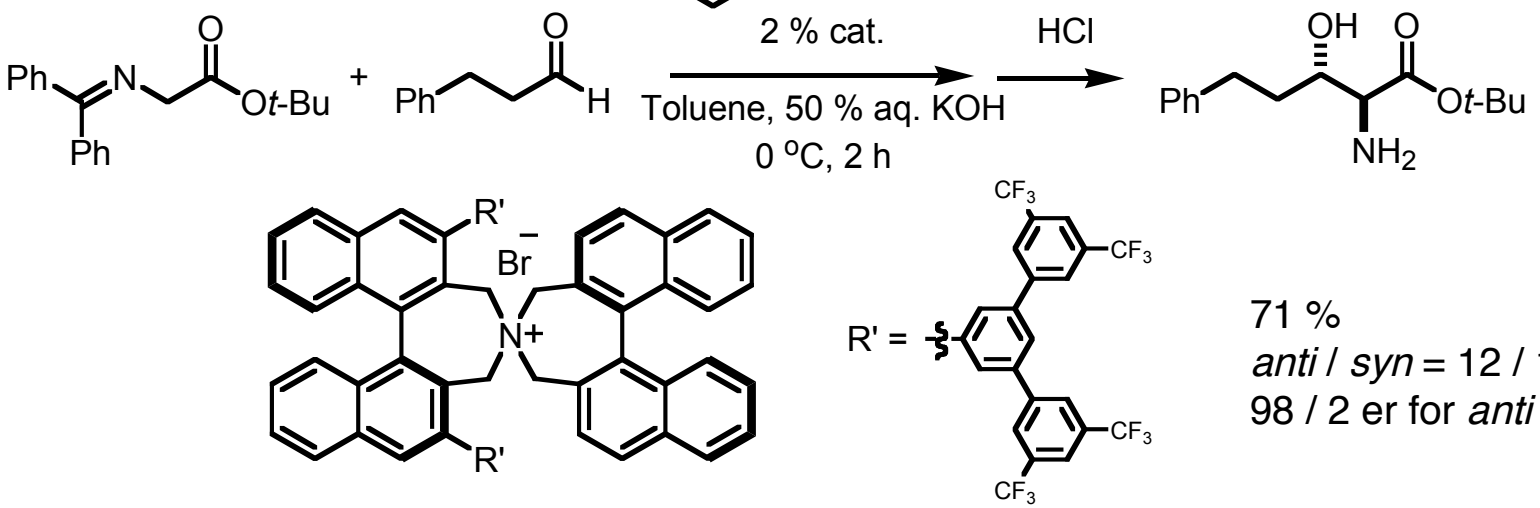




Asymmetric Alkylation – Other Electrophiles



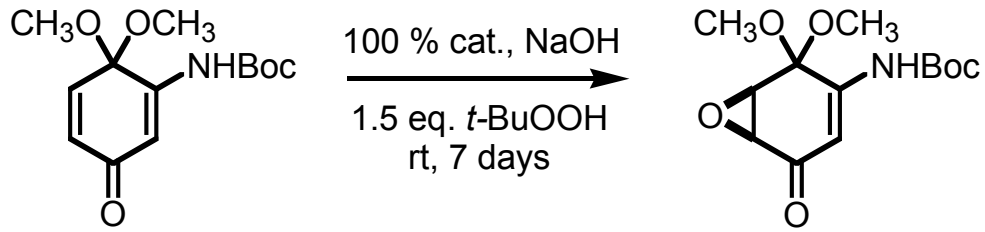
X = OCH_3 : 85 % yield, 97.5 / 2.5 er
X = Et : 85 % yield, 95.5 / 4.5 er

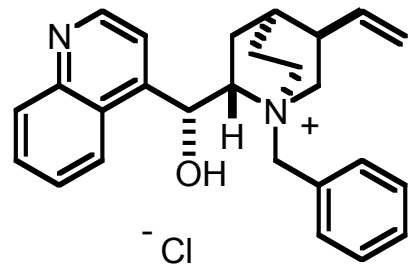


71 %
anti / *syn* = 12 / 1
98 / 2 er for *anti*

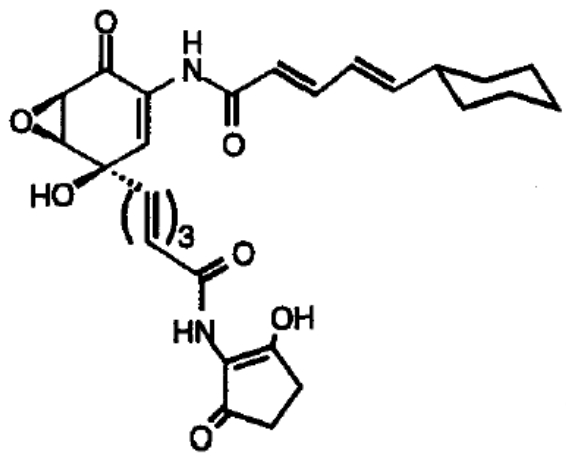
Corey, E. J. *et. al. Org. Lett.* **2001**, *3*, 639.
Maruoka, K. *et. al. Angew. Chem. Int. Ed.* **2002**, *41*, 4542.

Asymmetric Epoxidation – Synthetic Applicatio n





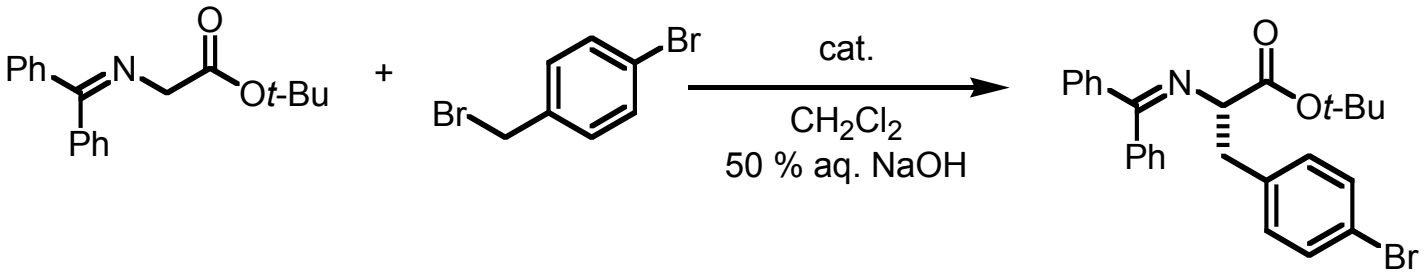
32 % yield
94.5 / 5.5 er

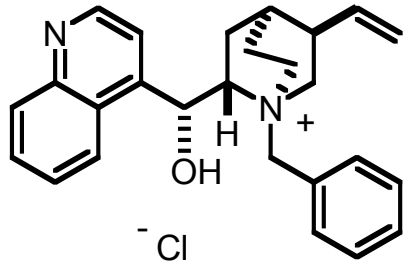


(-)-alismycin

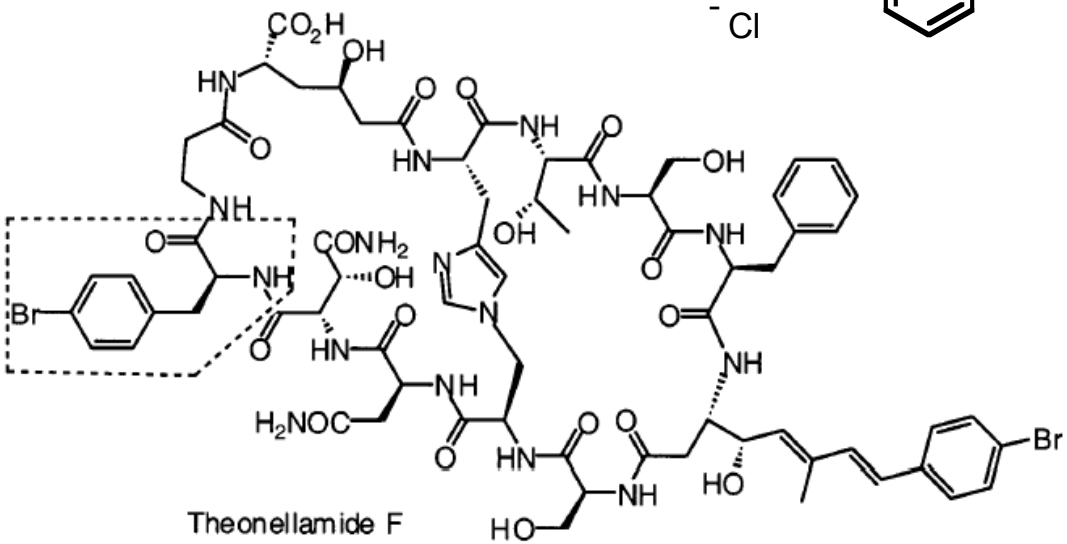
Taylor, J. K. *et. al. Tetrahedron Lett.* **1998**, *39*, 5433.

Asymmetric Alkylation – Synthetic Application





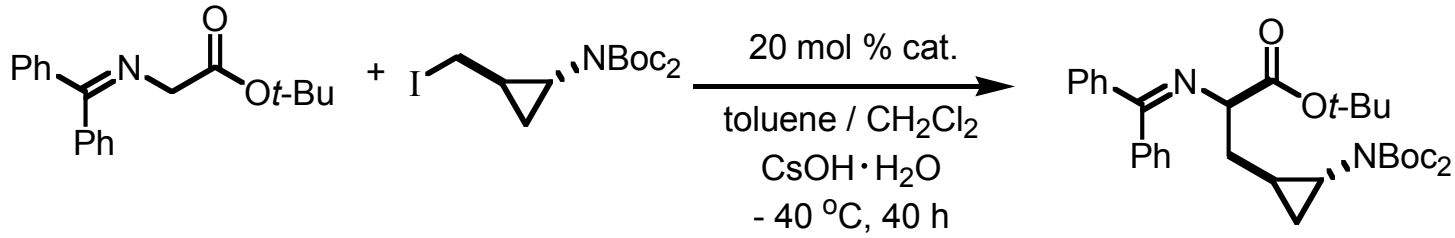
Quant.
76 / 24 er
After recrystallization
90 / 10 er

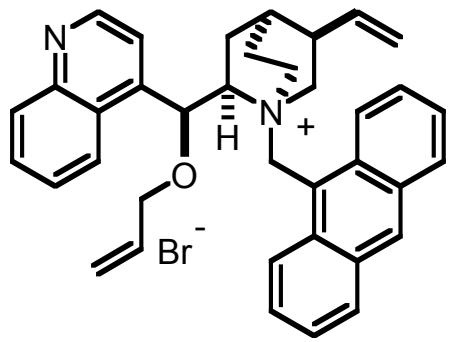


Theonellamide F

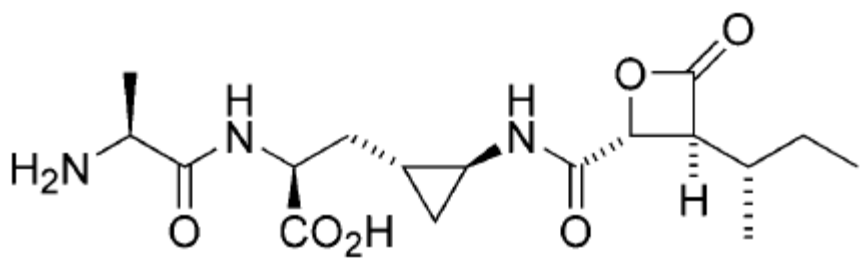
Shioiri, T. *et. al. Synlett* **1994**, 247.

Asymmetric Alkylation – Synthetic Application





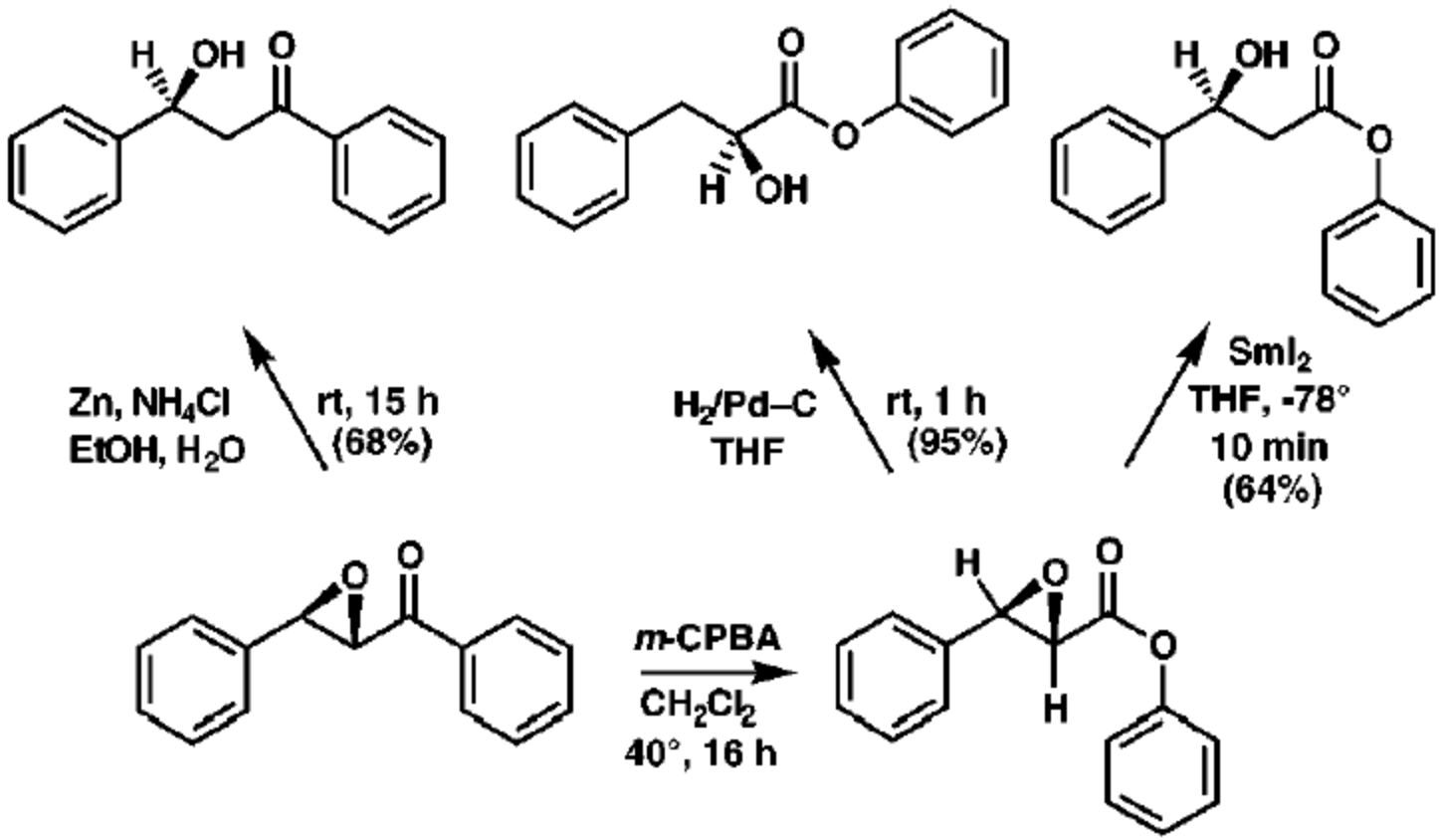
66 % yield
97 / 3 dr



belactosin A

Armstrong, A. *et. al. Org. Lett.* **2003**, *5*, 2331.

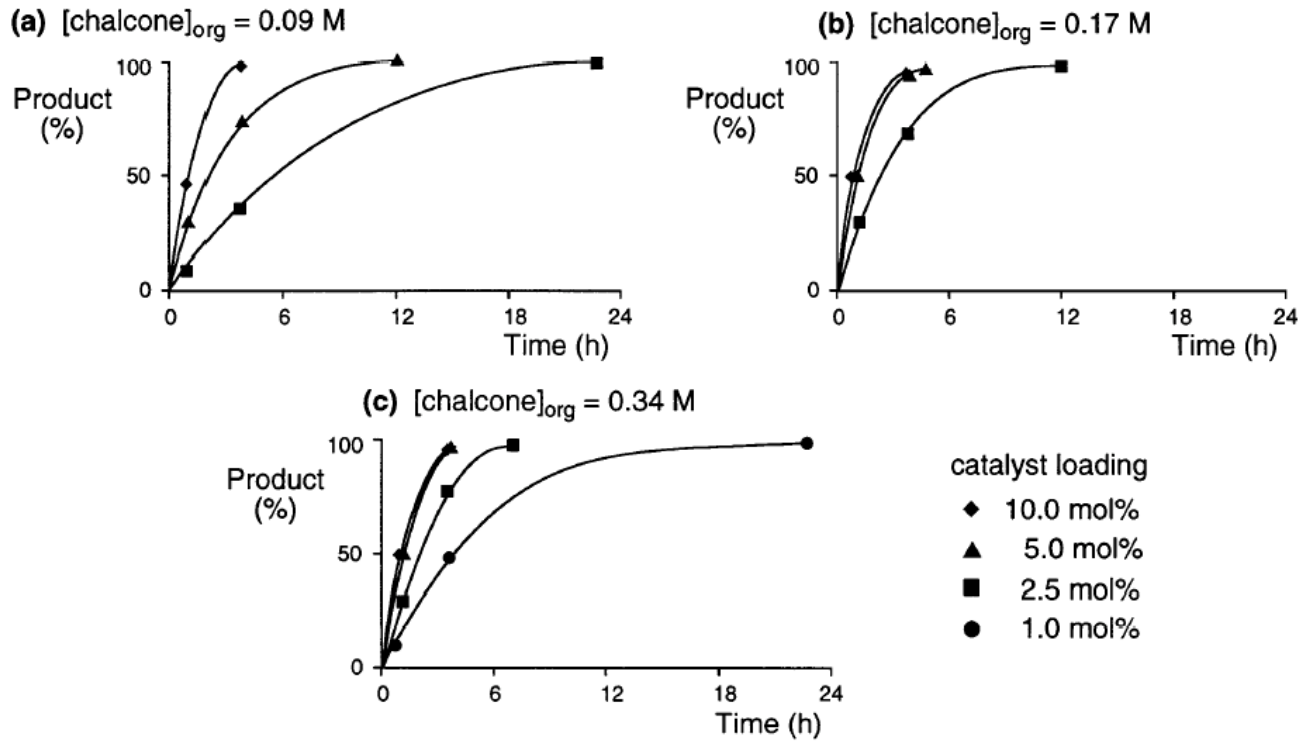
Asymmetric Epoxidation – Post Transformation



Corey, E. J. *et. al. Org. Lett.* **1999**, *1*, 1287.

Asymmetric Epoxidation – Kinetics

- Reaction rate
  - First order of hypochlorite concentration
  - For [cat.] > 0.008 M, 0th order of catalyst concentration
    : Solubility effect

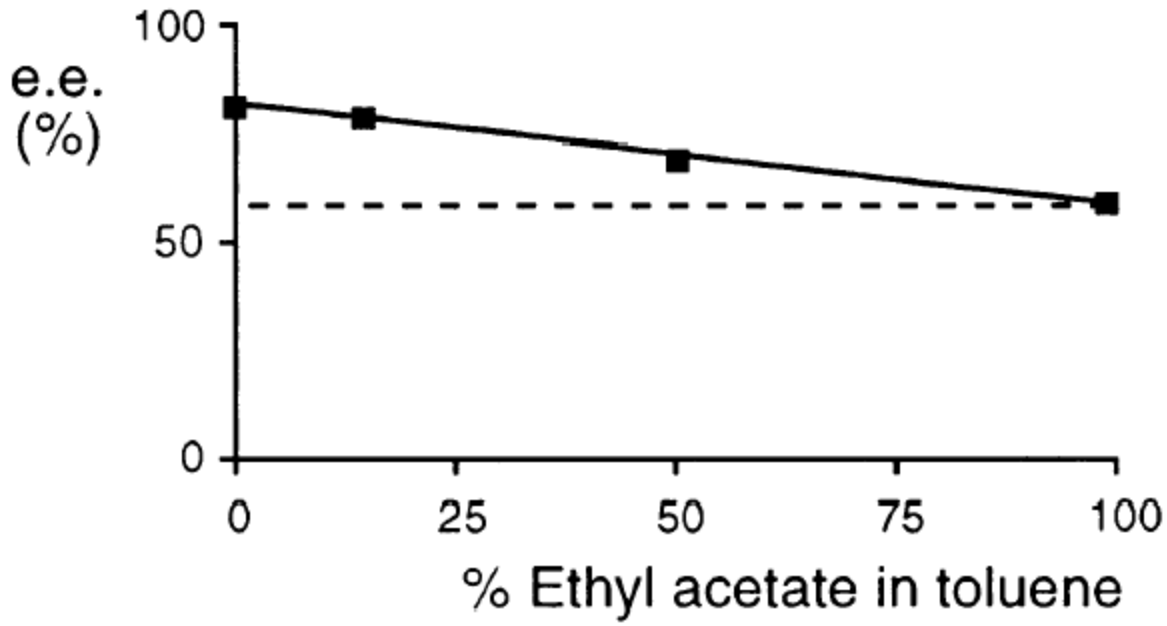


Rate limiting step : ion exchange between catalyst and NaOCl

Lygo B. *et. al. Tetrahedron Lett.* **2001**, *42*, 1343.

Asymmetric Epoxidation – Medium effect

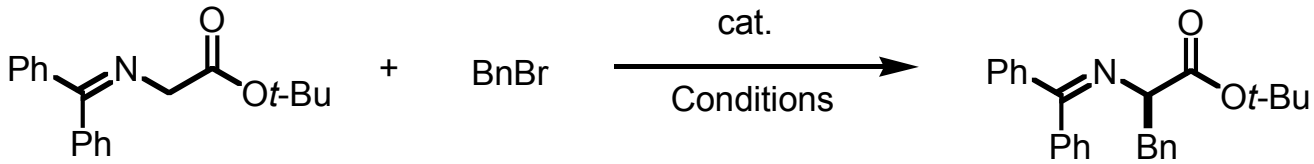
- 1 ~ 10 mol % cat., 0.09 ~ 0.34 M substrate : 93/7 er
- 0.1 mol % cat., 3.4 M substrate : 80/20 er

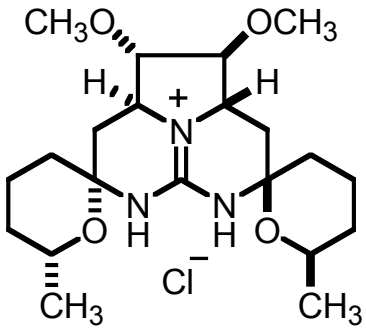


Enantioselectivity is linearly dependent on the concentration of EtOAc.
Polarity of organic phase significantly influences enantioselecitvity.

Lygo B. *et. al. Tetrahedron Lett.* **2001**, *42*, 1343.

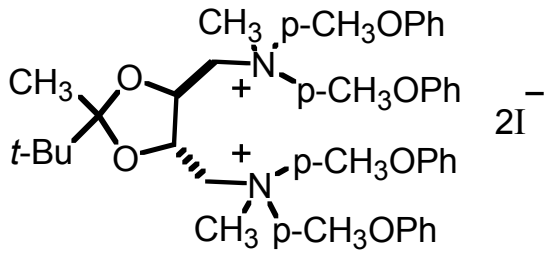
Asymmetric Alkylation – Miscellaneous





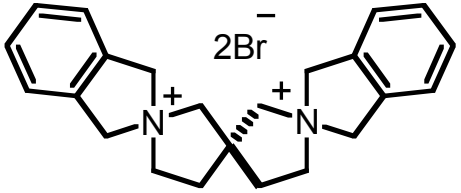
30 mol %
CH_2Cl_2
aq. KOH

55 % yield, 95 / 5 er



10 mol %
Toluene/CH_2Cl_2
$CsOH{\bullet}H_2O$

87 % yield, 97.5 / 3.5 er

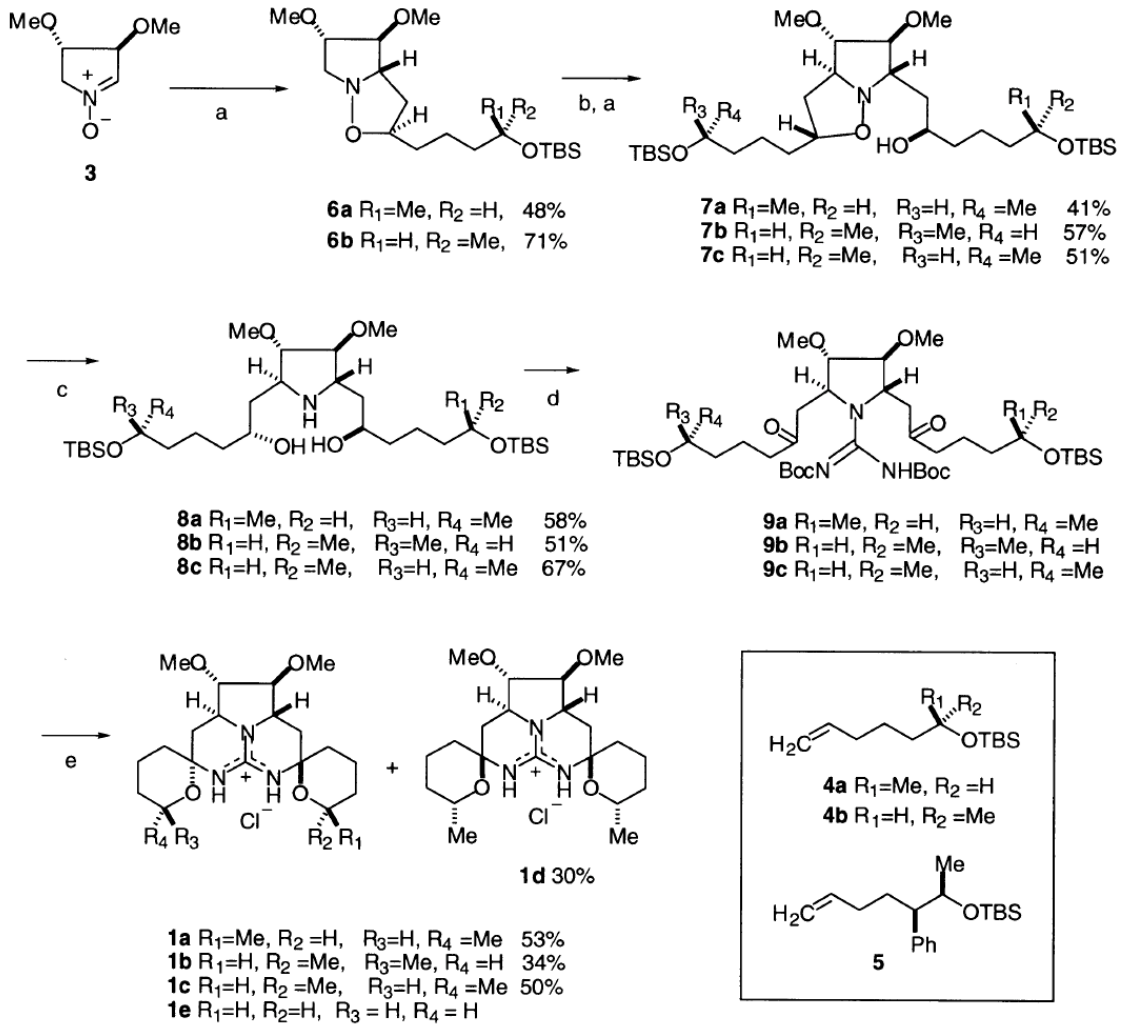


20 mol %
CH_2Cl_2
aq. KOH

95 % yield, 97.5 / 2.5 er

Nagasawa, T. *et. al. Angew. Chem. Int. Ed.* **2002**, *41*, 2832.
Shibasaki, M. *et. al. Tetrahedron Lett.* **2002**, *43*, 9539.
Sasai, H. *et. al.* unpublished result

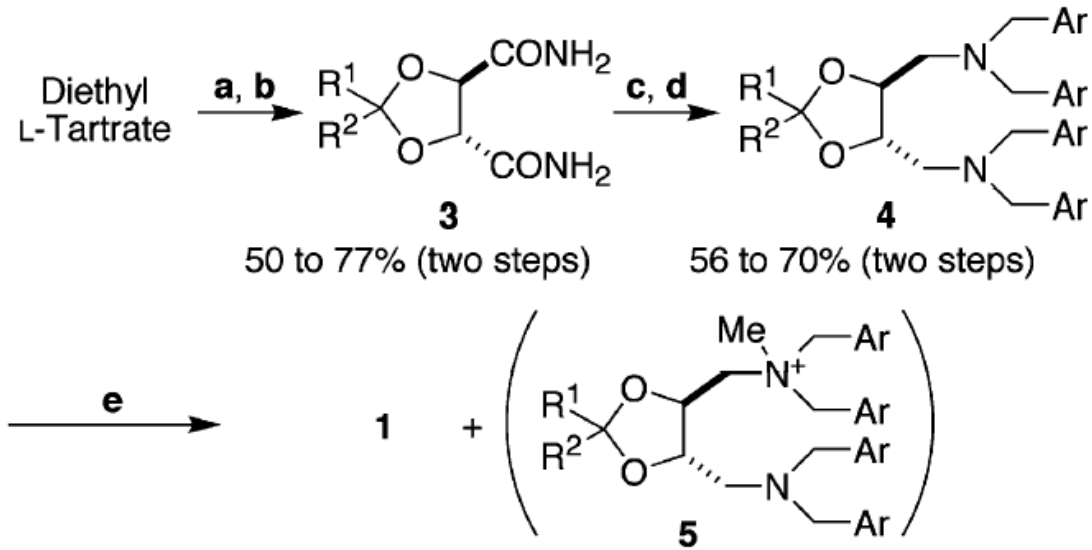
Asymmetric Alkylation – Miscellaneous



Scheme 1. (a) **4**, Toluene, reflux, 24 h; (b) mCPBA, 0°C, CH_2Cl_2, 10 min; (c) Pd/C, H_2, EtOH, rt, 24 h; (d) (i) bis-*N*-Boc thiourea, $HgCl_2$, DMF, rt, 1 h, (ii) TPAP, NMO, rt, 1 h, (e) HCl/MeOH, rt, 24 h.

Nagasawa, T. *et. al. Tetrahedron* **2001**, *57*, 8959.

Asymmetric Alkylation – Miscellaneous



	Yield of **1**	Yield of **5**
1aa (R^1=R^2=Me, Ar=Ph)	54%	44%
Others	57 to 89%	trace

Scheme 1. *Reagents and conditions*: (a) ketone (1.2 equiv.), $HC(OMe)_3$ (1.5 equiv.), cat. $TsOH{\cdot}H_2O$, MeOH, 70°C, then diethyl L-tartrate, toluene, 110°C; (b) NH_3 gas, MeOH, 4°C; (c) LAH (3.5 mol equiv.), THF, rt to reflux; (d) $ArCH_2Cl$ (7.0 mol equiv.), *i*-Pr_2NEt (7.2 mol equiv.), MeCN, rt; (e) MeI (40 mol equiv.), rt.

Shibasaki, M. *et. al. Tetrahedron Lett.* **2002**, *43*, 9539.

Asymmetric Alkylation – Catalyst Modification

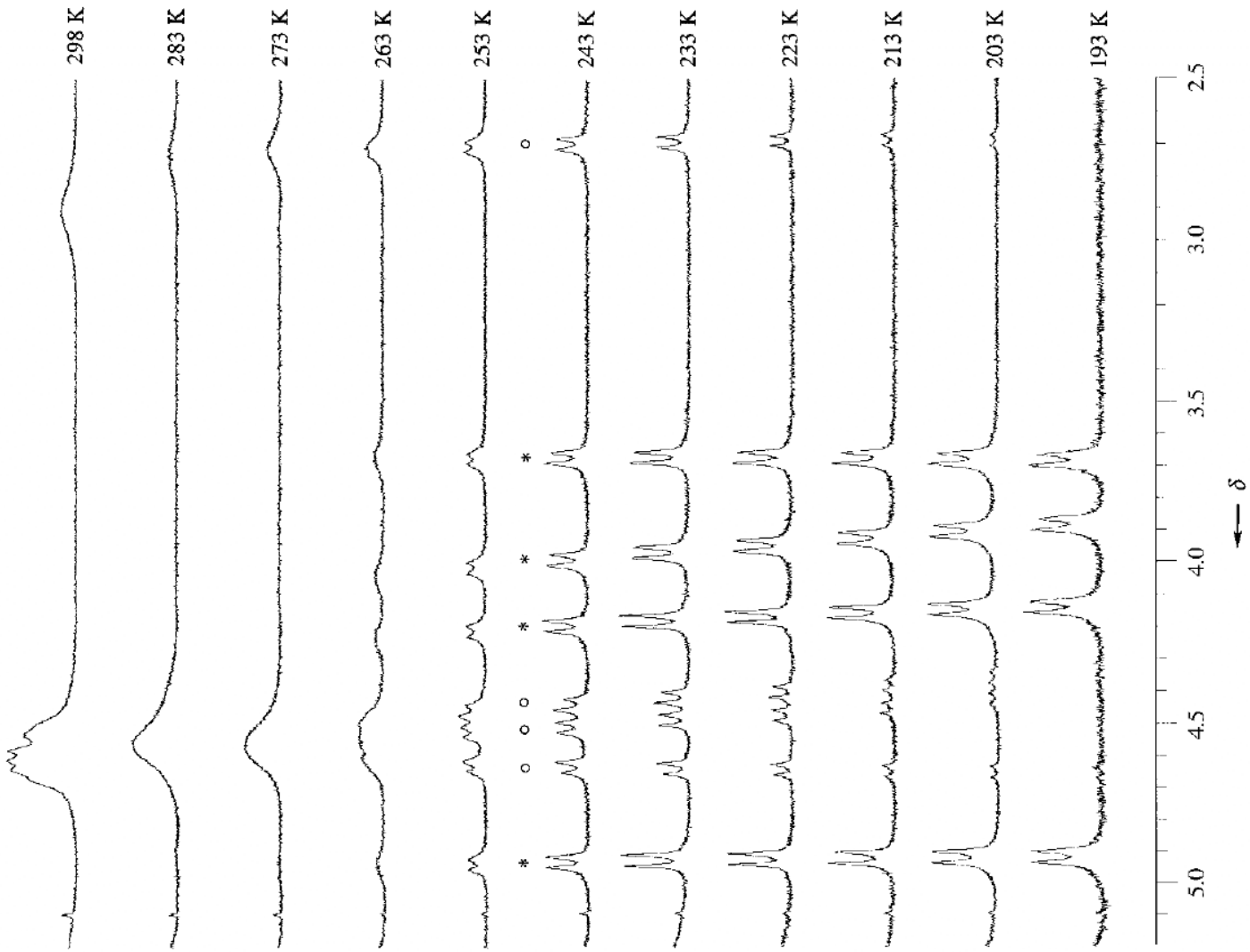
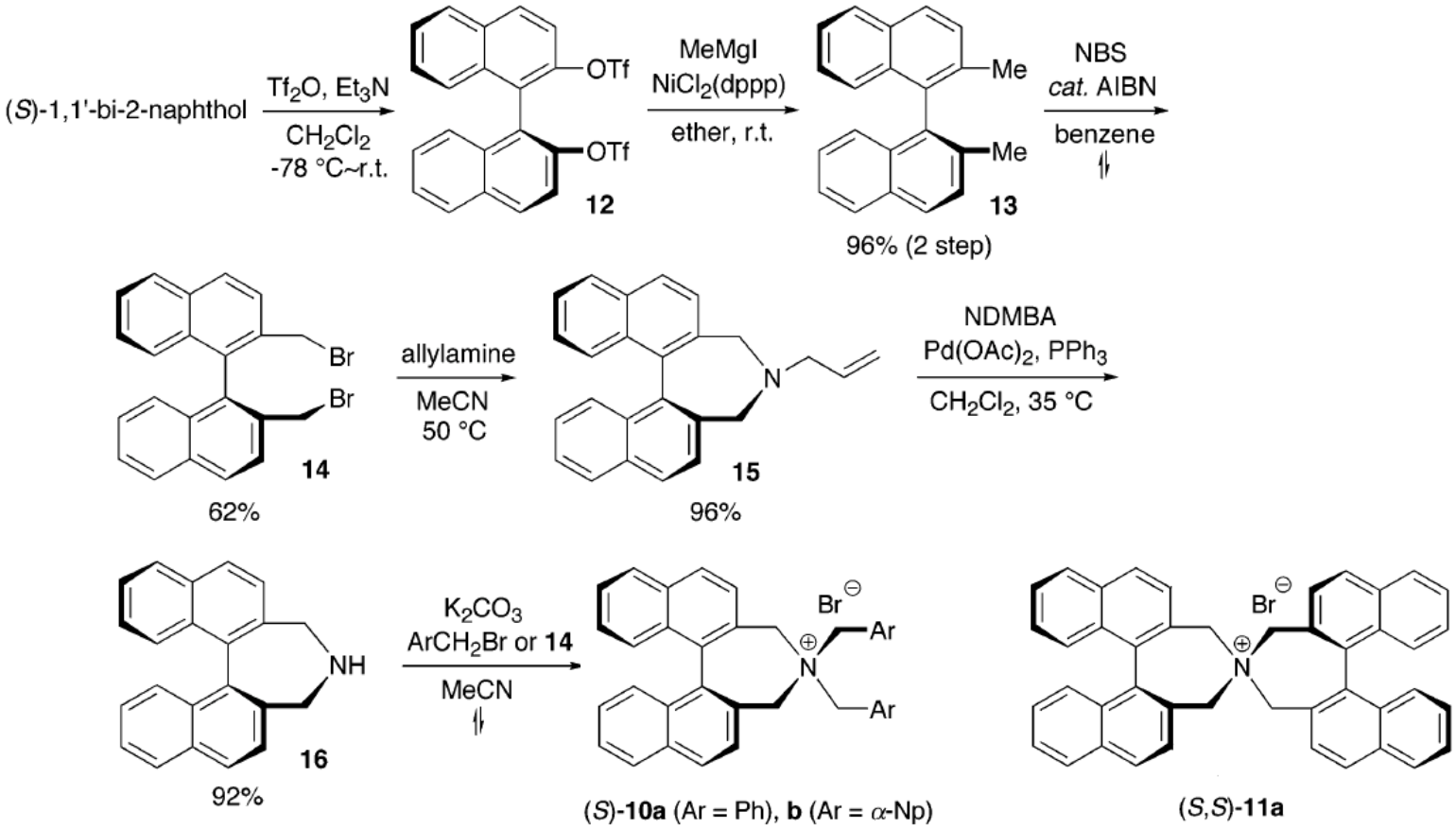


Figure 2. The temperature dependence of the ^{1}H NMR signals of the benzylic protons of homochiral (*) and heterochiral (○) conformers of **4c**.[10]

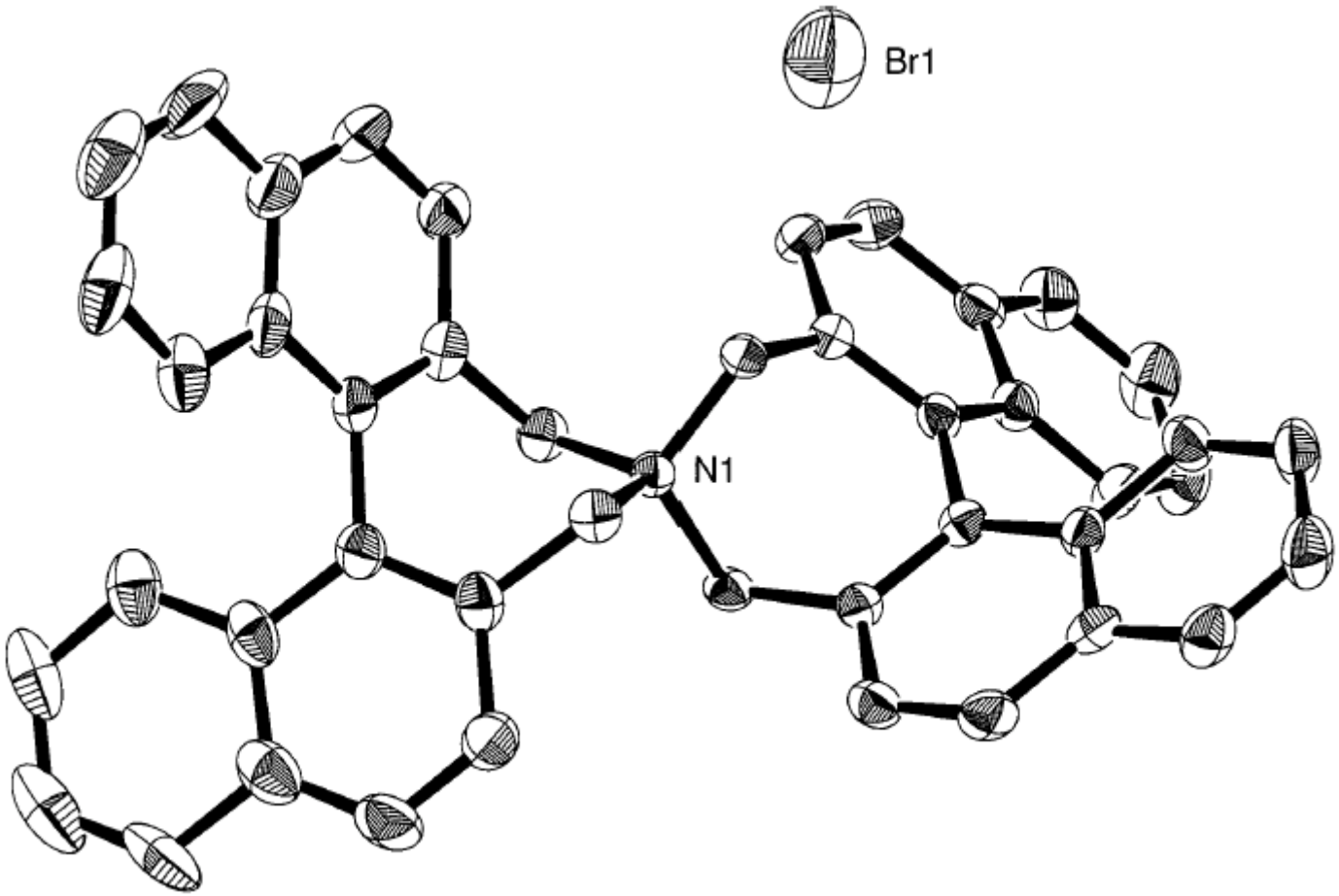
Maruoka K. *et. al. Angew. Chem. Int. Ed.* **2002**, *41*, 1551.

Asymmetric Alkylation – Preparation of PTC



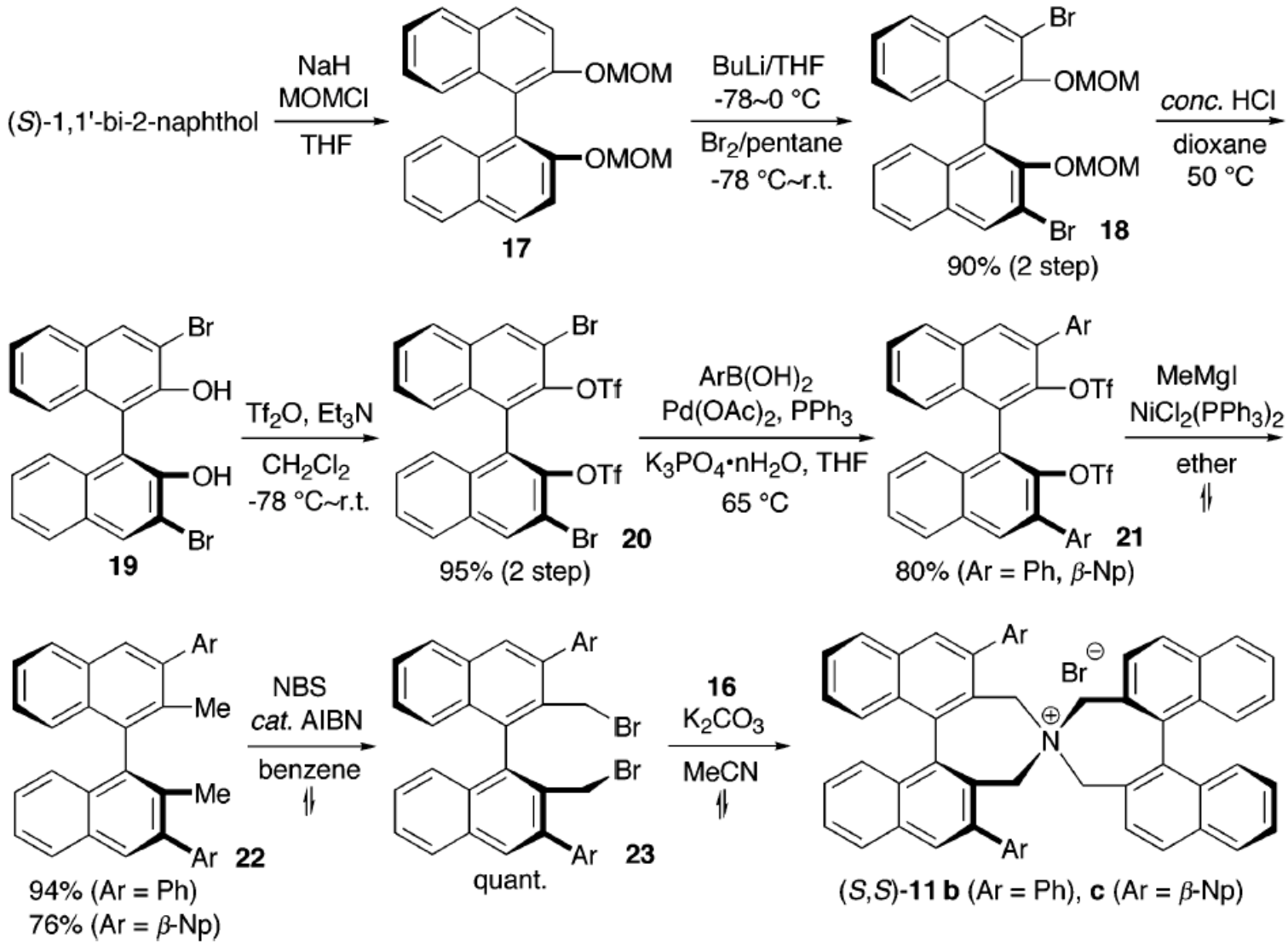
Maruoka K. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 5139.

Asymmetric Alkylation – Preparation of PTC



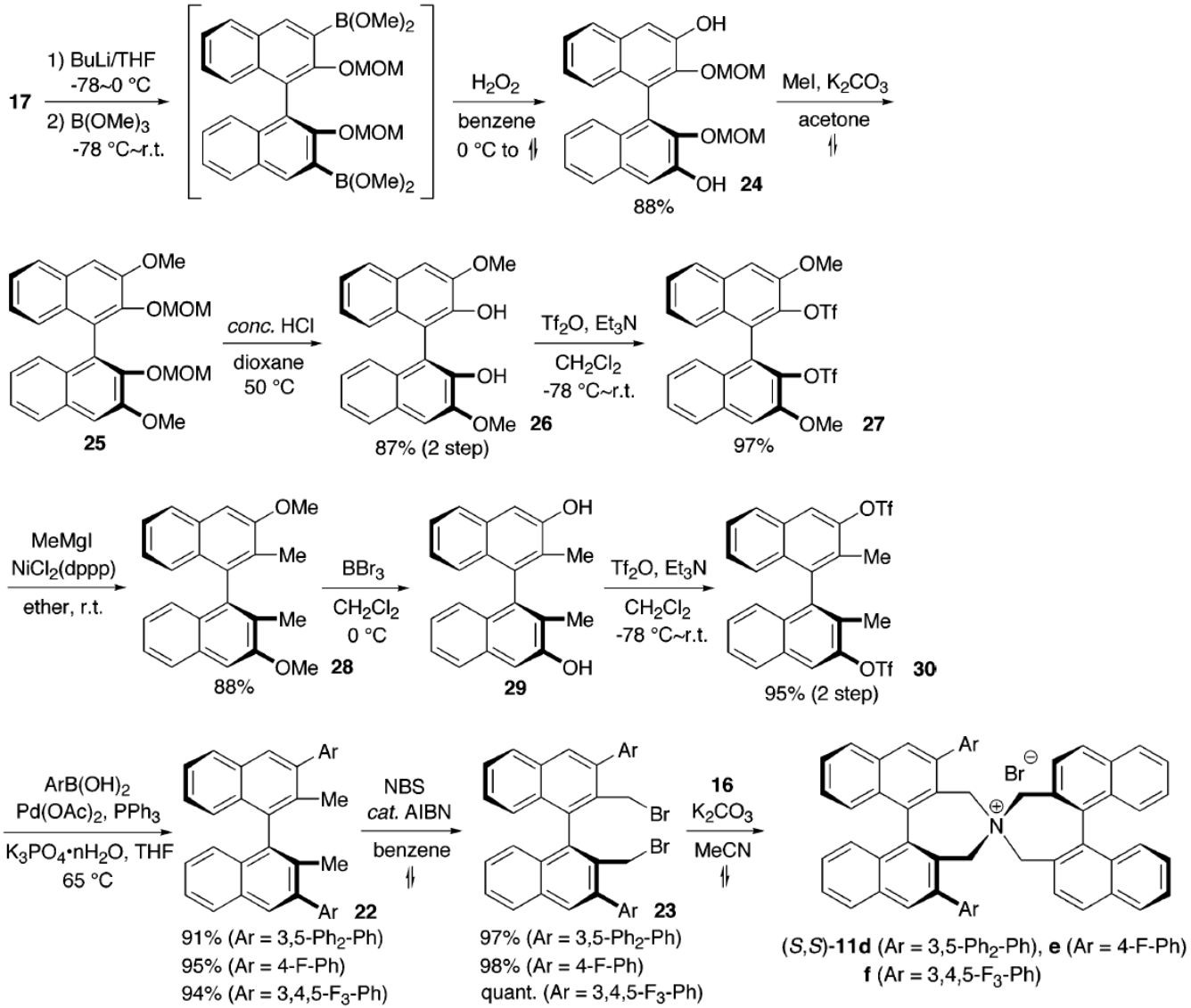
Maruoka K. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 5139.

Asymmetric Alkylation – Preparation of PTC



Maruoka K. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 5139.

Asymmetric Alkylation – Preparation of PTC



Maruoka K. *et. al. J. Am. Chem. Soc.* **2003**, *125*, 5139.