Nonmetal-Based Asymmetric Catalysis : Quaternary Ammonium Salts as Chiral Catalysts

Evans Group Friday Seminar
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March 16, 2001

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• Alkylations
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• Aldol Reactions
• Epoxidations
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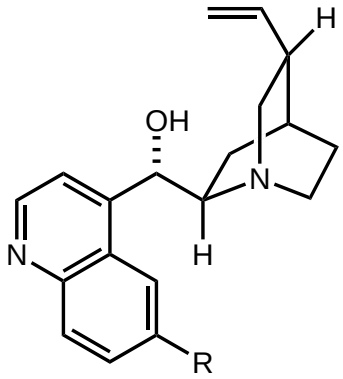
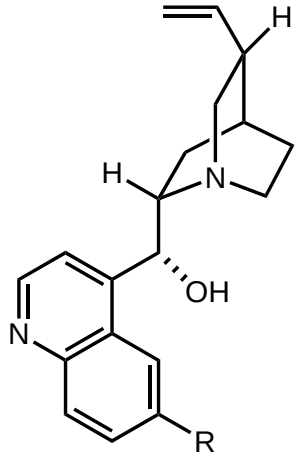
Leading References :

• O'Donnell, M., "Asymmetric Phase-Transfer Catalysis", *Catalytic Asymmetric Synthesis*, Ojima ed., Wiley-VCH, 1993
• Shioiri, T., "Use of Chiral Quaternary Salts in Asymmetric Synthesis", *Phase-Transfer Catalysis : Mechanisms and Syntheses*, Halpern, ed., ACS Symposium Series, 1997.

Introduction



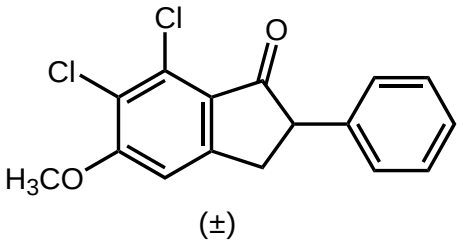
R = H : Chinconine ($1.70/g)
R = OCH_3 : Quinidine ($8.80/g)



R = H : Chinconidine ($ 0.78/g)
R = OCH_3 : Quinine ($3.15/g)

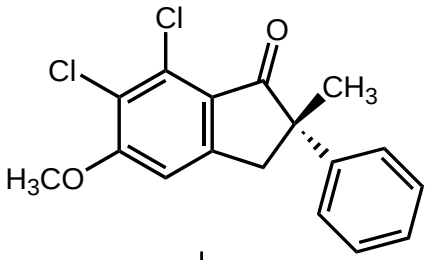
- The most common chiral quaternary ammonium salts for asymmetric catalysis are derived from the chincona alkaloid family of natural products *via* simple *N*-alkylation.
- The chinconine and chinconidine family of natural products are *pseudo*-enantiomeric.
- Once *N*-alkylated, these alkaloids have a rather rigid structure, and tight-ion pairing can be made only on one sterically unhindered face of the alkaloid nitrogen.
- Asymmetric catalysis with these ammonium salts have been documented in the literature since 1975. Early enantiomeric excesses were determined by rotation, and these results have been disputed since (see O'Donnell, M., *"Asymmetric Phase Transfer Reactions",* Catalytic Asymmetric Synthesis, Ojima ed., Wiley-VCH, 1993). Impurities from catalyst decomposition were thought to contaminate products, giving erroneous rotation values.
- For the enantioselective syntheses of chincona alkaloid derivatives, see Lygo *et al*, *Tetrahedron*, **1999**, *55*, 2795.

Synthesis of (+)-Indacrinone

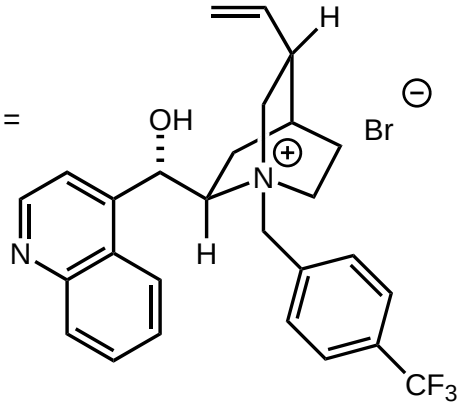


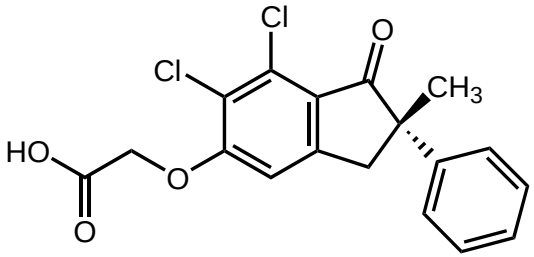
(±)

CH_3Cl, 10 mol% cat*
toluene/50% NaOH (5:1)
20 °C, 18h
92% *ee*, 95% yield

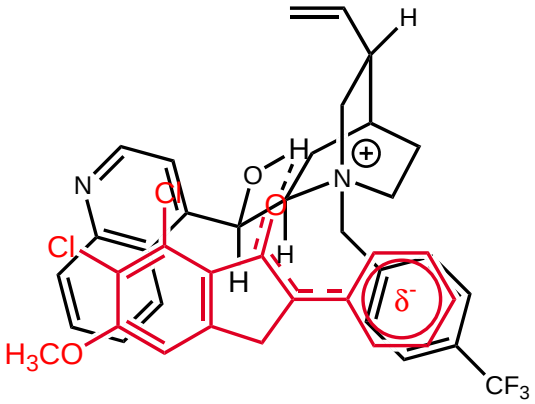


cat* =





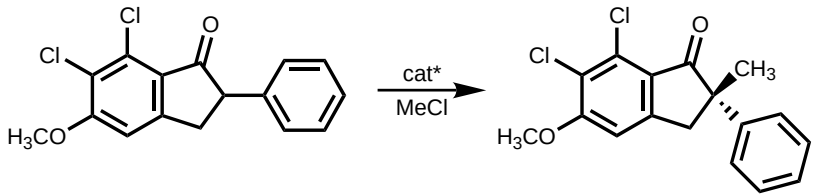
Author's Rationale :



- CH_3Cl was a superior electrophile to both CH_3Br or CH_3I.
- Increasing NaOH concentration improves selectivity.
- Catalyst *N*-benzyl substituent was critical for enantioselectivity, with electron withdrawing substituents enhancing selectivity.
- A very rigid transition state is proposed, where the substrate is bound to catalyst by a hydrogen bond as well as through π-stacking.
- Tight-ion pairing shown is consistent with computational modeling (*J. Org. Chem.*, **1991**, *56*, 5181).

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

Kinetic and Mechanistic Considerations for Enantioselective Phase Transfer Methylation



Step 1 : Enolate Anion Formation - Base concentration dependent!

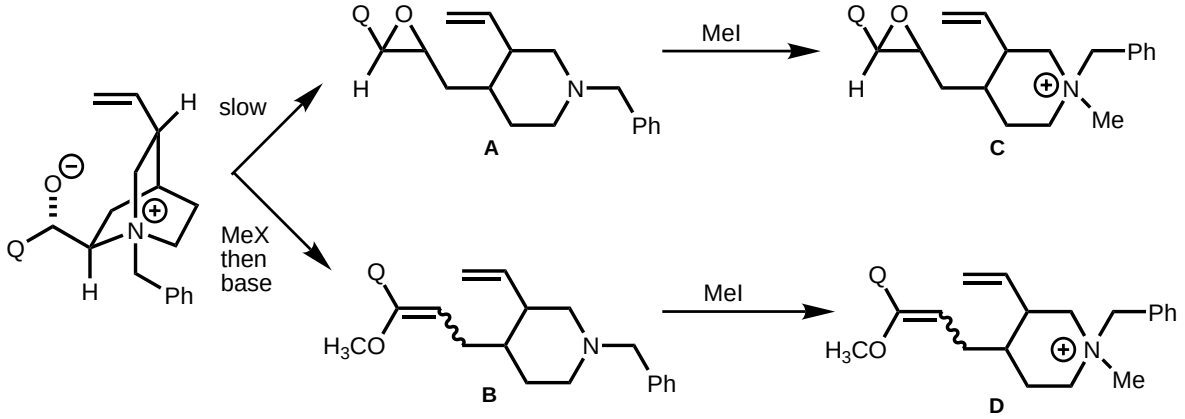
- In 50% NaOH, deprotonation is interfacial, and enolate forms a separate solid phase, even in the absence of catalyst. The deprotonation is complete when 20% of indanone has been alkylated.
- With 30% NaOH, indanone is much preferred to enolate at equilibrium.

Step 2 : Anion Extraction to Organic Phase - Dimeric or monomeric in catalyst?

- In toluene, the catalyst exisits as a dimer with its zwitterionic oxide. Catalyst could extract indanone enolate from aqueous or solid phases, or zwitterion could deprotonate residual indanone in organic phase.
- Tetraalkyl ammonium salts with a bromide counterion are 1000 times more soluble in organic solvents than with a hydroxide counterion.

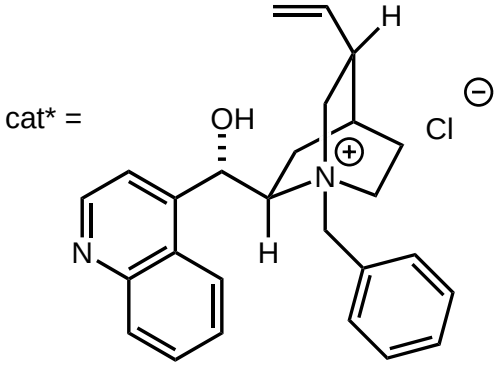
Step 3 : Chiral Methylation in the Organic Phase

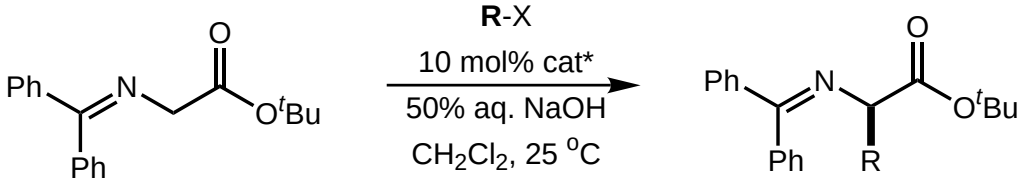
- Stirring rate has no effect on rate or *ee* of reaction.
- Higher *ee*'s with less polar solvents such as toluene support tight-ion pair theory. Non-polar, non polarizable solvents such as hexane slows reaction and lowers *ee* due to poor solubility of indanone.
- Under reaction conditions, catalyst can decompose to **A** and **B**. MeI can further alkylate decompositions adducts to give non-selective catalysts **C** and **D**.



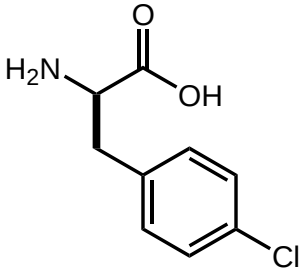
Hughes, Dolling *et al*, *J. Org. Chem.*, **1987**, *52*, 4745

Amino Acid Synthesis : Early Examples





R-X	**equiv.**	**% *ee* (*R*)**	**Yield(%)**	**Time(h)**
CH_2=$CHCH_2Br$	5	66	75	5
$PhCH_2Br$	1.2	66	75	9
MeBr	5	42	60	24
n-BuBr	5	52	61	14
4-Cl-$C_6H_4CH_2Br$	1.2	66	81	12
2-napthylCH_2Br	1.2	54	82	18

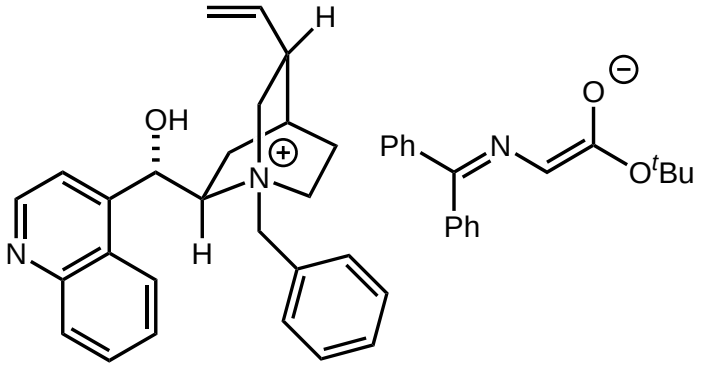


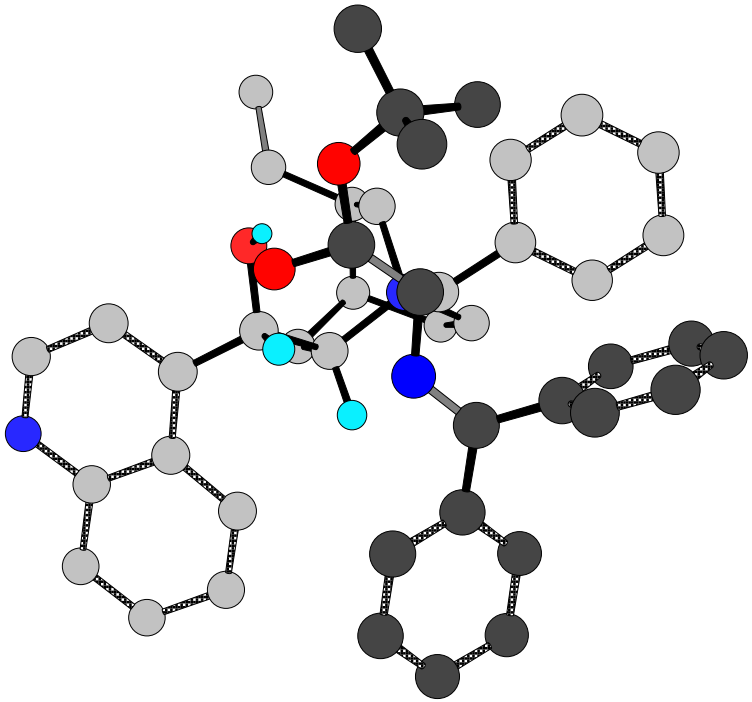
6.5 g prepared in >99% ee, two steps, 50% overall yield from alkylation precursor Schiff base.

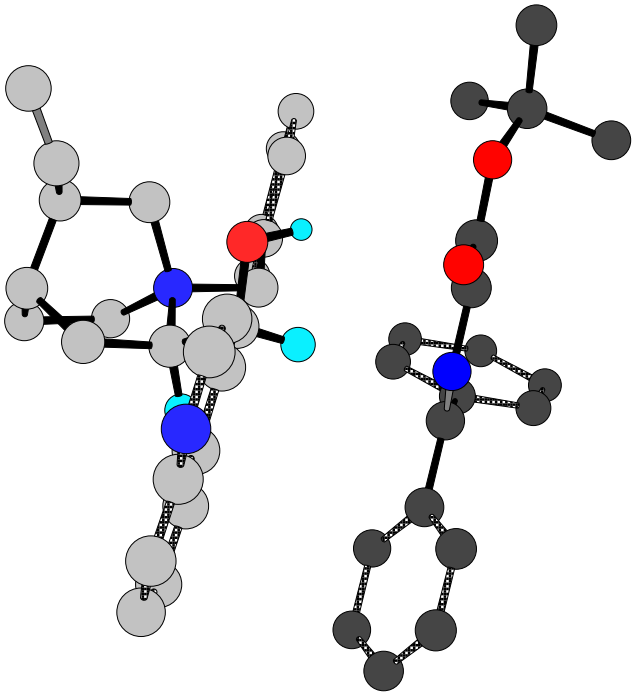
- *tert*-Butyl ester proved to be optimal for asymmetric induction
- *N*-benzyl catalyst shown above gave comparable results to the more expensive *N*-(4-(trifluoromethyl))benzyl catalyst
- Discovers that *O*-protection with allyl or benzyl does not changes yields or selectivities. Is the *O*-alkylated catalyst the actual "active species"? (*Tetrahedron*, **1994**, *50*, 2353)

O'Donnell *et al*, *J. Am. Chem. Soc.*, **1989**, *111*, 2353
O'Donnell *et al*, *Tetrahedron.*, **1994**, *50*, 2353

O'Donnell's Stereochemical Rationale



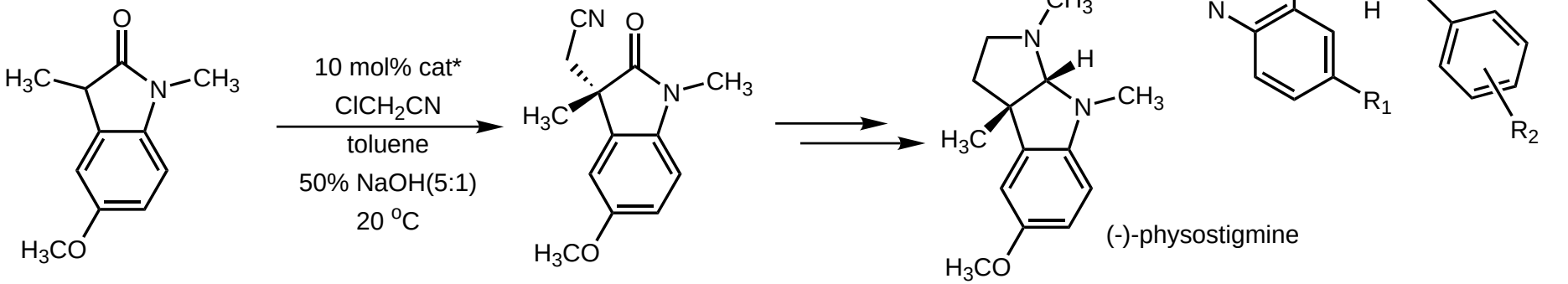




- These models represent MM2 minimizations of substrate enolate fitting into catalyst binding region.
- Very little energy difference between *Z* and *E* enolates in the absence of small counterions.
- *Z* enolate was more consistent with experimental *ee*'s.

Lipkowitz, O'Donnell *et al*, *J. Org. Chem.*, **1991**, *56*, 5181

Asymmetric Alkylations of Oxindoles



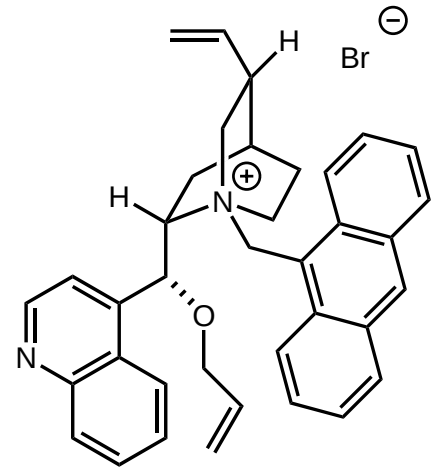
R_1	R_2	X	% *ee*
H	H	Br	10
H	2-CF_3	Br	4
H	3-CF_3	Br	69
H	4-CF_3	Br	72
H	3-Br	Br	48
H	4-Br	Br	68
H	4-Cl	Br	69
H	3,4-Cl_2	Br	77
H	3,4-Cl_2	Cl	78
H	2,6-Cl_2	Br	0
OCH_3	H	Br	39
OCH_3	3,4-Cl_2	Br	77

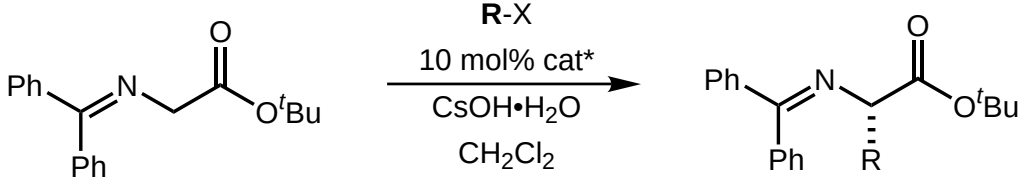
- Asymmetric induction is increased when *N*-benzyl group is substituted at the 3 and 4 positions with electron withdrawing groups.
- Little counterion effect observed
- Substitution at 2 and/ or 6 position of *N*-benzyl moiety severely erodes selectivity.
- Increasing catalyst loading up to 50 mol% does not improve enantiomeric excess

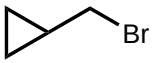
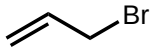
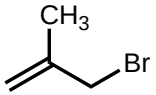
Wong *et al*, *J. Org. Chem.,* **1991**, *56*, 872

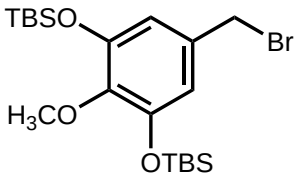
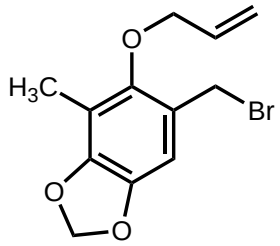
Corey's Amino Acid Synthesis Methodology

cat* =





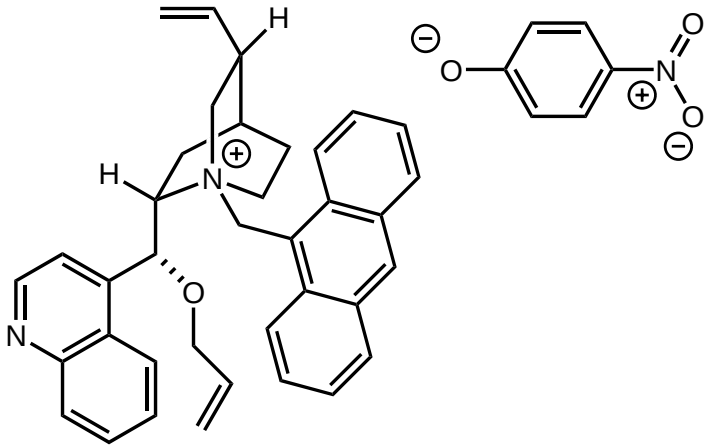
R-X	Temp (^{o}C), Time	%*ee*	yield
CH_3I	-60, 28h	97	71
CH_3CH_2I	-60, 30h	98	82
$CH_3(CH_2)_4CH_2I$	-60, 32h	99.5	79
	-60, 36h	99	75
	-78, 22h	97	89
	-78, 20h	92	91
	-78, 18h	95	68

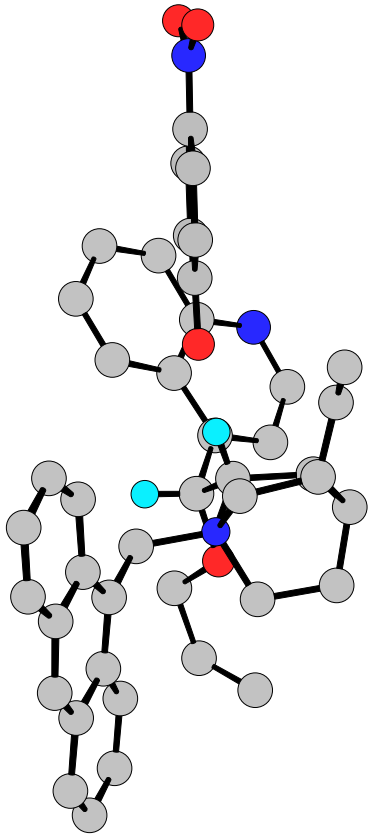
R-X	Temp (^{o}C), Time	%ee	yield
$PhCH_2Br$	-78, 23h	94	87
Ph_2CHBr	-78, 22h	99.5	73
	-78, 24h	97	67
	-78, 24h	96	81

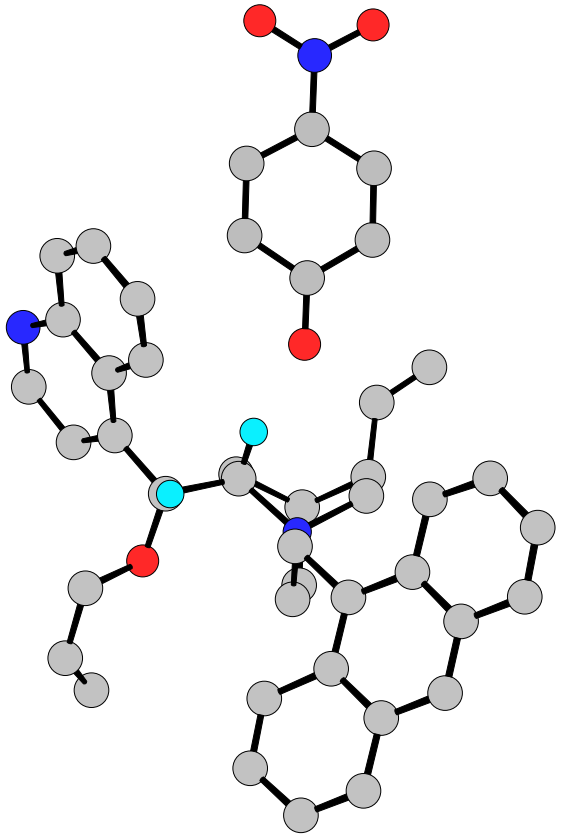
• Use of 50% aq. KOH at -20 ^{o}C gave slightly lower *ee*.

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

Stereochemical Model for Alkylations : X-Ray Evidence

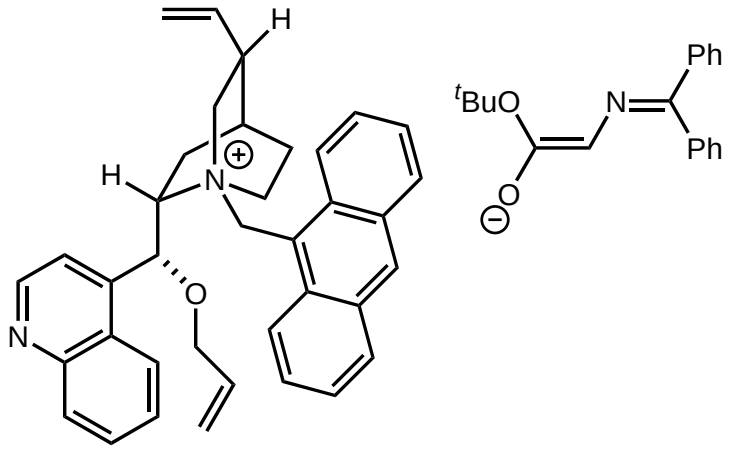


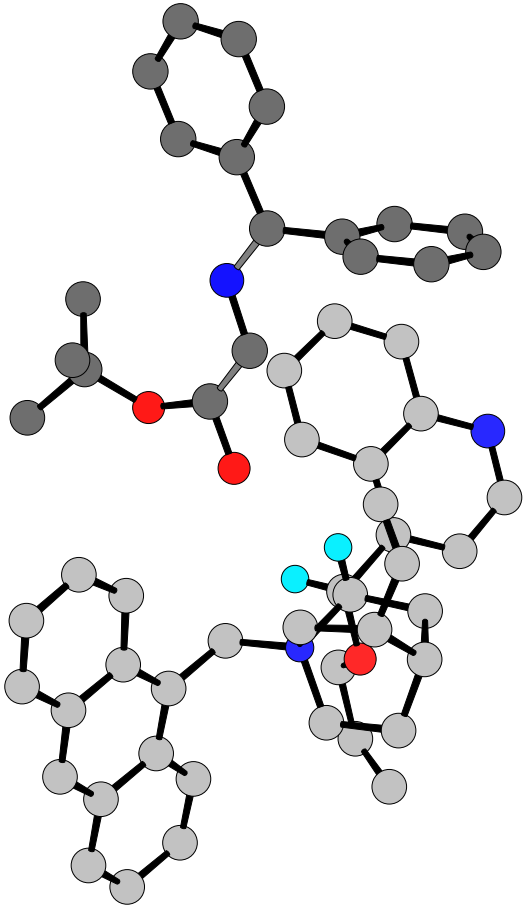


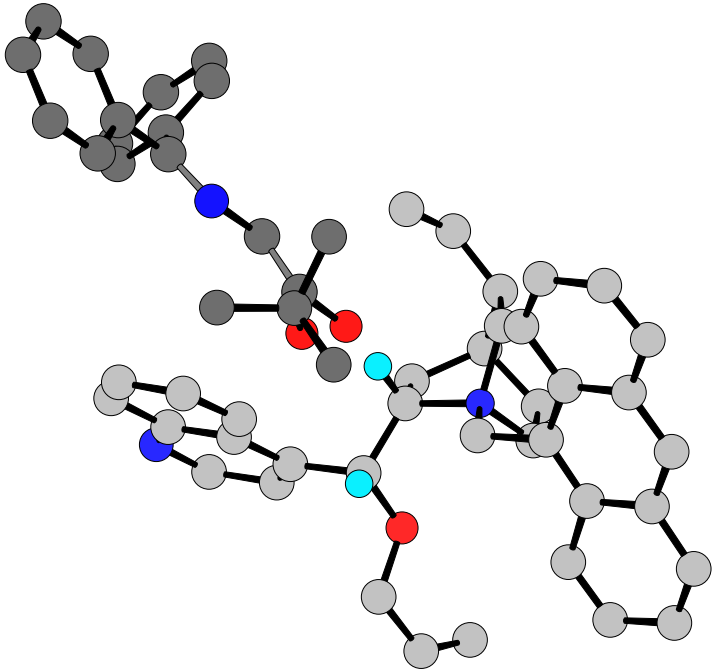


Corey *et al*, *J. Am. Chem. Soc.*, **1997**, *119*, 12414

Stereochemical Model for Alkylations



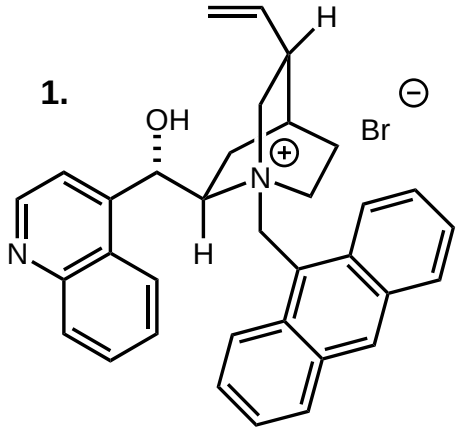




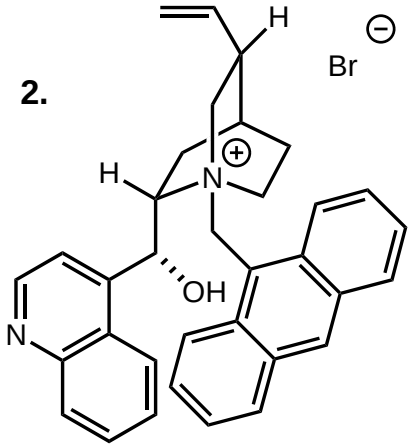
Corey *et al*, *J. Am. Chem. Soc.*, **1997**, *119*, 12414

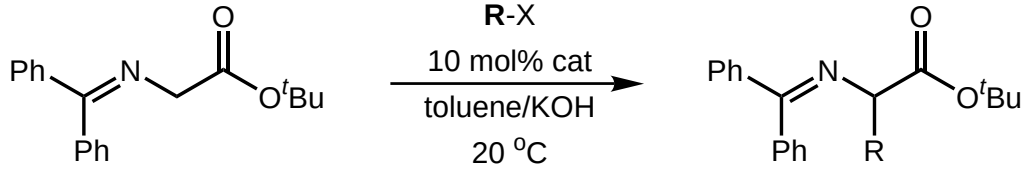
Lygo's Alkylations

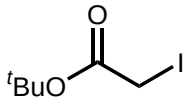
1.



2.





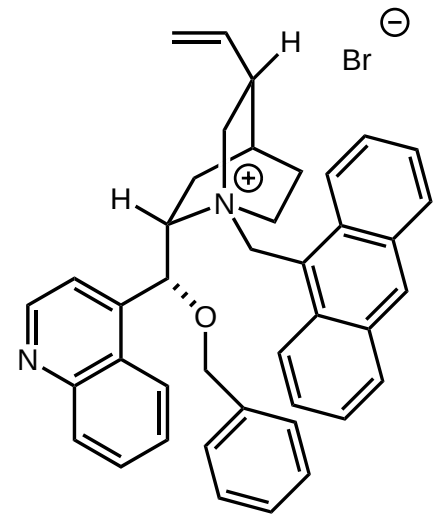
R-X	**cat**	**Time(h)**	**% *ee* (config)**	**Yield(%)**
$PhCH_2Br$	**1**	18	89(*R*)	63
	2	18	91(*S*)	68
$CH_2{=}CHCH_2Br$	**1**	18	88(*R*)	62
	2	18	88(*S*)	76
CH_3I	**1**	3	86(*R*)	40
	2	3	89(*S*)	41
$CH_3(CH_2)_3I$	**1**	18	87(*R*)	56
	2	18	88(*S*)	42
(β-naphthyl)CH_2Br	**1**	18	82(*R*)	86
	2	18	86(*S*)	75
	**1**	4	67(*R*)	83
	2	4	72(*S*)	84

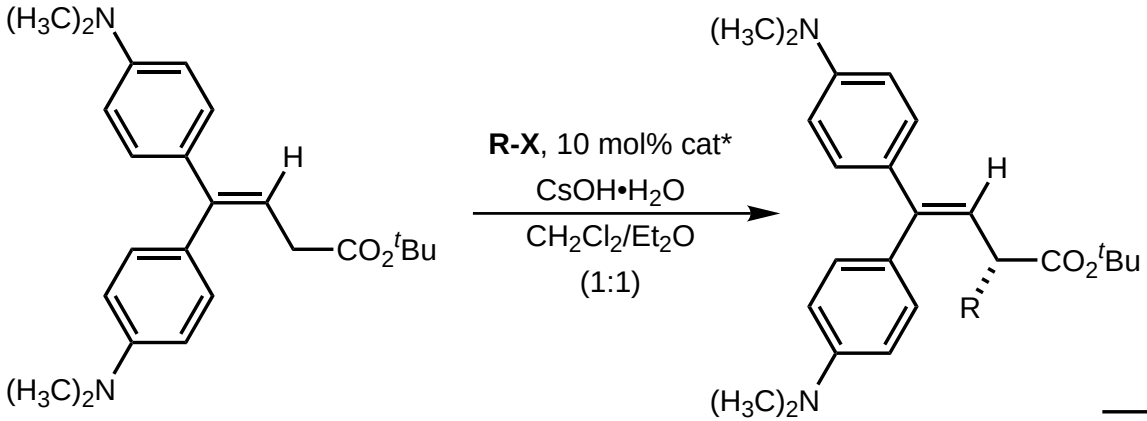
- Lygo also notes that the *O*-protected catalysts give identical results, and also suggests that the *O*-alkylated species may be the active catalyst.

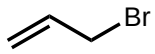
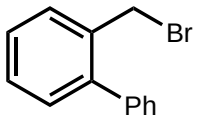
Lygo *et al*, *Tetrahedron Lett.*, **1997**, *38*, 8595

Synthesis of Chiral 1,3-Propane Diols

cat* =



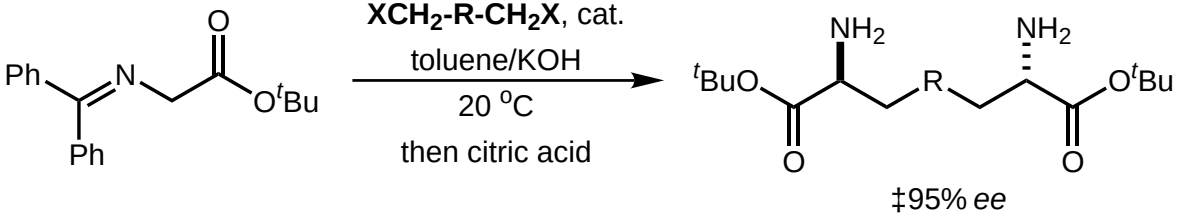


R-X	Temp(°C), Time(h)	Yield(%)	% *ee*
CH_3I	-50, 12	68	98
$CH_3(CH_2)_5I$	-45, 12	73	95
$Cl(CH_2)_3I$	-45, 12	71	95
$Cl(CH_2)_4I$	-45, 12	62	94
	-65, 36	76	96
$PhCH_2Br$	-65, 36	83	94
	-65, 12	81	98

- Strongly electron donating substituents on phenyl groups of nucleophile required for high enantioselectivity.
- Use of bifunctionalized electrophiles make the synthesis of chiral 3-susbtituted tetrahydrofurans and tetrahydropyrans possible.

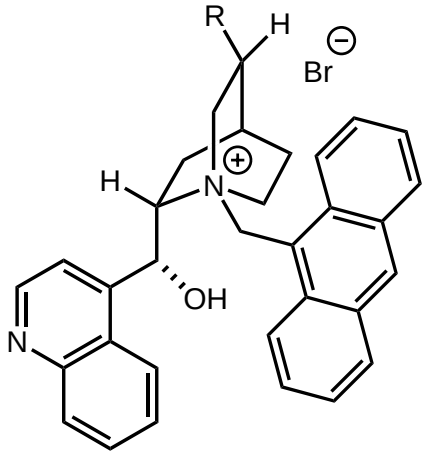
Corey *et al*, *J. Am. Chem. Soc.*, **1998**, *120,* 13000

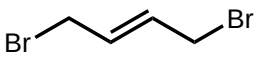
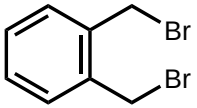
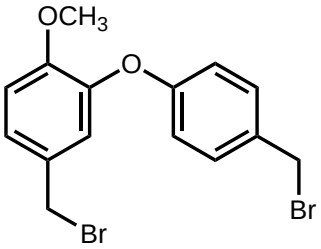
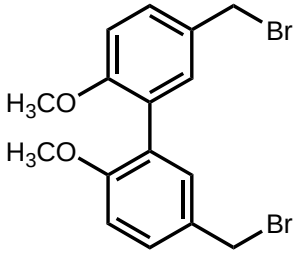
Synthesis of bis-α-Amino Acid Esters



‡95% *ee*

1 R = CH=CH$_2$
2 R = CH$_2$CH$_3$

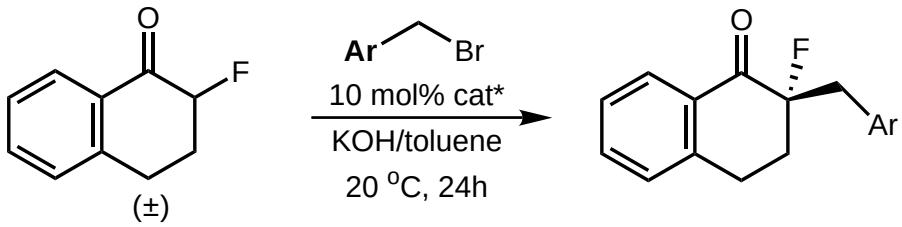


XCH$_2$-R-CH$_2$X	**cat.**	**% *de***	**Yield(%)**
	10 mol% **2**	82	49
	10 mol% **2**	75	48
	10 mol% **1**	80	63
	20 mol % **1**	80	65

- No explanation as to why the dihydro catalyst **2** was used in certain cases.
- One can control mono and *bis* alkylation by varying the equivalents of *bis*-allyl bromide. 0.5 eqv. gives a 10:1 ratio of *bis* : mono alkylation, 5.0 eqv. gives a 1:10 ratio.
- Useful methodology for the synthesis of natural and unnatural dityrosine type amino acids.

Lygo *et al*, *Tetrahedron Lett.*, **1999**, *40*, 1385
Lygo, *Tetrahedron Lett.*, **1999**, *40*, 1389

Asymmetric Alkylation of α-Fluorotetralone



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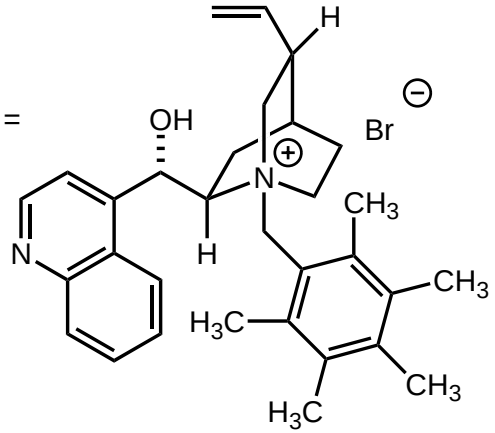
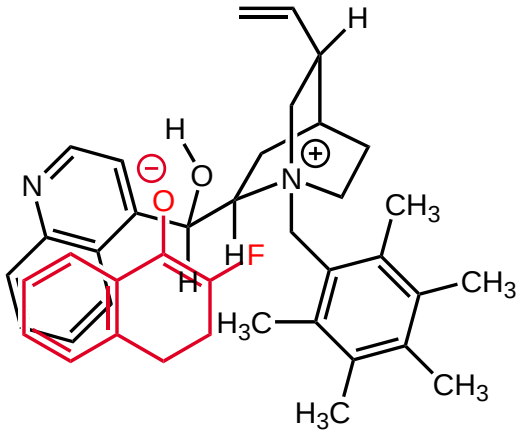


- Reaction was optimized extensively for solvent and base. RbOH•H_2O/THF systems gave comparable results.
- Again, substitution and electronics at *N*-benzyl group of alkaloid was critical to selectivity. In this case, electron withdrawing substituents had a detrimental effect.
- Analogous alkylation of α-methyltetralone with benzyl bromide gave a maximum of 55%*ee* and 18% yield with above catalyst.

Ar	% ee	Yield(%)
C_6H_5	80	71
2-Me-C_6H_4	84	60
3-MeC_6H_4	84	45
4-Me-C_6H_4	82	58
4-Br-C_6H_4	78	83
2,3,4,5,6-Me_5-C_6	91	44
β-Np	79	60
(*E*)-PhCH=CH	70	33

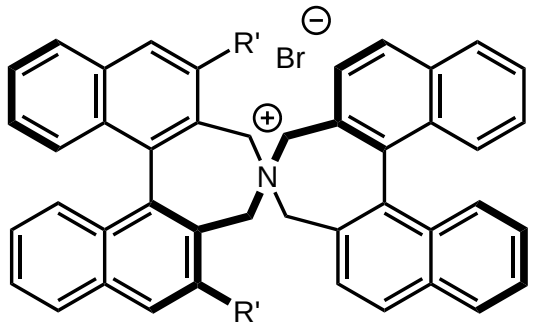


HAR Rationale :

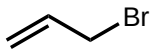
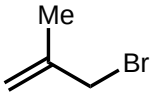
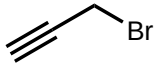
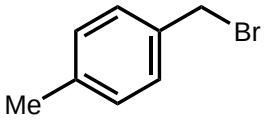
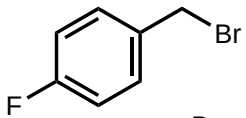
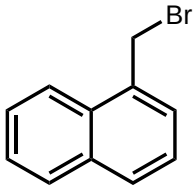
- Sterics of the N-benzyl group prevent the enolate from docking such that the *re* face is exposed.
- Electron withdrawing substituents on the *N*-benzyl group will enhace π-stacking with enolate, again promoting binding with *re* face exposed.

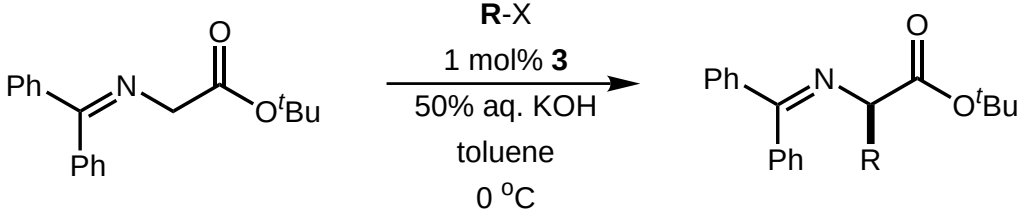
Arai *et al*, *Tetrahedron Lett.*, **1999**, *40*, 6785

A C_2-Symmetric Chiral Phase Transfer Catalyst for the Synthesis of Amino Acids



1 R'=H
2 R'=Ph
3 R'= β-Np

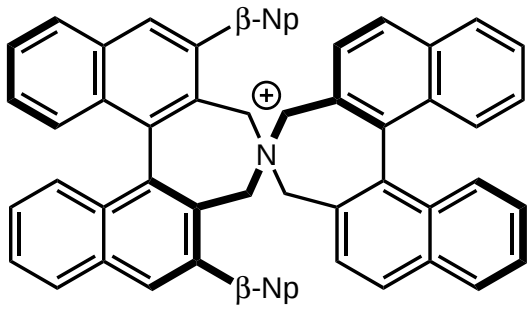
R-X	Temp (^{o}C), Time	Yield(%)	%*ee*
$PhCH_2Br$	0, 0.5h	95	96
CH_3I	0, 8h	64	90
CH_3CH_2I	0, 10h	41	95
	0, 1h	84	94
	0, 1h	82	93
	0, 1h	90	95
	0, 0.5h	80	96
	0, 1h	81	96
	0, 1.5h	60	96

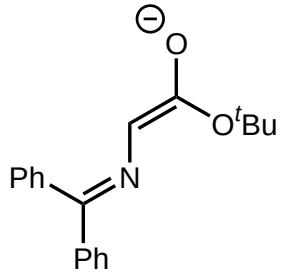


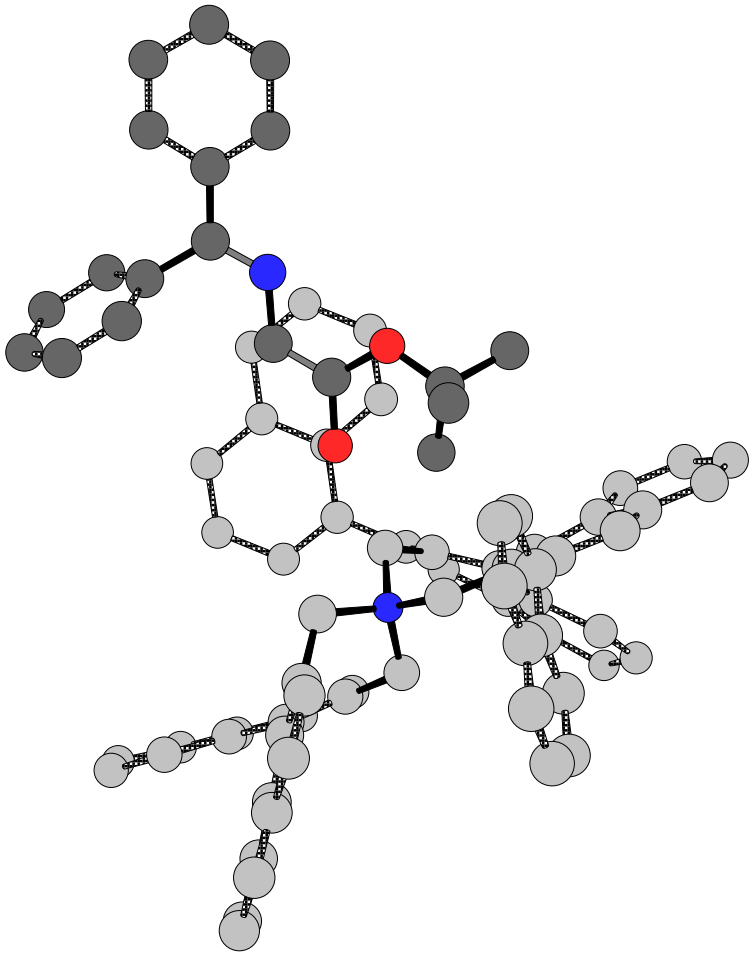
- Rigid, chiral spiro ammonium salts required for high enantioselectivity.
- R' substituent on catalyst critical for enentioselectivity, as **1** gives 79% *ee* and **2** gives 89% *ee* for the alkylation reaction with $PhCH_2Br$.
- The rate of reaction *increases* with the steric bulk of catalyst substituent R' (For R-X being $PhCH_2Br$, **1** takes 6h, **2** takes 30 min. at 0 ^{o}C). Solubility issue?

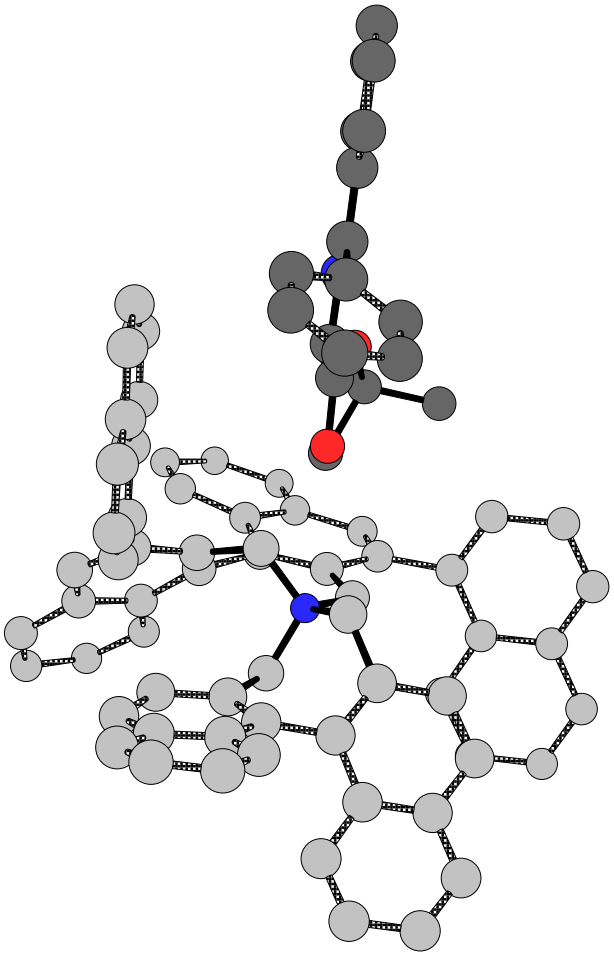
Maruoka *et al*, *J. Am. Chem. Soc.*, **1999**, *121*, 6519

Possible Rationalization of Observed Enantioselectivity







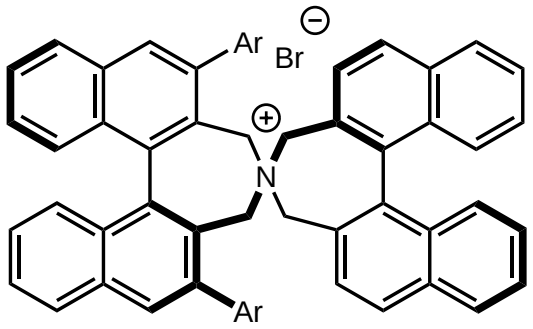


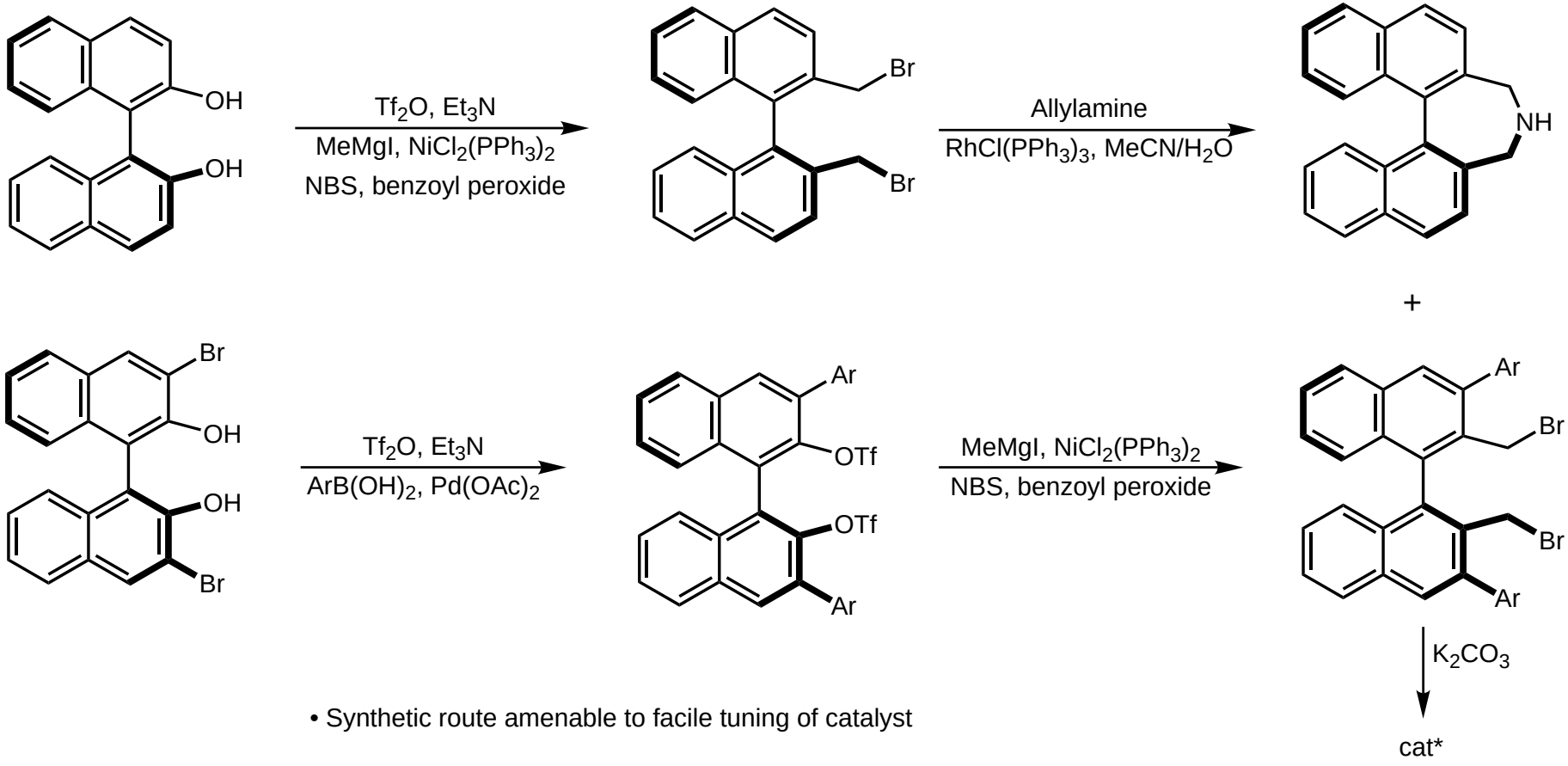
"The conformation of the E-enolate.....makes a good match for the molecular pocket of chiral catalyst....." - Maruoka

(Chem3D models by HAR)

Maruoka Catalyst Synthesis

cat* =



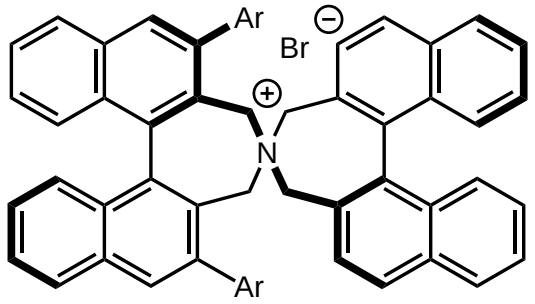


- Synthetic route amenable to facile tuning of catalyst

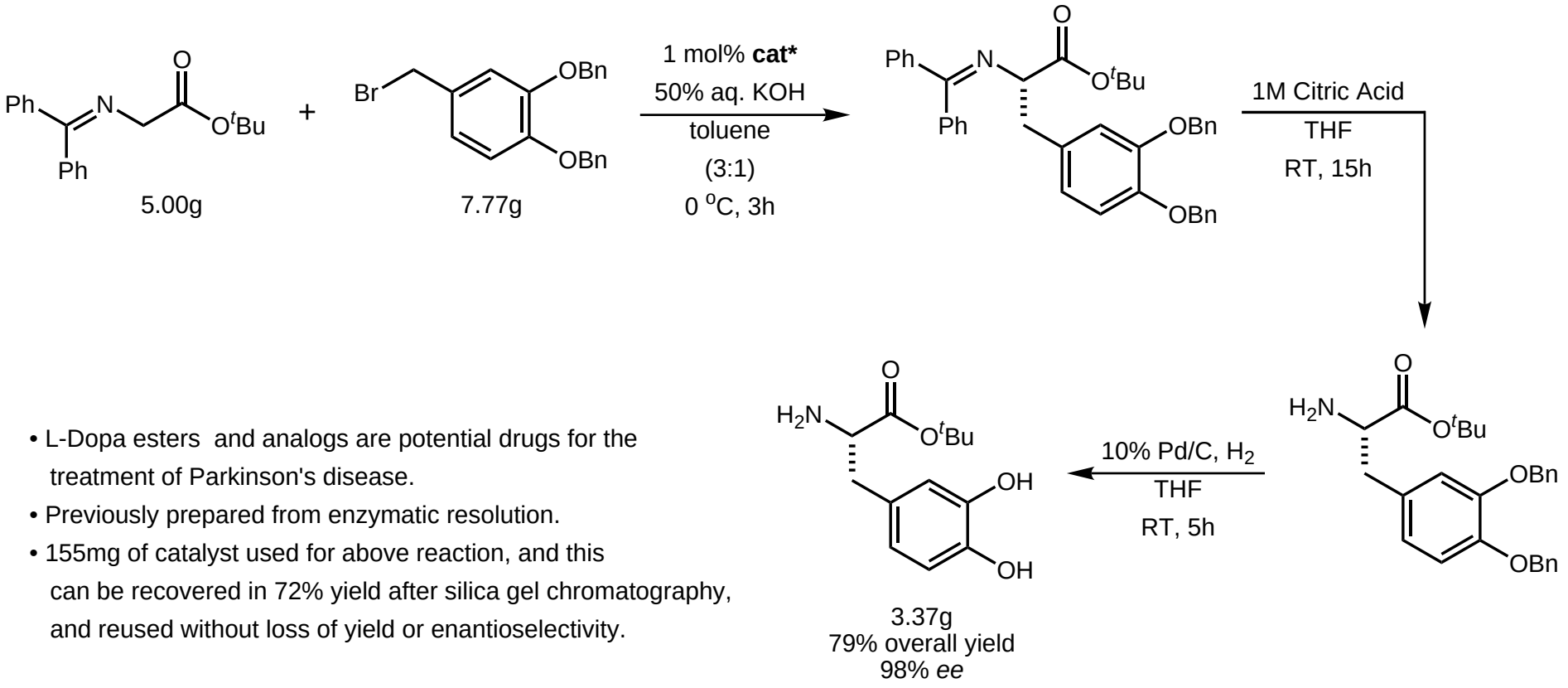
Maruoka *et al*, *J. Am. Chem. Soc.*, **1999**, *121*, 6519

Gram-Scale Synthesis of L-Dopa tert-Butyl Ester

cat* =



Ar = 3,4,5-F_3-Ph

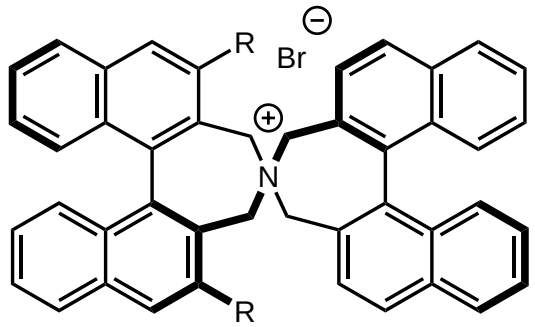


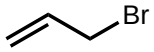
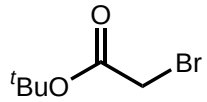
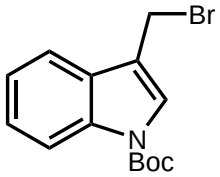
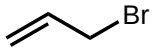
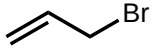
- L-Dopa esters and analogs are potential drugs for the treatment of Parkinson's disease.
- Previously prepared from enzymatic resolution.
- 155mg of catalyst used for above reaction, and this can be recovered in 72% yield after silica gel chromatography, and reused without loss of yield or enantioselectivity.

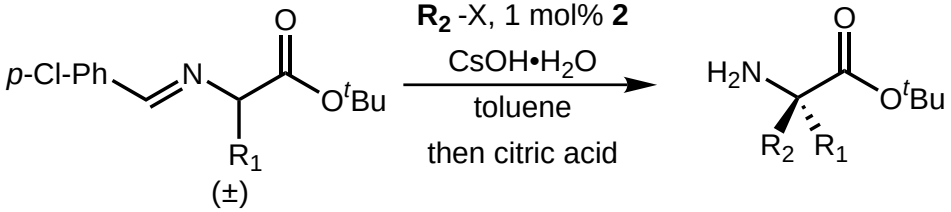
Maruoka *et al*, *Tetrahedron Lett.*, **2000**, *41*, 8339

Synthesis of α, α Dialkyl α-Amino Acids

1 R = β-Np
2 R = 3,4,5-F_3-Ph



R_1	R_2 -X	Temp (^{o} C), Time	Yield(%)	% *ee*
Me	$PhCH_2Br$	0, 0.5h	85	98
Me		0, 0.5h	73	98
Me	CH_3CH_2I	0, 0.3h	71	99
Me		-20, 2h	60	93
Me		-10, 0.7h	78	91
$PhCH_2$		0, 0.5h	71	97
^{i}Bu	$PhCH_2Br$	0, 0.5h	64	92
^{i}Bu		0, 1h	70	93

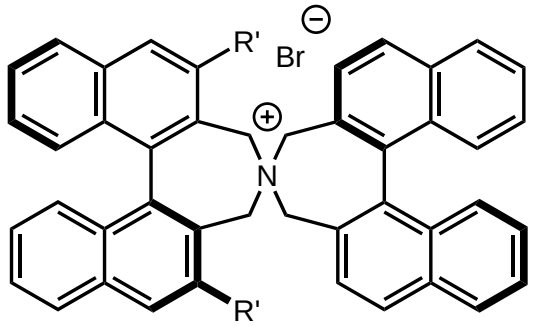


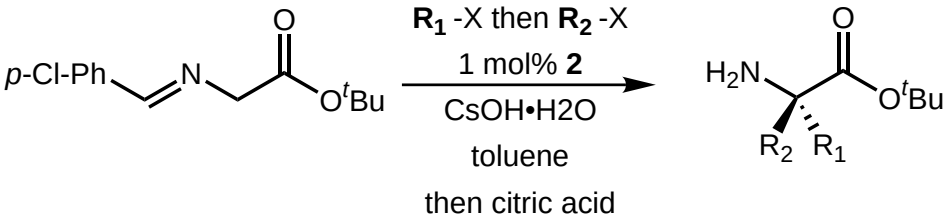
- Solid/liquid phase transfer reaction increases reactivity as well as selectivity.
- Enantiomerically pure starting material provide identical reactivity and results.
- Tuning the electronic properties of the catalyst important, as **2** ffered significantly higher levels of enantioselectivity than **1**.

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

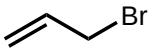
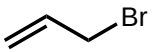
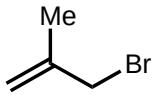
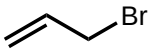
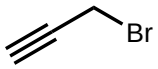
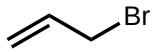
Synthesis of α, α Dialkyl α-Amino Acids via a One Pot, bis-*Alkylation Reaction*

1 R = β-Np
2 R = 3,4,5-F_3Ph



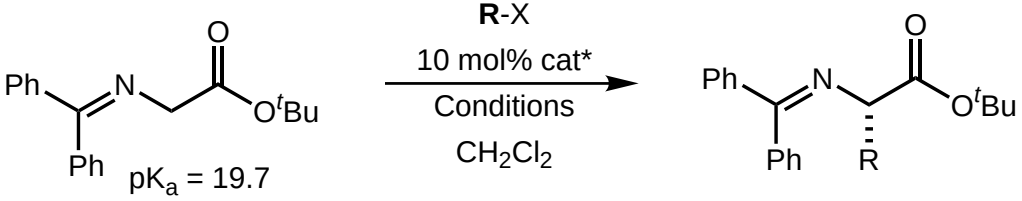


- Remarkable synthesis of α,α-dialkyl-α-amino acids!
- Either enantiomer can be prepared using the same reagents, by just inverting the order of addition of alyklating agents.

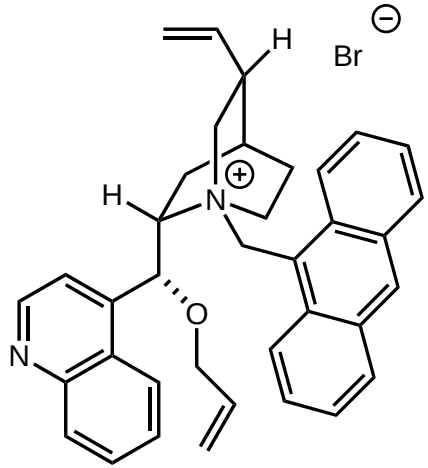
R_1-X	Temp(^{o}C), Time	R_2 -X	Temp (^{o}C), Time	Yield	%*ee*(config.)
	-10, 3.5h	$PhCH_2Br$	0, 0.5h	80	98(*R*)
	-10, 3.5h		0, 0.7h	60	97
	-10, 3.5h		0, 0.5h	58	96
$PhCH_2Br$	-10, 2h		0, 0.3h	74	92(*S*)

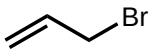
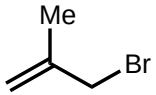
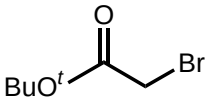
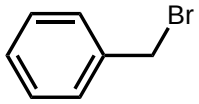
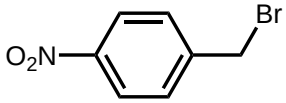
Maruoka *et al*, *J. Am. Chem. Soc.*, **2000**, *122*, 5228

Organic Soluble Bases Can Also Be Used.....

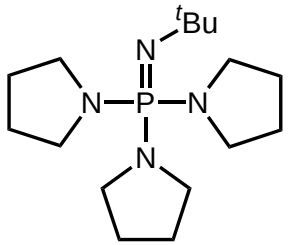


cat* =

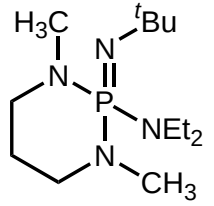


R-X	**Conditions**	**Time(h)**	**Yield(%)**	**% *ee***
CH_3I	A	4	92	94
CH_3CH_2I	B	6	98	89
$(CH_3)_2CHI$	B	24	93	97
	A	6	96	90
	A	4	91	94
	A	7	89	56
	A	4	88	91
	A	4	93	89

A : 1.5 eqv. BEMP, -78 ^oC
B : 5.0 eqv. BTPP, -50 ^oC



BTPP pK$_a$ = 17.0
non-active halides



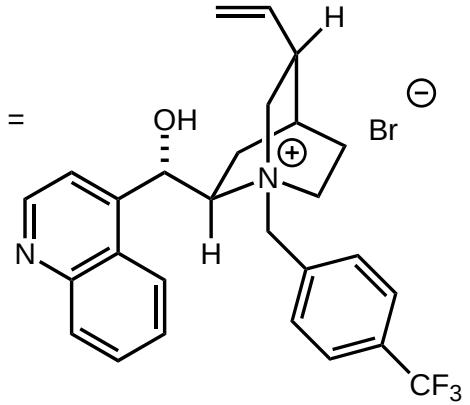
BEMP pK$_a$=16.2
active halides

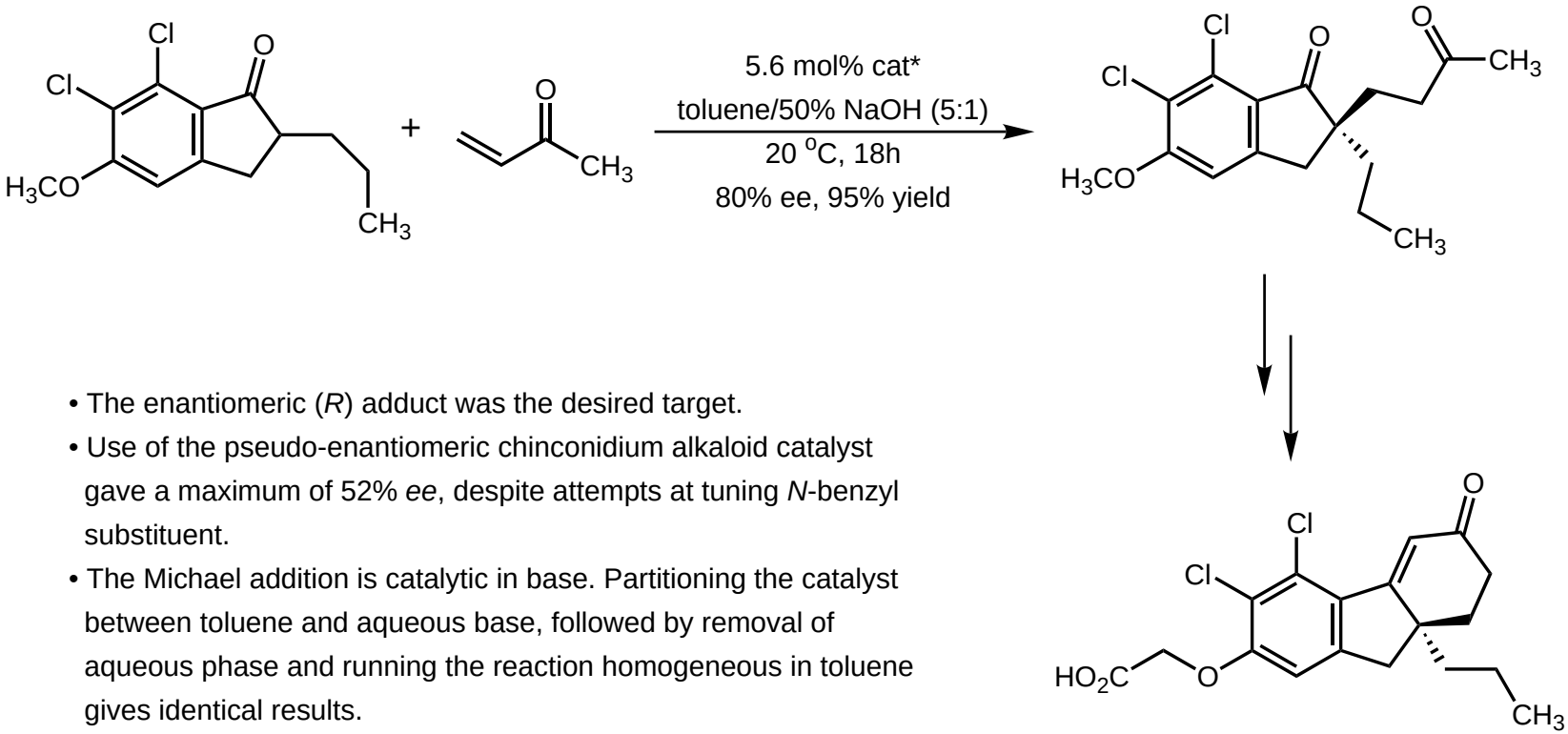
- Since both base and substrate are in the same phase, reaction times are generally faster than phase transfer reactions.
- No mention of base recovery in procedure.
- For Schwesinger base synthesis, see : *Chem. Ber.*, **1994**, *127*, 2435.

O'Donnell *et al*, *Tetrahedron Lett.*, **1998**, *39*, 8775

Michael Addition of Indanone to MVK

cat* =

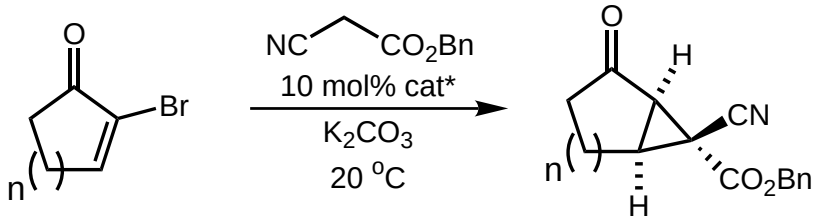


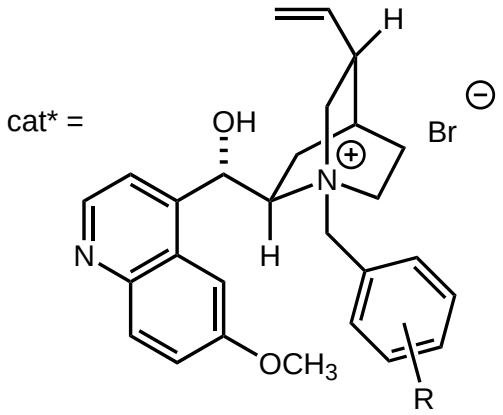


- The enantiomeric (*R*) adduct was the desired target.
- Use of the pseudo-enantiomeric chinconidium alkaloid catalyst gave a maximum of 52% *ee*, despite attempts at tuning *N*-benzyl substituent.
- The Michael addition is catalytic in base. Partitioning the catalyst between toluene and aqueous base, followed by removal of aqueous phase and running the reaction homogeneous in toluene gives identical results.
- Stereochemical rationale identical to that proposed by Dolling (See *J. Am. Chem. Soc.*, **1984**, *106*, 406)

Conn *et al*, *J. Org. Chem.*, **1986**, *51*, 4710

Cyclopropanation via *Michael Addition*



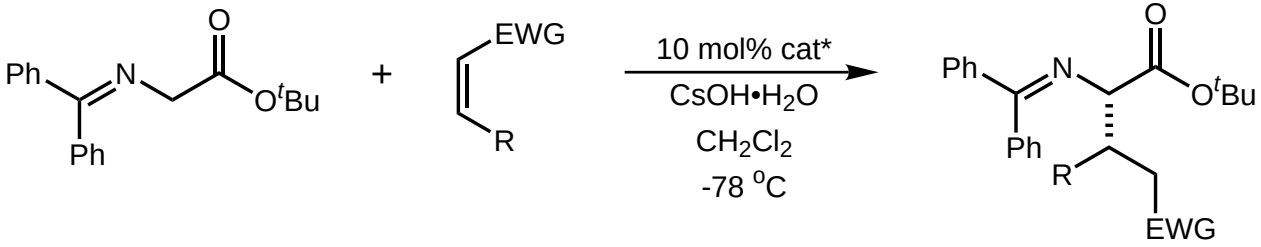


n	R	Solvent	Time(h)	Yield(%)	% *ee*
1	2,4-$(CF_3)_2$	toluene	34	76	31
1	2,4-$(CF_3)_2$	1,2-dichloroethane	34	74	44
1	2,4-$(CF_3)_2$	chlorobenzene	13	74	45
1	4-CF_3	chlorobenzene	26	82	25
1	2,4-$(CH_3)_2$	chlorobenzene	48	96	15
1	F_5	chlorobenzene	31	62	24
2	2,4-$(CH_3)_2$	chlorobenzene	112	51	6
2	2,4-$(CF_3)_2$	chlorobenzene	43	60	83

- Both nitromethane and cyanomethylsulfone can be used as a nucleophile, but the enantioselectivity is lower.
- Substitution at 2 position of *N*-benzyl with an electron withdrawing group crucial to good enanioselectivity .

Arai, Shioiri *et al*, *Tetrahedron Lett.*, **1999**, *40*, 4215

Corey's Michael Additions



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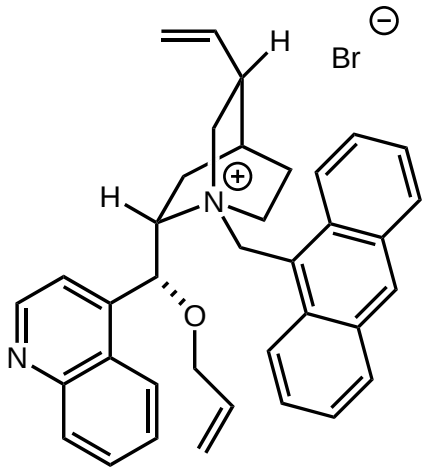
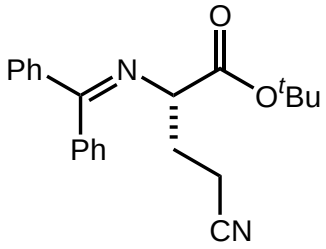
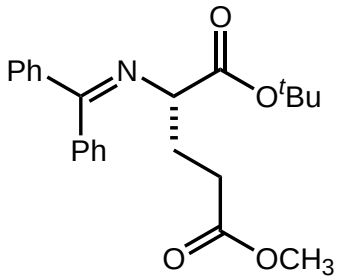


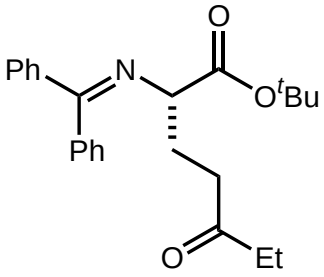


85%, 91% *ee*

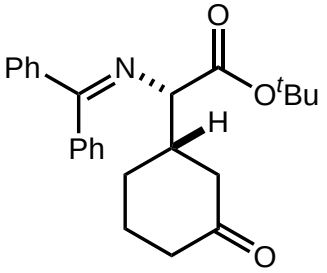
(reaction run at -55 ^{o}C)



85%, 95% *ee*

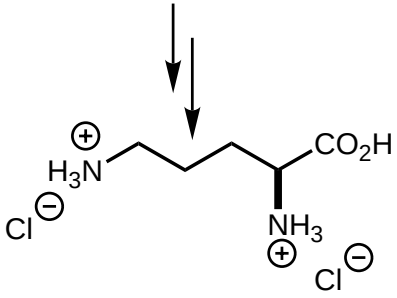


85%, 91% *ee*



88%, 91% *ee*

dr = 96:4

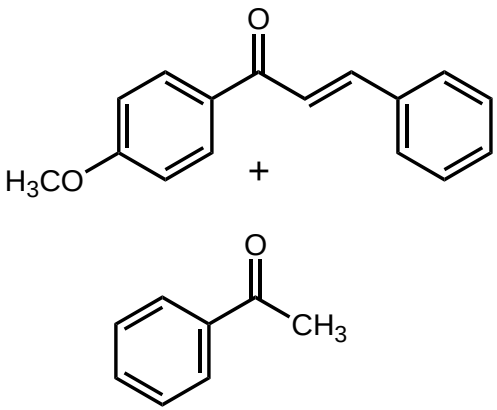


(*S*)-ornithine hydrochloride

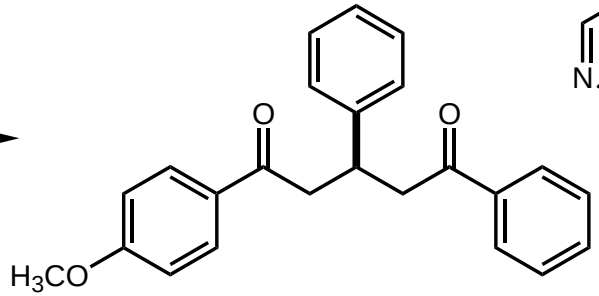
Corey *et al*, *Tetrahedron Lett.*, **1998**, *39*, 5347

Corey *et al*, *Org. Lett.*, **2000**, *2*, 1097

Corey's Syntheses of Chiral 2-Cyclohexenones



10 mol% **cat***
toluene/50% KOH
-10 °C, 36h
72%, 80% ee



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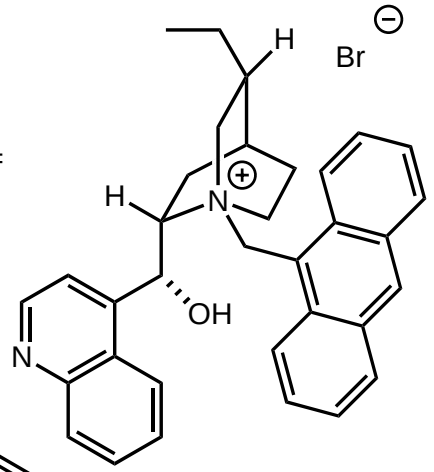
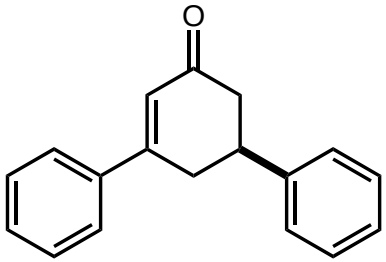
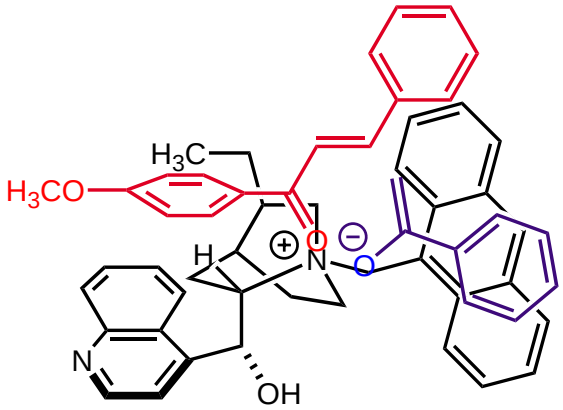




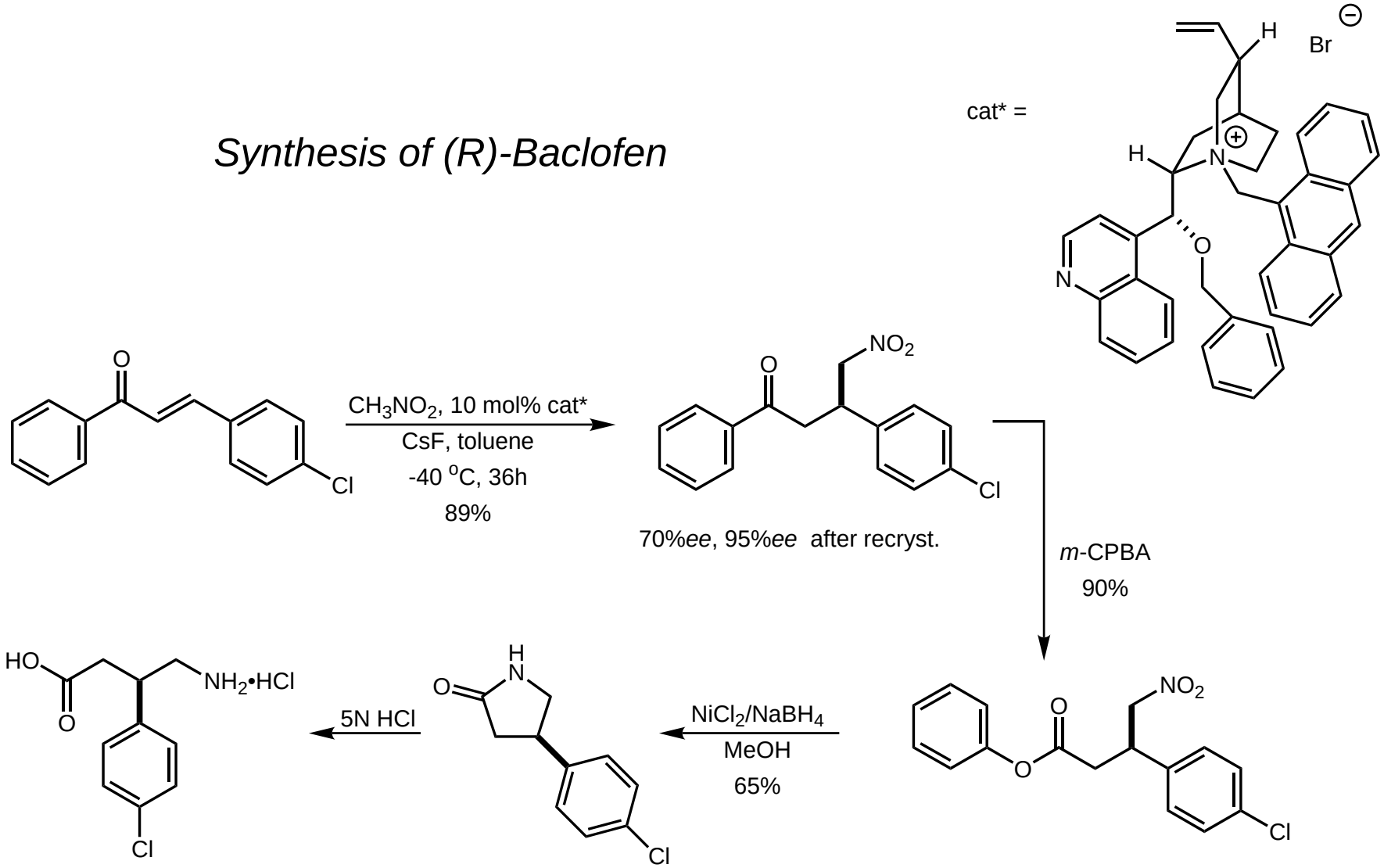
Author's Rationale:



- No explanation given for why free hydroxyl on chinconidium salt is used.

Corey *et al*, *Org. Lett.*, **2000**, *2*, 1097

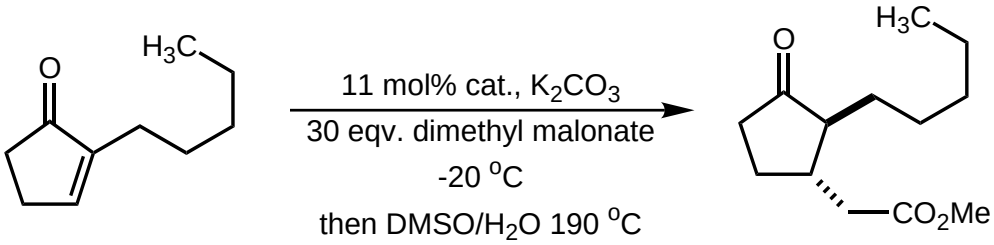
Synthesis of (R)-Baclofen



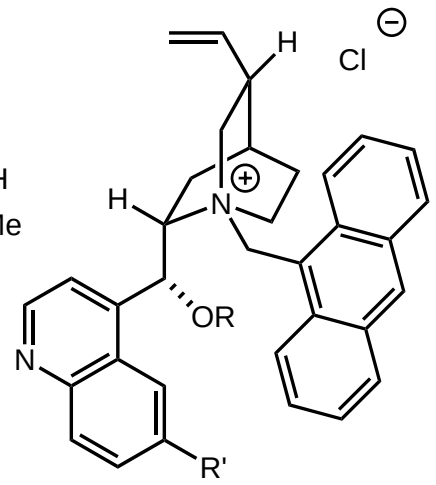
- (*R*)-baclofen hydrochloride is a therapeutically useful $GABA_B$ receptor agonist.
- Racemic baclofen is currently used to treat spasms caused by spinal chord injury or disease.
- Stereochemical model is identical to the Michael addition of acetophenone
  (Corey *et al*, *Org. Lett.*, **2000**, *2*, 1097).

Corey *et al*, *Org. Lett.*, **2000**, *2*, 4257

Enantioselective Synthesis of Methyl Dihydrojasmonate

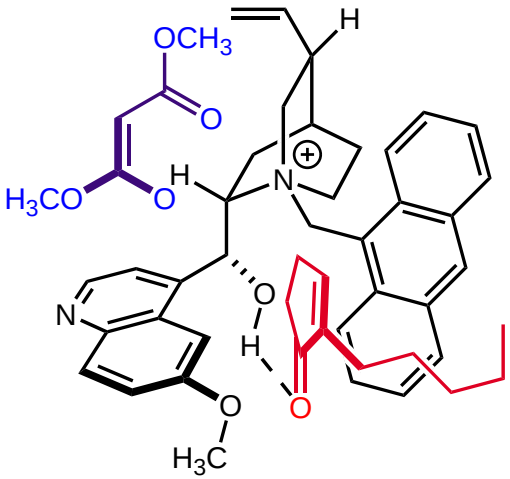


1 R = R' = H
2 R = allyl, R' = H
3 R = H, R' = OMe

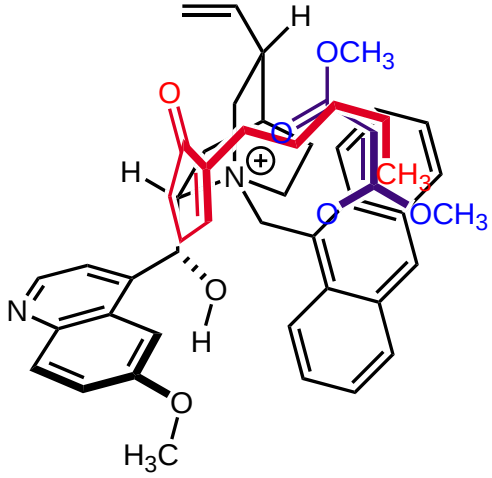


cat.	**% *ee***	**Yield(%)**
1	54	75
2	NR	NR
3	90	91

Author's Rationale :



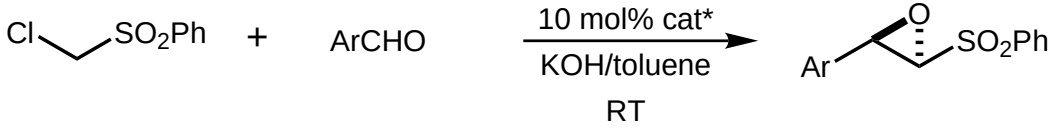
HAR Rationale :



- Both enantiomers of *trans*-dihydrojasmonate are constituents of commercial fragrances.
- Unprotected hydroxyl group of catalyst crucial to attain reactivity.
- *Pseudo*-enantiomeric quinidinium catalyst catalyst gives 80% *ee*.
- Dimethyl malonate is used as a reagent and also as a solvent. The use of any other solvent completely inhibits the reaction.

Plaquevent *et al*, *Org. Lett.*, **2000**, *2*, 2959

Asymmetric Darzens Reactions of Chloromethyl Phenylsulfone



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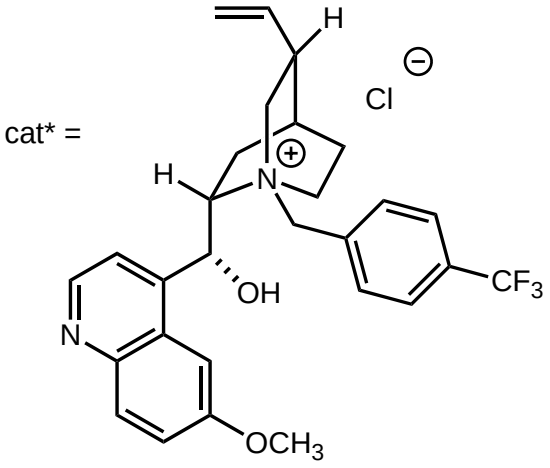
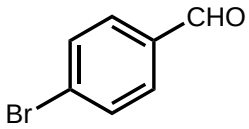
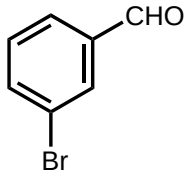
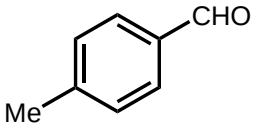
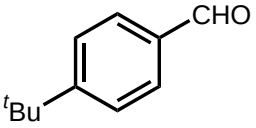
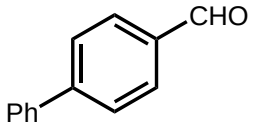
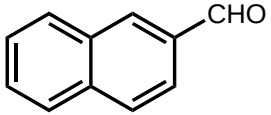
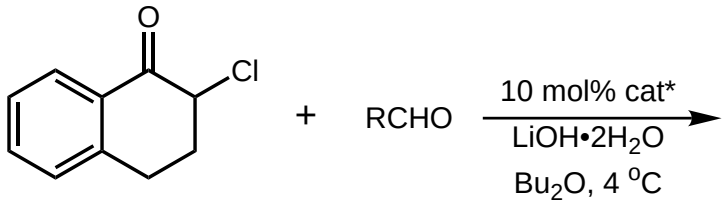


ArCHO	Time(h)	Yield(%)	% *ee*
	1	80	64
	1.5	69	71
	2	84	78
	2	70	81
	1.5	71	72
	1	94	68

- The use of a non-polar solvent is critical for both yield and enantioselectivity.
- Again, the electronics of the *N*-benzyl substituent significantly influences enantioselectivity.
- Generally, metal mediated asymmetric Darzens reactions are stoichiometric in chiral controller. For a chiral crown ether catalyzed Darzens reaction, see *Synlett*, **1997**, 291.
- For the synthetic utility of α,β epoxysulfones, see *J. Am. Chem. Soc.*, **1997**, *119*, 4557, and references cited therein.

Arai, Shioiri *et al*, *Tehtrahedron Lett.*, **1998**, *39*, 8299

Asymmetric Darzen's Reactions with α-Chloro Ketones



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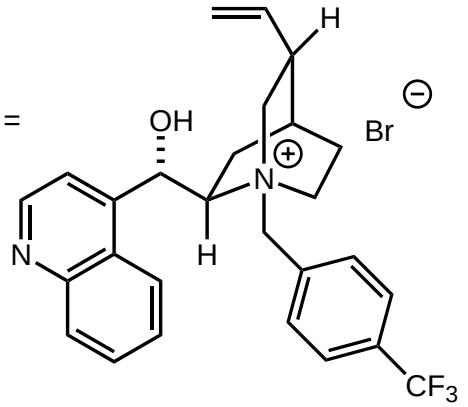
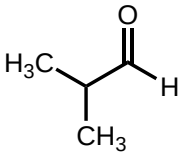
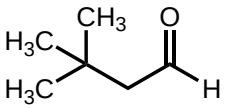
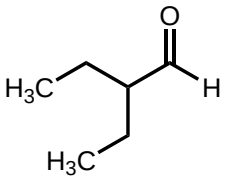
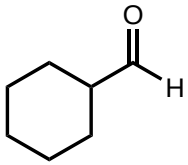
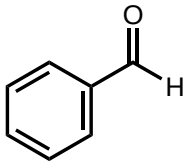
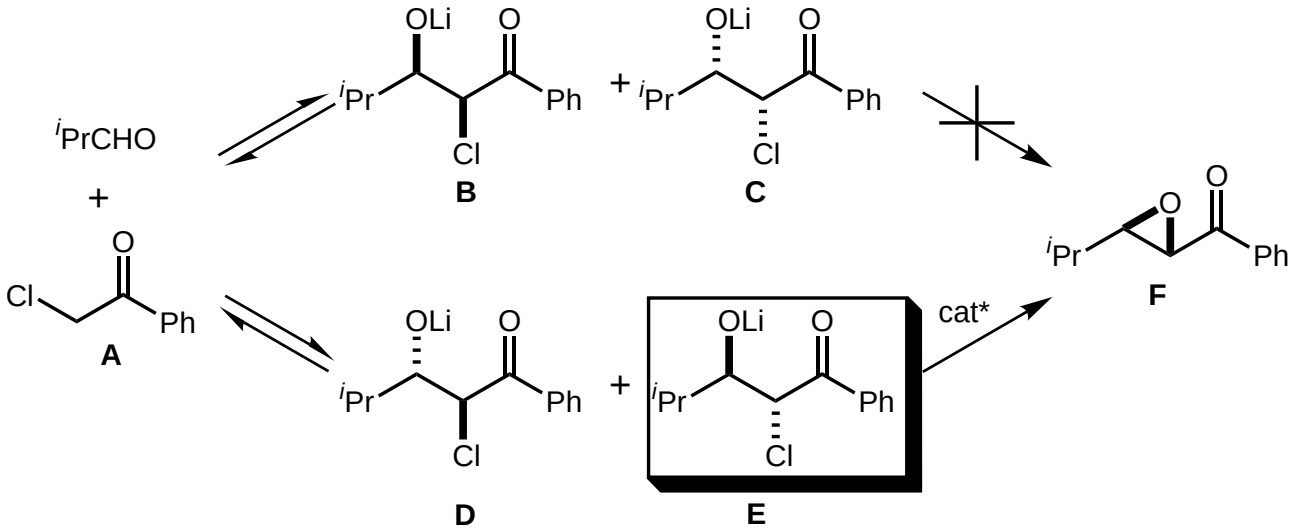


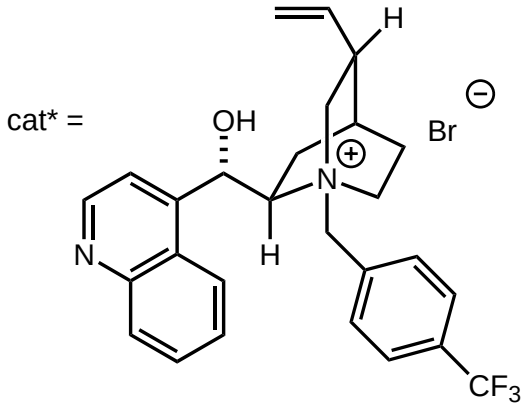
RCHO	Time(h)	Yield(%)	% *ee*
	61	99	69
	84	86	86
	252	67	84
	62	80	69
	43	67	59

- Rare case where etherial solvent is optimal for asymmetric induction.
- LiOH hydrate is the optimal base.
- Chloroenolate geometry is probably critical for enantioselectivity. Phenacyl chloride gives lower *ee*'s in reaction.
- More bulky aldehydes, such as pivaldehyde, do not react.
- *O*-protected catalyst gives almost racemic product.

Arai, Shioiri *et al*, *Tetrahedron*, **1999**, *55*, 6375

Proposed Mechanism for Asymmetric Darzens Reaction





- In a typical reaction, starting ketone is rapidly consumed, and aldol adduct is consumed slowly.
- The *syn*:*anti* ratio of aldol adducts remains constant at 33:66 throughout the reaction.
- Racemic *syn* and *anti* aldol adducts were separately subjected to reaction conditions.

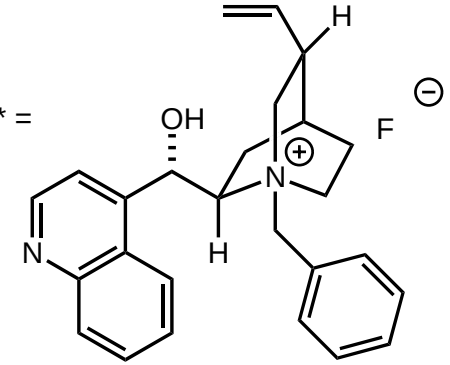
Substrates	%*ee* (yield) **F**	%*ee* **D**	**A**(% yield)
B + **C**	82(14)	47	30
D + **E**	69(21)	17	4

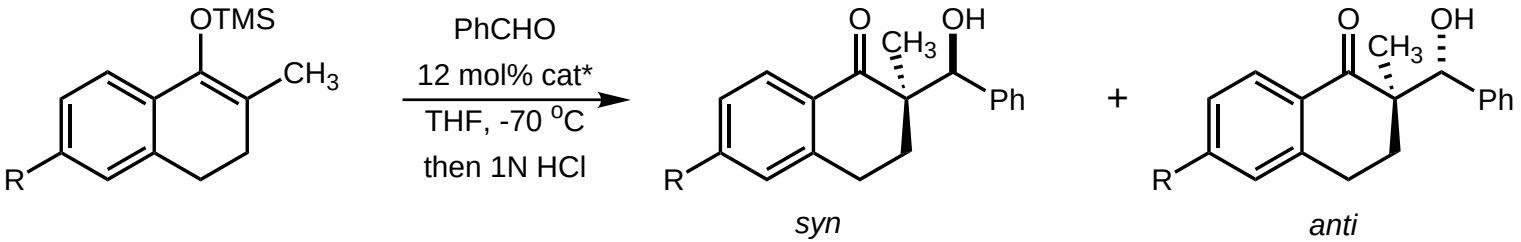
- Does *kinetic resolution* of the aldol adducts determine enantioselectivity?

Arai, Shioiri *et al*, *Tetrahedron*, **1999**, *55*, 6375

Shiori's Aldol

cat* =



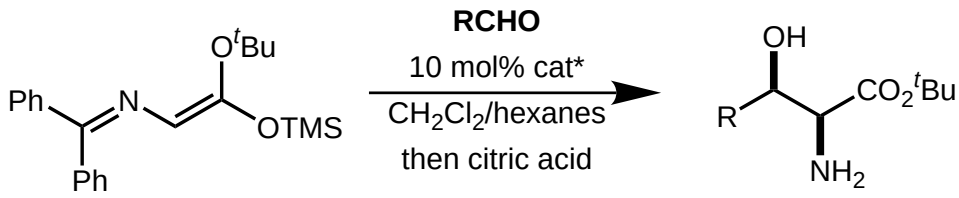


R	**Yield(%)**	***syn*:*anti***	% ***ee syn***	% ***ee anti***
H[a]	74	75:25	72	22
H[b]	65	73:27	44	6
OCH_3[b]	73	76:24	68	39
Cl[b]	73	82:18	66	21
Br[b]	67	81:19	66	15

Catalyst preps : [a]Amberlite IRA-410 (fluoride form), then evaporation.
[b]Amberlyst A-26 (hydroxide form), then HF, then evaporation.

Shiori *et al*, *Tetrahedron Lett.*, **1993**, *34*, 1507

Corey's Aldol Reaction



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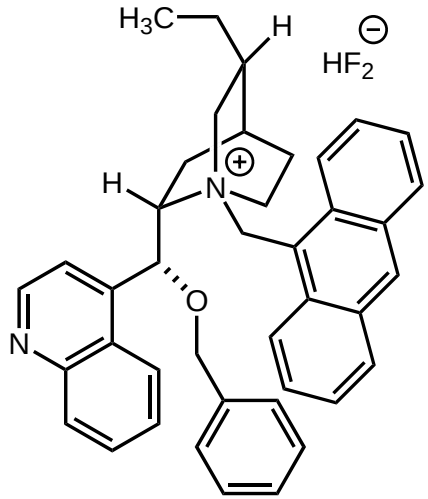
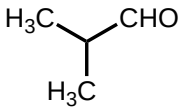
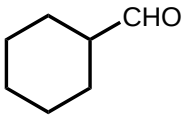
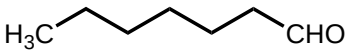
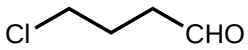
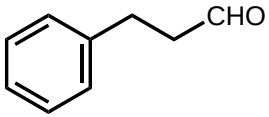
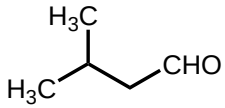
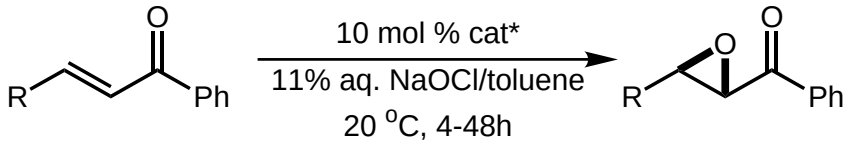


RCHO	Temp(^{o}C)	Time(h)	Yield(%)	*syn/anti*	% *ee syn*	%*ee anti*
	-78	7	70	86:14	95	83
	-50	1	81	93:07	88	46
	-78	2	79	75:25	89	91
	-78	2	48	50:50	82	86
	-78	6	64	50:50	72	86
	-45	2	61	75:25	76	70

- Bifluoride salt prepared from passing bromide salt through Amberlite A-26, then quenching the hydroxide salt with 1N HF, evaporation of solvent and drying over P_2O_5.
- Silyl ketene acetal was a 7:1 *E*:*Z* mixture of isomers.

Corey *et al*, *Tetrahedron Lett.*, **1999**, *40*, 3843

Asymmetric Epoxidation of Chalcone-type Compounds



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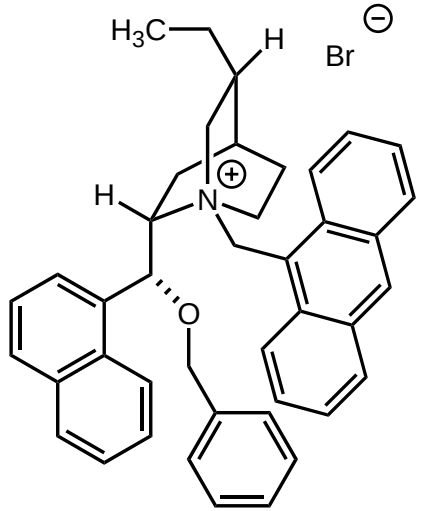
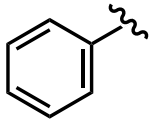
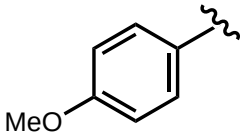
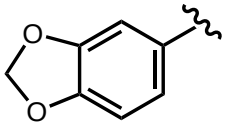
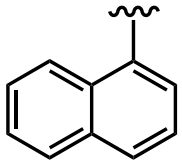
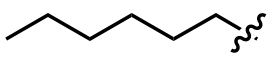
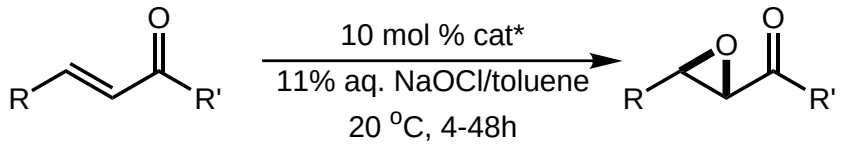


R	% *ee*	Yield(%)
	86	90
	82	87
	83	97
	82	86
	77	92

- Again, solvent efffects are dramatic, with non-polar solvents giving superior results.
- Hydroxyl protected catalyst affords much higher selectivity.
- Hydrogen peroxide can also function as an oxidant, but product is almost racemic.

Lygo *et al*, *Tetrahedron Lett.*, **1998**, *39*, 1599
Lygo *et al*, *Tetrahedron*, **1999**, *55*, 6289

Lygo's Epoxidation : Full Scope



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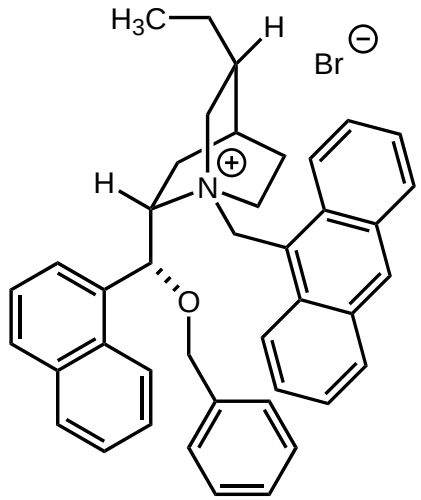
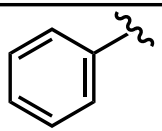
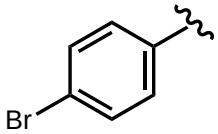
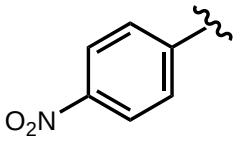
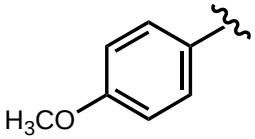
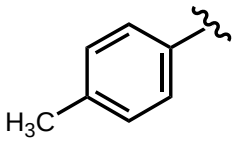
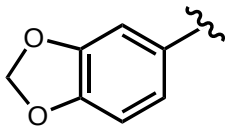
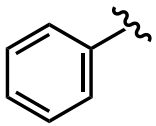
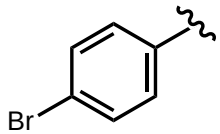
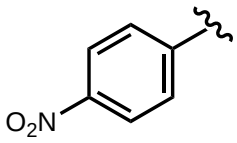
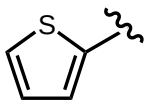
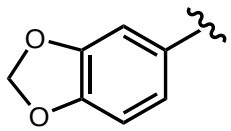
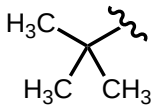


R = *n*-hexyl

R'	% *ee*	Yield(%)
	77	92
	84	89
	90	79
	84	94
	81	93
	86	87

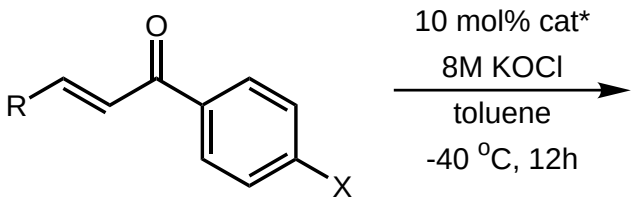
R = phenyl

R'	%*ee*	Yield(%)
	86	90
	88	99
	83	85
	85	82
	89	95
	85	40[a]

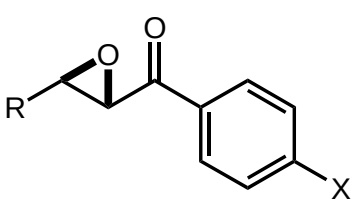
[a] reaction did not go to completion

Lygo *et al*, *Tetrahedron*, **1999**, *55*, 6289

Corey's Epoxidation



10 mol% cat*
8M KOCl
toluene
-40 ^{o}C, 12h



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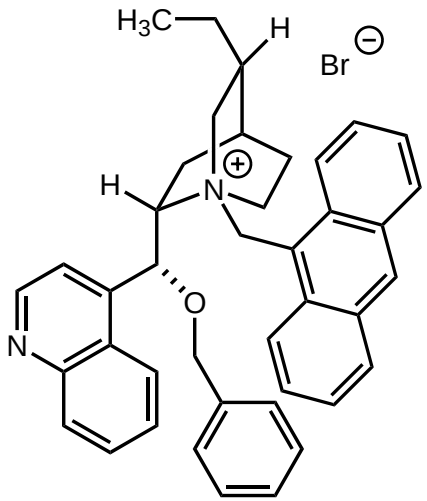
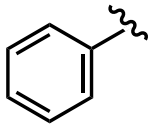
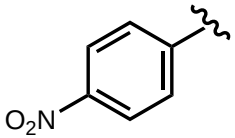
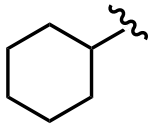
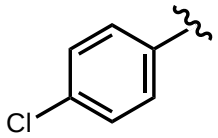
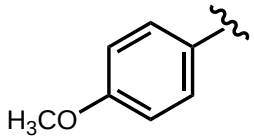
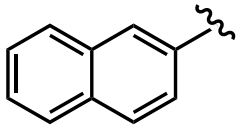
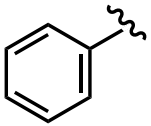
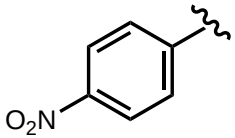
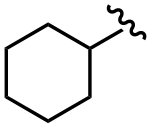
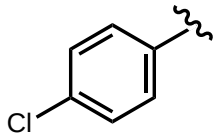
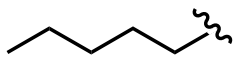


X = H

R	% *ee*	Yield(%)
	93	96
	94	90
	94	85
	92	94
	95	70
	93	87

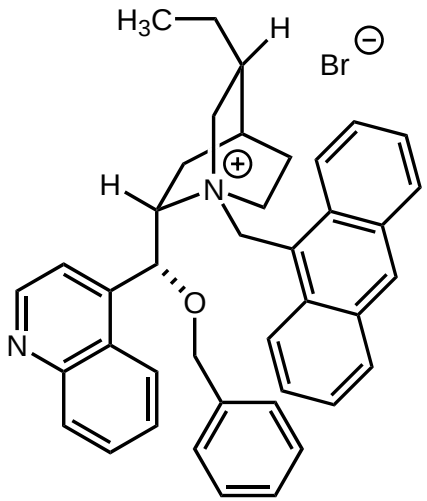
X = F

R	% *ee*	Yield(%)
	98	93
	95	97
	95	87
	99	94
	91	90

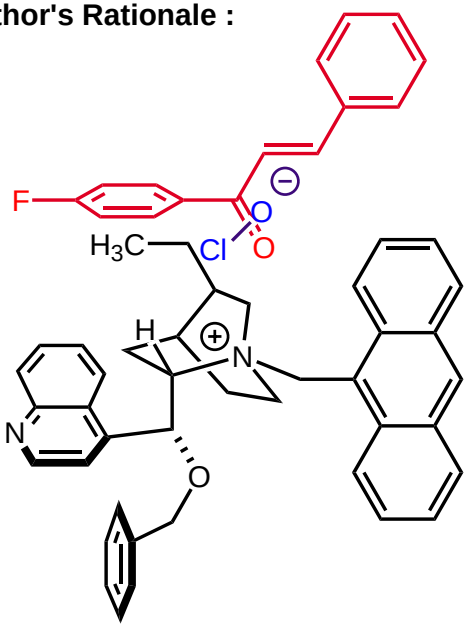
Corey *et al*, *Org. Lett.*, **1999**, *1*, 1287

Corey's Stereochemical Model

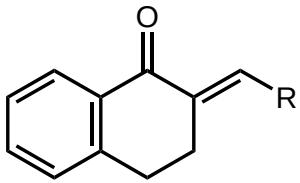
cat* =



Author's Rationale :



- When aromatic ring attached to carbonyl group is forced to be co-planar with the carbonyl σ-plane, low *ee*'s are obtained.

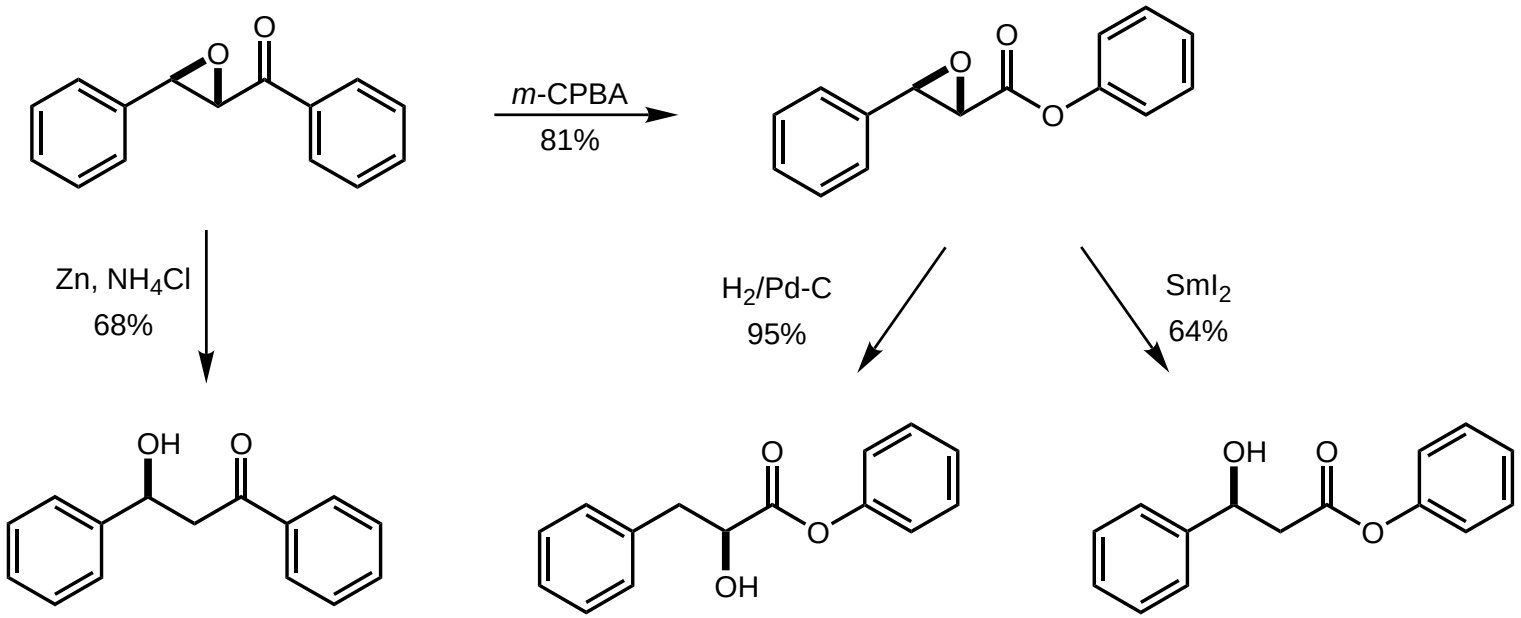


R = CH_3 76% *ee*
R = Ph 61% *ee*

- The described model is consistent with the observed sense of induction, but has enone approaching over bridgehead!
- Substrate organization allows the chinconidium salt to stabilize developing negative charge on enone oxygen, then as epoxide is formed, provides a counterion for the chloride.

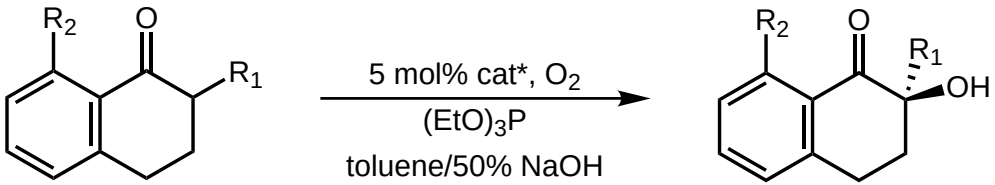
Corey *et al*, *Org. Lett.*, **1999**, *1*, 1287

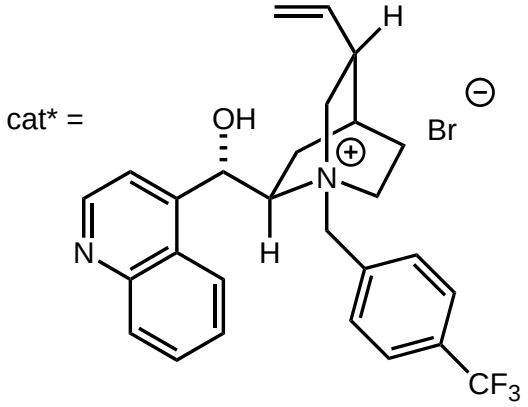
Elaboration of Epoxy Ketone Derivatives



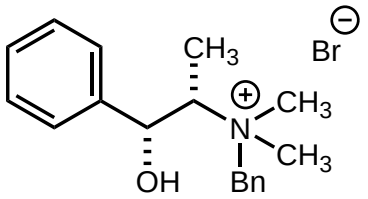
Corey *et al*, *Org. Lett.*, **1999**, *1*, 1287

Synthesis of α-Hydroxy Ketones

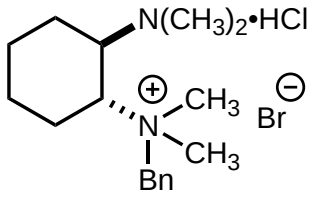




R_1	R_2	Time(h)	Yield(%)	% *ee*
CH_3	H	24	95	70
CH_2CH_3	H	24	98	72
$CH(CH_3)_2$	H	24	59	77
$CH(CH_3)_2$	H	48	87	56
CH_3	CH_3O	24	93	27
CH_3	Cl	5	95	79
Ph	Cl	5	95	48



A



B

- Triethyl phosphite is used to reduce the hydroperoxide *in situ*.
- Longer reaction times seem to decrease *ee*. Due to catalyst decomposition?
- Other ammonium salts, derived from ephedrine (**A**) or cyclohexane diamine (**B**) give <10% *ee*.

Shioiri *et al*, *Tetrahedron Lett.,* **1988**, *29*, 2835

Conclusions.....

- Quaternary ammonium salts are capable of catalyzing a broad range of asymmetric reactions with moderate to high selectivities.
- *N*-alkylated chincona alkaloids stand out as the most effective natural product derived catalysts.
- While chincona alkaloids are difficult to tune structurally, a new class of even more effective axially chiral ligands are emerging.
- Generally, these reactions are not well understood. Hydrogen bonding may or may not be operative.
- The reactions themselves are generally user friendly, and do not require strictly anhydrous conditions.
- A broad variety of chiral starting material can be made using this methodology, with important industrial applications.