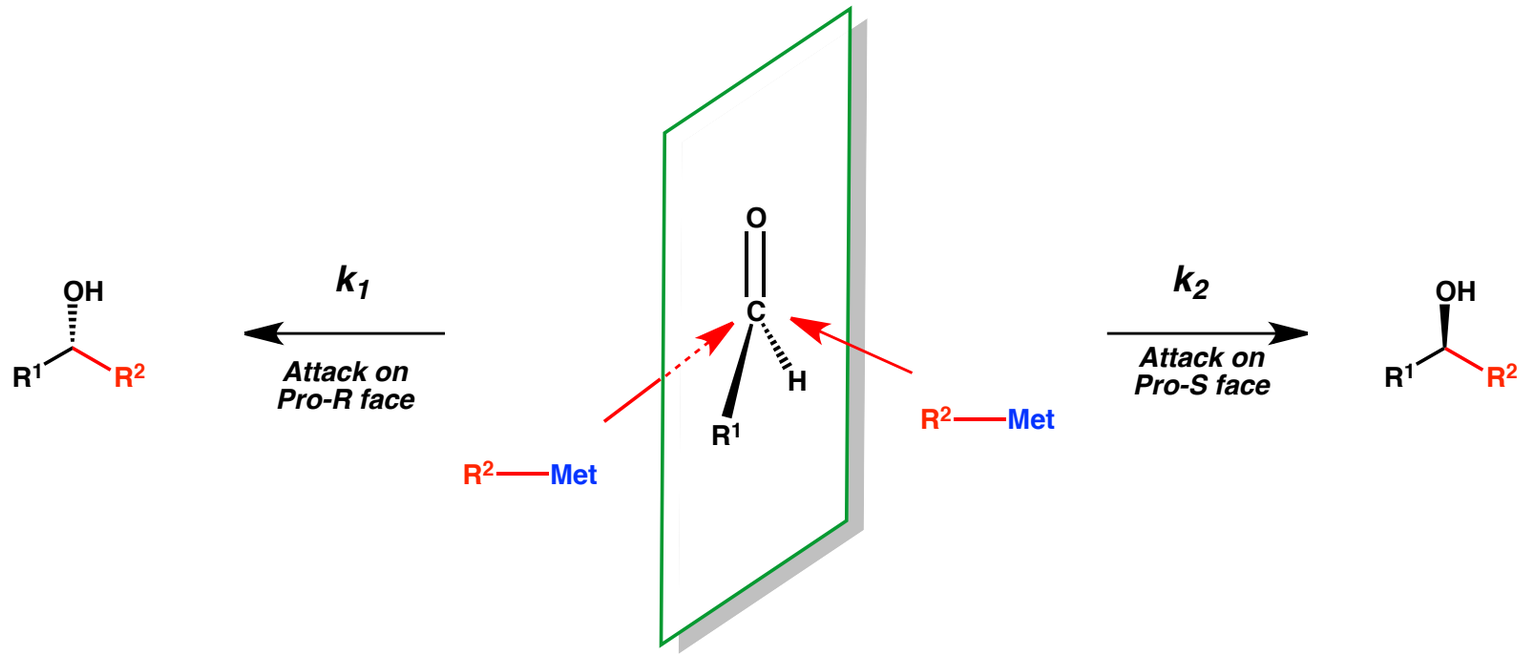
Nucleophilic Addition to C=O



General references:

(1) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) Aitken, R. A.; Kilényi, S. N. *Asymmetric Synthesis*; Blackie: London, 1992.

(3) Procter, G. *Asymmetric Synthesis*; Oxford University Press: Oxford, 1996.

(4) Gawley, S. E.; Aubé, J. *Asymmetric Synthesis, Volume 14*; Pergamon Press: Elmsford, NY, 1996.

(5) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, FL, 1996.

(6) Ojima, I. e. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(7) Seyden-Penn, J. *Chiral Auxiliaries And Ligands In Asymmetric Synthesis*; Wiley: New York, 1995.

(8) Atkinson, R. S. *Stereoselective Synthesis*; Wiley: New York, 1995.

(9) Ottow, E.; Schöllkopf, K.; Schulz, B.-G. *Stereoselective Synthesis*; Springer-Verlag: New York, 1993.

(10) Nógràdi, M. *Stereoselective Synthesis: A Practical Approach, 2nd Edition*; VCH: New York, 1995.

(11) Rahman, A.-U.; Shah, Z. *Stereoselective Synthesis in Organic Chemistry*; Springer-Verlag: New York, 1993.

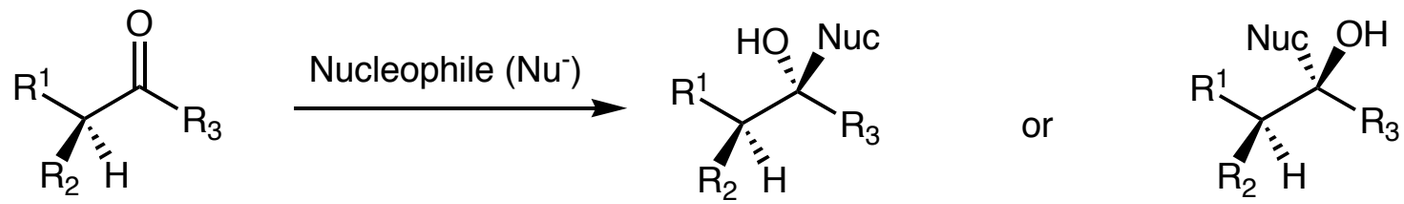
(12) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis;* Wiley-VCH, 2009. Chapter 2

(13) Stereoselective Synthesis 2

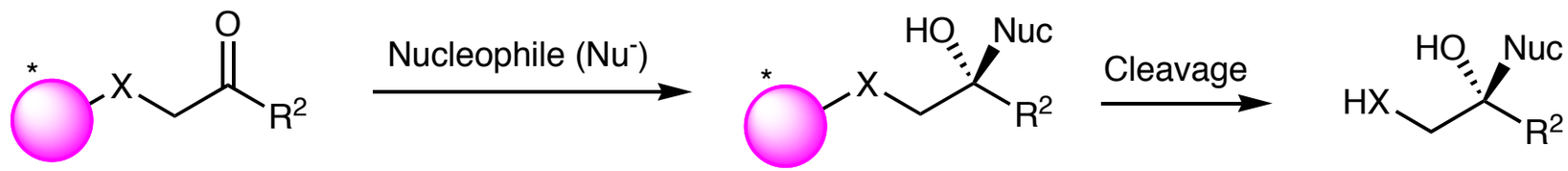
Stereocontrol in Nucleophilic Addition Reactions

1. Stereochemistry is controlled by adjacent stereogenic center

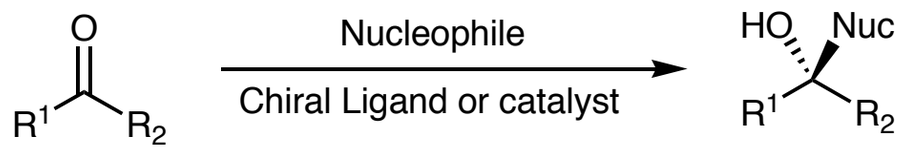
Nuc = C, H



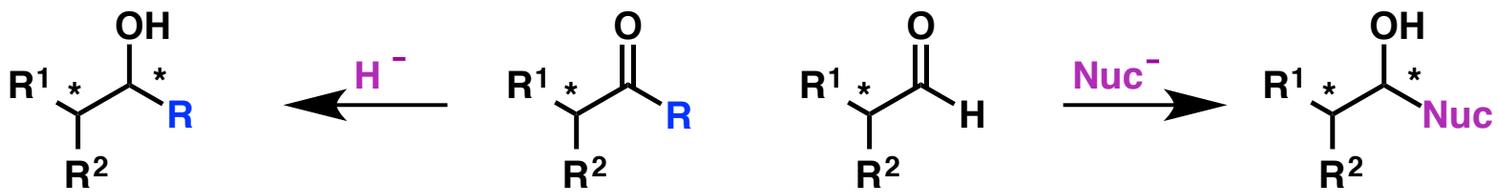
2. Removeable Chiral Auxiliary



3. Enantioselective Additions

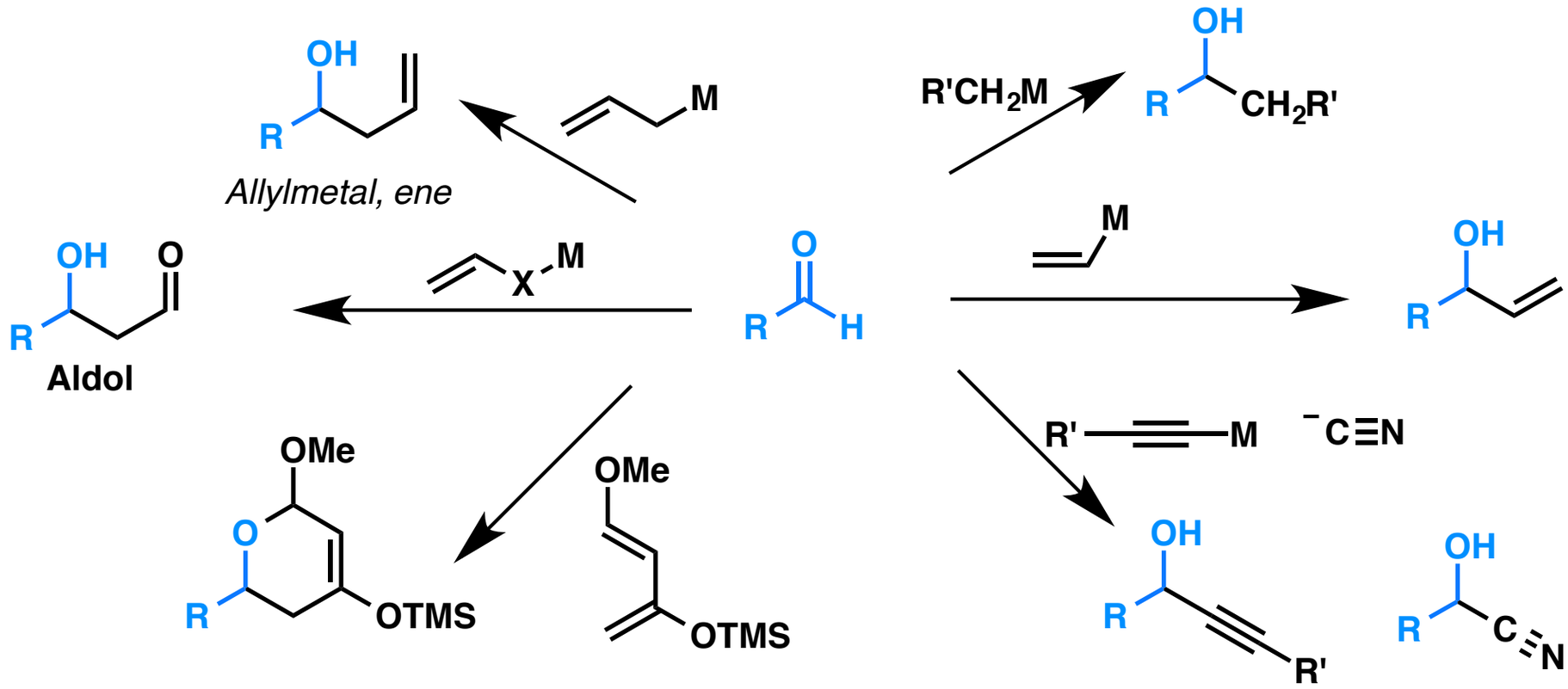


Nucleophilic Addition to C=O



Nuc

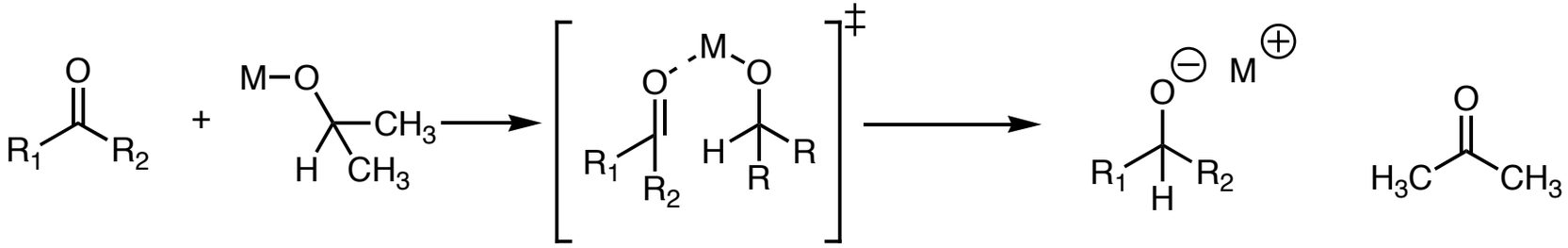
Organometallic, enolates (Aldol)
Dienophiles
(Felkin-Anh, Chelation control)



Reagents for the Reduction of Ketones

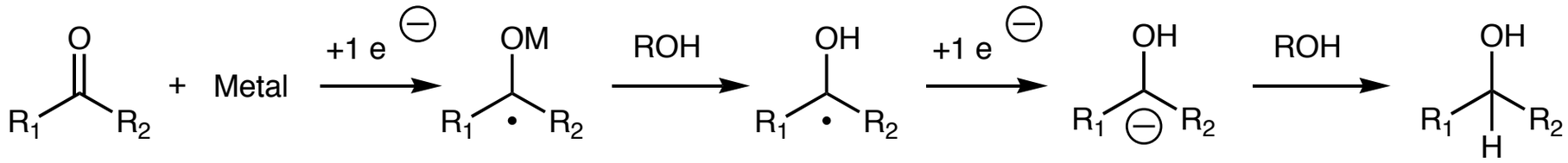
a. Metal hydrides

b. Hydride delivery from carbon: Meerwein-Ponndorf-Verley

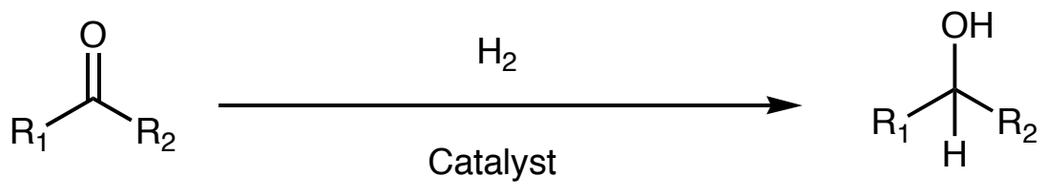


Reagents for the Reduction of Ketones

c. Dissolving metals



d. Catalytic hydrogenation

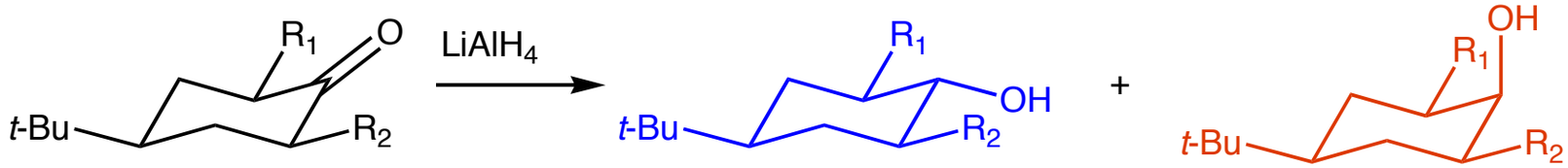


Reduction of Chiral Ketones

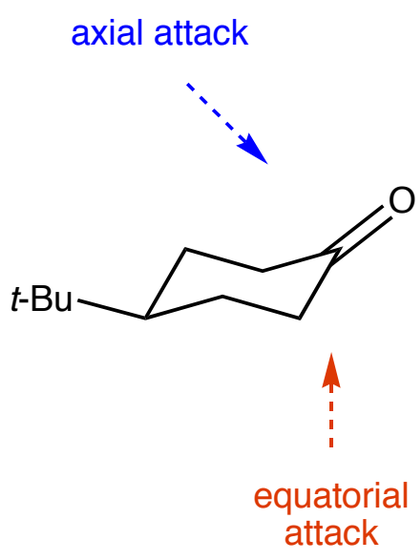
Cyclic Ketones

Acyclic Ketones

Reduction of Cyclic Ketones



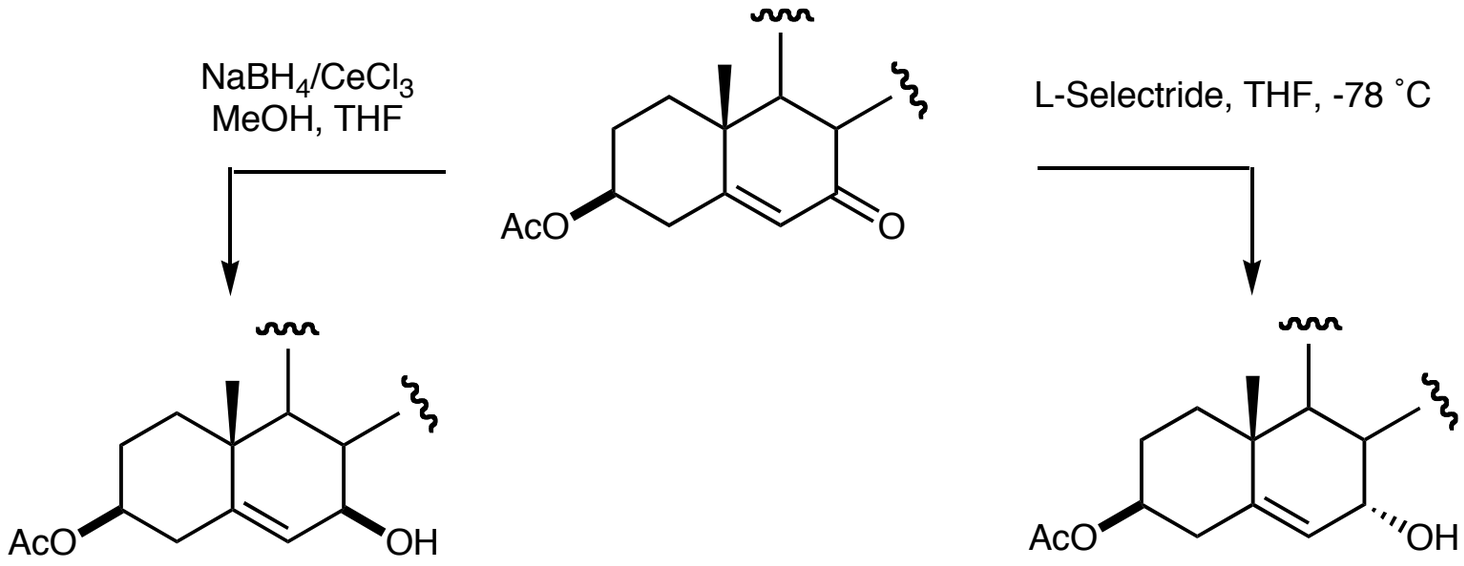
$R_1 = R_2 = H$	92	8
$R_1 = Me$, $R_2 = H$	83	17
$R_1 = R_2 = Me$	53	47



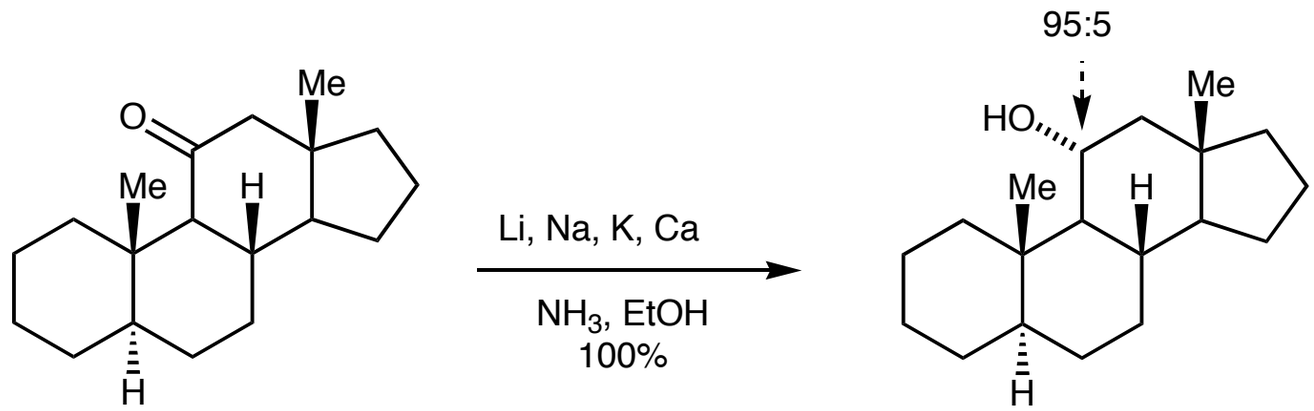
	axial:equatorial attack
$NaBH_4$:	86:14
$LiAlH_4$:	90:10
$LiBuBH_3$	98:2
$LiMeBH_3$	98.3:1.7
$Li(sec\text{-}Bu)_3BH$	3.5:96.5
$LiSia_3BH$	0.6:99.4

Reduction of Cyclic Ketones

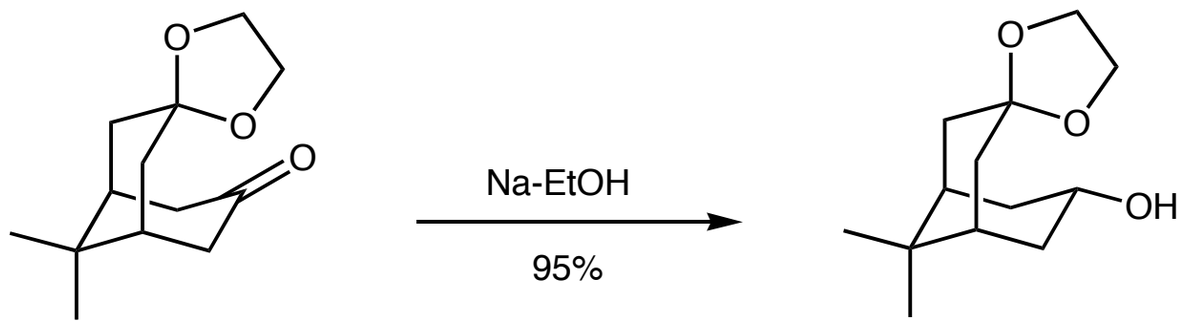
A. Amann, G. Ourisson and B. Luu *Synthesis* **1987**, 1002.



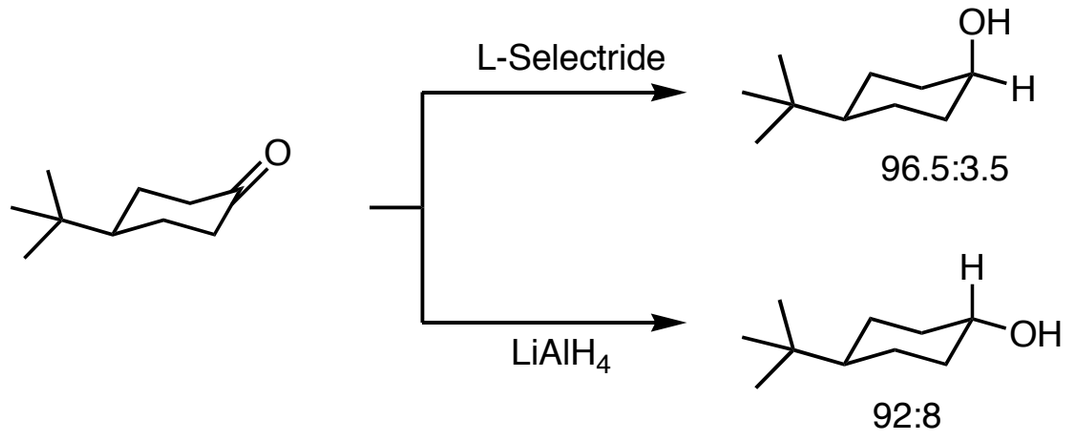
Reduction of Cyclic Ketones With Dissolving Metals



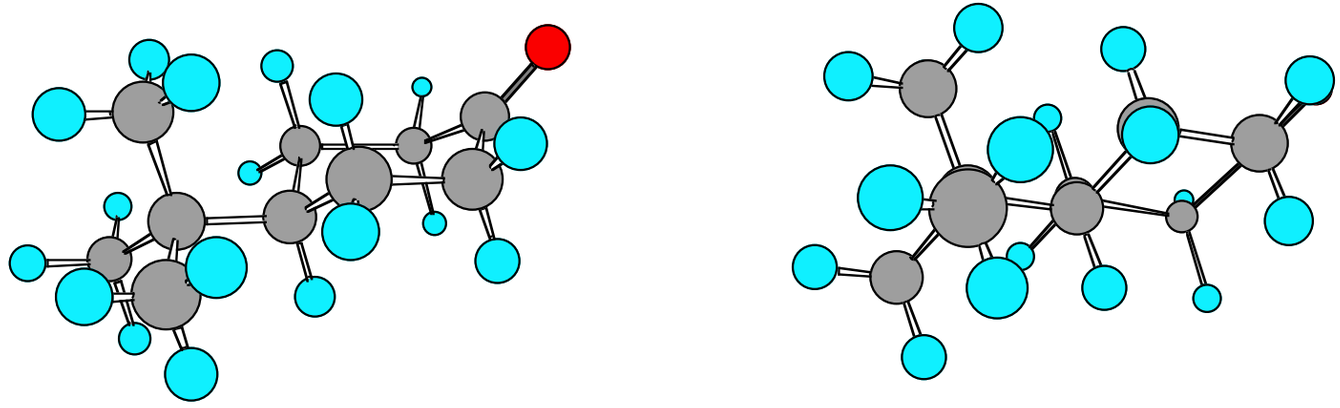
J. Org. Chem. **1985**, *50*, 1156



Nucleophilic Addition to C=O: Cyclic Systems

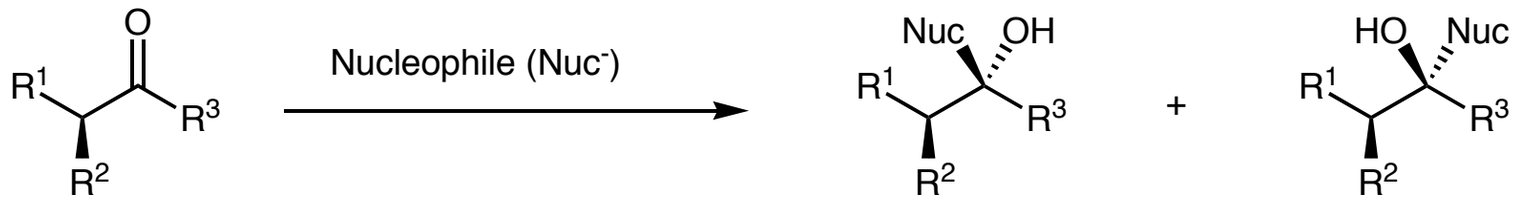


Torsional strain argument

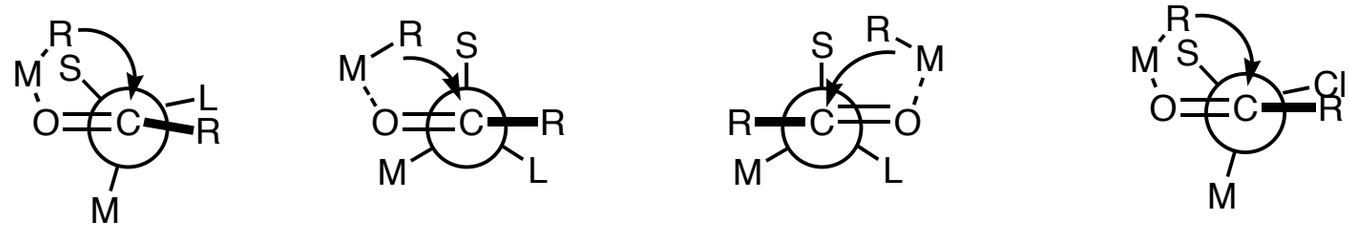


⇨ Equatorial hydride delivery produces an eclipsed transition state

Stereoselective Addition to Chiral C=O: Historical Perspective



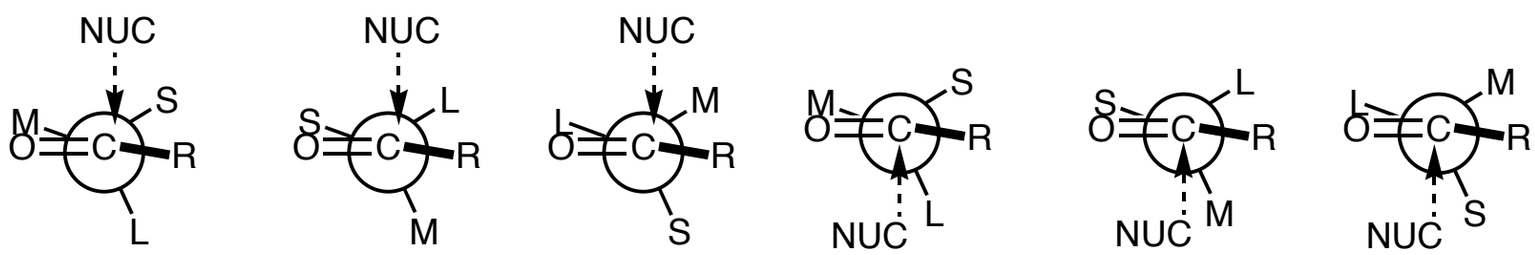
Cram's model for predicting the major isomer (1950's)



Favored TS (1952) *Favored TS (1959)* *disavored TS (1959)* *dipolar TS (1952) Conforth*

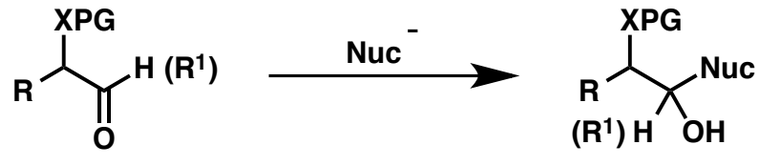
Karabatsos model (1967)

Karabatsos assumed that the transition state is early, so that there is little bond breaking or bond making in the transition states and that the arrangement of the three ligands on the α-carbon are therefore the same in the transition state as they are in the starting materials: eclipsed.



⇨ Neither one of this model predict the outcome of nucleophilic addition to cyclohexanones and they fail to account for the effect of the size of R on the selectivity.

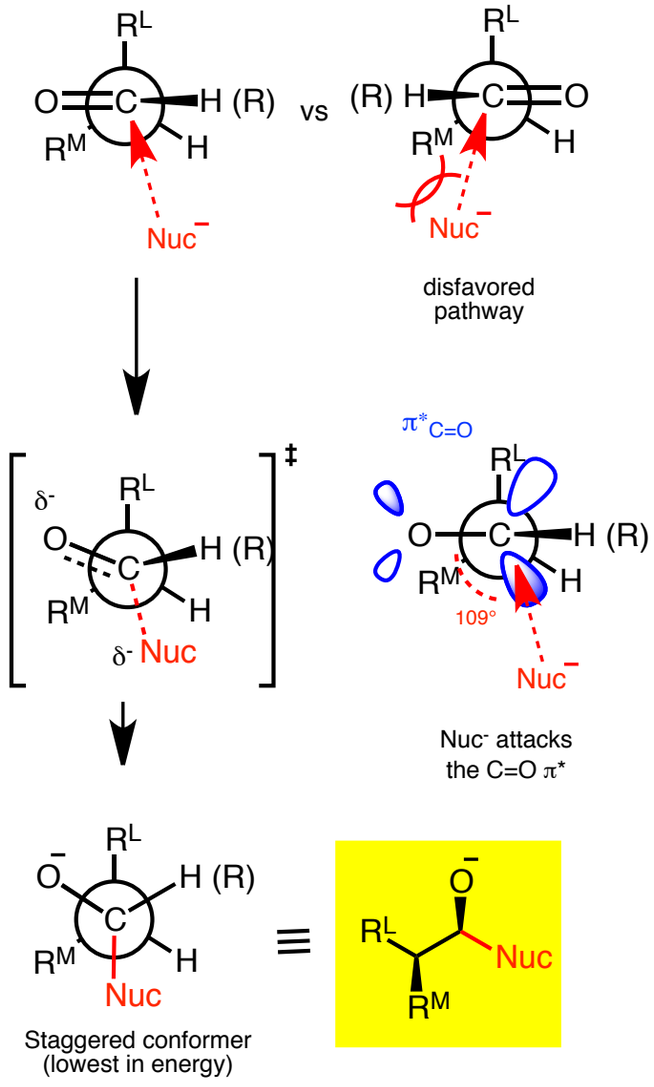
Overview: Carbonyl Addition Reactions



Which diastereomer will be the major?

Case 1. R^L and R^M = Carbon

R^L = Largest group (sterically)



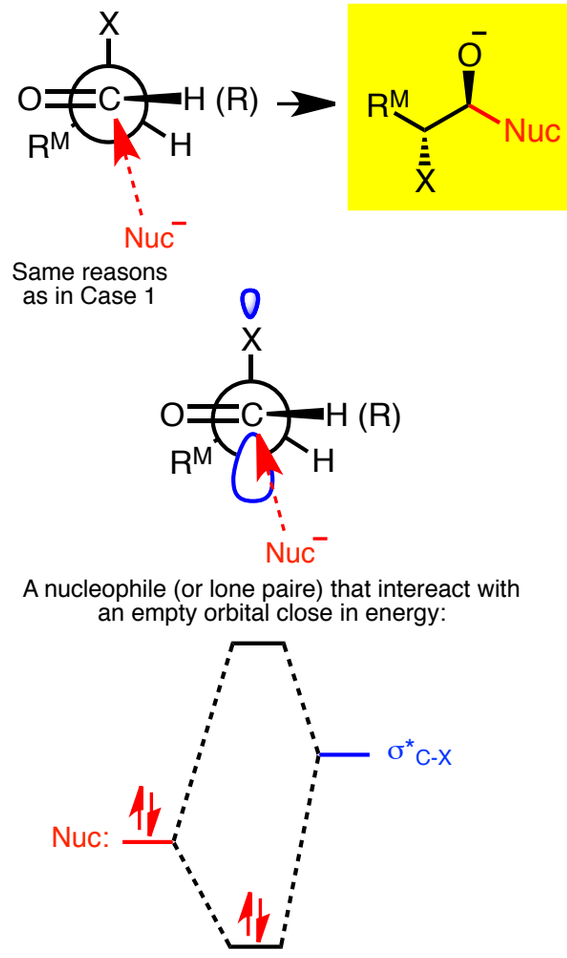
Case 2. R^L = X (O,N,S,halogen, etc.) and R^M = C

Non-accessible lone pairs on X

($OSiR_3$, $OCPh_3$)

or accessible lone pairs but metal cannot form a bidentate chelate

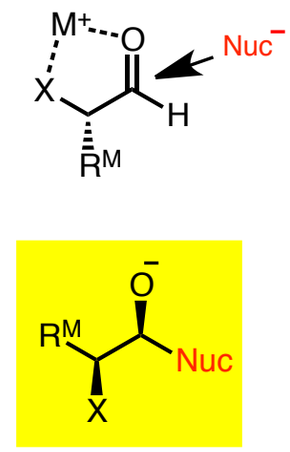
(wrong size - ionic radius or monovalent)



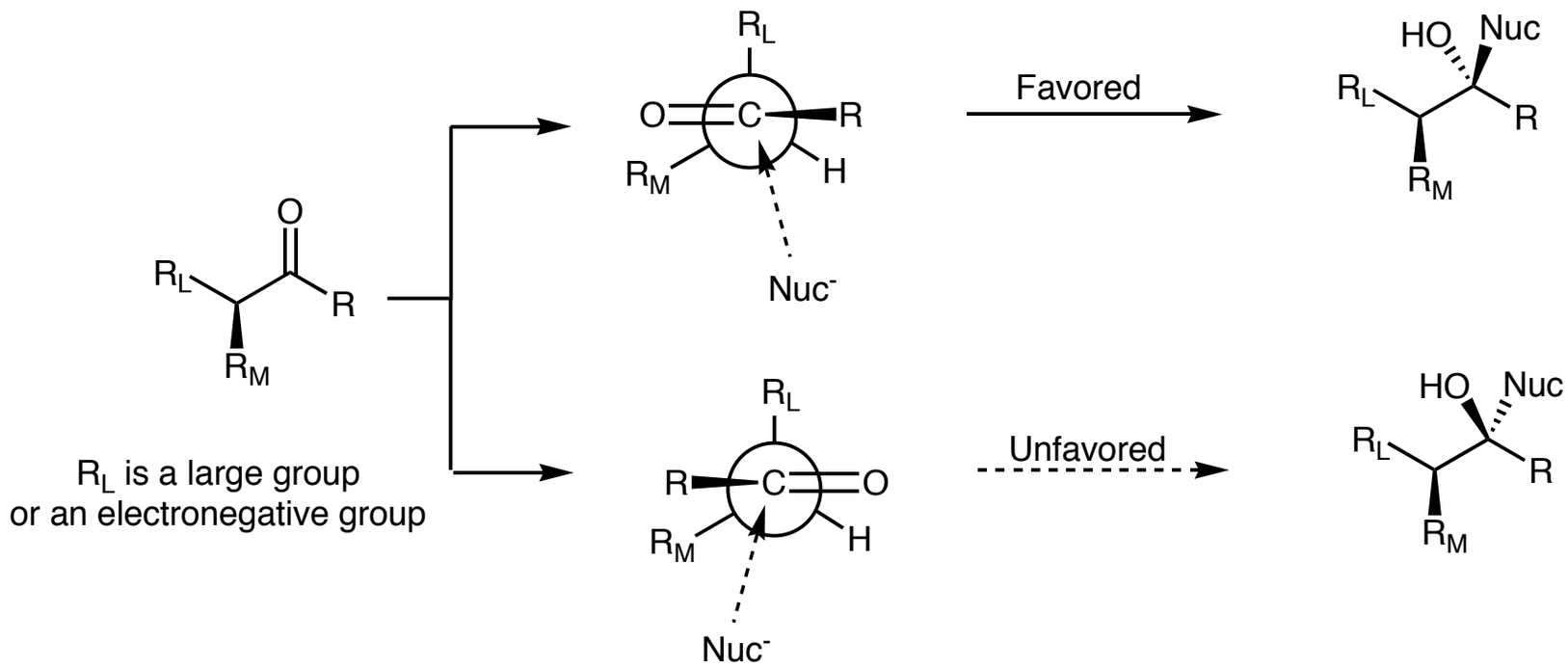
Case 3. Chelate formation

Requirements:

- Metal is Lewis acidic (good ionic radius + multivalent)
- X has an accessible electron pair

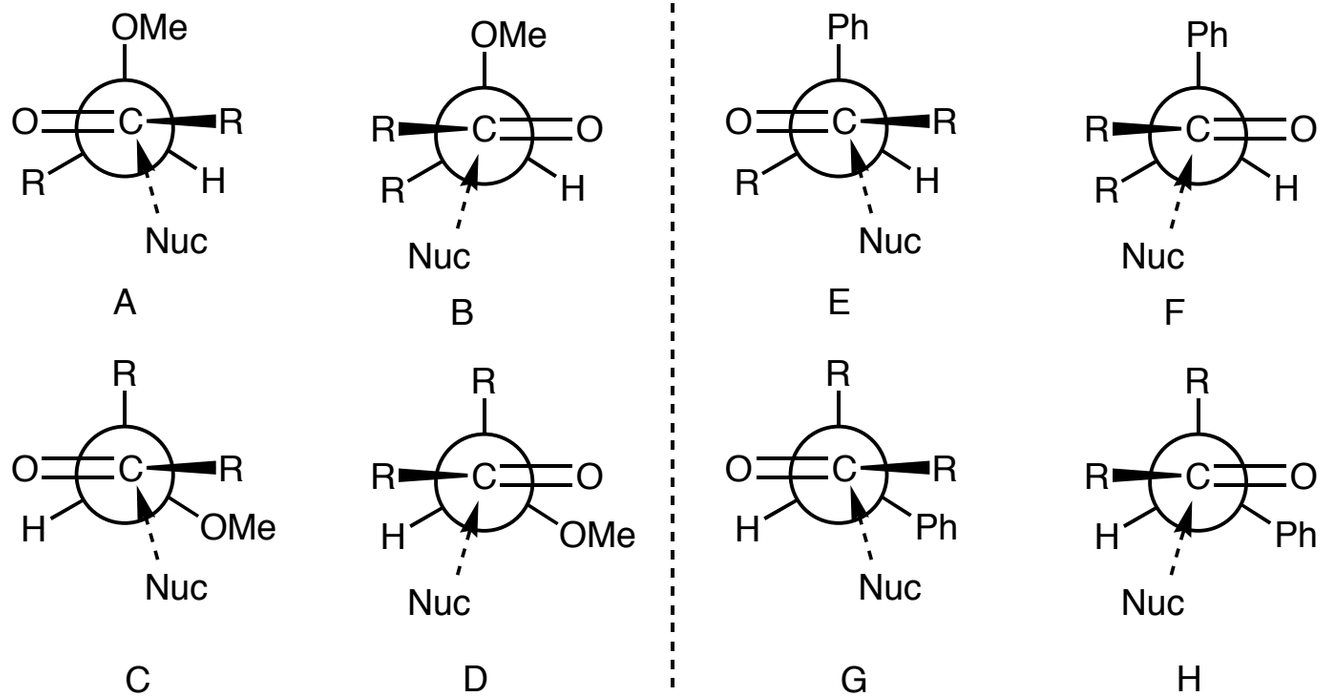


Felkin-Anh Model for Nucleophilic Addition to C=O



Felkin-Anh Model and Heathcock's Contribution

Stereoelectronic Model | *Steric Model*



Felkin-Anh Model and Heathcock's Contribution

⇨ Nucleophile will approach along the Burgi-Dunitz trajectory (103 °)

⇨ For ketone, the approach may be in or near the normal plane but for aldehydes, there will be a deviation from this plane, towards the H and away from the stereocenter.

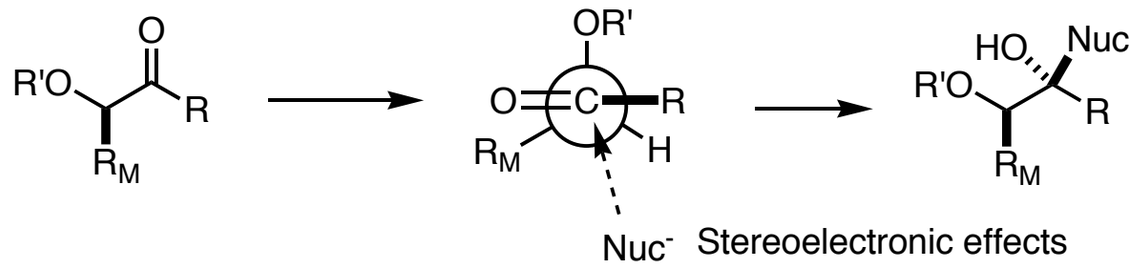
⇨ When strong electronic or steric preference by one ligand, the F-A two conformer model may be used with : MeO>*t*-Bu>Ph>*i*-Pr>Et>Me>H

⇨ Complete evaluation requires a four conformer analysis (above). Electronic anti preference is: MeO>Ph>R>H. Steric anti preference is: *t*-Bu>Ph>*i*-Pr>Et>Me>H.

Felkin-Anh vs Chelation-controlled Addition

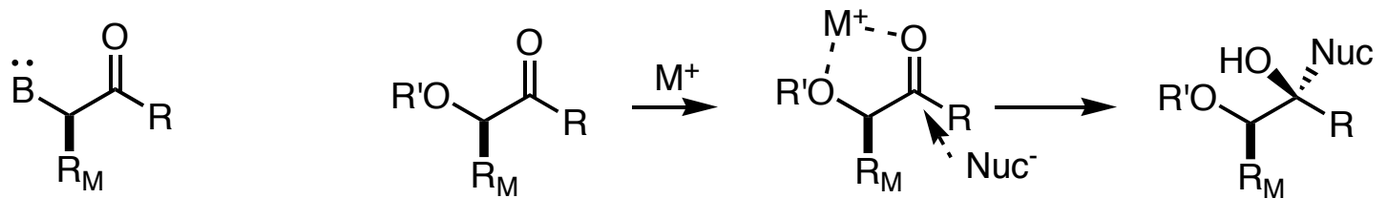
Felkin-Anh Stereoelectronic Model can be used to predict the stereochemical outcome of carbonyl addition reaction
but sometimes conditions to favor a chelation-controlled product can be used to generate another stereoisomer.

In the absence of chelation: R' = trityl, silyl (Felkin-Anh model)

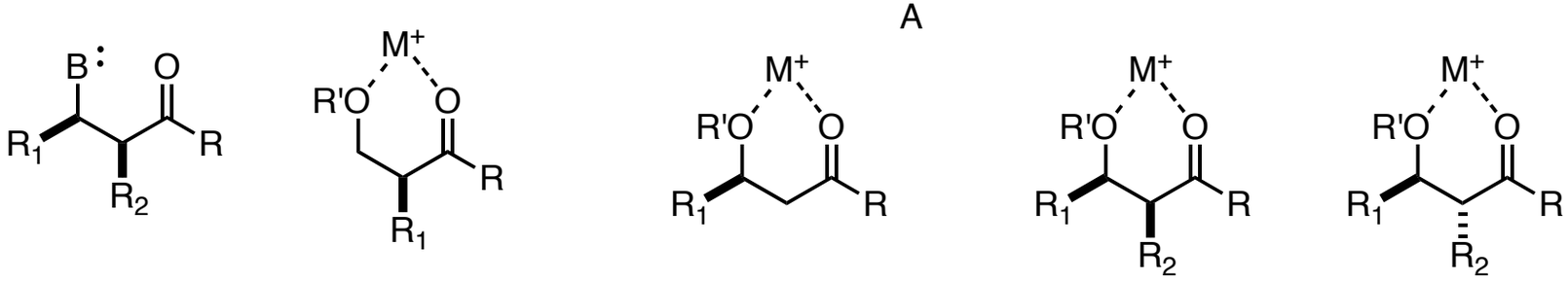


Conditions favor chelation (5, 6 and larger ring between substrate and metal):
- Lewis basic group
- Appropriate Lewis acid (M^+)

Diastereomers



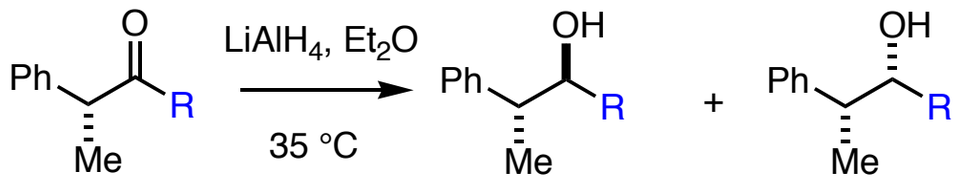
A



B C D E

Acyclic Ketone Reduction

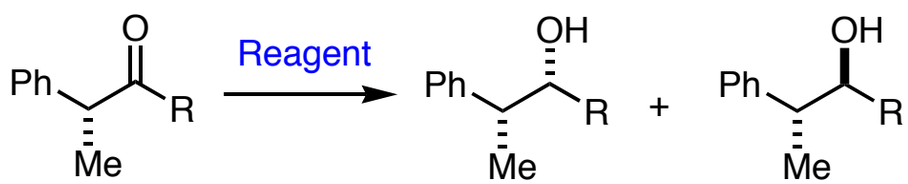
Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819.



R	Diastereoselectivity
Me	74:26
Et	76:24
i-Pr	83:17
t-Bu	98:2

Sterically hindered reagents:

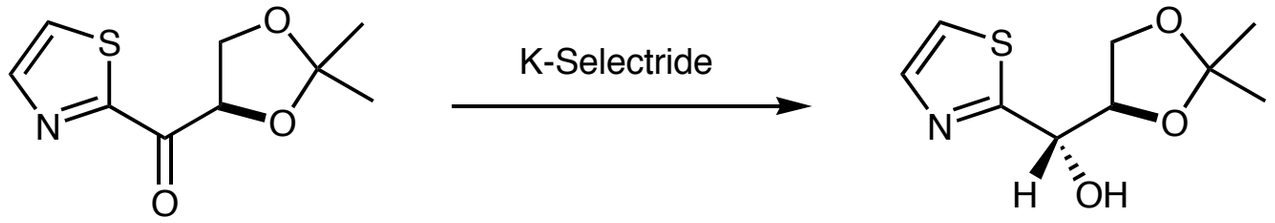
Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 4475.



R	Reagent	Diastereoselectivity
Me	$LiAlH_4$	26:74
	L-Selectride	<1:>99
Et	$LiAlH_4$	23:77
	L-Selectride	<1:>99

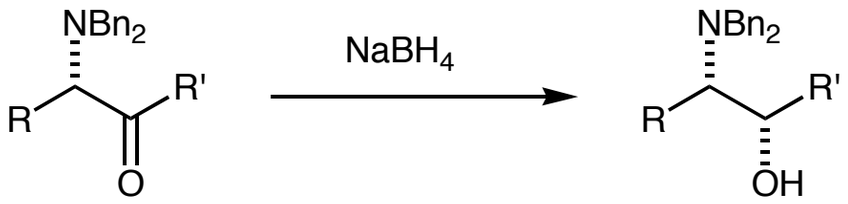
Acyclic Ketone Reduction

Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693, 702.



95 : 5

Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X.
Tetrahedron: Asymmetry **1990**, *1*, 375.
Angew. Chem. Int. Ed. Engl. **1991**, *30*, 1531.

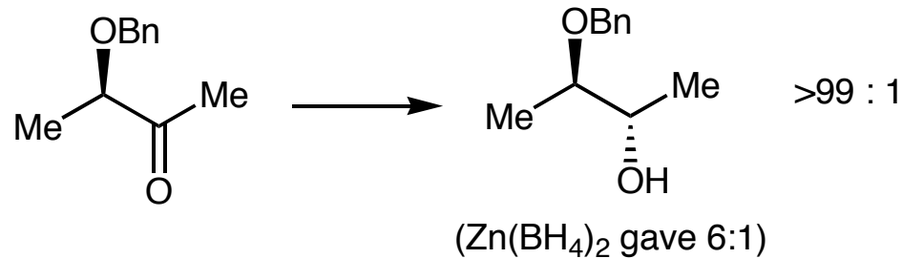


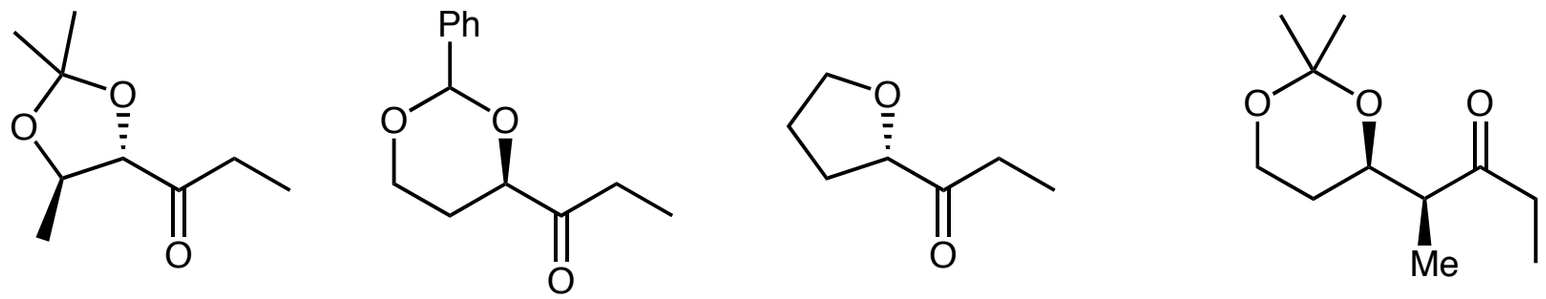
94 : 6

Chelation-controlled Reduction of Ketones

Faucher, A.-M. *Tetrahedron Lett.* **1998**, *39*, 8425-8428.

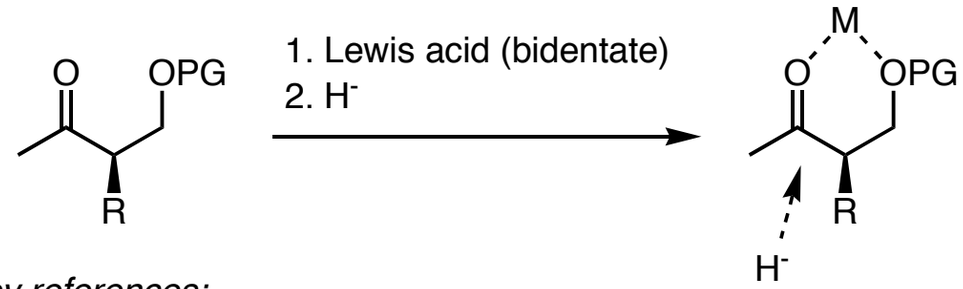
n-Bu_3BHLi (Et_2O, pentane), CH_2Cl_2 is a superieur reagent:





Bu_3BHLi	24:1	43:1	4.4:1	37:1
$Zn(BH_4)_2$	1 : 2	2.1 : 1	3.7 : 1	3.6 : 1

Diastereoselective Reduction of Ketones: β-Alkoxy Ketones



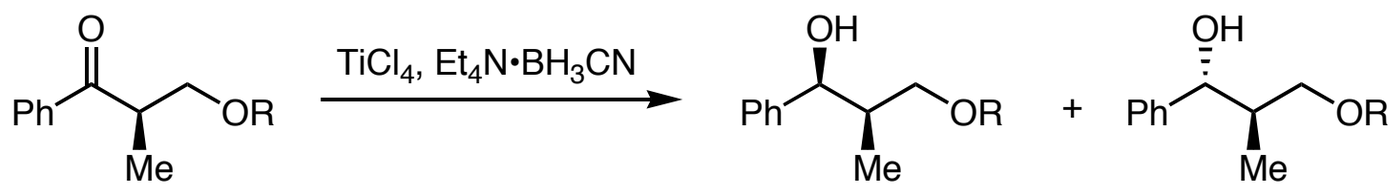
most common systems:

- α-alkoxycarbonyl
- β-alkoxycarbonyl

key references:

Mori, S. *J. Am. Chem. Soc.* **1995**, *117*, 5055-5065.
Eliel, E. L. *J. Am. Chem. Soc.* **1992**, *114*, 1778-1784.

M. DiMare *J. Org. Chem.* **1994**, *59*, 705-706. *J. Org. Chem.* **1996**, ?



R = MOM, Bn TBDPS

≥ 92 : 8

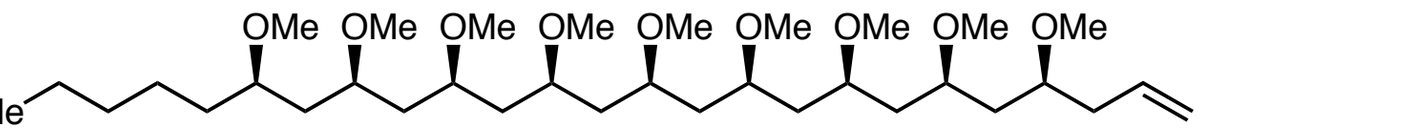
- Not good when the chiral center is β

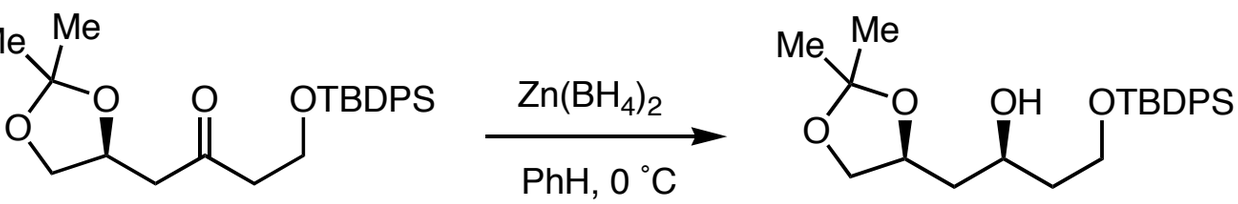
Diastereoselective Reduction of Ketones: β-Alkoxy Ketones

$Zn(BH)_4$ is usually efficient for the chelation-controlled reduction of β-alkoxy ketones

Review: Nakata, T.; Oishi, T. *Acc. Chem. Res.* **1984**, *17*, 338-344.

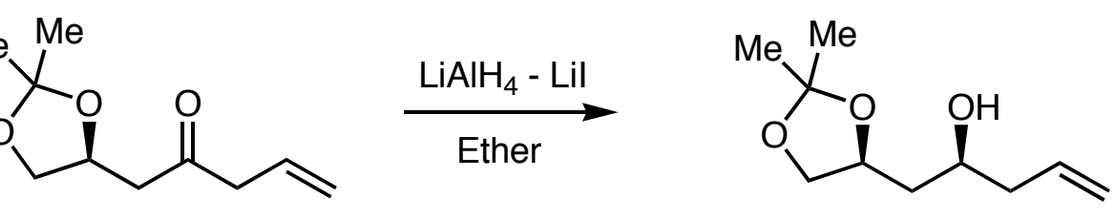
see also: Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529-6532.





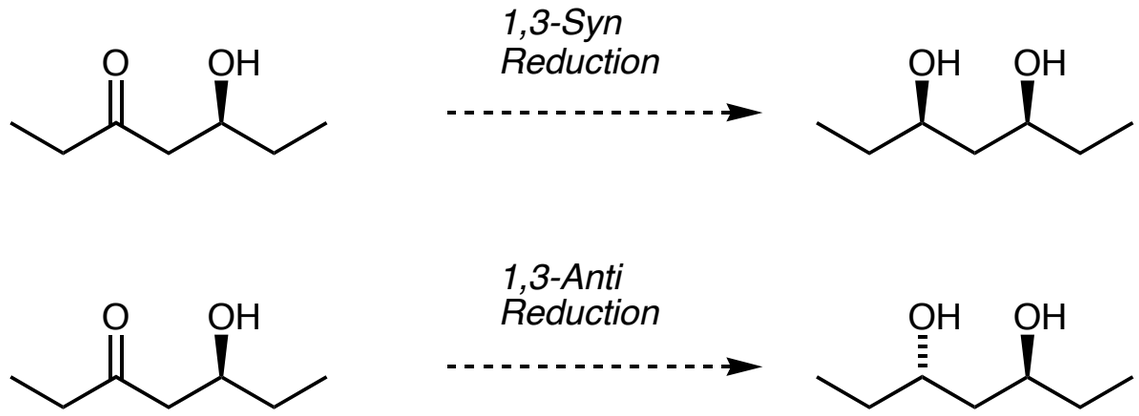
syn:anti
15.4:1

Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419-5422.

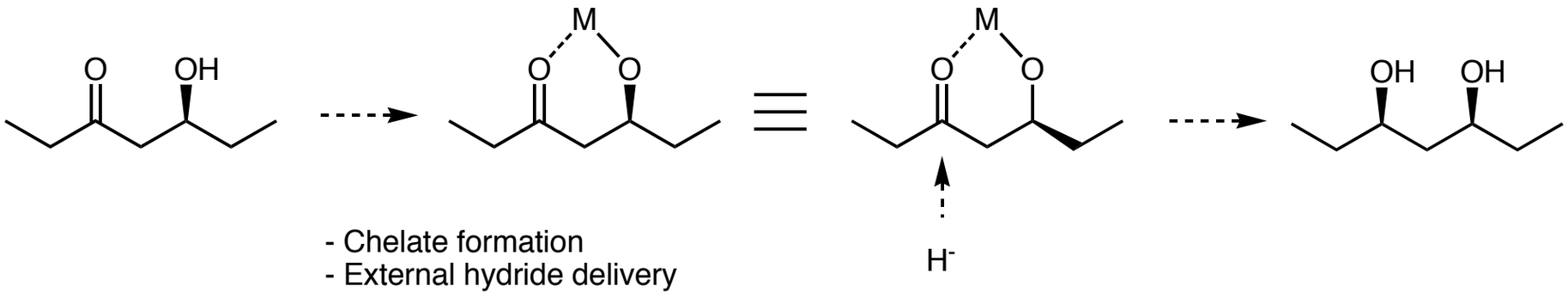


syn:anti
95:5
(82:18 without LiI)

Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis

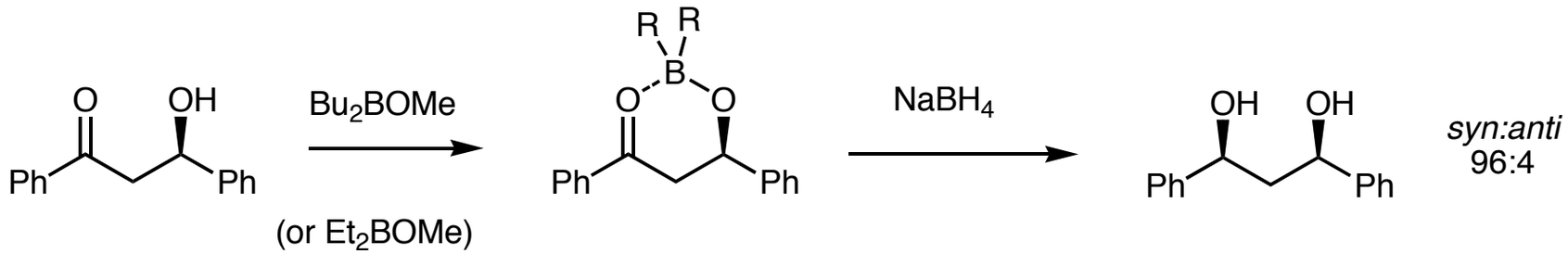


Syn reduction

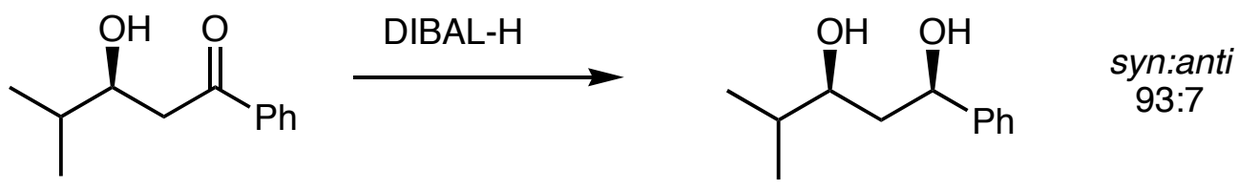


Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis

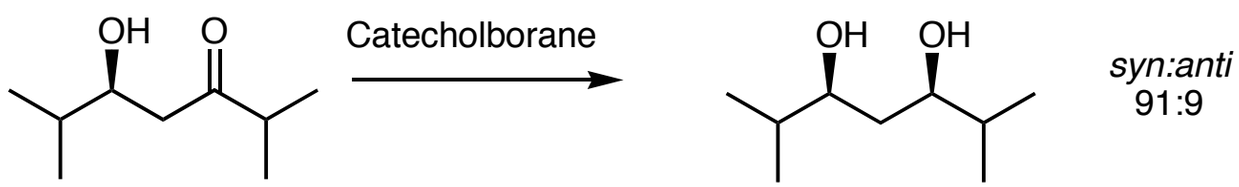
Narasaka *Chem. Lett.* **1980**, 1415.
Prasad *Tetrahedron Lett.* **1987**, *28*, 155. *Helv. Chim. Acta* **1986**, *69*, 803.



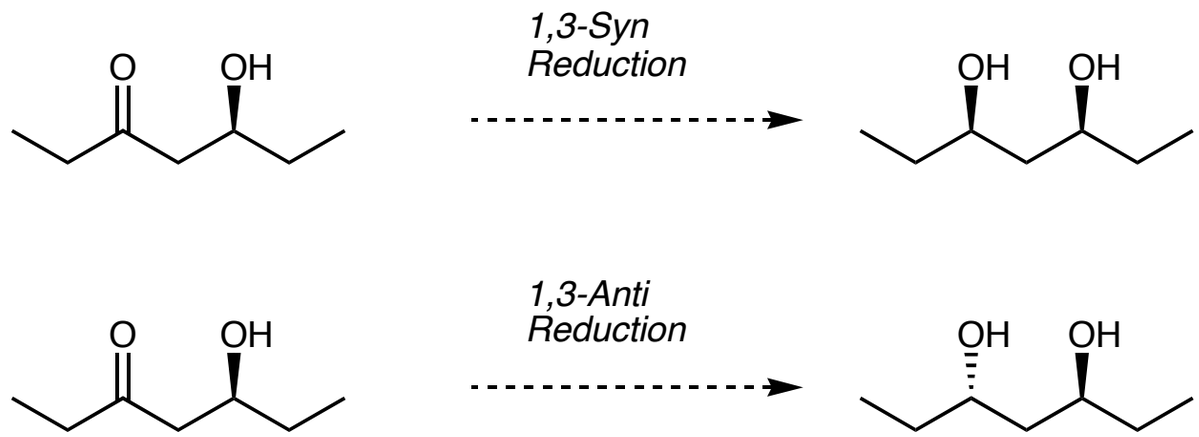
Kiyooka, S. *Tetrahedron Lett.* **1986**, *27*, 3009.



Evans, D. A. *J. Org. Chem.* **1990**, *55*, 5190-5192.

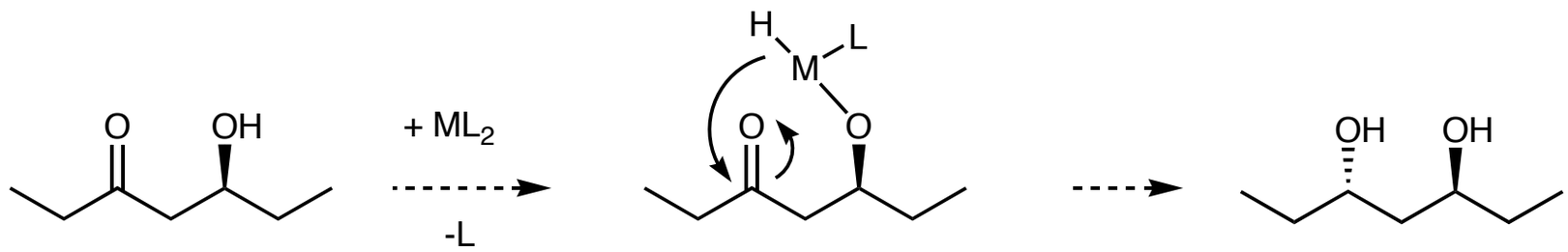


Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis



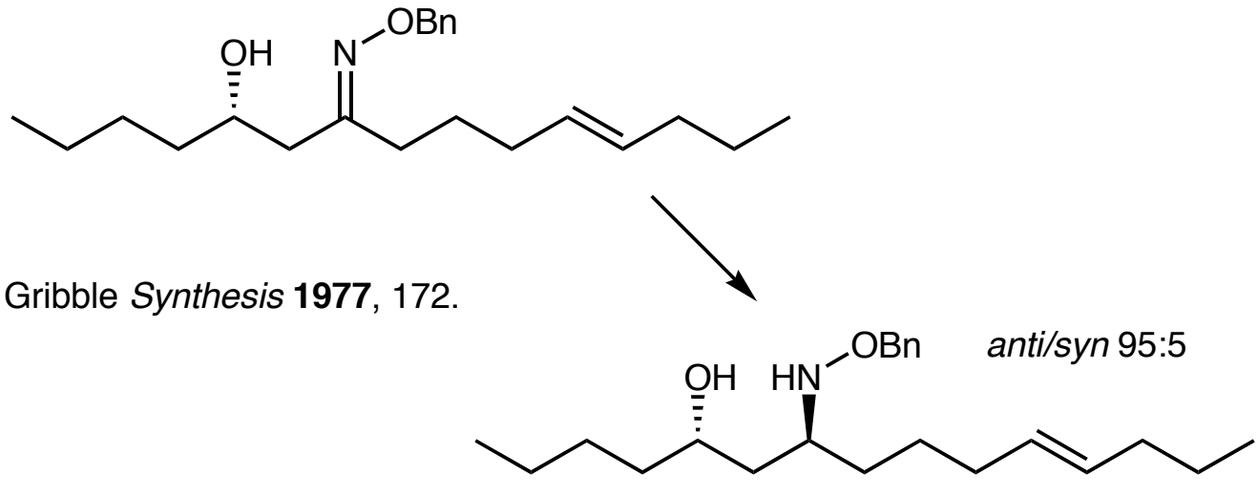
Reagent: Gribble, G. *J. Am. Chem. Soc.* **1974**, *96*, 7812.
Review: Gribble *Chem. Soc. Rev.* **1998**, *27*, 395.

Anti reduction



- Hydride is delivered internally
- requirement: the intermolecular process must be slow

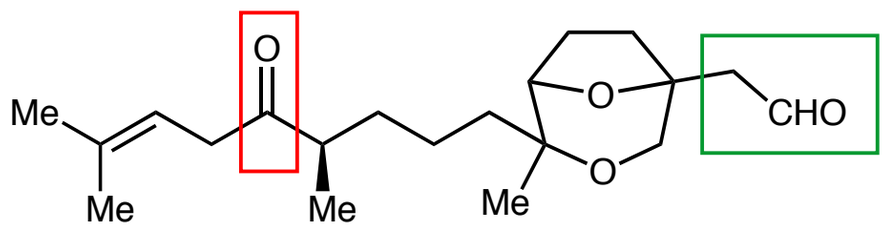
Triacetoxyborohydride Reagents



Gribble *Synthesis* **1977**, 172.

anti/syn 95:5

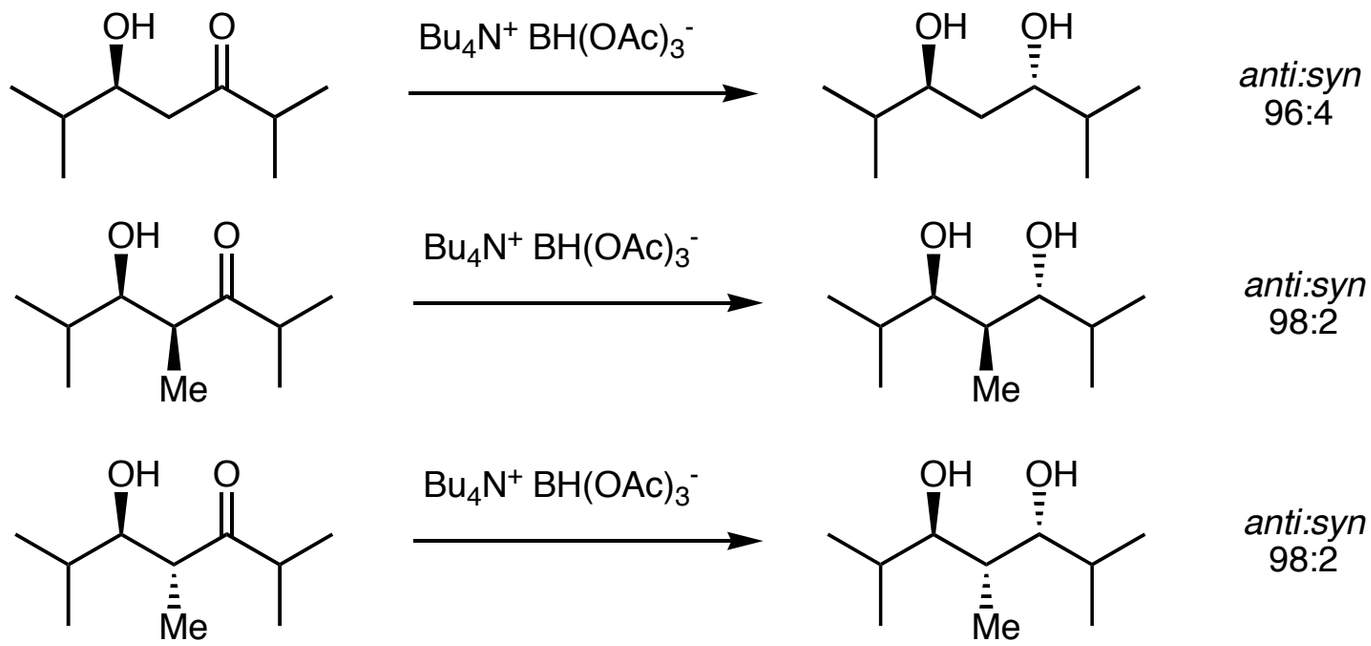
⇨ Reagent reduces aldehydes in the presence of ketones.



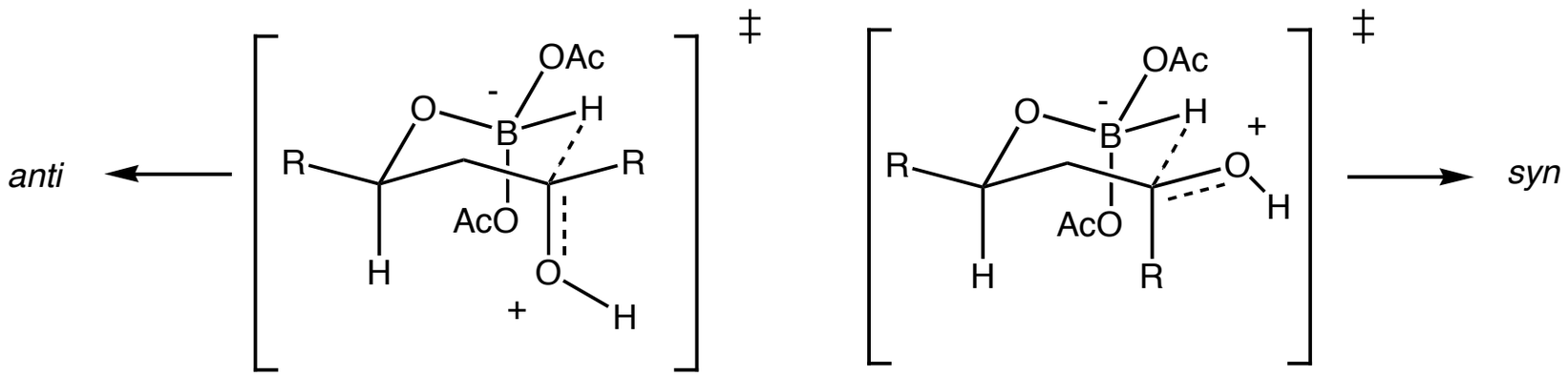
$NaBH(OAc)_3$
HOAc, PhH
76%

Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis

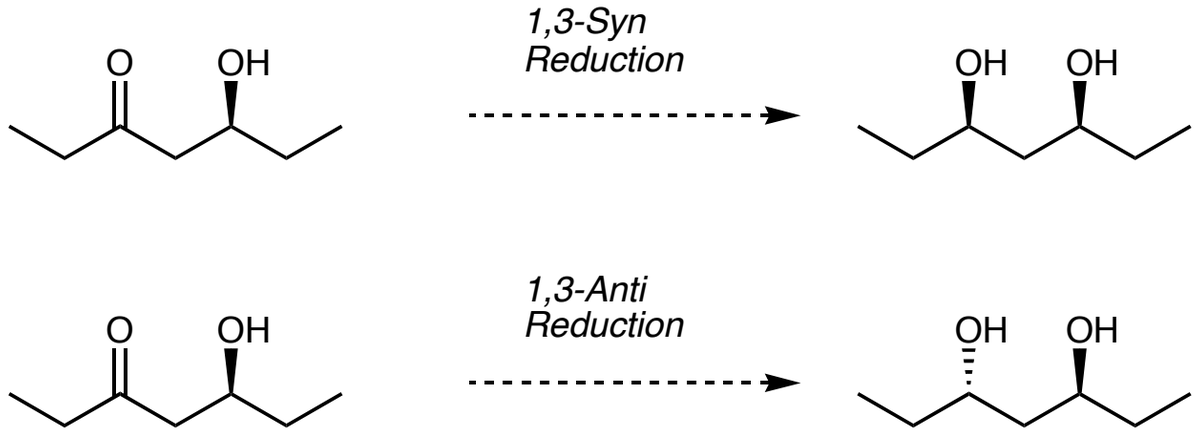
Evans *J. Am. Chem. Soc.* **1988**, *110*, 3560.



Transition state model:

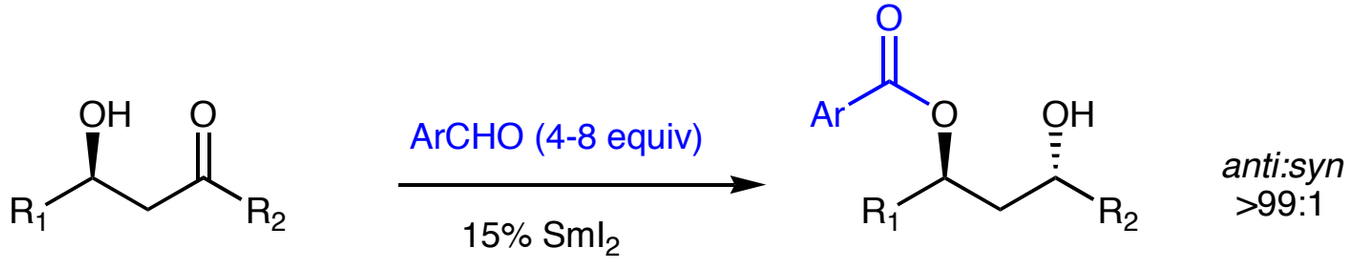


Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis

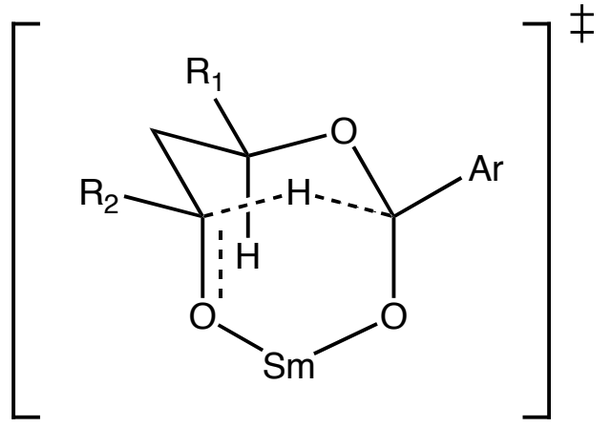


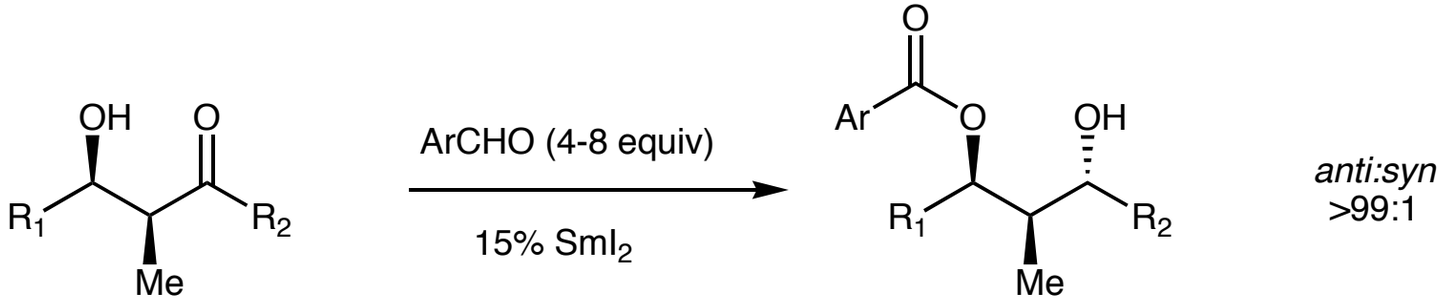
Anti reduction

Intramolecular Tishchenko Reduction: Evans *J. Am. Chem. Soc.* **1990**, *112*, 6447.

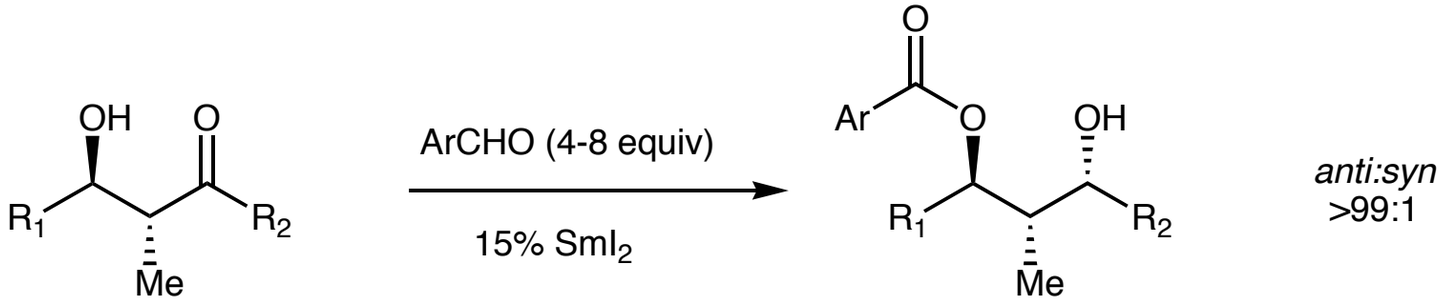


Diastereoselective Carbonyl Reduction: 1,3-Diol Synthesis



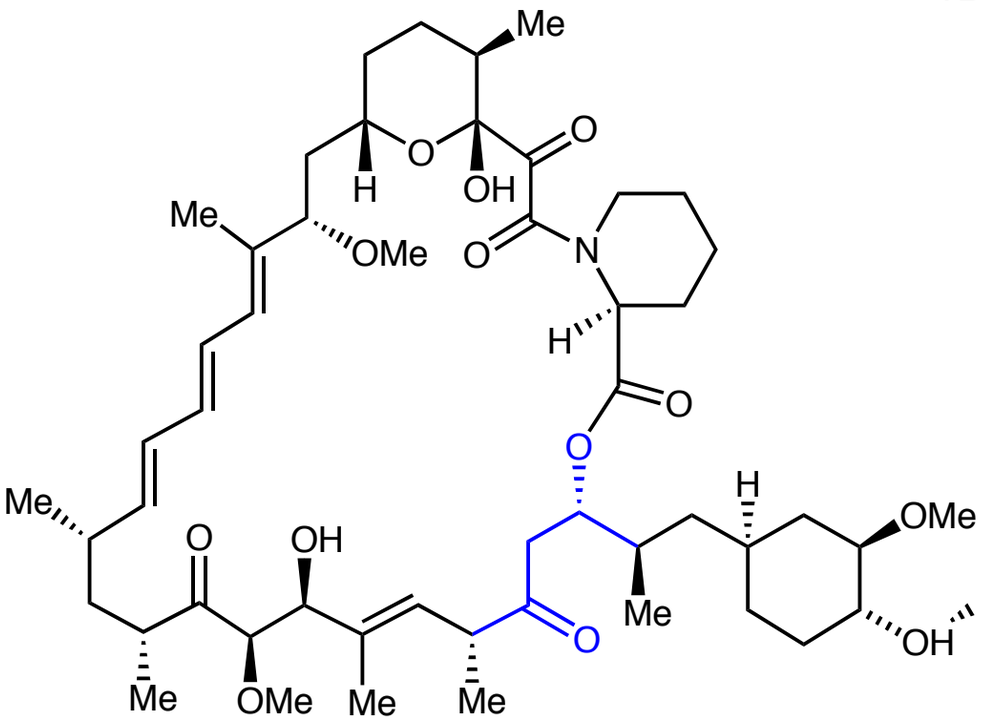


anti:syn
>99:1

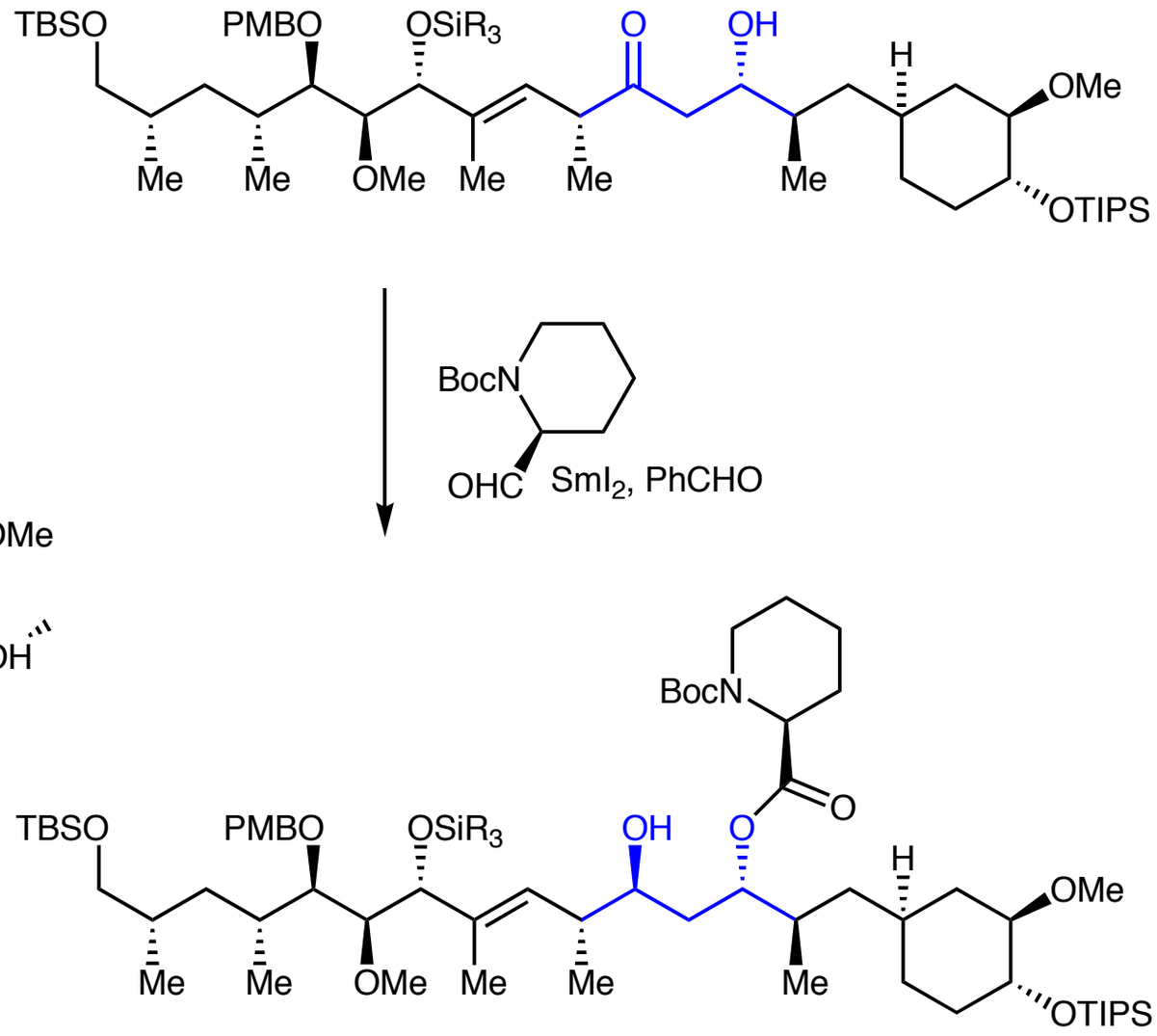


anti:syn
>99:1

Application of Evans-Tishchenko Reduction

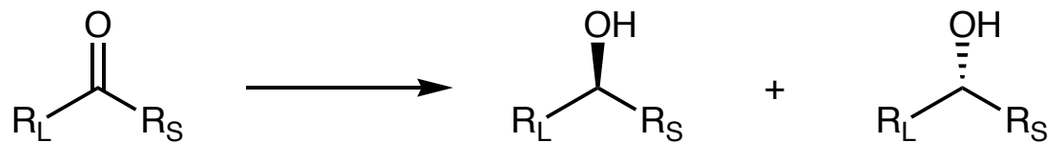


Rapamycin



(Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 7906)

Enantioselective Reduction of Ketones



Stoichiometric chiral hydride
borane, borohydride, aluminum hydride

Chiral catalyst with
stoichiometrichydride source
borane

Asymmetric hydrogenation
H_2 is used as hydrogen donor

Transfer hydrogenation
i-PrOH, HCOOH are used as
hydrogen donor

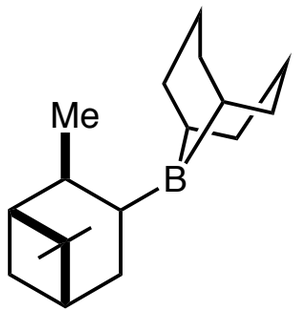
- experimentally simple
- low reactions temperatures
- high loading (low TON)

- may require high pressure
- may require high temperature
- very high TON

Enantioselective Carbonyl Reduction: Non-Catalytic Chiral Reducing Agent

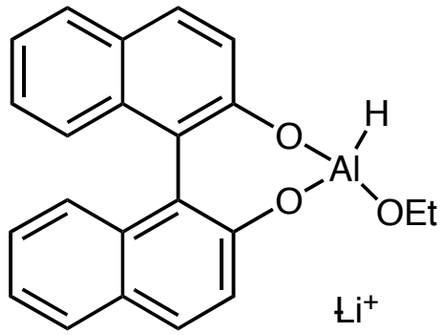
* Chiral aluminum hydrides

* Chiral boranes and borohydrides



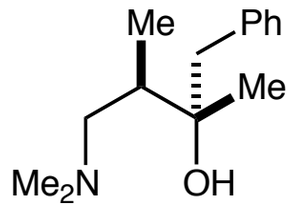
(*R*)-Alpine-Borane,
33$ for 100 mL (0.5M)

(A)



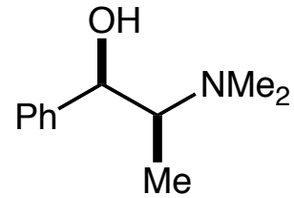
(s)-Binal-H

(B)



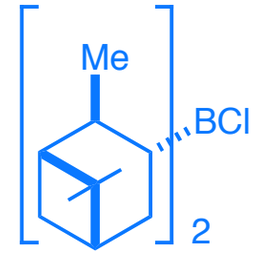
Darvon alcohol
$LiAl(L)_2H_2$

(C)



N-Methylephedrine
$LiAl(lig)(OAr)_2H$
Ar = 3,5-Xylenol

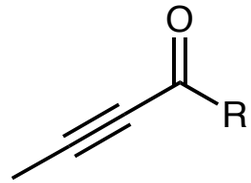
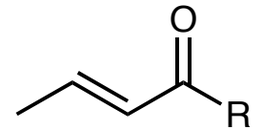
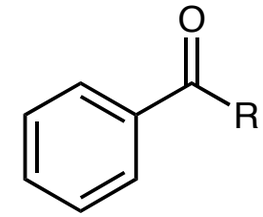
(D)



DIP-Chloride

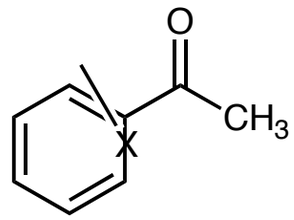
(E)

Scope: Stoichiometric Reagents

Reagent			
Alpine-borane	72 - 92% ee	59 - 89% ee	78% ee
BINAL-H	84 - 96% ee	>95% ee	95 - 100% ee
Darvon	34 - 90% ee	25% ee	15 - 75% ee
N-methylephedrine	75 - 90% ee	78 - 98% ee (cyclic ketones) 25 - 58% ee (acyclic ketones)	----
DIP-Cl	17 - >99% ee	76 - 85% ee	>87% ee

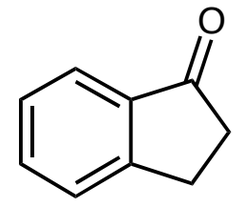
Reduction of Ketones With DIP-Cl: Scope and Limitations

Aryl methyl ketones



81 - 98% ee

Cyclic aryl alkyl ketones

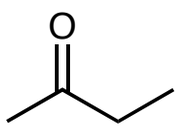


97% ee

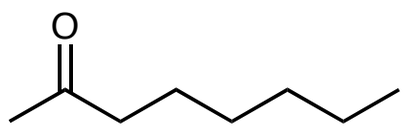
X = F, Br, Cl, I, NO_2, CN, COOH, $CONR_2$, Me, OH, OMe, CF_3

exceptions: 4-OH (10% ee) but 4-OLi (90% ee) and 2-COOH (25% ee)

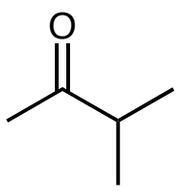
Dialkylketones



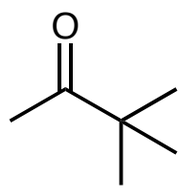
4% ee



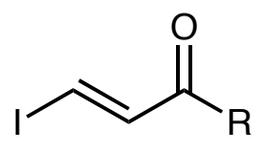
7% ee



32% ee

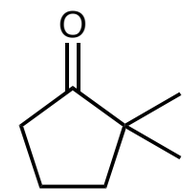


95% ee

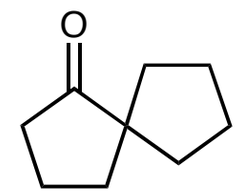


R = pentyl (85% ee)
R = c-pentyl (78% ee)

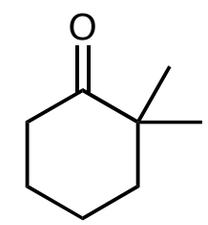
Cyclic alkyl ketones



98% ee

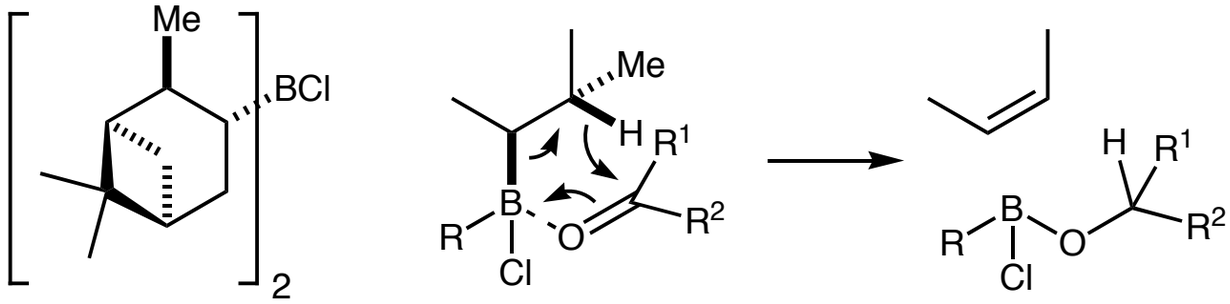


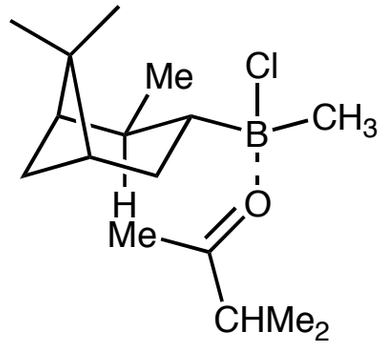
95% ee



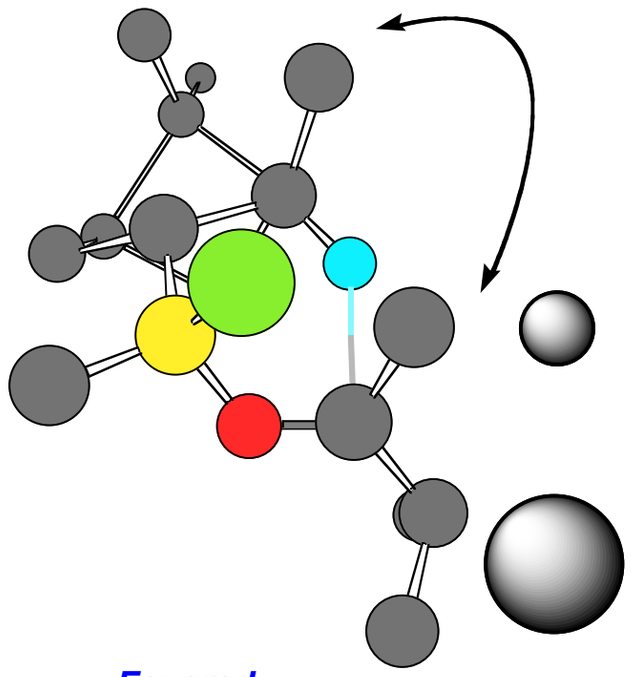
91% ee

Chiral Reagents for the Reduction of C=O: DIP-Cl

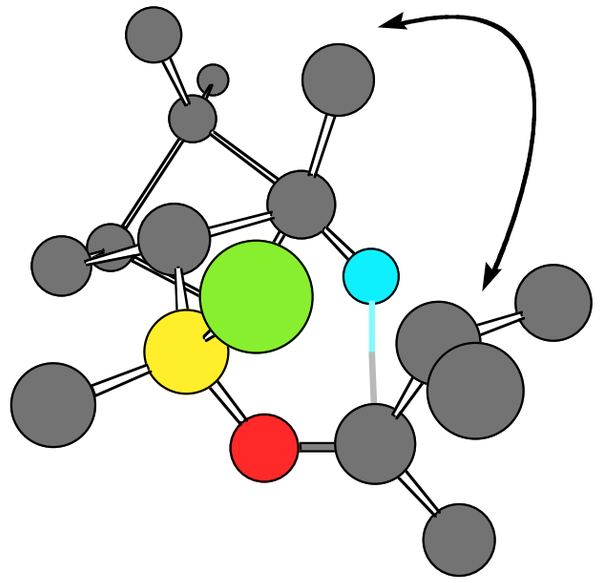




Chiral Reagents for the Reduction of C=O: DIP-Cl

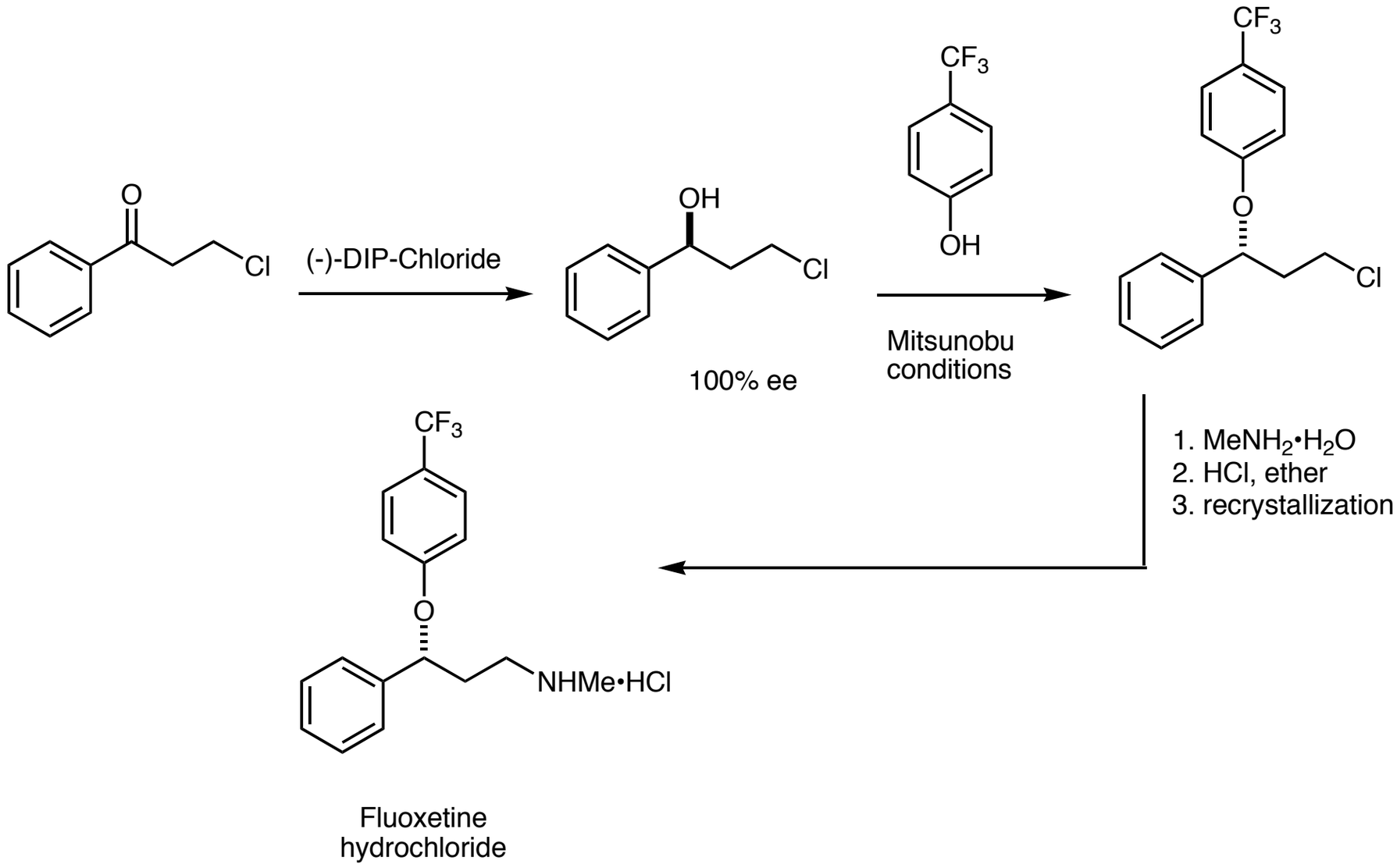


Favored

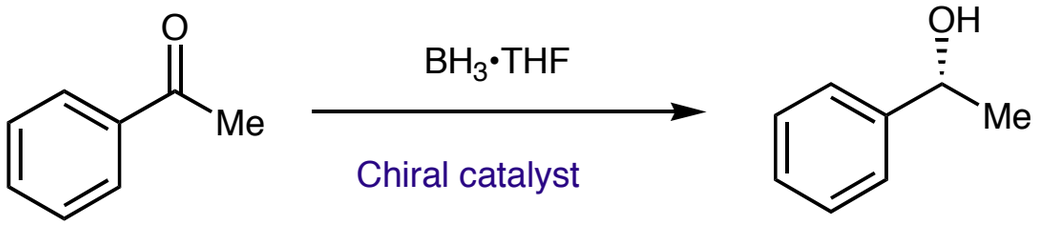


Disfavored

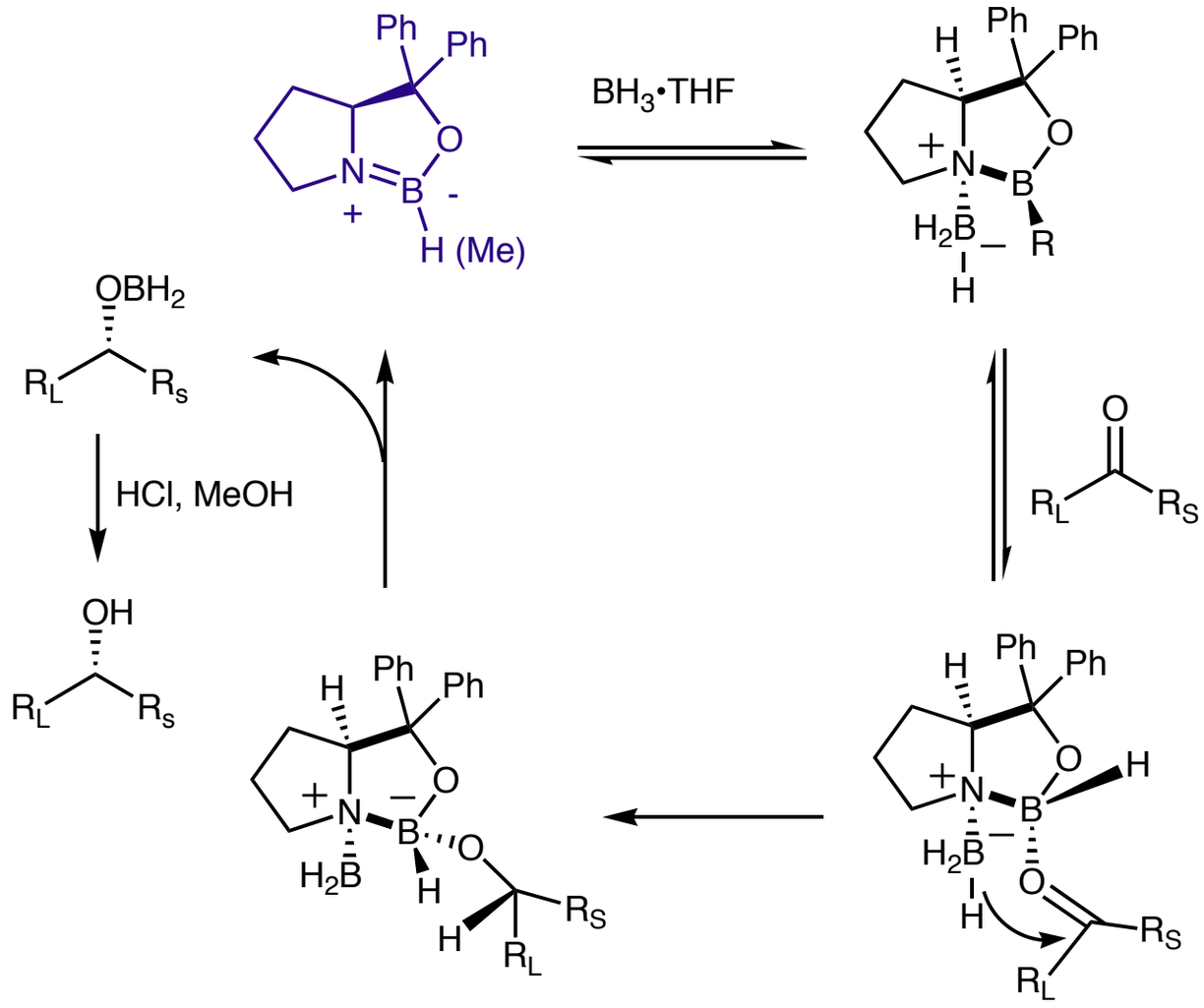
Reduction of Ketones With DIP-Cl: Scope and Limitations



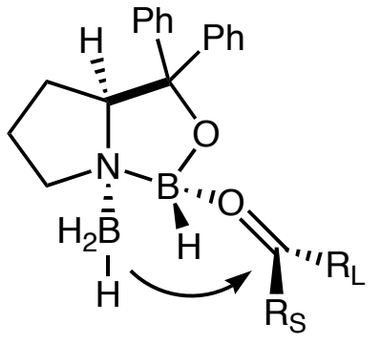
Corey-Bakshi-Shibata (CBS) Catalytic System (Corey-Itsuno)

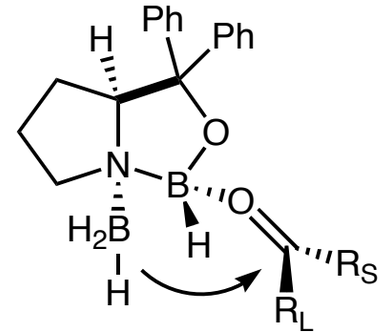


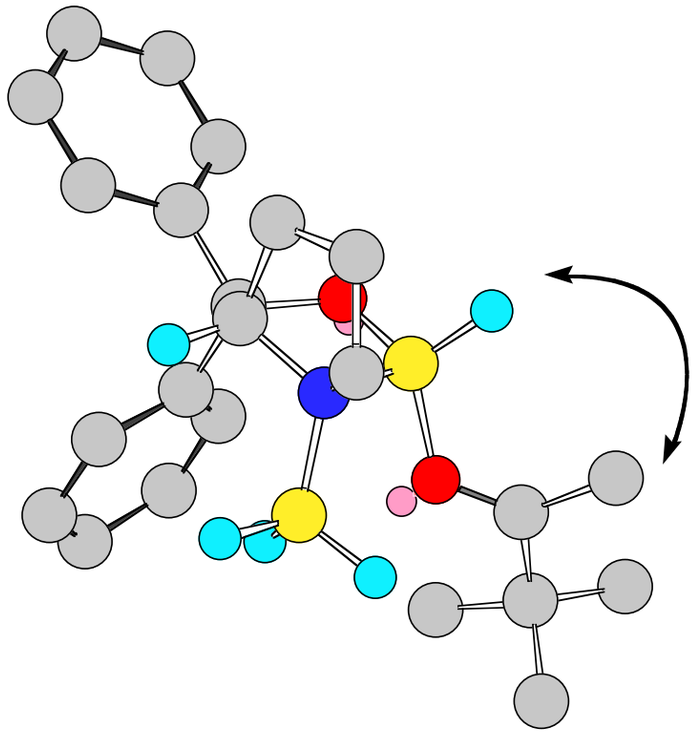
Chiral catalyst (equiv)	BH_3 (equiv)	% ee
1.0	2.0	97
0.1	1.0	97
0.025	1.2	95

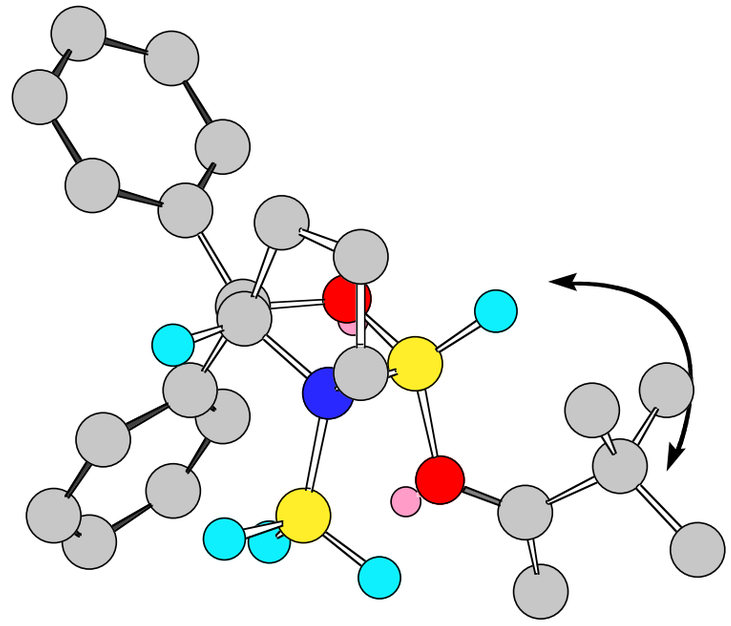


CBS Catalyst: Postulated Transition State Model



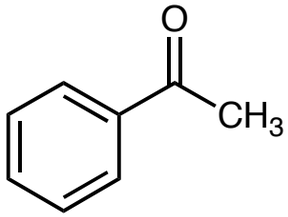




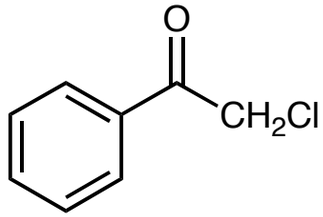


CBS Enantioselective Reduction: Scope

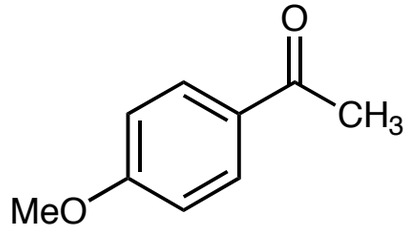
Aryl ketones



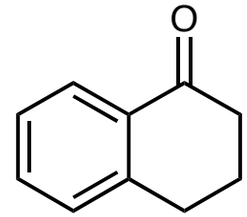
99% ee



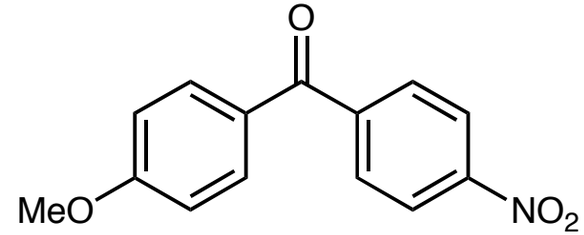
98% ee



99% ee

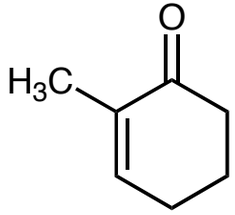


≥99% ee

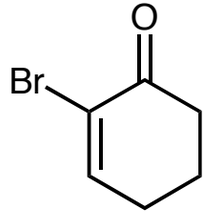


95% ee

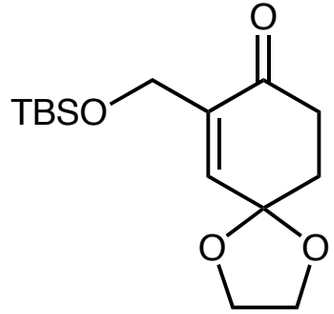
Cyclic α,β–enones



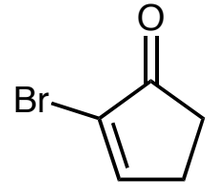
93% ee



96% ee



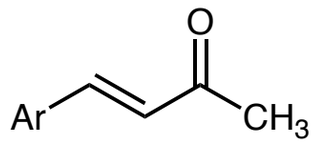
92% ee



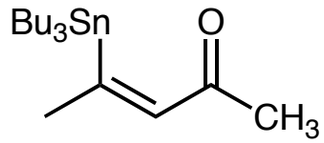
90% ee

CBS Enantioselective Reduction: Scope

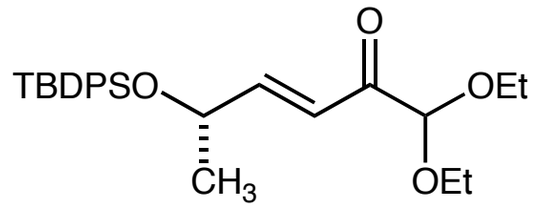
Acyclic α,β-enones



95-97% ee

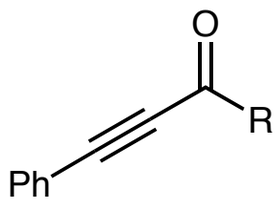


85% ee

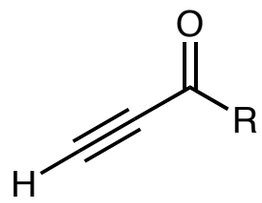


95% ee

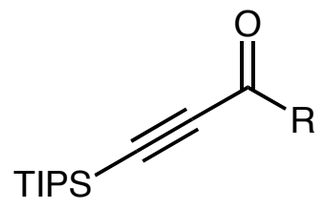
α,β-ynones



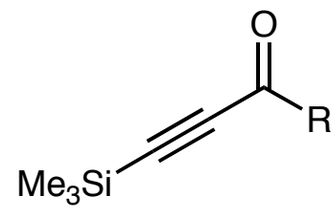
R = n-alkyl, 71-88% ee
R = s-alkyl, 94-96% ee



R = n-alkyl, 95% ee
R = c-hexyl, 98% ee

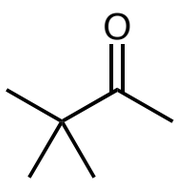


R = n-alkyl, 90-97% ee

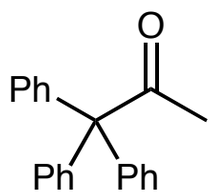


R = n-alkyl, 91-97% ee

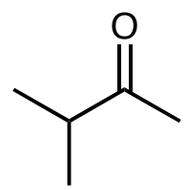
Dialkyl ketones



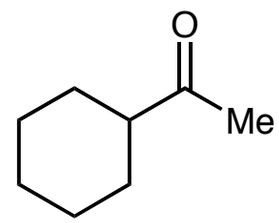
97.4% ee



97% ee

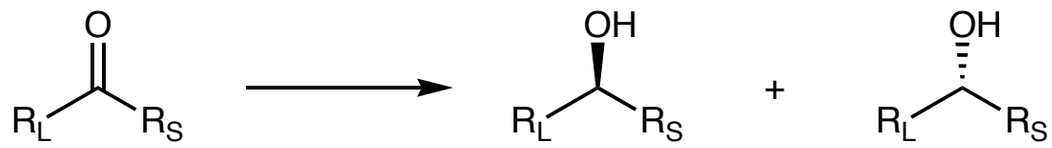


91% ee



≥ 99% ee

Enantioselective Reduction of Ketones



Stoichiometric chiral hydride
borane, borohydride, aluminum hydride

Chiral catalyst with
stoichiometrichydride source
borane

Asymmetric hydrogenation
H_2 is used as hydrogen donor

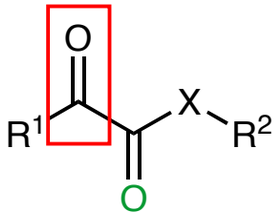
Transfer hydrogenation
i-PrOH, HCOOH are used as
hydrogen donor

- experimentally simple
- low reactions temperatures
- high loading (low TON)

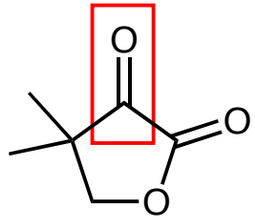
- may require high pressure
- may require high temperature
- very high TON

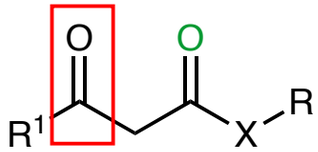
Asymmetric Hydrogenation of Ketones: Introduction

Functionalized Ketones

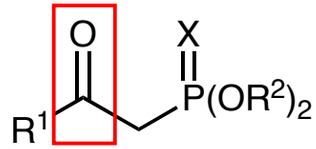


(X = O, NH)

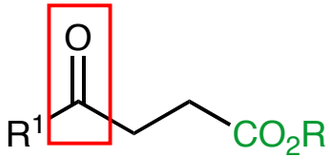


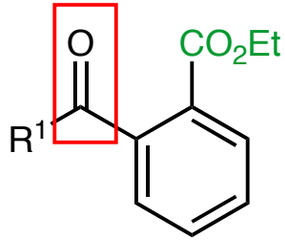


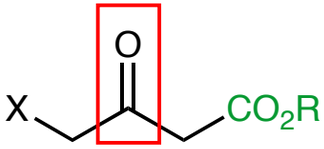
(X = O, NMe, S)

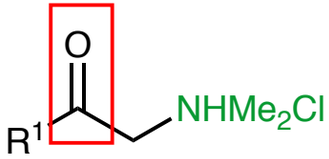


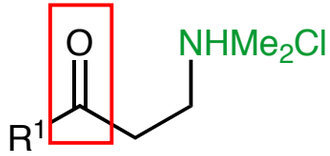
X = O, S



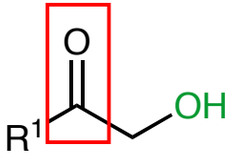


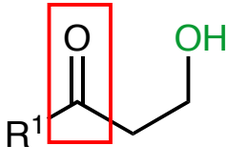


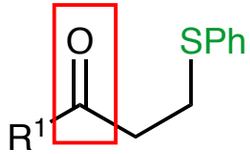


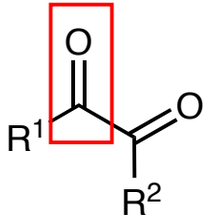


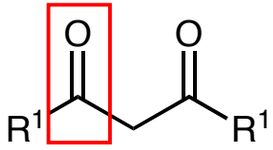
(X = OR', Cl, $NHMe_2$, NMe_3)



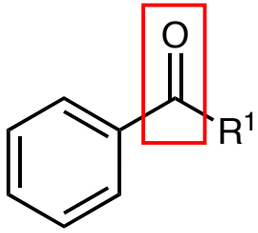


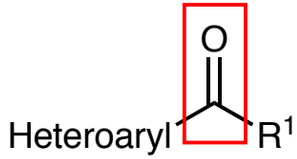


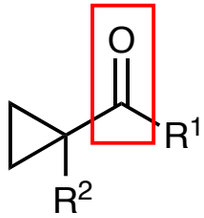


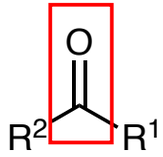


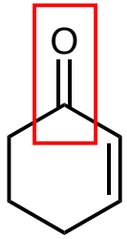
Unfunctionalized Ketones

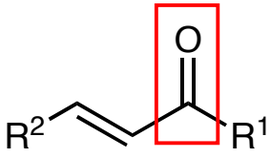


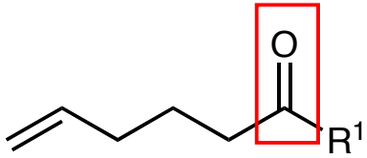








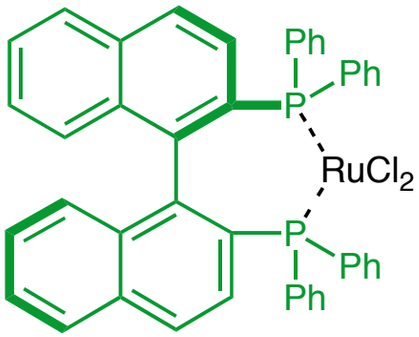




chemoselectivity

Noyori's Chemistry: Three Classes of Catalytic Systems

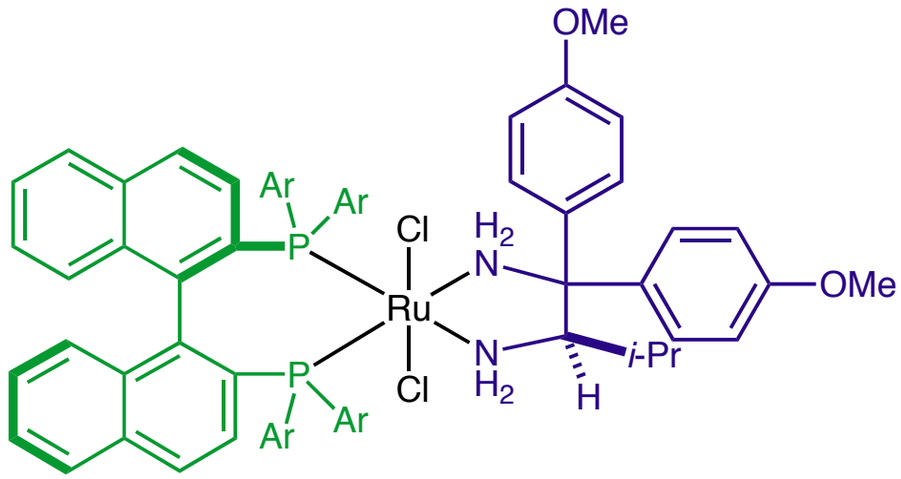
Enantioselective Hydrogenation



DIPHOSPHINE LIGAND

CH_3OH, 100 atm H_2
S/C = 700-10000

FUNCTIONALIZED KETONES

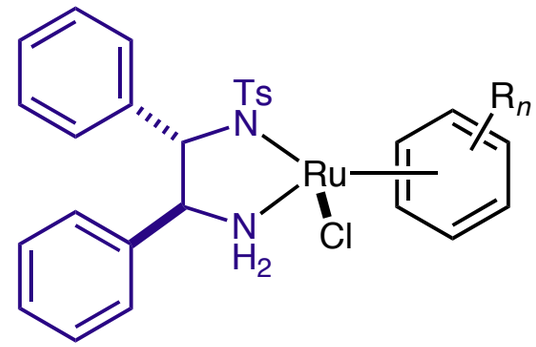


DIPHOSPHINE LIGAND
DIAMINE LIGAND

i-PrOH, 1-10 atm H_2
higher pressure: more turnovers
t-BuOK (cat.)
S/C = 2000-100000

UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

Enantioselective Hydrogen Transfer

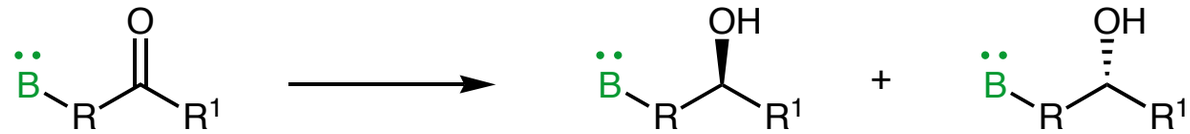


DIAMINE LIGAND

i-PrOH or HCO_2H (solv)
rt, *t*-BuOK (cat.)
S/C 200-2000

UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

Enantioselective Hydrogenation of Functionalized Ketones



- Ruthenium or Rhodium complex (halide counterions)
- Chiral Diphosphine ligand
- In most cases, high hydrogen pressure (100 atm) required
- Sometimes, higher enantioselectivities are higher temperature

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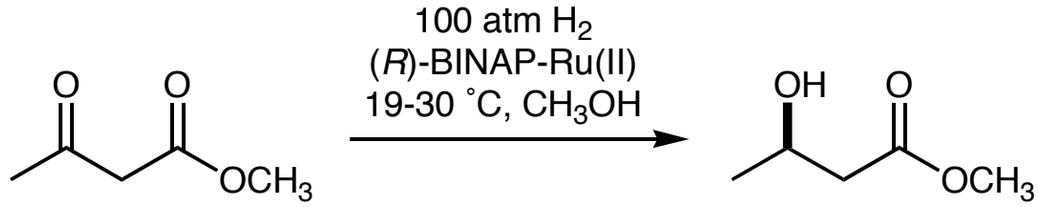
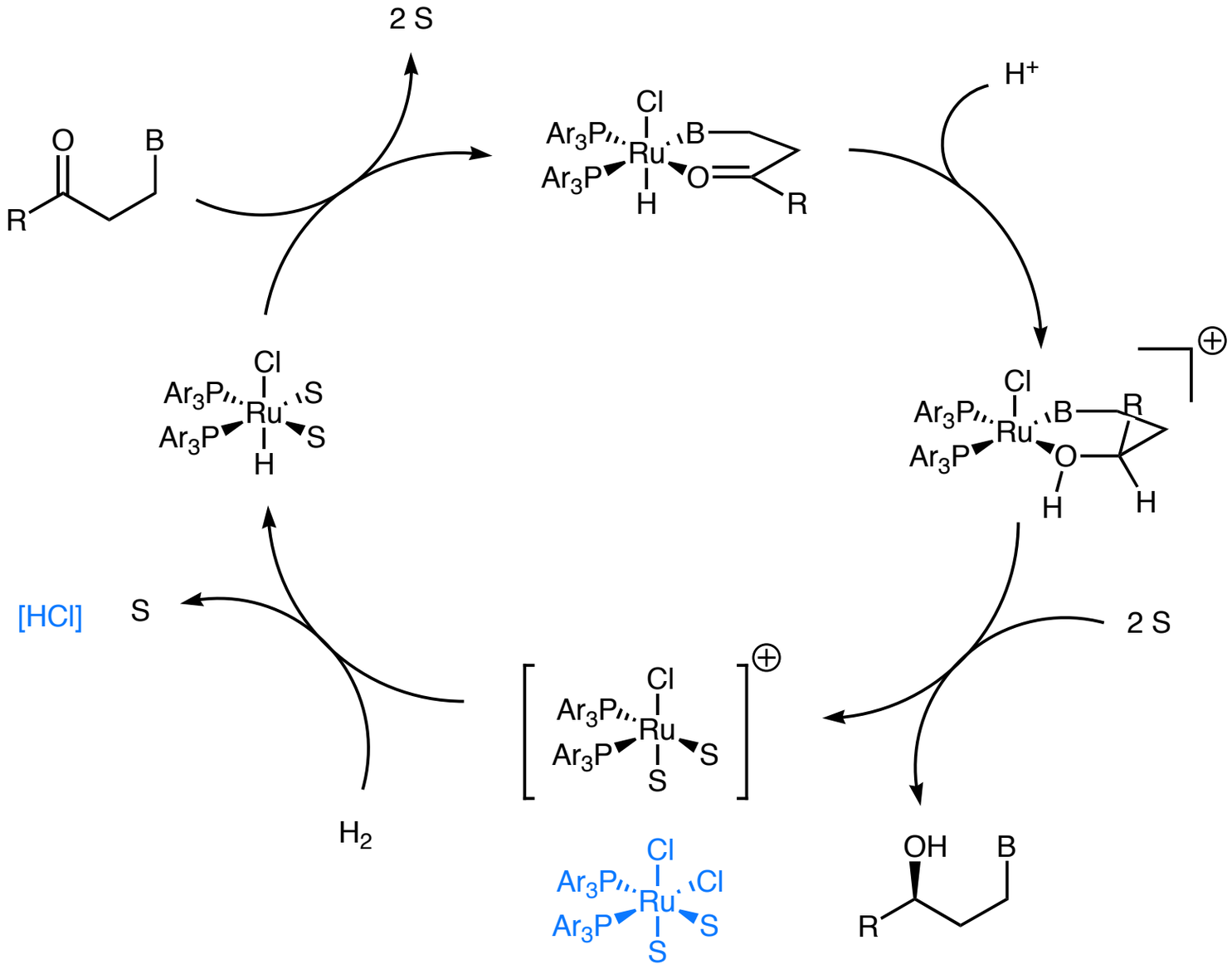
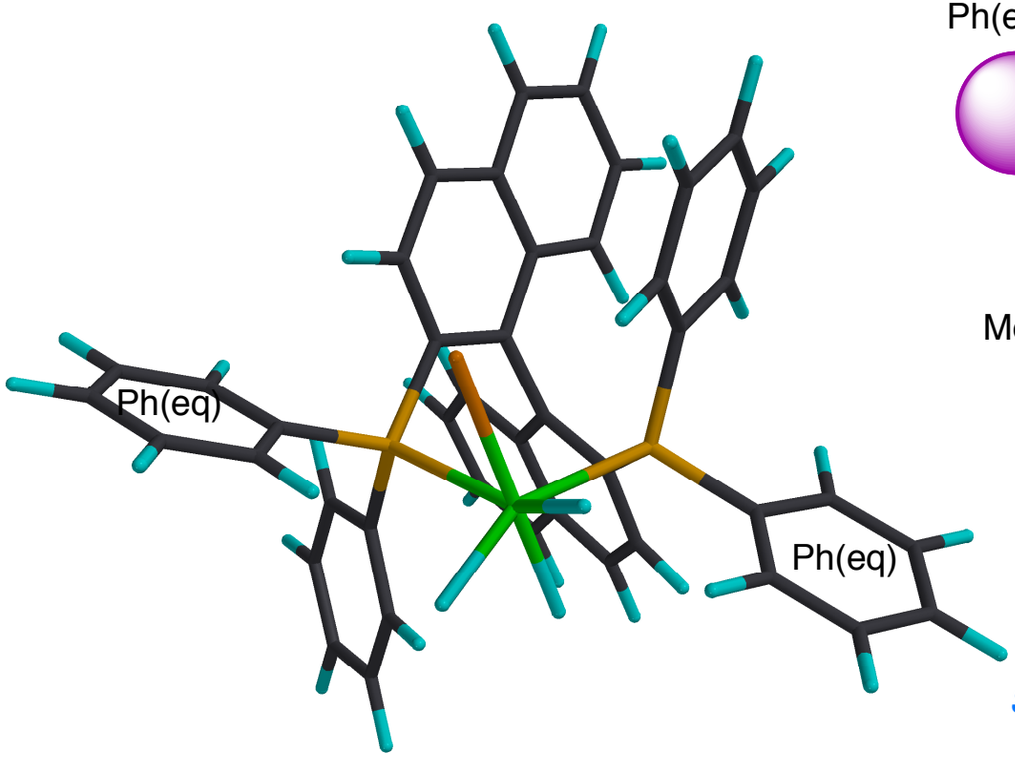


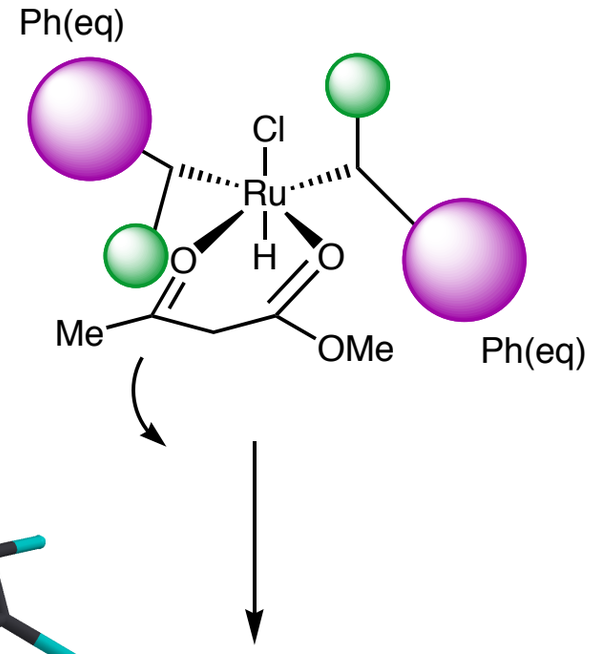
catalyst	S/C	time (h)	%	%ee
$Ru(OCOCH_3)$(binap)	1400	60	1	---
$Ru(OCOCH_3)$(binap) + 2TFA	1620	32	99	15
$Ru(OCOCH_3)$(binap) + $2HClO_4$	1620	32	99	51
$Ru(OCOCH_3)$(binap) + 2HCl	1800	32	99	99
$Ru(OCOCH_3)$(binap) + 2HCl	10000	64	98	96
$RuCl_2$(binap)	10000	64	98	96
$RuBr_2$(binap)	10000	64	98	96
RuI_2(binap)	10000	64	98	96

(R)-BINAP/Ru Reduction of C=O: Postulated Transition Structures

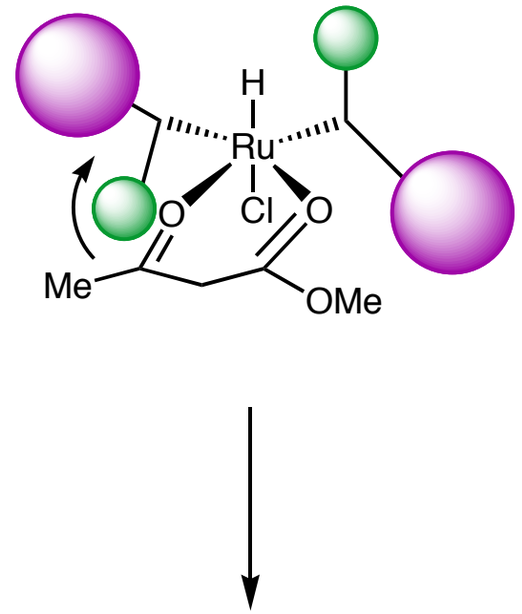


(R)-BINAP-Ru Complex: Importance of the Diphenylphosphine Unit





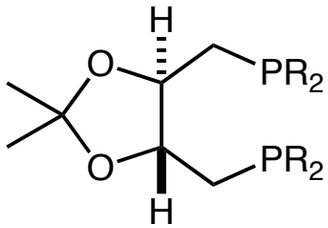
Si-Face attack: Favored



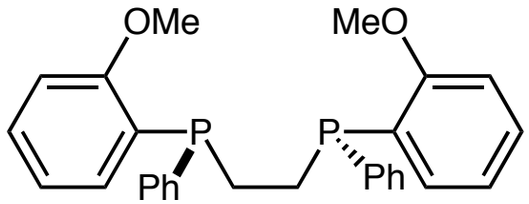
Re-Face attack: Disfavored

⇨ Equatorial phenyl groups are "bulkier"

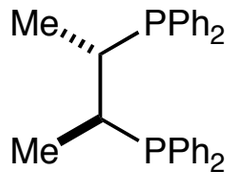
Chiral Diphosphine Ligands for Enantioselective Transformations



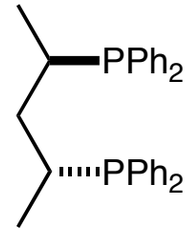
(*R*,*R*)-DIOP (R = Ph)



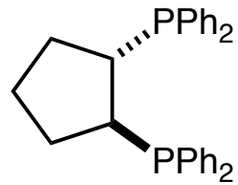
(*R*,*R*)-DIPAMP



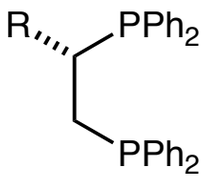
(*S*,*S*)-CHIRAPHOS



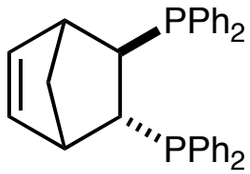
(*R*,*R*)-BDPP



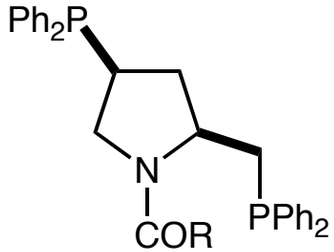
(*S*,*S*)-DPCP



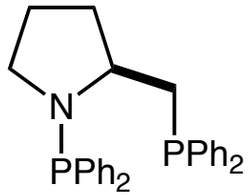
R = Me: (*S*)-PROPHOS
R = Ph: (*S*)-PHENPHOS
R = c-C_6H_{11}: (*S*)-CYCPHOS



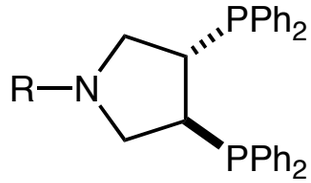
(*R*,*R*)-NORPHOS



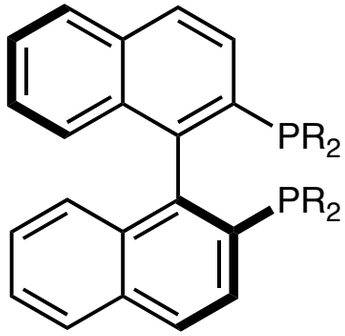
R = t-BuO: (*S*,*S*)-BPPM
R - R'NH- (*S*,*S*)-R'-CAPP
R' = Ar



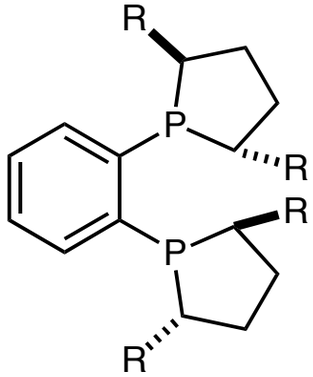
ProNOP



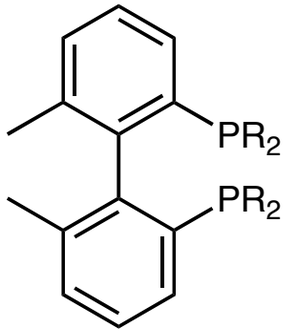
(*S*,*S*)-PYRPHOS



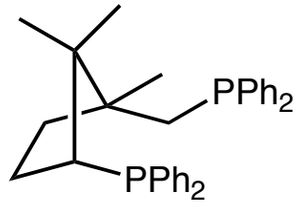
(*S*)-BINAP (R = Ph)
(*S*)-TolBINAP (R = tolyl)



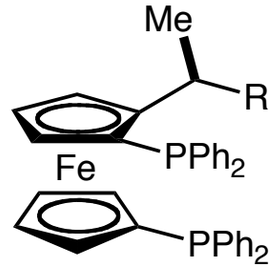
DuPHOS (R= Me, Et)



BIPHEMP (R = Ph)
BICHEP (R = c-C_6H_{11})



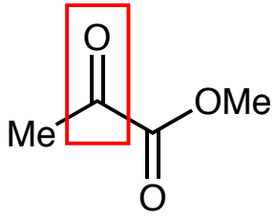
CAMPHOS



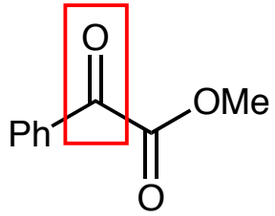
R = NMe_2 : BPPFA
R = OH: BPPFOH

Enantioselective Hydrogenation of Functionalized Ketones

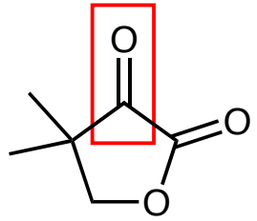
1,2-dicarbonyl: Not good substrates with BINAP-Ru



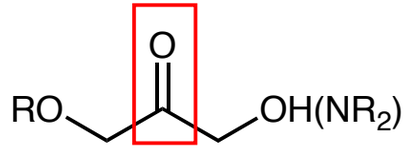
87% ee (*R*)
20 atm
THF
(2S,4S)-MCCPM-Rh
Synlett **1992**, 169



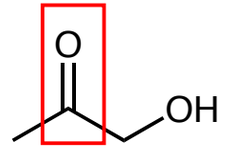
99% ee (*S*)
5 atm
EtOH
(R)-BICHEP-Ru
TL **1993**, 2351



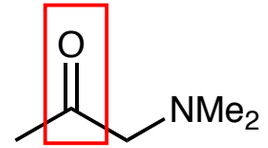
99% ee (*R*)
1 atm
PhMe
(S)-Cp,Cp-isoAlaNOP-Rh
Synlett **1995**, 358
Organomet. **1996**, 15, 2440



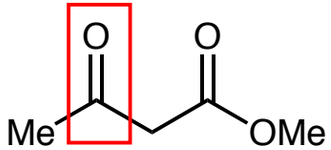
93->95 ee% (*S*)
94-97 atm
(*S*)-BINAP
TL **1991**, 4381
HCA **1993**, 2344
TA **1993**, 2451



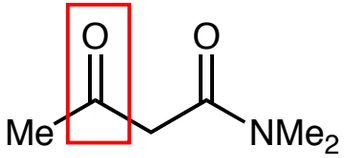
92 ee% (*R*)
93 atm
(*R*)-BINAP
JACS **1988**, 629



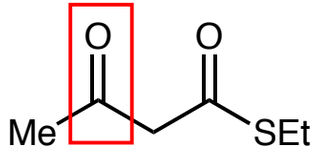
99 ee% (*S*)
102 atm
(*S*)-BINAP
JACS **1988**, 629



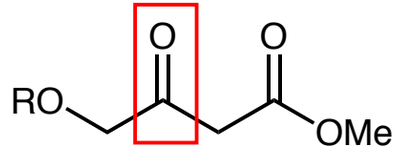
>99 ee% (*R*)
100 atm
MeOH (rt)
(*R*)-BINAP
ACR **1990**, 345



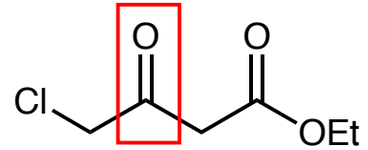
96 ee% (*S*)
63 atm
EtOH (27 ˚C)
(*S*)-BINAP
JACS **1988**, 629



93 ee% (*R*), 42% yield
95 atm
EtOH (27 ˚C)
(*R*)-BINAP
JACS **1988**, 629



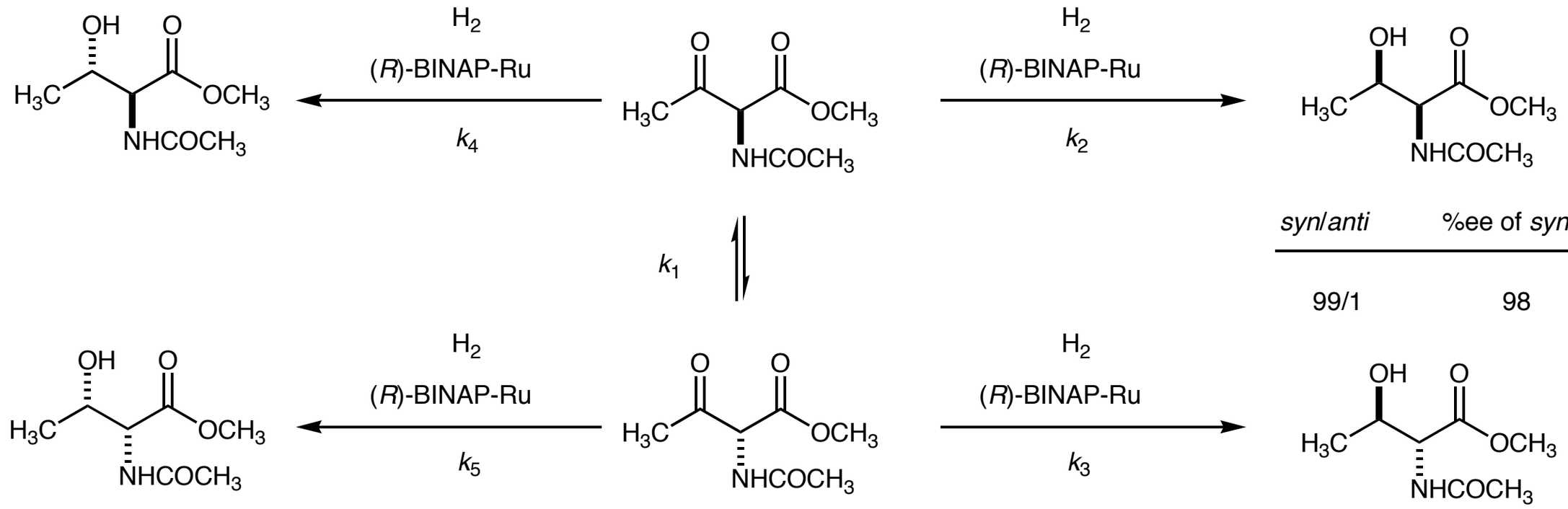
>95 ee% (*R*)
100 atm
MeOH (rt)
(*S*)-BINAP
JACS **1988**, 629



97 ee% (*R*)
100 atm
MeOH (100 ˚C)
(*S*)-BINAP
TL **1988**, 1515

Dynamic Kinetic Resolution With BINAP-Ru

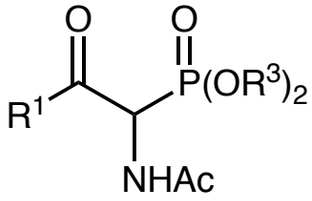
R. Noyori et al. *J. Am. Chem. Soc.* **1989**, *111*, 9134-9135.



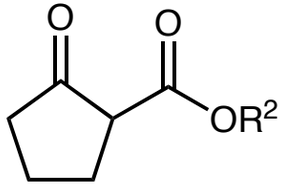
syn/*anti*	%ee of *syn*
99/1	98

$k_1 >> k_2 >> k_3 >> k_4, k_5$

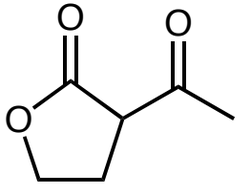
Other substrates:



JACS **1995**, 2931
TL **1995**, 769



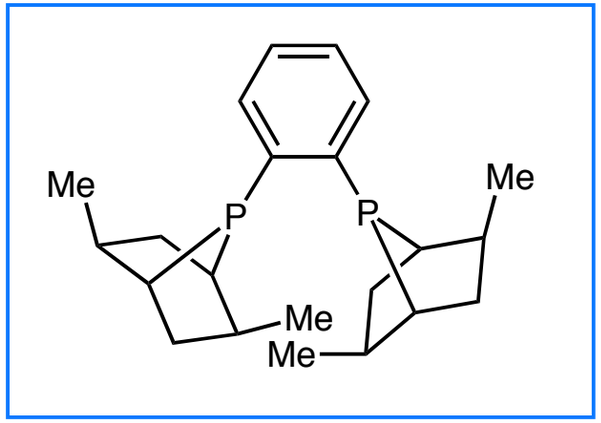
JACS **1995**, 4423
PAC **1996**, 37
JOC **1996**, 6244

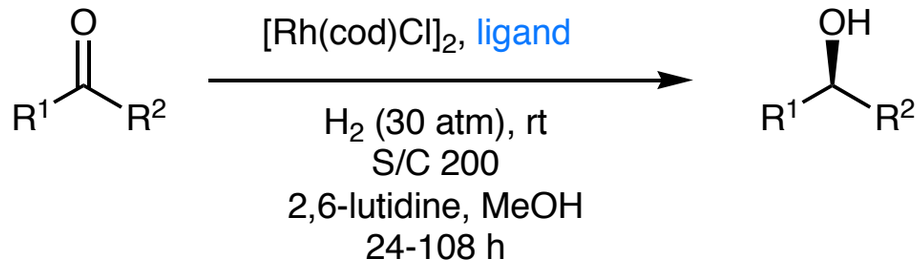


JOC **1994**, 3064
TA **1990**, 1

Hydrogenation of Alkyl Ketones With PennPHOS

X. Zhang *Angew. Chem. Int. Ed.* **1998**, *37*, 1100-1103

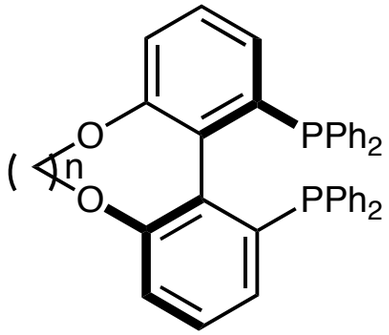




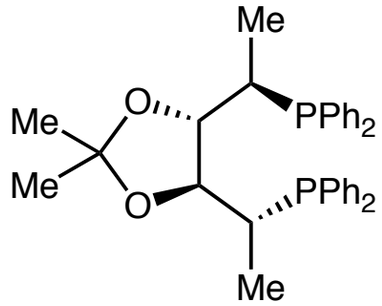
R^1	R^2	Yield	ee
Ph	Me	97	95
4-MePh	Me	94	95
4-MeOPh	Me	56	91
Ph	Et	95	93
Ph	*i*-Pr	20	72
2-Furyl	Me	99	96
$PhCH_2CH_2$	Me	99	73
Bu	Me	96	75
i-Bu	Me	66	85
i-Pr	Me	99	84
c-C_6H_{11}	Me	90	92
t-Bu	Me	51	94

- Relatively low S/C
- KBr sometimes added to improve yields and ee's

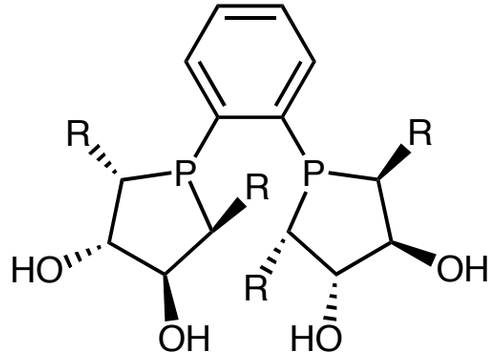
Some Other Chiral Ligands From Zhang



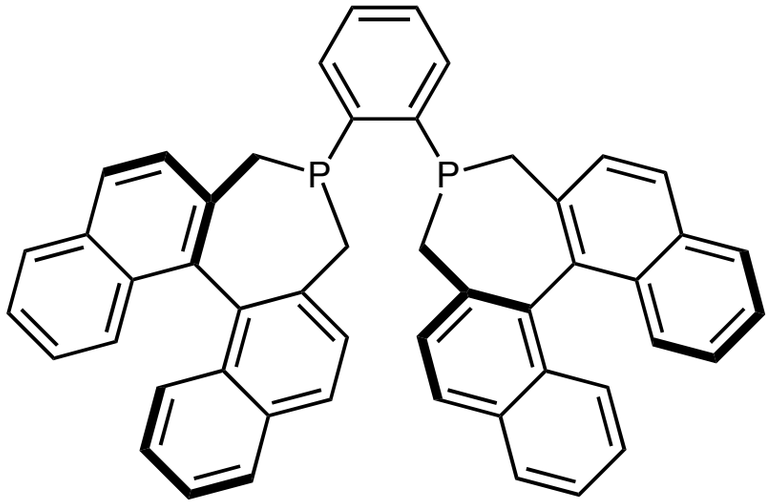
J. Org. Chem. **2000**, 6223
β-keto esters



J. Org. Chem. **2000**, 5871
enamides



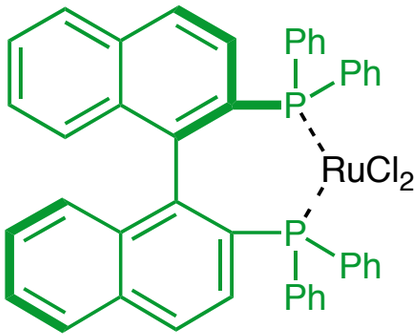
R = Me, Et
J. Org. Chem. **2000**, 3489
enamides, Baylis-Hillman



Org. Lett. **1999**, 1679
enamides

Noyori's Chemistry: Three Classes of Catalytic Systems

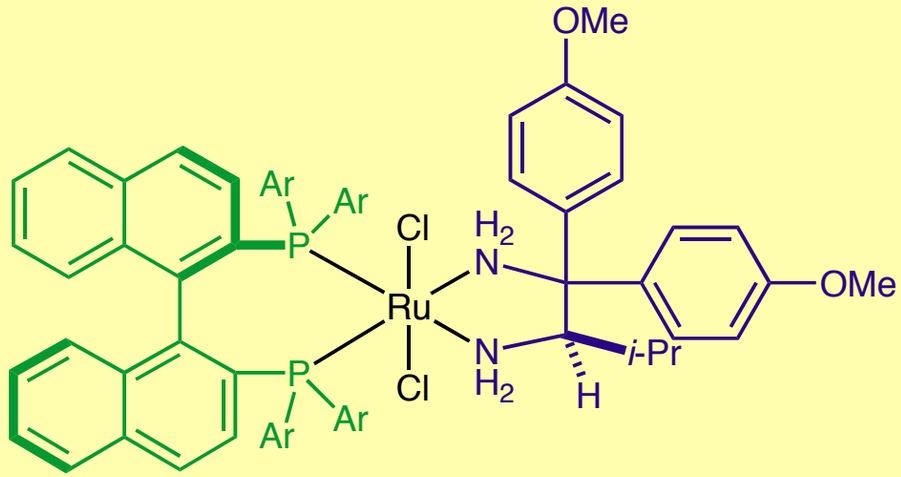
Enantioselective Hydrogenation



DIPHOSPHINE LIGAND

CH_3OH, 100 atm H_2
S/C = 700-10000

FUNCTIONALIZED KETONES

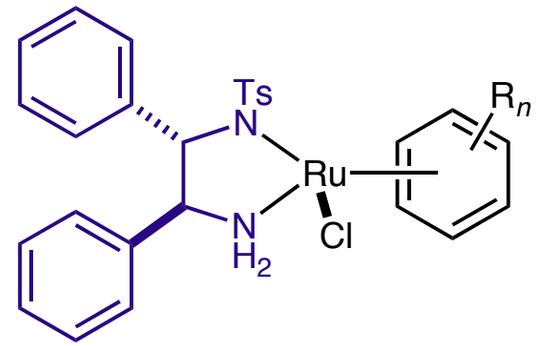


DIPHOSPHINE LIGAND
DIAMINE LIGAND

i-PrOH, 1-10 atm H_2
higher pressure: more turnovers
t-BuOK (cat.)
S/C = 2000-100000

UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

Enantioselective Hydrogen Transfer

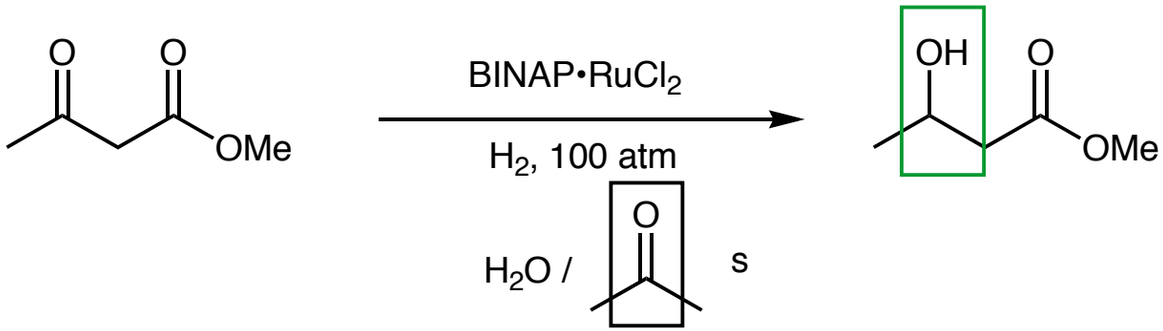


DIAMINE LIGAND

i-PrOH or HCO_2H (solv)
rt, *t*-BuOK (cat.)
S/C 200-2000

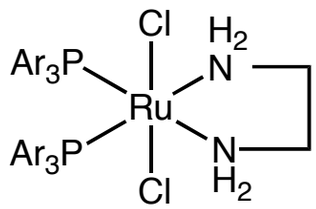
UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

BINAP-Ru Chemistry: Ineffective for Unfunctionalized Ketones

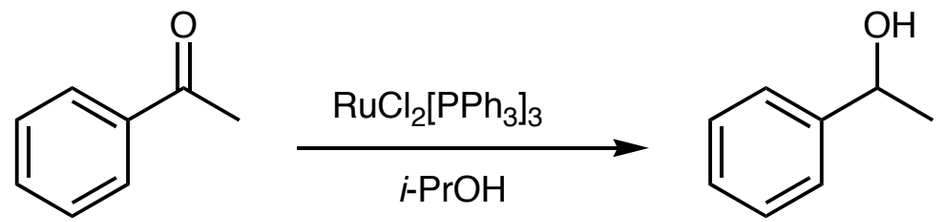


- second basic group is necessary
- rate is increased in the presence of strong acid
- σ- to π-complex between C=O and Ru in the reduction process

Effect of protic ligand (hydrogen bond donor ligands)



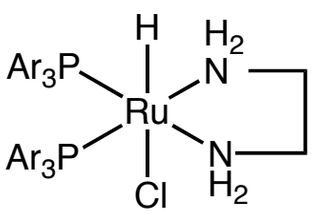
precatalyst



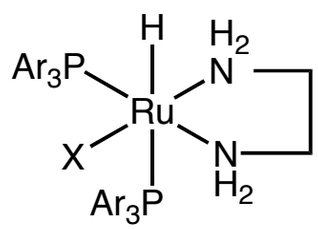
ketone/Ru = 5000

TOF = moles of product/mole of Ru per h

H_2, no base	<5
H_2, KOH	70
H_2, $H_2NCH_2CH_2NH_2$	<5
no H_2, $H_2NCH_2CH_2NH_2$, KOH	7
H_2, $H_2NCH_2CH_2NH_2$, KOH	6700 (28 ˚C, 3 atm H_2)



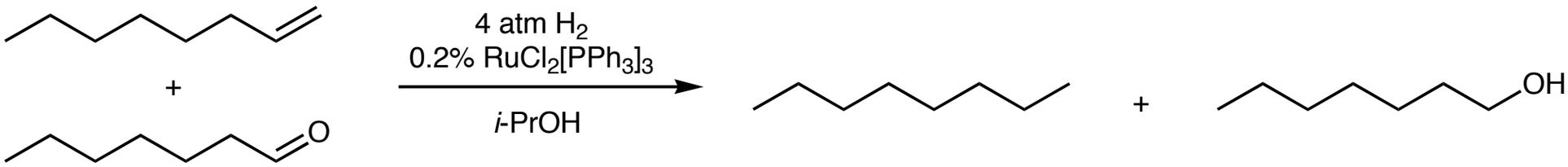
trans



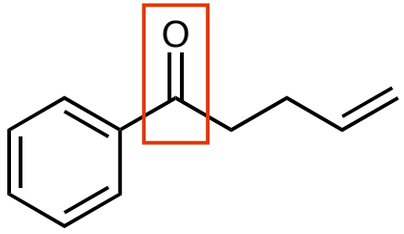
cis

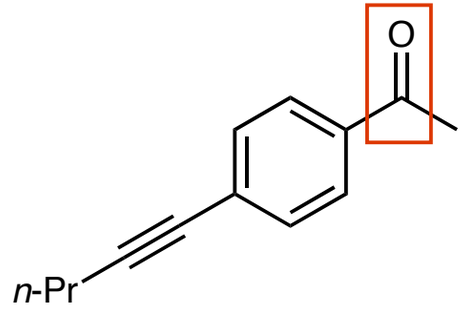
Chemoselective Hydrogenation

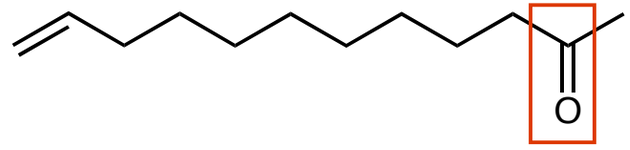
Noyori *JACS* **95**, 10417

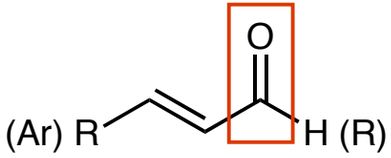


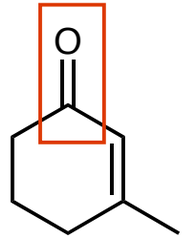
no additive	250	:	1 (150 min)
$H_2NCH_2CH_2NH_2$, KOH Ru:diamine:KOH = 1:1:2	1	:	1500 (10 min)

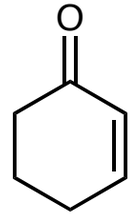








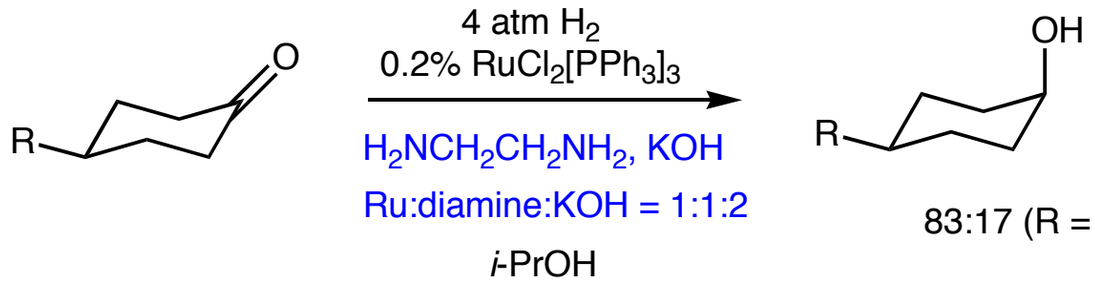




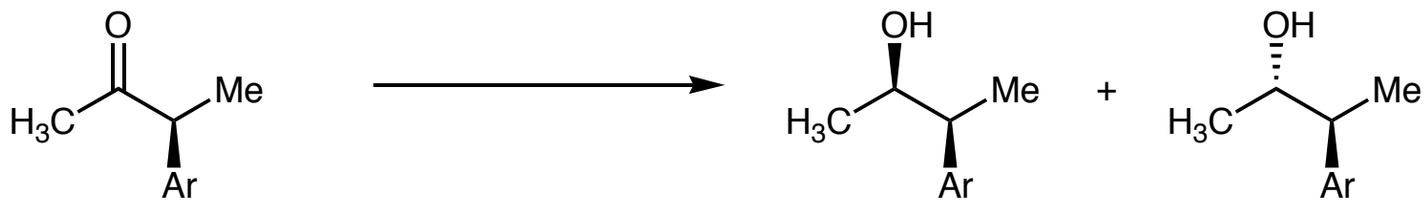
70% selectivity

Diastereoselective Hydrogenation

Noyori *JOC* **1996**, 4872



83:17 (R = OH) to 98.4:1.6 (R = *t*-Bu)

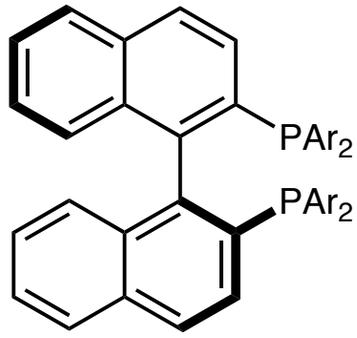


78:22 (Ar = 4-FC_6H_4)
to
96:4 (Ar = 4-$MeOC_6H_4$)

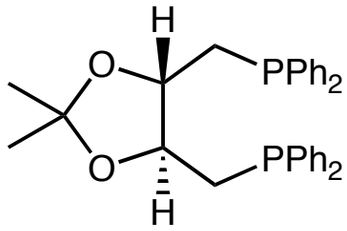
⇨ It behaves as a bulky hydride to give Felkin-Anh selectivity

Enantioselective Hydrogenation: Catalysts

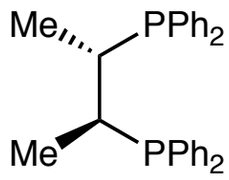
Diphosphine



(*S*)-BINAP: Ar = Ph
(*S*)-TolBINAP: Ar = 4-MeC_6H_4
(*S*)-XylBINAP: Ar = 3,5-$Me_2C_6H_3$

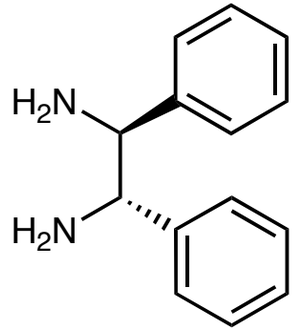


(*S,S*)-DIOP

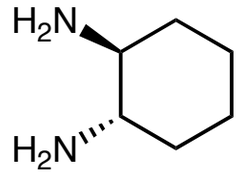


(*S,S*)-CHIRAPHOS

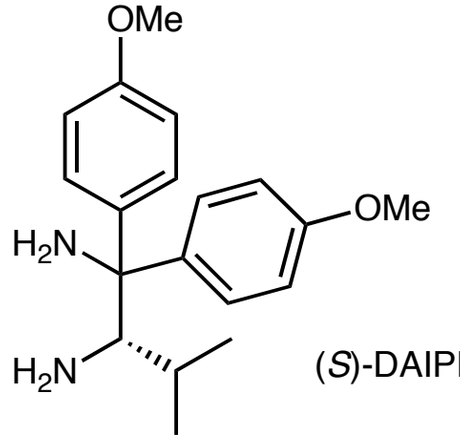
1,2-Diamine



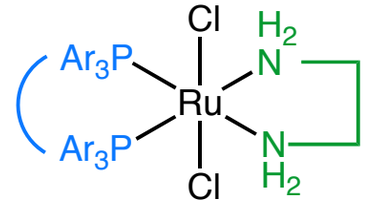
(*S,S*)-DPEN



(*S,S*)-cyclohexane-1,2-diamine



(*S*)-DAIPEN

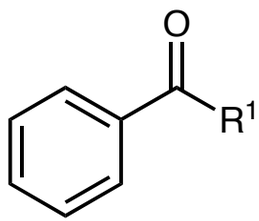


precatalyst
(shelf stable)

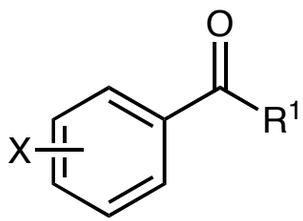
X-ray of several complexes are available

Scope of the Hydrogenation - 1

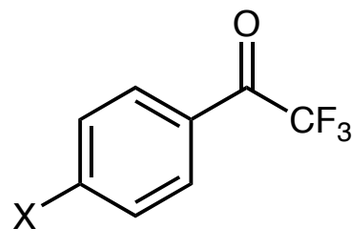
Aryl ketones (Typical conditions: S/C 100 000/1, 8 atm H_2)



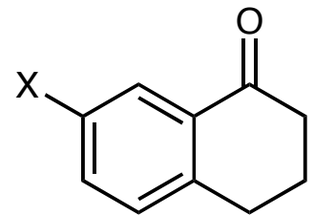
90-99% ee



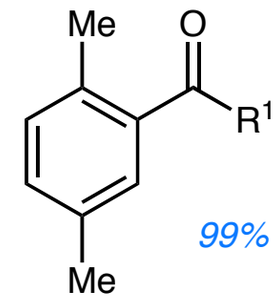
95-100% ee



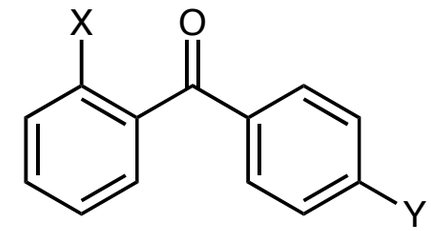
94-96% ee



94-95% ee



99% ee

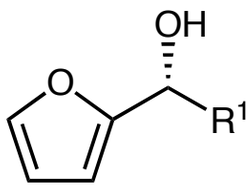


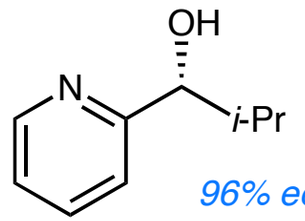
X ≠ H

96-99% ee

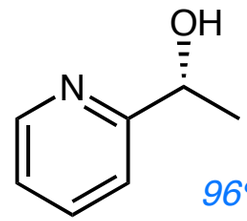
Heteroaromatic ketones ((*S*)-xylbinap:(*S*)-daipen, *t*-BuOK, *i*-PrOH, 8 atm H_2, 25-30 ˚C)

97-99% ee

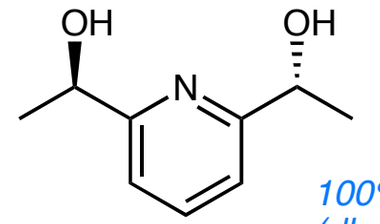




96% ee

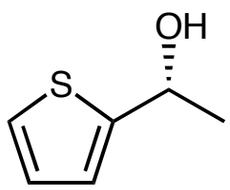


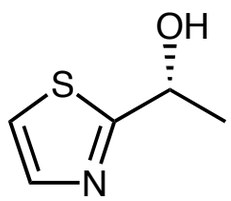
96% ee



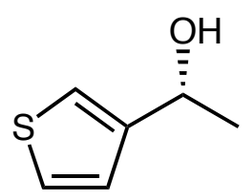
100% ee
(dl:meso 100:0)

99% ee

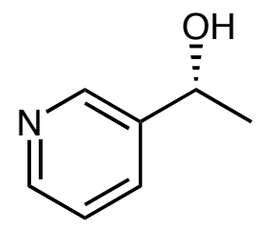




96% ee
(add B(Oi-Pr)$_3$)

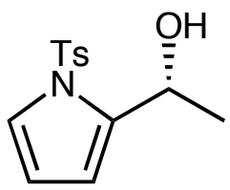


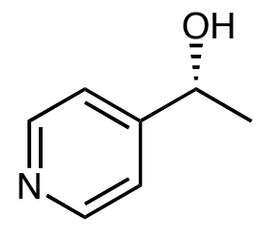
99.7% ee



99.6% ee

98% ee

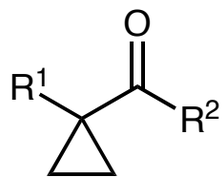




99.8% ee

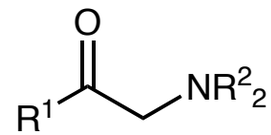
Scope of the Hydrogenation - 2

Cyclopropyl ketones
(*S*)-xylbinap:(*S*)-daipen,
t-BuOK, *i*-PrOH, 8 atm H_2, 25-30 ˚C)



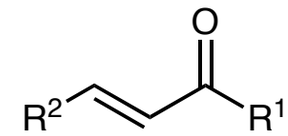
95-98% ee

Amino ketones

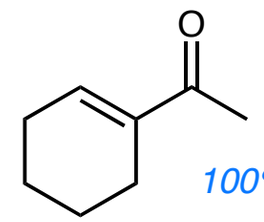


Usually >90% ee
with R^2 = alkyl, COR, H, etc.

α,β-Usaturated ketones

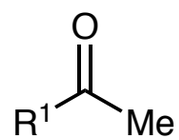


86-99% ee
R^1,R^2 = Ph, 42% ee



100% ee

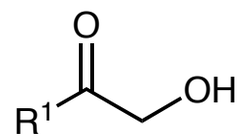
Alkyl ketones



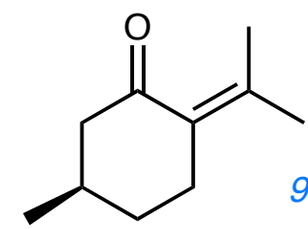
R^1 = Bu 75% ee
R^1 = $PhCH_2CH_2$ 73% ee
R^1 = i-Pr 84% ee
R^1 = c-C_6H_{11} 92% ee
R^1 = t-Bu 94% ee

PennPhos
is better

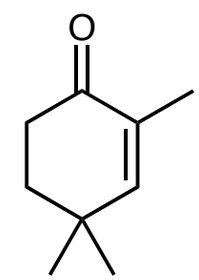
α-Hydroxy ketones



37-98% ee
(substrate-dependant)

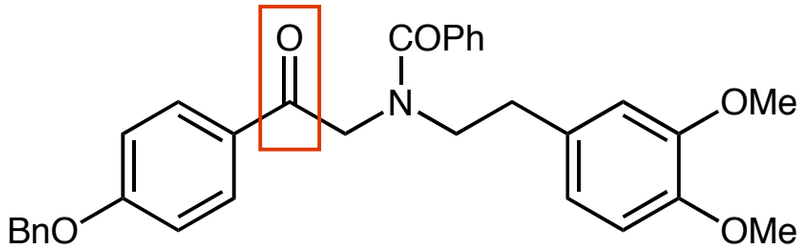


98:2 (cis:trans)

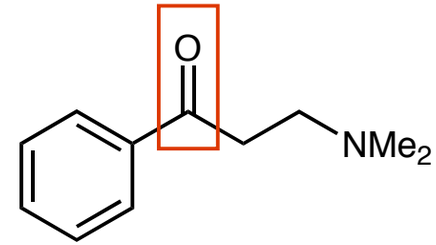


94-96% ee

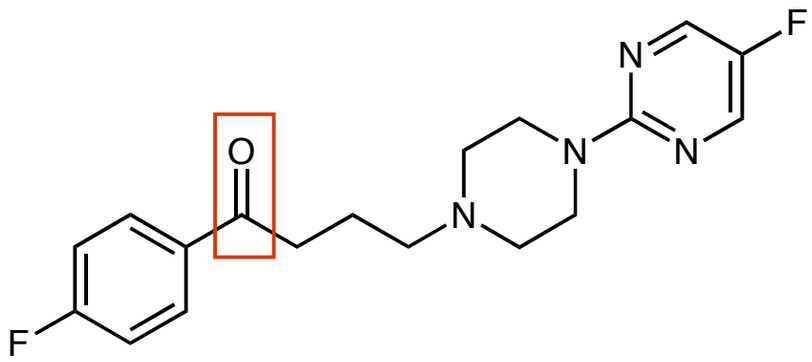
More Practical Examples



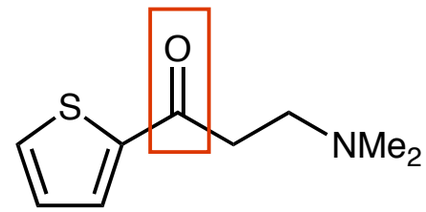
97% ee, 100% yield
denopamine hydrochloride synthesis



97.5% ee, 96% yield
fluoxetine hydrochloride synthesis



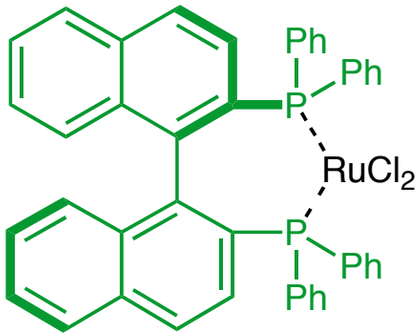
99% ee, 97% yield
BMS 181100



92% ee, 100% yield

Noyori's Chemistry: Three Classes of Catalytic Systems

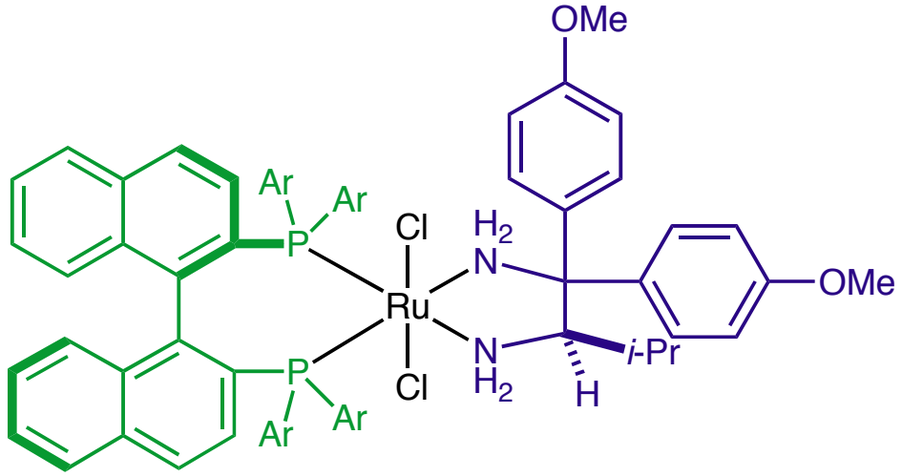
Enantioselective Hydrogenation



DIPHOSPHINE LIGAND

CH_3OH, 100 atm H_2
S/C = 700-10000

FUNCTIONALIZED KETONES

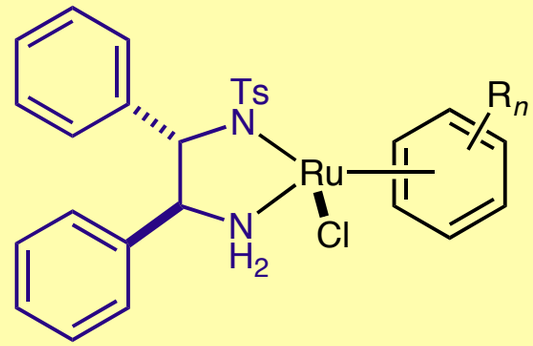


DIPHOSPHINE LIGAND
DIAMINE LIGAND

i-PrOH, 1-10 atm H_2
higher pressure: more turnovers
t-BuOK (cat.)
S/C = 2000-100000

UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

Enantioselective Hydrogen Transfer



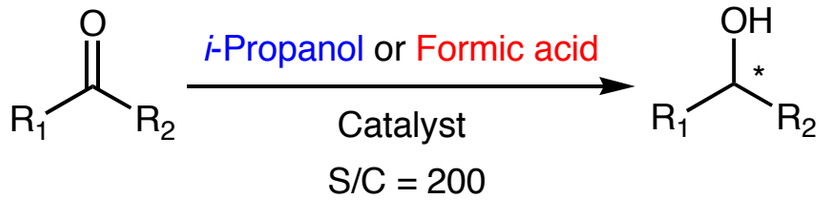
DIAMINE LIGAND

i-PrOH or HCO_2H (solv)
rt, *t*-BuOK (cat.)
S/C 200-2000

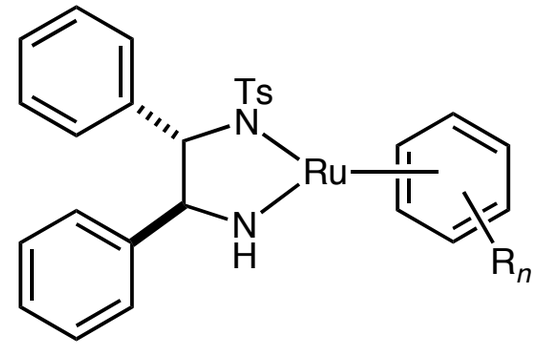
UNFUNCTIONALIZED AND FUNCTIONALIZED KETONES

Noyori's Ru(II)-Promoted Asymmetric H Transfer for Ketone Reduction

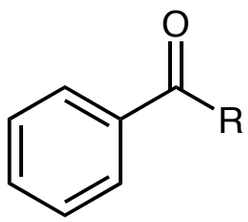
Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563. *Acc. Chem. Res.* **1997**, *30*, 97-102.
J. Am. Chem. Soc. **1996**, *118*, 2521-2522.



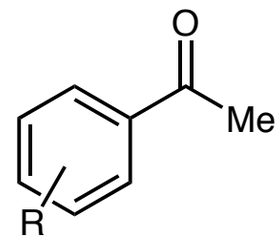
Catalyst:



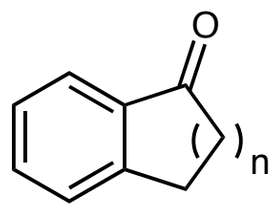
Mechanism: Meerwein-Ponndorf-Verlay (?) or other (see later)



R = H	95% ee	>99% ee
R = Et	94% ee	>96% ee
R = i-Pr	22% ee	41% ee
R = t-Bu	22	<1



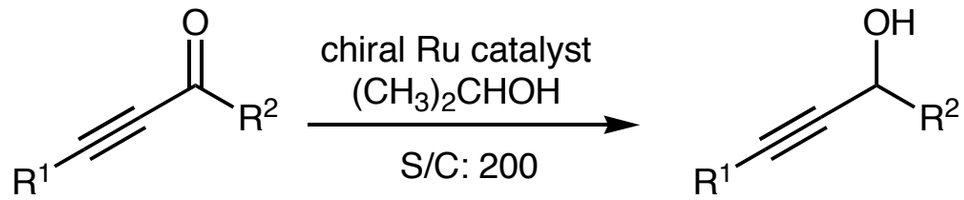
R = o-Cl	95	--
R = m-Cl	98	>99
R = p-Cl	95	>99
R = o-OMe	24	---
R = m-OMe	96	>99
R = p-OMe	53	>99



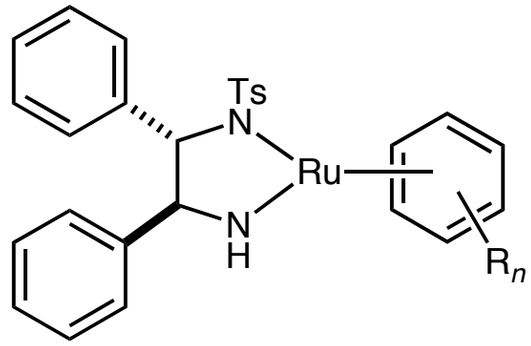
n = 1 >99% ee
n = 2 >99% ee

Hydrogenation of α,β-Acetylenic Ketones

R. Noyori *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.



R^1 = Ph, Bu, TMS



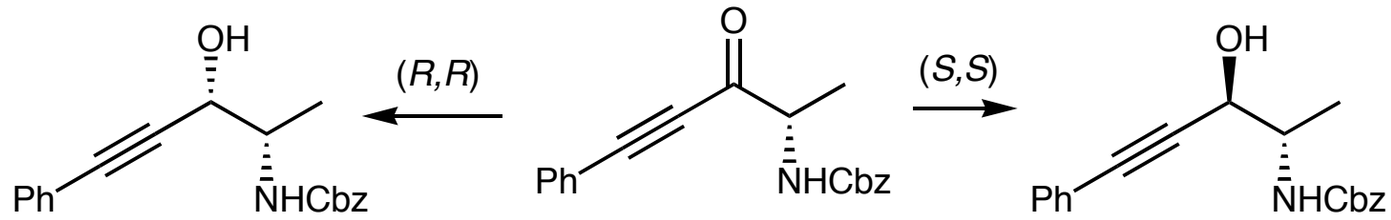
(*S*,*S*)-Catalyst

R^2	Yield	ee	config
Me	>99	98	S
Et	97	97	S
i-Pr	98	99	S
c-Hex	>99	98	S

Hydrogenation of Ketones: Scope

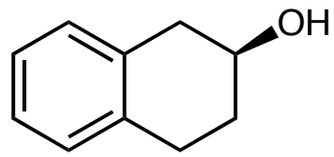
R. Noyori *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.

Catalyst-controlled enantioselectivity:

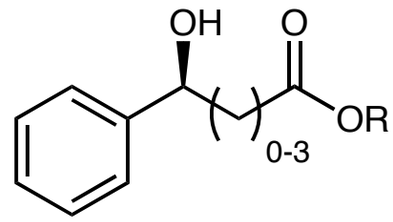


>99% ee, >97% yield

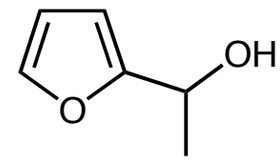
>99% ee, >97% yield



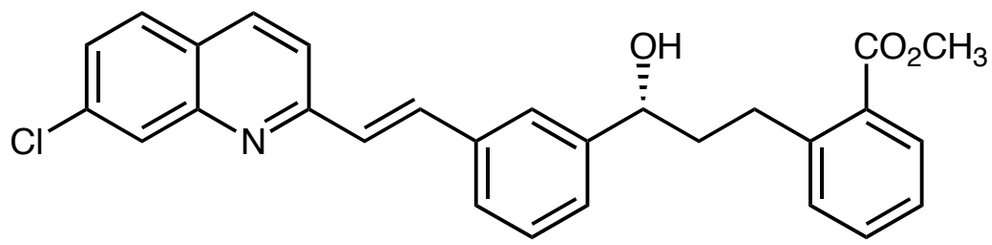
82% ee



0, 75% ee
1, 93% ee
3, 95% ee

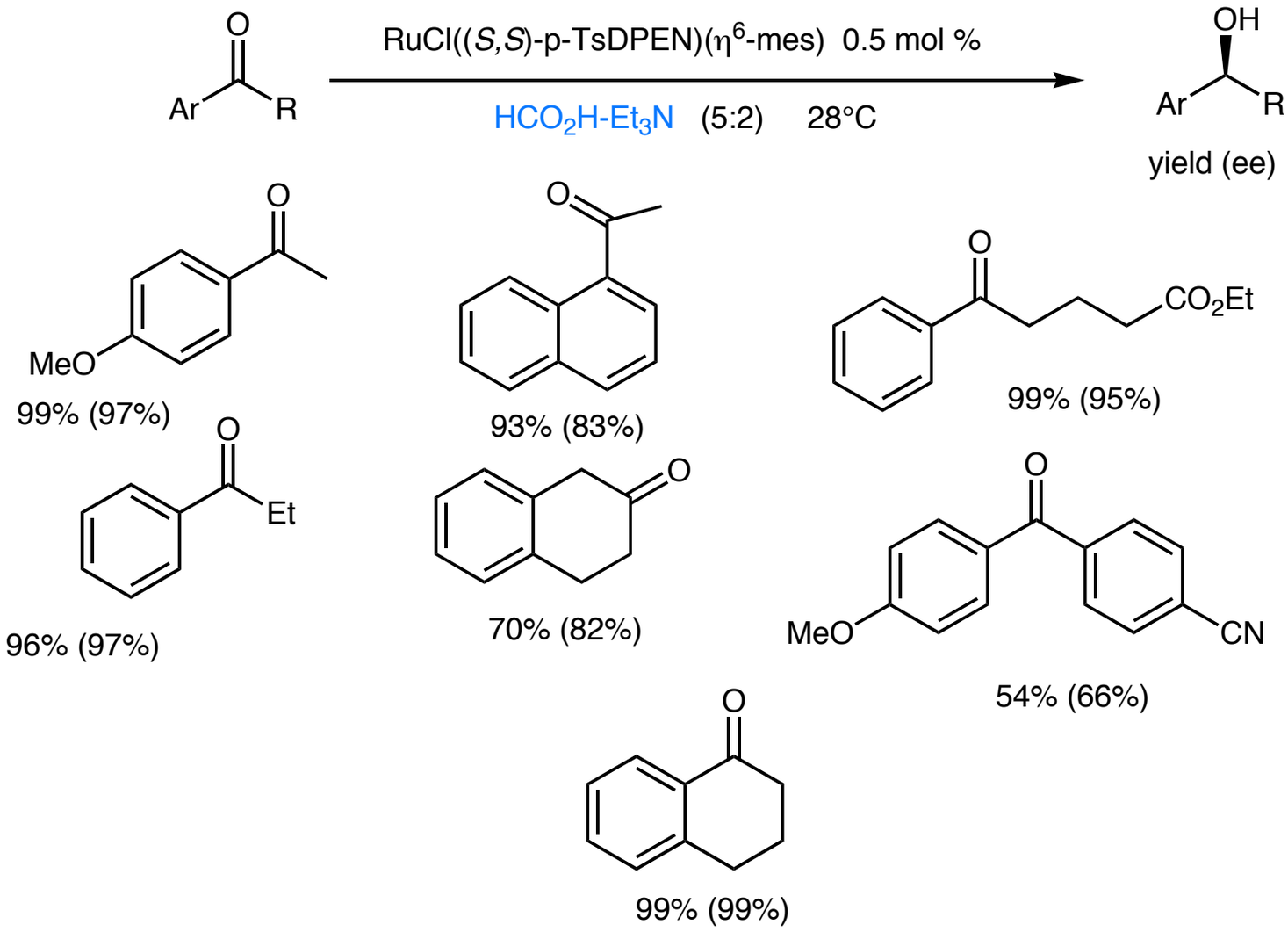


98% ee



92% ee

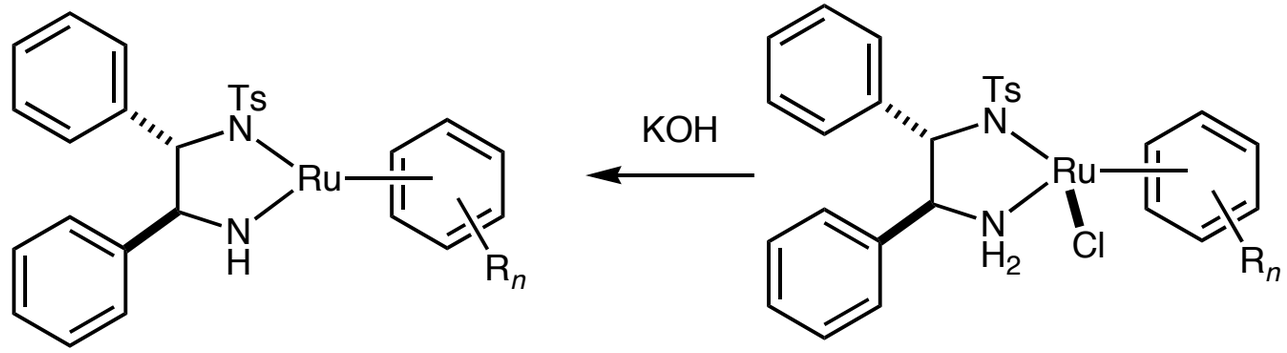
Modification of the Reagent: HCO_2H/Et_3N as H Transfer Precursor



J. Am. Chem. Soc. **1996**, *118*, 2521.

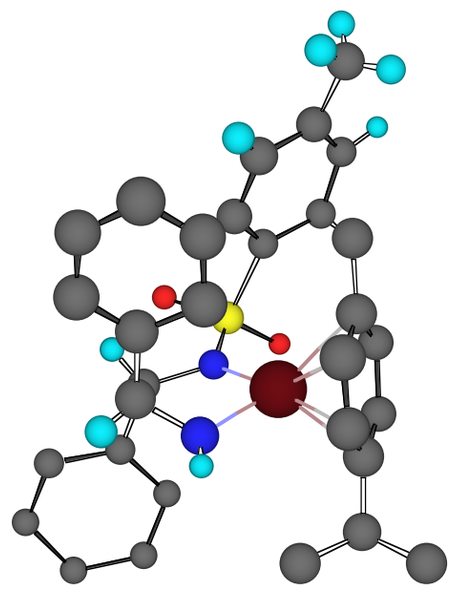
Noyori's Ru(II)-Promoted Asymmetric H Transfer: Mechanism

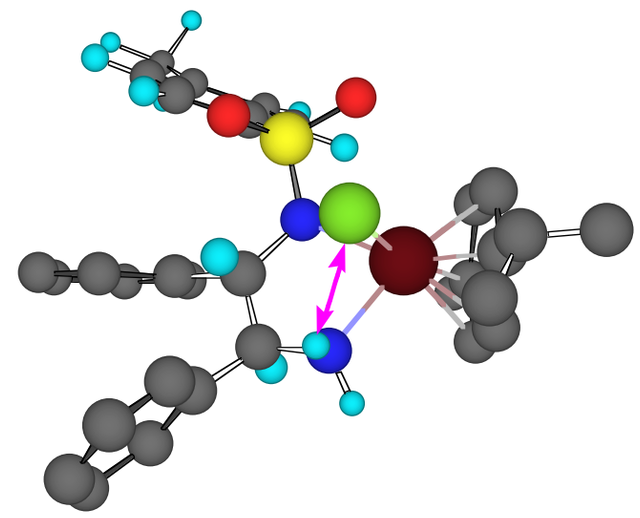
Noyori, *Ang. Chem. Int. Ed. Engl.* **1997**, *36*, 285-288



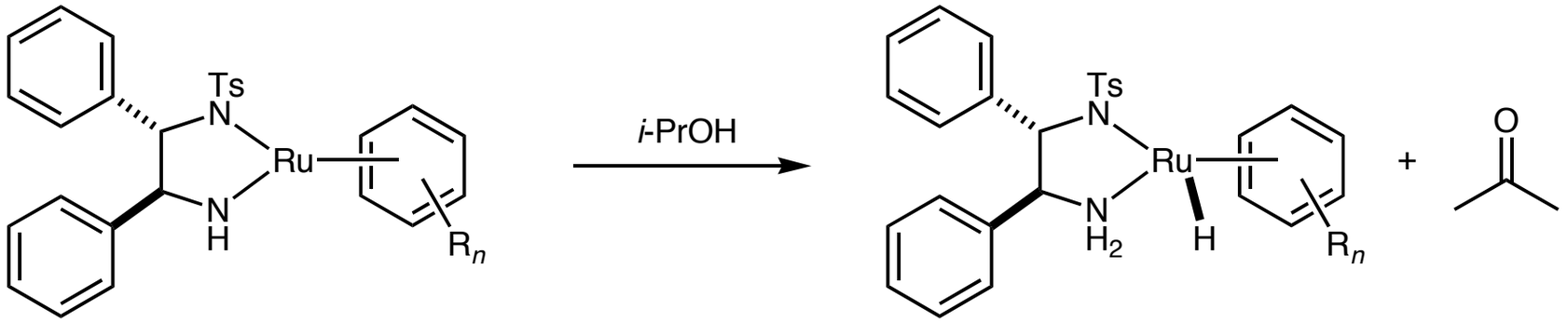
16-electron complex

18-electron complex

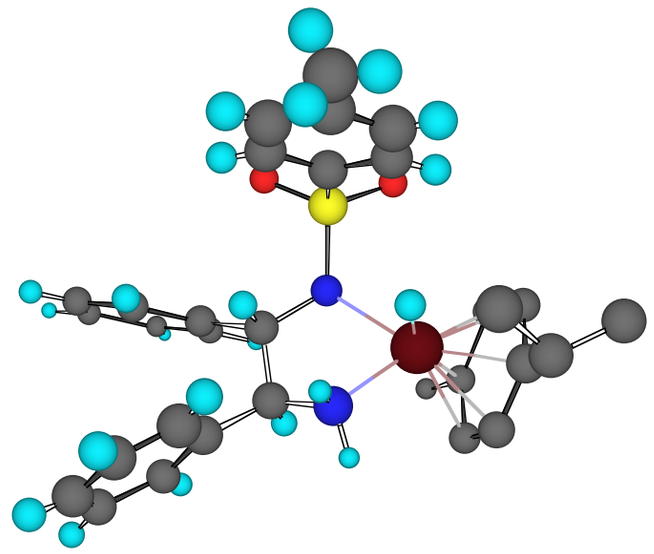




Structure of the Activated, Reactive Catalyst



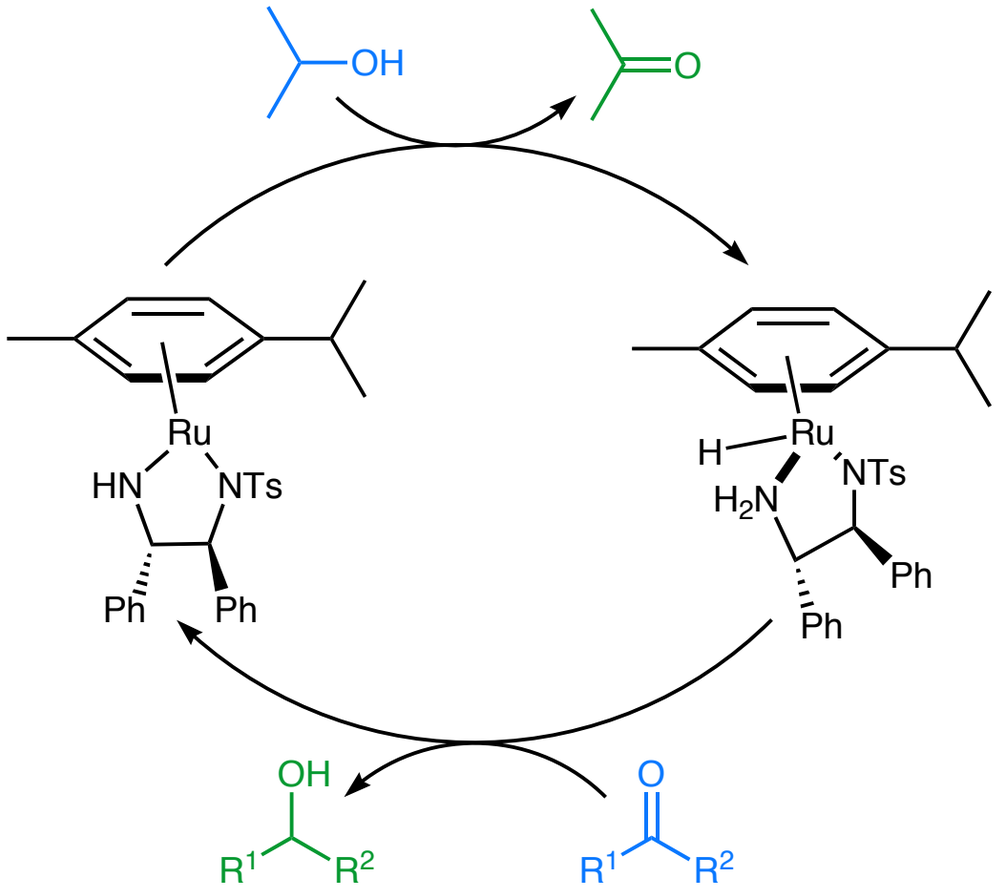
16-electron complex

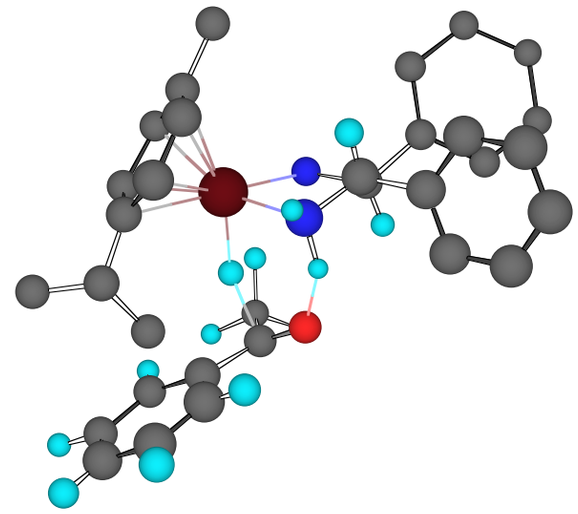


Reversible reaction; with formic acid/triethylamine: irreversible reduction

Catalytic Cycle and Proposed Transition Structure

Oxidation of stoichiometric reagent: reductionof the catalyst





Reduction of the substrate: oxidation of the catalyst

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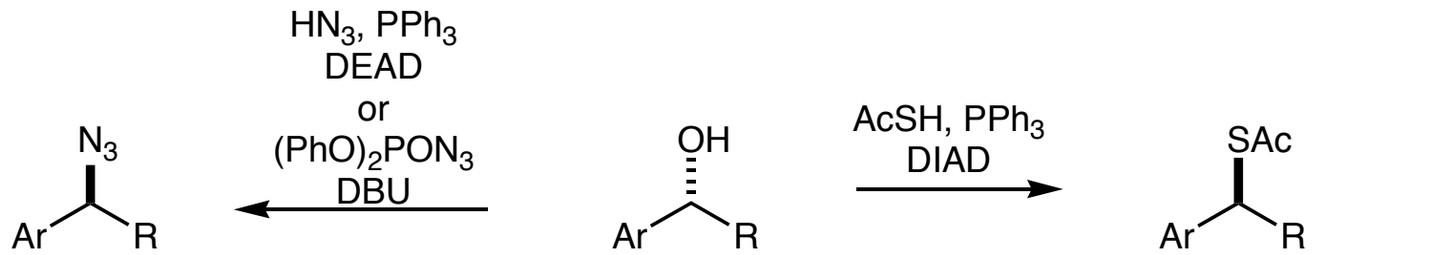
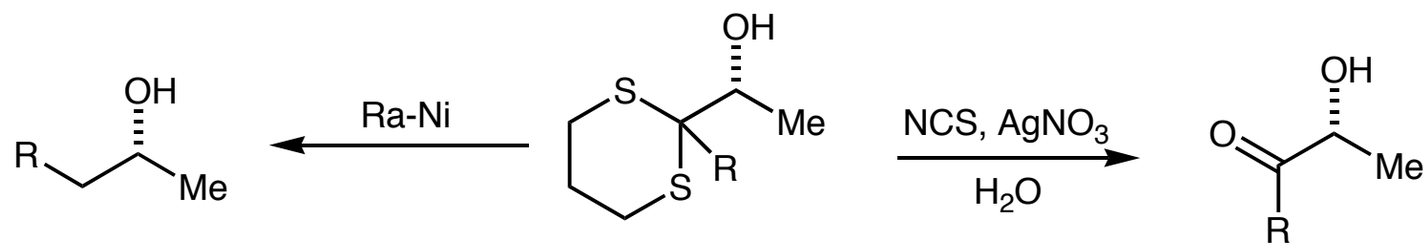
Mitsunobu inversion:
(review on Mitsunobu reaction: Hughes, D. L. *Organic Reactions* **1992,** ***42***, 335-656.
Org. Prep. Proced. Int. **1996**, *28*, 127-164)



TL **1991**, 7175
JOC **1993**, 5886

Tet. Asymm. **1997**, 1773
TL **1994**, 1087



TL **1990**, 7415
TL **1992**, 4967

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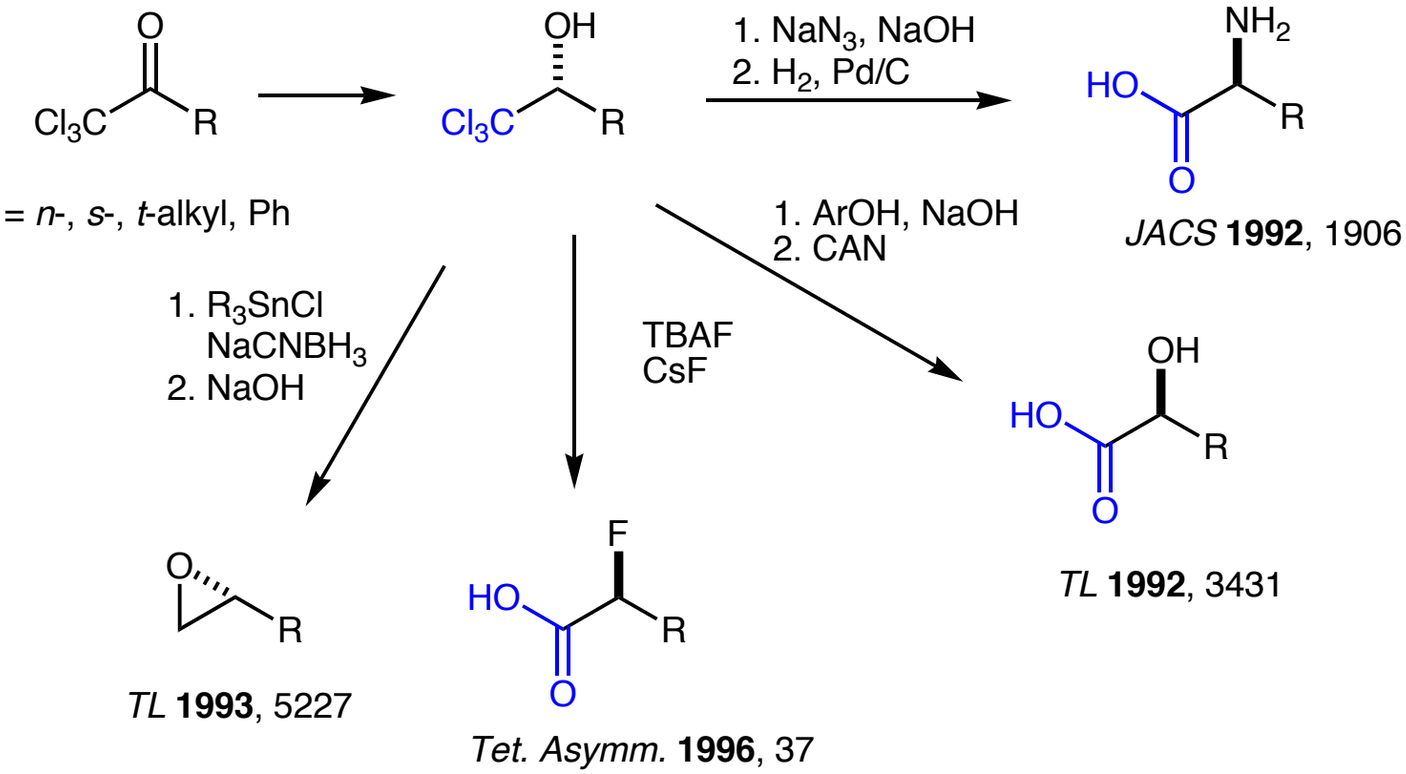
TL **1992**, 3435



R = *n*-, *s*-, *t*-alkyl, Ph

JACS **1992**, 1906

TL **1992**, 3431

TL **1993**, 5227

Tet. Asymm. **1996**, 37