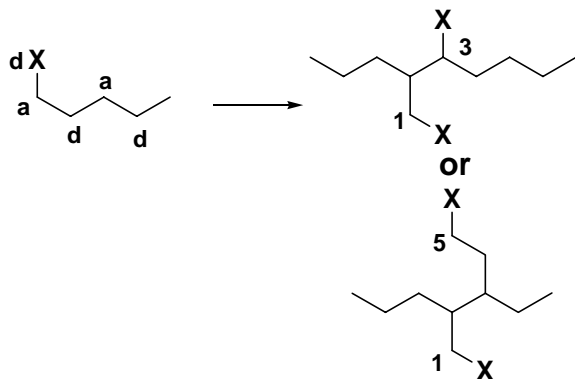


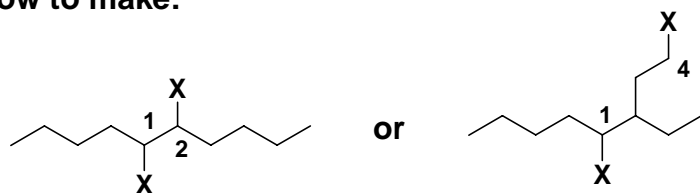
Reactivity Umpolung: reversal of normal polarity
 electrophiles become nucleophiles
 nucleophiles become electrophiles

Normal reactivity:

x = heteroatom
 d = donor (Nu^-)
 a = acceptor (E^+)



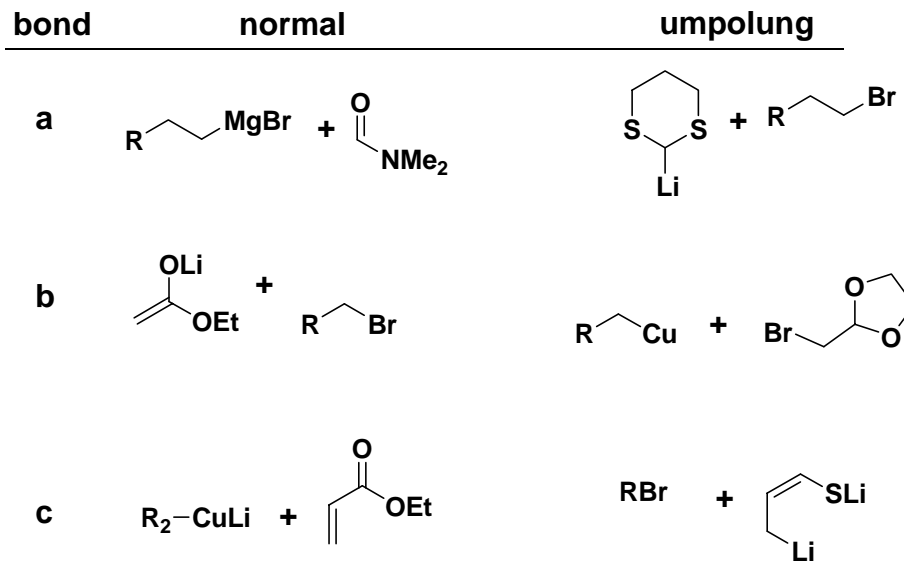
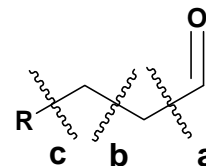
How to make:



Outline:

1. electrophilic heteroatoms
2. acyl anions
3. homoenolates
4. the cyclopropane trick
5. sulfone chemistry

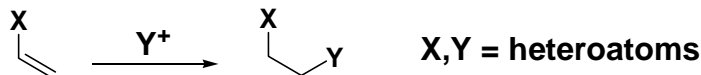
complimentary disconnections



General Review: ACIEE, 1979, 239
 Carey and Sundburg, sec 13.2

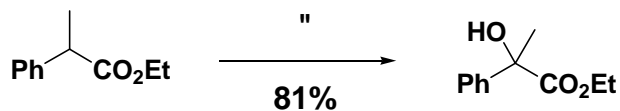
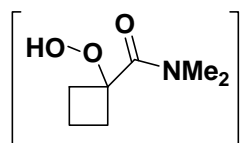
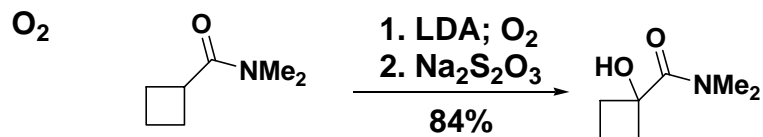
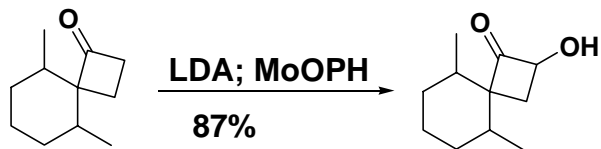
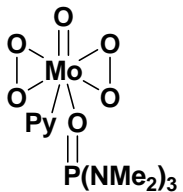
Electrophilic Heteroatoms

General form:



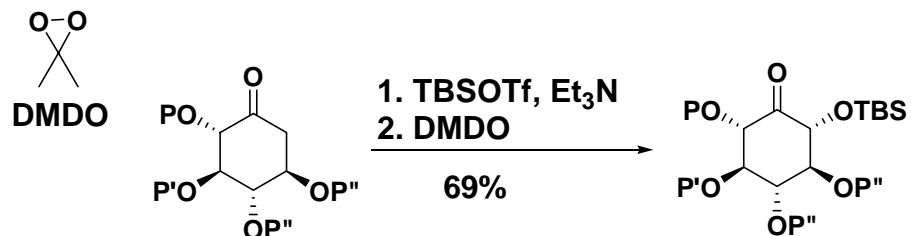
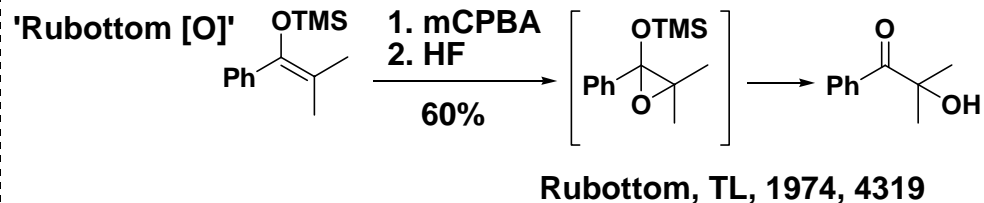
Electrophile

Examples


 Wasserman and Lipshutz
TL, 1975, 1731


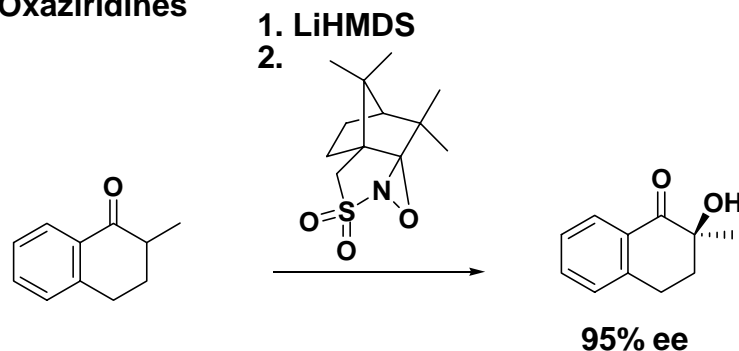
Vedejs, JOC, 1978, 188

mCPBA



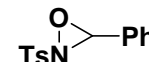
Falck, JOC, 1995, 3385

Oxaziridines



Davis, Chem. Rev. 1992, 919

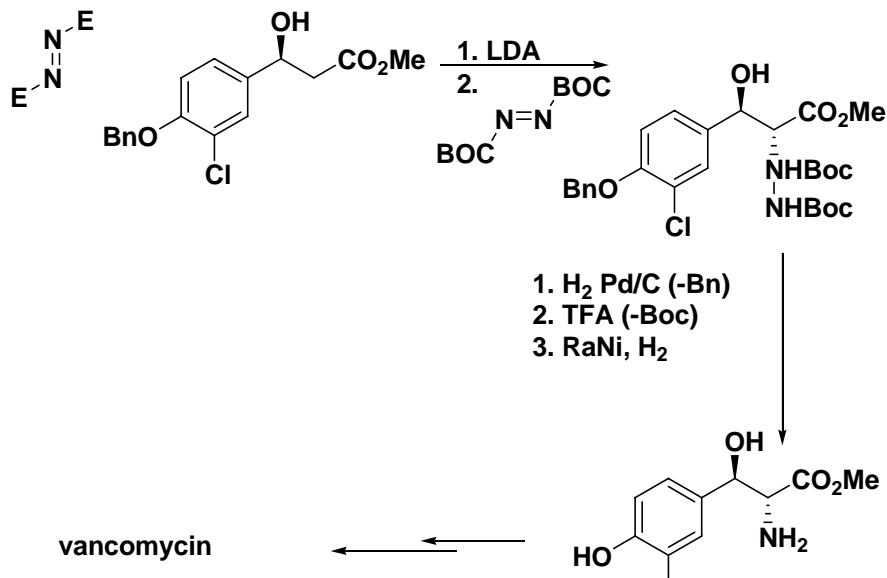
not a general asymmetric method. For racemic, most commonly used is 'Davis Oxaziridine'



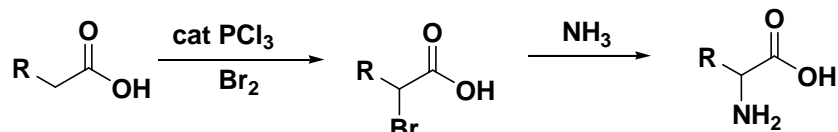
Aminations (Review: Syn Lett, 1997, 741)

Electrophile

Examples

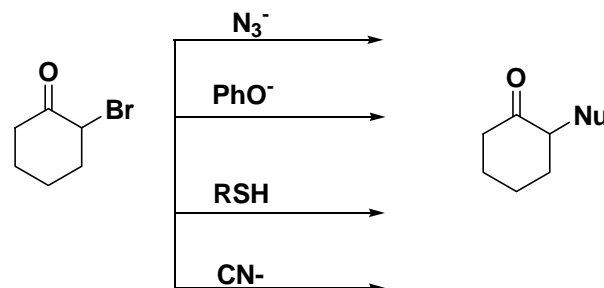


Heteroatom exchange: Most commonly with Br, Cl

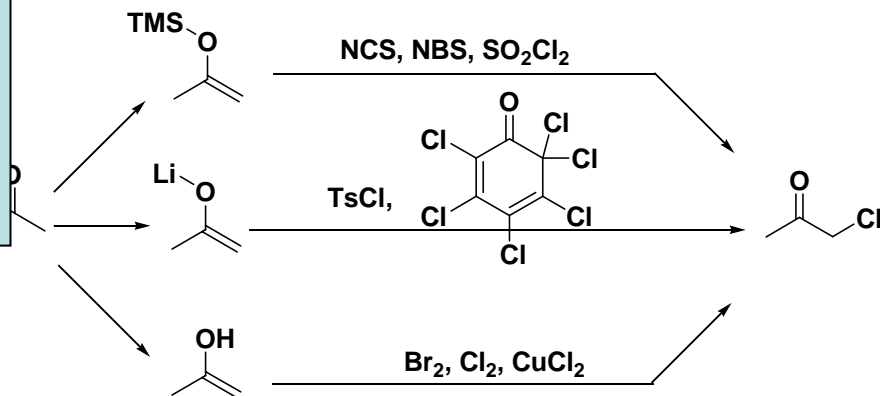


can you name this rxn?

α -halo carbonyls are excellent electrophiles (recall S_N2 rxn accelerated by either electron withdrawing or electron releasing groups)

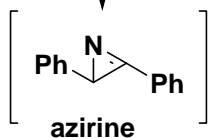
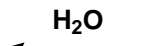
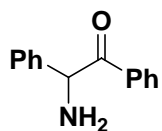


Synthesized from enolate (or equiv) and electrophilic halogen:



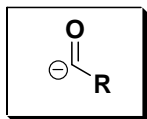
Lead references: Brummond, TL, 1999, 2231;
enantioselective chlorination: Jorgensen, ACIEE, 2004, 5507

Include stoltz use of neber in dragmacidin,
JACS, 2005, 5970

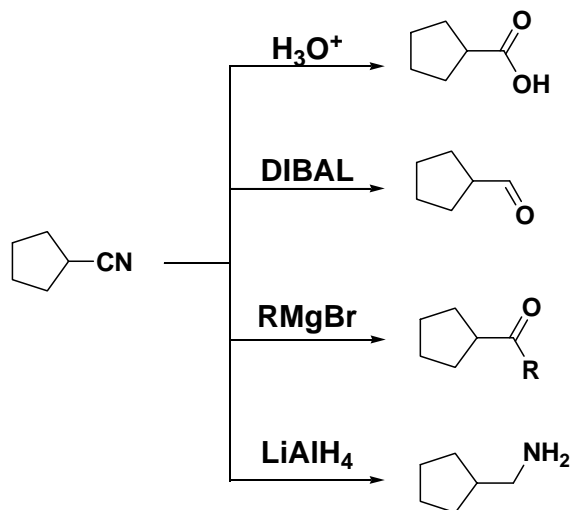
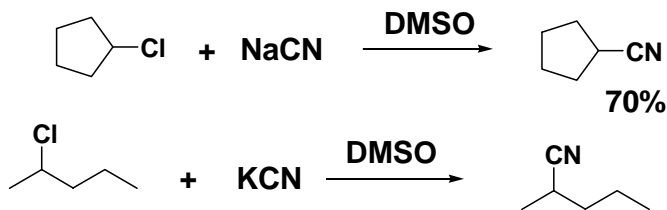


Maruoka, JACS, 2002, 7640

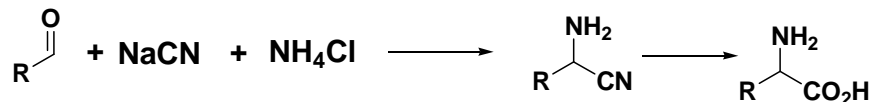
Acyl anions are the most sought umpolung reagents



Cyanide: Super nucleophile (small, non-basic), can be converted into amine, aldehyde, acid, ketone.

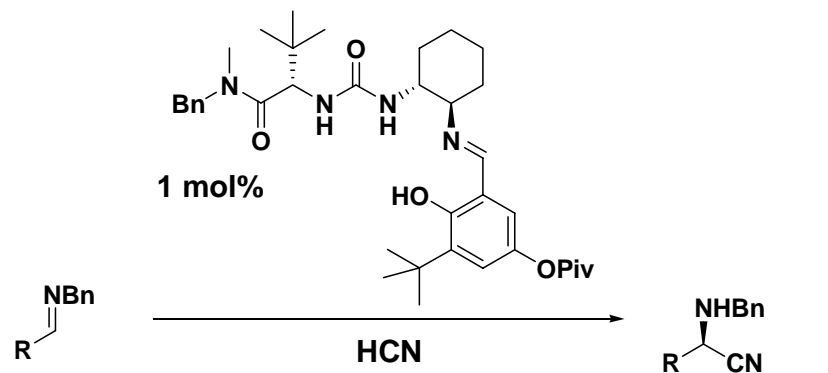


Strecker amino acid synthesis: One of the oldest and most effective ways to make amino acids



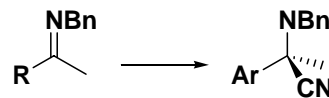
Recently has become hot topic for asymmetric catalysis.
Review: Chem Rev. 2003, 2795

Jacobsen JACS 2002, 10012



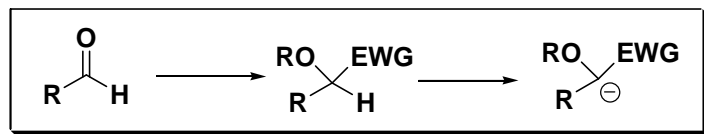
R	%ee
Ph	99
iPr	97
tBu	99
nPent	96

With keto-imines

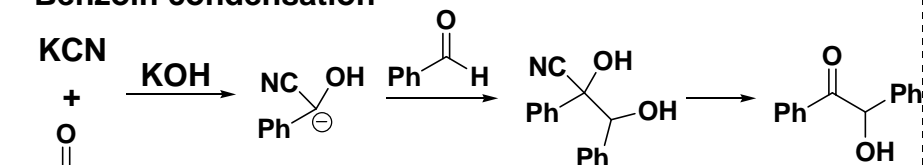


ee's 88-95 for 3- or 4-substituted Ar

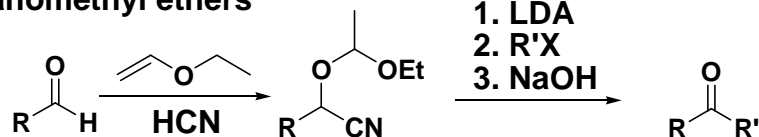
Increasing the acidity of the formyl proton



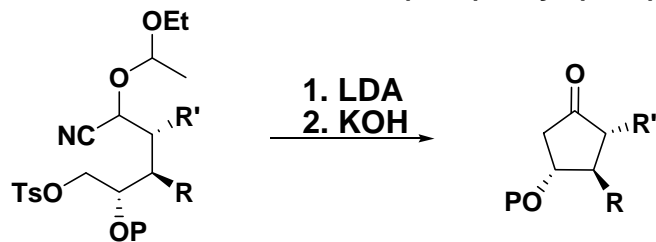
Benzoin condensation



Cyanomethyl ethers



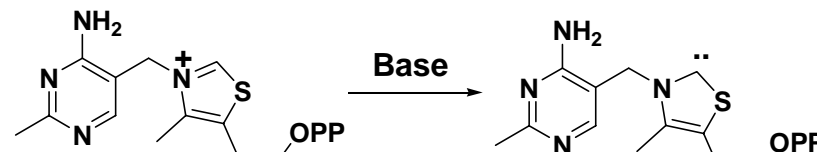
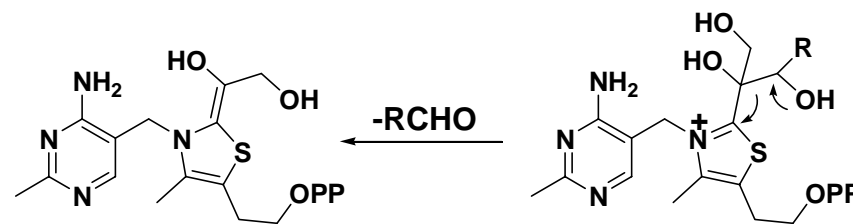
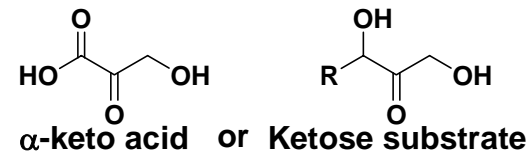
Stork, JACS, 1971, 5286

 R=Me; R' = n-hex (85%)
iPr (80%); allyl (76%)


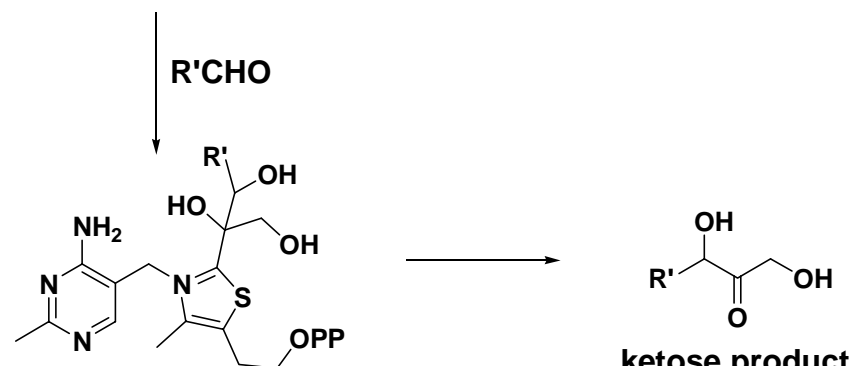
Related Chemistry:


 Review: Chem. Soc. Rev
2000, 359

Nature uses carbenes:


 Vitamin B1 (thiamine)
Coenzyme: thiamine pyrophosphate


enamine intermediate

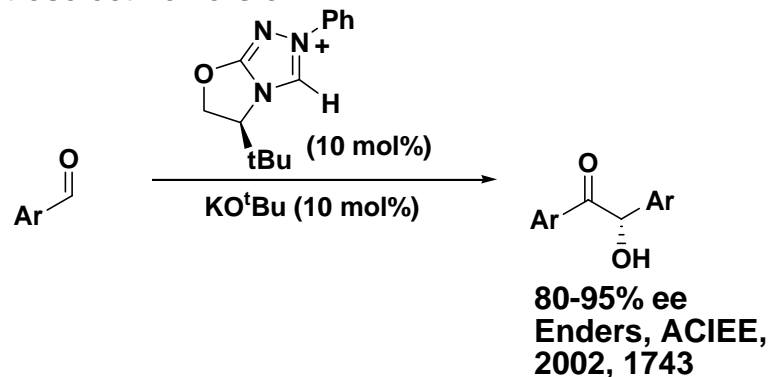


ketose product

In the lab: Review: Org. Rxn. 1991, 407; ACIEE 2004, 1326

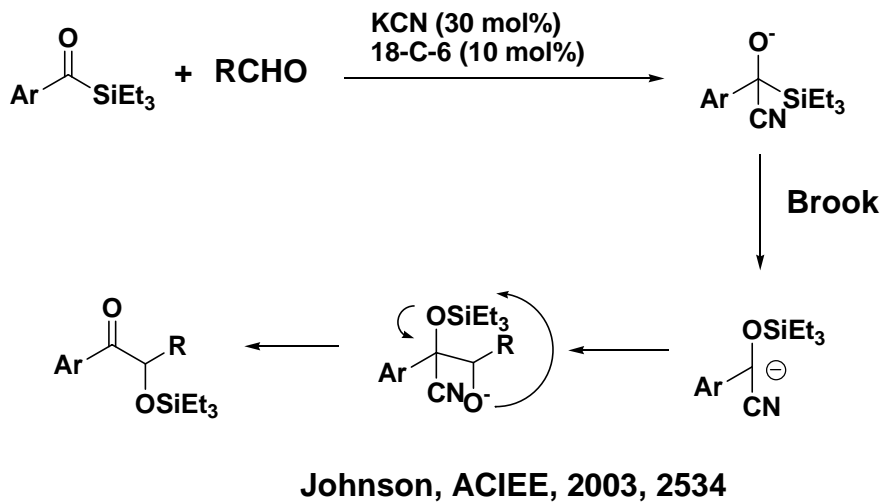
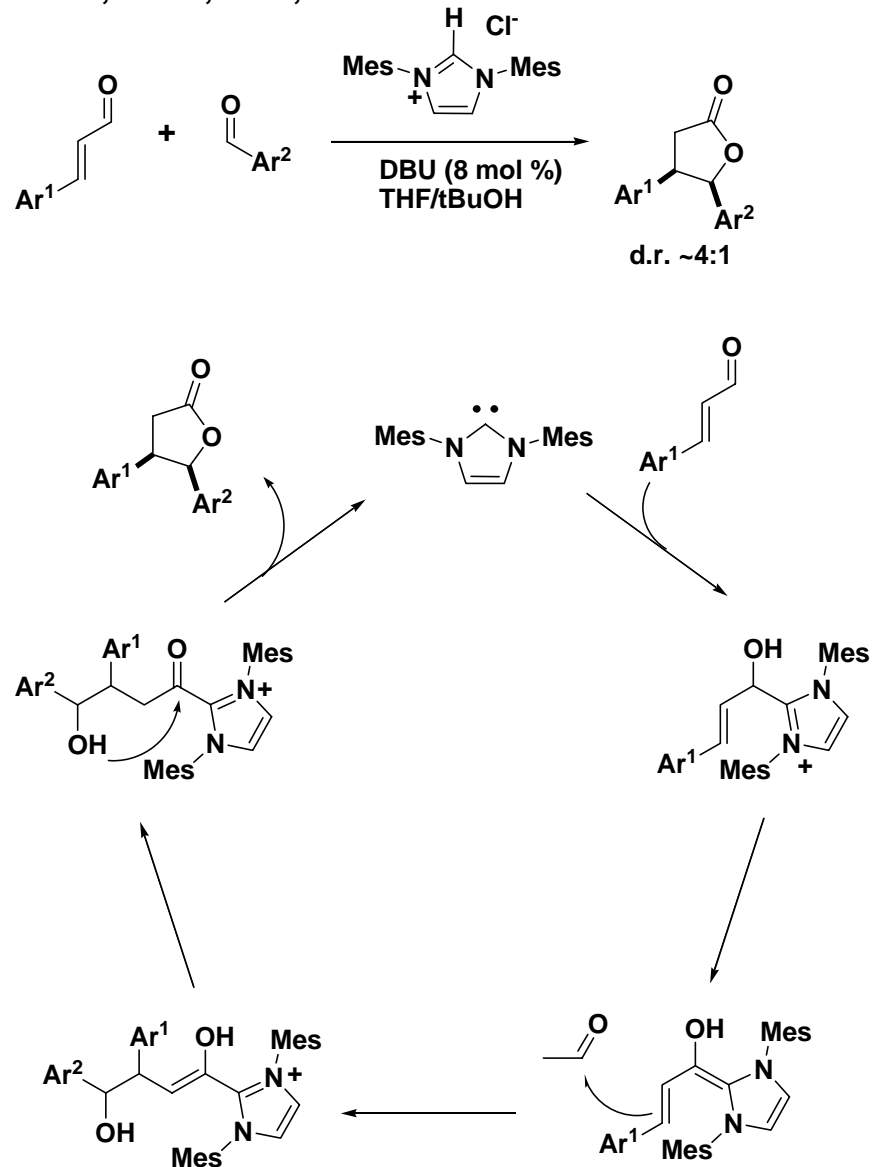
Benzoïn reaction

enantioselective version:



Problem: crossed benzoïn gives mixture of homo and hetero dimers.

Soln: Acyl silanes

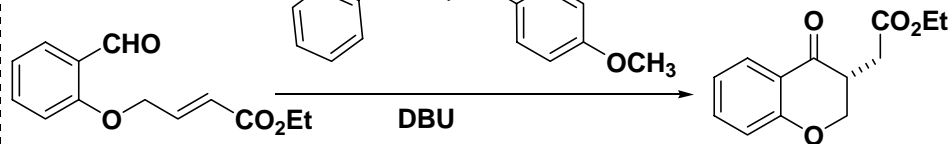

 Catalytic homoenolate generation
 Bode, JACS, 2004, 14370


Reactivity Umpolung-7a

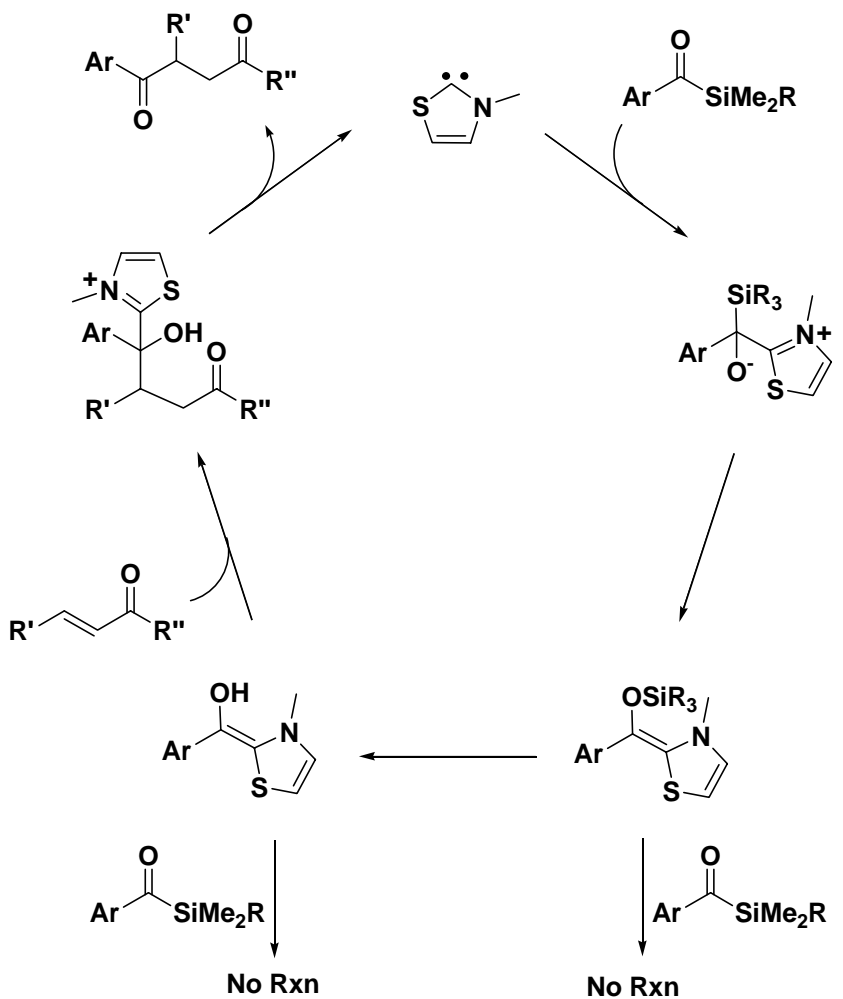
Ready

catalytic Sila-Stetter Reaction
Schiedt, JACS, 2004, 2314

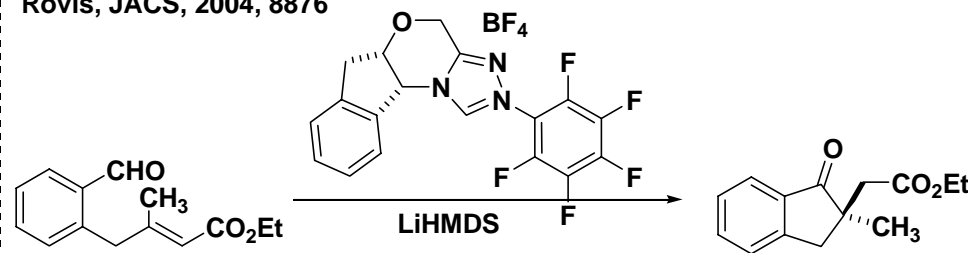
Rovis, JACS, 2002, 10298



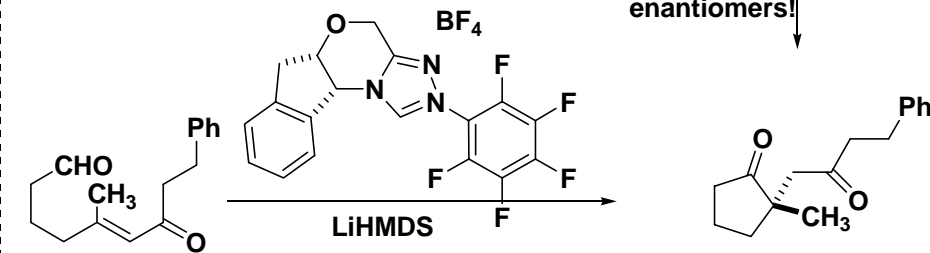
94% ee
94% y



quaternary stereocenters with activated catalyst:
Rovis, JACS, 2004, 8876



99% ee
95% y



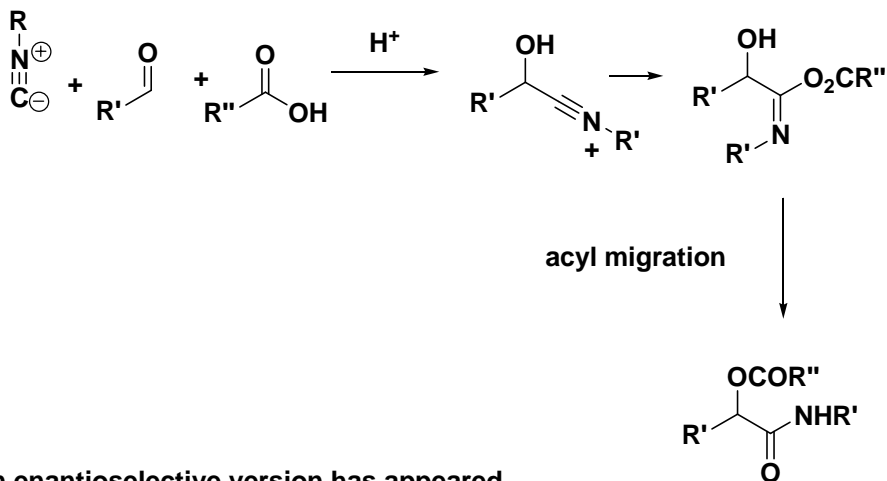
opposite enantiomers!

99% ee
63% y

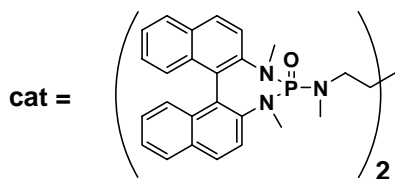
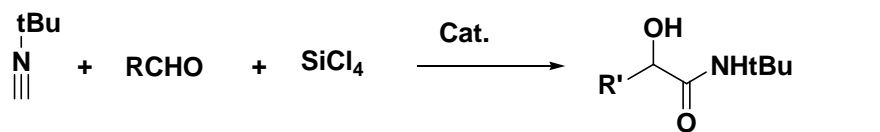
Isonitriles

Versatile C1 synthons; often act as acyl anion

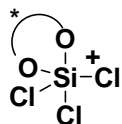
Passerini Rxn:

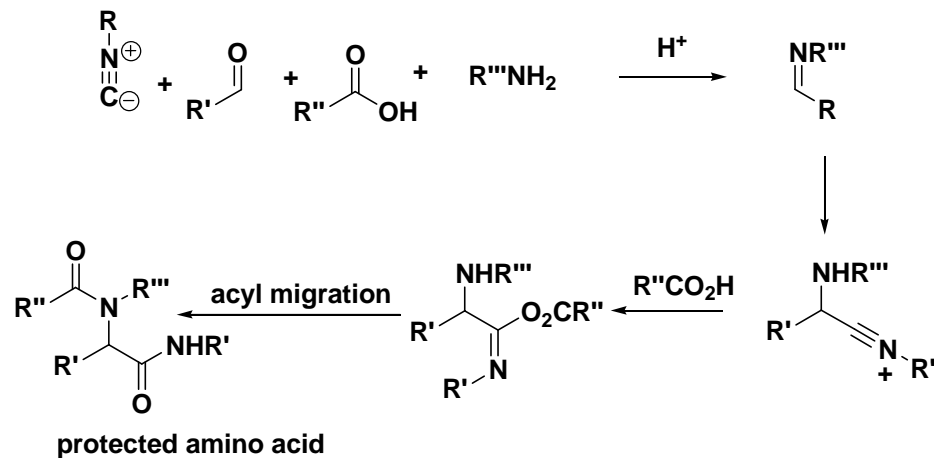


an enantioselective version has appeared

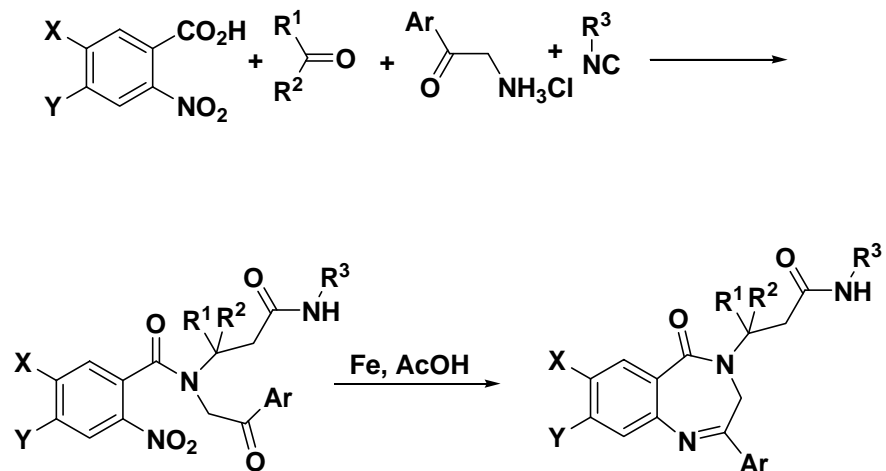


R	ee
tol	99
naphthyl	99
2-furyl	92
c-hex	64

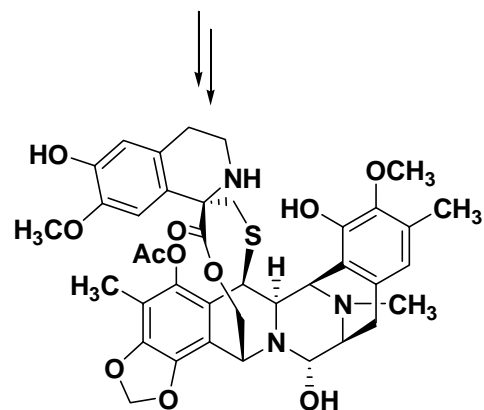
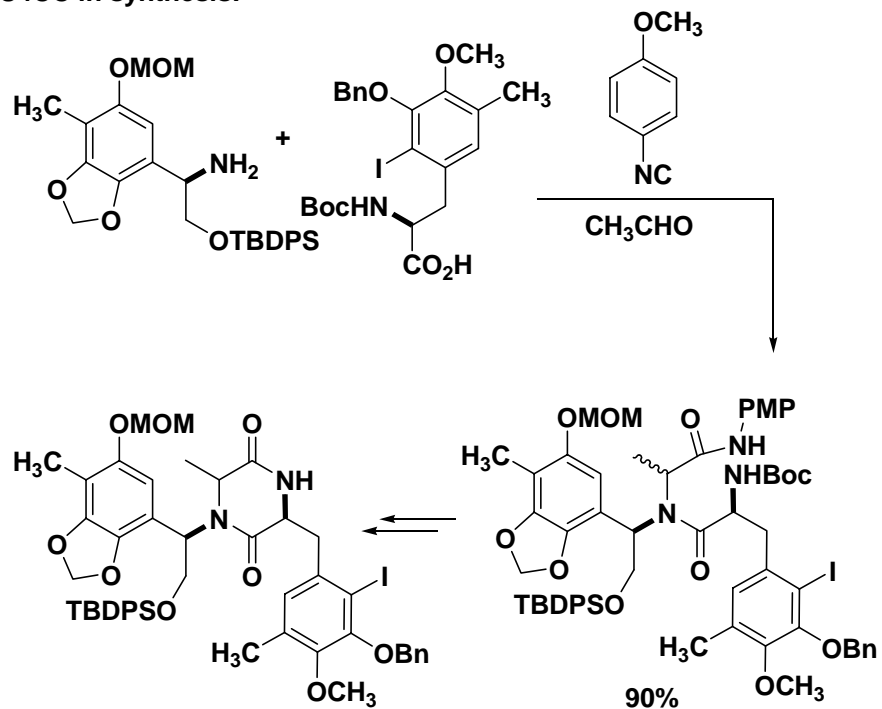
 Propose silyl cation
 lewis acid:

 JACS,
 2003, 7825

Ugi Four-component coupling (U4CC)


Has been applied extensively for library synthesis:



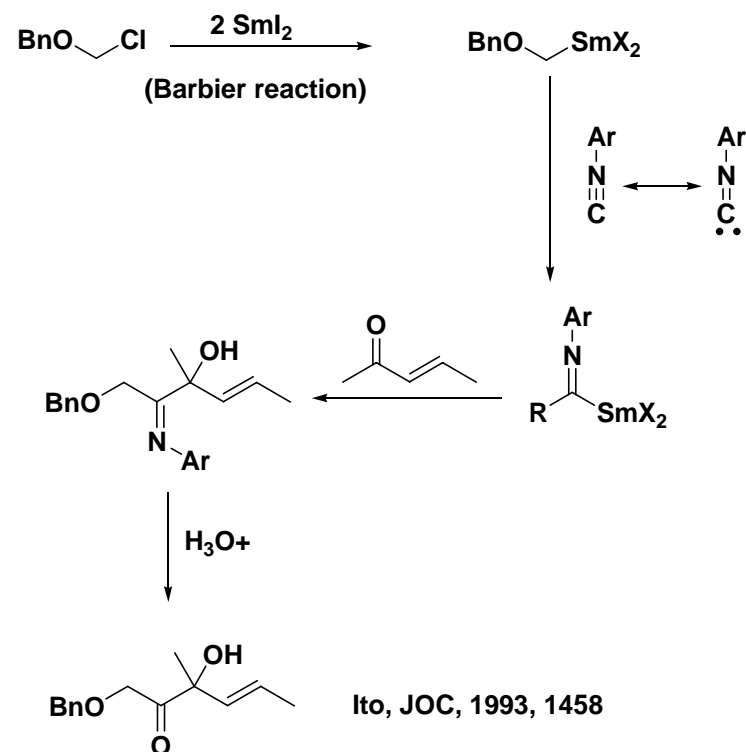
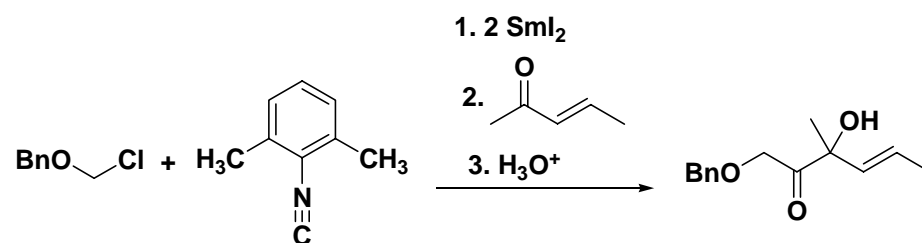
U4CC in synthesis:



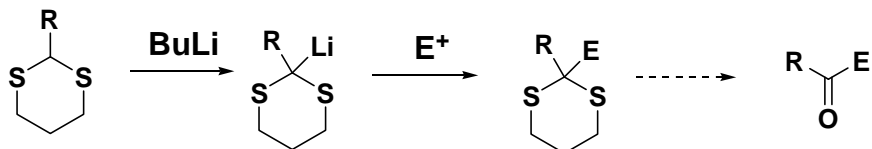
Ecteinascidin 743

 Antiproliferative ($IC_{50} = 0.2 - 1$ nM)

Fukuyama, JACS, 2002, 6552

 Isonitriles as linchpins (first as E^+ , then as Nu^-)


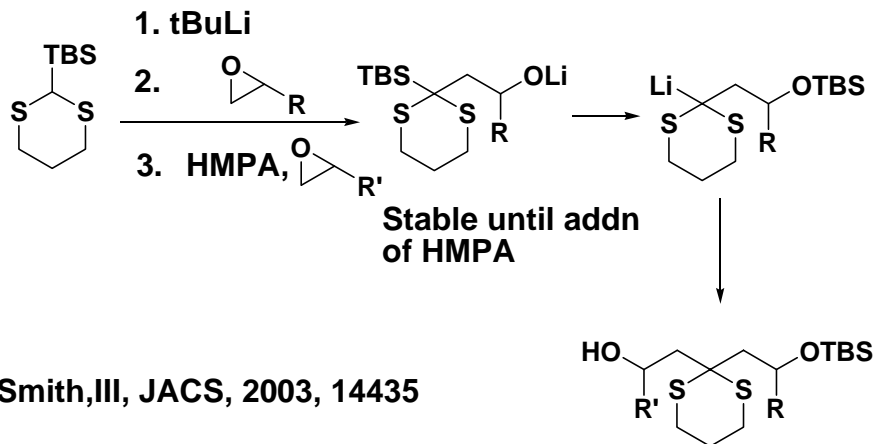
Dithiane anions



Corey, Seebach, JOC, 1975, 231

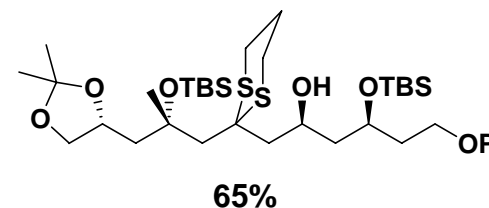
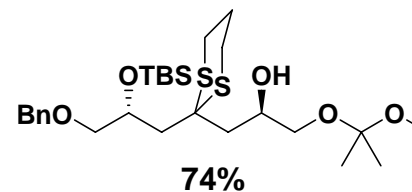
R	E	% yield
H	Et-I	85
Me	iPr-I	83
Ph	iPr-I	97
H	PhCHO	99
n-pent		95
H		77

An extension: dithianes as linchpins

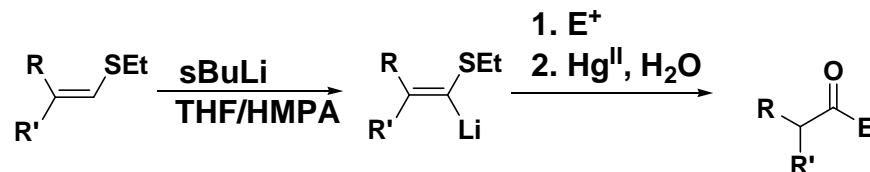


Smith, III, JACS, 2003, 14435

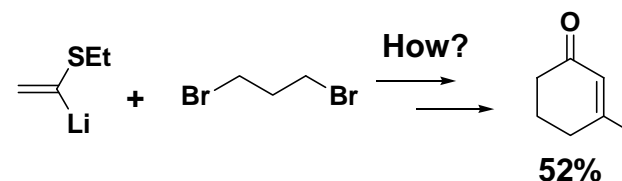
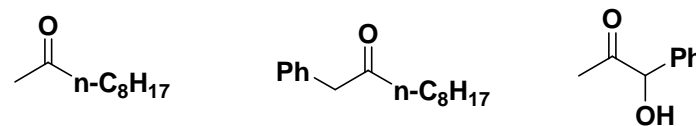
sample products:



Vinyl thioether anions

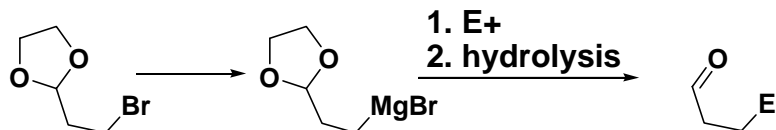
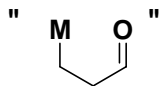


sample products:



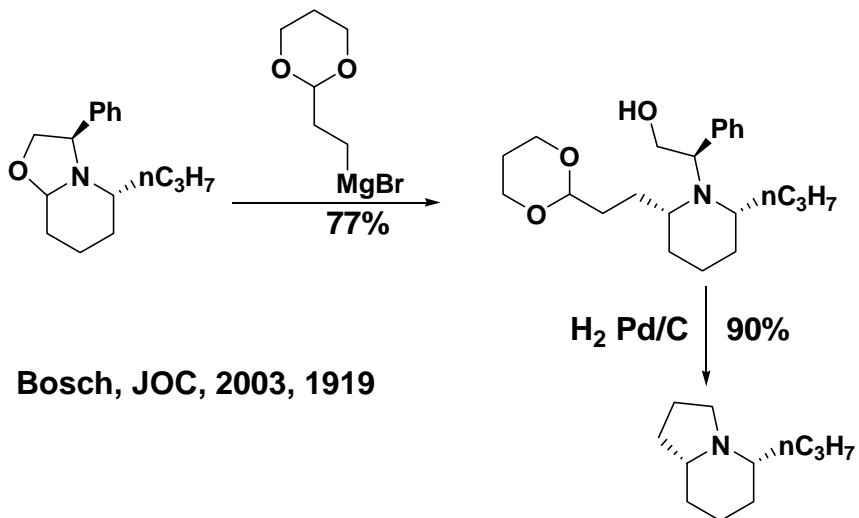
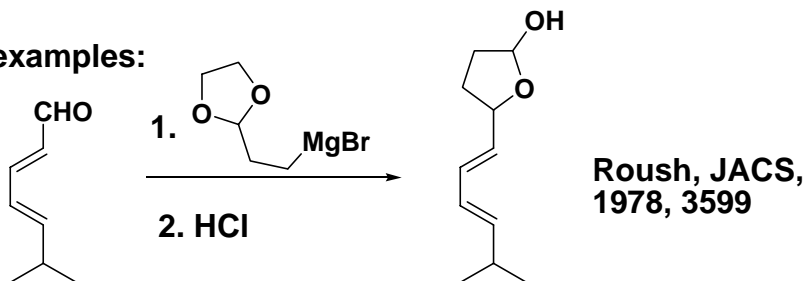
Yamamoto, JACS, 1973, 2694

Homoenoate equivalents

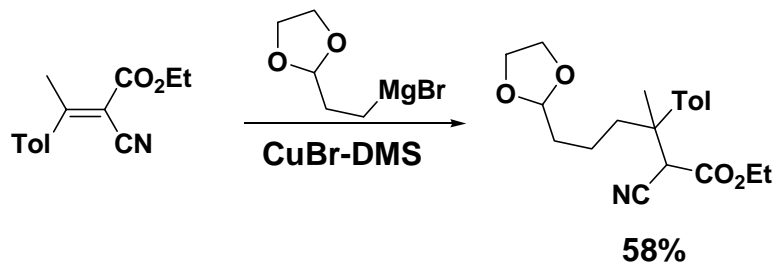


available from aldrich

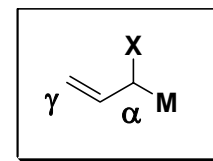
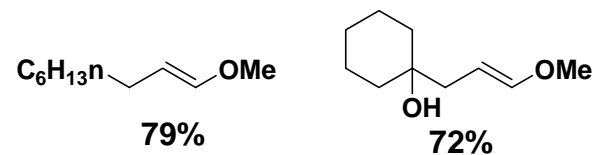
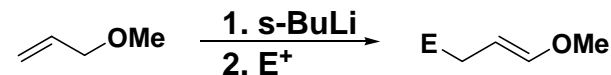
examples:



conjugate addn.

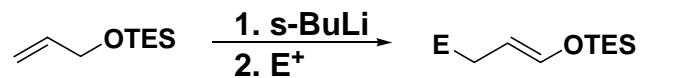


TL, 2003, 737


 Many examples. Few work well.
Selectivity (α vs. γ) usually poor


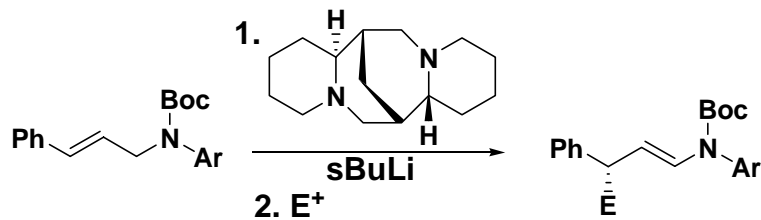
Evans, JACS, 1974, 5560

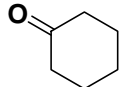
homoenolates, cont.



E	Yield (%)
Me	95
Et	83
Allyl	68

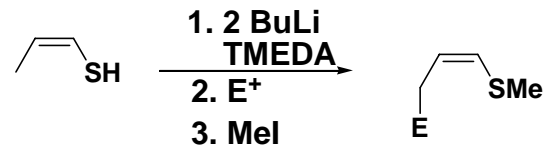
Still, JACS, 1974, 5561



E ⁺	% yield	% ee
Me	73	95
Allyl	72	94
	77	98

Review: ACIEE, 1997, 2282

Seebach:



E⁺ = n-alkyl Br
EtCHO
PhCHO
c-pentanone

yields = 65-95
α:γ = 1:3 - 1:4

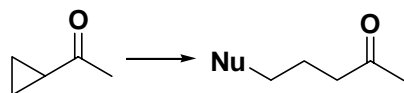
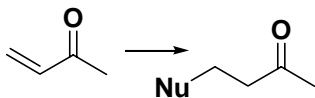
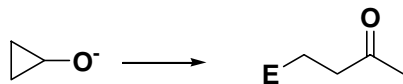
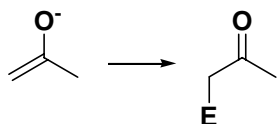
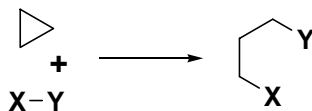
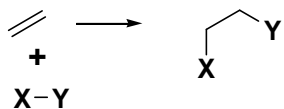
Review: Tet, 1983, 205

The Cyclopropane Trick

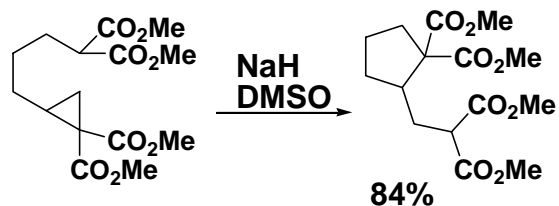
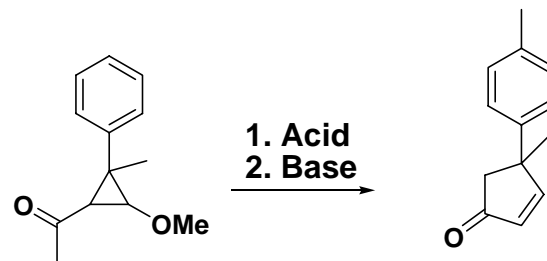
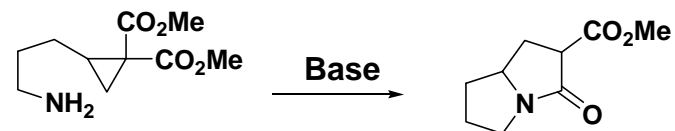
cyclopropanes convert even to odd, odd to even:

normal reactivity mode

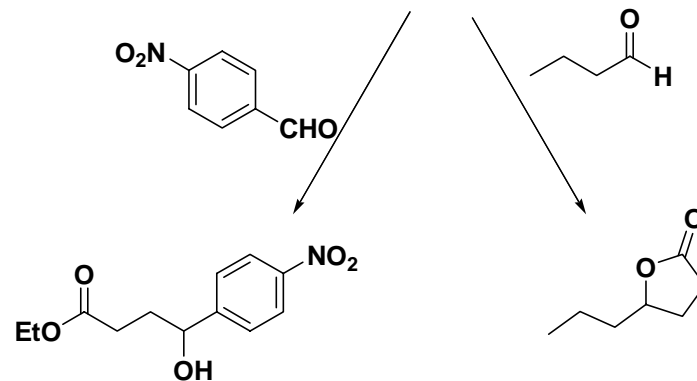
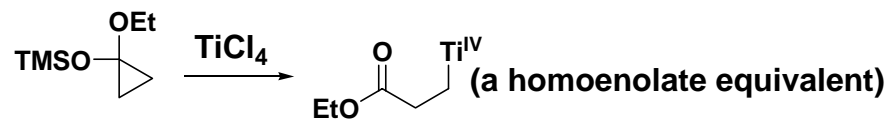
with cyclopropane



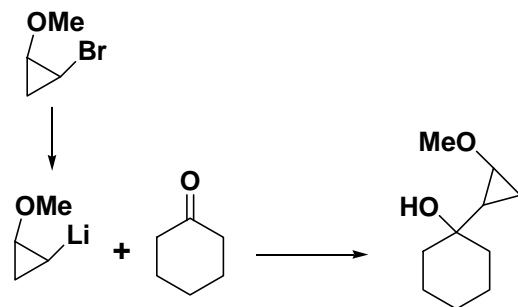
examples


 Danishefsky
 JACS, 1974, 1256


Wenkert, JOC, 1978, 1267

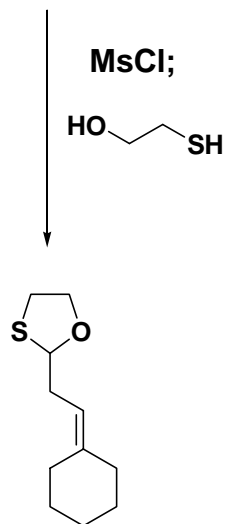


Kuwajima, JACS, 1977, 7360



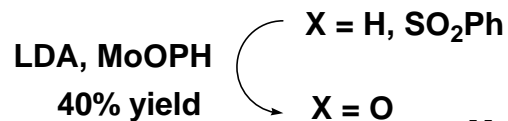
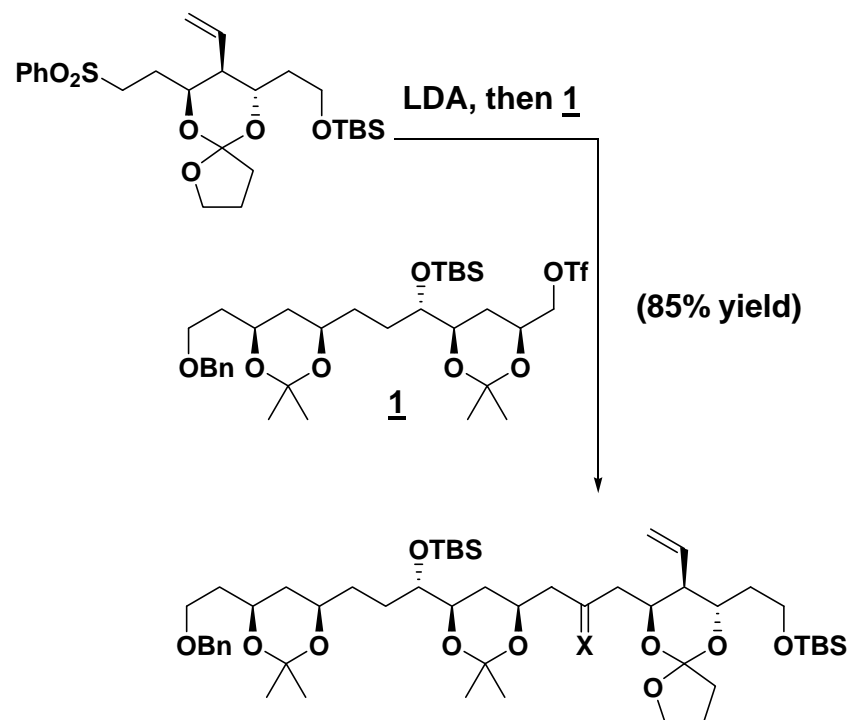
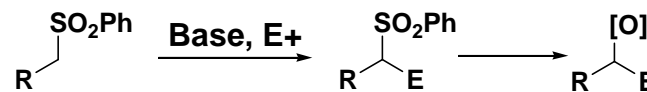
Note: leaving group β to lithium, but no cyclopropene formed from elimination

Corey, TL, 1975, 3685

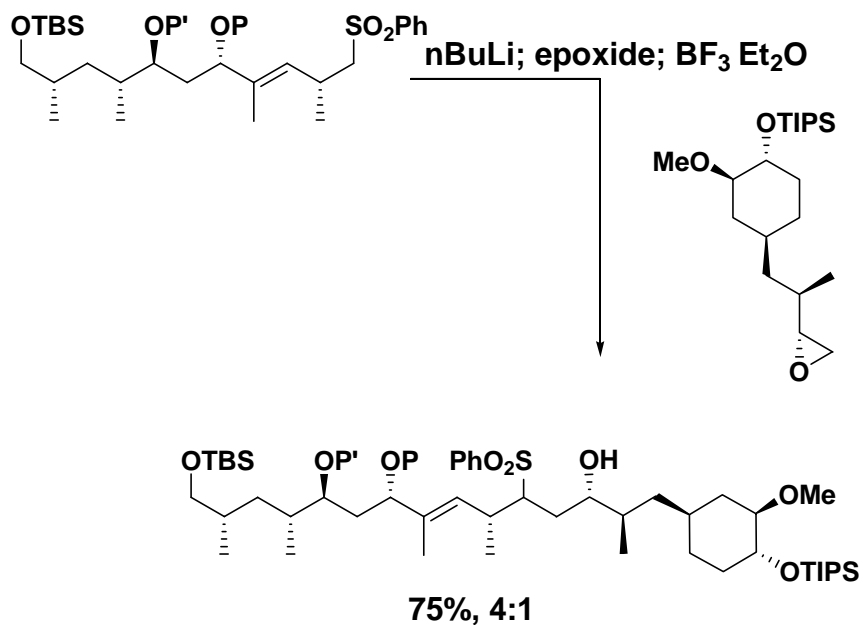


Sulfones

sulfones display amphoteric reactivity pattern:
they can be either electrophilic or nucleophilic

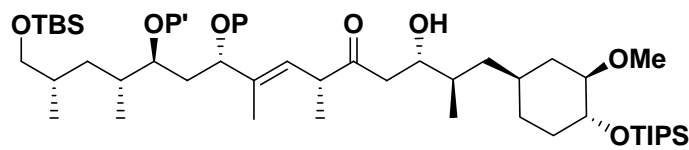


Masamune, TL, 1988, 451



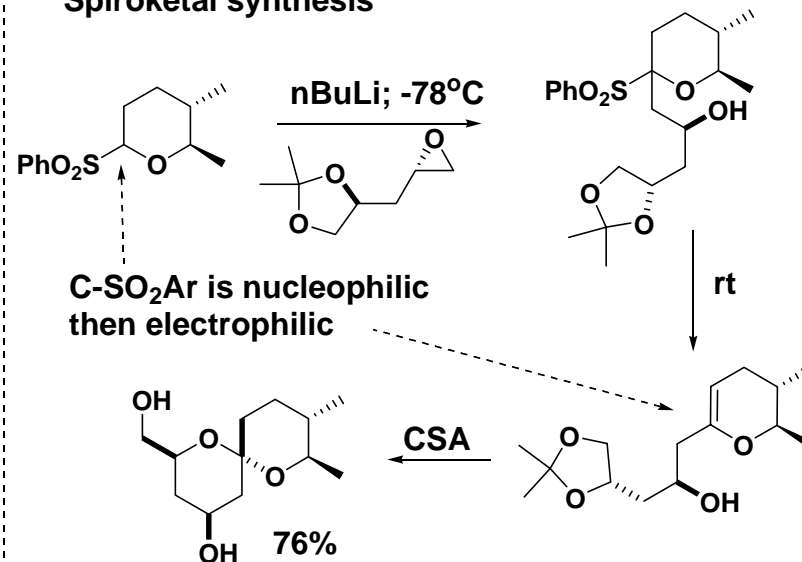
1. $\text{nBuLi; CH}_2\text{I}_2\text{-iPrMgBr}$
2. OsO_4, Pyr
3. $\text{NaIO}_4, \text{pH7}$

69%



Schreiber, JACS, 1993, 7906

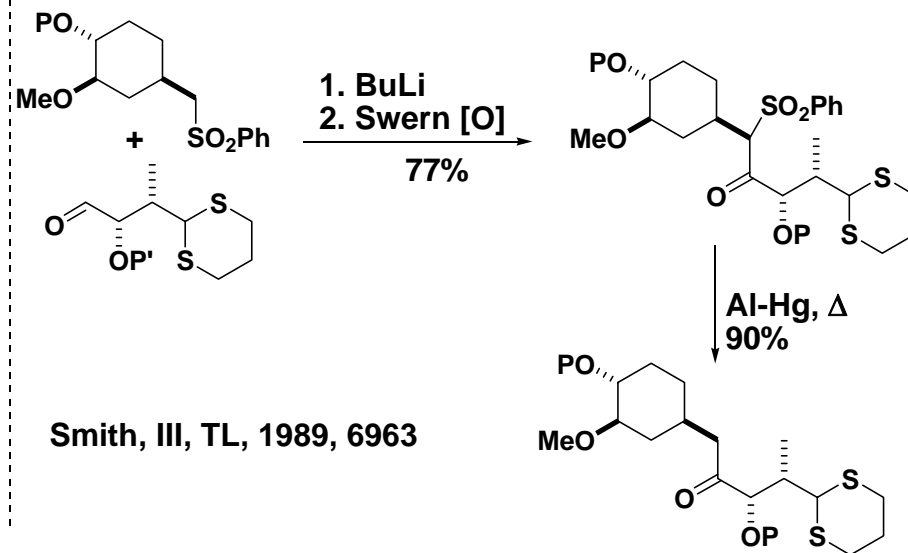
Spiroketal synthesis



Ley, TL, 1986, 5277

Perkin, 1991, 25

Strategies & Tactics in Organic Synthesis, 1991, 237



Smith, III, TL, 1989, 6963