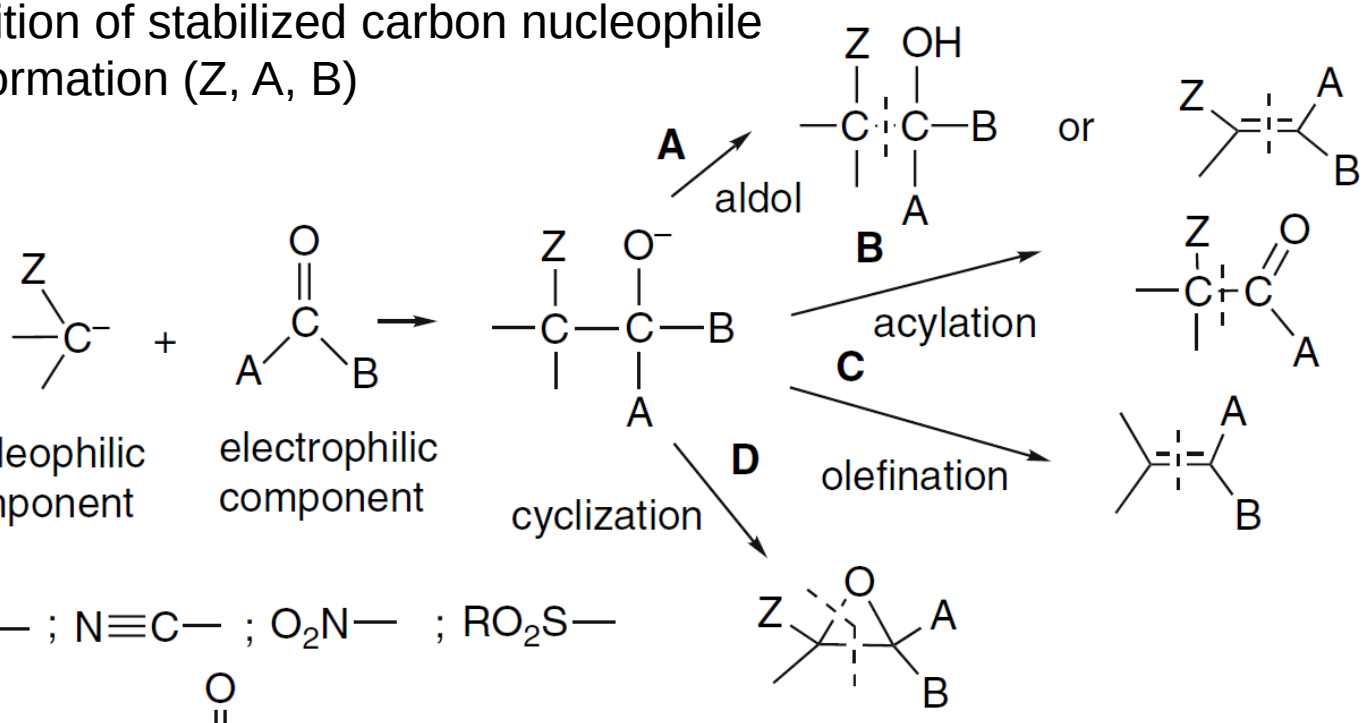
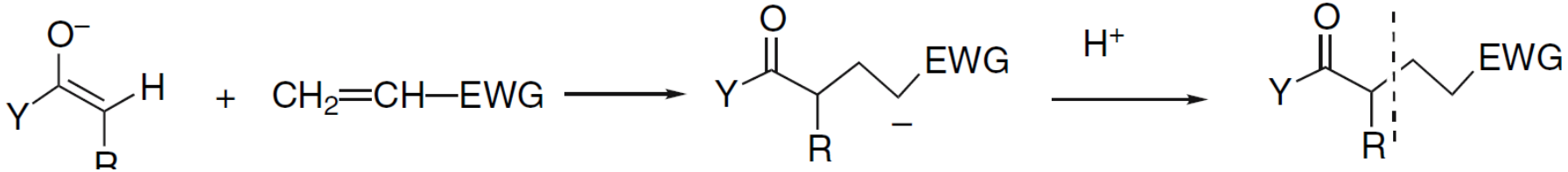
Reactions of Carbon Nu with C=O Compounds

- 1. step: addition of stabilized carbon nucleophile
- 2. product formation (Z, A, B)





Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

- hydroxylic solvents and under *thermodynamic control*
- preparation of α,β-usaturated aldehydes
- ArCHO + RCHO
- regiochemistry and stereochemistry - accomplished under *kinetic control*

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

- „*directed aldol addition*“
- one as nuclephile, one as electrophile

- kinetic control - no equilibrium

= stochiometrically generated enolate, Li^+, aprotic solvent, low temperature

- thermodynamic control

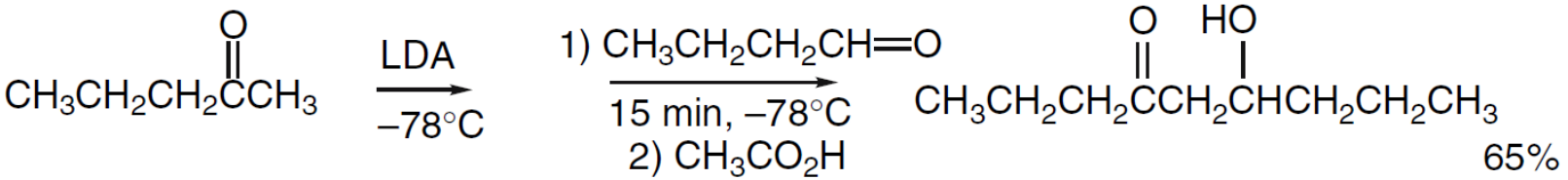
= less then 1.0 eq. of base, weakly coordinating cations, protic or polar solvents, higher reaction temperatures

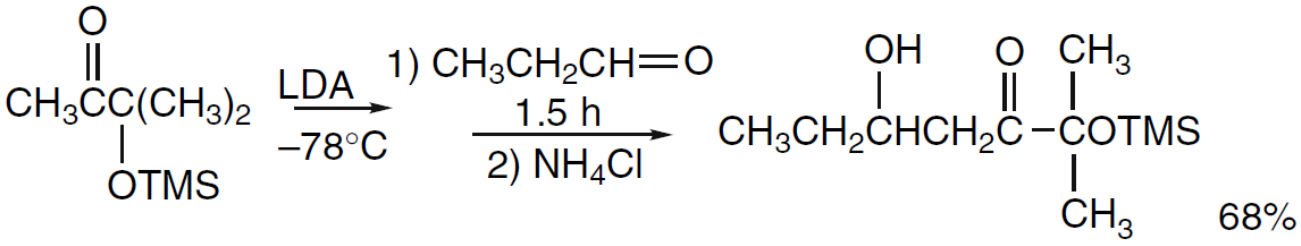
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

Examples



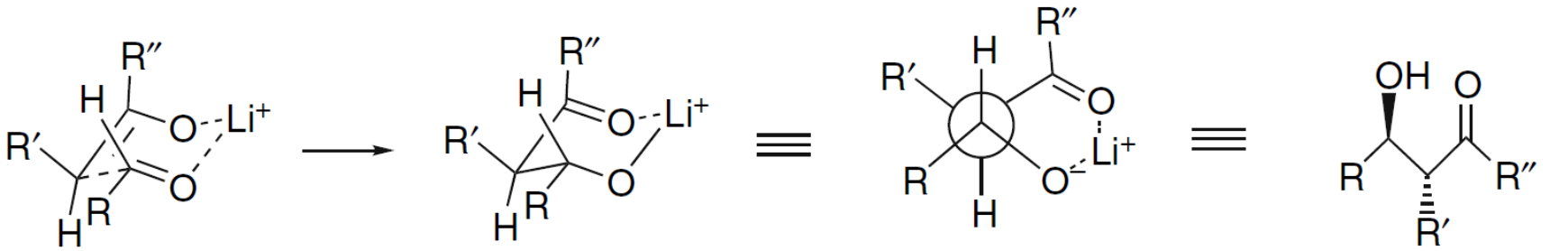


Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

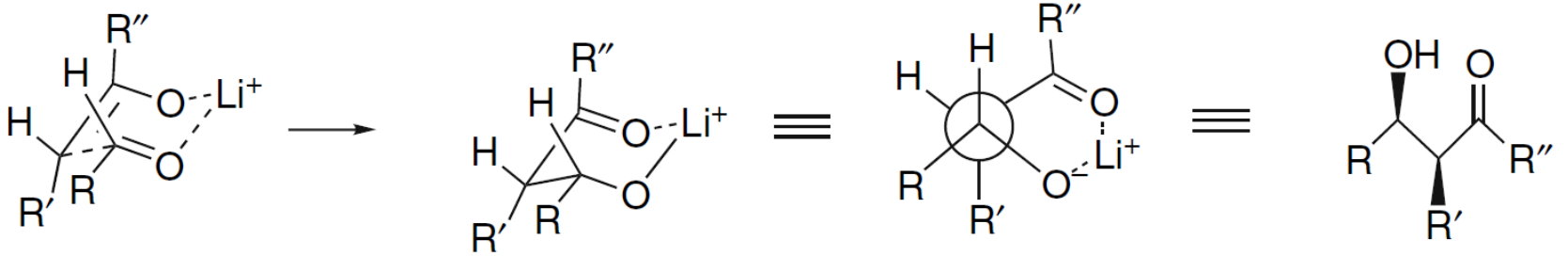
Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

- stereospecific with respect to E/Z-configuration of enolate
- *E*-enolate → *anti*
- *Z*-enolate → *syn*



E-enolate

2,3-anti product



Z-enolate

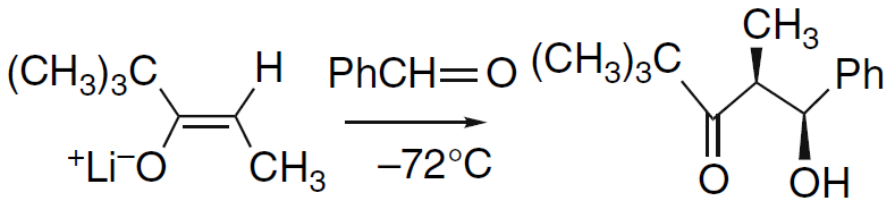
2,3-syn product

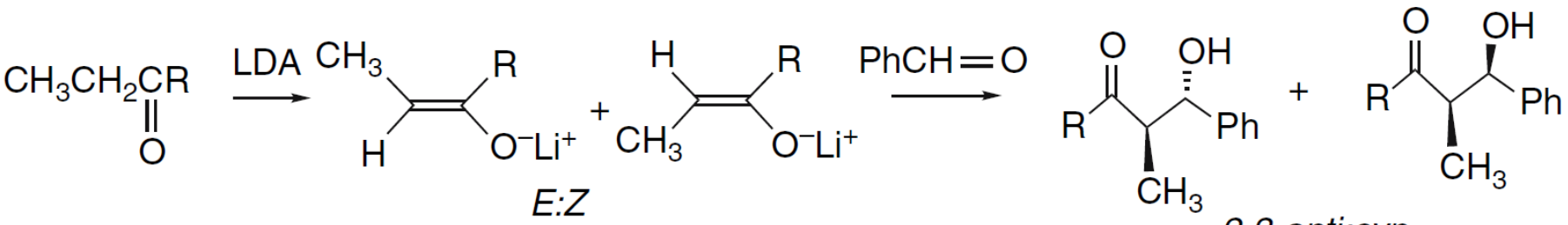
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

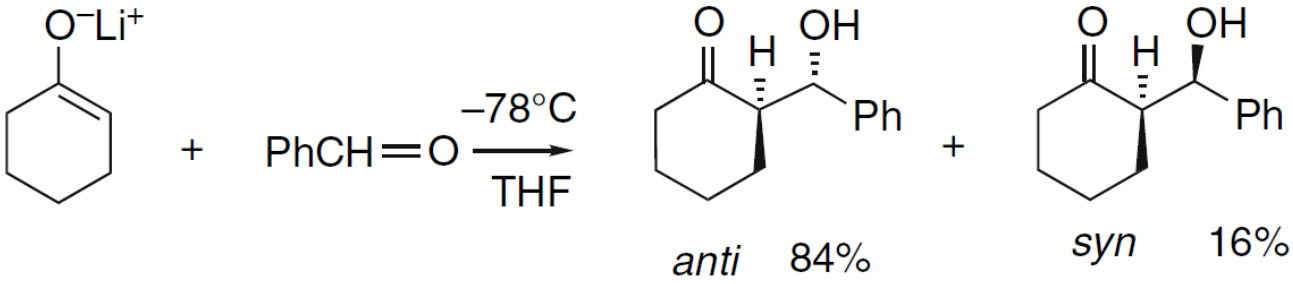
Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

Examples





R =	*E:Z*	*2,3-anti:syn*
C_2H_5	70:30	36:64
$CH(CH_3)_2$	40:60	18:82
$C(CH_3)_3$	2:98	2:98



anti 84% *syn* 16%

Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

- kinetic stereoselection in aldol additions of lithium enolates:
  (1) *Z*-enolate → *syn* aldol, *E*-enolate → *anti* aldol
  (2) no bulky substituent → low stereoselectivity
  (3) *Z*-enolates more stereoselective than *E*-enolates

- ketone with one tertiary alkyl substituent → *Z*-enolate
- less substituted ketone → mixture of *E*- and *Z*-enolates

$LiNH(C_6H_2Cl_3)$

$LiNPh_2$

$LiN(Ph)Si(CH_3)_3$

- increasing the stereoselectivity of aldol additions:
  (1) better control of enolate stereochemistry (LiBr /*E*-enolate/, aromatic amides /Z-enolate/, etc.)*
  (2) enhancement of stereoselectivity in the addition step

Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

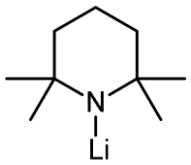
Example

	E:Z Stereoselectivity		
	LDA	LiTMP	LiTMP + LiBr
$CH_3CH_2C(=O)CH_2CH_3$	3.3:1	5:1	50:1
$(CH_3)_2CHC(=O)CH_2CH_3$	1.7:1	2:1	21:1
$(CH_3)_3CC(=O)CH_2CH_3$	1: >50	1: >20	1:>20

$LiNH(C_6H_2Cl_3)$

$LiNPh_2$

$LiN(Ph)Si(CH_3)_3$



Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

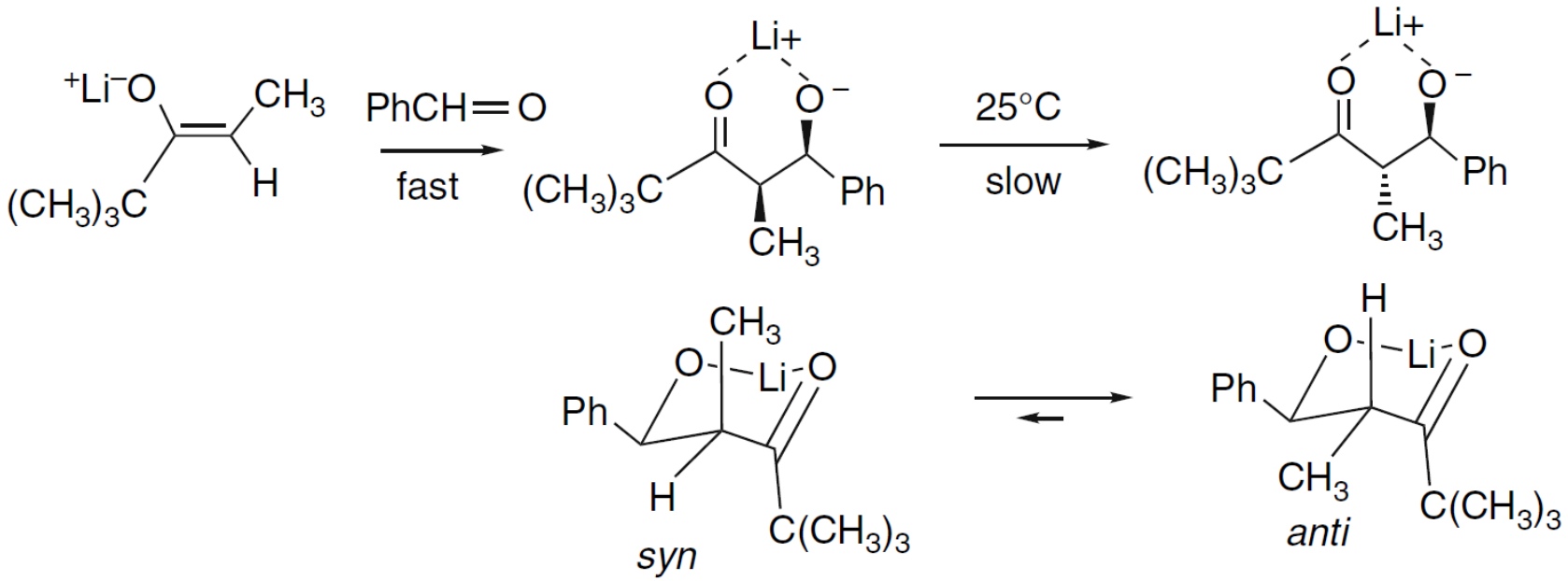
Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

thermodynamic stereoselection ($MgBr_2$)– lower:

(1) all the regio and stereoisomeric enolates can participate as nucleophiles

(2) the adducts can return to reactants → so the difference in *stability* of the stereoisomeric *anti* and *syn* products determines the product composition

Example



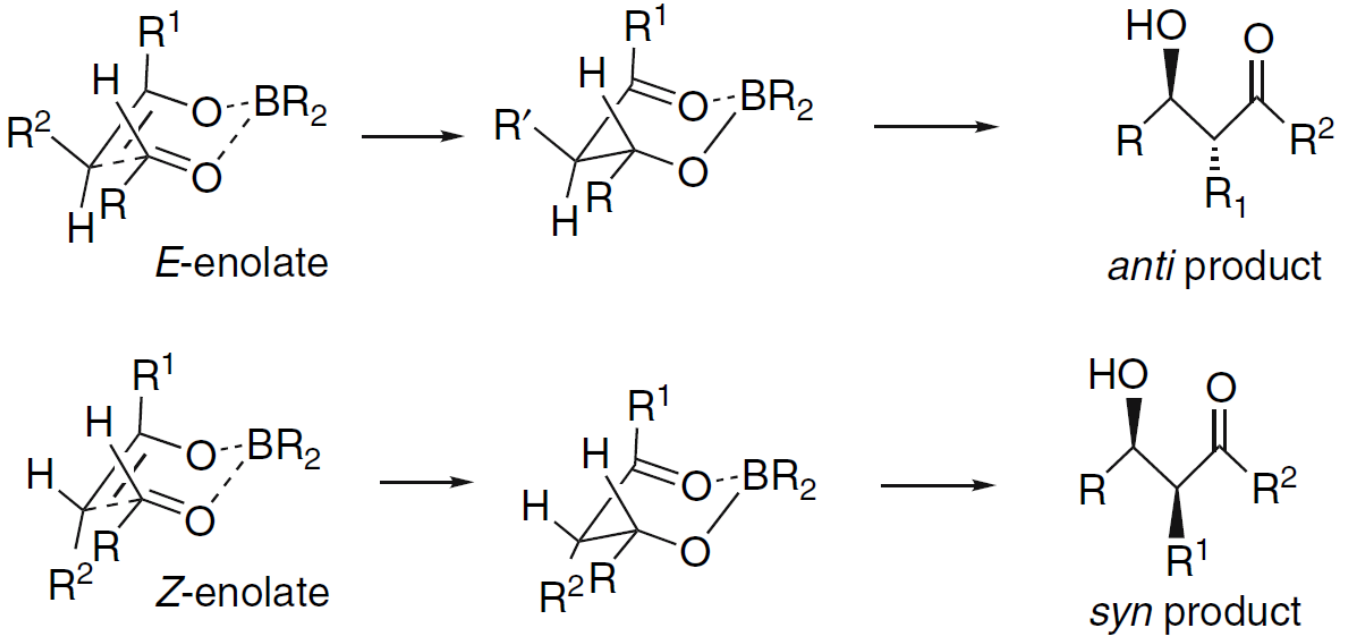
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

Aldol Reaction of Boron Enolates:

- higher stereoselectivity
- similar TS (more compact)
- *Z*-enolate → *syn* aldol, *E*-enolate → *anti* aldol
- R_2BOTf/R_3N → *Z*-enolate, R_2BX → *E*-enolate



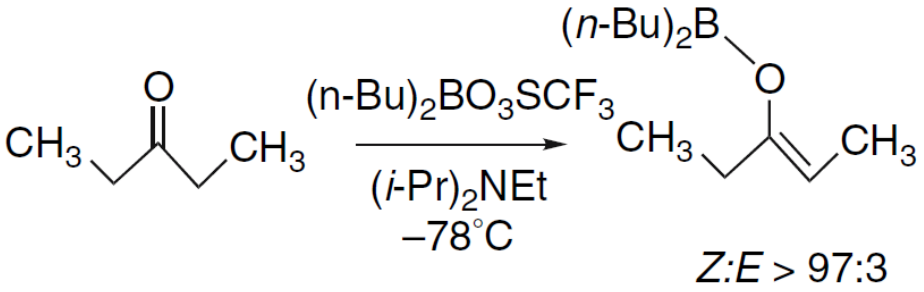
Reactions of Carbon Nu with C=O Compounds

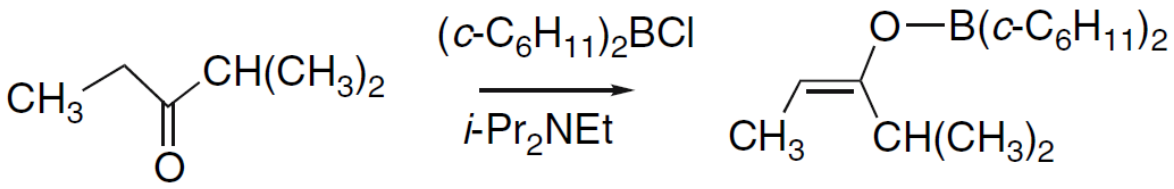
Aldol Addition and Condensation Reactions

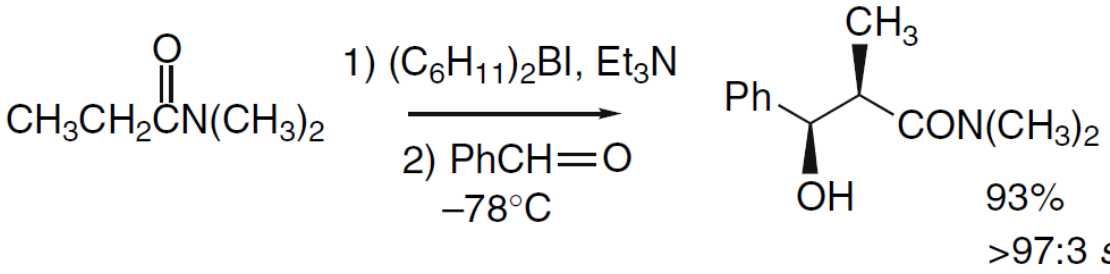
Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

Aldol Reaction of Boron Enolates:

Examples







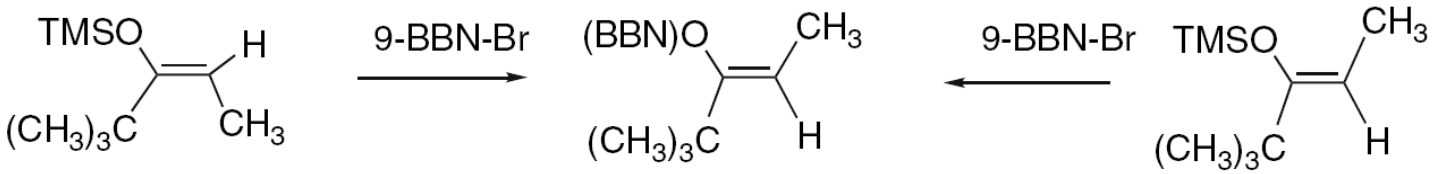
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

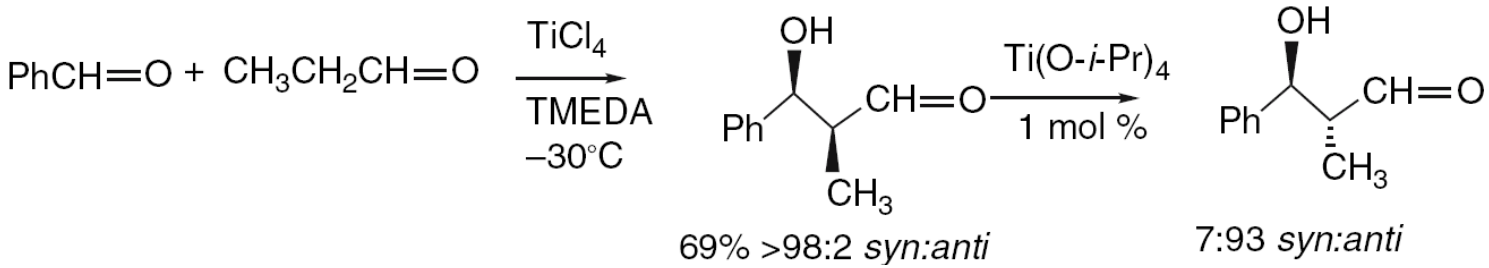
Aldol Reaction of Boron Enolates:

- 9-BBNBr + TMS enolether



Aldol Reactions of Titanium, Tin, and Zirconium Enolates

- stereoselectivity: $Bu_2B > Cp_2Zr > Li$



69% >98:2 *syn:anti*

7:93 *syn:anti*

Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

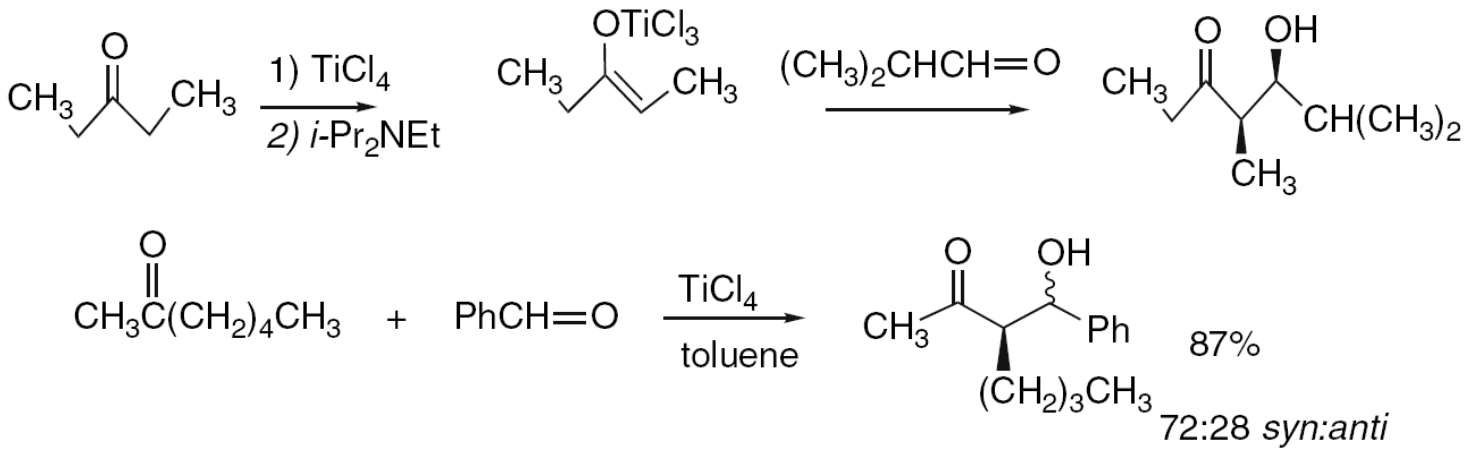
Aldol Reactions of Titanium, Tin, and Zirconium Enolates

- Ti, Sn, Zr (ligands – tetra, penta, hexacoordinated structures)
- chelated TS

Titanium Enolates

- preparation: a) from Li^+ enolates (RO_3TiCl)
  b) from ketones ($TiCl_4/R_3N$) – *Z*-enolates (formation of *syn* products)

Examples



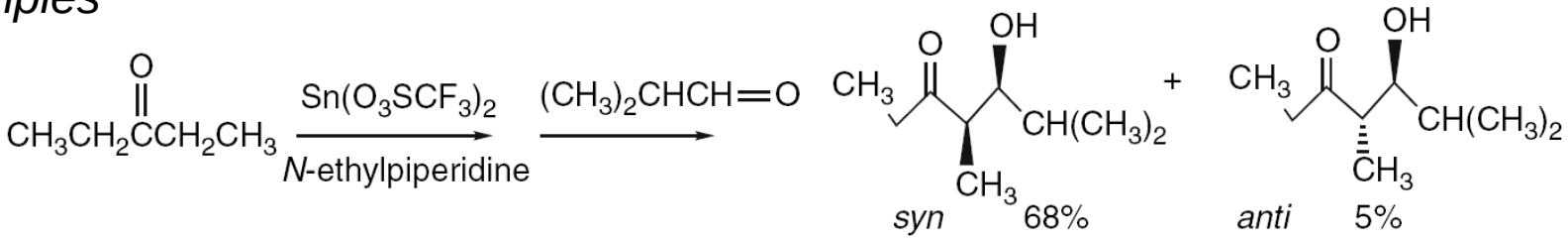
Aldol Addition and Condensation Reactions

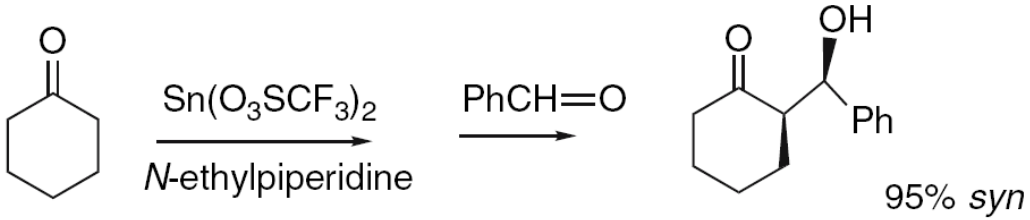
Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

Tin Enolates (Sn^{2+})

- preparation from ketones ($Sn(OTf)_2/R_3N$)
- formation of *syn* products only (from *E/Z*-enolate -open TS)
- even cyclic enolates → *syn* products

Examples





Reactions of Carbon Nu with C=O Compounds

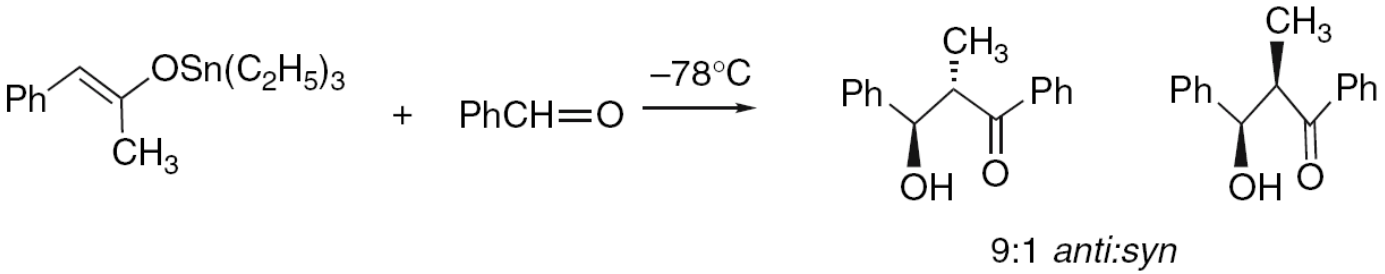
Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

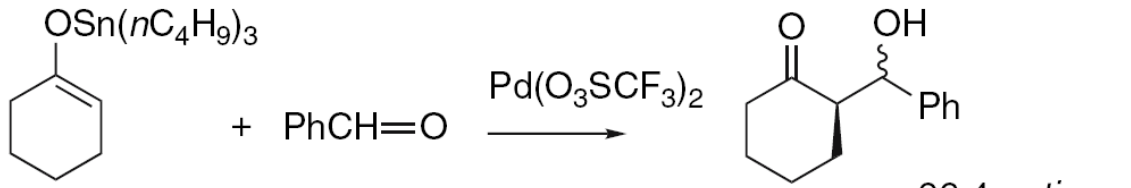
Tin Enolates (Sn^{4+})

- preparation from enolacetates (R_3SnOR)
- formation of a*nti* products only (catalysts: $Pd(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$)

Examples



9:1 *anti:syn*



96:4 *anti:syn*

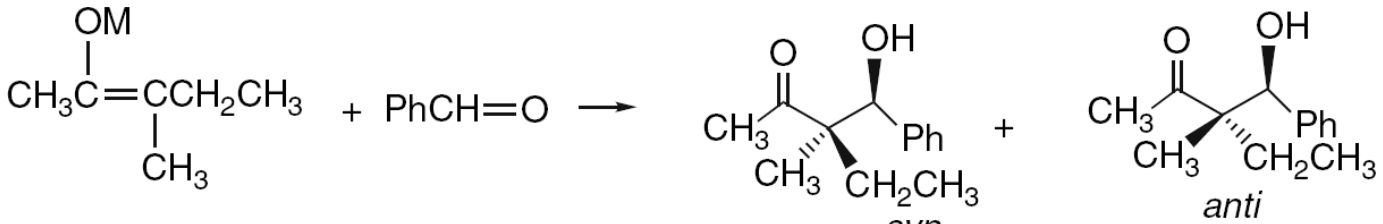
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Control of Regio- and Stereoselectivity of Aldol Reactions of RCHO and RCOR´

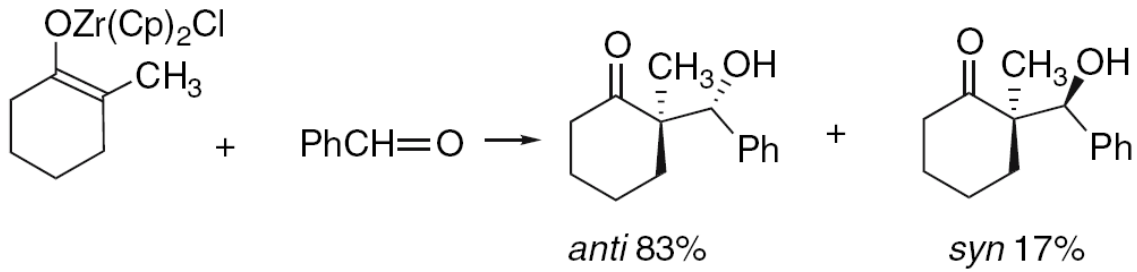
Zirconium Enolates

- preparation from enolacetates (Cp_2ZrCl_2)
- aldol reaction – stereoselectivity: $Bu_2B > Cp_2Zr > Li$



E-enolate	*syn*:*anti*	*Z*-enolate	*syn*:*anti*
Li	17:83	Li	45:55
Bu_2B	3:97	Bu_2B	94:6
$(Cp)_2ZrCl$	9:91	$(Cp)_2ZrCl$	86:14

Example



Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

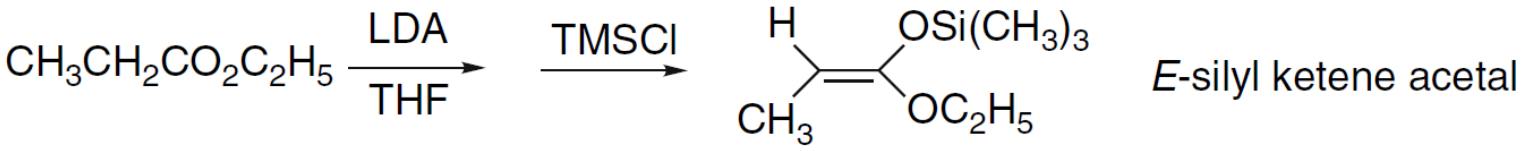
Aldol Addition Reactions of Enolates of Esters and Other Derivatives

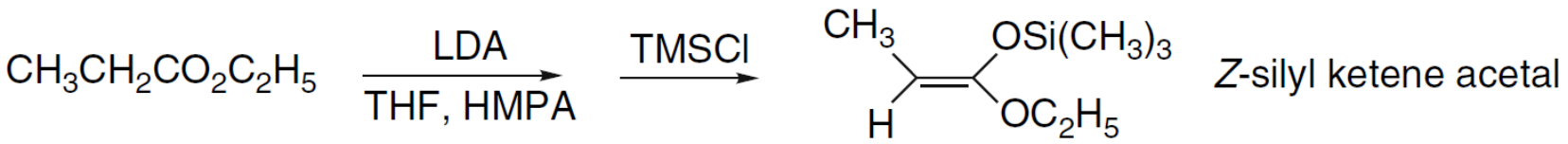
- esters, thiol esters, amides, and imides
- lithium, boron, titanium, and tin derivatives

Silyl Ketene Acetals

- reactivity analogous to silyl enol ethers
- *E*-enolates - preferred under kinetic conditions (LDA/THF)
- *Z*-enolate - inclusion of a strong cation-solvating cosolvent (HMPA or DMPU)

Example





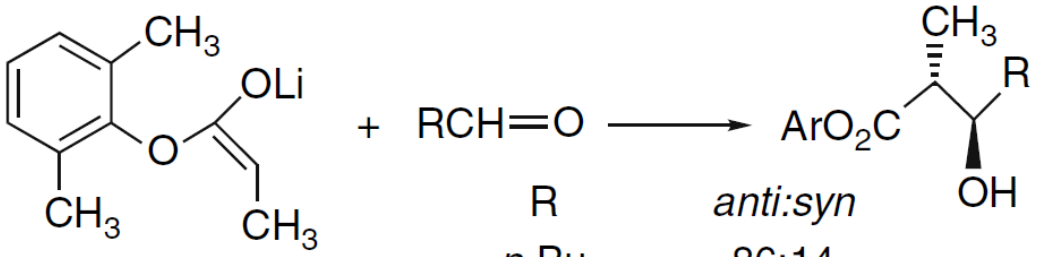
Aldol Addition and Condensation Reactions

Aldol Addition Reactions of Enolates of Esters and Other Derivatives

Silyl Ketene Acetals

- aldol addition of unhindered ester enolate - not very stereoselective
- stereoselectivity can be improved - use of a very bulky group
  → *E*-enolate – *anti* product

Example



R	*anti:syn*
n-Bu	86:14
i-Pr	>98:2
t-Bu	>98:2
Ph	88:12

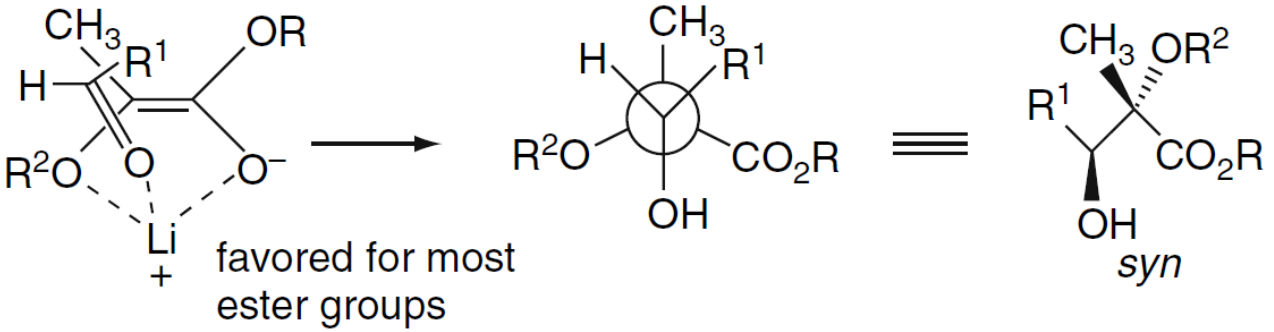
Reactions of Carbon Nu with C=O Compounds

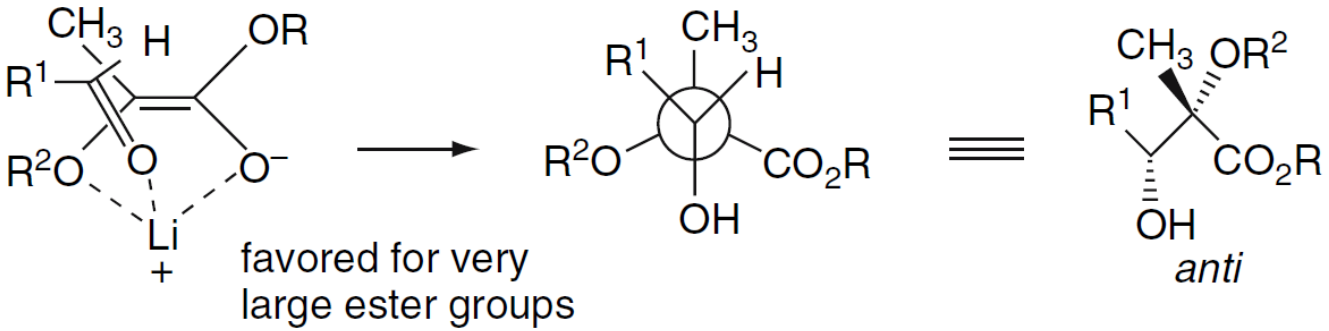
Aldol Addition and Condensation Reactions

Aldol Addition Reactions of Enolates of Esters and Other Derivatives

Lithium Enolates of Esters

- Li enolates of α-alkoxy esters - high stereoselectivity
  - *syn* product favored
  - *anti* product (extremely bulky groups)





Reactions of Carbon Nu with C=O Compounds

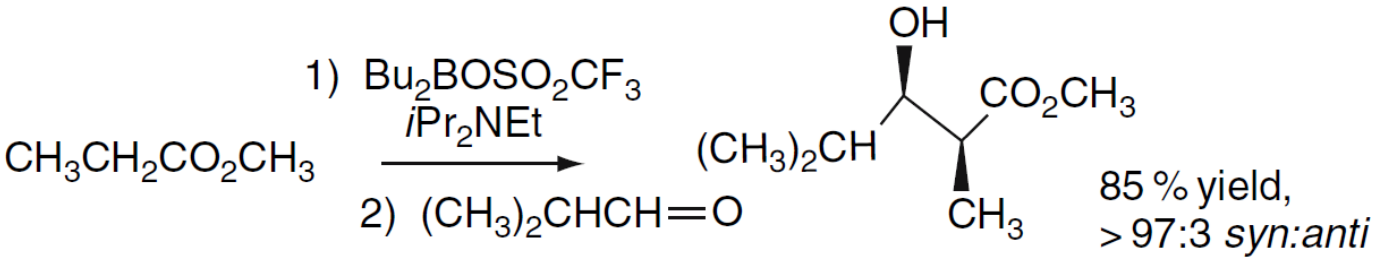
Aldol Addition and Condensation Reactions

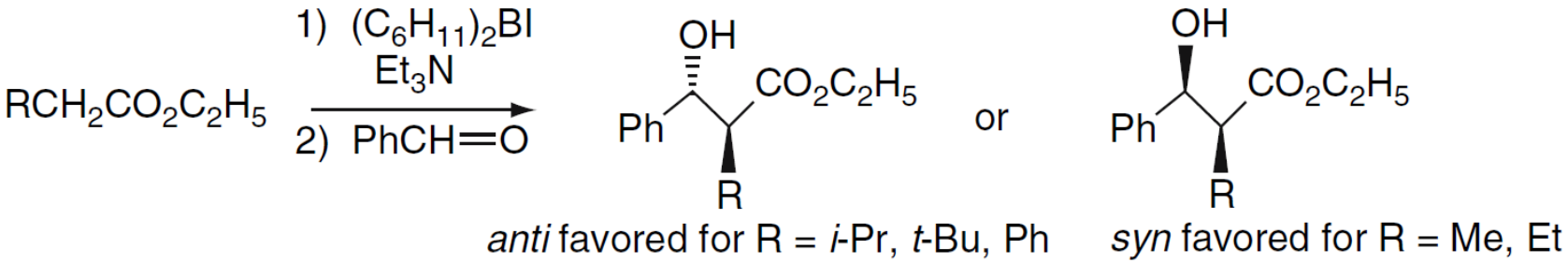
Aldol Addition Reactions of Enolates of Esters and Other Derivatives

Boron Enolates of Esters

- *Z*-enolates - *syn* product favored
- branched-chain alcohol $(C_6H_{11})_2BI$) or esters (R_2BOTf)- *anti* product

Examples





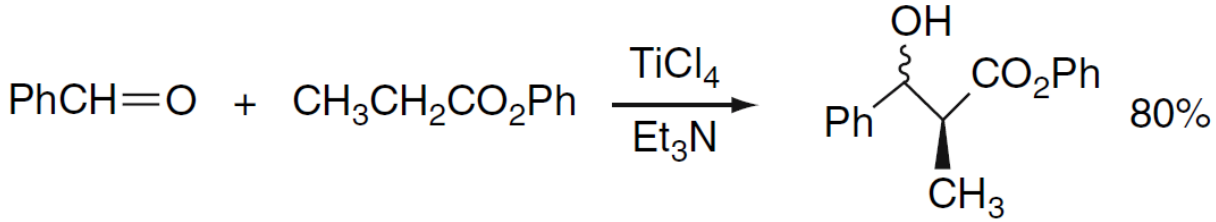
Reactions of Carbon Nu with C=O Compounds

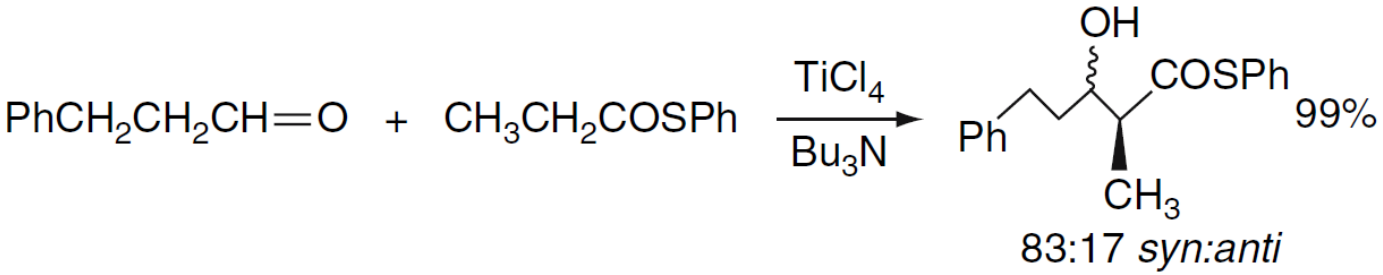
Aldol Addition and Condensation Reactions

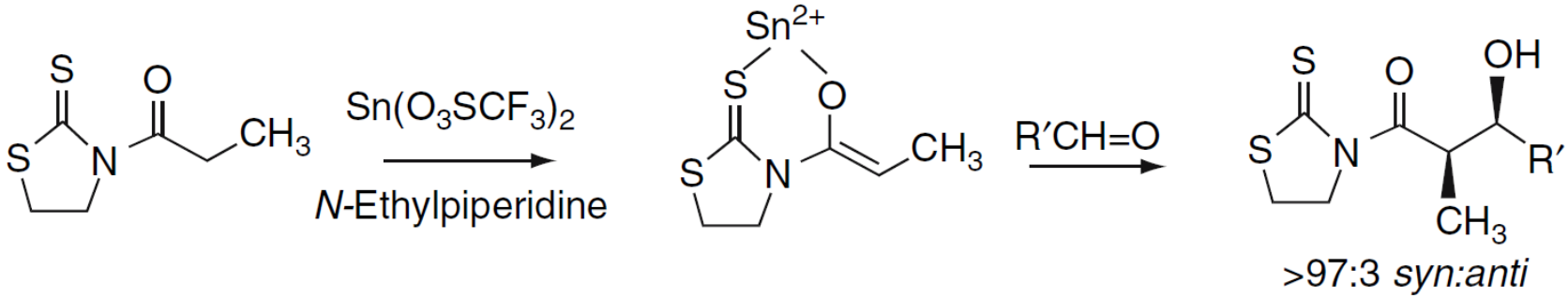
Aldol Addition Reactions of Enolates of Esters and Other Derivatives

Other Enolates of Esters

Examples





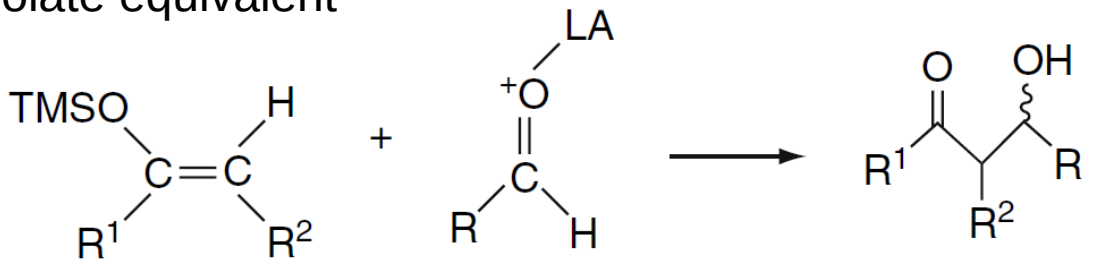


Reactions of Carbon Nu with C=O Compounds

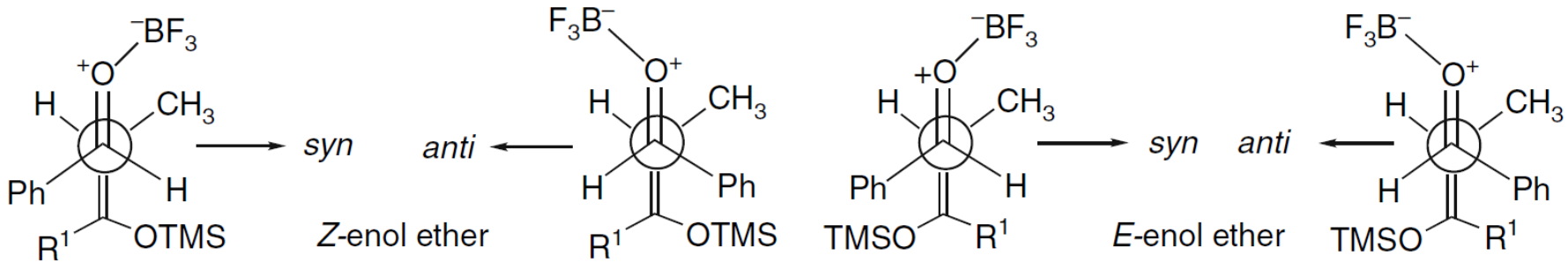
Aldol Addition and Condensation Reactions

Mukaiyama Aldol Reaction

- Lewis acid–catalyzed aldol addition reactions of silyl enol ethers, silyl ketene acetals and similar enolate equivalent



- LA: $TiCl_4$, $SnCl_4$, BF_3, $Bu_2Sn(OTf)_2$, Bu_3SnClO_4, $Sn(OTf)_2$, $Zn(OTf)_2$, $LiClO_4$, etc.
- open TS (steric factors)

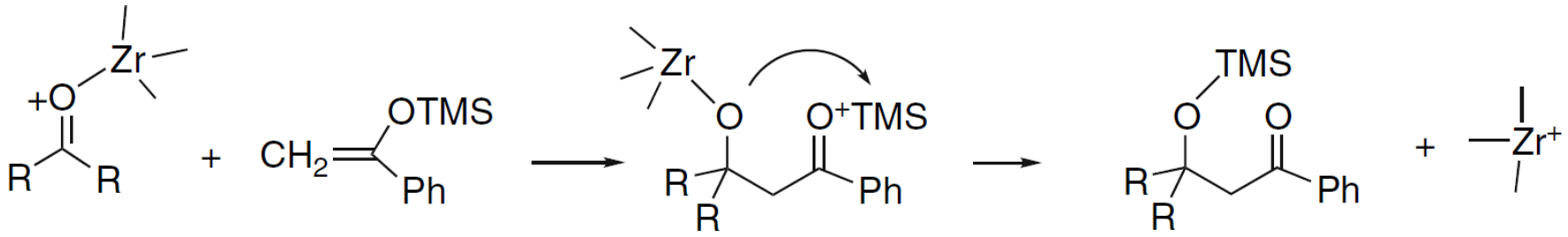


Reactions of Carbon Nu with C=O Compounds

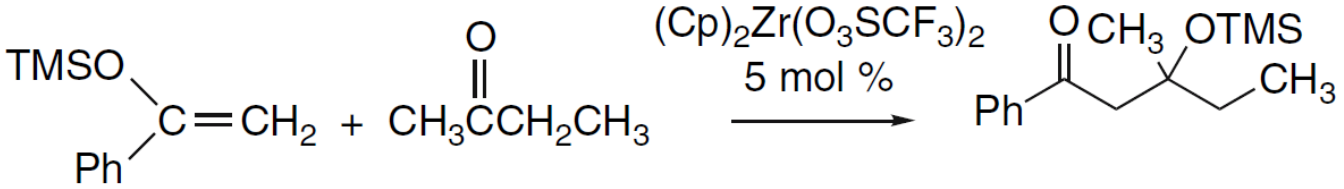
Aldol Addition and Condensation Reactions

Mukaiyama Aldol Reaction

- catalytic versions ($Cp_2Zr(OTf)_2 \rightarrow Cp_2Zr^{2+}$)



Example



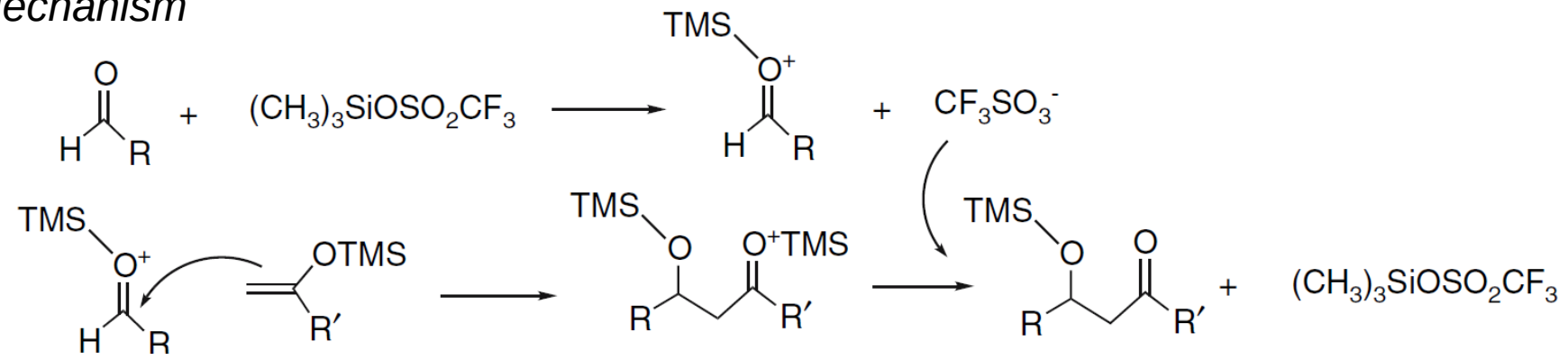
Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

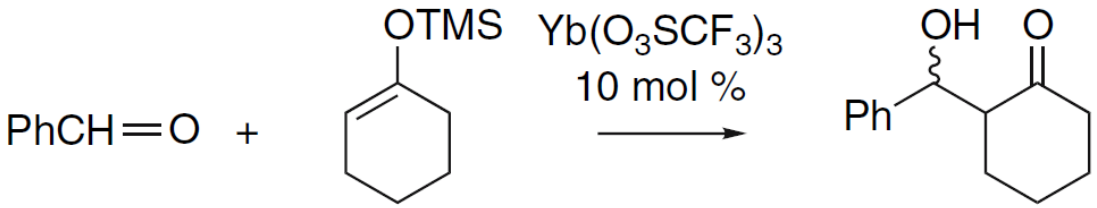
Mukaiyama Aldol Reaction

- TMS-mediated Mukaiyama aldol reaction

Mechanism



- lanthanide salts – Yb(OTf)3, (aqueus solvents, H_2O-THF)



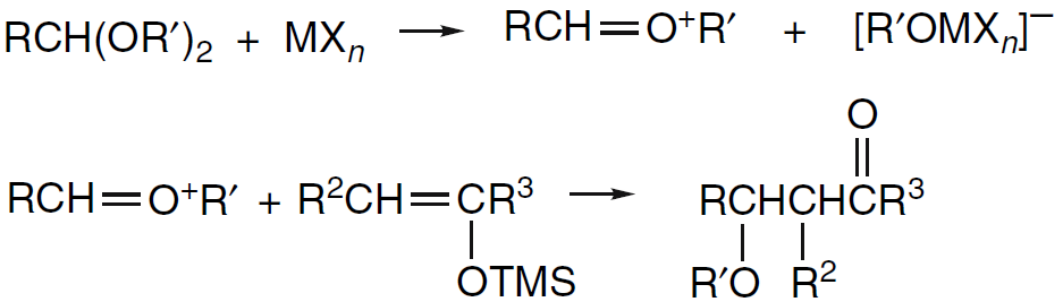
91% yield, 73:27 *syn*:*anti*

Reactions of Carbon Nu with C=O Compounds

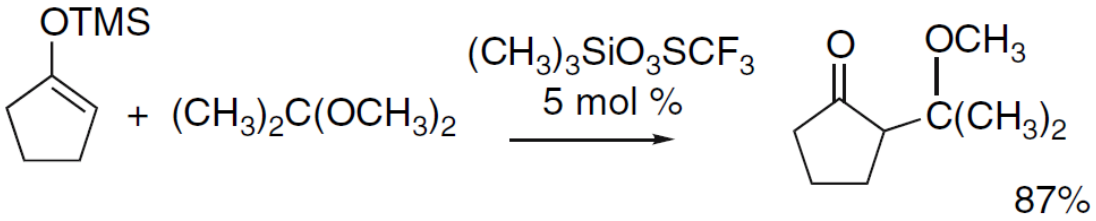
Aldol Addition and Condensation Reactions

Mukaiyama Reaction with Acetals

- other type electrophile (acetals)
- LA: $TiCl_4$, $SnCl_4$, TMSOTf, $Bu_2Sn(OTf)_2$ – ionization (oxonium ion)
- products: β-alkoxy ketones



Example

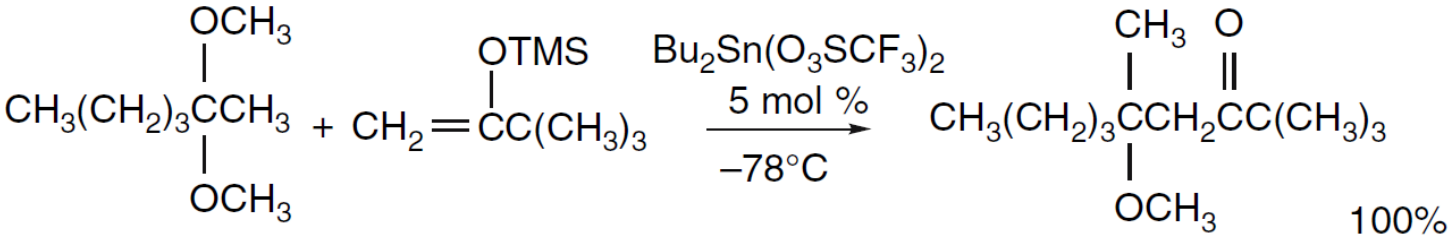


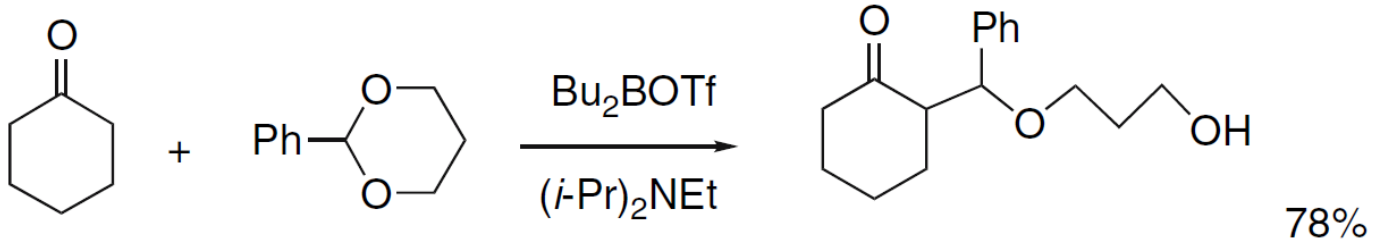
Reactions of Carbon Nu with C=O Compounds

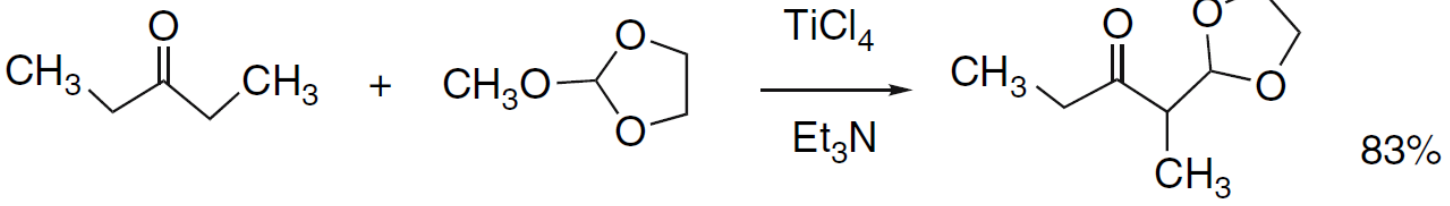
Aldol Addition and Condensation Reactions

Mukaiyama Reactions and Related Reactions

Examples





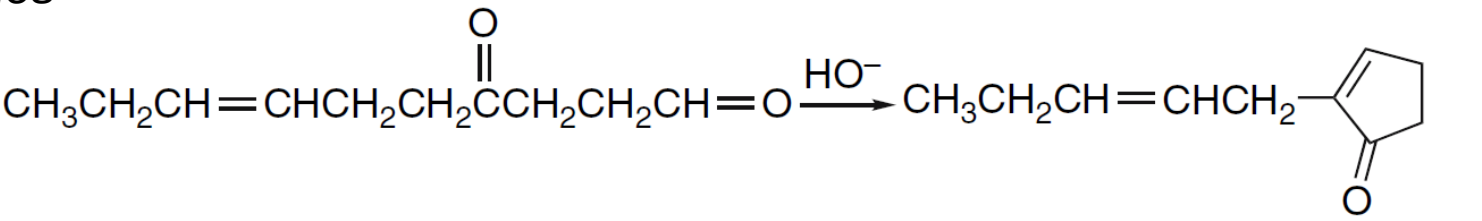


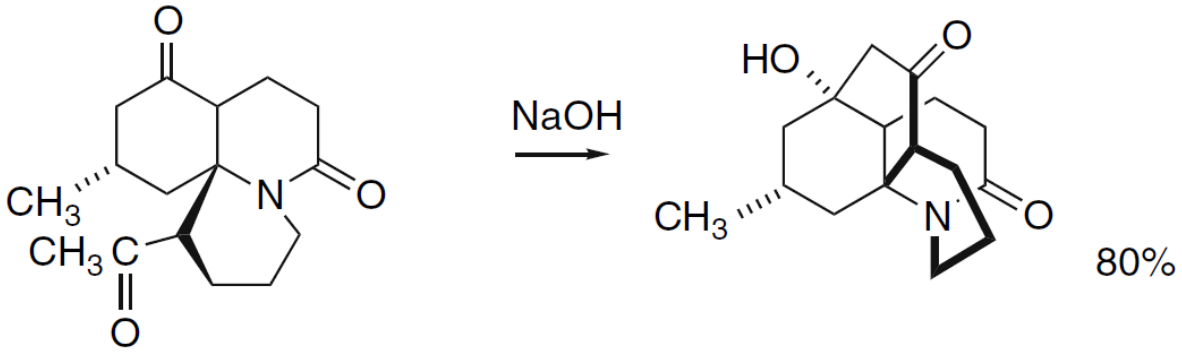
Aldol Addition and Condensation Reactions

Intramolecular Aldol and Mukaiyama Aldol Reactions

- aldol reaction of dicarbonyl compounds
- five-membered ring – thermodynamically favored
- six-membered ring – 10^3 faster formation

Examples

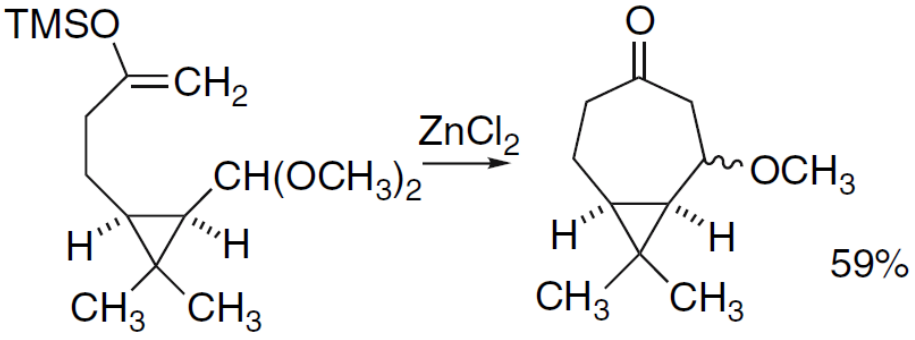


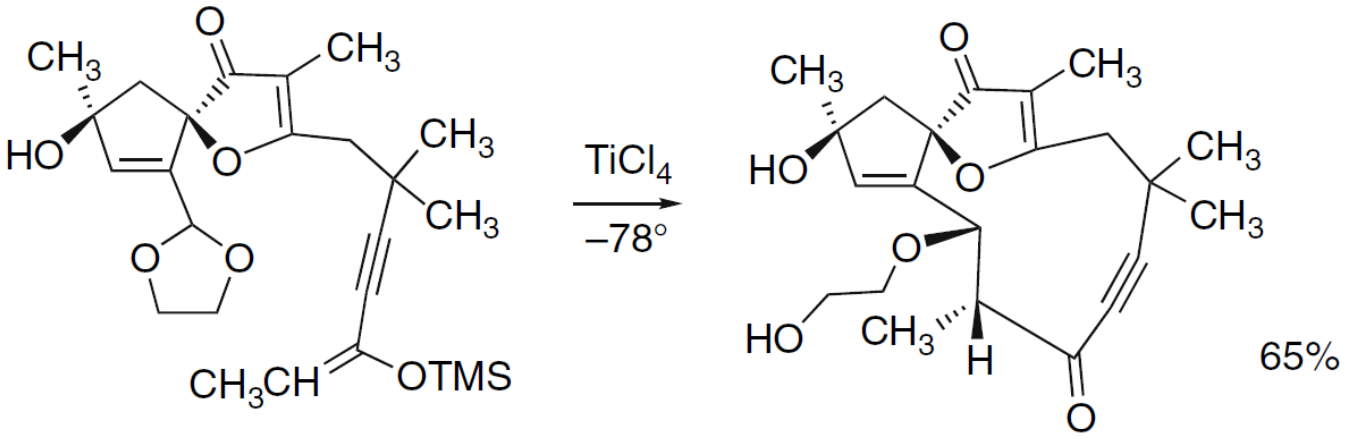


Aldol Addition and Condensation Reactions

Intramolecular Aldol and Mukaiyama Aldol Reactions

Examples



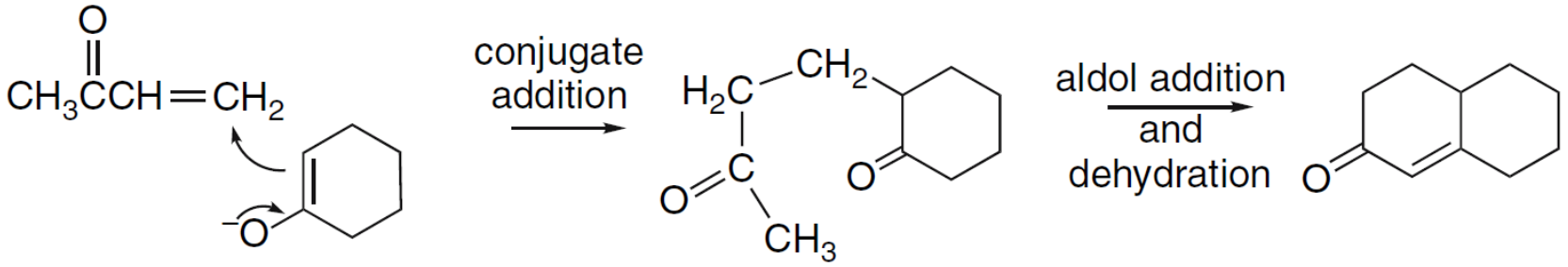


Reactions of Carbon Nu with C=O Compounds

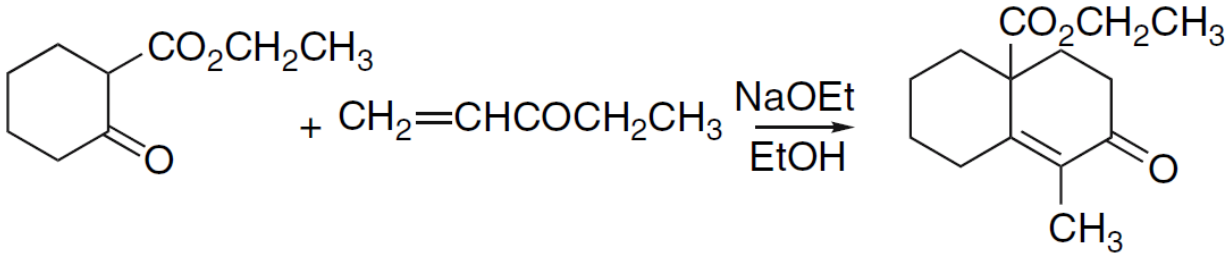
Aldol Addition and Condensation Reactions

Robinson Annulation

- construction six-membered ring from a ketone
- 1. step: conjugate addition
- 2. step: cyclization
- 3. dehydration



Example



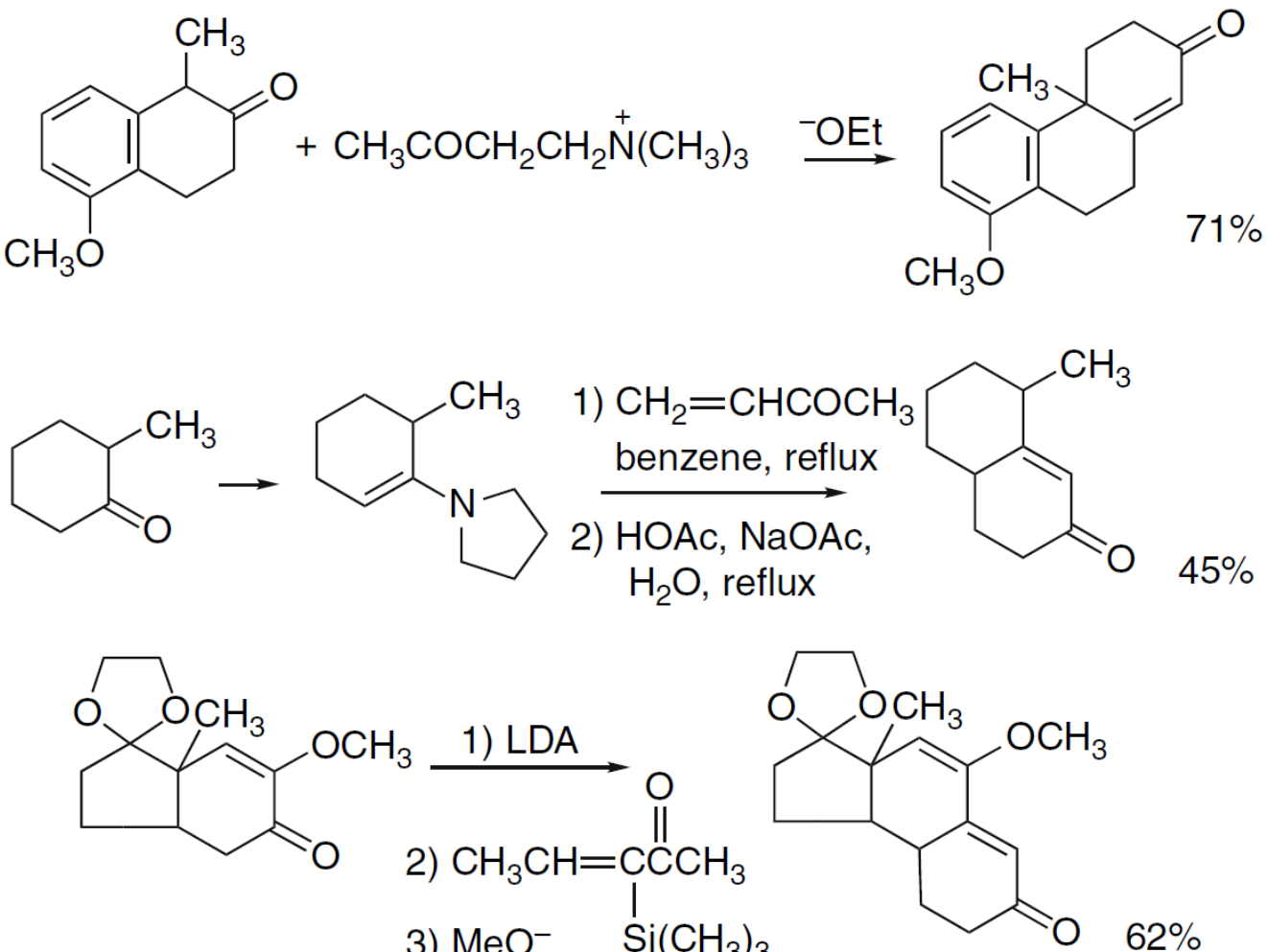
59%

Reactions of Carbon Nu with C=O Compounds

Aldol Addition and Condensation Reactions

Robinson Annulation

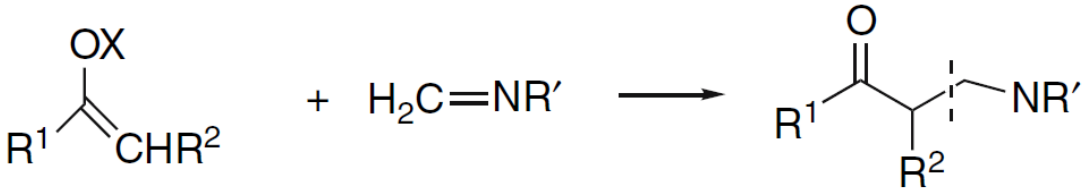
Examples



Reactions of Carbon Nu with C=O Compounds

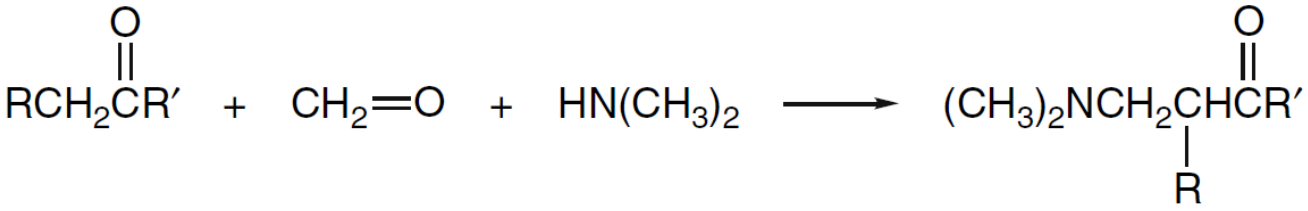
Addition Reactions of Imines and Iminium Ions

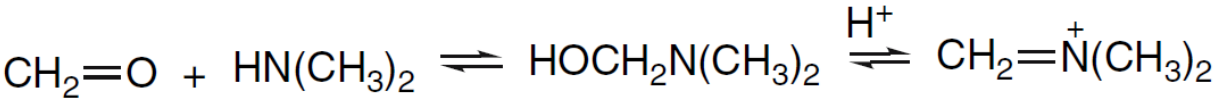
- reactivity: C=NR < C=O < $C=NR_2^+$ < $C=OH^+$
- preparation of β-amino ketones:



Mannich Reaction

- condensation of an enolizable carbonyl compound with an iminium ion



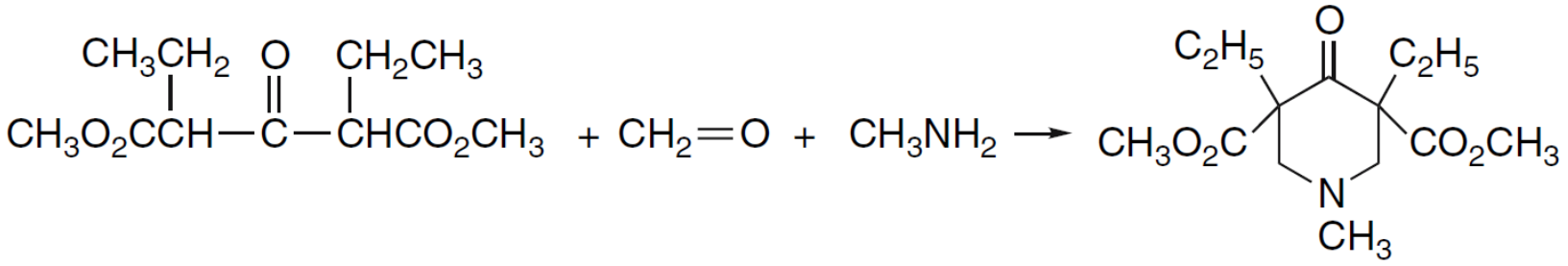


Reactions of Carbon Nu with C=O Compounds

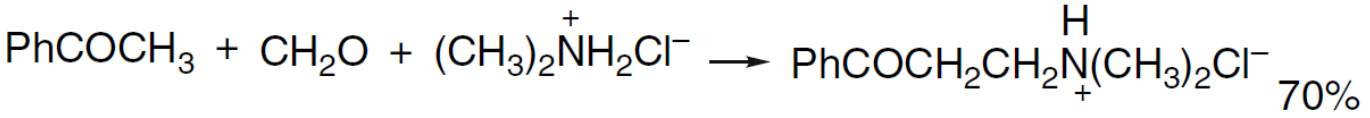
Addition Reactions of Imines and Iminium Ions

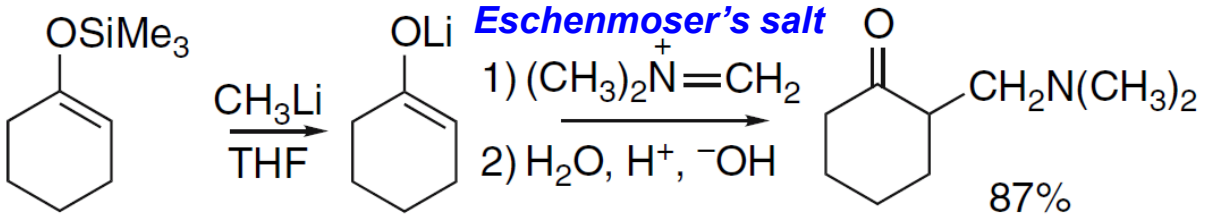
Mannich Reaction

- formation of electrophile
  - formaldehyde, benzaldehyde
  - secondary amine
  - primary amine (dialkylation)



Examples



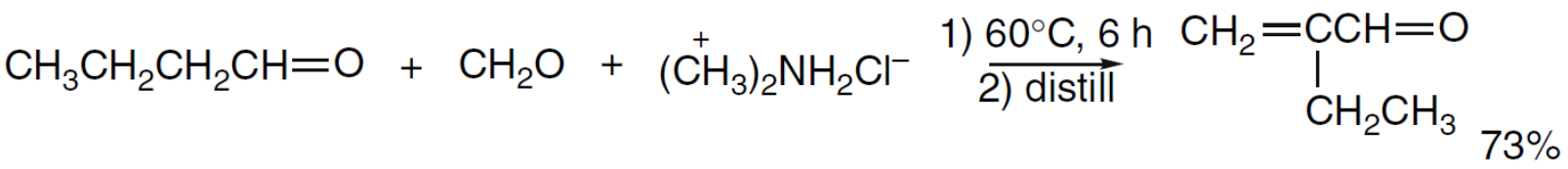


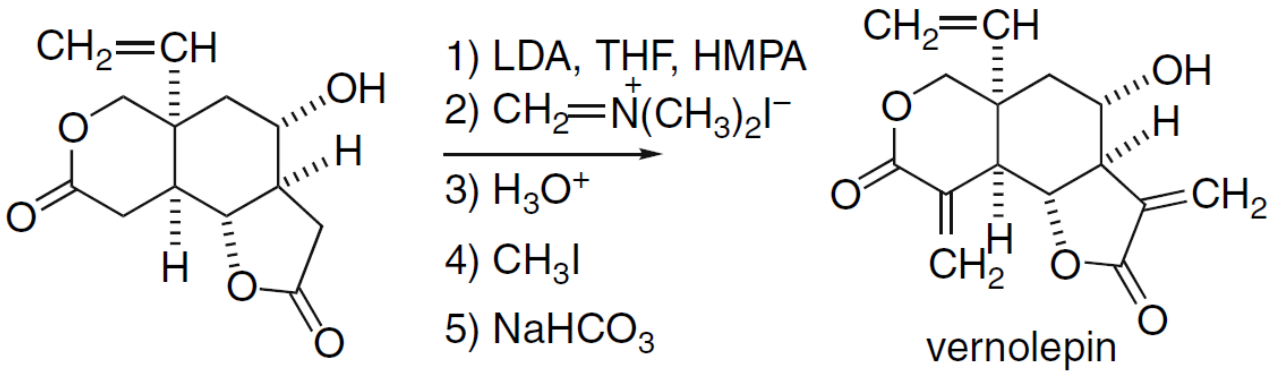
Reactions of Carbon Nu with C=O Compounds

Addition Reactions of Imines and Iminium Ions

Mannich Product Transformation

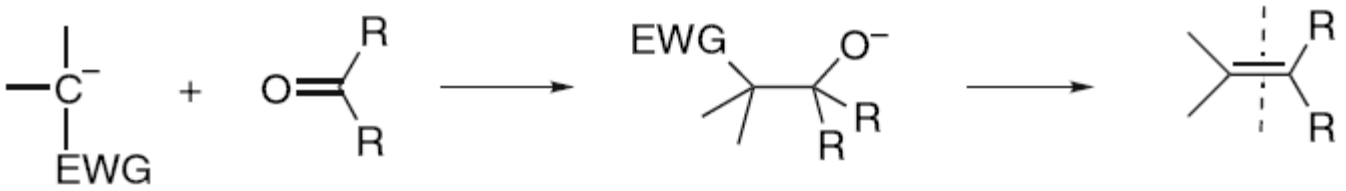
- α,β-unsaturated aldehydes and ketones





Reactions of Carbon Nu with C=O Compounds

Olefination Reaction of Stabilized Carbon Nu



Conversion of CO compounds into alkenes (*Pathway C*)

1.step: addition of Nu
2. step: elimination

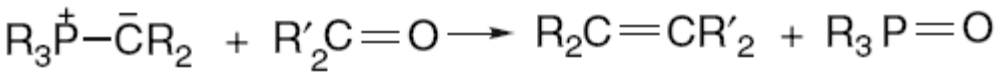
Named reactions:

- Wittig and related reactions (phosphor containing compounds)
- Peterson reaction (α-silyl compounds)
- Julia olefination (α-sulfonyl compounds)

Reactions of Carbon Nu with C=O Compounds

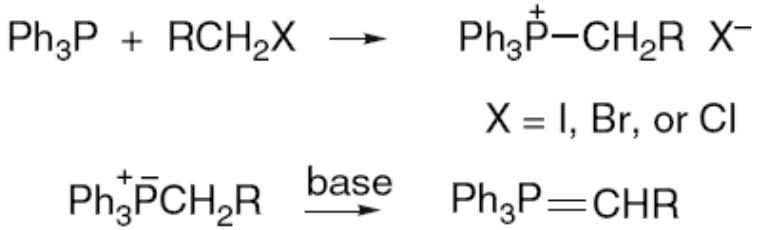
Wittig reaction

- reaction of phosphonium ylide with aldehydes or ketones to give olefins and Ph_3PO



Ylide structure:

Preparation of ylides:



Base - strong base used for deprotonation
organolithium reagents (BuLi, PhLi), dimsyl anion, amide ion or substituted amide anions (LDA, NaHMDS)

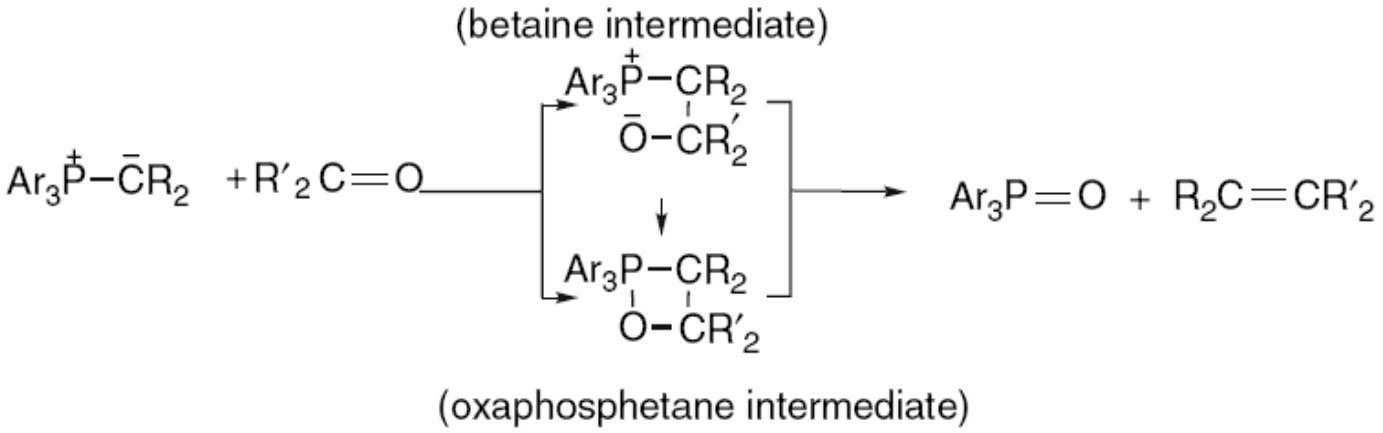
Reactions of Carbon Nu with C=O Compounds

Wittig reaction

Unstabilized Ylides
- ylides with nonpolar substituents (alkyl, aryl)
- reactive toward both ketones and aldehydes

Stabilized Ylides
- *y*lides with α-EWG substituent (COR, COOR, etc.),
- less reactive

Mechanism of Wittig reaction
- dipolar intermediate (betaine)
- low temperature (oxaphosphetane)



Reactions of Carbon Nu with C=O Compounds

Stereoselectivity of Wittig reaction

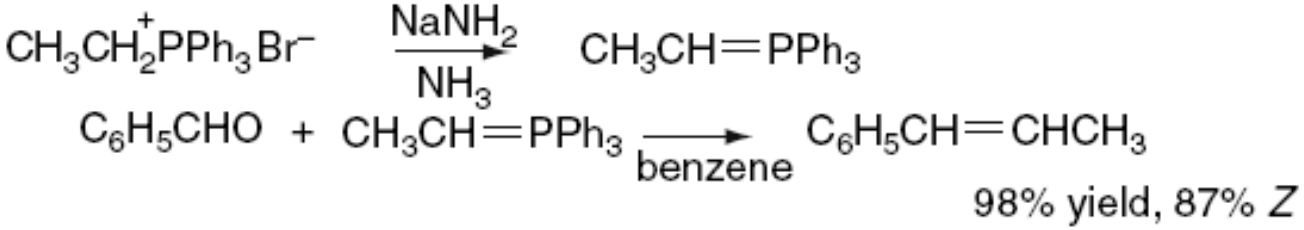
Structure of ylide

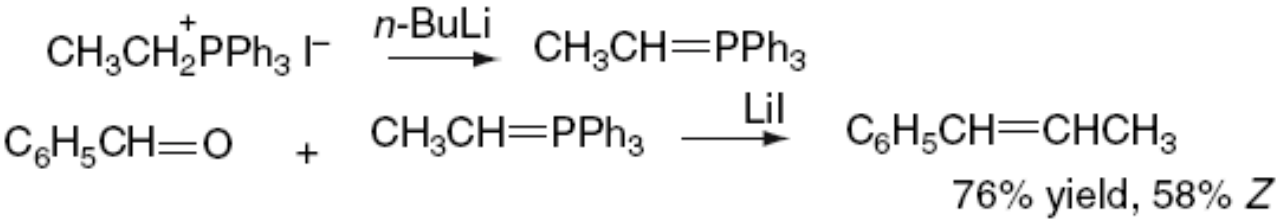
Stabilized ylides – formation of *E-alkenes*

Unstabilized ylides – formation of *Z-alkenes*

Effect of base used for ylide formation

formation of *Z*-alkenes dominates (amides, silazides more than ylides generated by organolithium compounds)





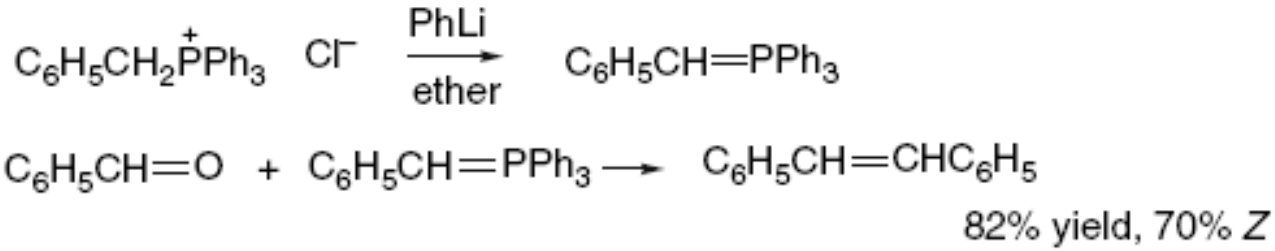
Solvent effect

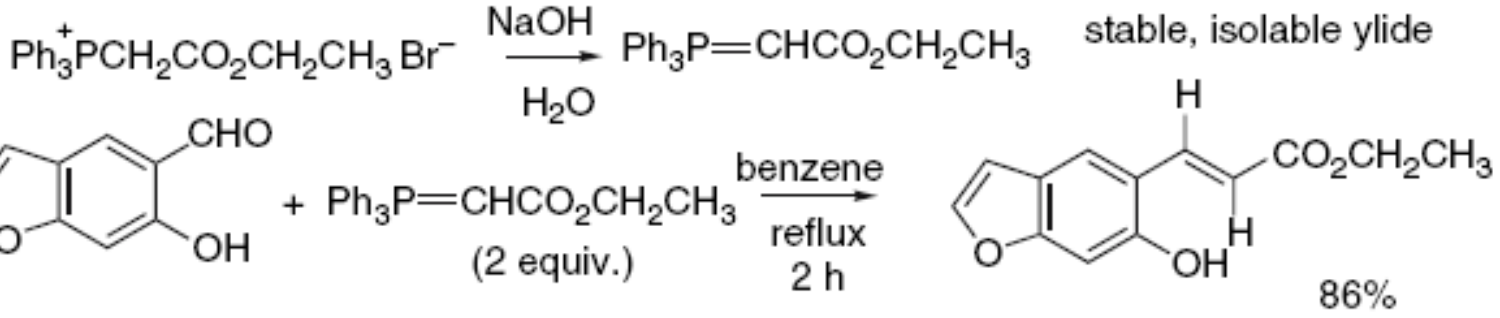
Temperature

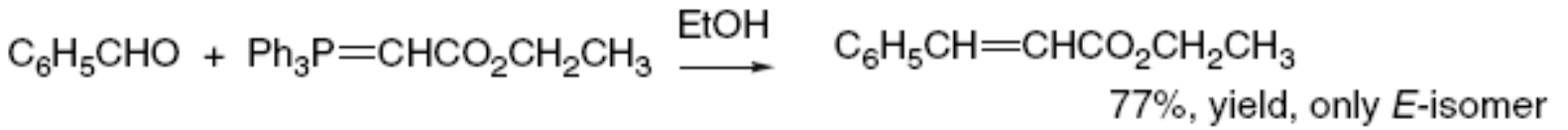
Reactions of Carbon Nu with C=O Compounds

Stereoselectivity of Wittig reaction

Examples - Unstabilized x stabilized ylides







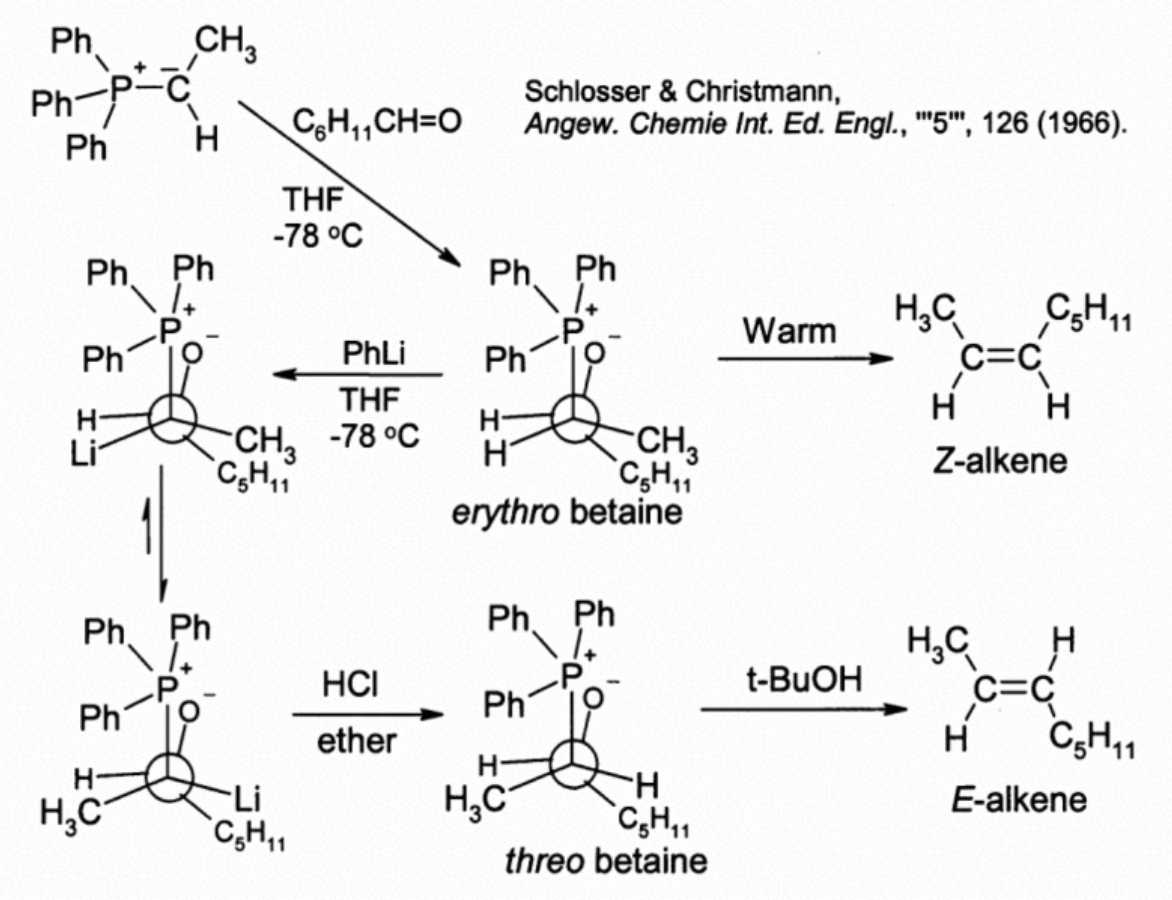
Reactions of Carbon Nu with C=O Compounds

Wittig reaction (Horner-Wittig)

- aldehydes, ketones (not hindered)
- olefination reaction with unstabilized ylides with high *Z*-stereoselectivity

- solvent: DMF
- additive: LiI, NaI
- heating or r.t.

- method:



tolerance to OH, OR, NO_2 (arom.), ester, etc.

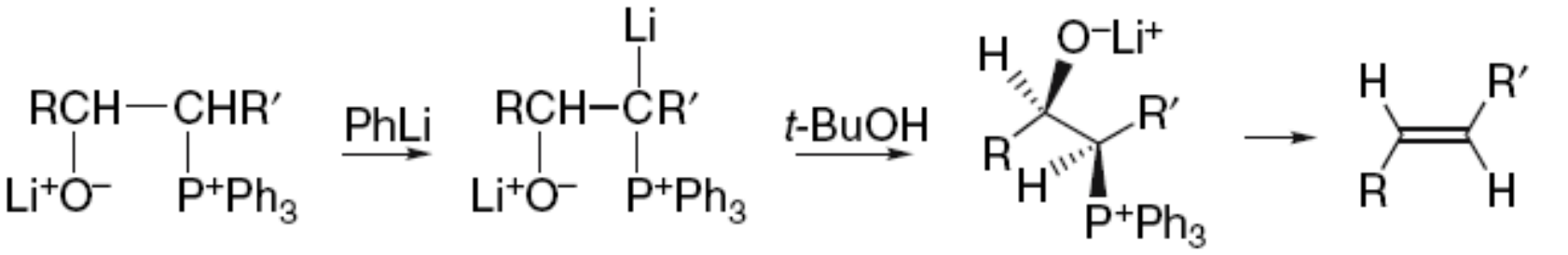
Reactions of Carbon Nu with C=O Compounds

Wittig reaction (Schlosser modification)

- olefination reaction with unstabilized ylides with high *E*-stereoselectivity

- method:

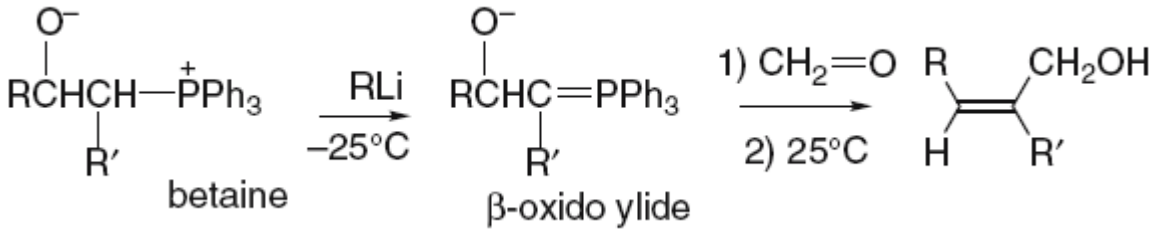
  ylide generated as *lithium halide complex*
  reaction with an aldehyde at low temperature
  formation of a mixture of diastereomeric *betaine-lithium halide complexes*
  formation of *β-oxidoylide* with 1.0 eq. of strong base (PhLi)
  addition of 1.0 eq. of *tBu*OH *alcohol* to protonate the *β-oxidoylide*
  formation of high *syn-betaine complex* with high stereoselectivity
  syn elimination of betaine-lithium halide complex to give *E-alkene*

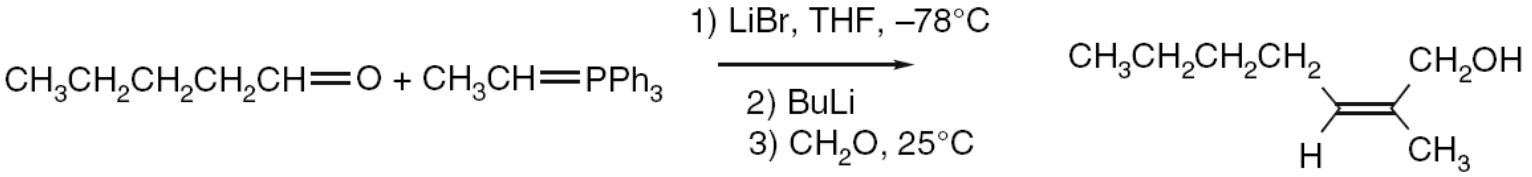


Reactions of Carbon Nu with C=O Compounds

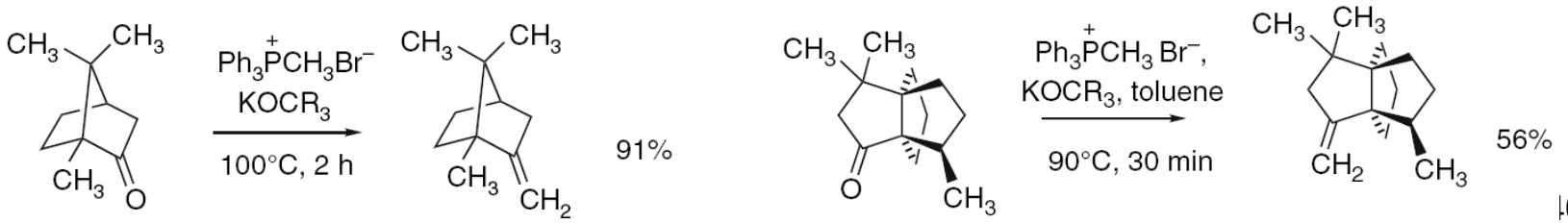
Wittig reaction (Schlosser modification)

- allylation with CH_2O
- stereoselective synthesis of *Z-allylic alcohols* from aldehydes





Examples

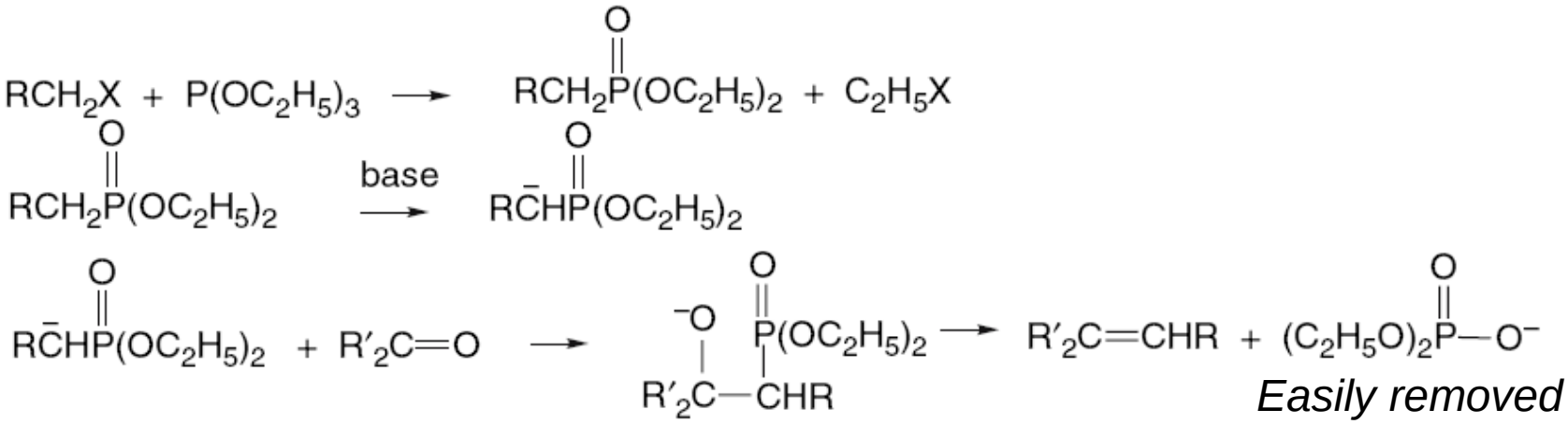


Reactions of Carbon Nu with C=O Compounds

Olefination Reactions Involving Phosphonate Anions

- reaction of phosphonate carbanions with carbonyl compounds to prepare α,β – unsaturated esters
- phosphonate carbaninons:
  stabilized
  more nucleophilic and basic

- preparation of phosphonate carbanions:
  alkylphosphonate esters with a base such as NaH, BuLi, EtONa
  synthesis of alkylphosphonate esters by the reaction of an alkyl halide with a phosphite ester



Easily removed by aqueous extraction

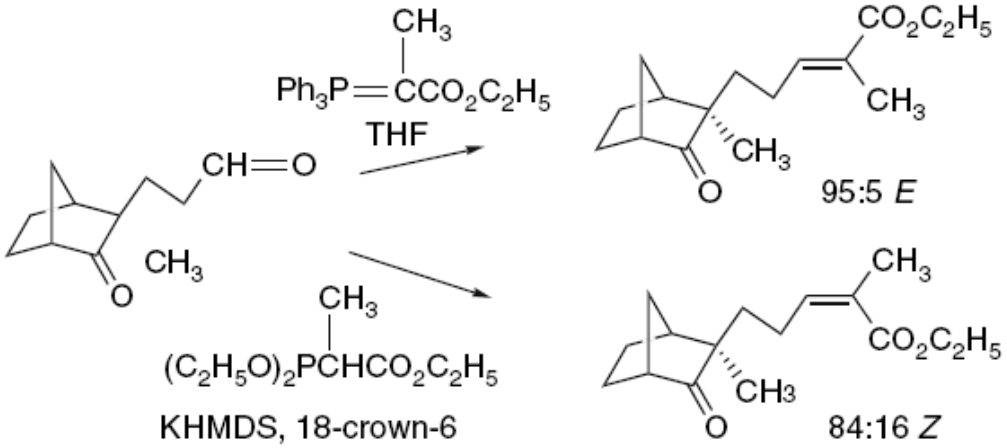
Reactions of Carbon Nu with C=O Compounds

Olefination Reactions Involving Phosphonate Anions

Horner - Wadsworth - Emmons reaction

- disubstituted, trisubstituted alkenes, aldehydes-ketones (poor)
- olefination reactions leading to the *E*-isomers predominantly (increasing steric bulk of the aldehyde, higher reaction temperatures (23 °C), Li > Na > K salts, using the solvent DME over THF)
- olefination reactions leading to the *Z*-isomers **(*Still modification*** - use of KHMDS with 18-crown-6, THF, -78 °C)

Example

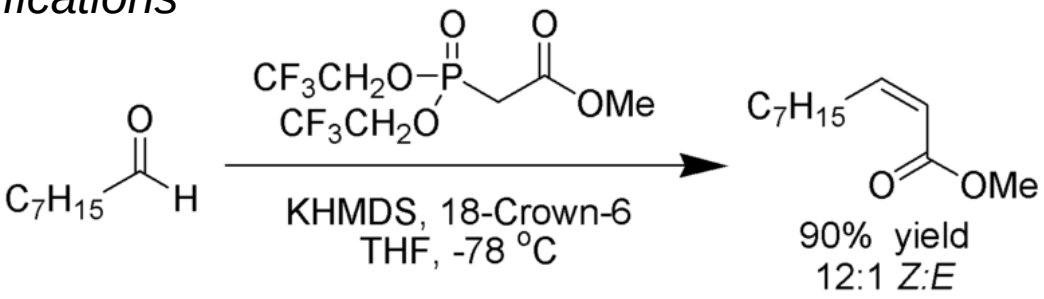


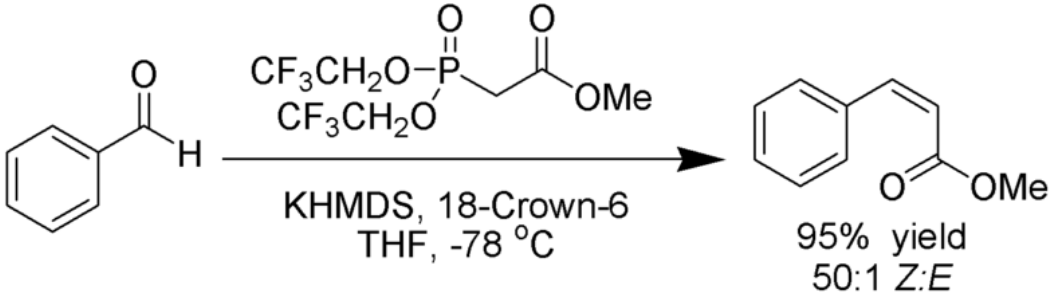
Reactions of Carbon Nu with C=O Compounds

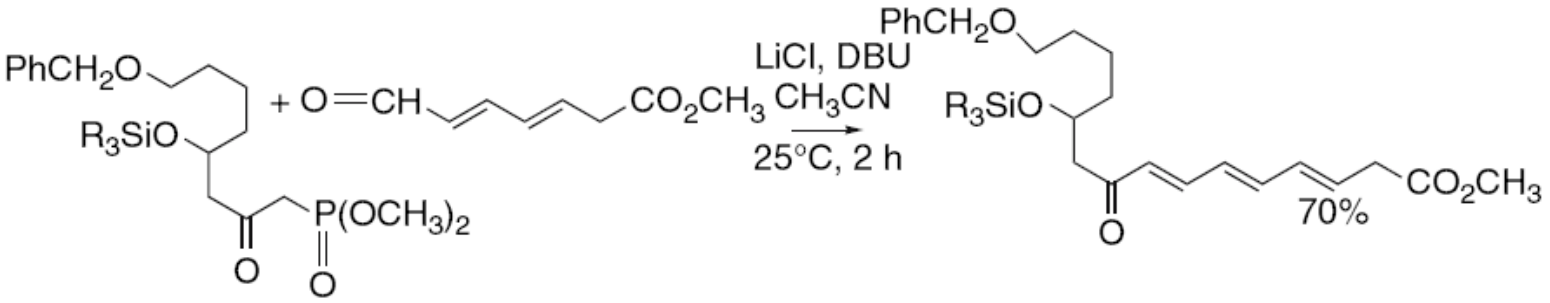
Olefination Reactions Involving Phosphonate Anions

- Some modified phosphonoacetate esters show selectivity for the *Z*-product
- *many modifications*

Examples





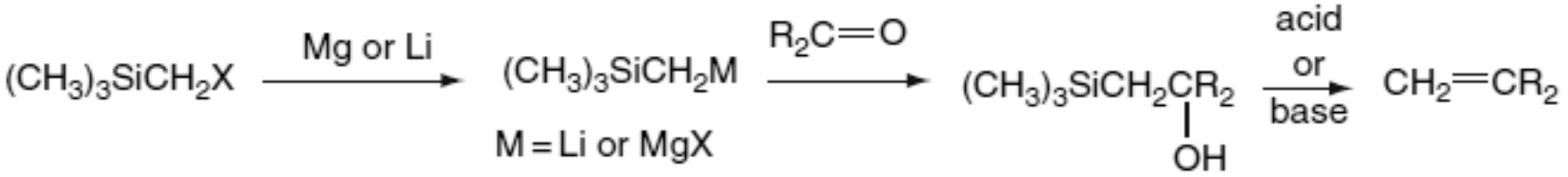


Reactions of Carbon Nu with C=O Compounds

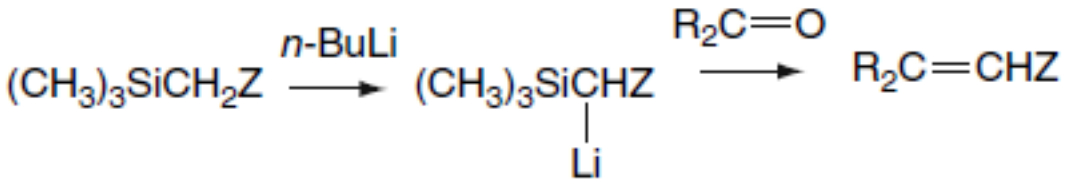
Reations of α-Trimethylsilylcarbanions with C=O

Peterson reaction

- reaction of α-silyl carbanions with ketones (aldehydes) to form β-hydroxysilanes
- β-hydroxyalkylsilanes are converted to alkenes by either acid or base
- advantage: E or Z with high stereoselectivity (base or acid)



- acidic substrates: organilithium reagents of the type $(CH_3)_3SiCH(Li)Z$, where Z is a carbanion-stabilizing substituent

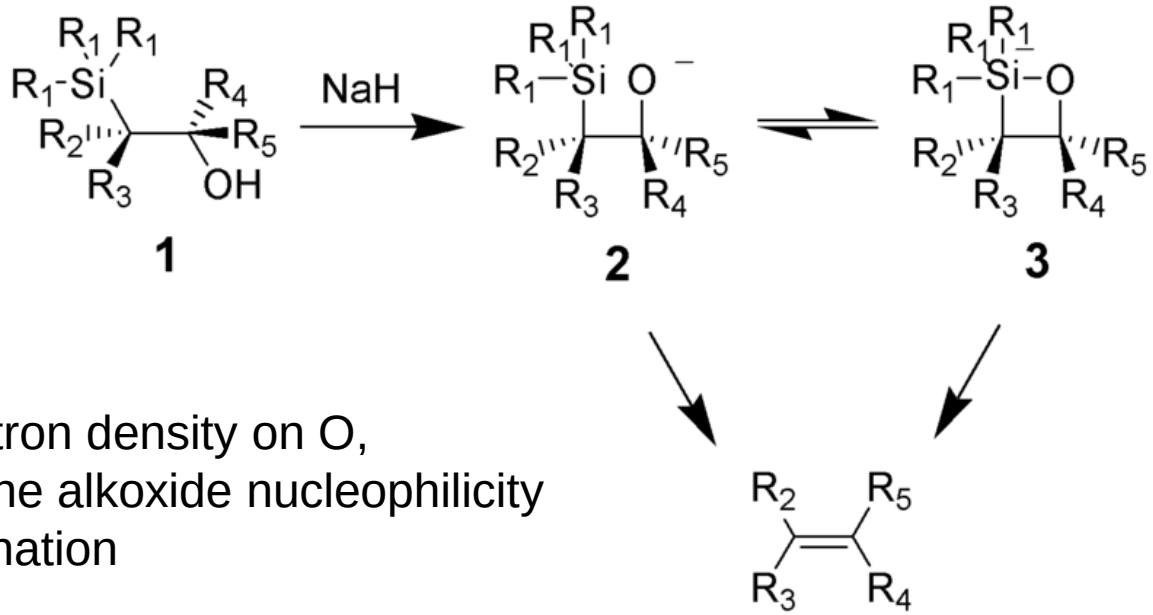


Reactions of Carbon Nu with C=O Compounds

Reations of α-Trimethylsilylcarbanions with C=O

Peterson reaction

- *basic elimination:*



- higher electron density on O,
  increased the alkoxide nucleophilicity
  faster elimination

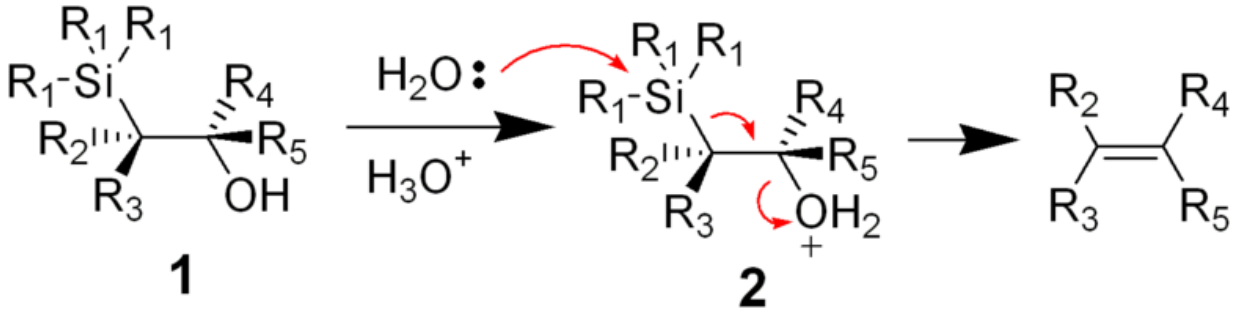
- rate of elimination: K > Na >> Mg
  (K alkoxides eliminate quickly, Na alkoxides require heating, Mg alkoxides extreme conditions).

Reactions of Carbon Nu with C=O Compounds

Reations of α-Trimethylsilylcarbanions with C=O

Peterson reaction

- *acidic elimination:*



- protonation and an *anti* elimination to form the desired alkene
- typical conditions: H_2SO_4 or AcOH, H_2O, THF

Stereoselectivity:

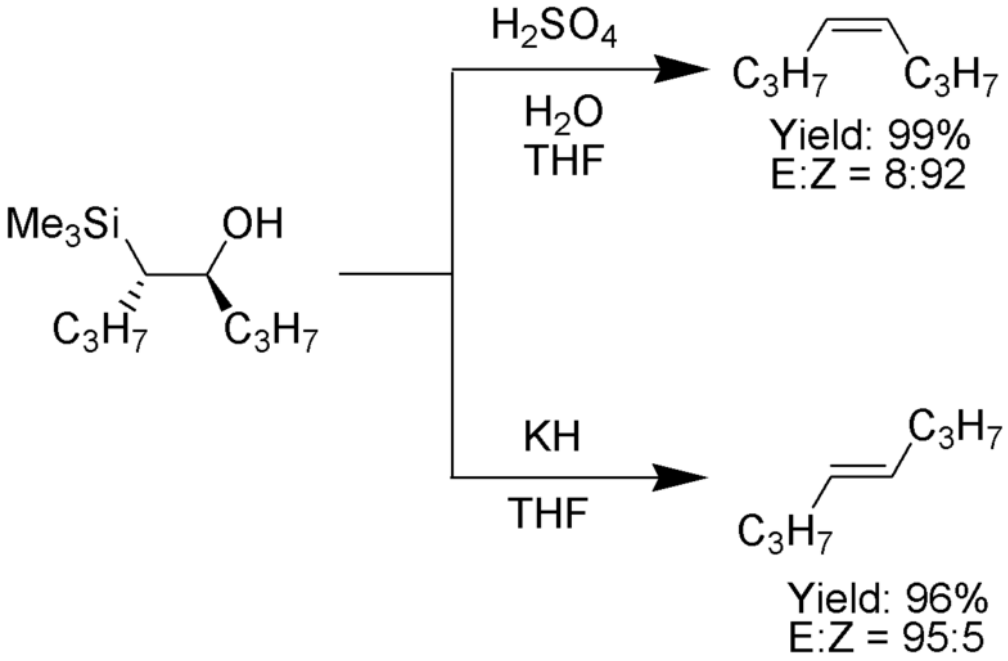
- unter basic conditions an cyclic mechanism of elimination– syn
- unter acidic conditions an acyclic β-eliminations occurs – anti

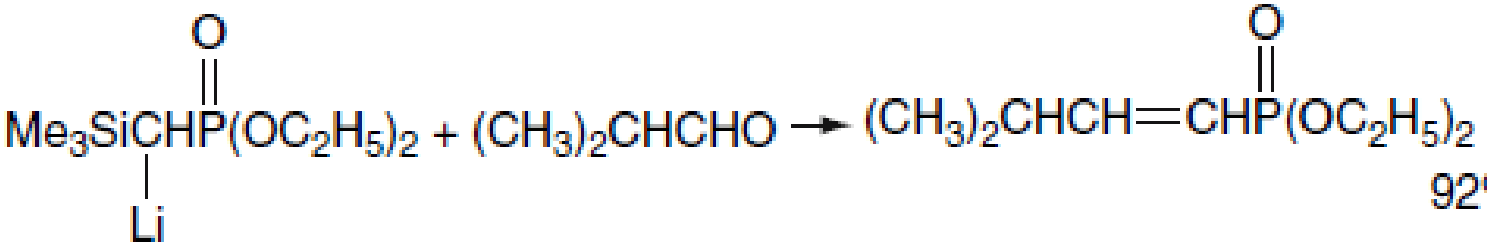
Reactions of Carbon Nu with C=O Compounds

Reations of α-Trimethylsilylcarbanions with C=O

Peterson reaction

Examples





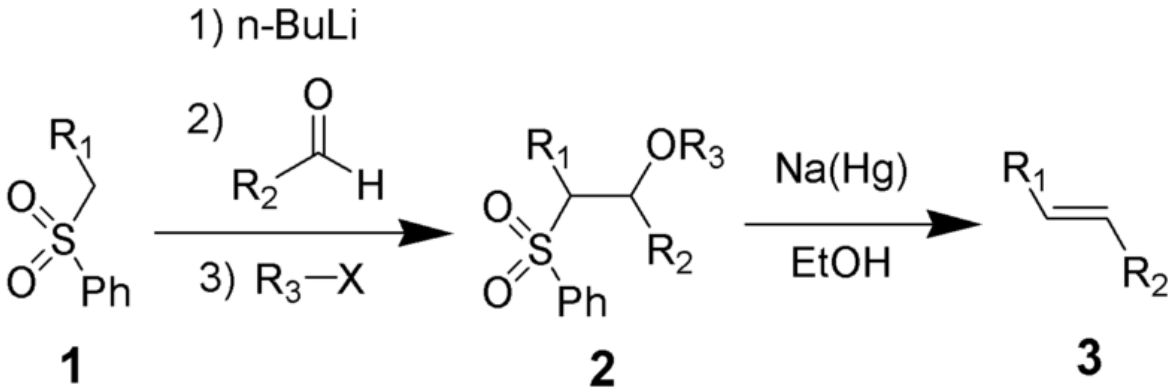
Reactions of Carbon Nu with C=O Compounds

Reations of alkylsulfonylcarbanions with C=O

Julia olefination (Julia–Lythgoe olefination)

- 1.step: the addition of sulfonyl-stabilized carbanions to carbonyl compounds
- 2.step: the alcohol functionalization
- 3. step: the elimination under reductive condition - formation of alkenes

- this transformation highly favors formation of the *E*-alkenes



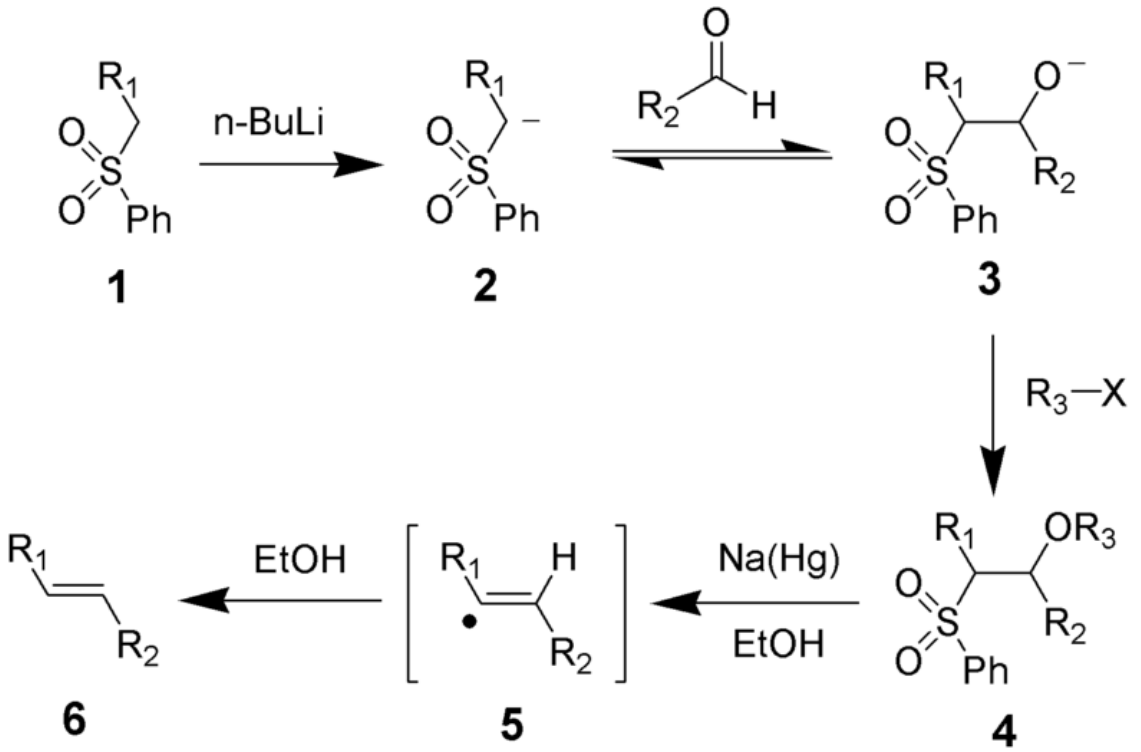
- functionalization (R^3 = Bz, Ac…with Ac_2O or BzCl)
- reductive elimination (Na/Hg or SmI_2)

Reactions of Carbon Nu with C=O Compounds

Reations of alkylsulfonylcarbanions with C=O

Julia olefination

- mechanism:



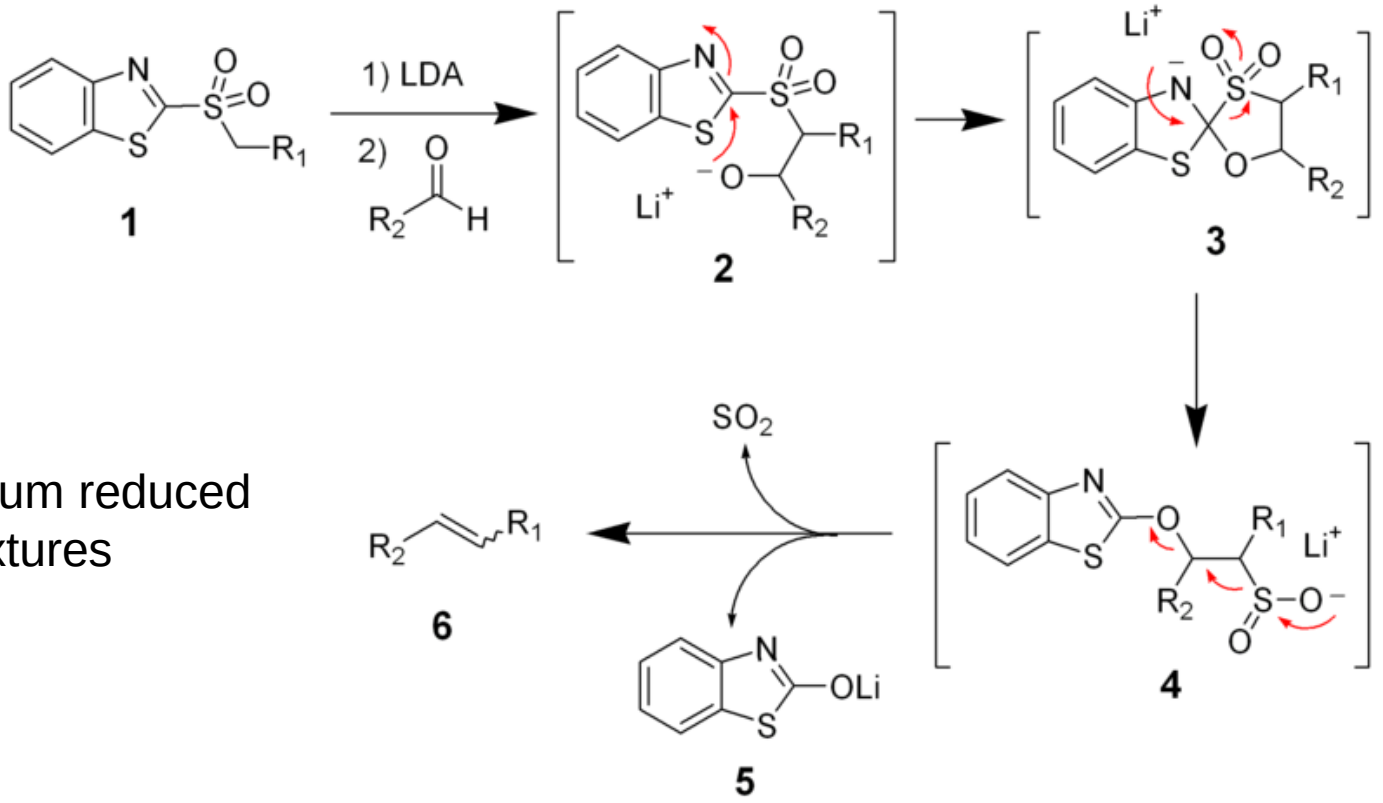
- the stereochemistry of the alkene (6) is independent of the stereochemistry of the sulfone intermediate 4
- *via* the radical intermediates, that are able to equilibrate
- more thermodynamically stable *E*-olefin is produced

Reactions of Carbon Nu with C=O Compounds

Reations of alkylsulfonylcarbanions with C=O

Julia – Kocienski olefination

- number of variations
- the replacement of the phenyl sulfones with heteroaryl sulfones (benzothiazole sulfones, *tetrazole sulfones*)

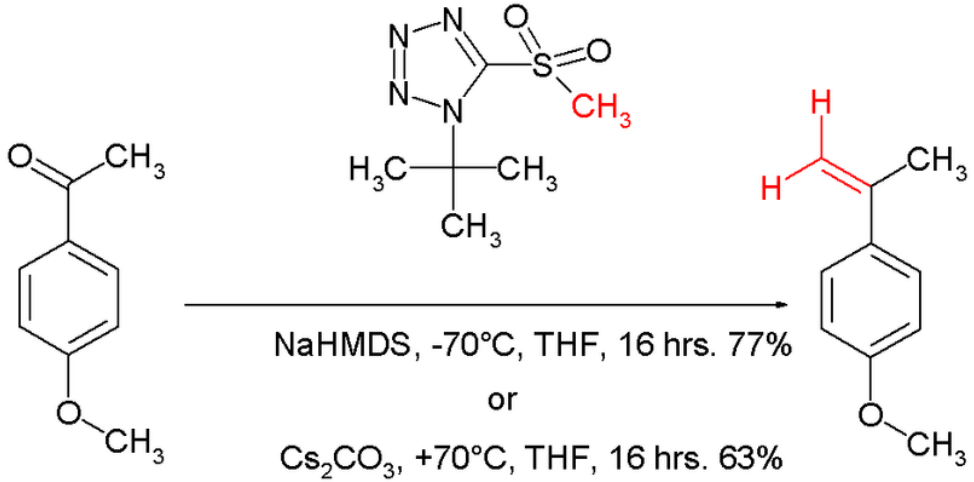


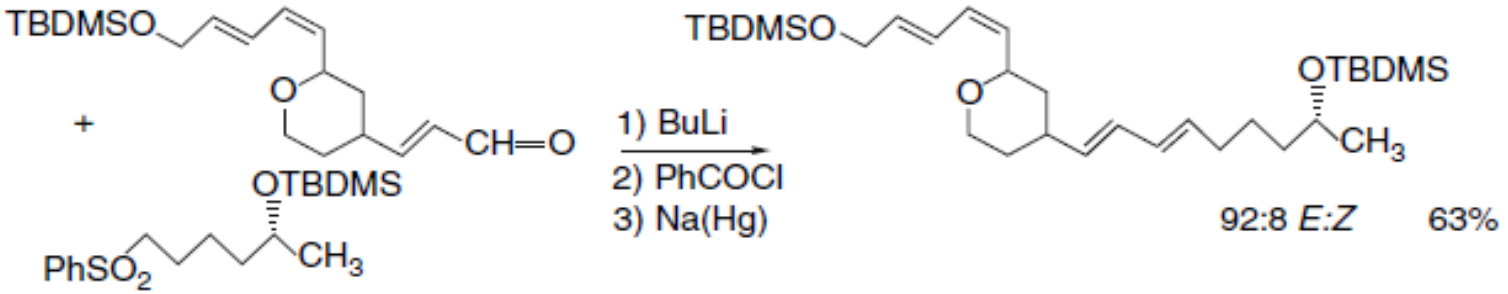
- equlibrium reduced
- E/Z mixtures

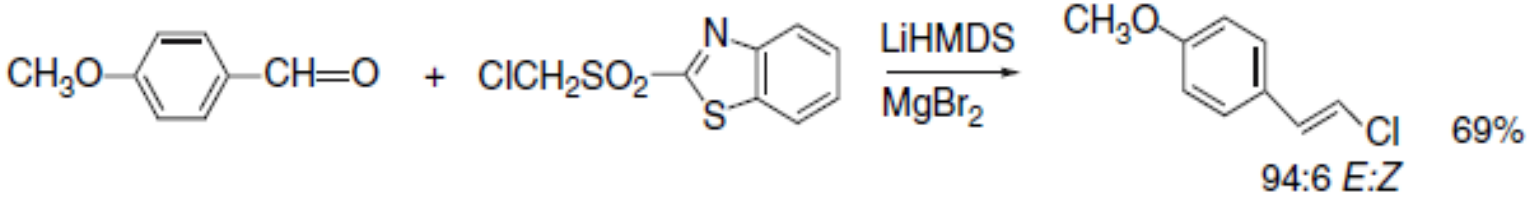
Reactions of Carbon Nu with C=O Compounds

Reations of alkylsulfonylcarbanions with C=O

Examples



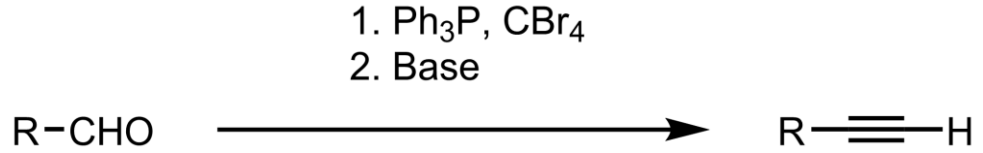




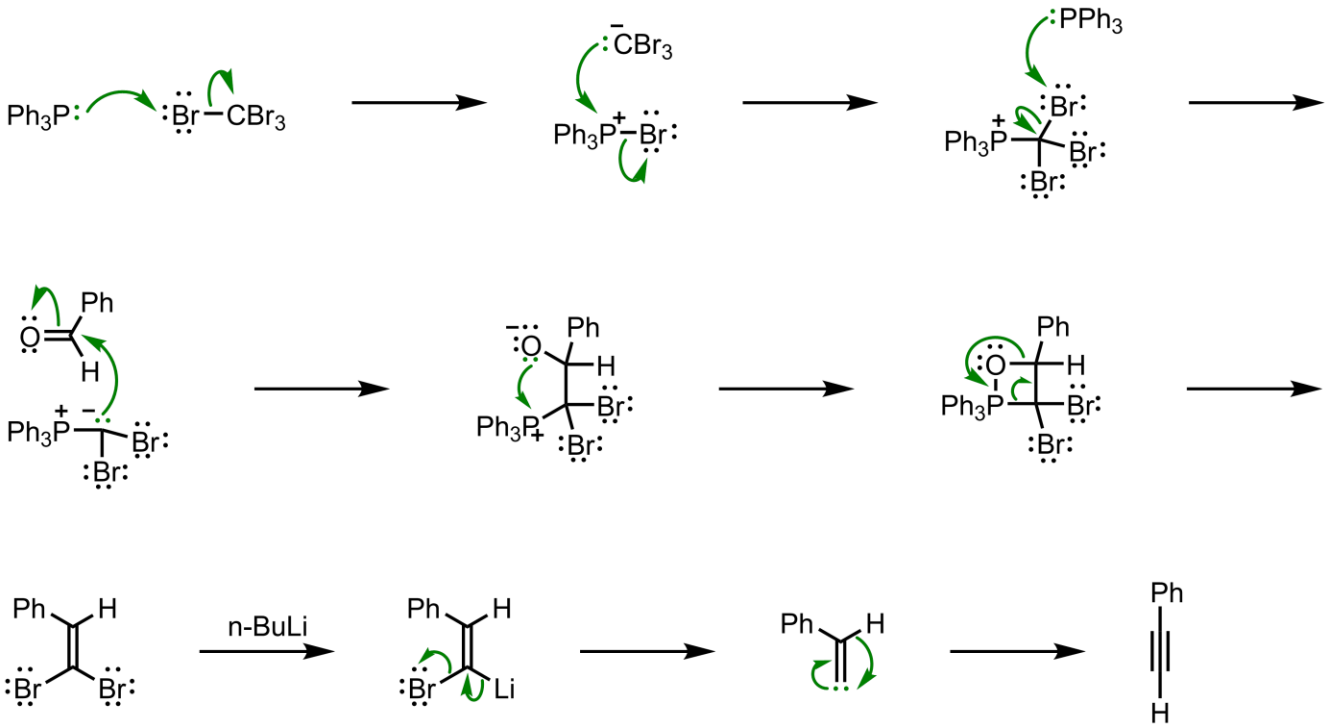
Reactions of Carbon Nu with C=O Compounds

Corey-Fuchs Reaction

- alkyne formation



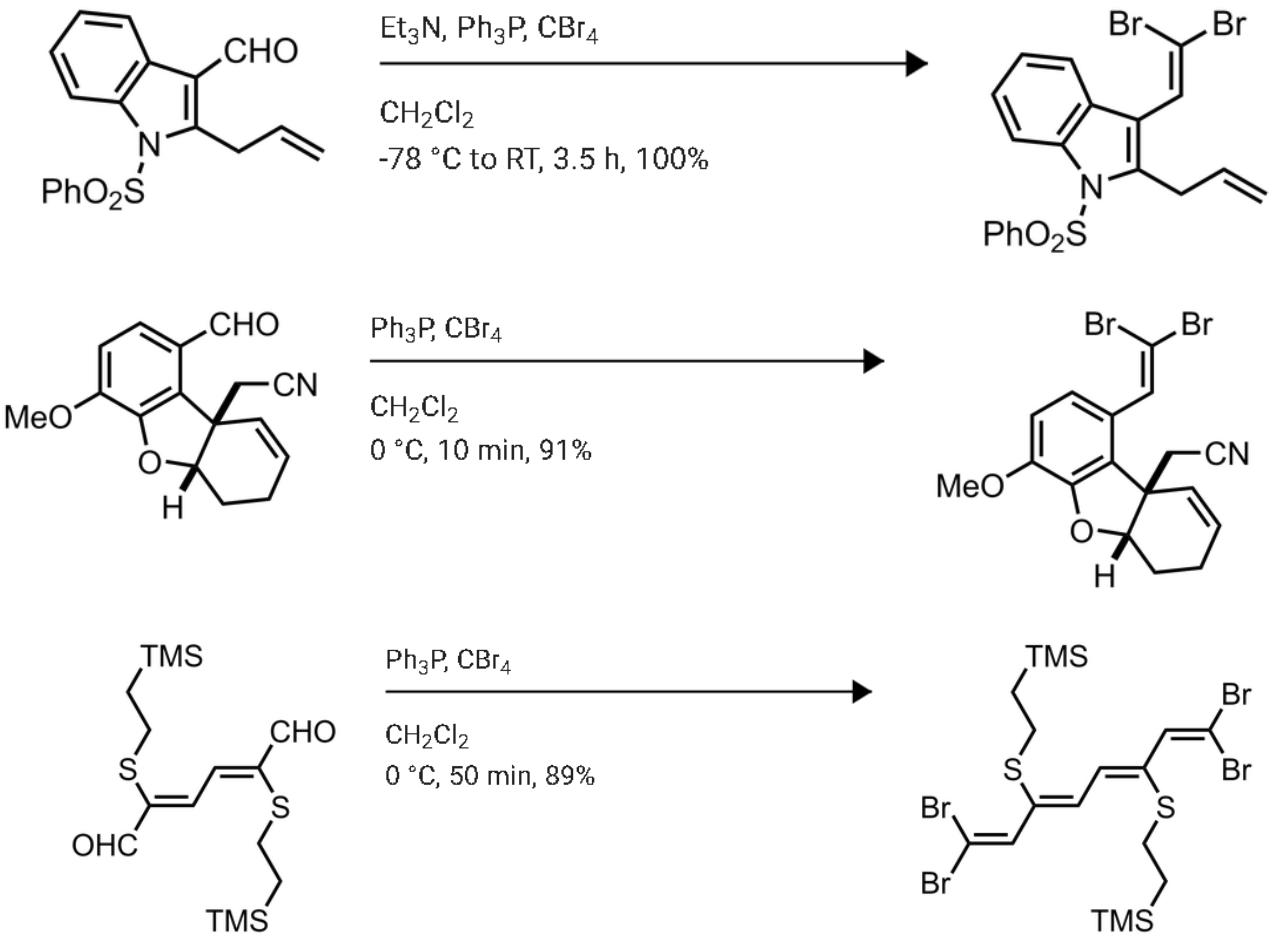
- mechanism



Reactions of Carbon Nu with C=O Compounds

Corey-Fuchs Reaction

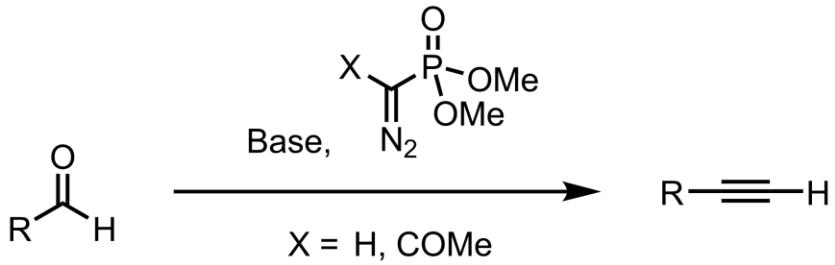
Samples



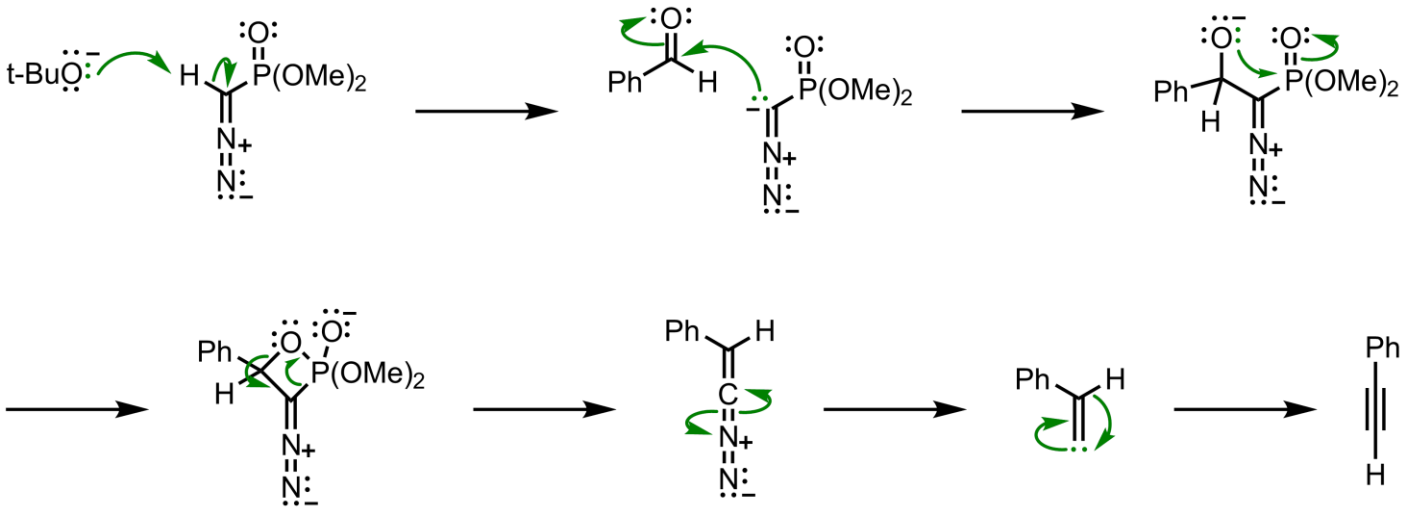
Reactions of Carbon Nu with C=O Compounds

Seyfert-Gilbert Homologation

- alkyne formation
- Base: K_2CO_3



- mechanism



Reactions of Carbon Nu with C=O Compounds

Seyfert-Gilbert Homologation

Samples