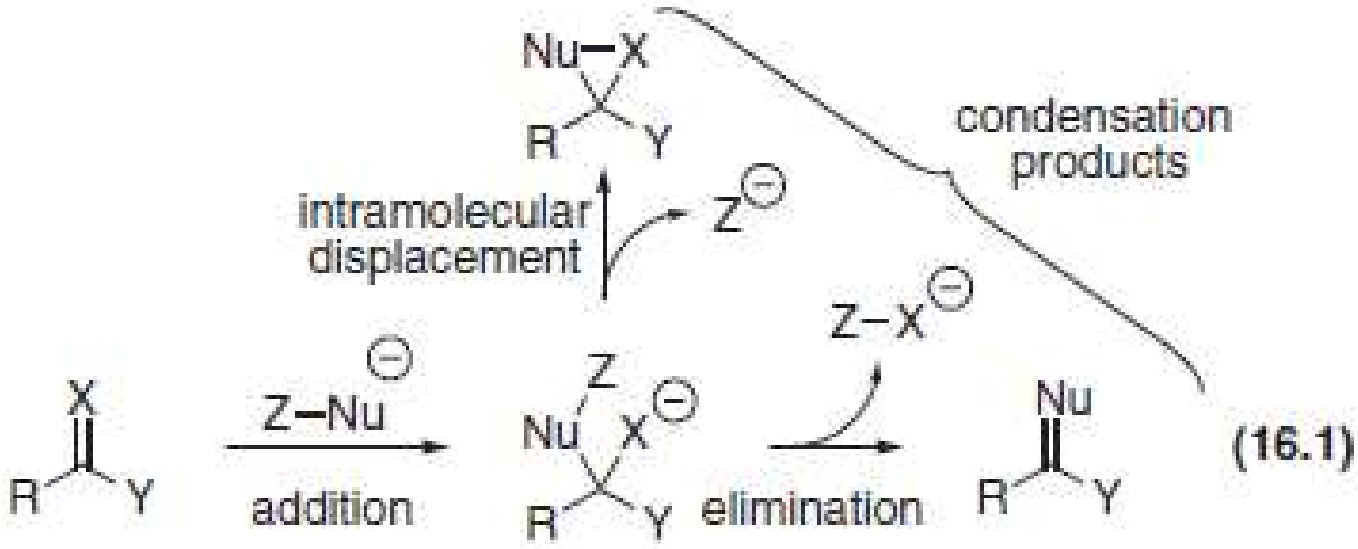
Chapter 16



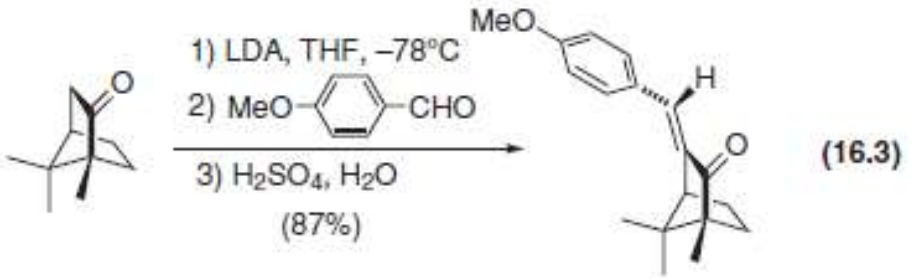
During a condensation reaction, a small molecule is eliminated from the initial adduct.

Condensations of enolate anions with aldehydes

Condensations can be carried out using ketones (G=alkyl; Claisen-Schmidt condensation), esters (G=OR; Knoevenagel condensation), or mixed anhydrides (G=OCOR; Perkin condensation)

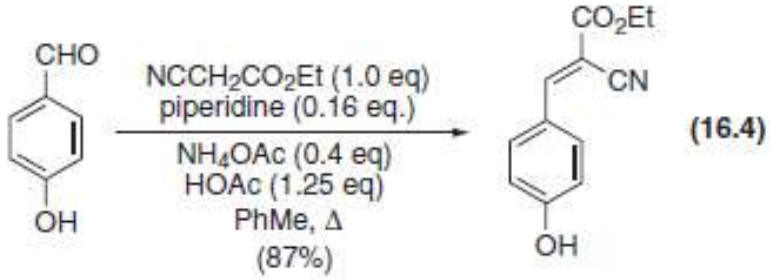
Claisen-Schmidt and Knoevenagel condensations

Claisen-Schmidt reaction: ketone enolate nucleophile, aldehyde electrophile



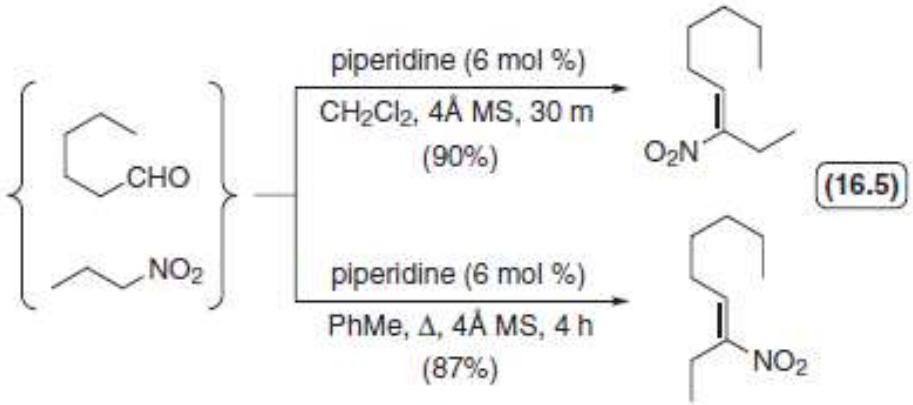
(16.3)

Knoevenagel condensation: cyanoacetate ester enolate nucleophile, aldehyde electrophile



(16.4)

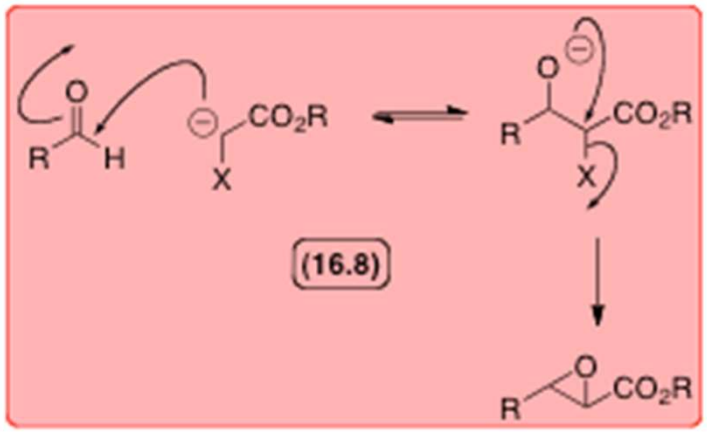
Knoevenagel condensation: nitroalkane enolate nucleophile, aldehyde electrophile



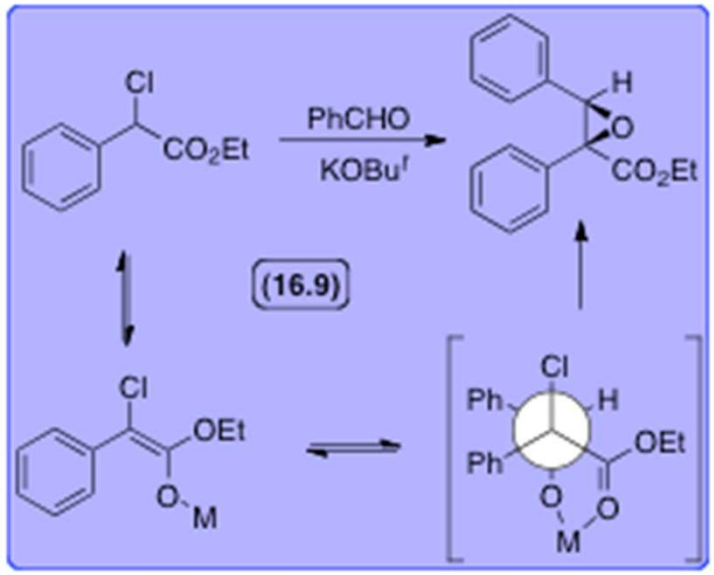
(16.5)

Darzens condensation

Alkoxide anion generated by addition to the aldehyde is trapped by the alkyl halide as an intramolecular electrophile



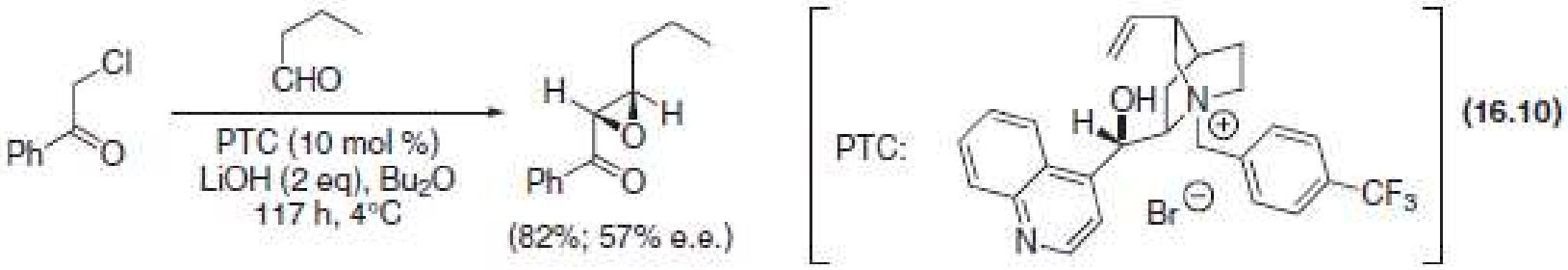
The *E(O)* enolate of the haloester reacts through a chelated transition state to give the *cis*-2,3-diphenyl-oxirane: the alkyl group of the aldehyde ends up *trans* to the carbonyl group.



Asymmetric Darzens condensation

Using a chiral phase transfer catalyst and lithium hydroxide as the base in a non-polar ether solvent allows the enantiomerically enriched epoxide to be formed.

Note how the alkyl group of the aldehyde again ends up *trans* to the carbonyl group in this reaction

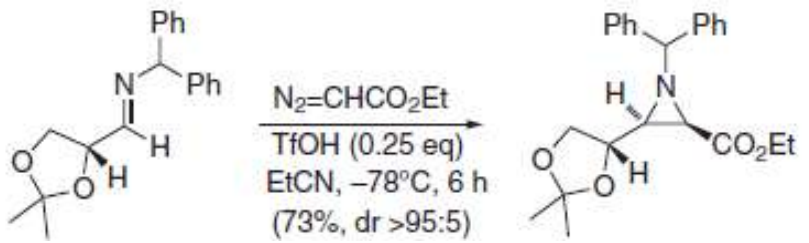


(16.10)

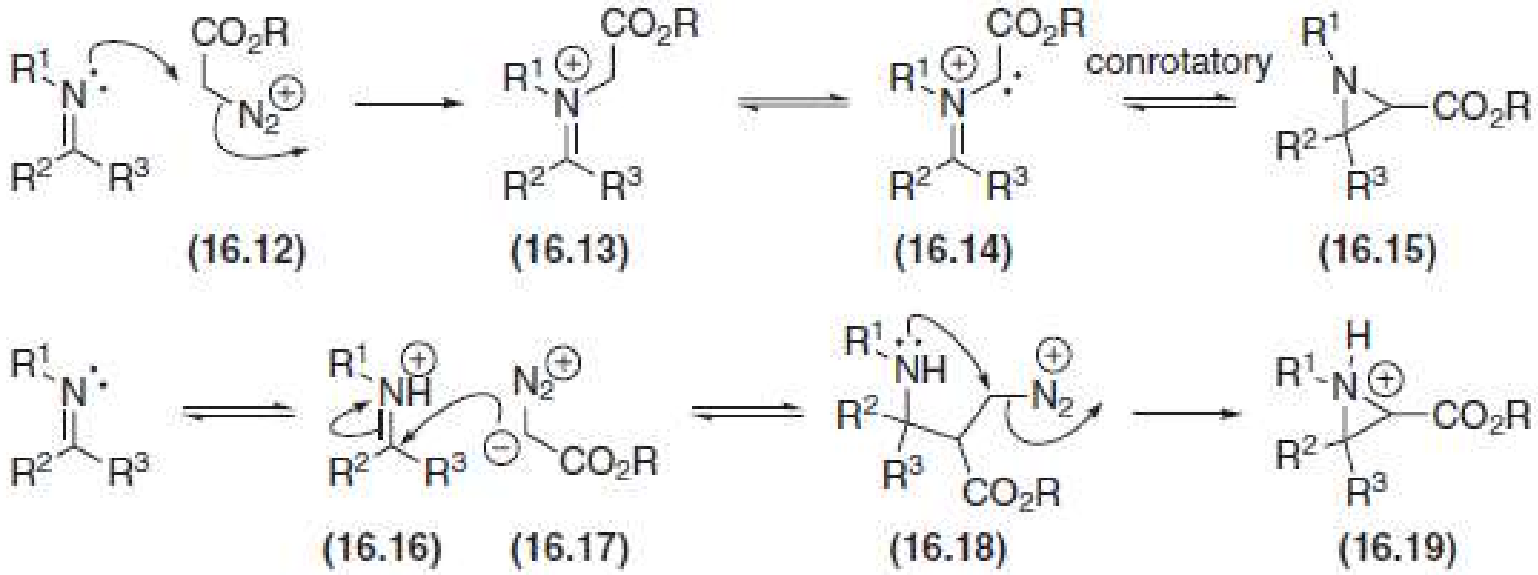
Aza-Darzens condensation

Addition of a diazoester to an imine constitutes a formal nitrogen analog of the Darzens condensation.

The reaction may proceed by either of two mechanisms depending on the exact reaction conditions.



(16.11)

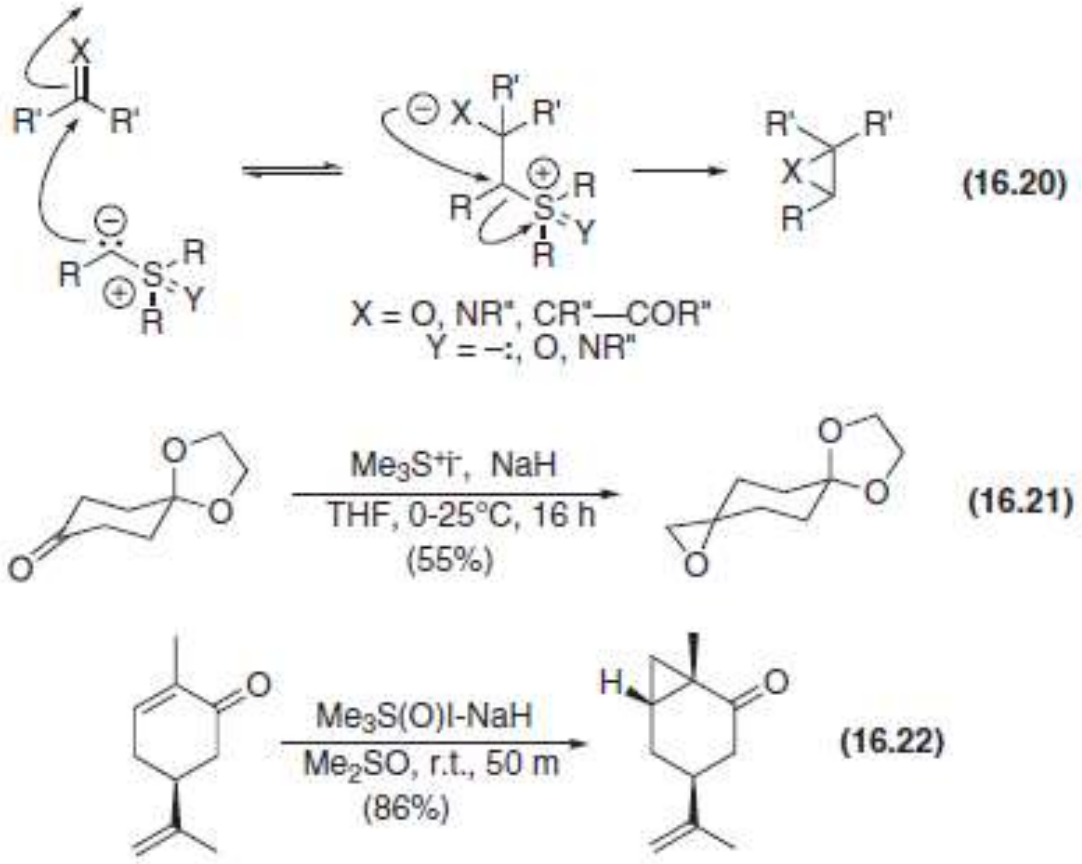


Corey-Chaykovsky reaction

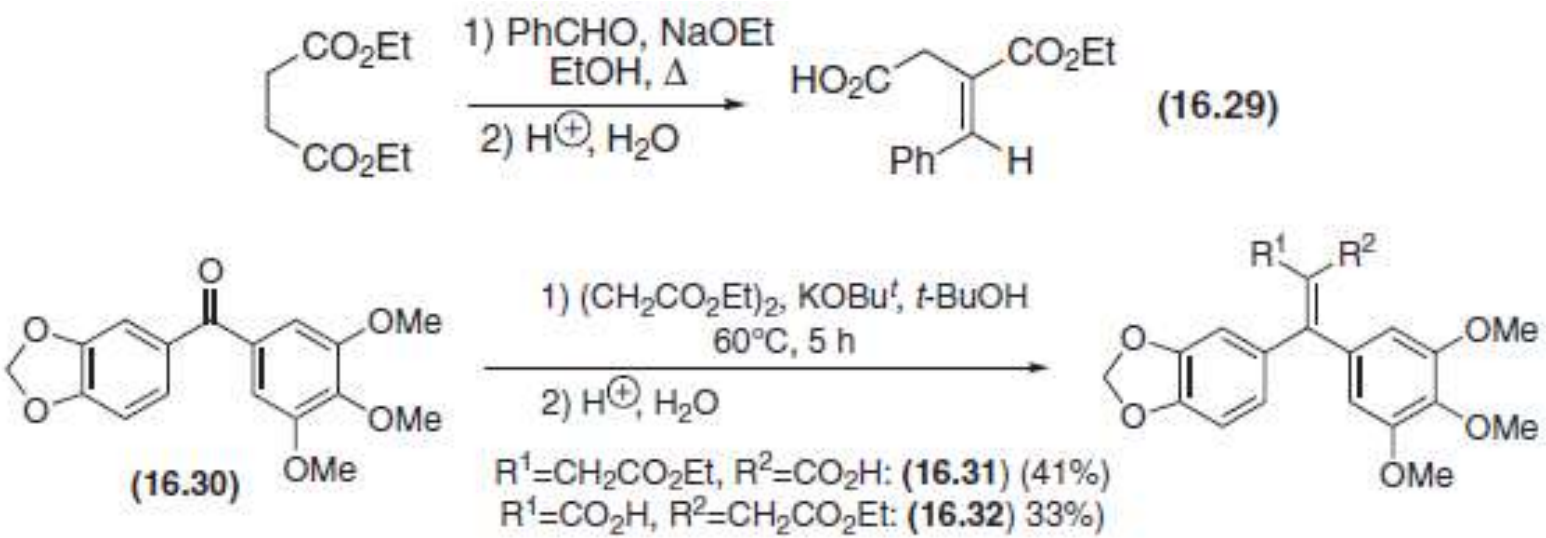
Sulfur ylides add to carbonyl and imine groups to give three-membered heterocycles.

Addition of sulfonium ylides to ketones and aldehydes gives epoxides.

Addition of sulfoxonium ylides to α,β-unsaturated ketones gives cyclopropyl ketones



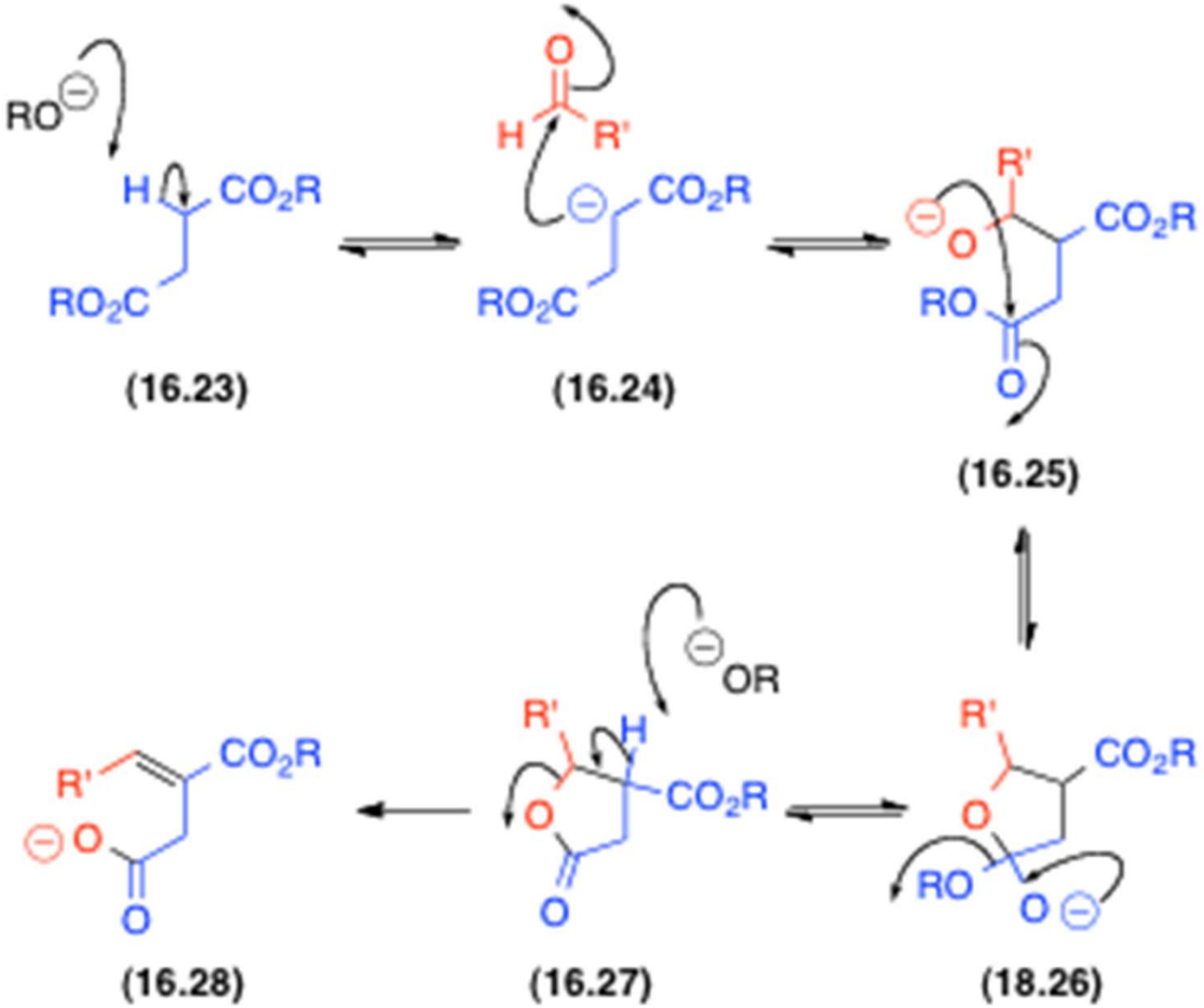
Stobbe condensation



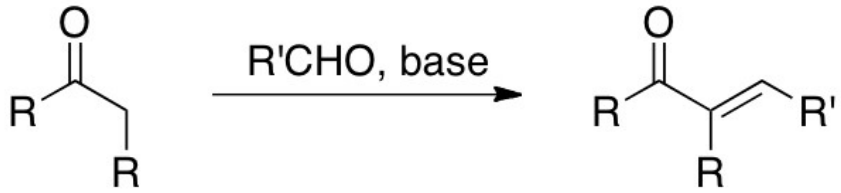
The Stobbe condensation involves the addition of the enolate of a succinate ester to an aldehyde or ketone. The product of the reaction is a half-ester, where the ester is conjugated, and the carboxylic acid is not.

Figure 16.1

The course of the Stobbe condensation

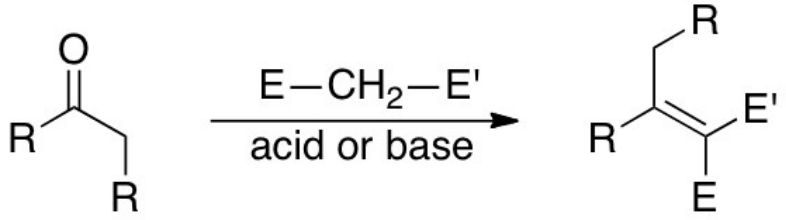


Reaction synopsis: Claisen-Schmidt reaction



Reagents: NaOH, EtOH; KOH, EtOH; NaOEt, EtOH; etc.
Works best if the aldehyde is aromatic

Reaction synopsis: Knoevenagel condensation



E, E' = COR', CO_2R', CN, NO_2, SO_2R', etc.

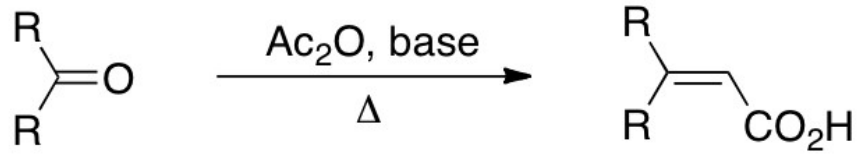
Reagents (all Doebner modifications):

$CH_2(CO_2Et)_2$, NH_4OAc, piperidine, AcOH, Δ;

$N{\equiv}CCH_2CO_2Et$, NH_4OAc, piperidine, AcOH, Δ;

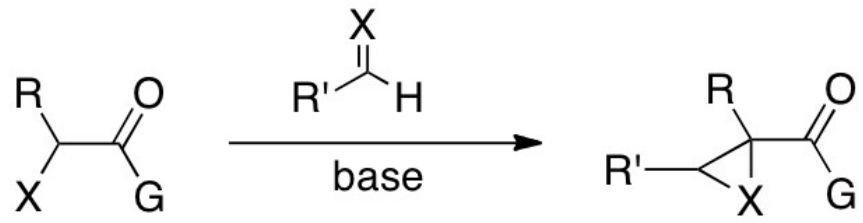
$MeCOCH_2CO_2Et$, NH_4OAc, piperidine, AcOH, Δ; etc.

Reaction synopsis: Perkin condensation



Reagents: Ac_2O, NaOAc, Δ; Ac_2O, Et_3N, Δ; etc.
Reaction proceeds more slowly with other anhydrides to give α-substituted cinnamic acids.

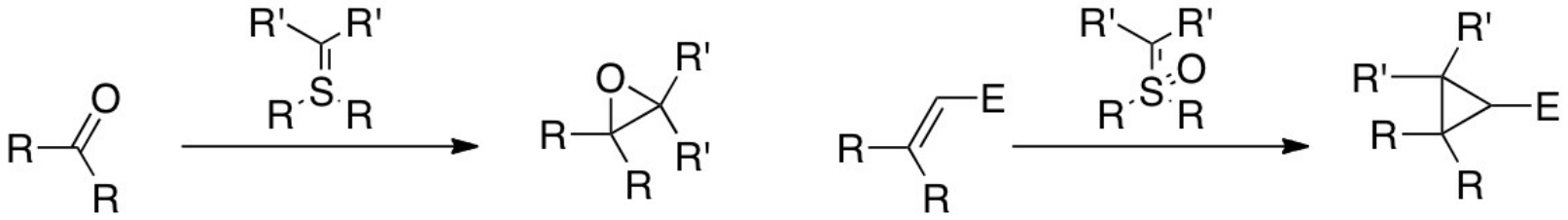
Reaction synopsis: Darzens condensation



G=R, Ar, OR;
X=O, NR, C(R)—E (E=CO_2R, COR, CN, NO_2, etc,)

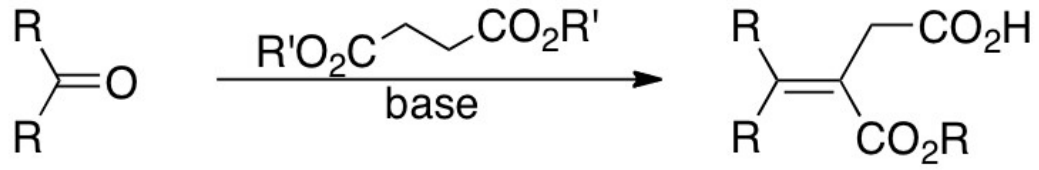
Reagents: $RCH(Cl)CO_2Et$, ArCHO, $KOBu^t$, THF; etc.

Reaction synopsis: Corey-Chaykovsky reaction



Reagents: $Me_3S^+I^-$, NaH, Me_2SO; $Me_3S^+I^-$, $KOBu^t$, THF; etc.
or $Me_3S(O)^+I^-$, NaH, Me_2SO; $Me_3S(O)^+I^-$, $KOBu^t$, THF; etc.

Reaction synopsis: Stobbe condensation

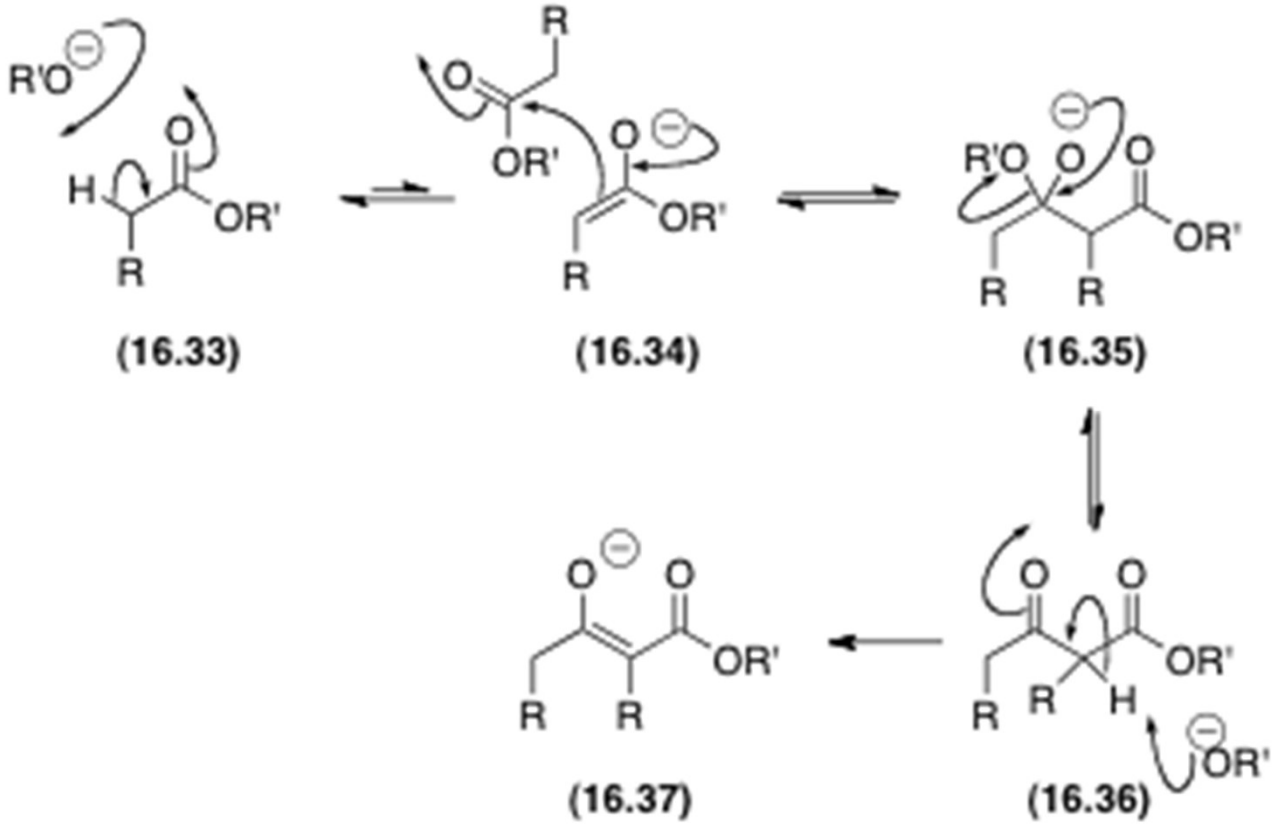


Reagents: $(CH_2CO_2Et)_2$, NaOEt, EtOH, Δ; etc.

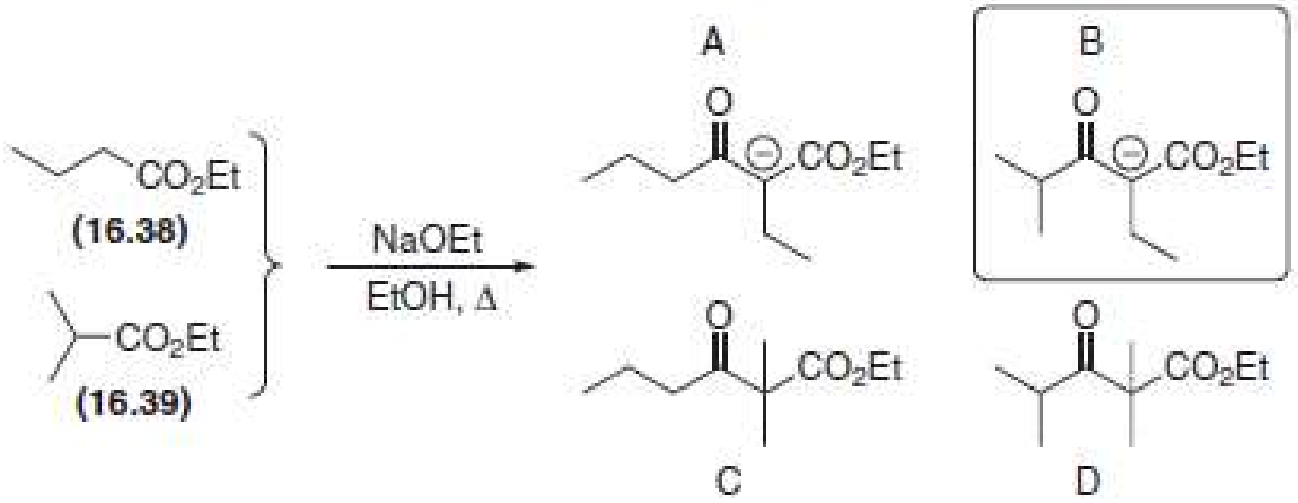
Stereochemistry: with aldehydes, *E* isomer predominates; with ketones product is close to stereorandom

Figure 16.2

The path of the Claisen condensation



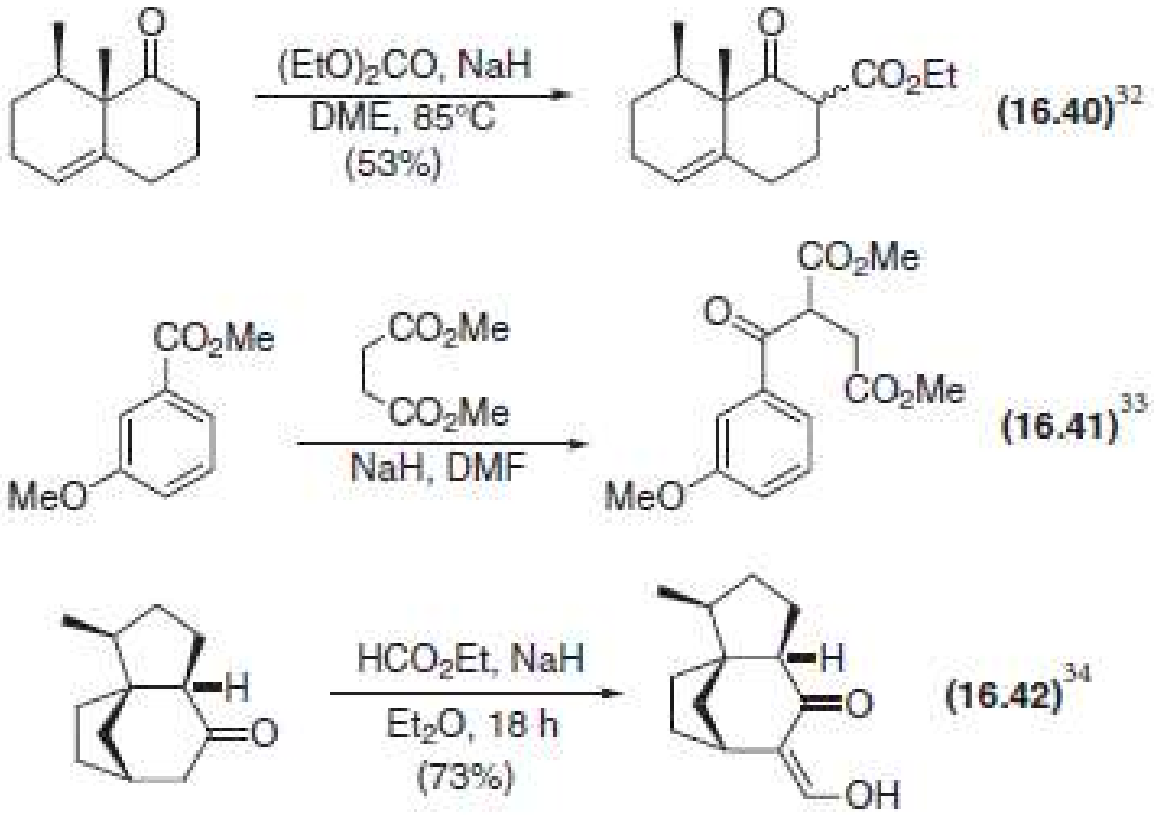
Crossed Claisen condensation: A



- β-ketoester A is the homocoupling product of ester **16.38**
- β-ketoester D is the homocoupling product of ester **16.39**
- β-ketoesters C and D lack an acidic hydrogen between the two carbonyl groups, so these condensation reactions are easily reversed
- β-ketoester B is the heterocoupling product of the two esters, and it has the acidic hydrogen between the carbonyl groups. This product is favored with long reaction times

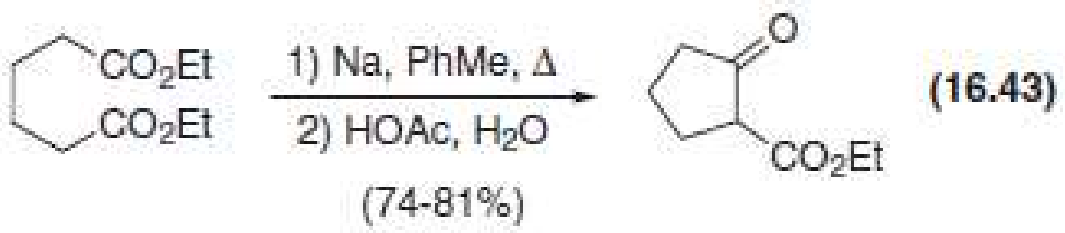
Crossed Claisen condensation: B

- the esters in red have no acidic α hydrogens, so none of them can form an enolate anion
- the product of the crossed Claisen condensation is the only one obtained in these reactions



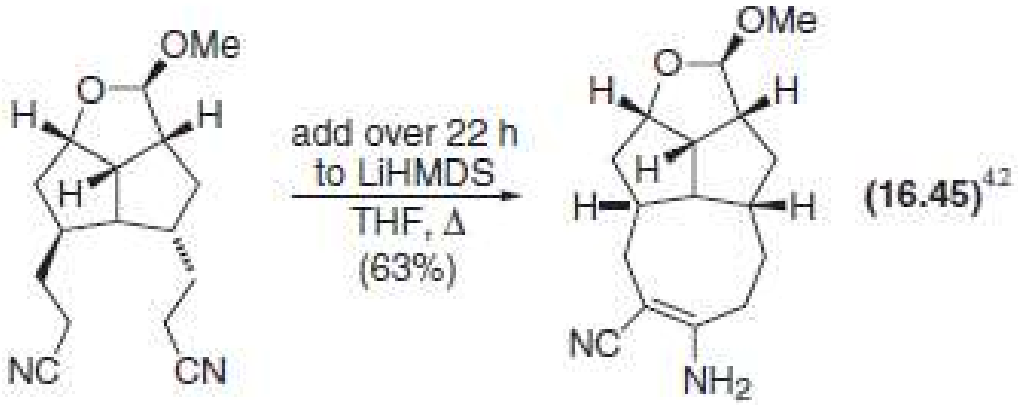
Dieckmann and Thorpe-Ziegler condensations

- The intramolecular variant of the Claisen condensation is known as the Dieckmann condensation. The rpoduct is a cyclic β-ketoester



(16.43)

- The nitrile analog of the Dieckmann condensation is known as the Thorpe-Ziegler condensation. The product is a β-amino-α, β-unsaturated nitrile

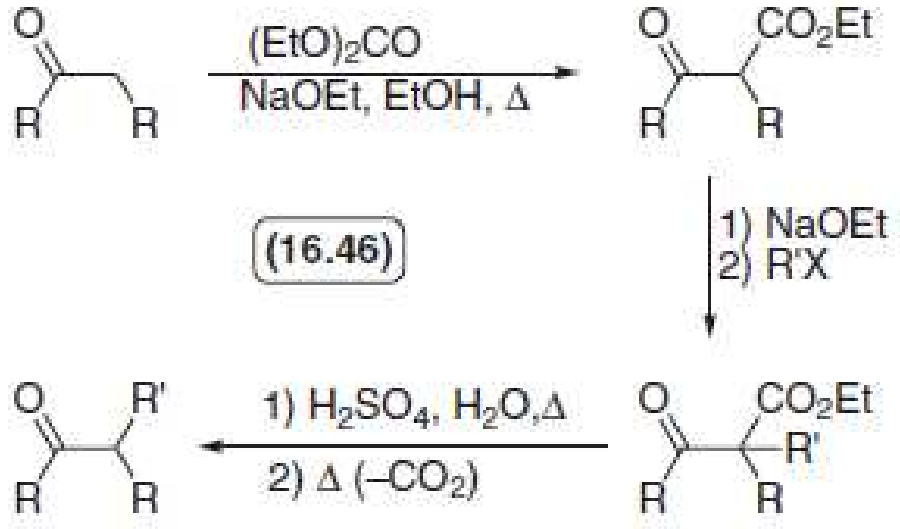


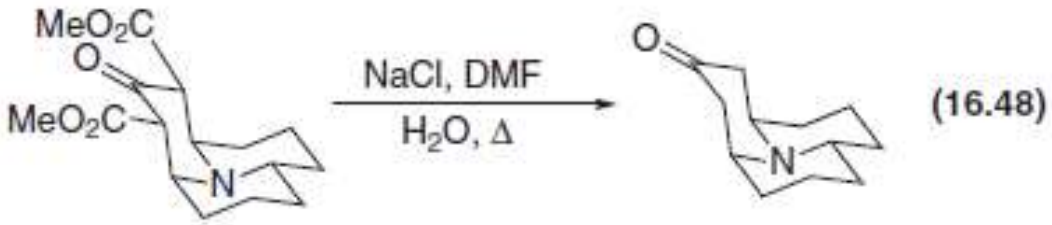
(16.45)[42]

Decarboxylation of β-ketoacids

- β-ketoacids are susceptible to decarboxylation under conditions of acid hydrolysis

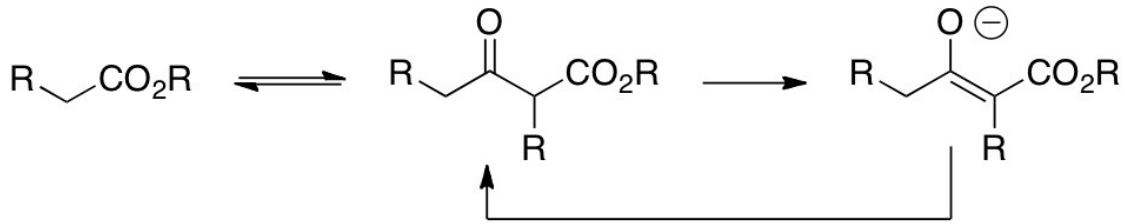
- the Krapcho decarboxylation involves S_N2 attack of chloride anion on the methyl group of a methyl ester, and decarboxylation of the revealed β-ketoacid





(16.48)

Reaction synopsis: Claisen condensation

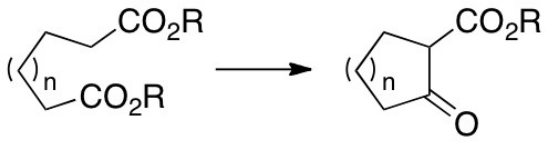


Reagents: 1) NaOEt, EtOH, Δ, then 2) HCl, H_2O; etc.

Equilibrium is favored by deprotonation of β-ketoester product

Crossed Claisen condensation works best when only one product can deprotonate to shift equilibrium

Reaction synopsis: Dieckmann condensation



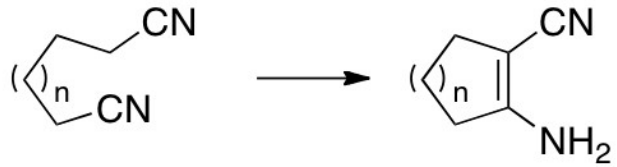
n=1, 2, 3, >11

Reagents: 1) NaOEt, EtOH, Δ, then 2) HCl, H_2O; etc.

Reaction works well to form 5- and 6-membered rings, and large rings

Reaction does not work well to form medium-sized rings

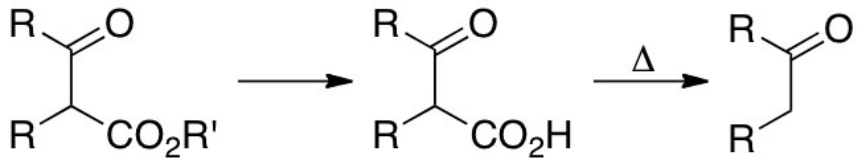
Reaction synopsis: Thorpe-Ziegler condensation



Reagents: 1) NaOEt, EtOH, Δ, then 2) HCl, H_2O; etc.

Reaction can be used to form medium-sized rings

Reaction synopsis: Decarboxylation



Reagents: 1) H_2SO_4, H_2O, Δ, then 2) Δ; etc.
or LiI, DMF, Δ; LiBr, Me_2SO, H_2O, Δ; etc.
(Krapcho)

Figure 16.3

The models of the C—X bond in heteroatom-stabilized carbanions. The resonance description of the bonding is shown below the orbital diagram.

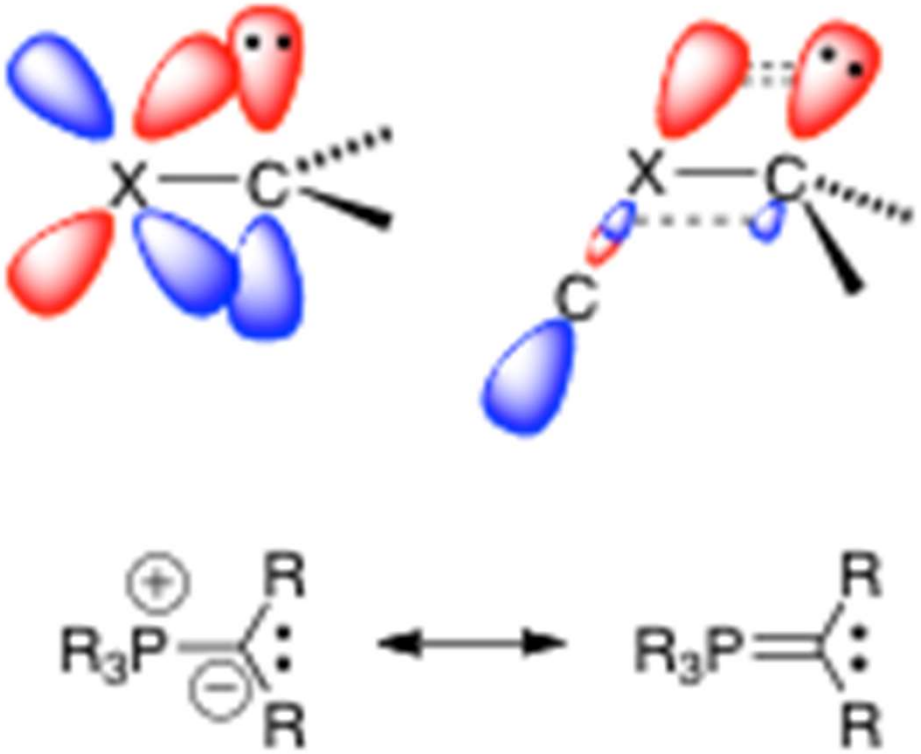
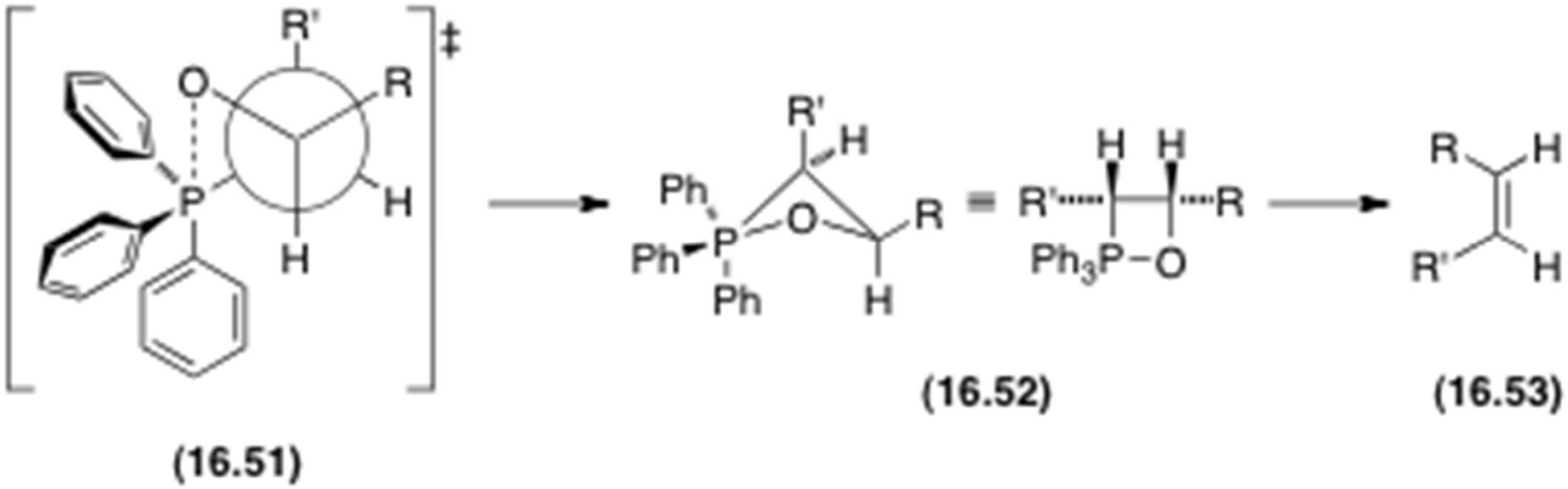


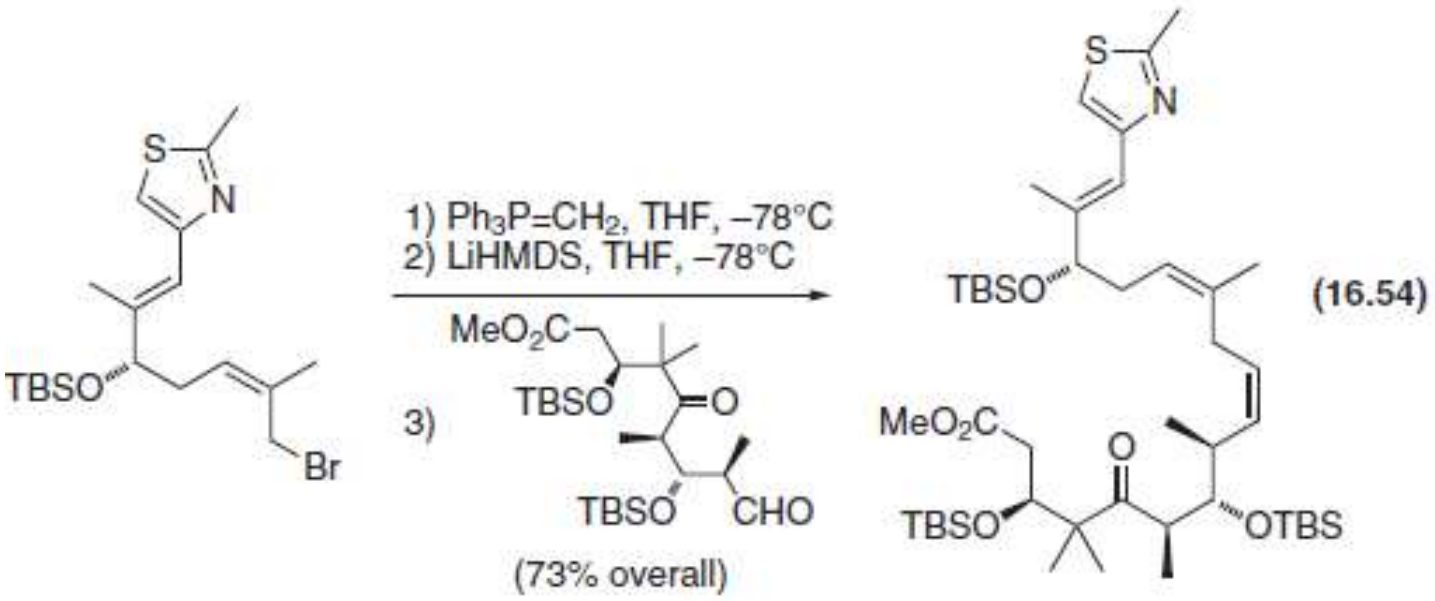
Figure 16.4



(16.51) (16.52) (16.53)

Rationalizing the stereochemistry of the concerted mechanism for the Wittig reaction

Tandem reaction of phosphorus ylide



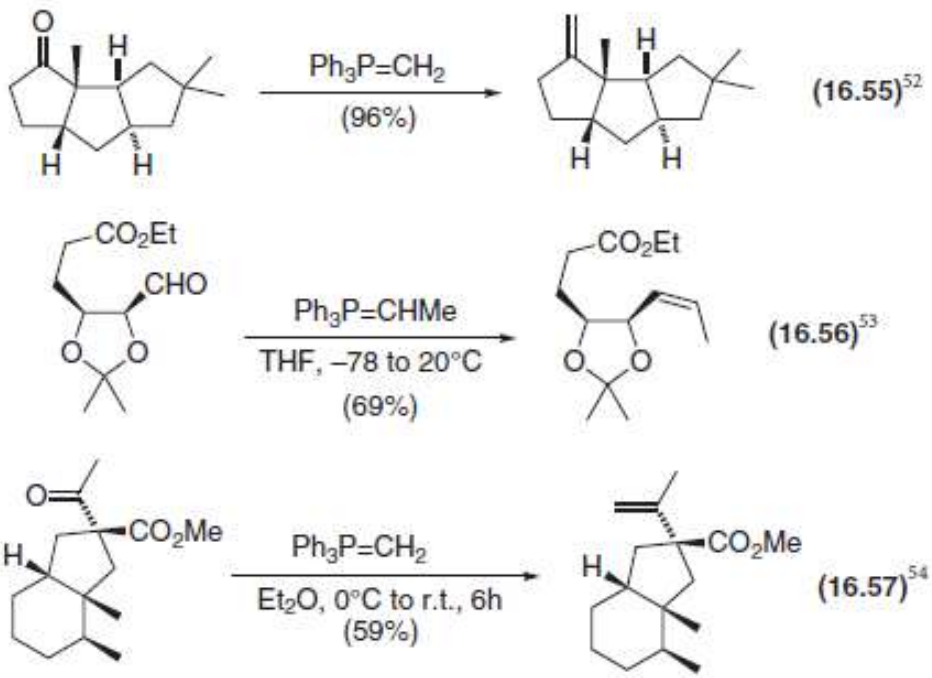
In step 1, the ylide acts as a carbon nucleophile to effect the S_N2 displacement of bromide anion, giving a new phosphonium salt

In step 2, the new phosphonium ion is deprotonated to a new phosphonium ylide

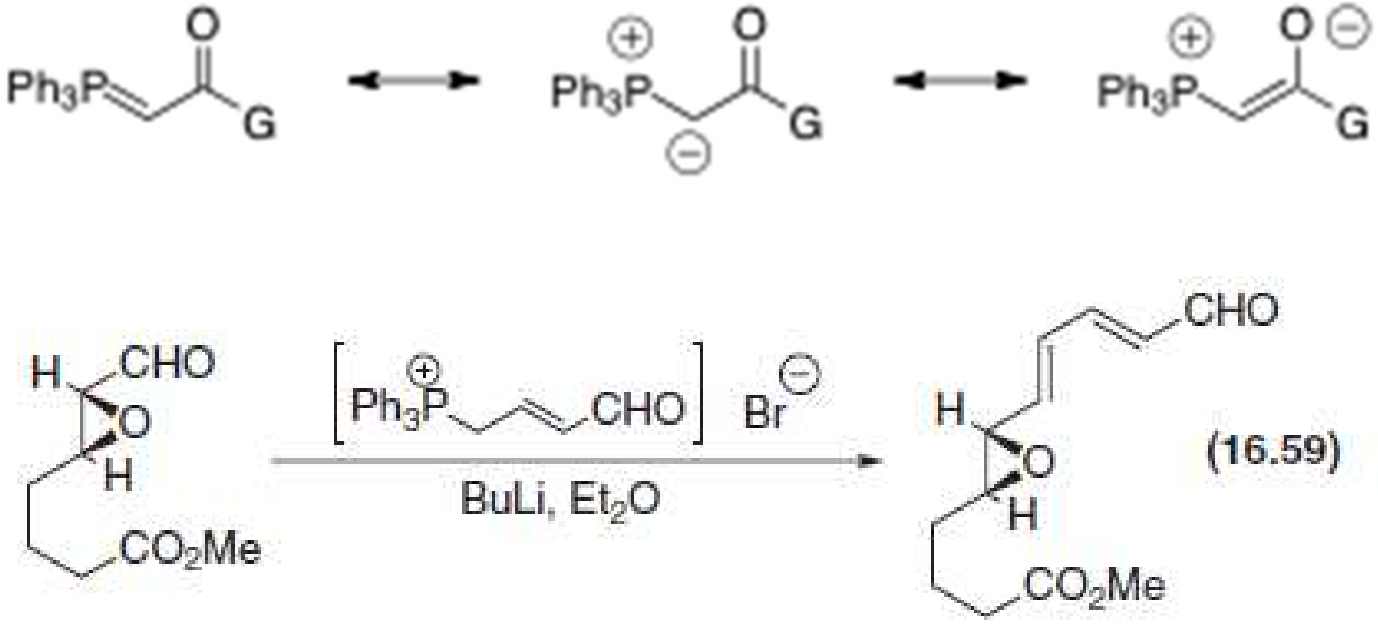
In step 3, the Wittig reaction is carried out

Representative Wittig reactions with unstabilized phosphonium ylides

Note the *Z* stereochemistry in the new alkene double bonds



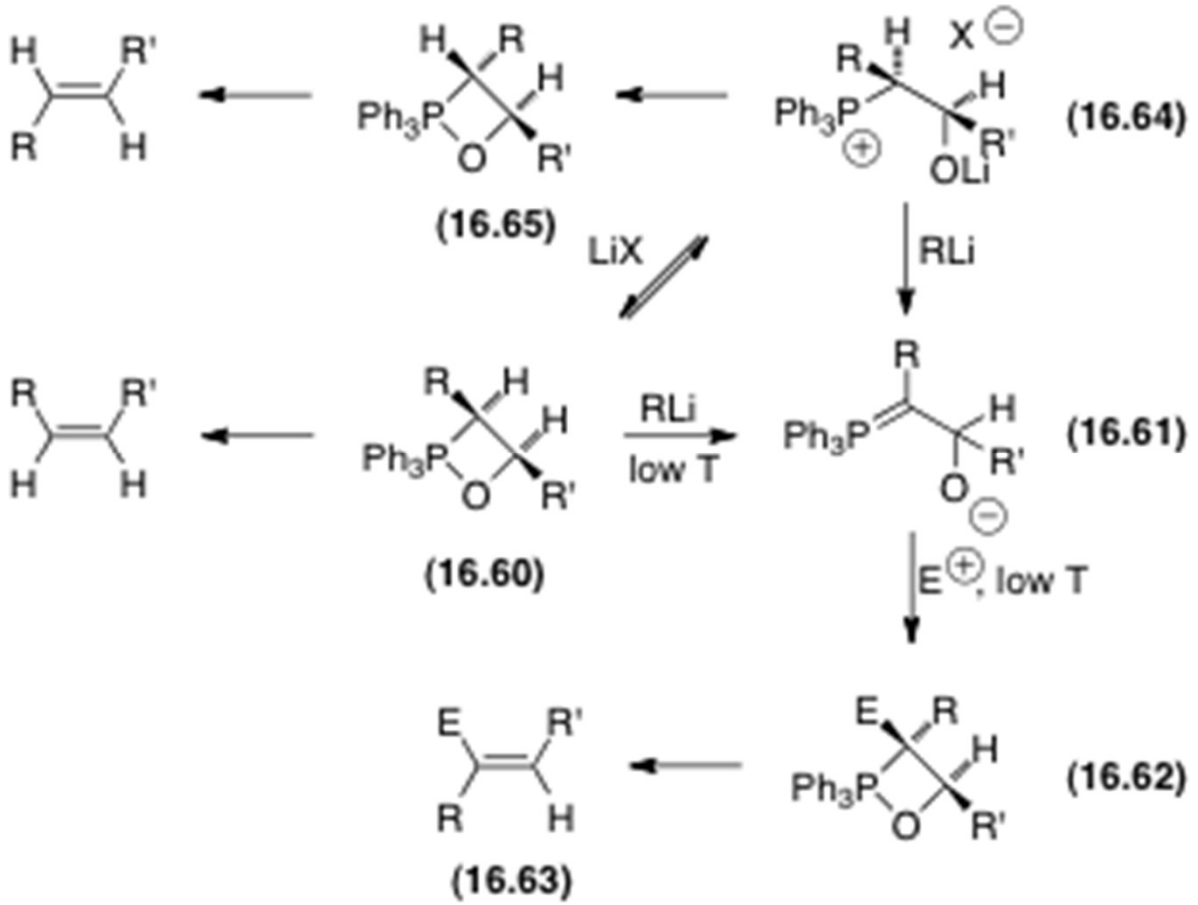
Wittig reactions with stabilized phosphonium ylides



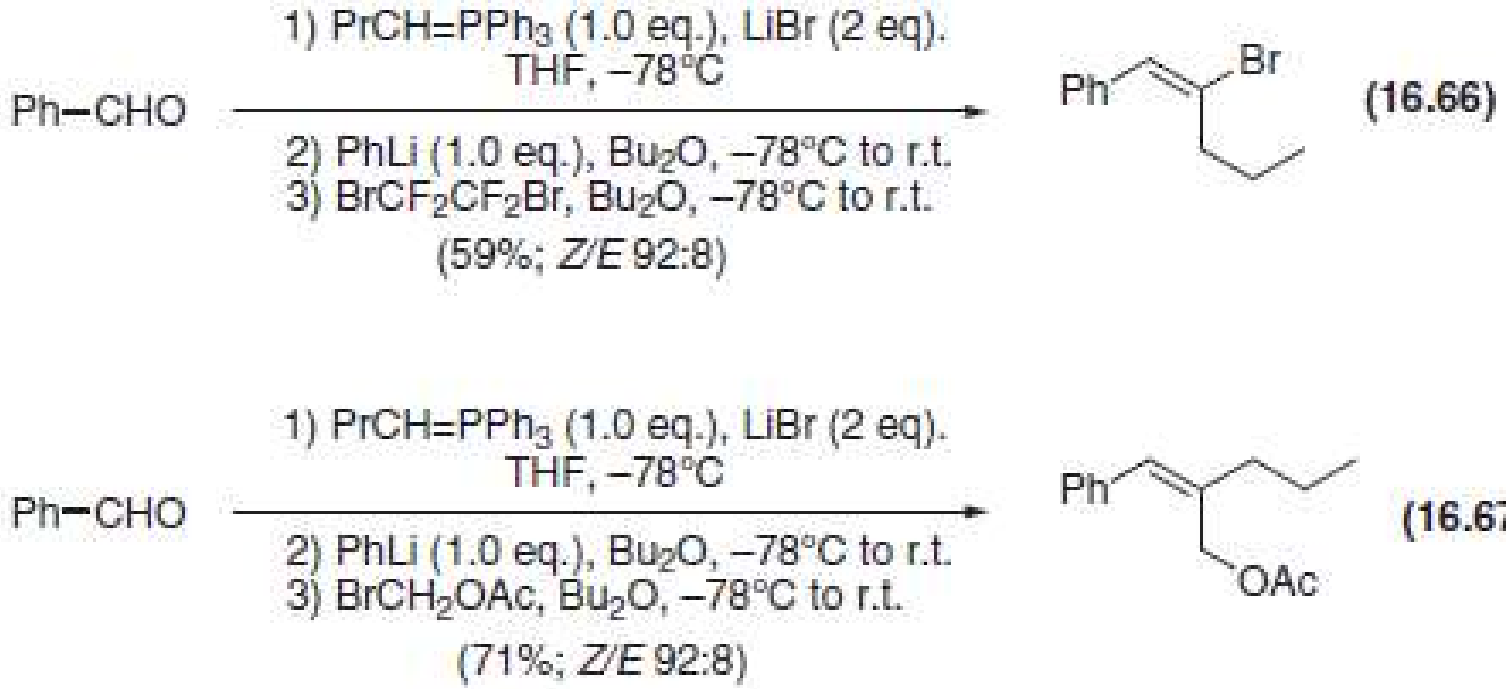
Stabilized phosphonium ylides preferentially form *E* alkenes

Figure 16.5

The possible outcomes of the Schlosser modification of the Wittig reaction



Representative Schlosser modifications of the Wittig reaction

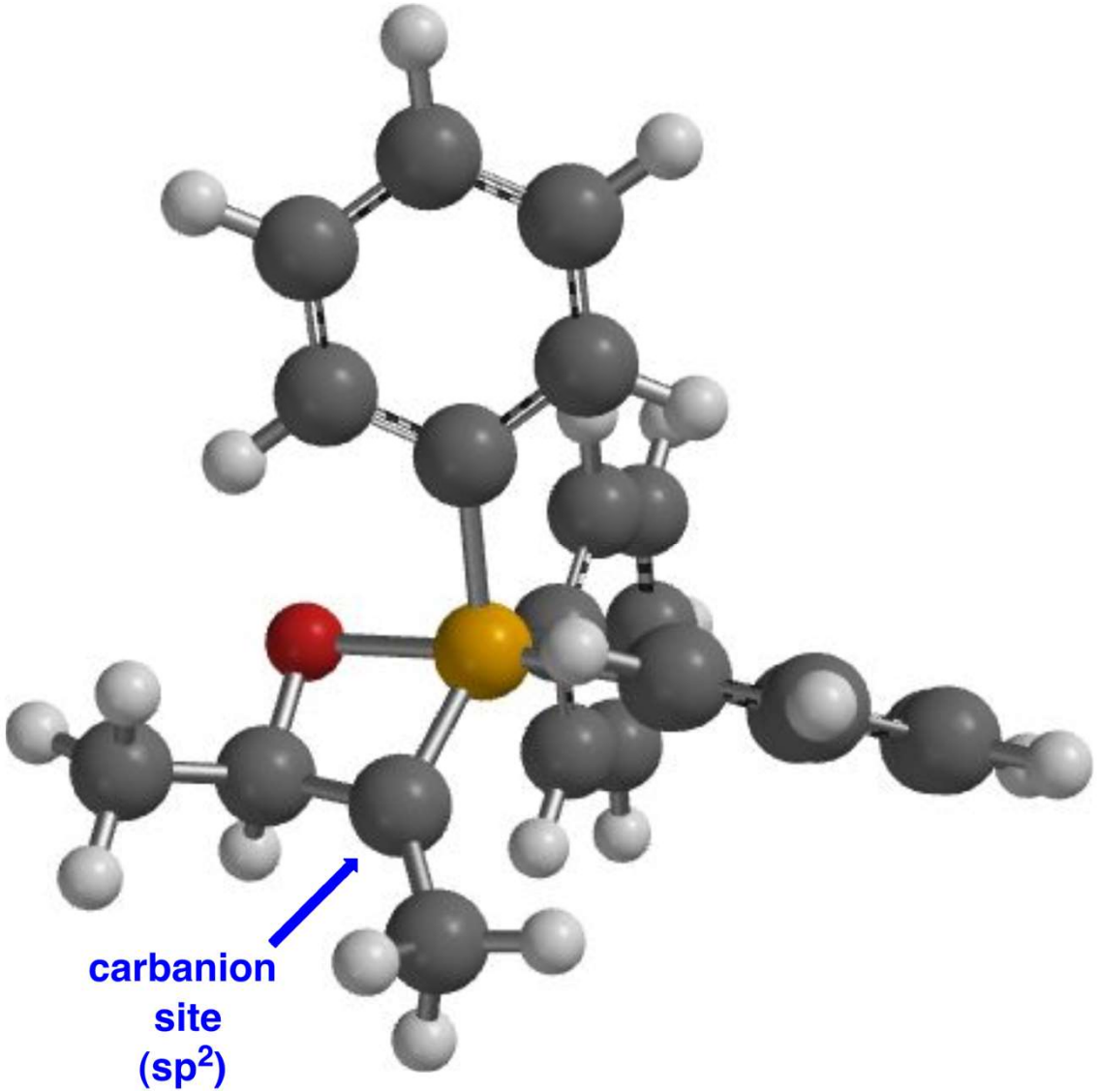


Trapping of the oxidophosphorane with a halogen or an electrophile *larger than formaldehyde* leads to the *E* alkene.

[The oxidophosphorane may have the structure of the conjugate base of the oxaphosphetane]

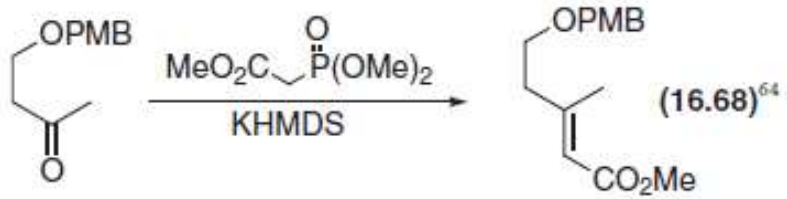
Figure 16.6

The computational model of an oxaphosphetane conjugate base

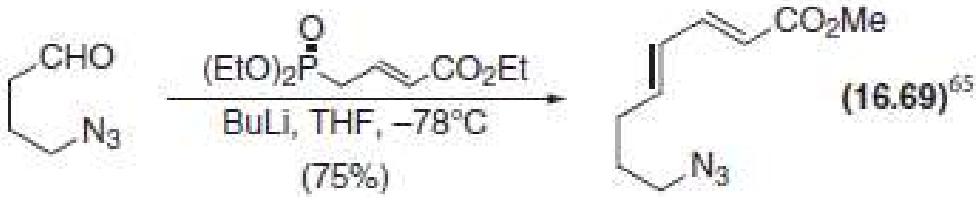


Representative Horner-Wadsworth-Emmons reactions

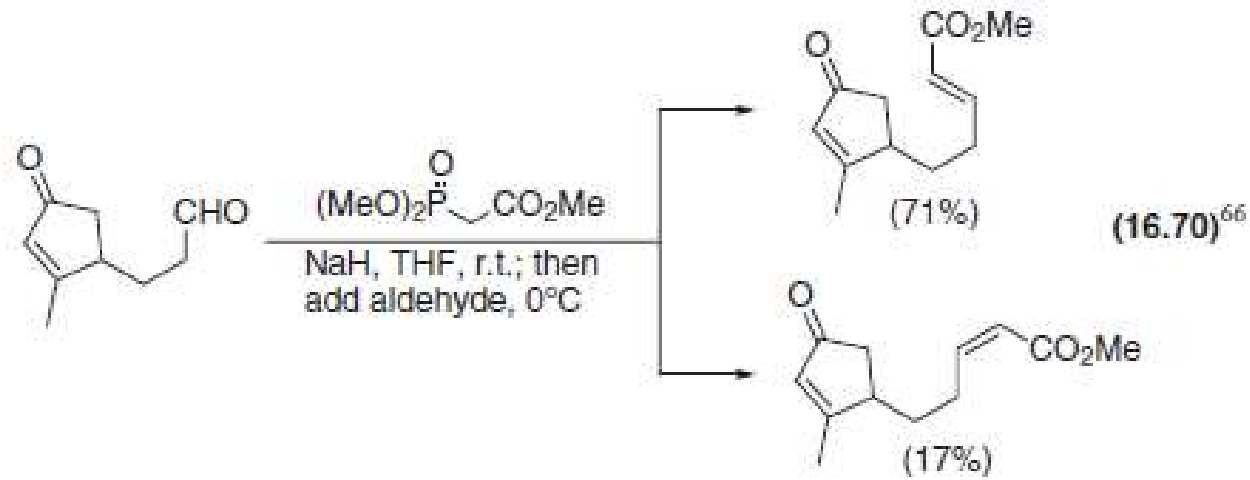
The *E* isomer is the major product, or the only product of the reaction



(16.68)[64]

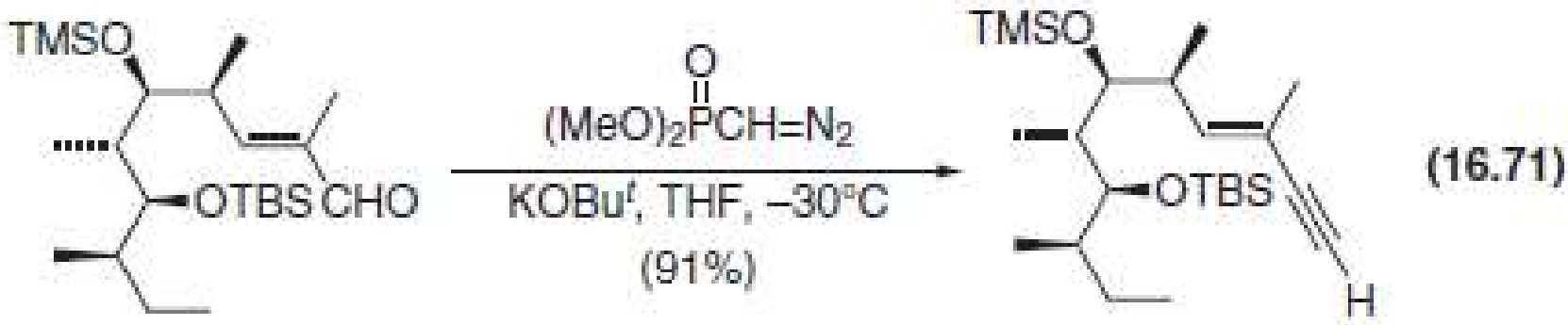


(16.69)[65]



(16.70)[66]

Seyferth-Gilbert homologation



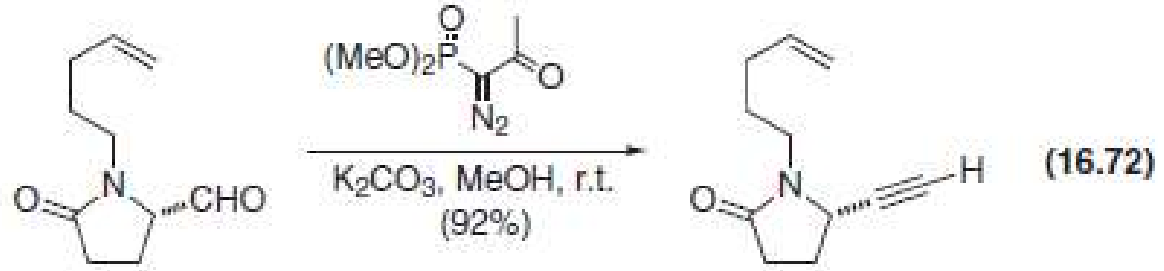
(16.71)

Reaction converts an aldehyde into an alkyne

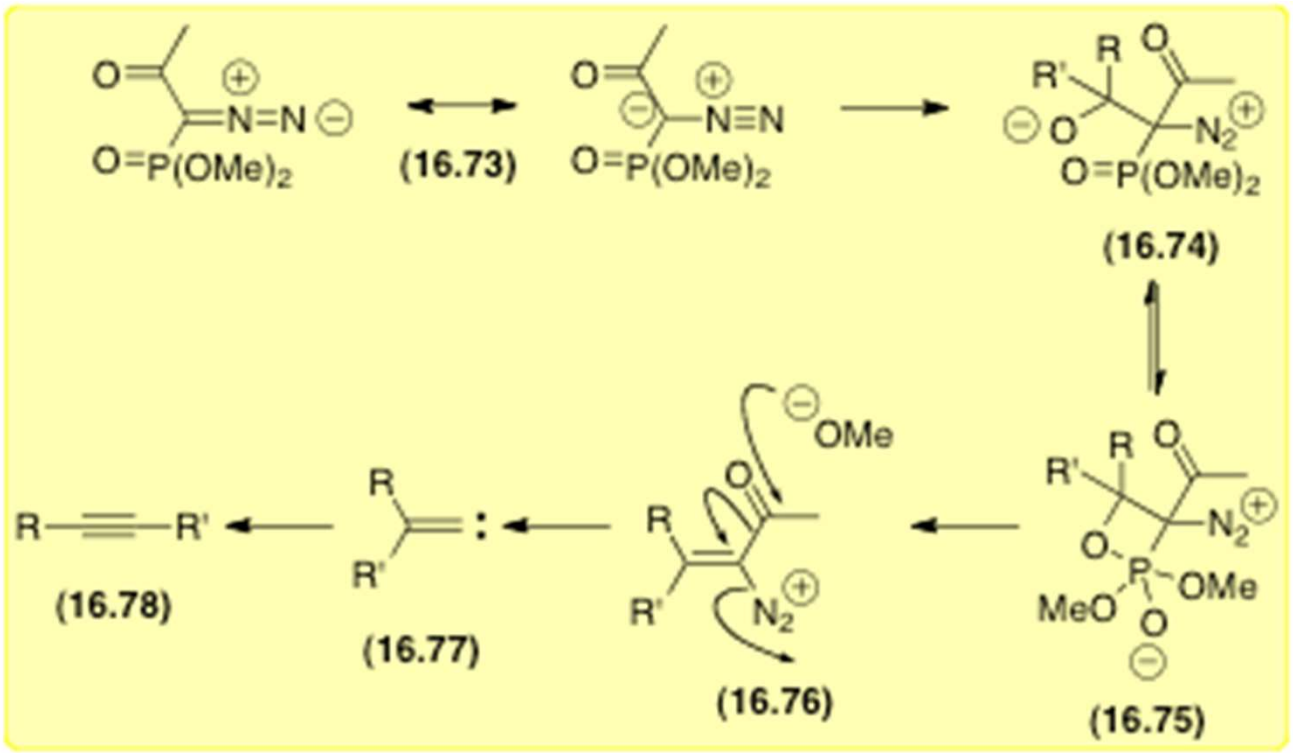
The carbon skeleton is extended by one carbon

The Bestmann modification of the Seyferth-Gilbert homologation

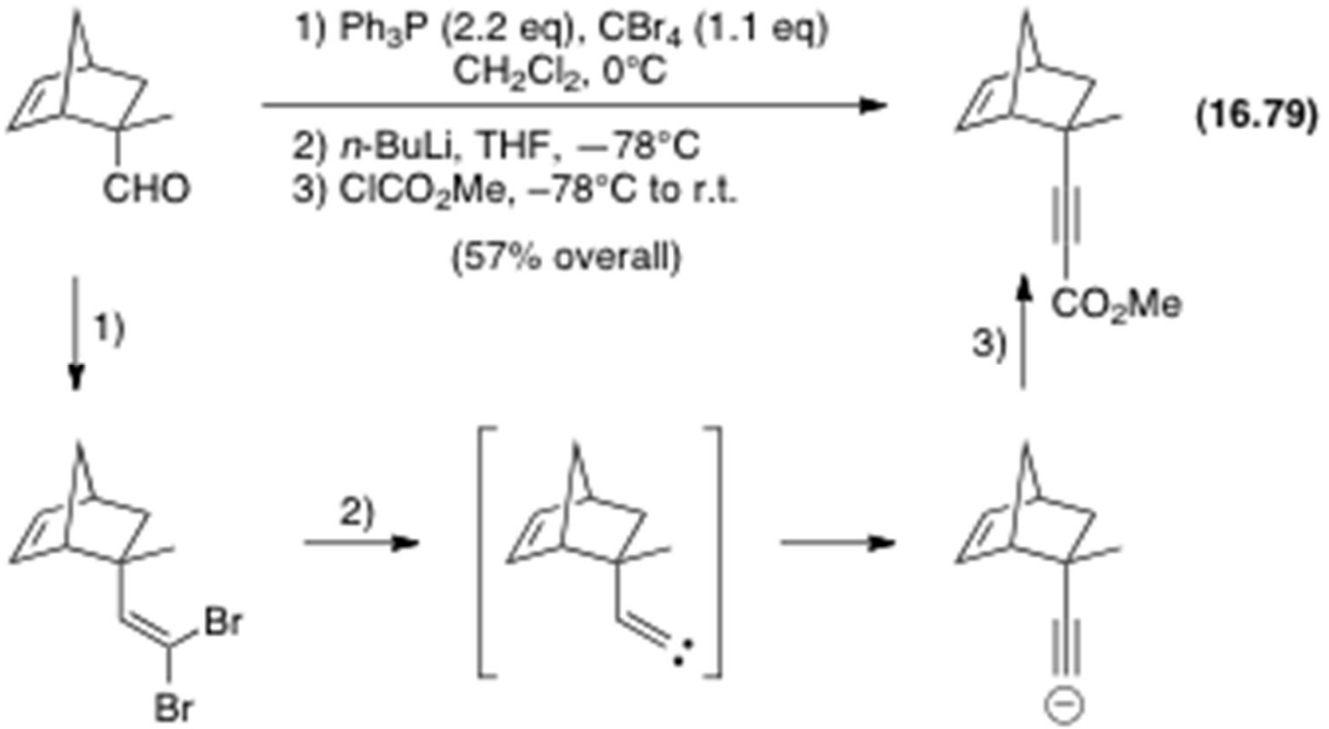
Figure 16.7



The reaction path of the Bestmann modification of the Seyferth-Gilbert homologation (in highlight box)

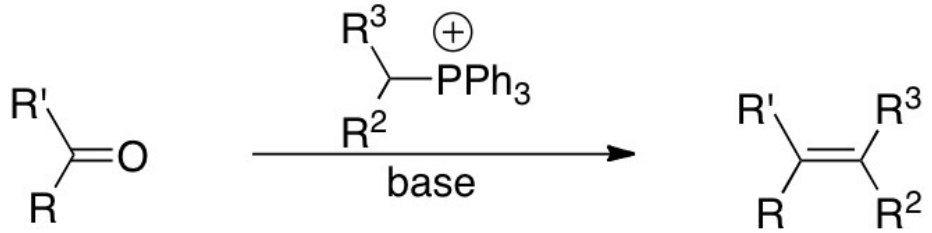


Corey-Fuchs homologation



Step 1 of this sequence is the Corey-Fuchs reaction. Treatment of the resulting vinylidene dibromide gives a vinylidene carbene that rearranges to the alkyne.

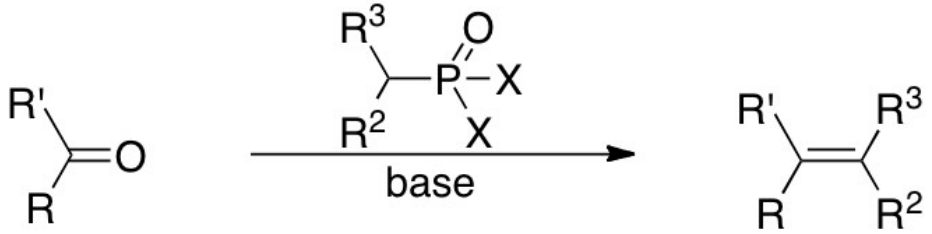
Reaction synopsis: Wittig reaction



Base: NaH/Me_2SO; BuLi; NaH/THF; LDA/THF; etc.

Stereochemistry: R=alkyl, predominantly *Z*;
R= COR, CO_2R, CHO, CN, Ph, etc.; predominantly *E*

Reaction synopsis: Horner-Wadsworth-Emmons (HWE) reaction

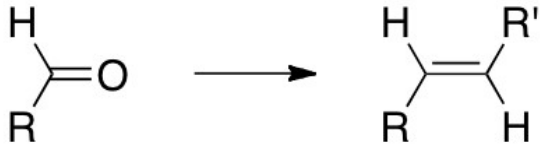


Base: NaH/Me_2SO; BuLi; NaH/THF; LDA/THF; etc.

X = alkyl, Ph (Horner); X = alkoxy (Wadsworth-Emmons)

Stereochemistry: predominantly *E*.

Reaction synopsis: Schlosser modification of the Wittig reaction

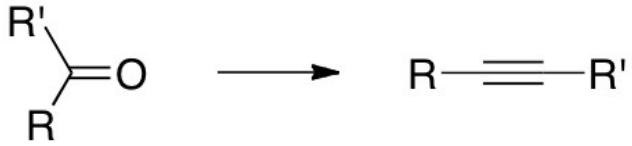


Reagents: 1) $Ph_3P{=}CHR'$, –78°C; 2) BuLi, –78°C; 3) HCl, Et_2O.

Stereochemistry: predominantly (almost exclusively) *E*

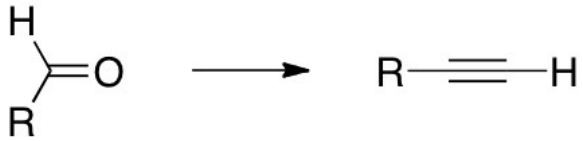
Intermediate anion that can be intercepted by electrophiles ($H_2C{=}O$; $BrCH_2CO_2Et$; $BrCF_2CF_2Br$; etc.)

Reaction synopsis: Seyferth-Gilbert homologation



Reagents: $(MeO)_2P(O)CH{=}N_2$, $KOBu^t$, THF;
or $(MeO)_2P(O)C(=N_2)COMe$, K_2CO_3, MeOH

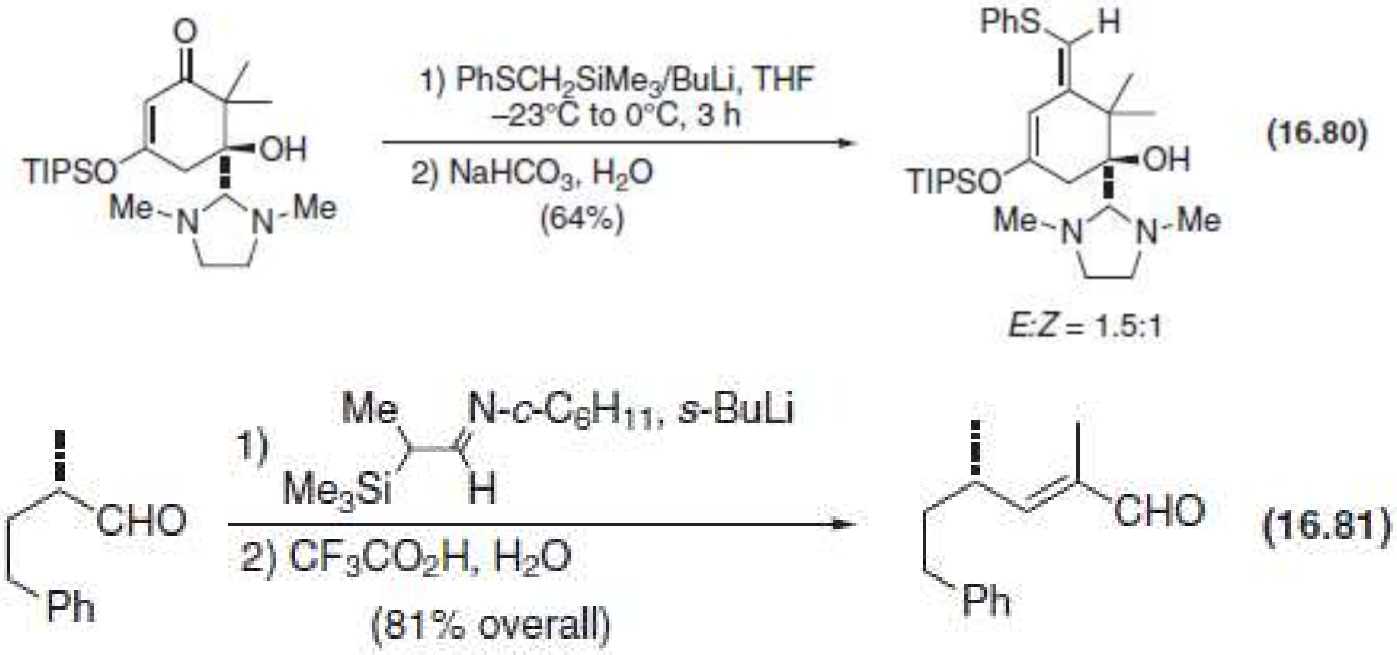
Reaction synopsis: Corey-Fuchs homologation



Reagents: 1) Ph_3P, CBr_4, CH_2Cl_2; 2) BuLi, THF, –78°C.

Alkynide anion may be intercepted by a variety of electrophiles.

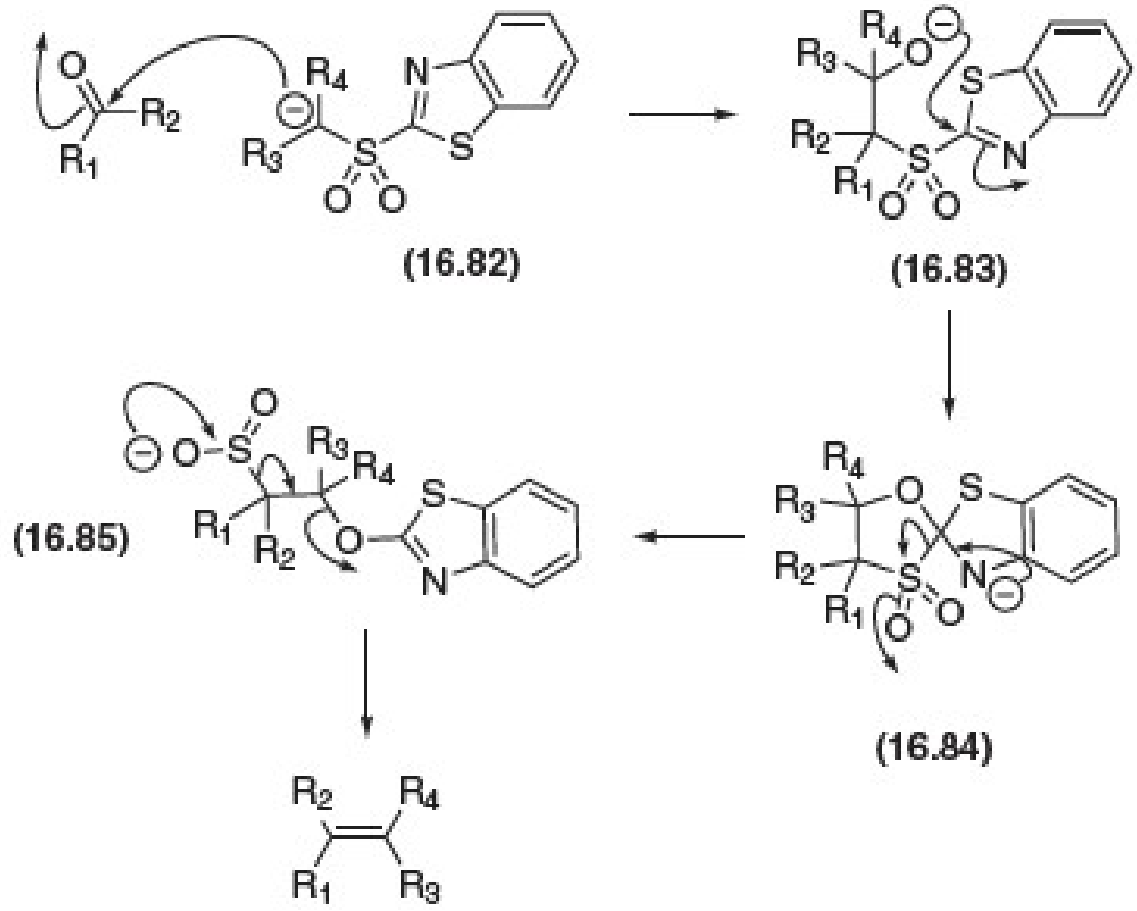
Peterson olefination



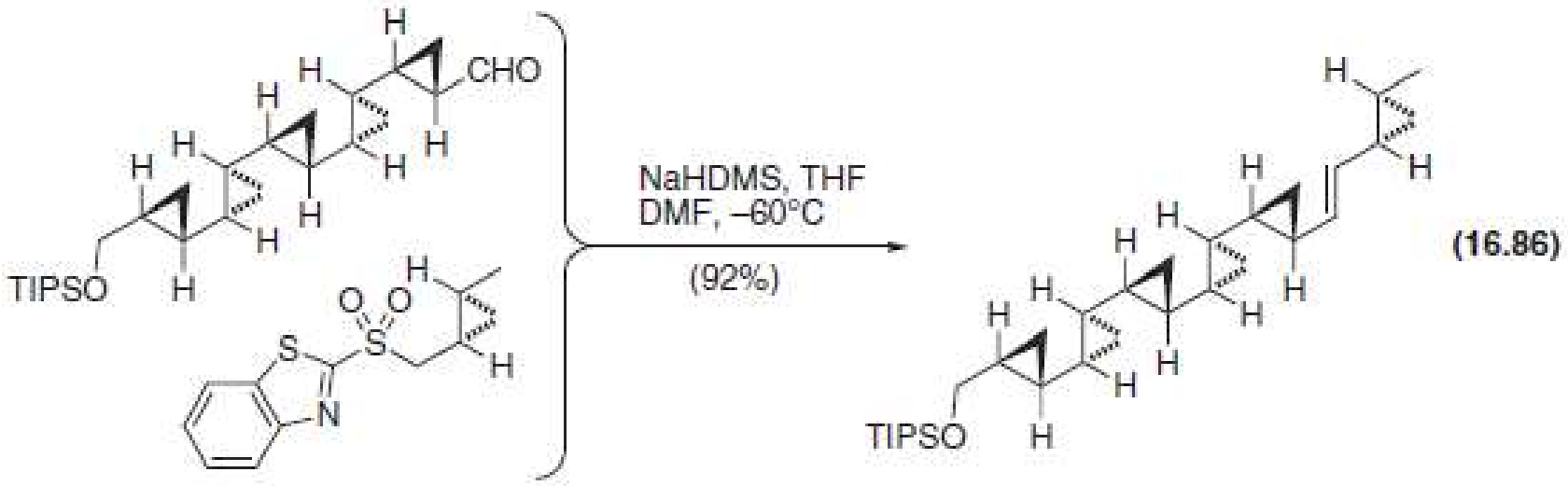
- a two-step process involving sequential addition to the carbonyl group and elimination to give the alkene
- initial adduct will fragment under either acidic or basic conditions
- stereochemistry of fragmentation of the same adduct changes when the reaction is carried out under acidic, rather than basic conditions

Figure 16.8

Mechanism of the Julia-Kocieński reaction

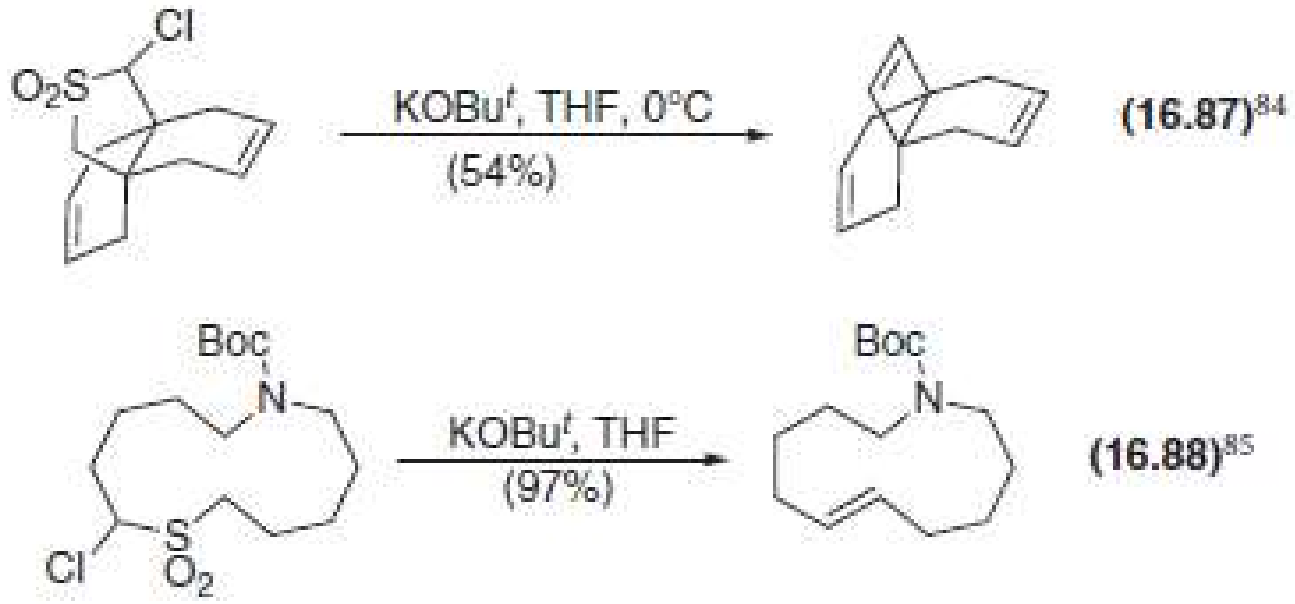


Julia-Kocieński reaction



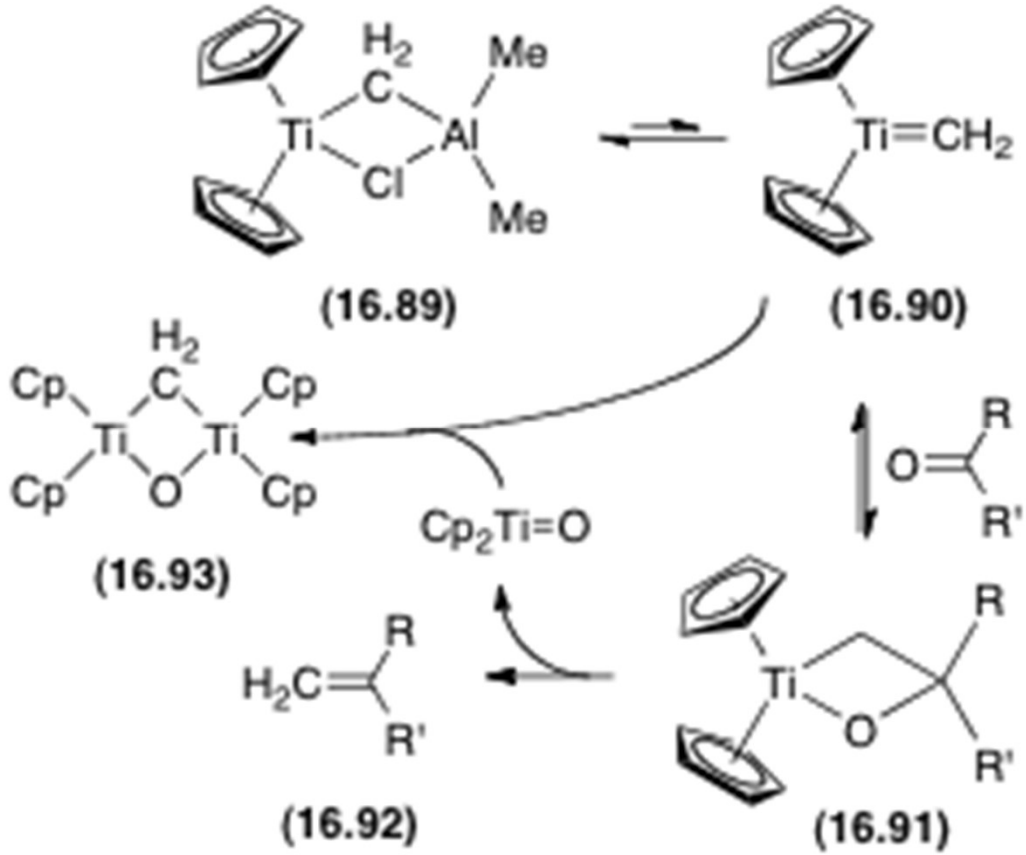
the reaction is especially compatible with functional groups sensitive to reduction

Ramberg-Bäcklund reaction



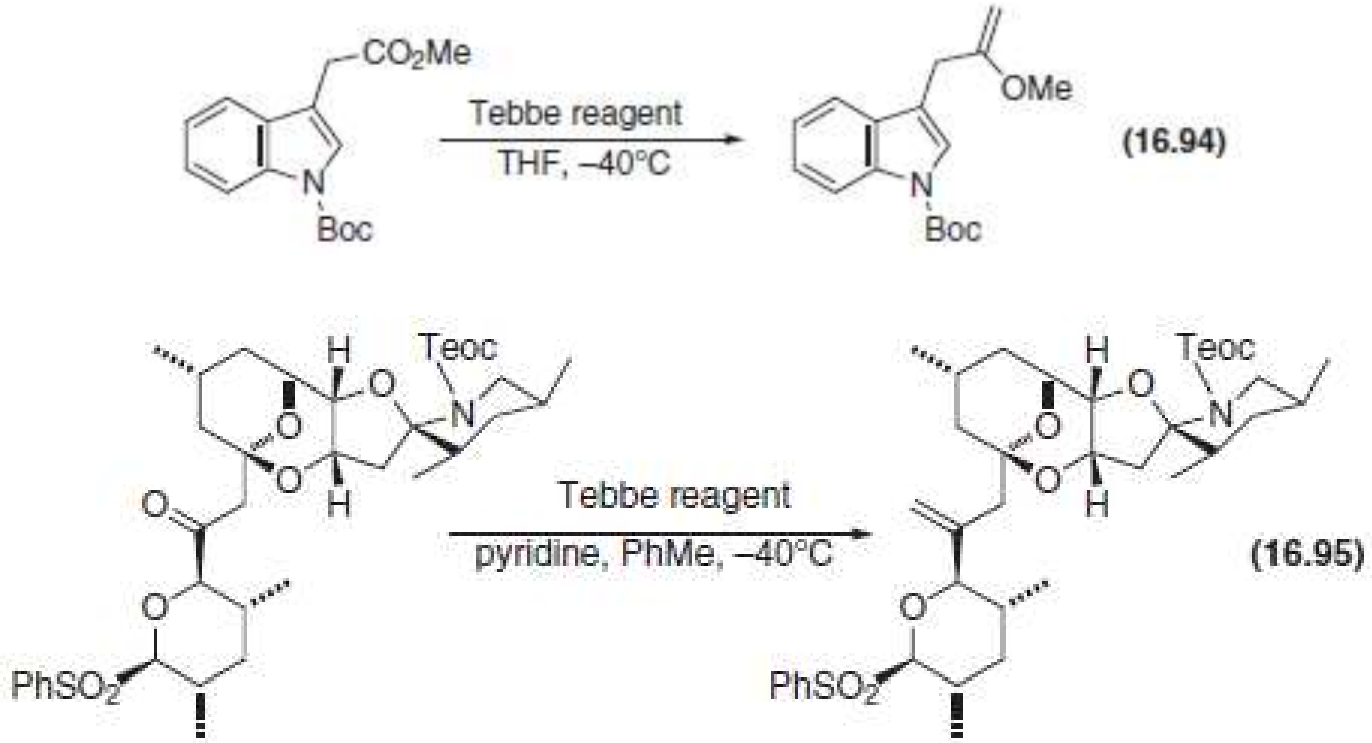
- first step of the reaction is a nucleophilic ring closure to give the thiirane dioxide
- suprafacial extrusion of SO_2 from the thiirane dioxide gives the alkene

Figure 16.9



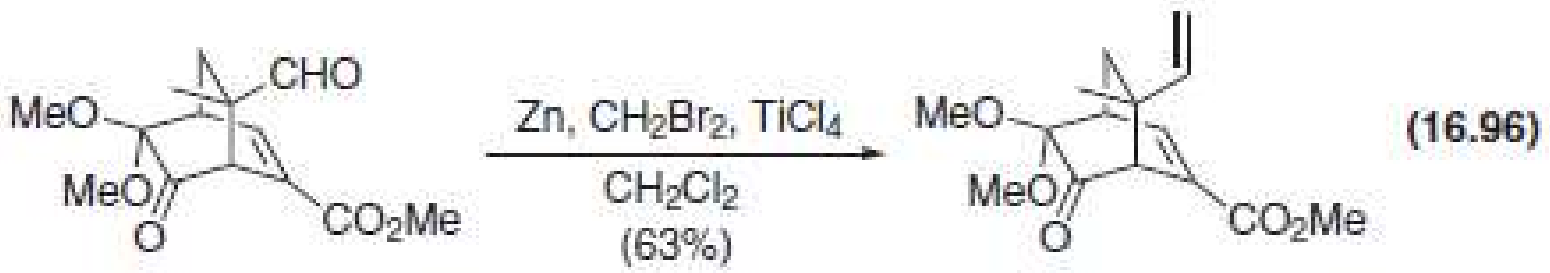
Olefination with methylenetitanocene reagents

Representative olefinations with Tebbe reagent



The reagent reacts with esters to give enol ethers

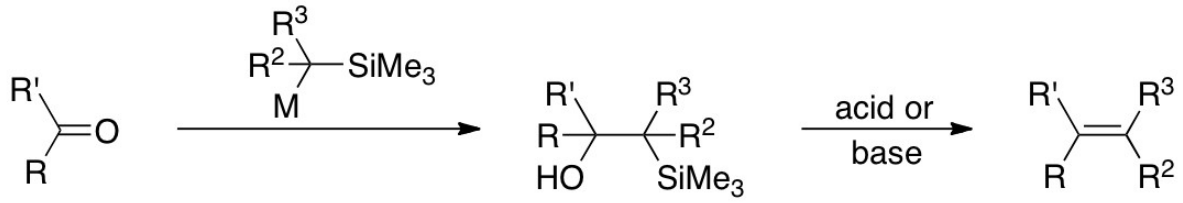
Olefination with the Lombardo reagent



(16.96)

- reagent tolerates sensitive functionality
- unhindered aldehydes tend to give pinacols as products instead of the alkene
- best used with ketones and hindered aldehydes

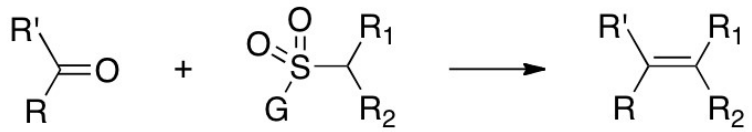
Reaction synopsis: Peterson olefination



M = Li, Mg, etc.;

Stereochemistry: elimination by base is *syn*; elimination by acid is *anti*. Alkene stereochemistry can be defined by choice of reagent to fragment the β-hydroxysilane.

Reaction synopsis: Julia-Lythgoe olefination

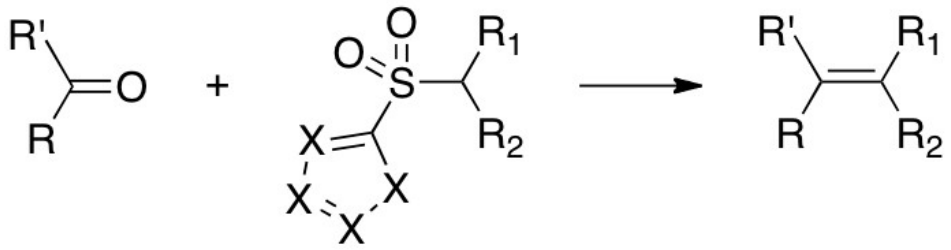


G = Ph or substituted phenyl

Reagents: 1) BuLi, THF; 2) add aldehyde; 3) Na(Hg), THF, ROH; etc.
or 1) BuLi, THF; 2) add aldehyde; 3) SmI_2, DMPU, THF; etc.

Stereochemistry: mainly *E*, with two largest groups *trans* to each other.

Reaction synopsis: Julia-Kocieńsky Olefination

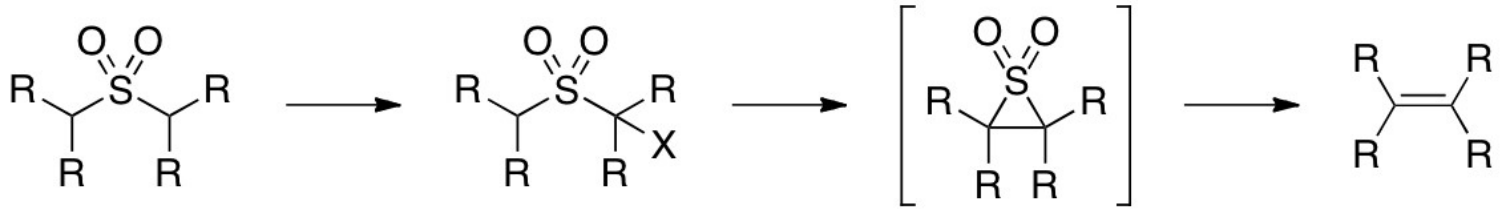


X = N, S (tetrazoles, thiazoles, benzothiazoles)

Reagents: strong, non-nucleophilic base (LDA, BuLi, etc.)

Reduction step is not needed with this reaction
Stereochemistry: as for the Julia-Lythgoe olefination.

Reaction synopsis: Ramberg-Bäcklund reaction

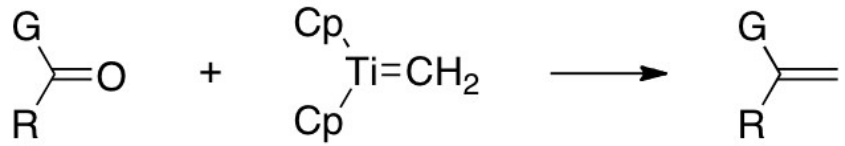


Reagents:

from unsubstituted sulfone: $KOBu^t$, THF, CF_2Br_2; etc.
from α-halosulfone: $KOBu^t$, THF.

Stereochemistry: mixture of *E* and *Z* isomers is obtained.

Reaction synopses: Tebbe, Petasis, and Lombardo olefinations



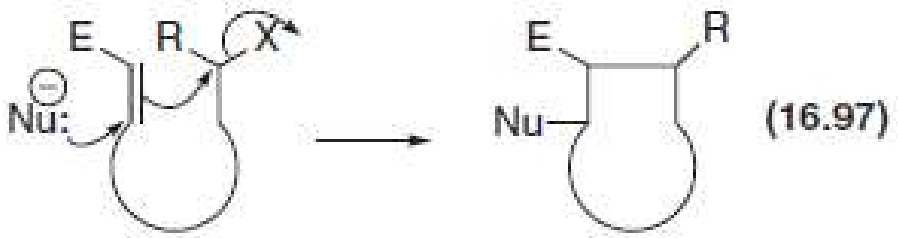
G = H, R', OR', NR'_2, etc.

Reagents:

Tebbe: Cp_2TiCl_2, Me_3Al, PhMe, THF; etc.
Petasis: Cp_2TiMe_2, PhMe, Δ
Lombardo: Zn, CH_2Br_2, $TiCl_4$, PhMe (age 3 days)

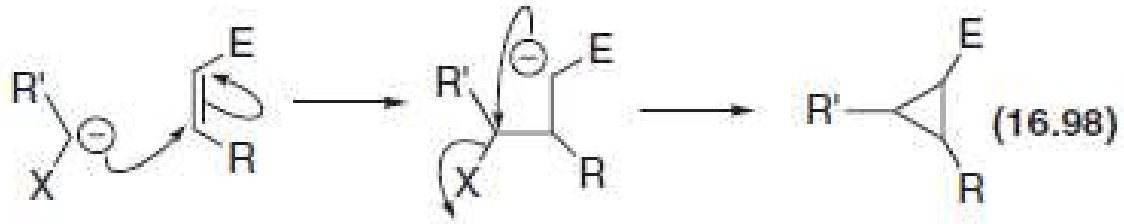
Michael-initiated ring closures (MIRC)

- leaving group is in the Michael acceptor in this reaction



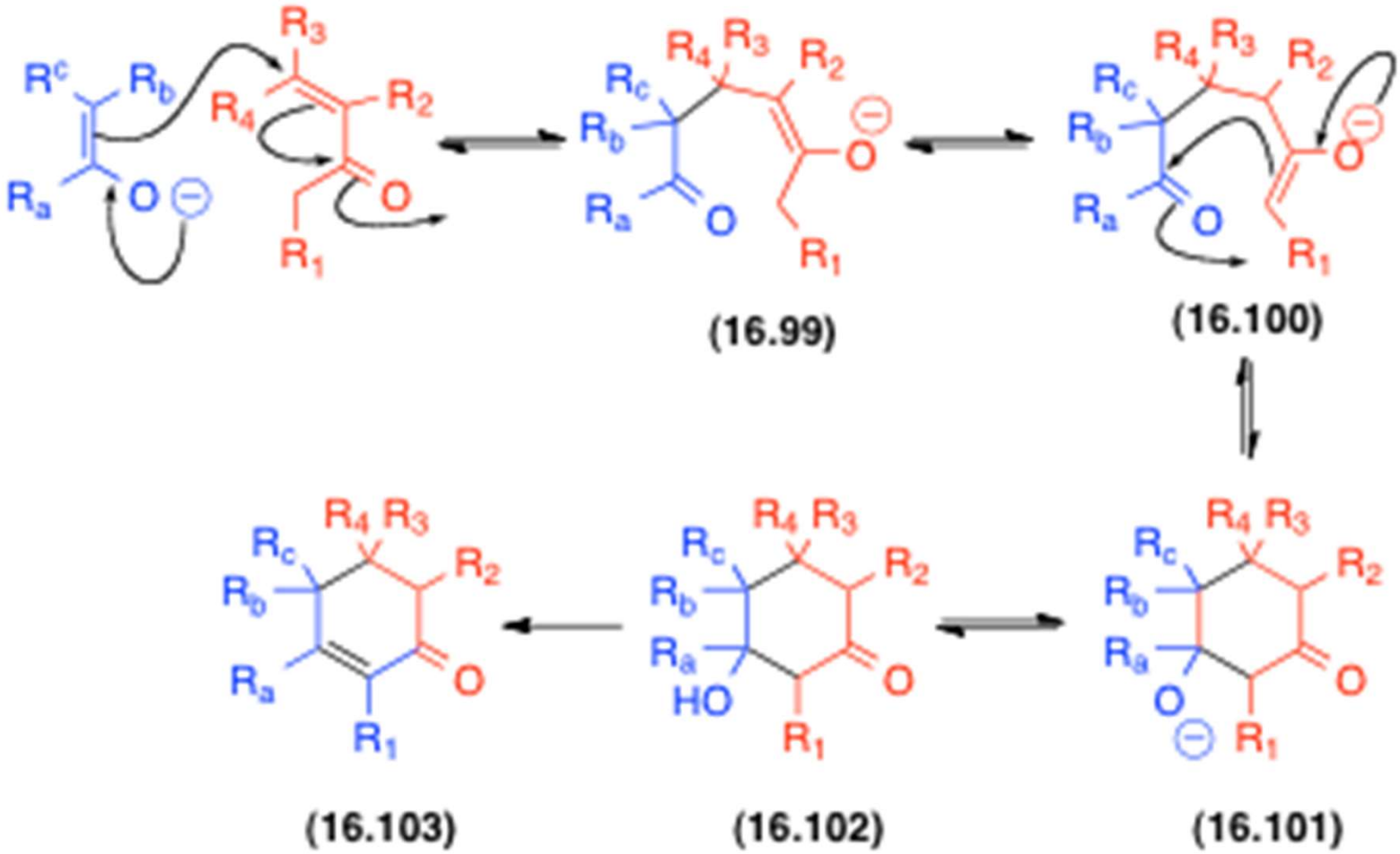
$CN^{\ominus}$, $R_2Cu(CN)Li_2$, enolate, etc.
E: CN, COR, CO_2R; X: Cl, Br, I, OTs, epoxide, etc.

- leaving group is in the initiating nucleophile in this reaction



E: CN, COR, CO_2R, etc.
X: SMe_2, $S(O)Me_2$, Cl, Br, I, OTs, epoxide, etc.

Figure 16.10



The mechanism of the Robinson annelation (annulation)

Robinson annelations in steroid synthesis

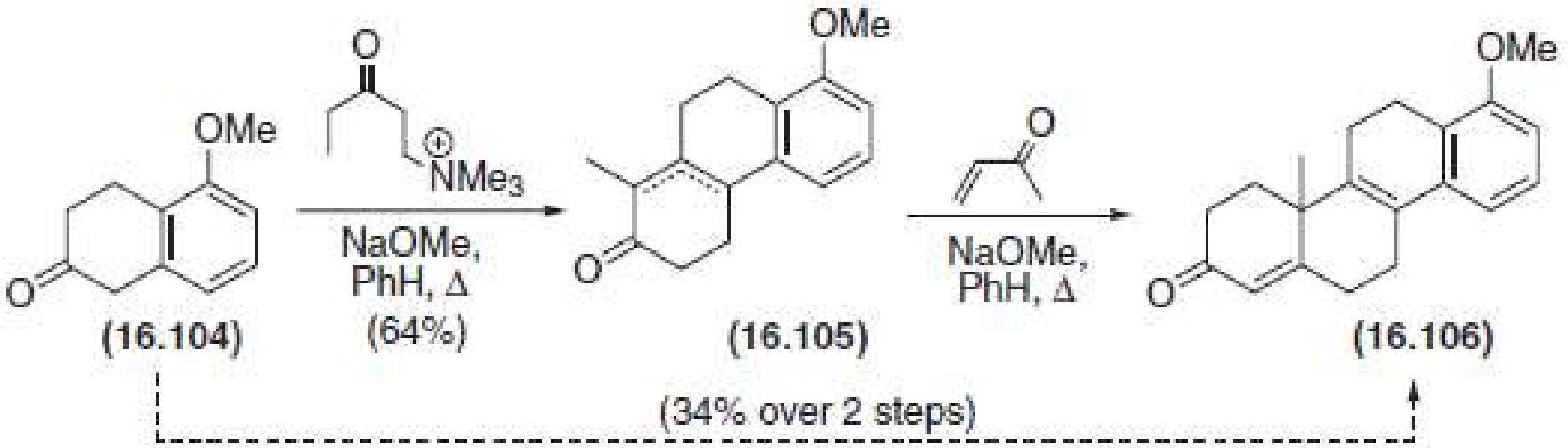
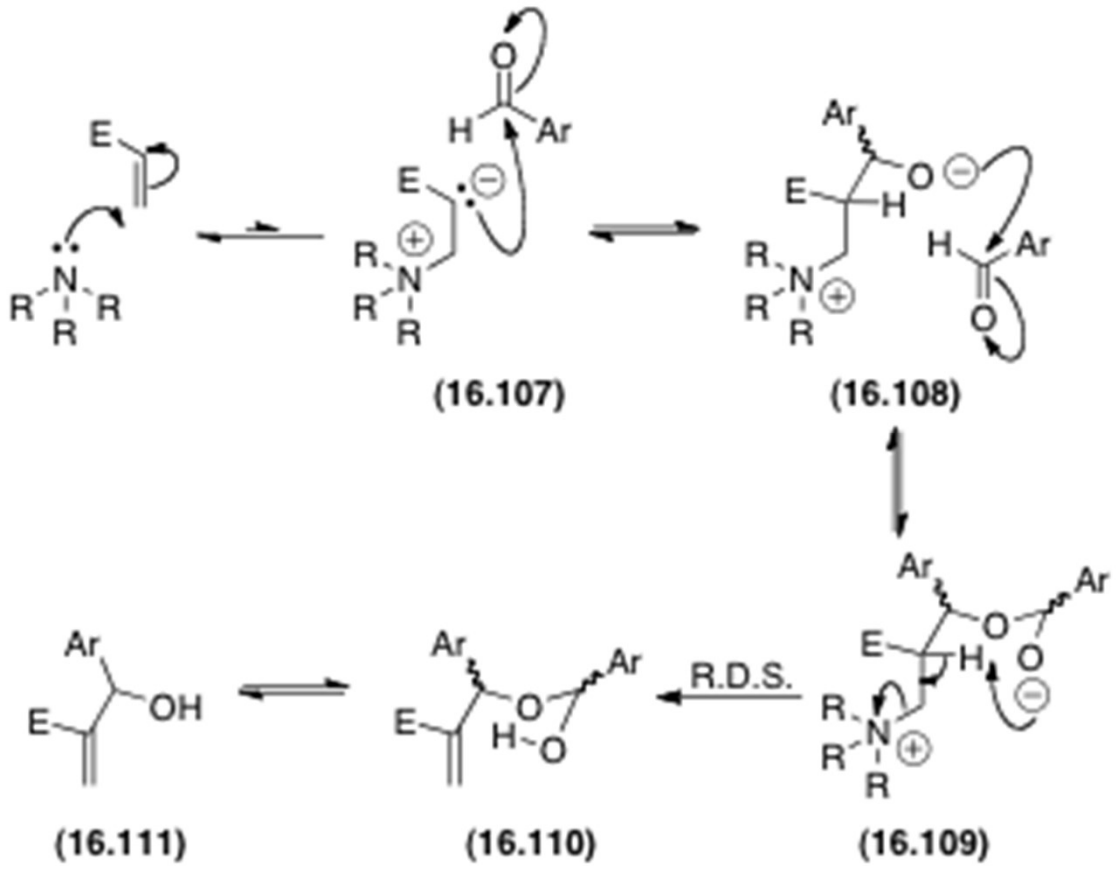
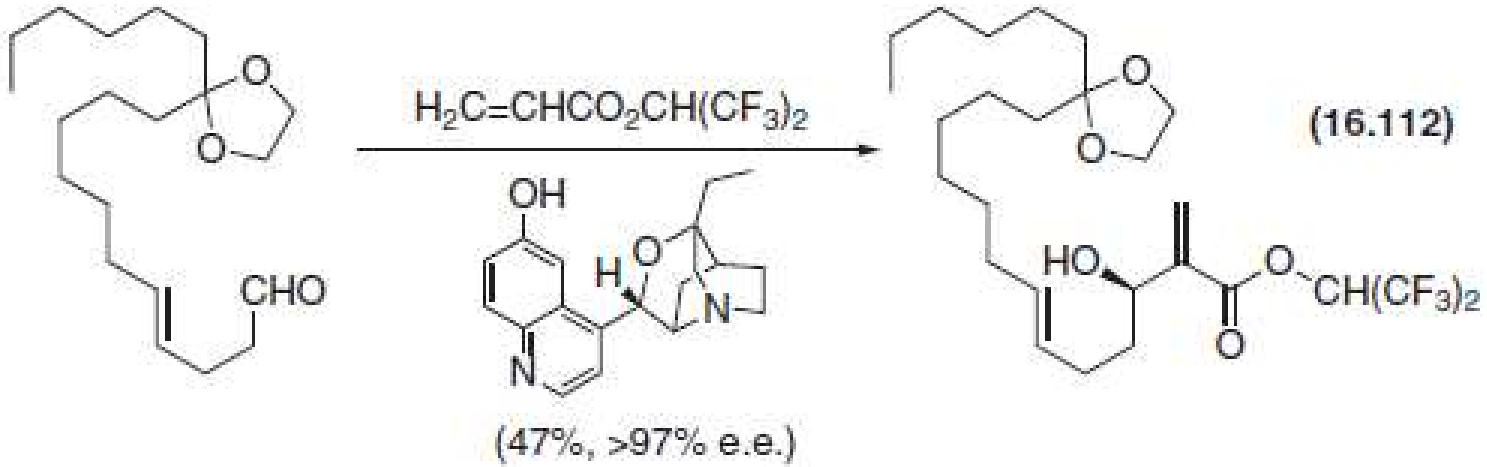


Figure 16.11



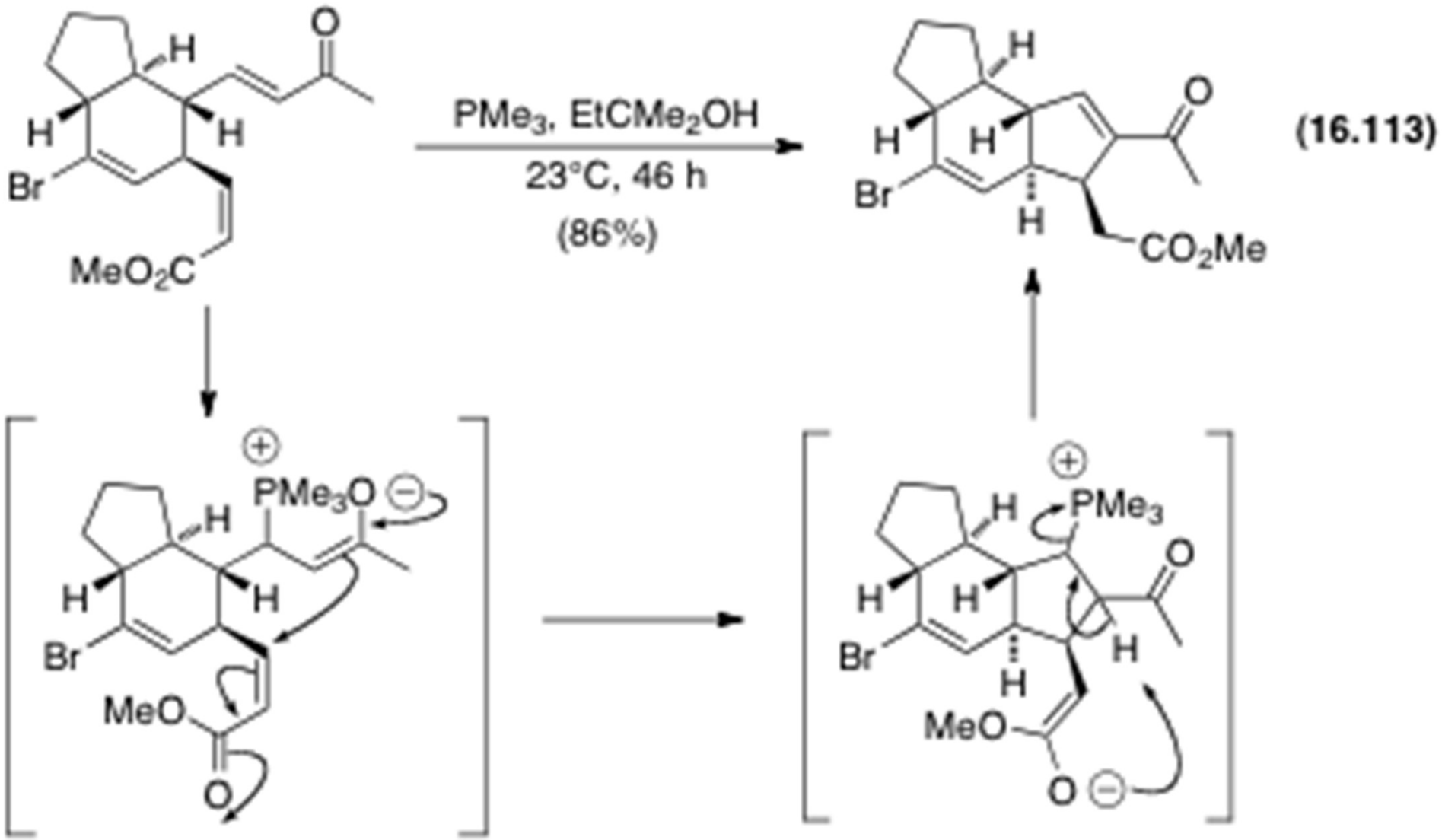
The mechanism of the Morita-Baylis-Hillman reaction

Asymmetric Morita-Baylis-Hillman reaction

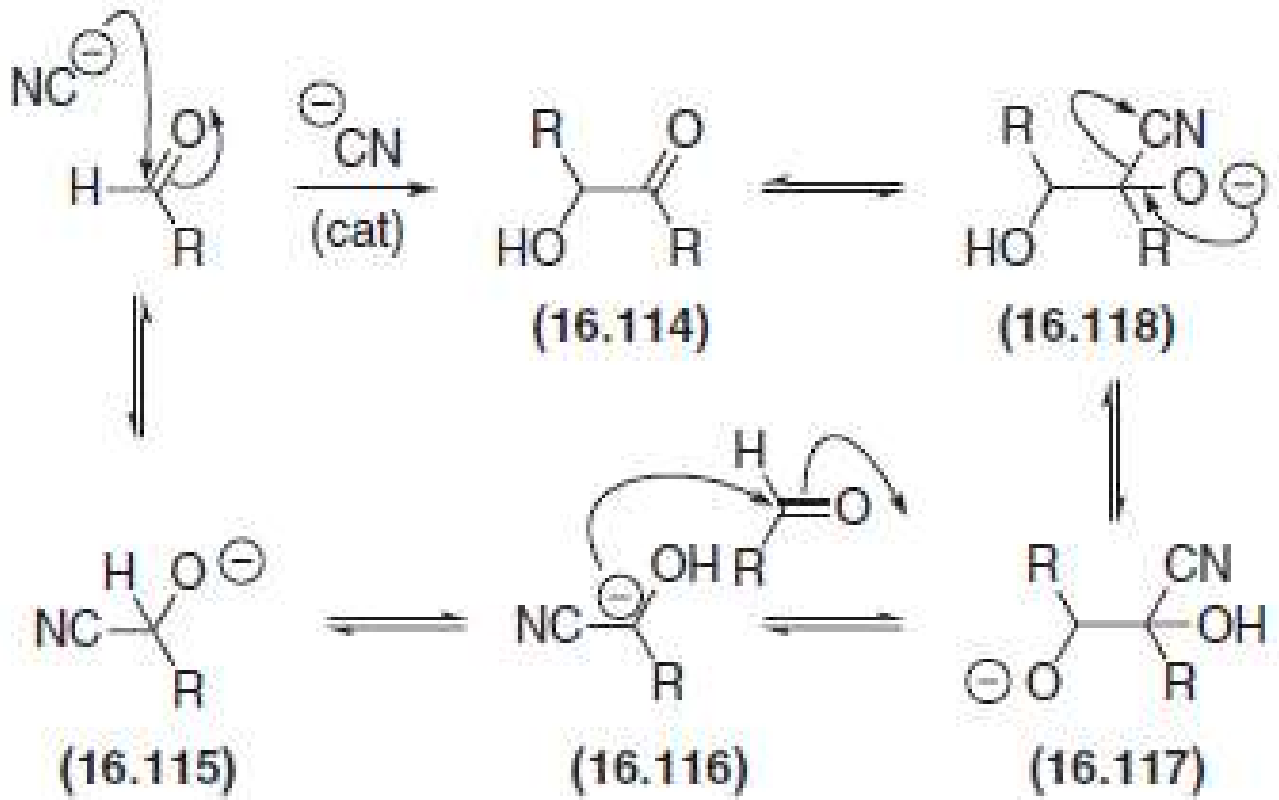


- In this reaction, the chiral catalyst derived from the quinine skeleton gives the *R* allylic alcohol in high enantiomeric excess

MBH-initiated cyclization

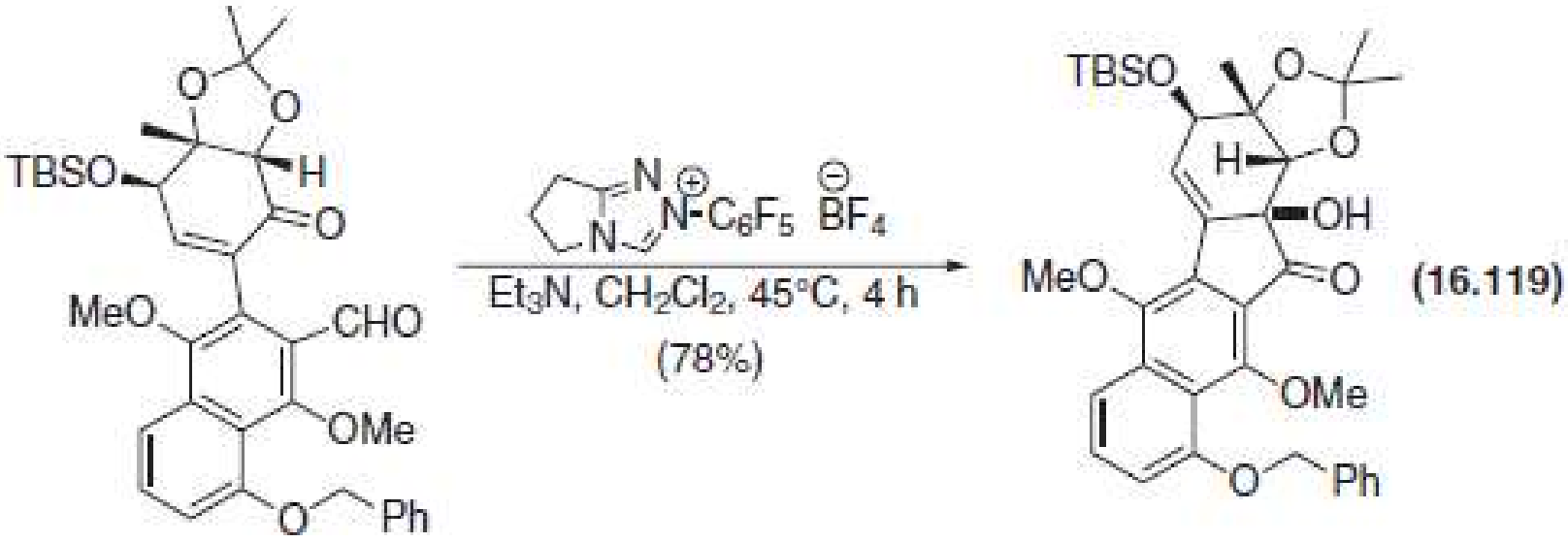


Benzoin condensation



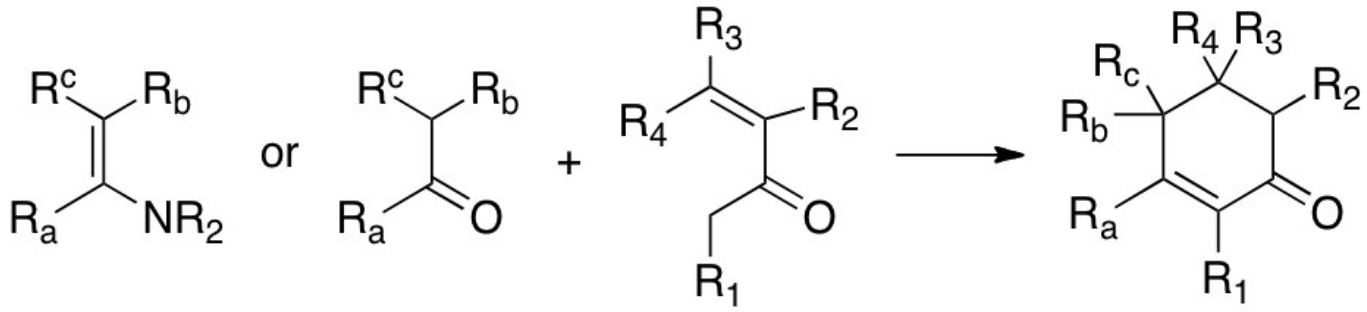
reaction is catalyzed by cyanide anion and by NHCs

Intramolecular benzoin condensation catalyzed by an NHC



- the triazolium ion reacts with the triethylamine to generate the *N*-heterocyclic carbene catalyst

Reaction synopsis: Robinson annelation (annulation)



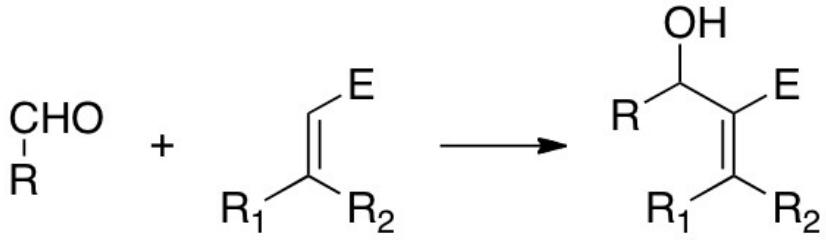
Reagents:

from ketone: KOBu^t, THF; NaOEt, EtOH; etc.

from enamine: PhH, Δ; etc.

Enone may be replaced by Mannich base.

Reaction synopsis: Morita-Baylis-Hillman reaction

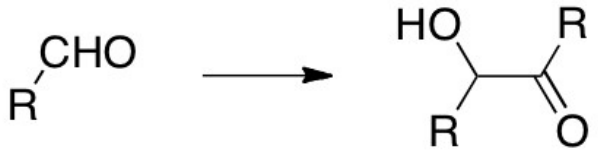


E: CO_2R, CN, COR, NO_2, etc.

Reagents: DABCO; DMAP; R_3P; etc.

Reaction is accelerated by protic solvents and by Lewis acids (e.g. Y^{+3})

Reaction synopsis: Benzoin condensation



Reagents: KCN, EtOH, Δ; NHC, CH_2Cl_2, Δ; etc.