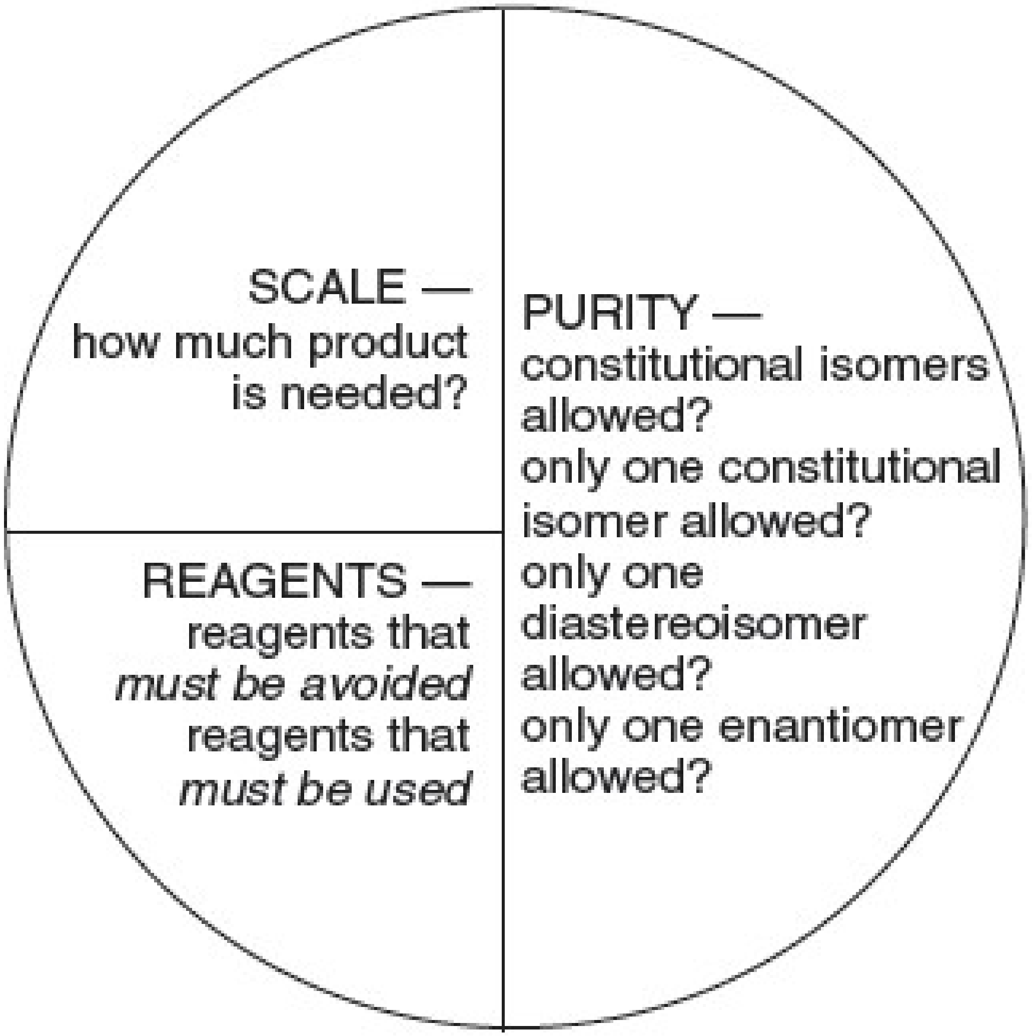
Chapter 15

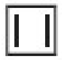
Figure 15.1

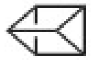
The three critical determinants of a synthesis



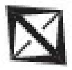
Synthetic targets of theoretical interest

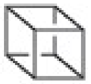
- highly strained and energetic molecules: cyclobutadiene and Ladenburg benzene (prismane)

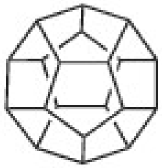

(15.1)


(15.2)

- Platonic solid hydrocarbons: tetrahedrane, cubane and dodecahedrane


(15.3)


(15.4)


(15.5)

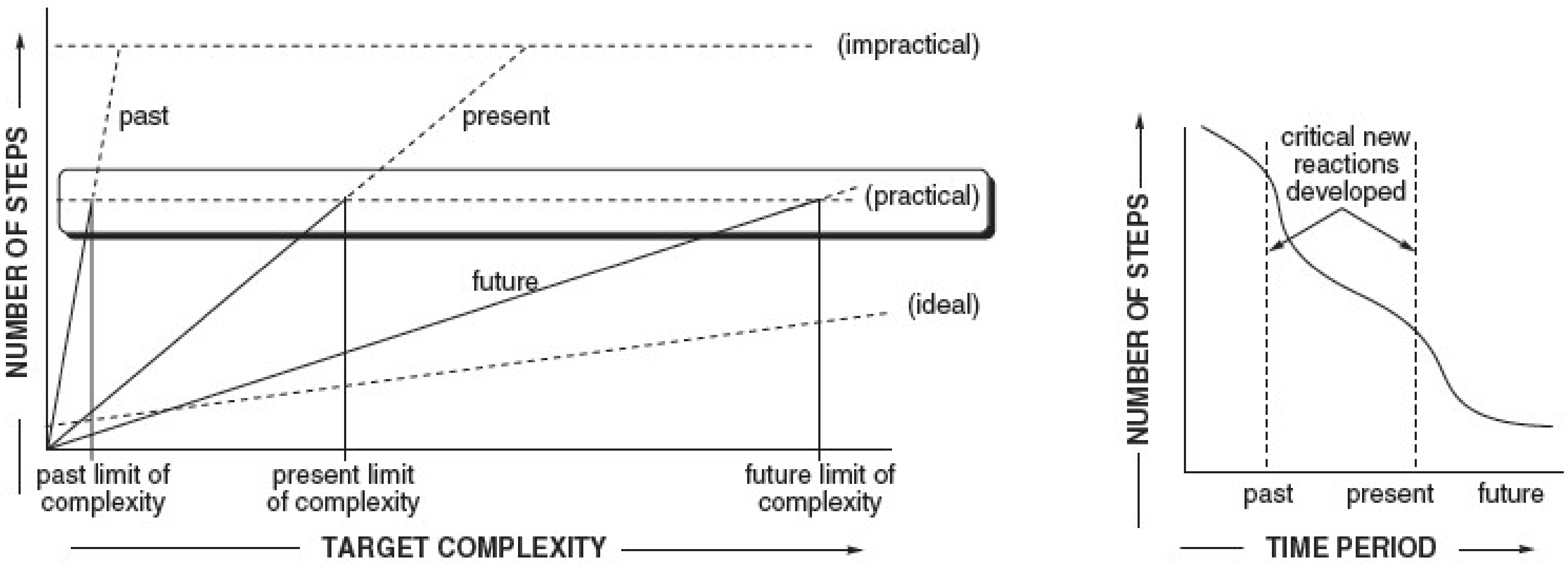
- Stable carbenes: *N*-heterocyclic carbenes

(15.6)

Elegance or, "What constitutes a good organic synthesis?”

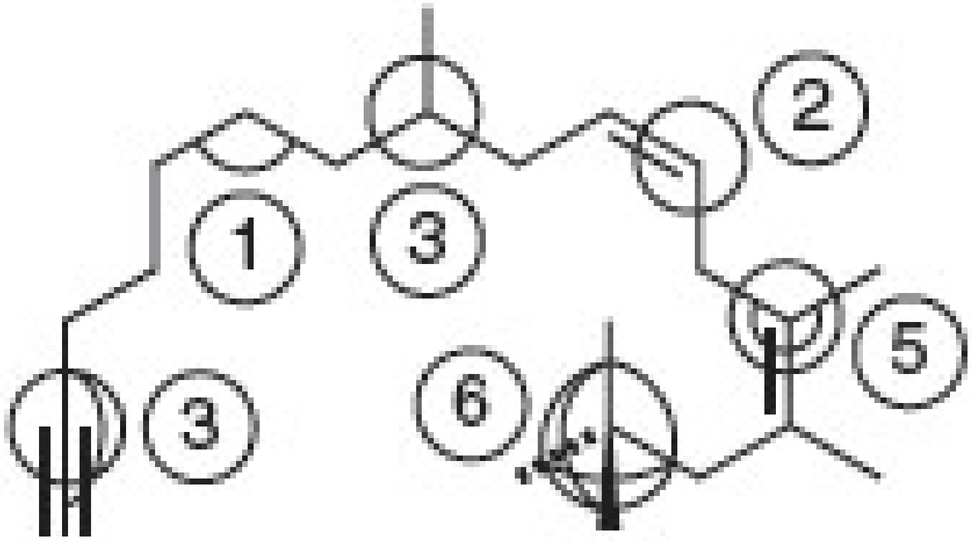
- Generally agreed features of an elegant synthesis
  - regiochemical control
  - stereochemical control
- Hendrickson definition of an “ideal synthesis” (1975):
  - A synthesis which: "...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality.”
- Atom economy (Trost, 1991):
  - the major goal is to minimize the number of atoms in the reactants that do not end up in the final product
  - dramatically affected by the advent of transition metal-catalyzed synthetic reactions
- Step economy (Wender, 1997):
  - every step in a synthesis costs time, money, and effort, and every step of a synthesis has an economic and environmental impact.
  - reducing the number of steps in a synthesis is critically important.
- Redox economy (Baran, 2010):
  - $\%\ \text{ideality} = 100\left[\dfrac{(\#\ \text{of construction rxns}) + (\#\ \text{of strategic redox rxns})}{(\text{total}\ \#\ \text{of steps})}\right]$

Figure 15.2



The relationship between target complexity and step economy over time

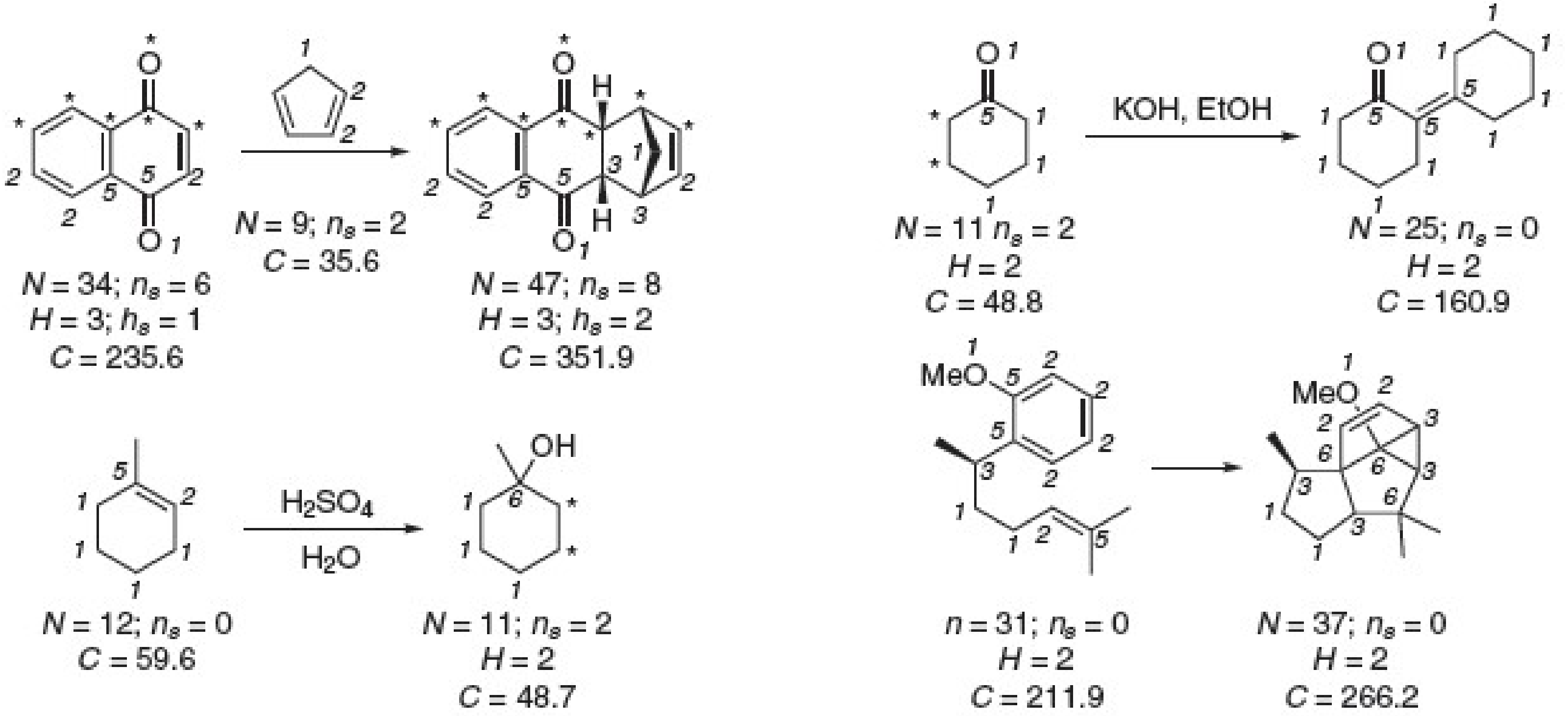
Modified Bertz fragment complexity indexes (*N*)



Calculating Bertz complexity indexes

- Complexity index, $C_c = (2N \ln N)$.
  - N = sum of fragment indexes
- $C_c = (2N \ln N - n_s \ln n_s)$.
  - n_s = number of pairs of atoms related by the symmetry of the molecule
- heteroatom coefficient, $H = n_h + 1$
- n_h = number of heteroatoms
- Heteroatom complexity index, $C_h = (2H \ln H - h_s \ln h_s)$
  - h_s = number of heteroatom pairs related by molecular symmetry
- Total complexity index, $C_{tot} = C_c + C_h$

Figure 15.4



Complexity indexes for some common reactions

Organic reactions in synthesis

- How we learn reactions first

A + B → C

- Different ways to look at a particular reaction

A + B → ? [Answer: C]

A + ? → C [Answer: B]

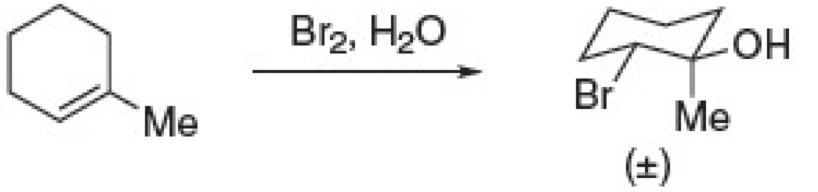
? + B → C [Answer: A]

- The question posed by synthesis

? + ? → C

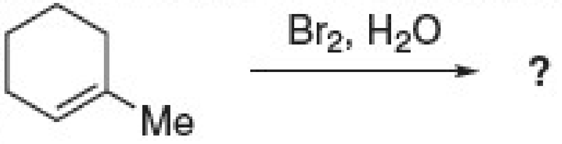
A specific example

- How we first learn the reaction



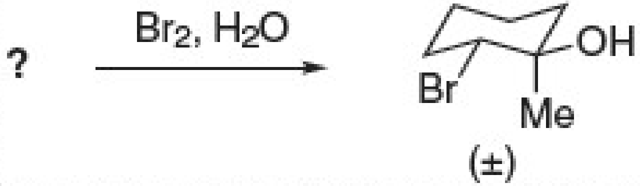
(15.7)

- Different ways to look at this particular reaction



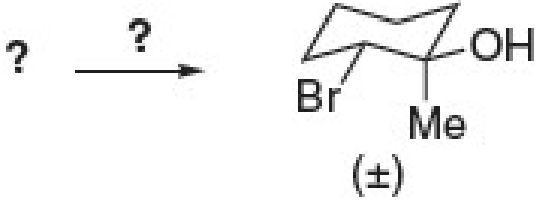
(15.8)

(15.9)



(15.10)

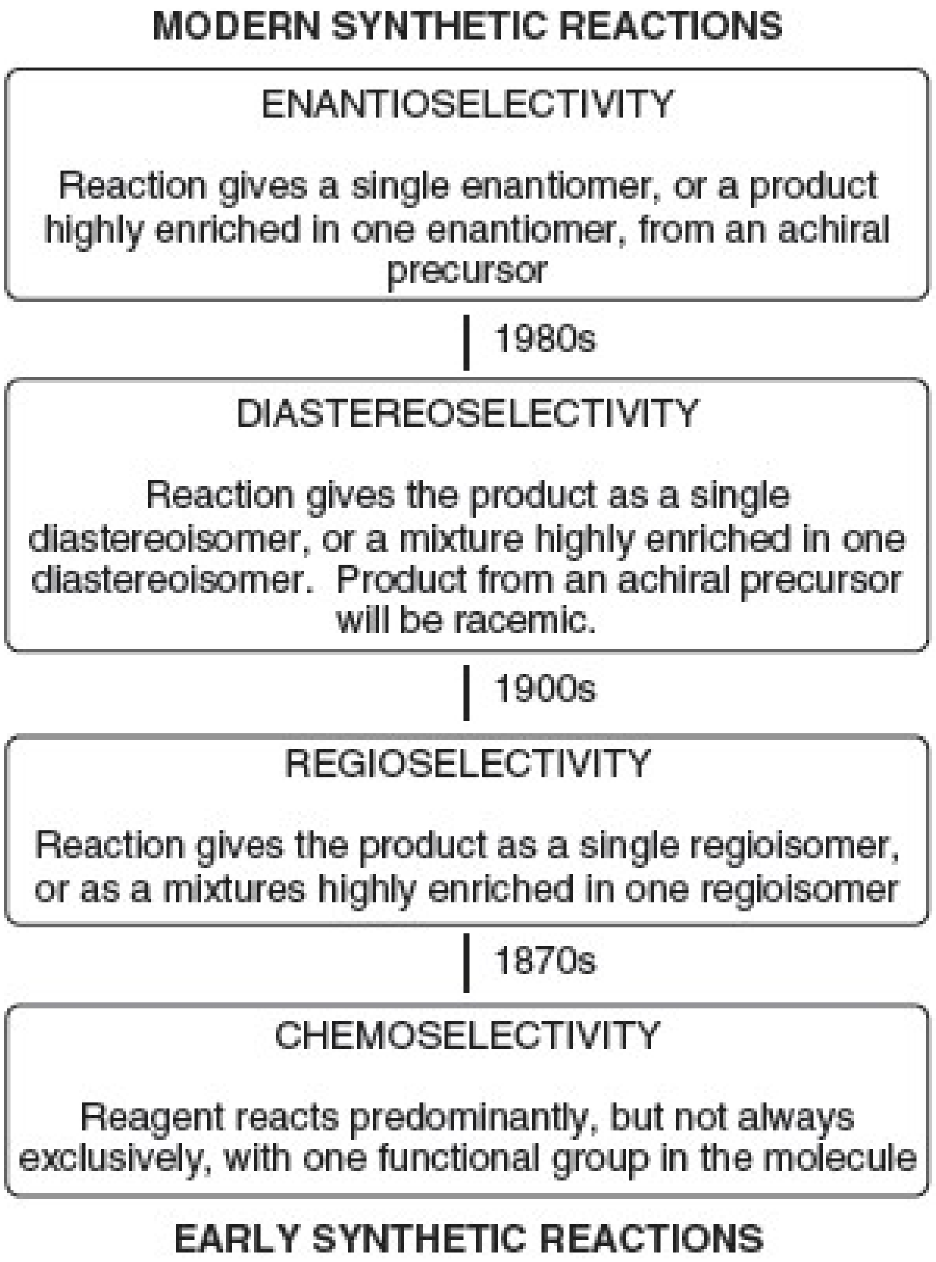
- The question posed by this reaction in synthesis



(15.11)

Figure 15.5

The rise of sophistication in organic synthesis



MODERN SYNTHETIC REACTIONS

ENANTIOSELECTIVITY

Reaction gives a single enantiomer, or a product highly enriched in one enantiomer, from an achiral precursor

1980s

DIASTEREOSELECTIVITY

Reaction gives the product as a single diastereoisomer, or a mixture highly enriched in one diastereoisomer. Product from an achiral precursor will be racemic.

1900s

REGIOSELECTIVITY

Reaction gives the product as a single regioisomer, or as a mixtures highly enriched in one regioisomer

1870s

CHEMOSELECTIVITY

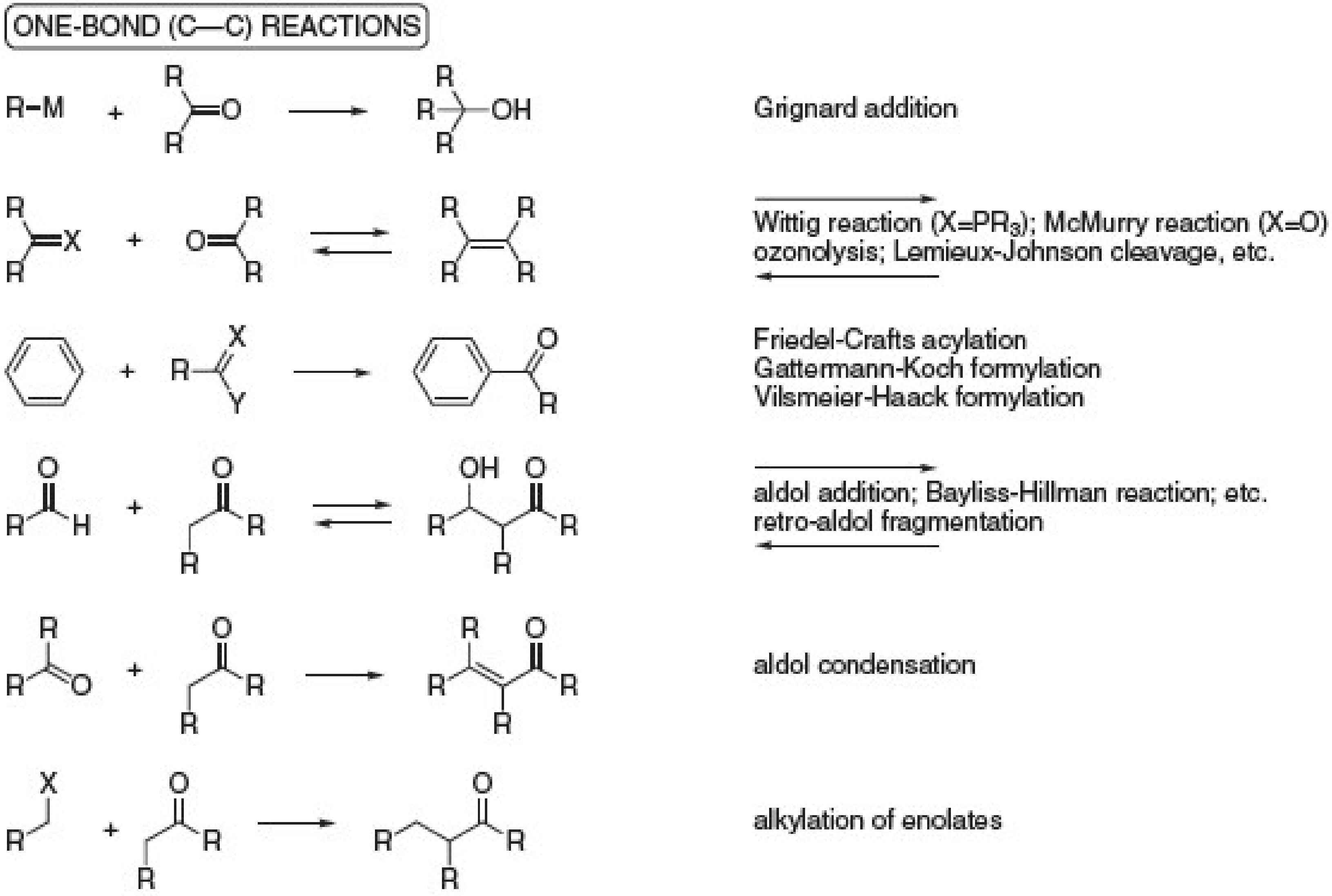
Reagent reacts predominantly, but not always exclusively, with one functional group in the molecule

EARLY SYNTHETIC REACTIONS

Table 15.1

- The reactions in this table are grouped according to the number and type of bonds involved into the following categories:
  - one-bond C—C bond-forming reactions
  - one-bond C—X bond-forming reactions
  - multibond reactions
  - oxidation and reduction reactions
  - rearrangement reactions

Table 15.1 A: One-bond (C—C) reactions



ONE-BOND (C—C) REACTIONS

Grignard addition

→
Wittig reaction (X=PR_3); McMurry reaction (X=O)
ozonolysis; Lemieux-Johnson cleavage, etc.
←

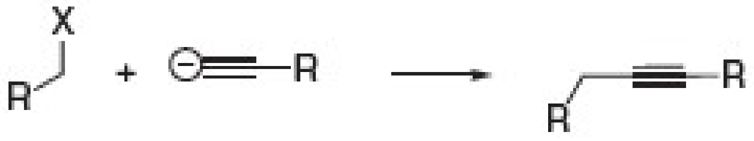
Friedel-Crafts acylation
Gattermann-Koch formylation
Vilsmeier-Haack formylation

→
aldol addition; Bayliss-Hillman reaction; etc.
retro-aldol fragmentation
←

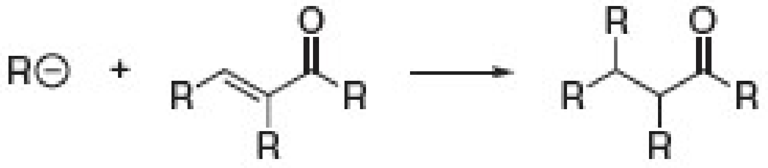
aldol condensation

alkylation of enolates

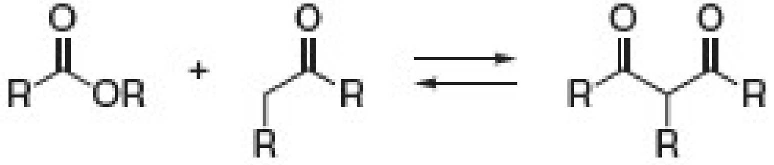
Table 15.1 B: One-bond (C—C) reactions



alkylation of alkynides



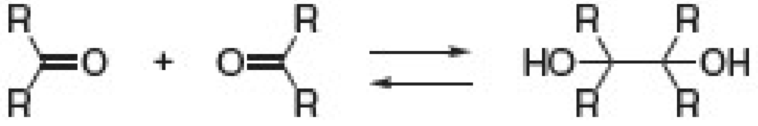
Michael addition



→

Claisen condensation
retro-Claisen fragmentation

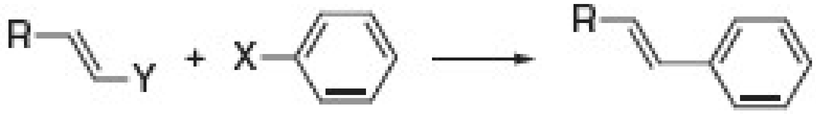
←



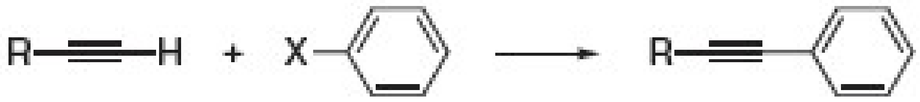
→

pinacol reaction
glycol cleavage

←

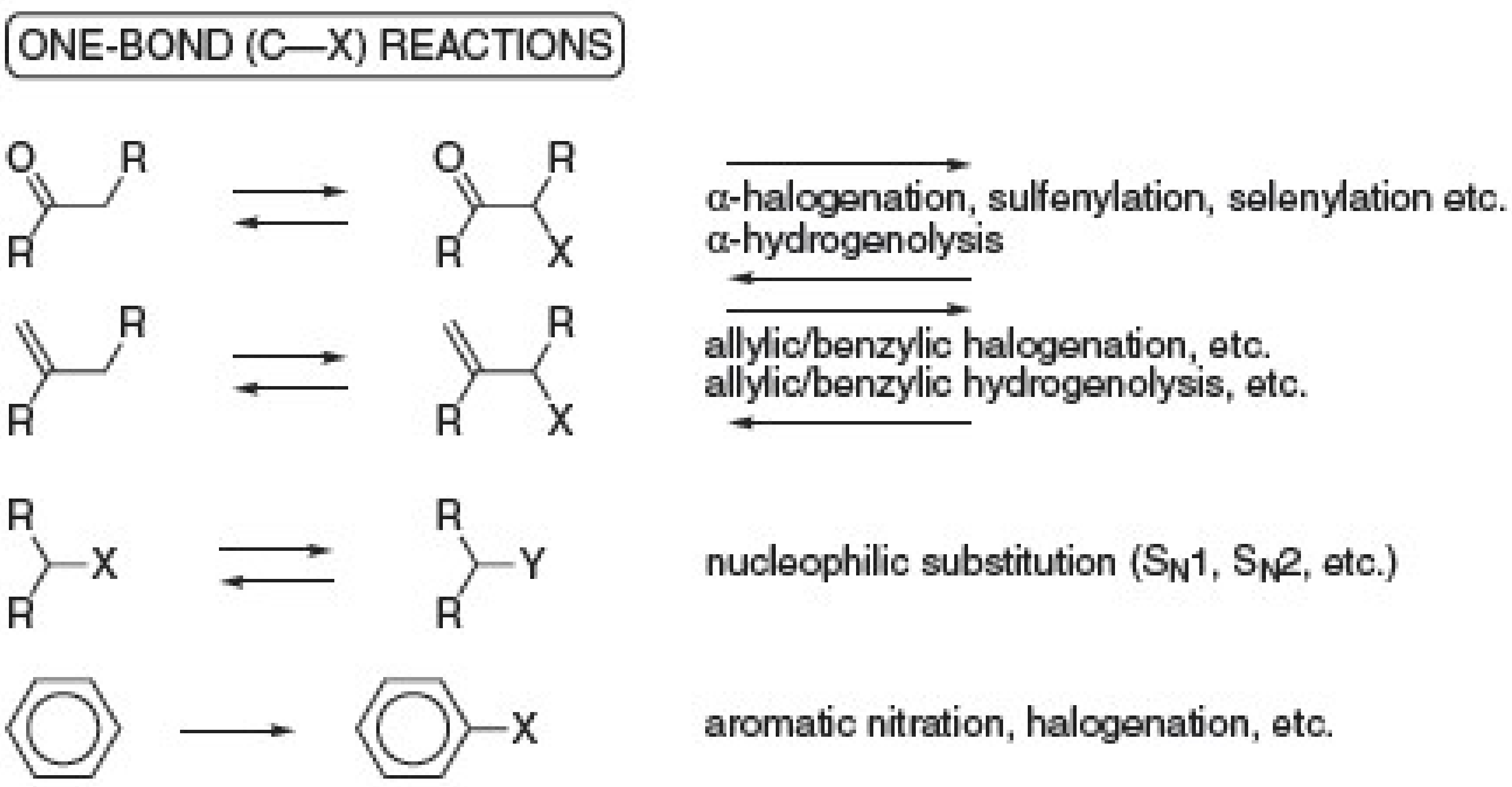


Heck coupling (X=halogen; Y=H)
Suzuki coupling (X=halogen; Y=$B(OR_2)$)



Sonogashira coupling

Table 15.1 C: One-bond (C—X) reactions



ONE-BOND (C—X) REACTIONS

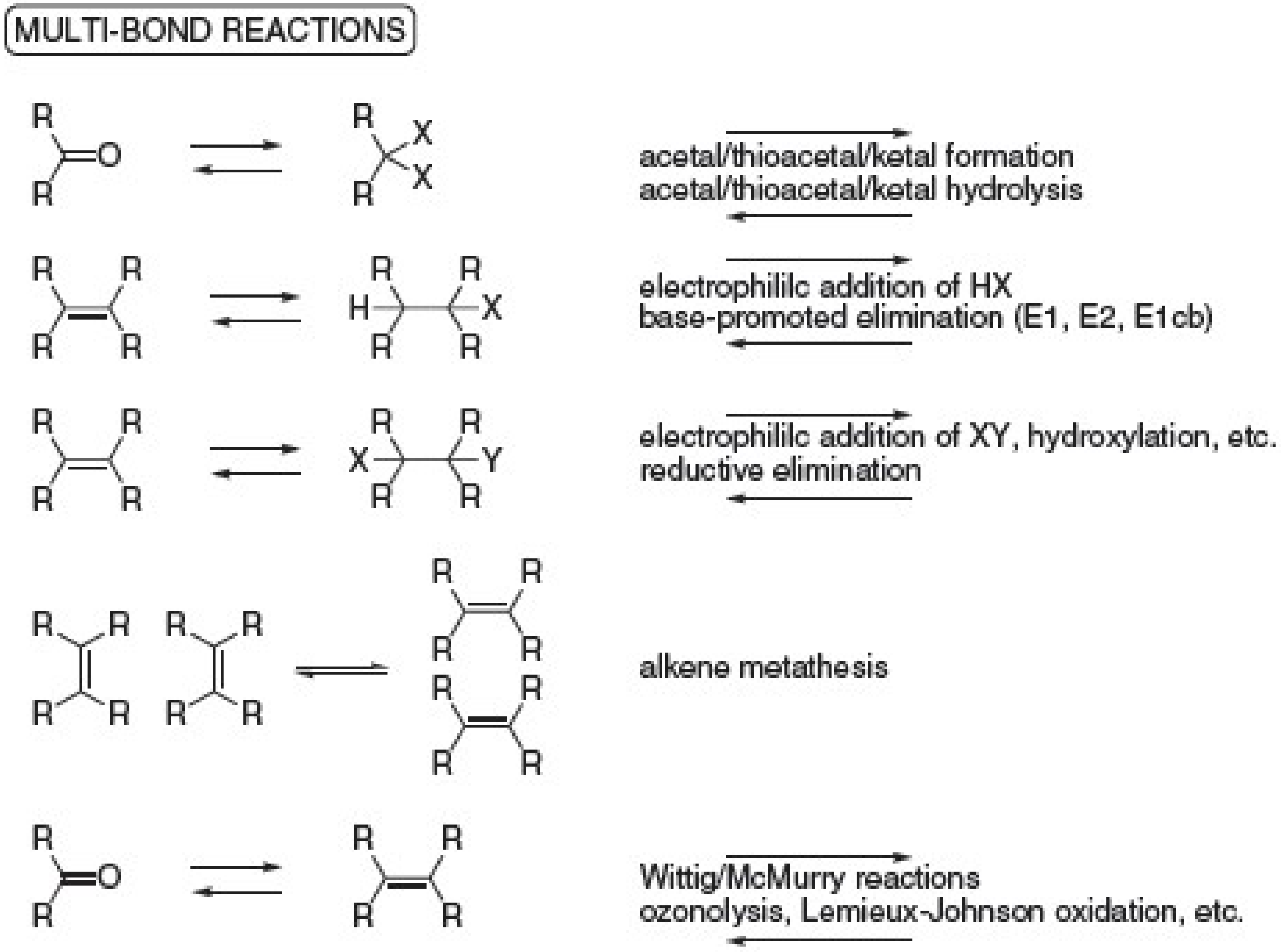
α-halogenation, sulfenylation, selenylation etc.
α-hydrogenolysis

allylic/benzylic halogenation, etc.
allylic/benzylic hydrogenolysis, etc.

nucleophilic substitution (S_N1, S_N2, etc.)

aromatic nitration, halogenation, etc.

Table 15.1 D: Multibond reactions



MULTI-BOND REACTIONS

acetal/thioacetal/ketal formation
acetal/thioacetal/ketal hydrolysis

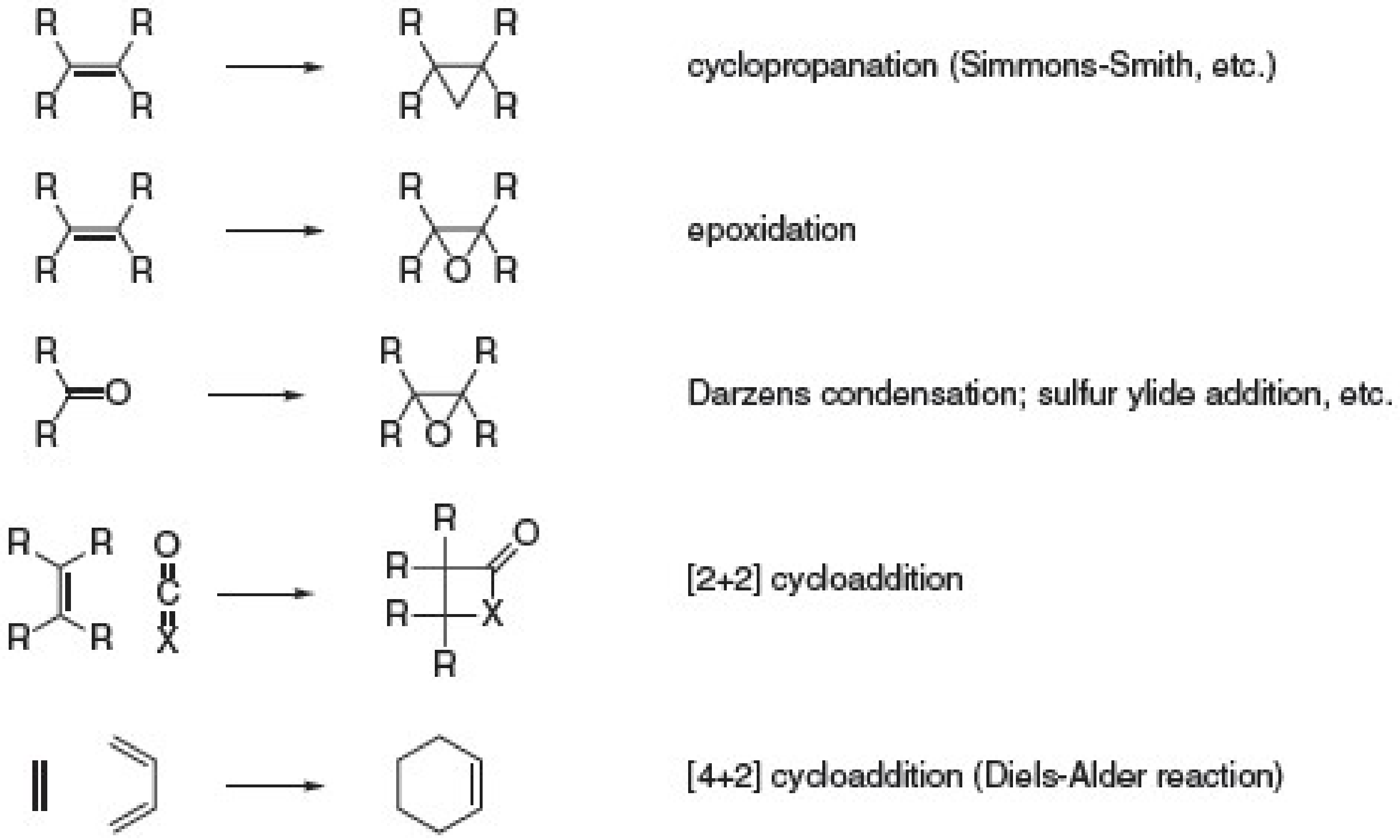
electrophililc addition of HX
base-promoted elimination (E1, E2, E1cb)

electrophililc addition of XY, hydroxylation, etc.
reductive elimination

alkene metathesis

Wittig/McMurry reactions
ozonolysis, Lemieux-Johnson oxidation, etc.

Table 15.1 E: Multibond reactions



cyclopropanation (Simmons-Smith, etc.)

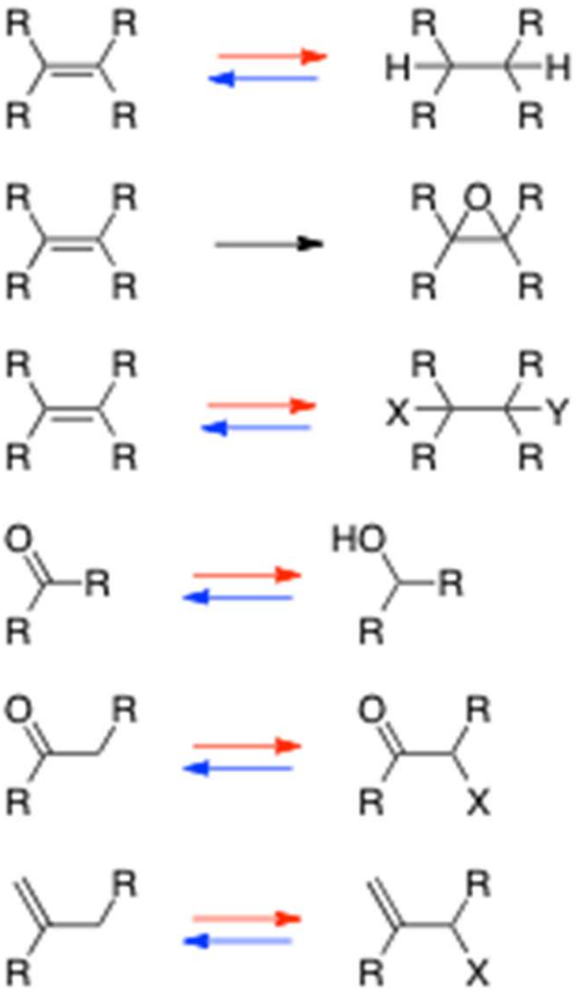
epoxidation

Darzens condensation; sulfur ylide addition, etc.

[2+2] cycloaddition

[4+2] cycloaddition (Diels-Alder reaction)

Table 15.1 F: Oxidation and reduction reactions



hydrogenation
dehydrogenation

epoxidation

addition of halogens; hydroxylation, etc.
reductive elimination

reduction of carbonyl compounds
oxidation of alcohols

α-halogenation, sulfenylation, sulfonation, etc.
hydrogenolysis of α-halocarbonyl compounds, etc.

allylic halogenation, oxidation, etc.
allylic hydrogenolysis

Table 15.1 G: Oxidation and reduction reactions

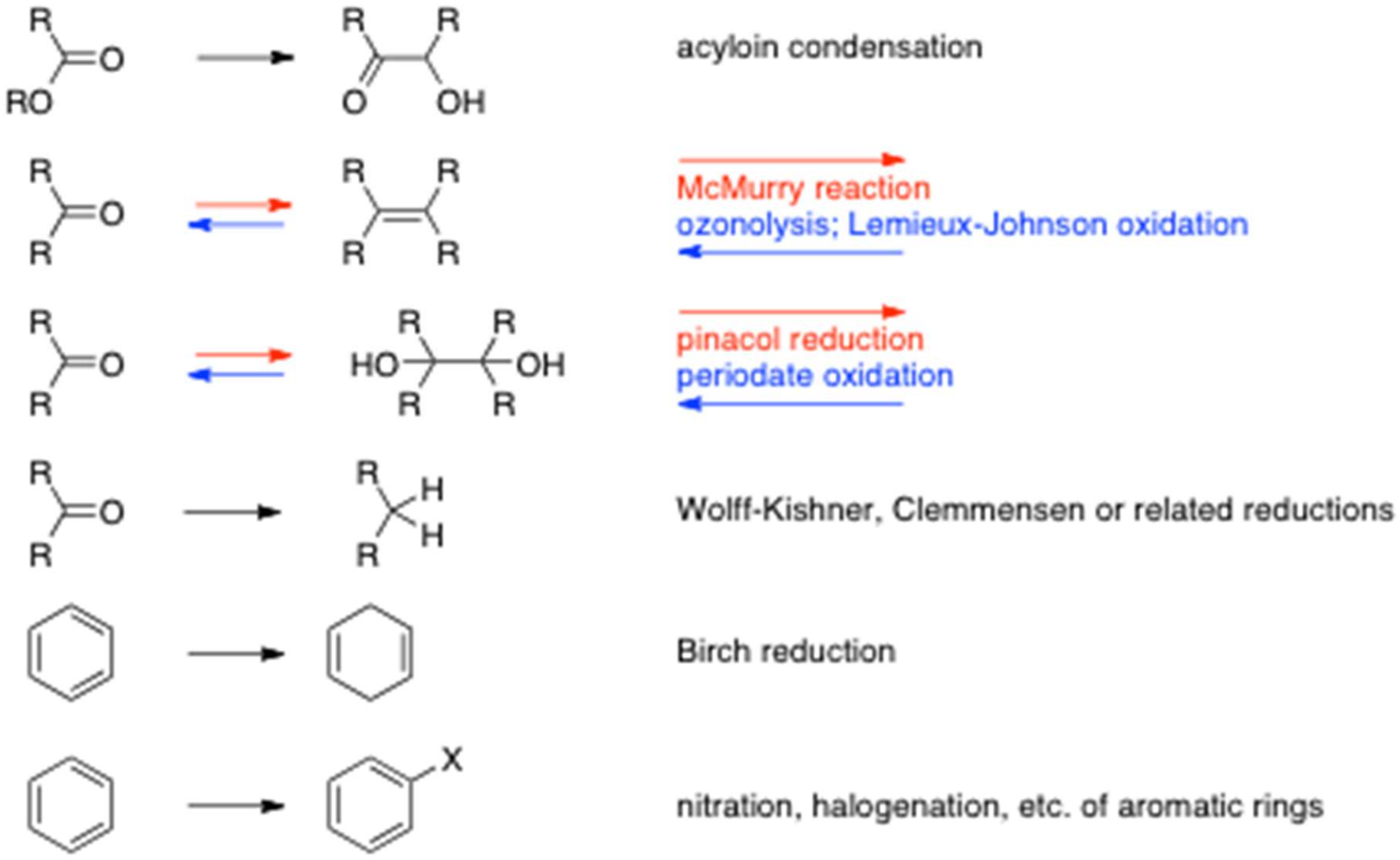


Table 15.1 H: Rearrangement reactions

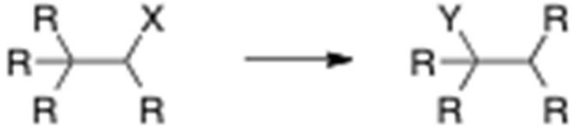
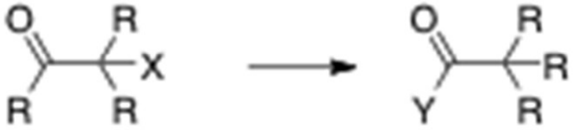
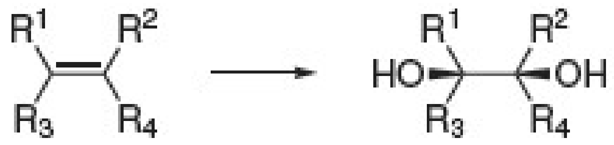
	Wagner-Meerwein rearrangement of cations
	pinacol rearrangement
	Favorskii rearrangement
	Hofmann, Curtius, Lossen rearrangements
	Baeyer-Villiger rearrangement (X=O; Y=O) Beckmann rearrangement (X=NOH; Y=NH) Schmidt reaction (X=O; Y=NH)
	Cope (X=CR$_2$) and Claisen (X=O) rearrangements other sigmatropic rrearrangements
	electrocyclization

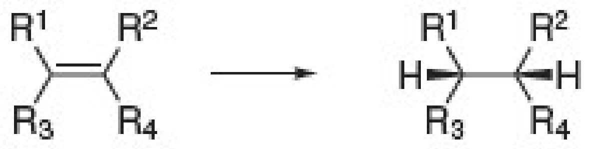
Table 15.2

- The reactions in this table are are grouped according to their stereochemistry into the following categories:
  - suprafacial (*syn*) additions
  - antarafacial (*anti*) additions
  - eliminations
  - reactions with retention of configuration
  - reactions with inversion of configuration

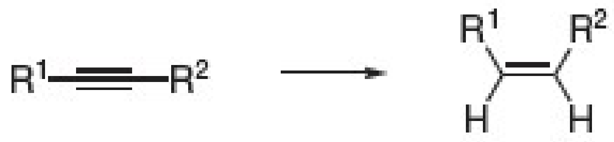
Table 15.2 A: Stereocontrolled reactions—suprafacial additions (1)



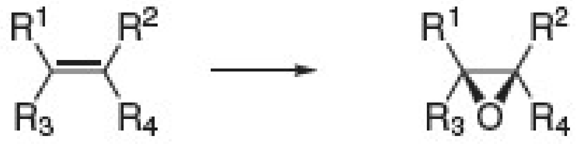
hydroxylation



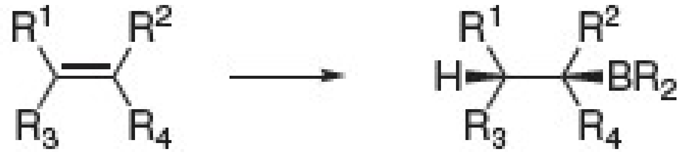
hydrogenation



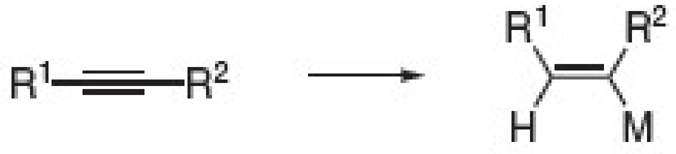
Lindlar hydrogenation



epoxidation

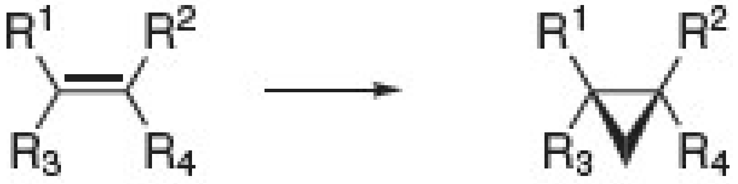


hydroboration

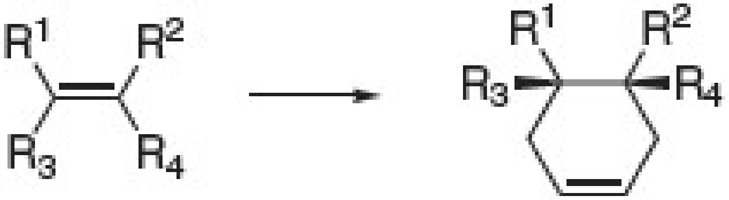


hydrometallation;
M=Al, Zr, etc.

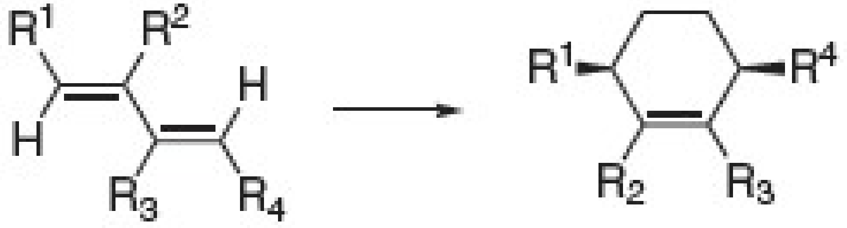
Table 15.2: Stereocontrolled reactions—suprafacial additions (2)



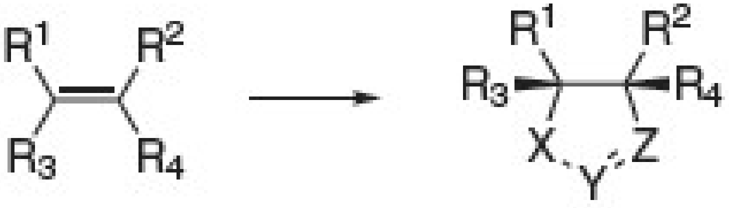
cyclopropanation



Diels-Alder cycloaddition



Diels-Alder cycloaddition



1,3-dipolar cycloaddition

Table 15.2 C: Stereocontrolled reactions—antarafacial additions

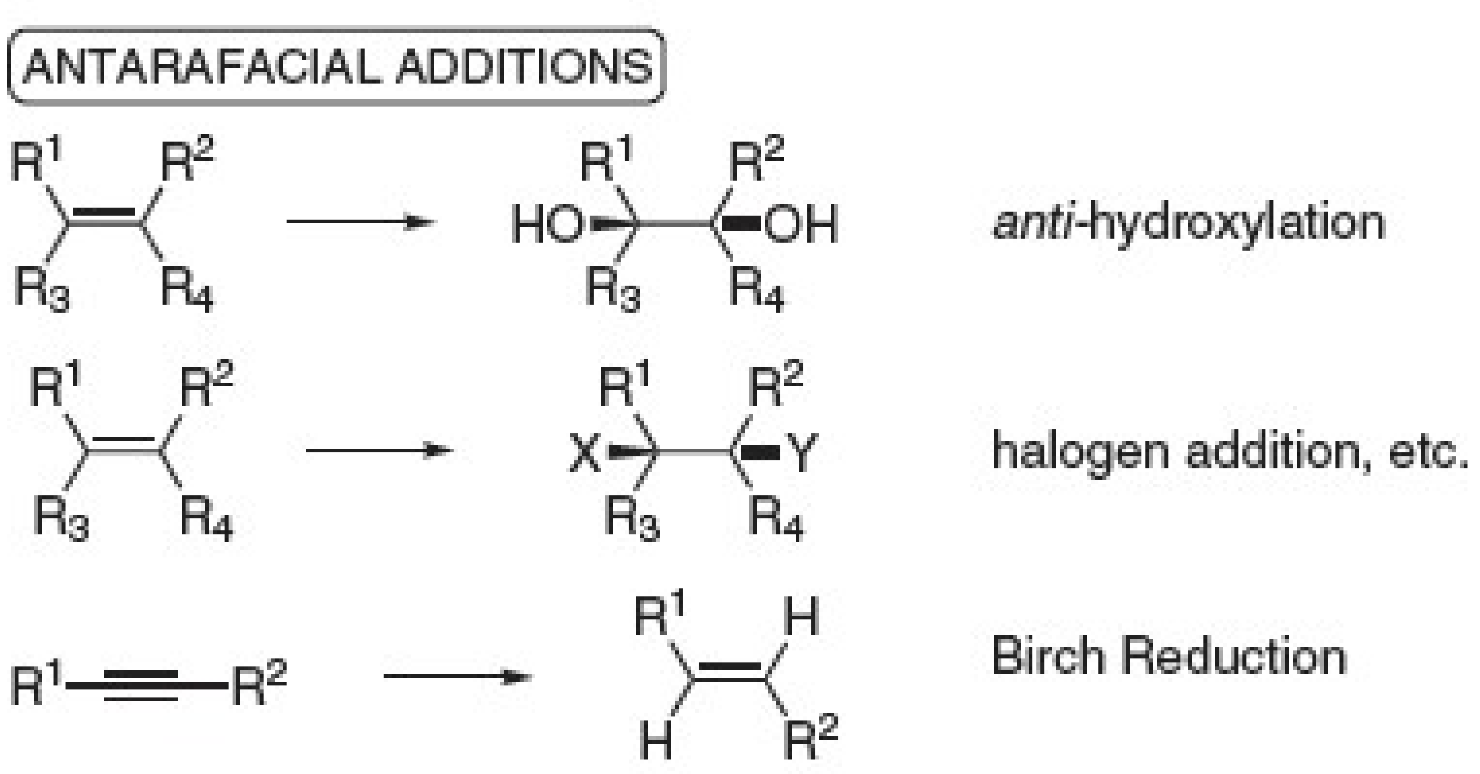
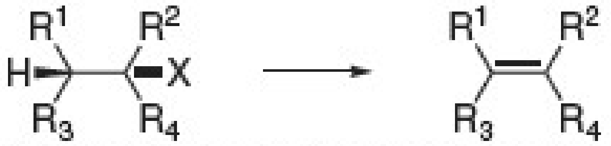
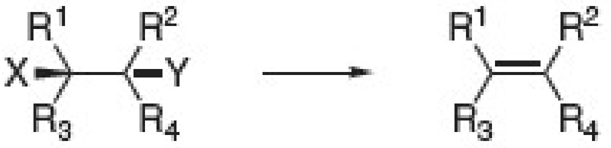


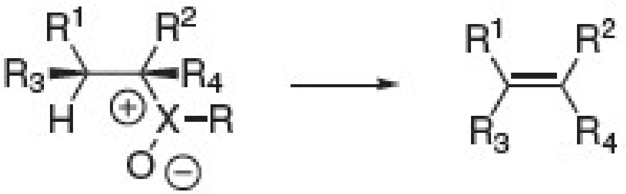
Table 15.2 D: Stereocontrolled reactions—eliminations



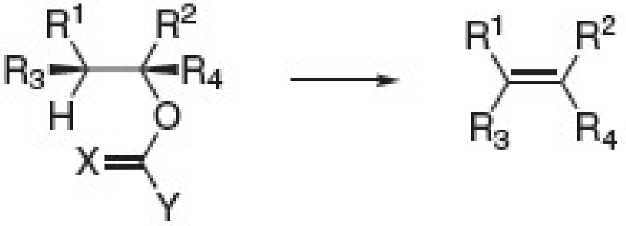
E2 elimination
(*anti*)



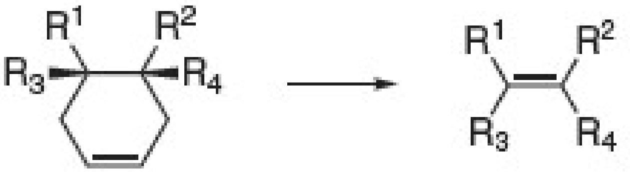
reductive elimination
syn or *anti*, depending on
leaving group)



Cope elimination (X=N)
(*syn* at low temperatures)
selenoxide elimination (X=Se)
(*syn*)

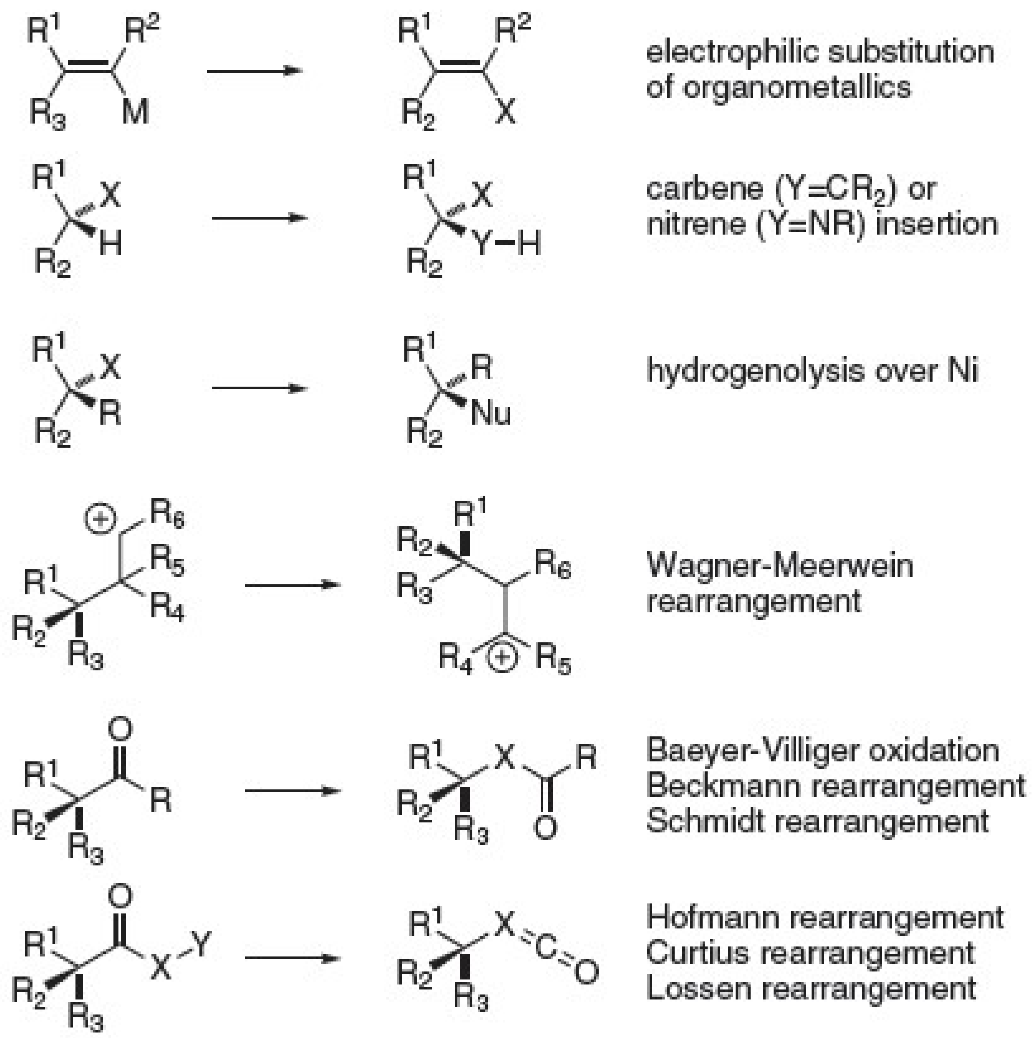


ester pyrolysis (X=O, Y=alkyl)
xanthate pyrolysis (X=S, Y=SR)
(*syn*)



Diels-Alder cycloreversion
(*syn*)

Table 15.2 E: Stereocontrolled reactions—retention of configuration



electrophilic substitution of organometallics

carbene ($Y=CR_2$) or nitrene ($Y=NR$) insertion

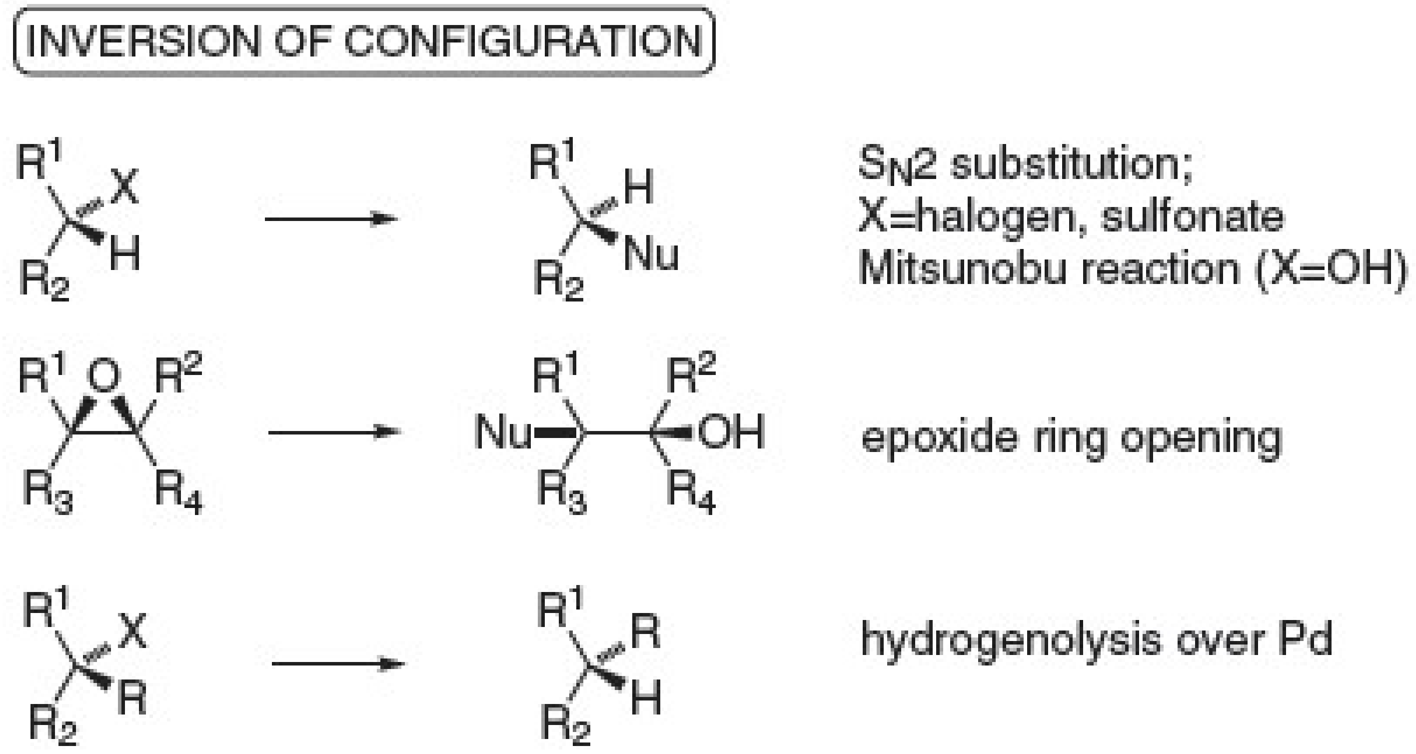
hydrogenolysis over Ni

Wagner-Meerwein rearrangement

Baeyer-Villiger oxidation
Beckmann rearrangement
Schmidt rearrangement

Hofmann rearrangement
Curtius rearrangement
Lossen rearrangement

Table 15.2 F: Stereocontrolled reactions—inversion of configuration



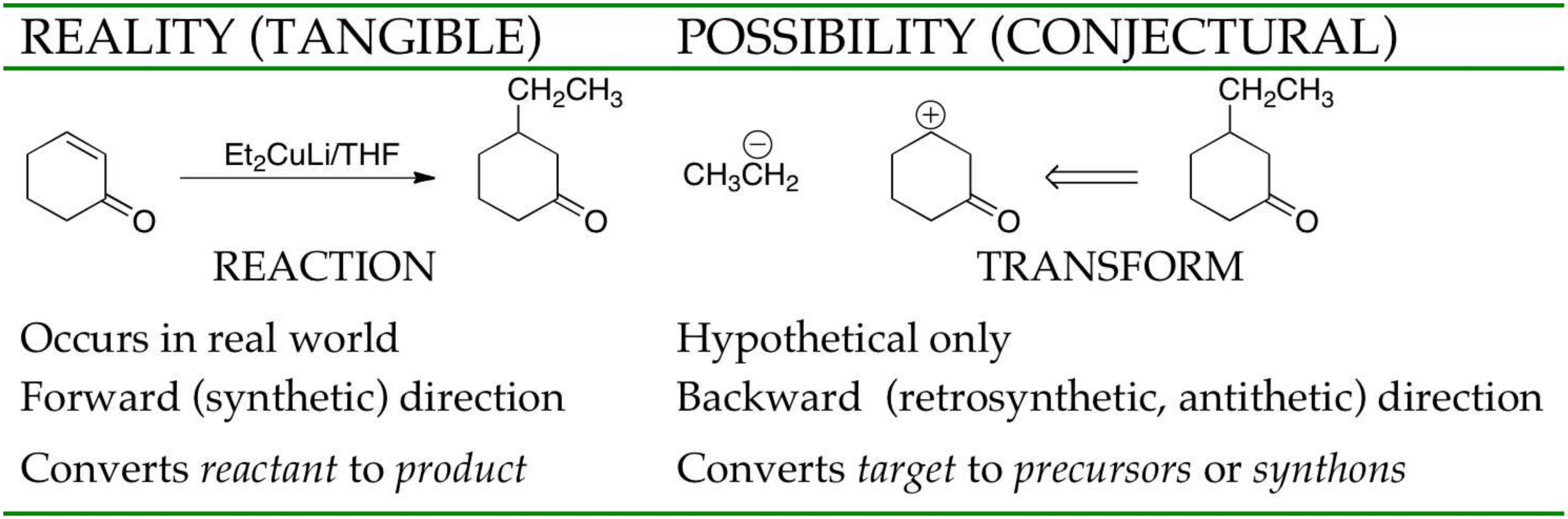
INVERSION OF CONFIGURATION

S_N2 substitution;
X=halogen, sulfonate
Mitsunobu reaction (X=OH)

epoxide ring opening

hydrogenolysis over Pd

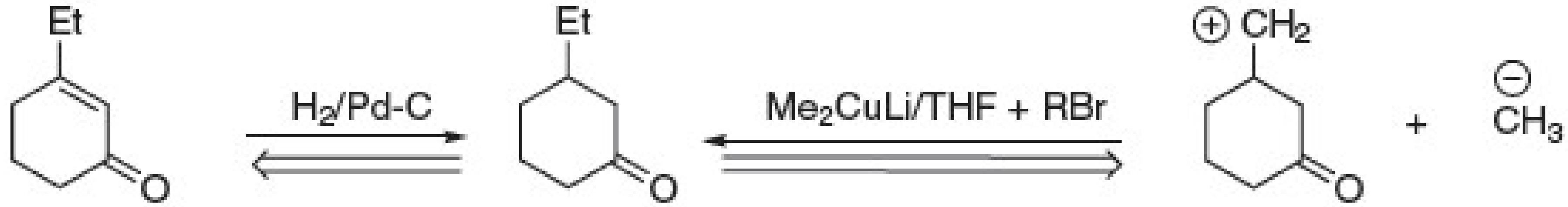
Figure 15.6



REALITY (TANGIBLE)	POSSIBILITY (CONJECTURAL)
REACTION	TRANSFORM
Occurs in real world	Hypothetical only
Forward (synthetic) direction	Backward (retrosynthetic, antithetic) direction
Converts *reactant* to *product*	Converts *target* to *precursors* or *synthons*

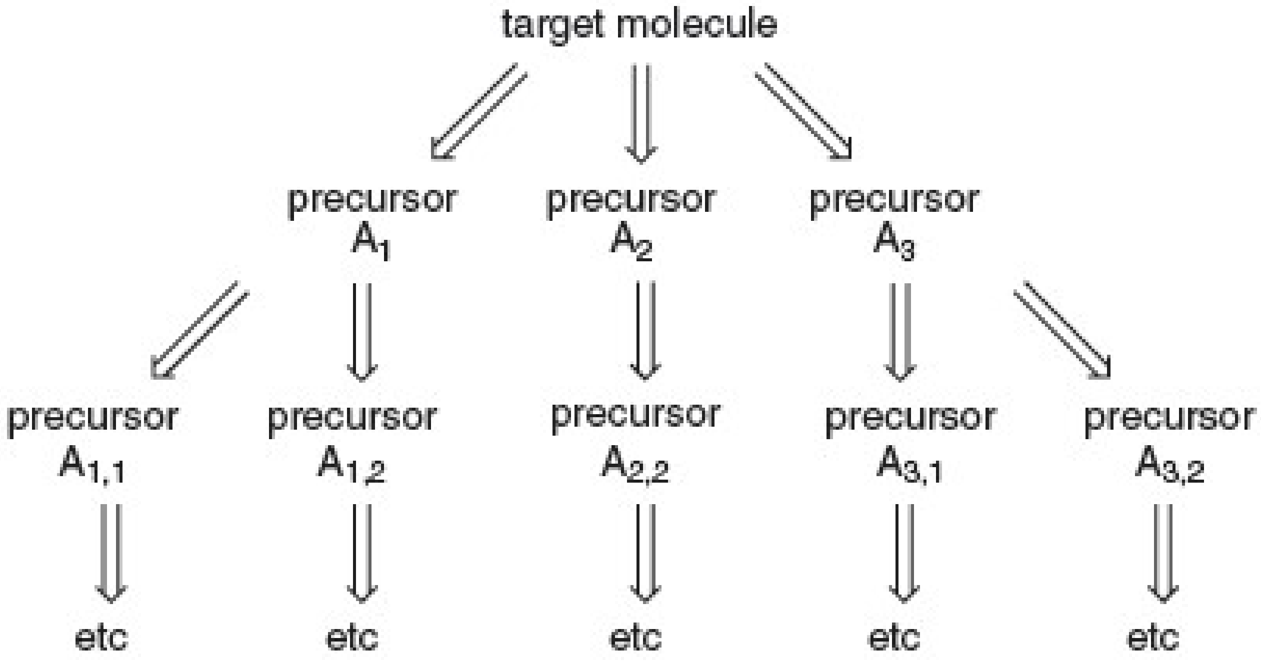
- Comparing reactions and transforms
  - reactions describe real events
  - transforms describe conjectural possibilities

Figure 15.7



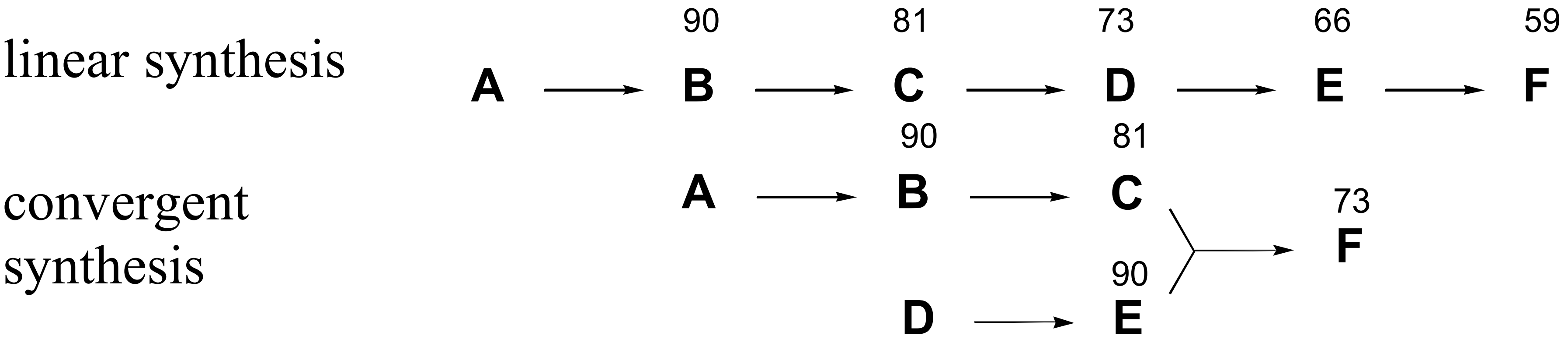
Alternative synthons for 3-ethylcyclohexanone.

Figure 15.8



A retrosynthetic tree

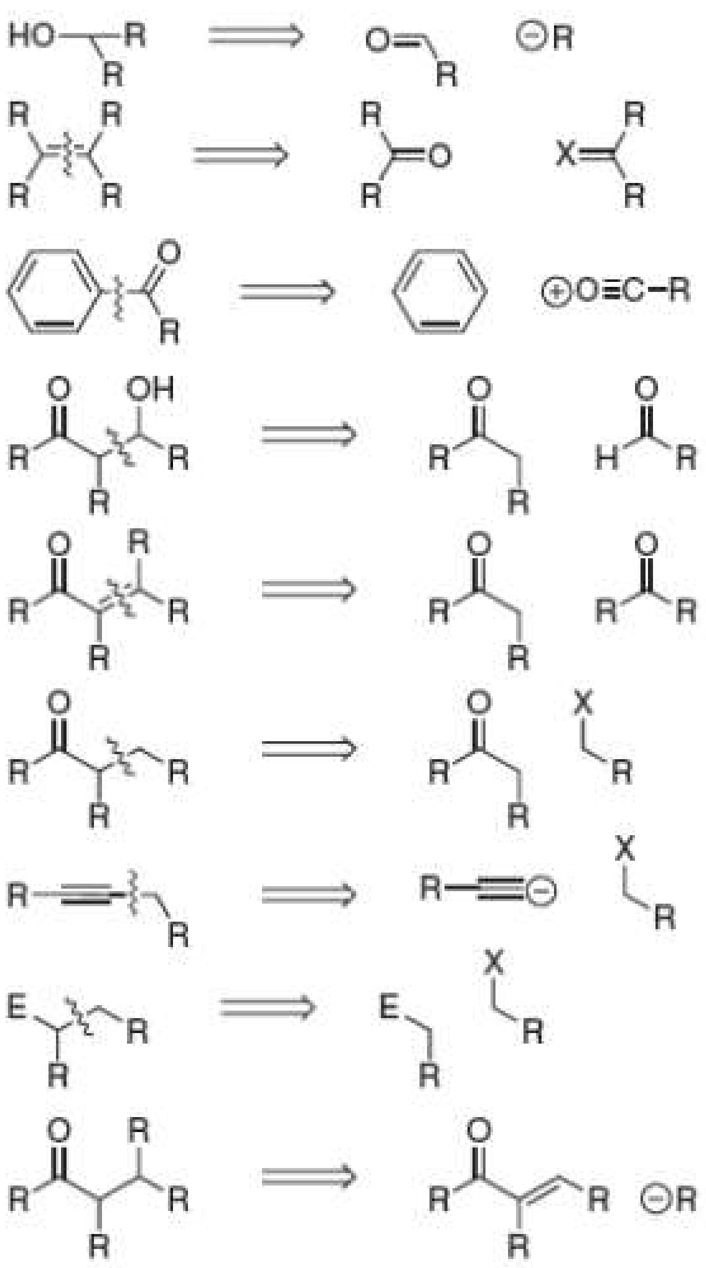
Figure 15.9



Comparing linear and convergent syntheses

Table 15.3 A

Bond disconnection (DIS) transforms



retro-Grignard addition
retro-alkynide anion addition

retro-Wittig transform
retro-McMurry transform

retro-acylation
retro-formylation

retro-aldol transform
retro-Reformatskii transform

retro-aldol condensation transform

retro-alkylation of enolate

retro-alkylation of alkynide anion

retro-alkylation of nitro compounds ($E=NO_2$), sulfoxides (E=SOR), dithianes ($E=(SR)_2$), etc.

retro-Michael addition transform

Table 15.3 B

Bond disconnection (DIS) transforms

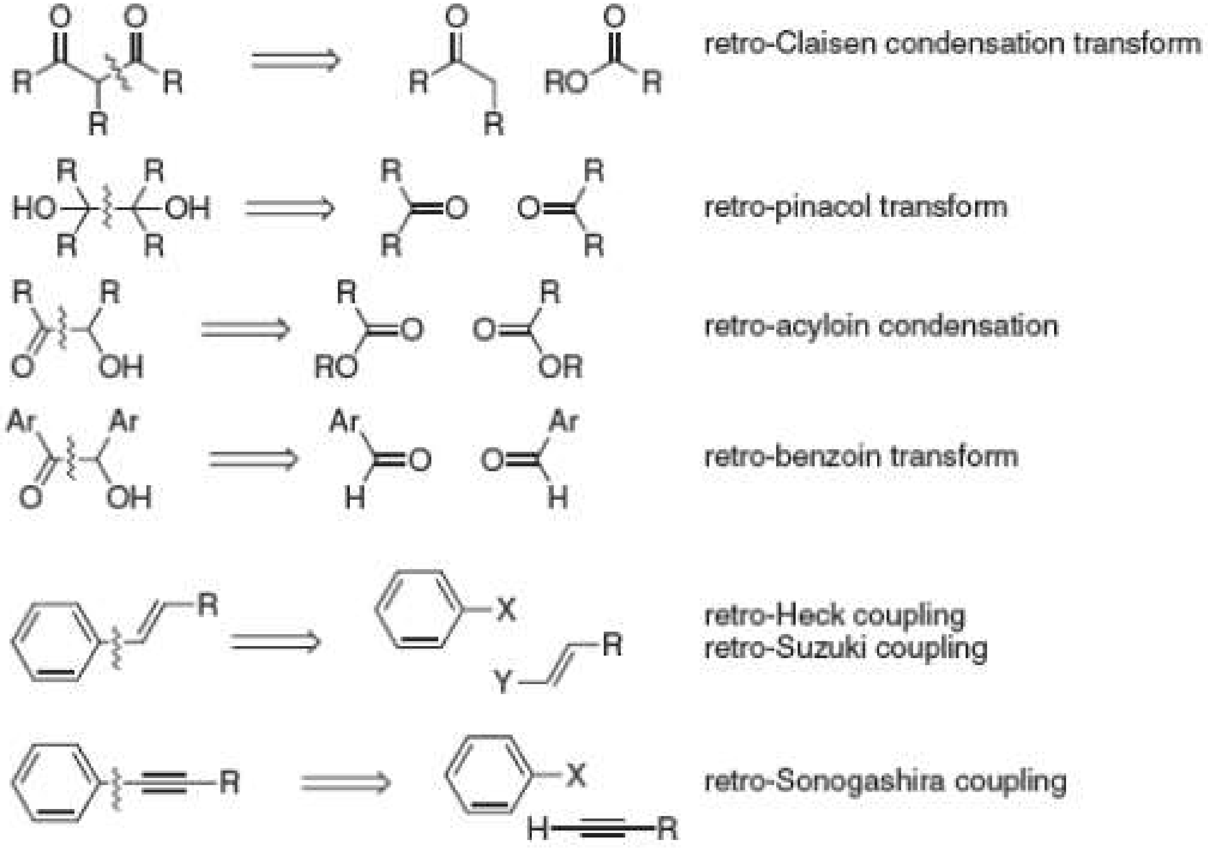


Table 15.3 C: Fuctional Group Interchange (FGI) transforms

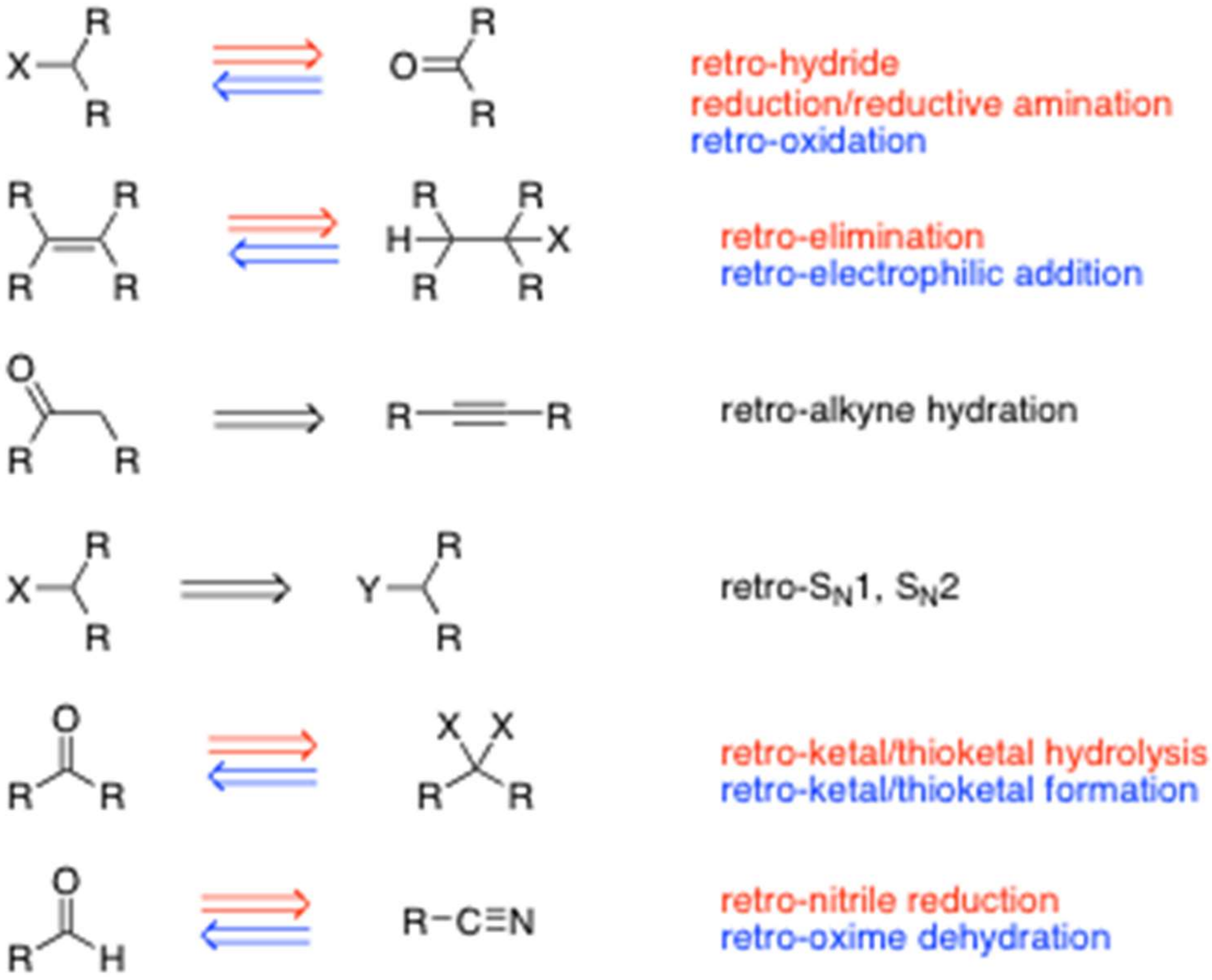


Table 15.3 D: Fuctional Group Interchange (FGI) transforms

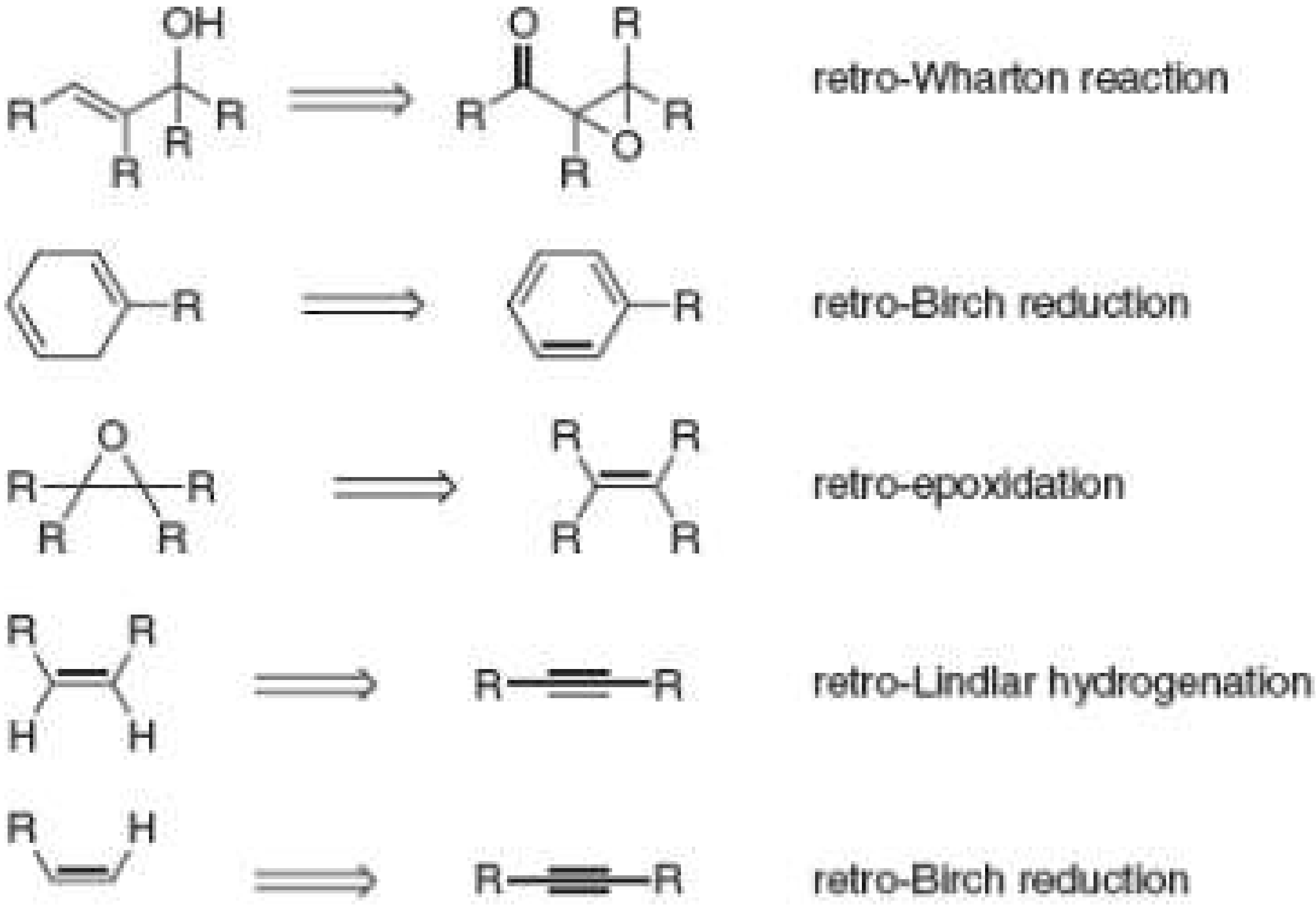


Table 15.3 E: Fuctional Group Removal (FGR) transforms

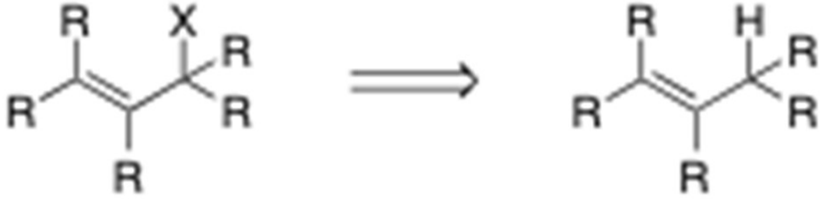
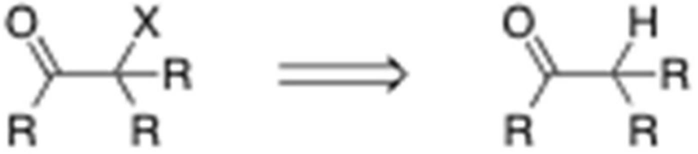
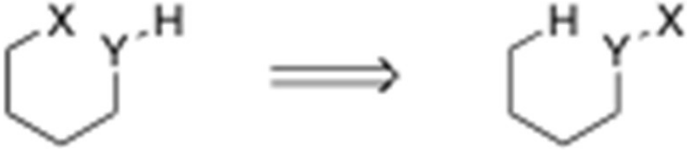
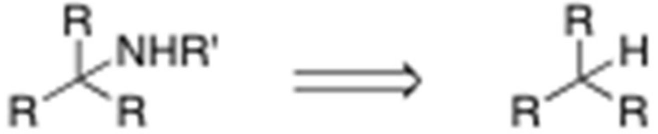
	retro-allylic halogenation, oxidation, etc.
	retro-α-halogenation, sulfenylation, selenylation, etc.
	retro-nitration, halogenation, etc.
	retro-Hofmann-Löffler-Freytag reaction; retro-Barton reaction, etc.
	retro-nitrene insertion

Table 15.3 F: Fuctional Group Addition(FGA) transforms

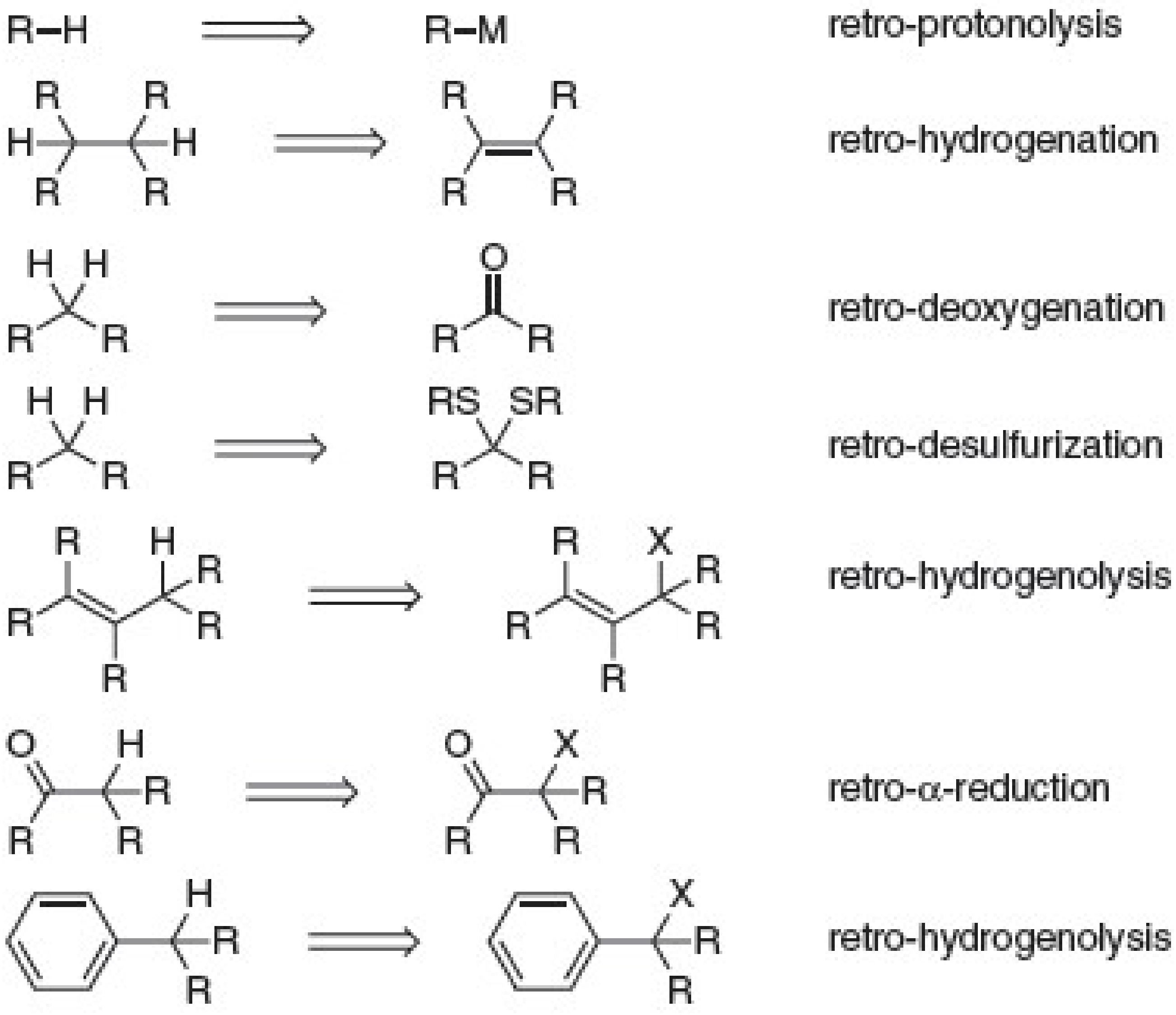


Table 15.3 F: Rearrangement (REARR) transforms

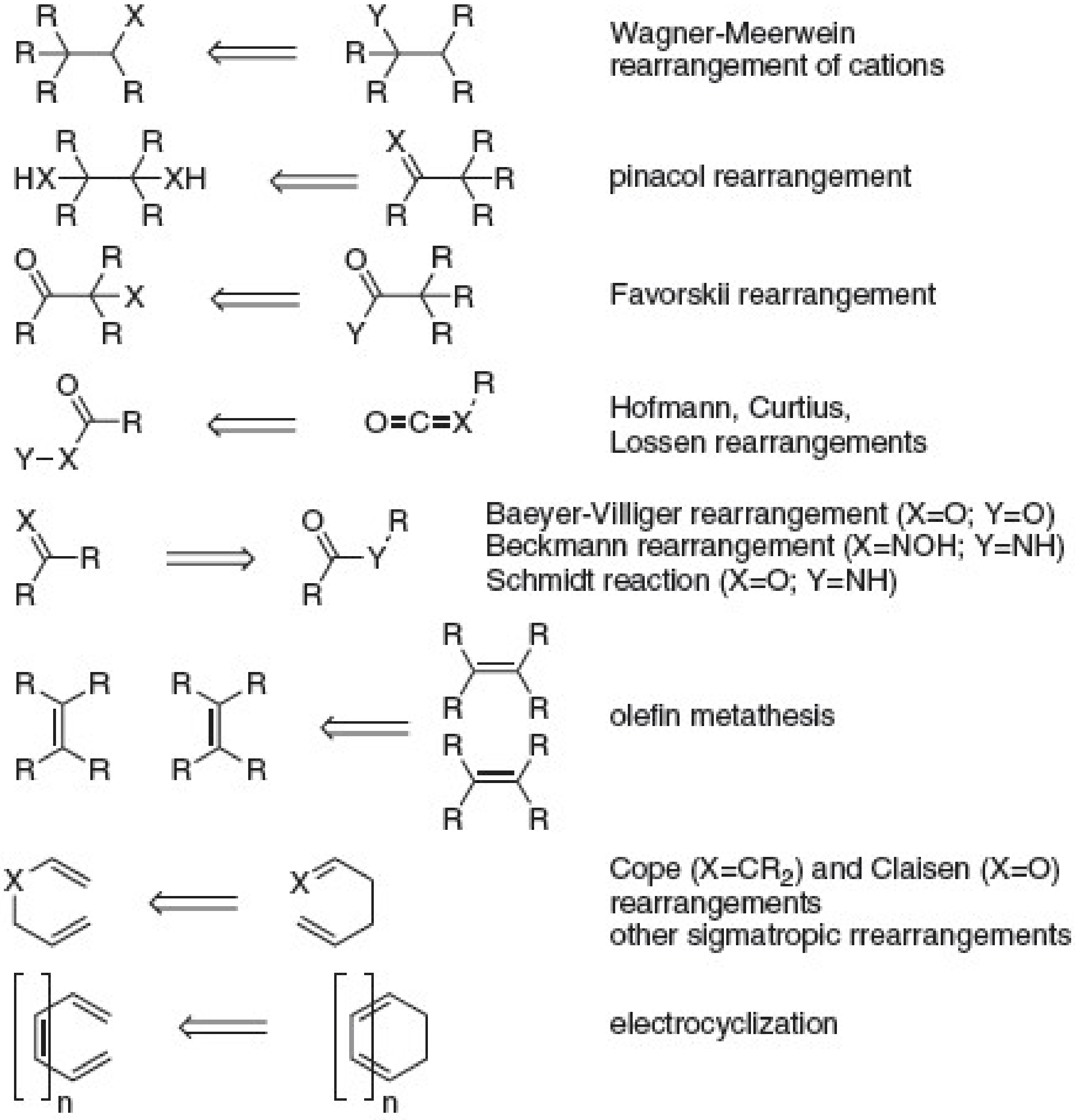
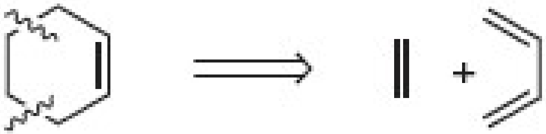
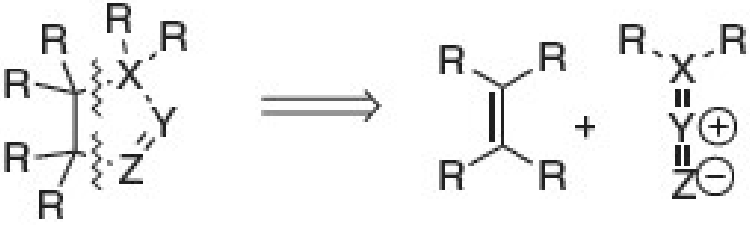


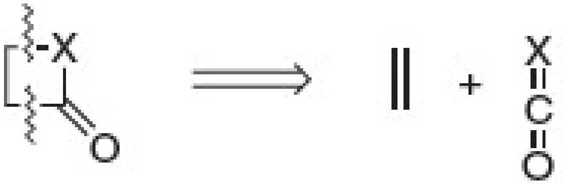
Table 15.3 G: Ring Disconnection (DIS) transforms



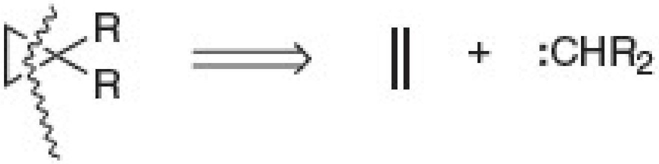
retro-Diels-Alder cycloaddition



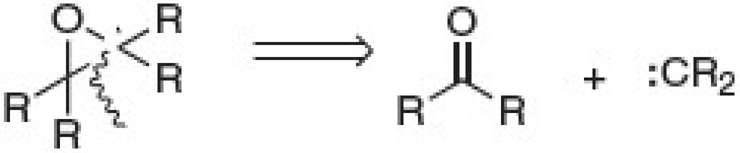
retro-[3+2] dipolar cycloaddition



retro-[2+2] cycloaddition

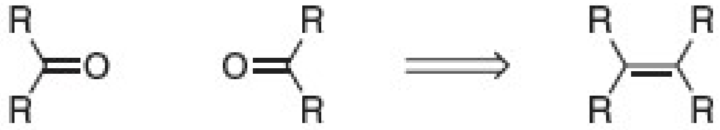


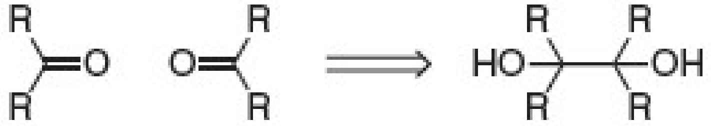
retro-carbene addition



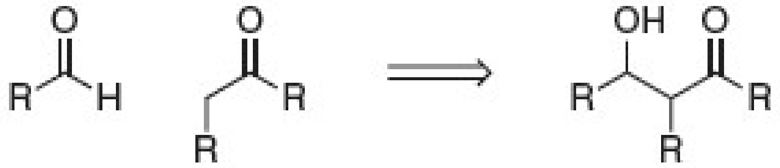
retro-Darzens condensation
retro-sulfonium ylide addition

Table 15.3 G: Ring Reconnection (REC) transforms

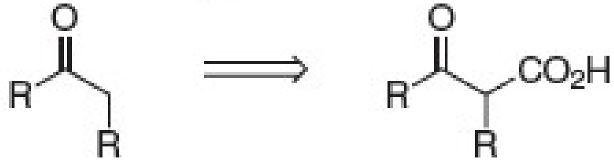

retro-ozonolysis transform
retro-Lemieux-Johnson transform


retro-glycol cleavage transform


aldol condensation transform

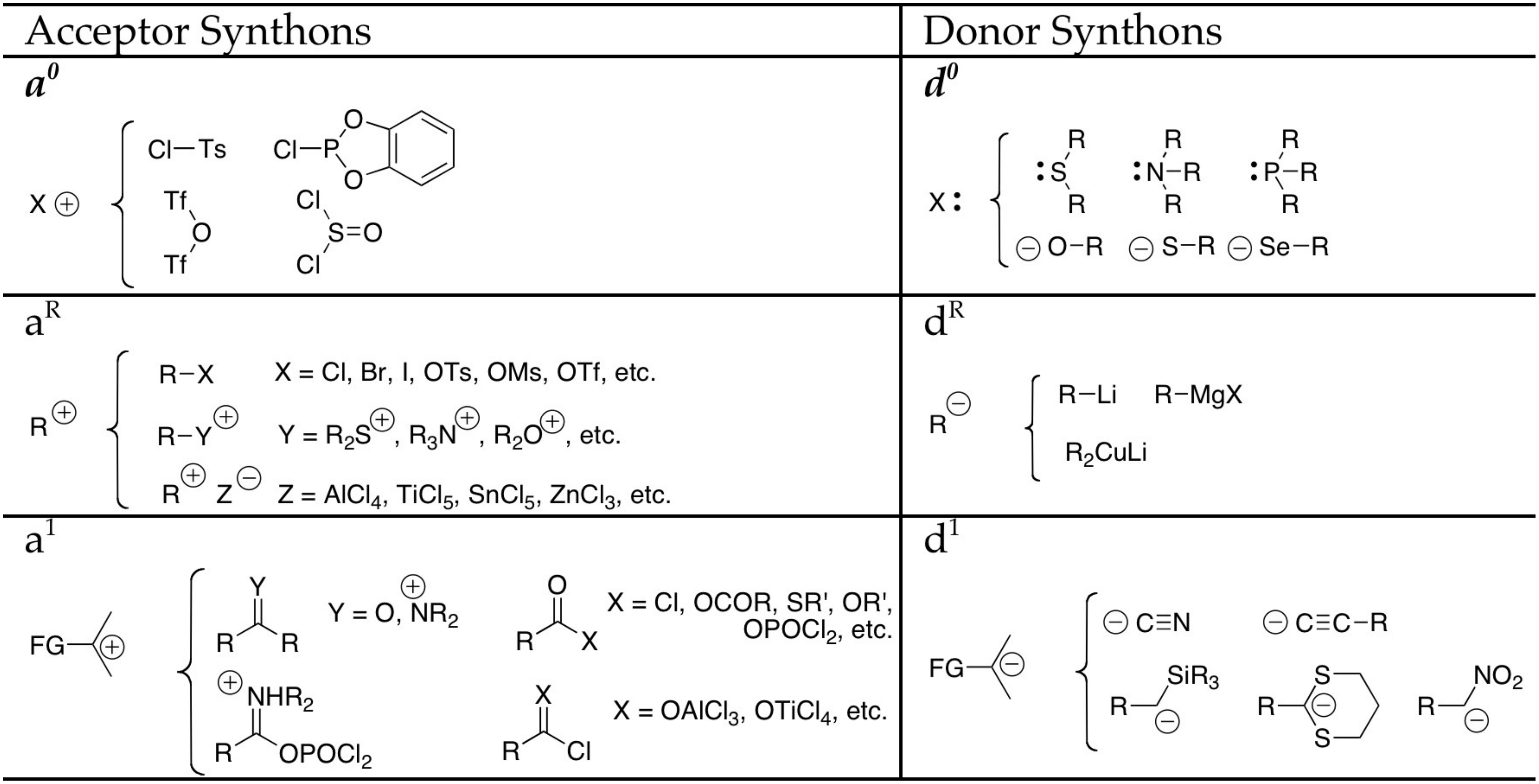

aldol addition transform


Claisen transform


retro-decarboxylation transform


retro-Eschenmoser-
Tanabe fragmentation

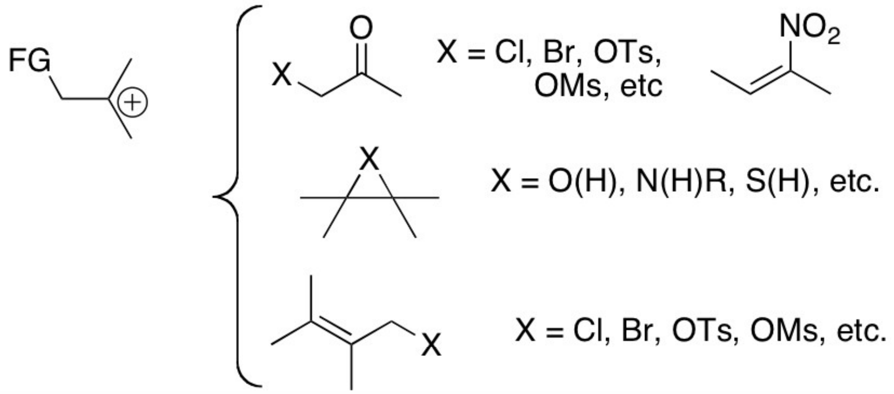
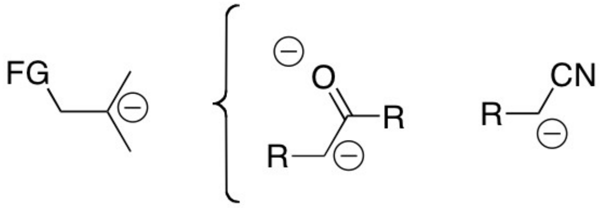
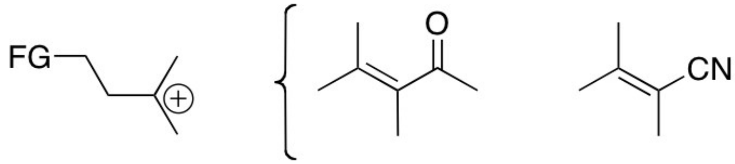
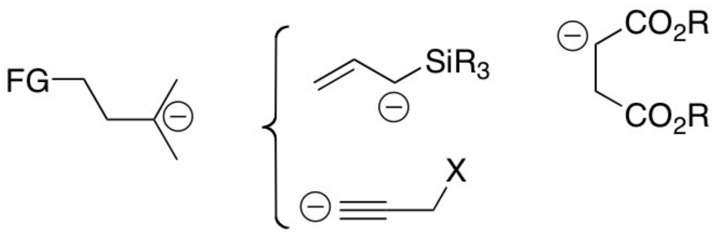
Table 15.4 A



Acceptor Synthons	Donor Synthons
a⁰	***d⁰***
$X^{\oplus}$: $Cl-Ts$, $Cl-P(O_2C_6H_4)$, $Tf-O-Tf$, $Cl_2S=O$	$X:$: $:SR_2$, $:NR_3$, $:PR_3$ $^{\ominus}O-R$, $^{\ominus}S-R$, $^{\ominus}Se-R$
a^R	d^R
$R^{\oplus}$: $R-X$ X = Cl, Br, I, OTs, OMs, OTf, etc. $R-Y^{\oplus}$ $Y = R_2S^{\oplus}, R_3N^{\oplus}, R_2O^{\oplus}$, etc. $R^{\oplus}\ Z^{\ominus}$ $Z = AlCl_4, TiCl_5, SnCl_5, ZnCl_3$, etc.	$R^{\ominus}$: $R-Li$ $R-MgX$ R_2CuLi
a^1	d^1
$FG-C^{\oplus}$: $R_2C=Y$ $Y = O, \overset{\oplus}{N}R_2$ $RC(=O)X$ $X = Cl, OCOR, SR', OR', OPOCl_2$, etc. $RC(=\overset{\oplus}{N}HR_2)OPOCl_2$ $RC(=X)Cl$ $X = OAlCl_3, OTiCl_4$, etc.	$FG-C^{\ominus}$: $^{\ominus}C\equiv N$, $^{\ominus}C\equiv C-R$ $R-\overset{\ominus}{C}H-SiR_3$, 2-R-1,3-dithian-2-ide, $R-\overset{\ominus}{C}H-NO_2$

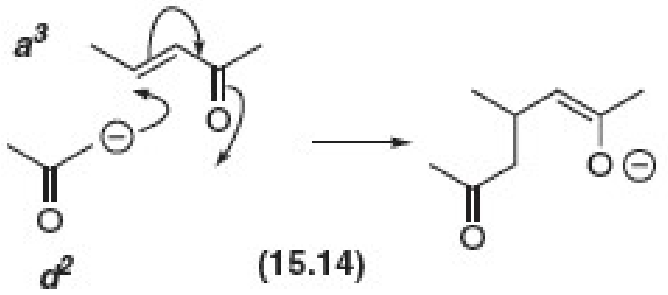
Fuhrhop-Penzlin designation of synthons (1)

Table 15.4 B

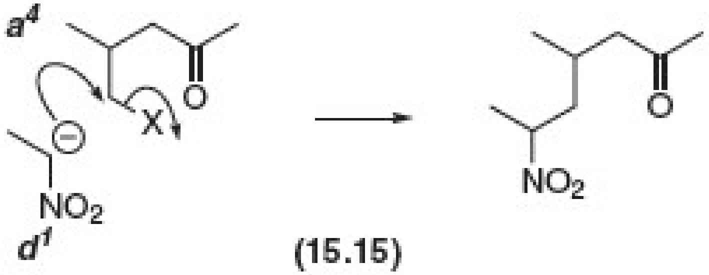
a^2  X = Cl, Br, OTs, OMs, etc X = O(H), N(H)R, S(H), etc. X = Cl, Br, OTs, OMs, etc.	d^2 
a^3 	d^3 

Fuhrhop-Penzlin designation of synthons (2)

Fuhrhop-Penzlin disconnections

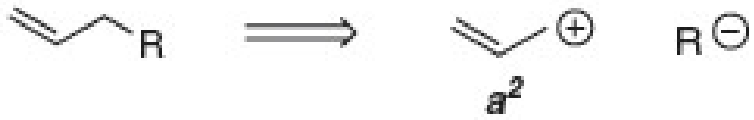


(15.14)



(15.15)

(15.16)



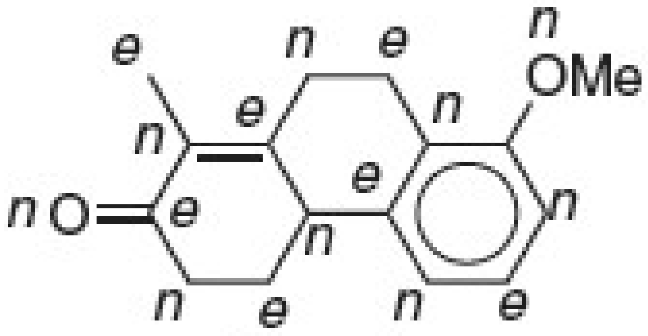
(15.17)

Disconnections reveal ***a*** and ***d*** synthons

- the ***a*** synthon may be a ***R*** synthon
- the ***d*** synthon may be a ***R*** synthon

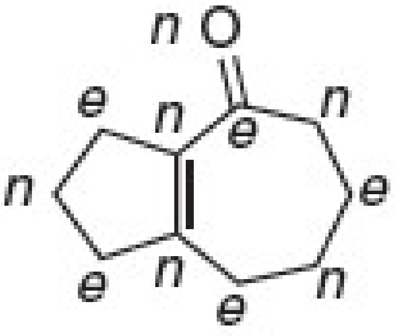
Figure 15.10

Consonant and dissonant molecules



(15.20)

Dissonalt difunctional relationship is enclosed in the red highlight box



(15.21)

Figure 15.11

FGA transforms applied to the twistane target molecule.

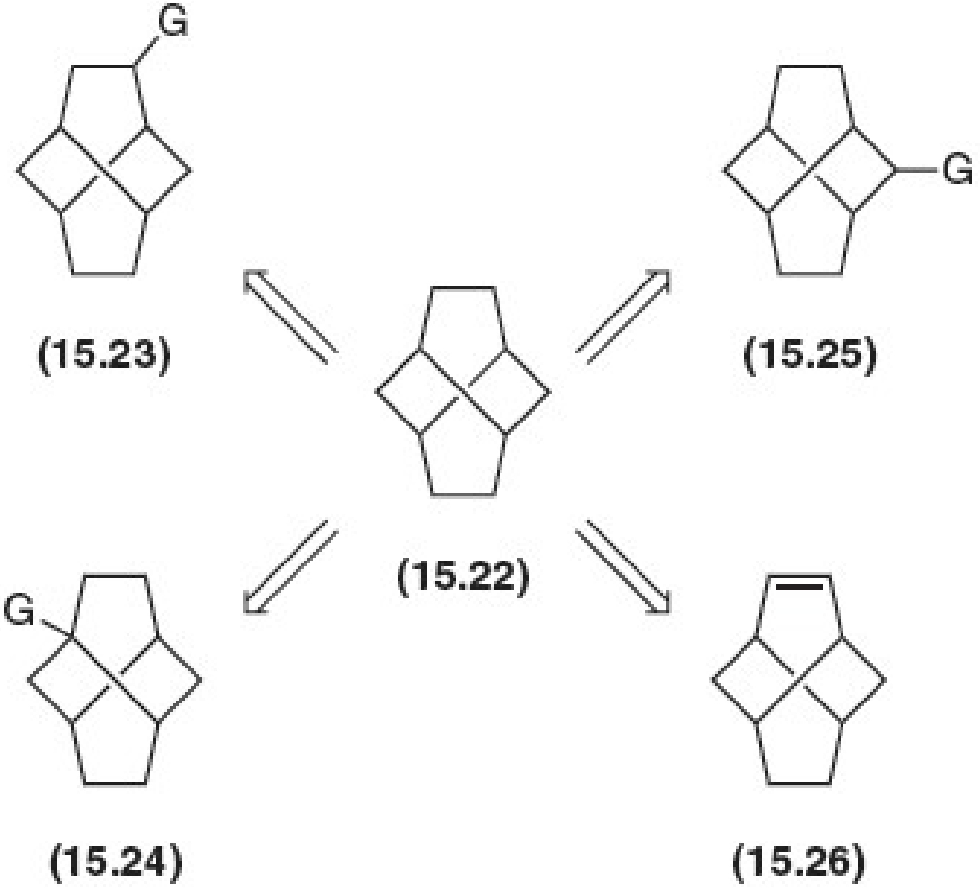
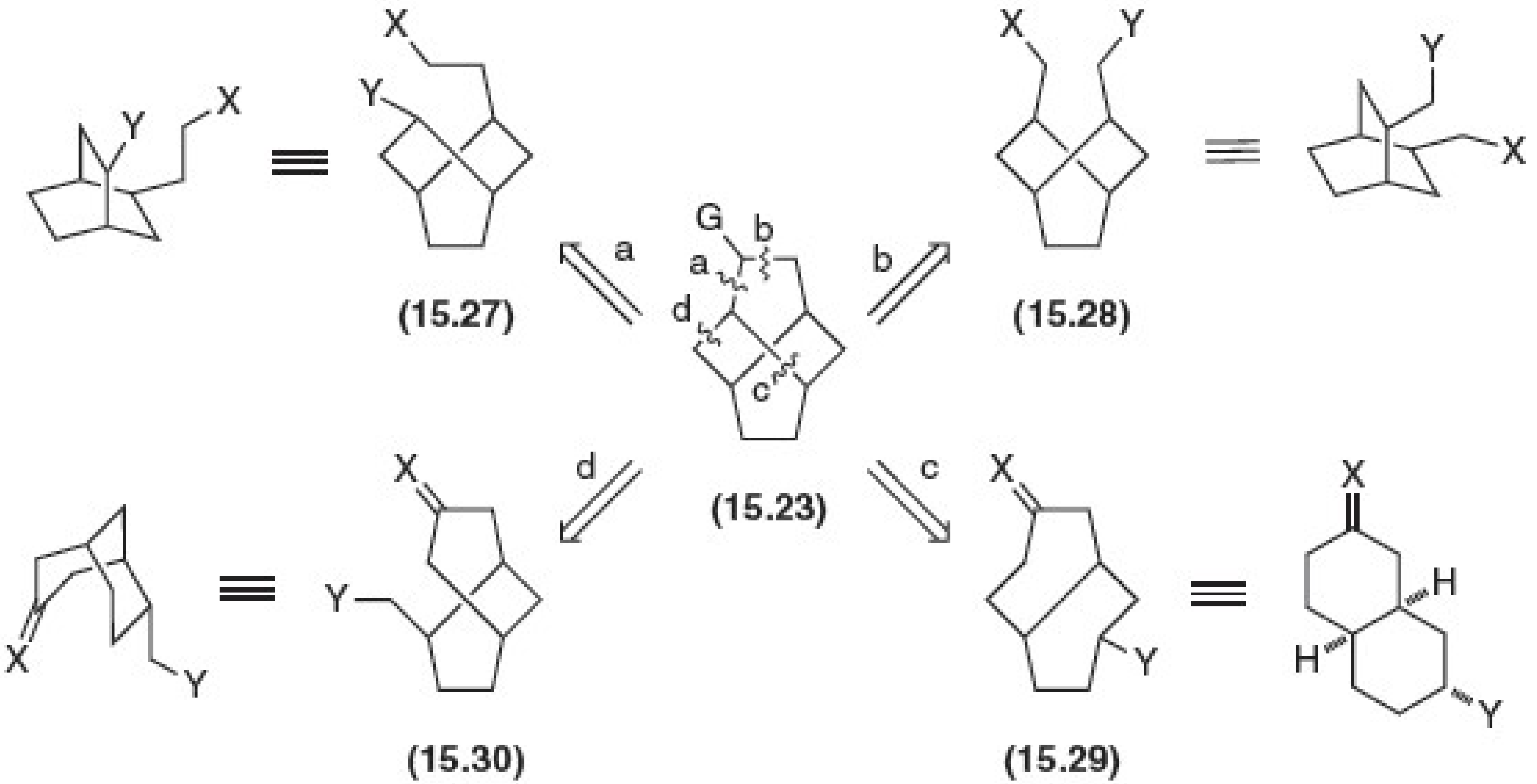


Figure 15.14

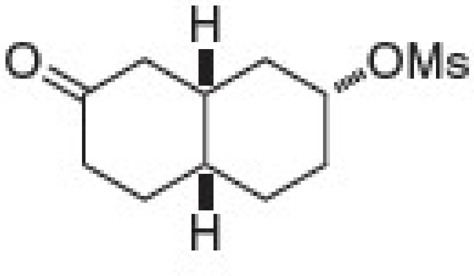


- Possible DIS transforms of the first-generation synthon **15.14**

One compound that can act as synthon **15.29**

The decalin must be *cis* fused or the required ring closure cannot happen.

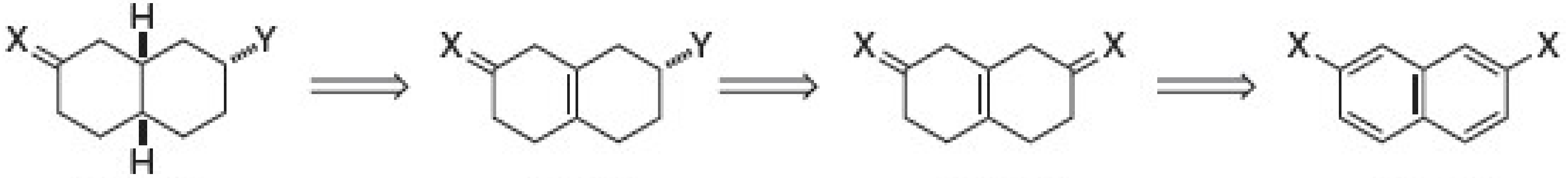
The reactive conformation is shown in red.



(15.31)

Figure 15.13

Retrosynthesis
of synthon
15.29



(15.29) (15.32) (15.33) (15.34)

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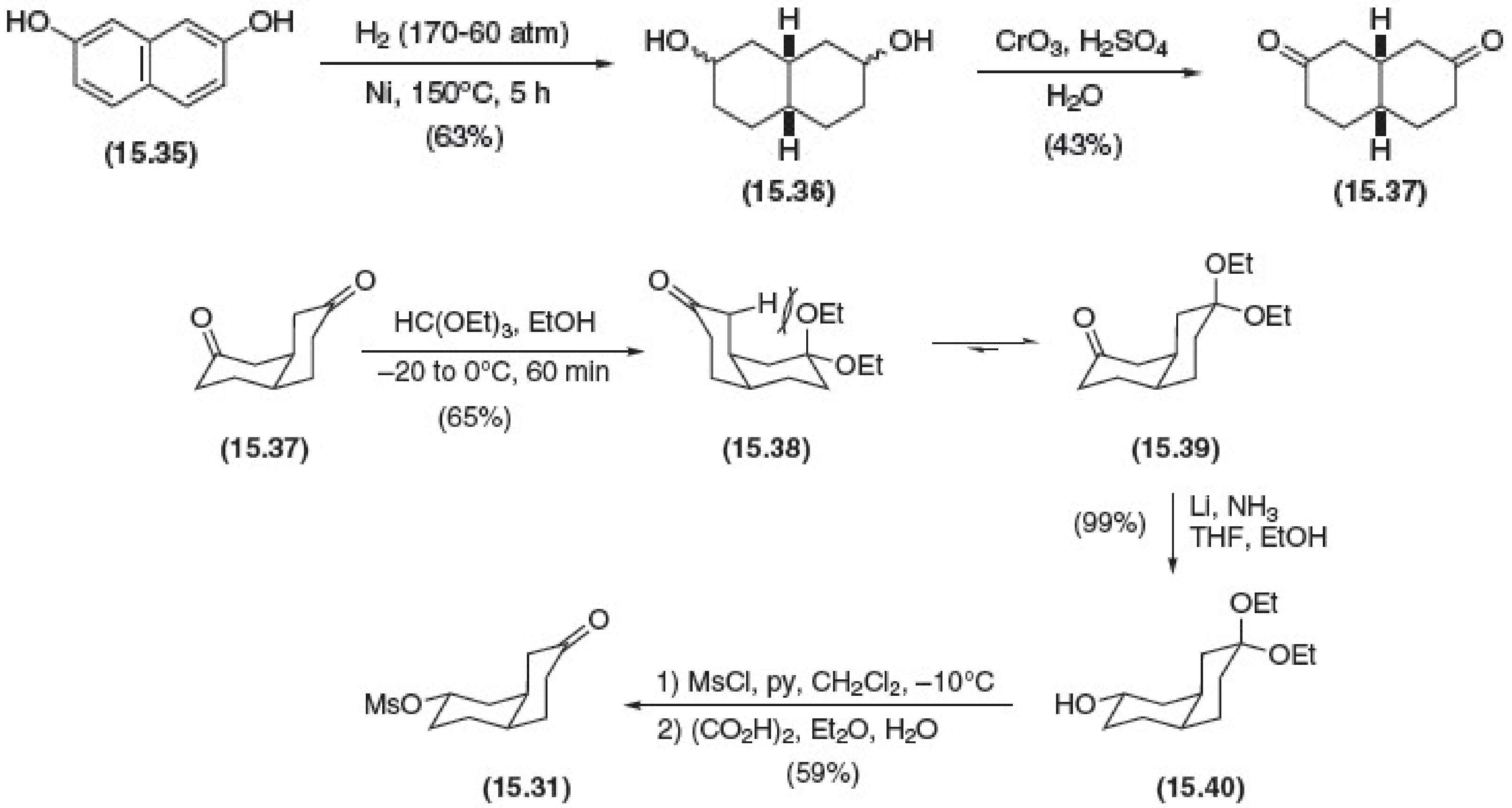
39. Gauthier, J.; Deslongchamps, P. *Can. J. Chem.* 1967, 45, 297.

Figure 15.14

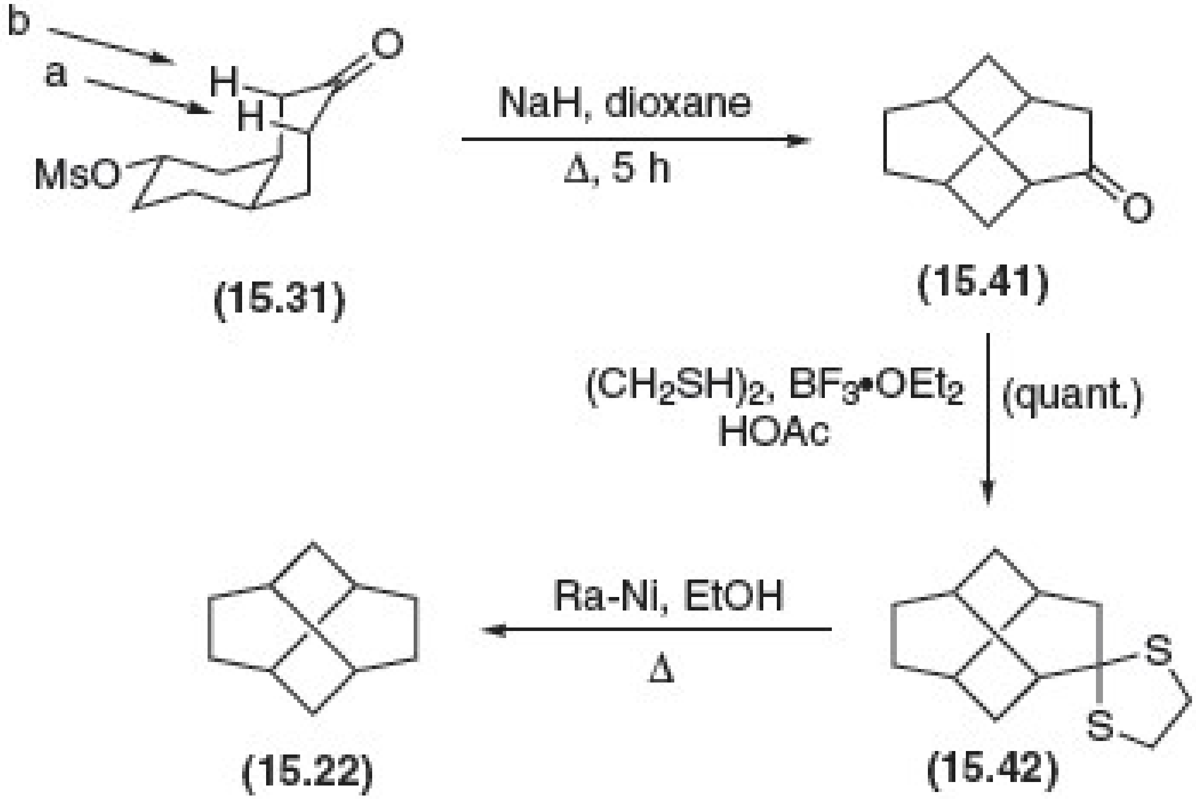


Synthesis of the key intermediate **15.31** for cyclization to the twistane ring system.

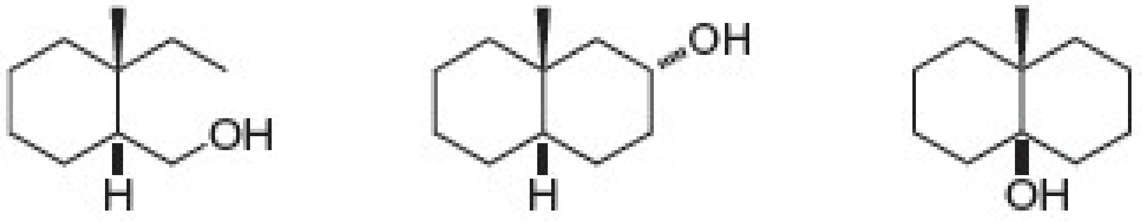
Figure 15.15

Completion of the synthesis of twistane

- proton a is sterically more accessible to the base than proton b, so its abstraction is favored kinetically



Chemoselectivity

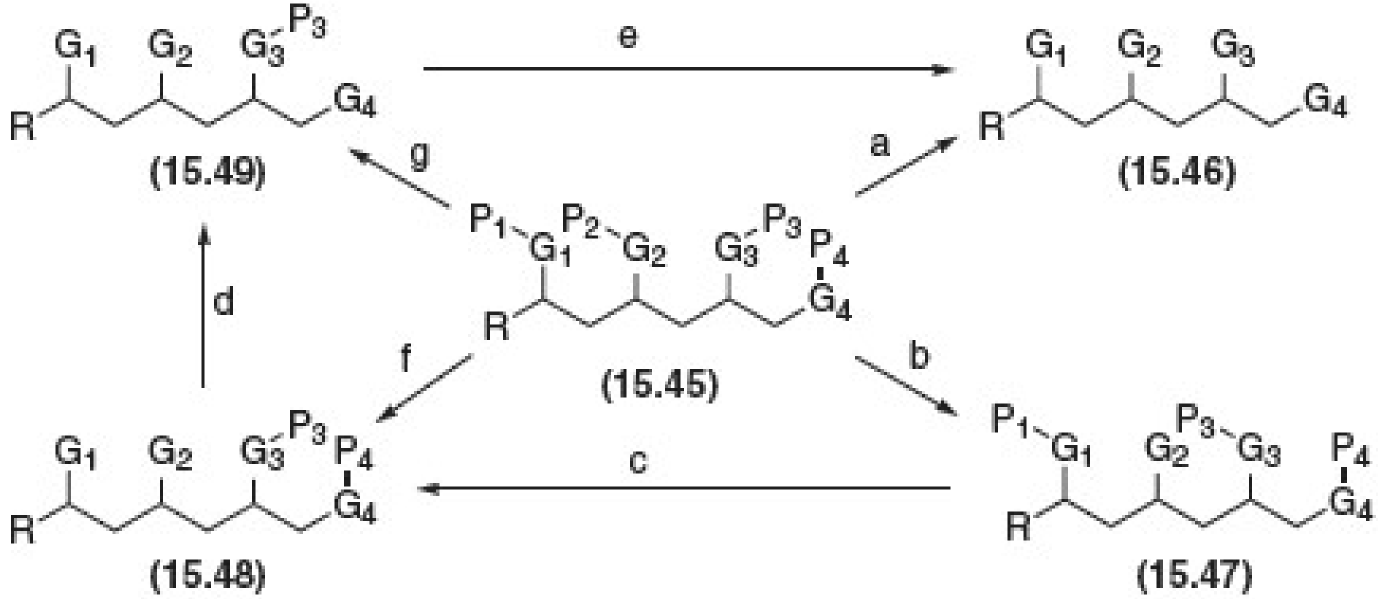


(15.43)

These three different alcohols can be distinguished by acetylation with acetic anhydride in pyridine

- primary alcohols react rapidly with this reagent
- secondary alcohols react at a moderate rate with this reagent
- tertiary alcohols do not react with this reagent

Figure 15.16



Orthogonality in protection of functional groups

- Note how it is possible to remove just one, or a select set of protecting groups

Figure 15.17 A

The reaction of a prochiral substrate with an achiral reagent proceeds through enantiomeric transition states of equal energy, and gives a racemic product; the same reaction in a chiral environment (e.g. with a chiral reagent, or in the presence of a chiral catalyst) proceeds through diastereoisomeric transition states of different energy, and thus gives a product enriched in one enantiomer.

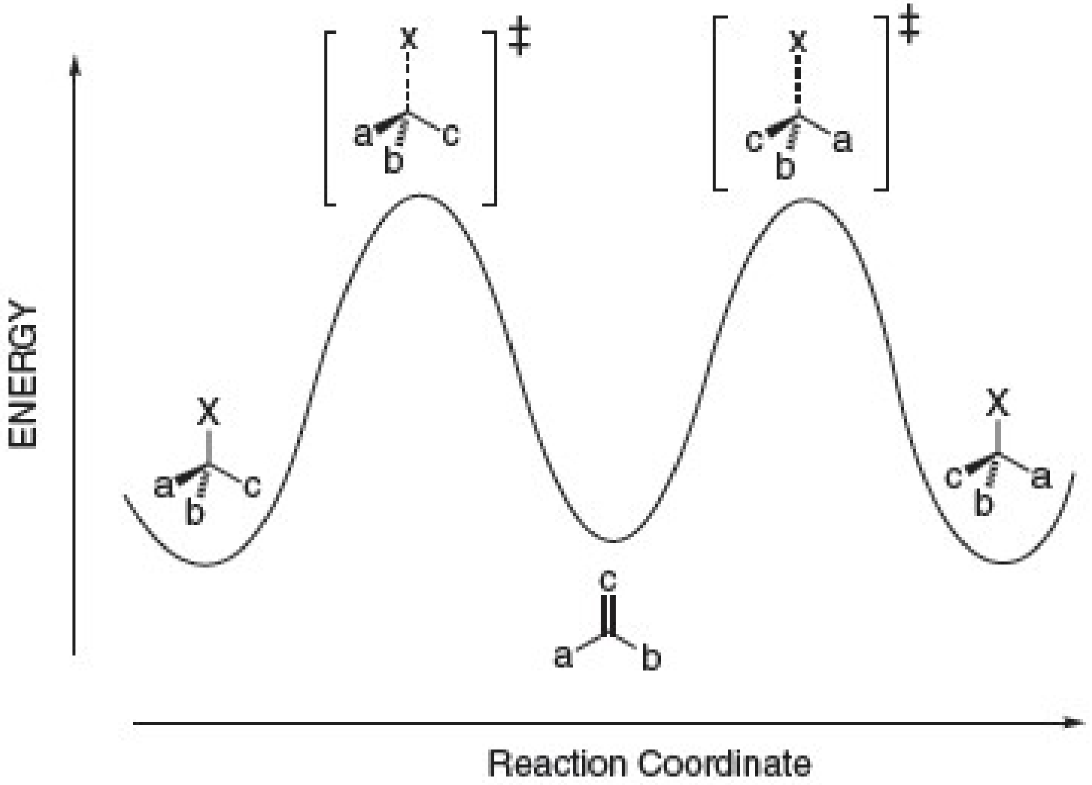


Figure 15.17 B

The reaction of a prochiral substrate in a chiral environment (e.g. with a chiral reagent, or in the presence of a chiral catalyst) proceeds through diastereoisomeric transition states of different energy, and thus gives a product enriched in one enantiomer.

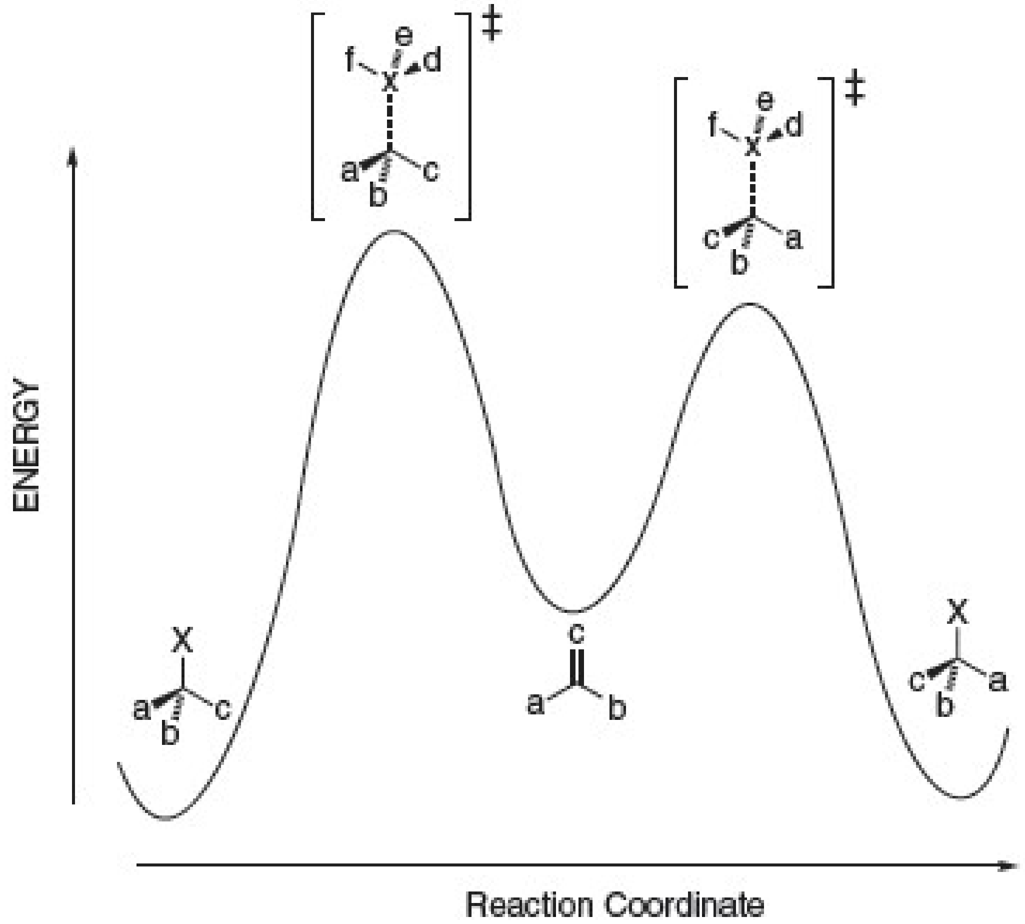
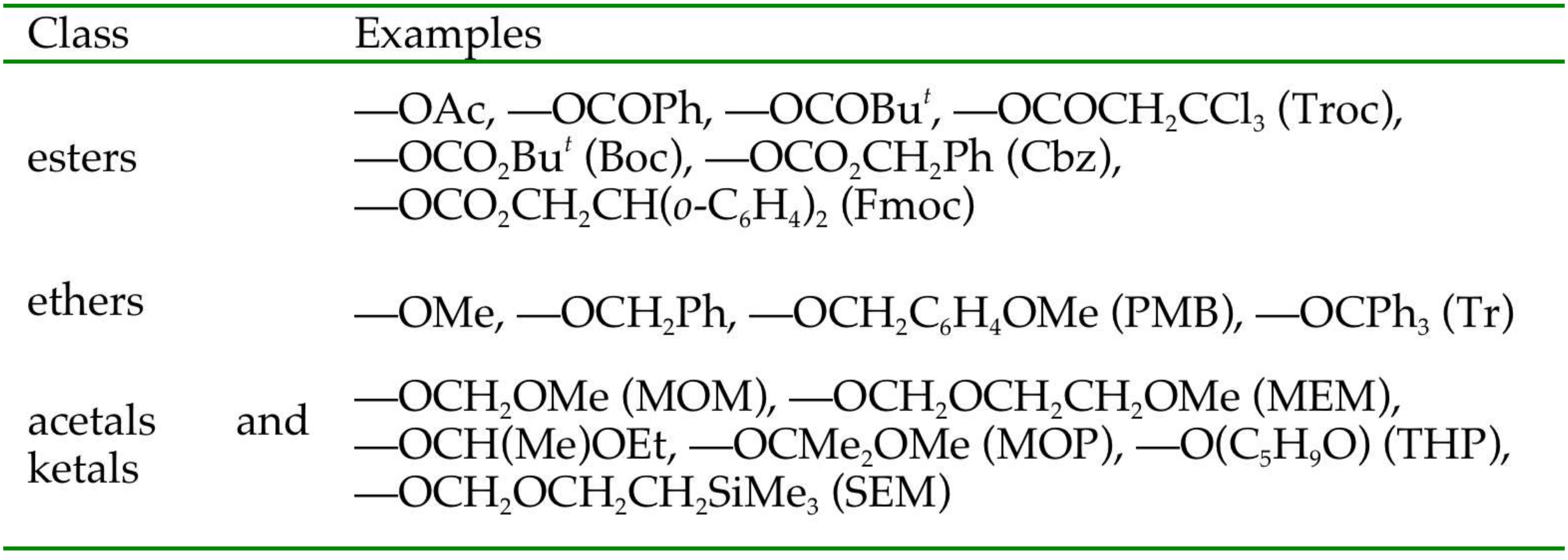


Table 15.5

Protecting groups for alcohols



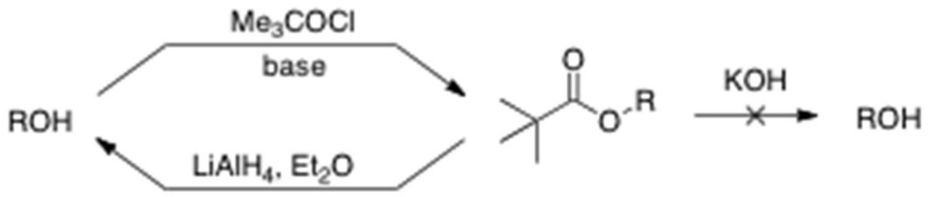
Class	Examples
esters	—OAc, —OCOPh, —OCOBu^t, —OCOCH$_2$CCl$_3$ (Troc), —OCO$_2$Bu^t (Boc), —OCO$_2$CH$_2$Ph (Cbz), —OCO$_2$CH$_2$CH(o-C$_6$H$_4$)$_2$ (Fmoc)
ethers	—OMe, —OCH$_2$Ph, —OCH$_2$C$_6$H$_4$OMe (PMB), —OCPh$_3$ (Tr)
acetals and ketals	—OCH$_2$OMe (MOM), —OCH$_2$OCH$_2$CH$_2$OMe (MEM), —OCH(Me)OEt, —OCMe$_2$OMe (MOP), —O(C$_5$H$_9$O) (THP), —OCH$_2$OCH$_2$CH$_2$SiMe$_3$ (SEM)

Table 15.6

Conditions for removing protecting groups from alcohols

Class	Conditions
esters	KOH, H_2O (base hydrolysis); HCl, H_2O (acid hydrolysis); $LiAlH_4$, Et_2O (reduction); H_2, Pd-C (Cbz esters)
ethers	BBr_3, CH_2Cl_2; $TiCl_4$, CH_2Cl_2, –78°C; Ce^{4+}, EtOH (PMB ethers); H_2, Pd-C (benzyl ethers)
acetals and ketals	H_2SO_4, H_2O, THF; Bu_4NF, THF (SEM)

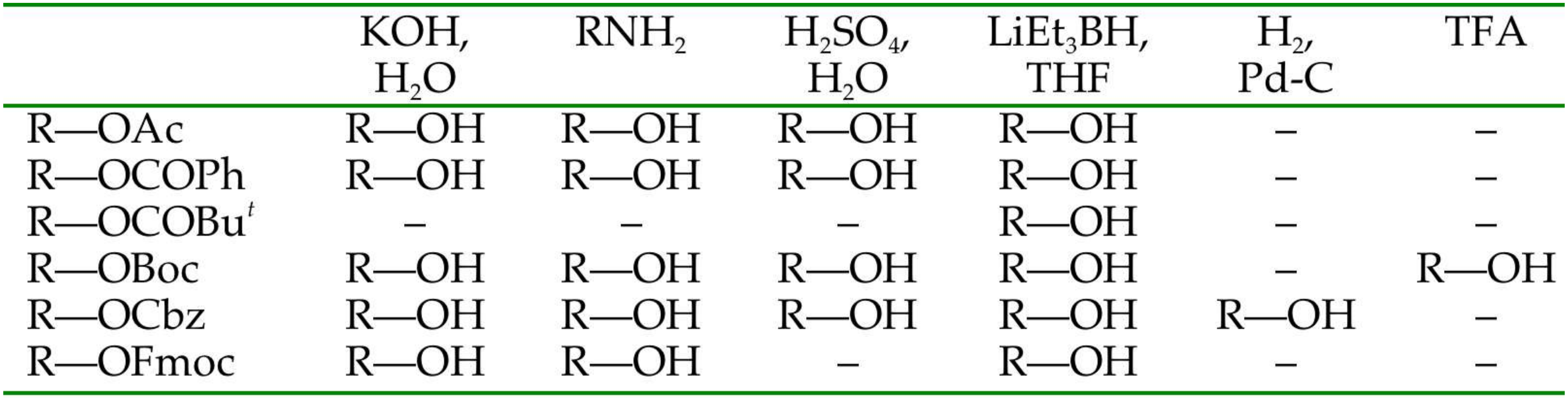
pivalate esters are highly hindered, and resist standard hydrolysis conditions



(15.50)

Table 15.7

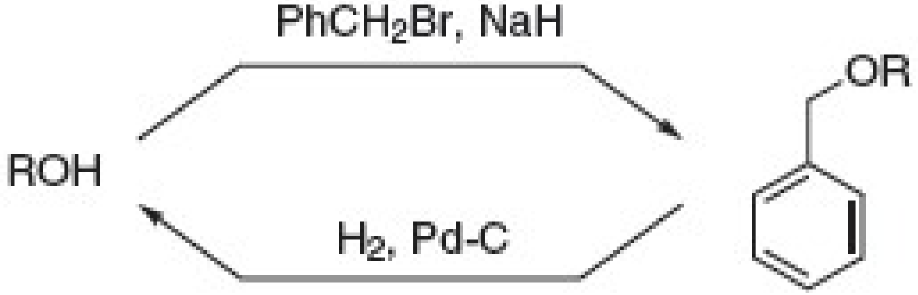
Representative conditions for the removal of ester protecting groups



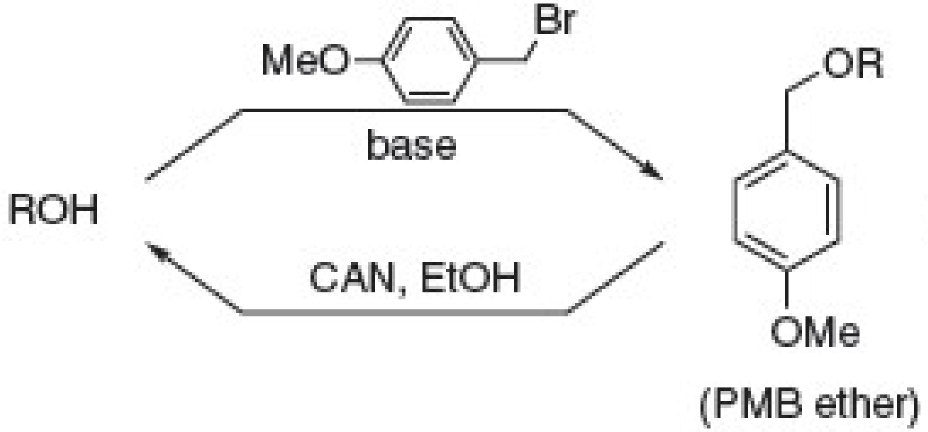
	KOH, H_2O	RNH_2	H_2SO_4, H_2O	$LiEt_3BH$, THF	H_2, Pd-C	TFA
R—OAc	R—OH	R—OH	R—OH	R—OH	–	–
R—OCOPh	R—OH	R—OH	R—OH	R—OH	–	–
R—OCOBu^t	–	–	–	R—OH	–	–
R—OBoc	R—OH	R—OH	R—OH	R—OH	–	R—OH
R—OCbz	R—OH	R—OH	R—OH	R—OH	R—OH	–
R—OFmoc	R—OH	R—OH	–	R—OH	–	–

Benzylic ether protecting groups

- benzyl ethers are formed under Williamson ether conditions
- simple benzyl etehrs are best cleaved by hydrogenolysis
- *p*-methyxybenzyl (PMB) ethers can be cleaved by oxidation with ceric amminium nitrate (CAN)



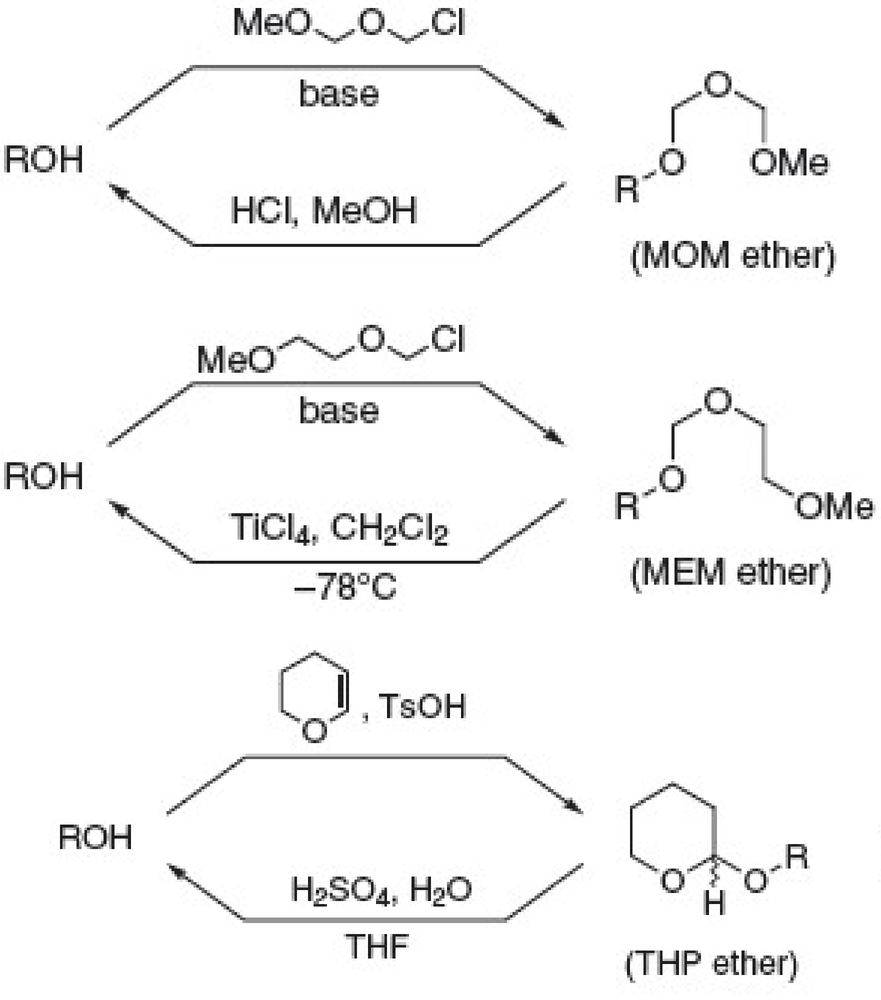
(15.51)



(15.52)

Acetals and Ketals

- formaldehyde acetals include methoxymethyl (MOM) and (2-methoxyethoxy)methyl (MEM) ethers
- tetrahydropyranyl ethers are easily formed, but have the disadvantage that a new chiral center is formed



(15.53)

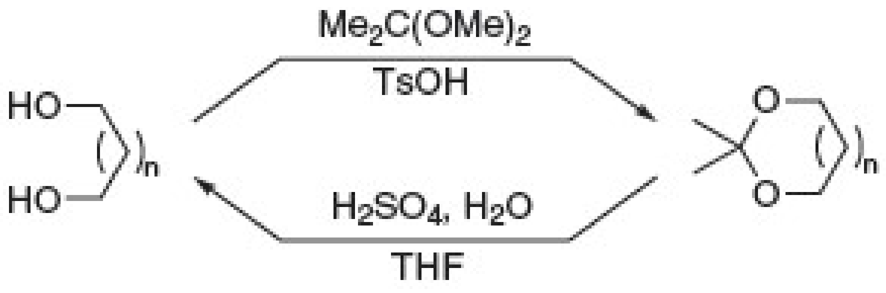
(15.54)

(15.55)

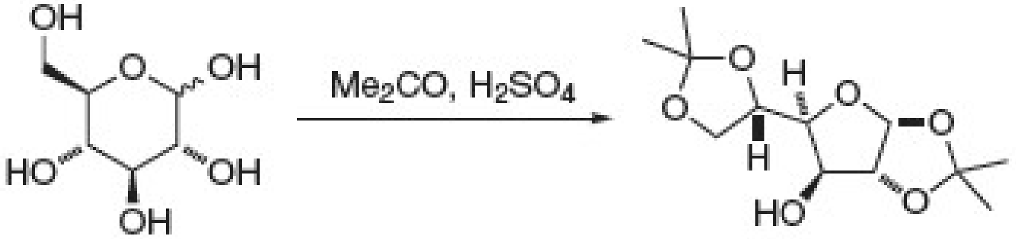
Protection of 1,2- and 1,3-diols

- cyclic ketals based on acetone (acetonides) are widely used to protect diols

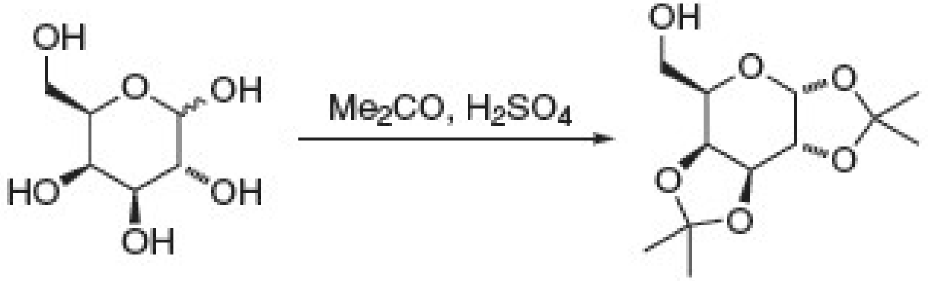
- acetonides are much more readily formed from *cis*-1,2-cyclohexanediols than from the *trans* isomers, as illustrated by the acetonides of glucose (**15.57**) and galactose (**15.58**)



(15.56)



(15.57)



(15.58)

Table 15.8: Stability of protecting groups toward various reagents

Conditions→ Group↓	Aqueous acid	Aqueous base	TFA	Lewis acid	Strong base	Metal alkyls	Fluoride anion	Hydrogen, catalyst	Hydride reductant	Oxidation
—OR				a						
—OCH$_2$Ar				a				b		c
—OTr			d	a				b		
—OCOR	e	f			g				h	
—OCbz	e	f				h		b	h	
—OFmoc	e	f			i	h		b	h	
—OBoc	e	f	k	a		h			h	
—OSiR$_3$	e	f				l	m			
—OMOM	e				a					
—OMEM	e				a					
—OTHP	e									
—OSEM							n			

Where no indication is given, one may assume that the group is generally stable under the conditions specified.

a. Susceptible to strong Lewis acids (BBr_3, $TiCl_4$, etc.)

b. Susceptible to hydrogenolysis, especially over Pd

c. Electron-rich benzyl ethers can be cleabed by oxidation with reagents such as CAN and DDQ

d. Usually used with trifluoroacetic anhydride

e. Susceptible to acid-catalyzed hydrolysis or alcoholysis

f. Susceptible to base-promoted hydrolysis or alcoholysis

g. Only esters that have an α hydrogen; generally a problematic side reaction in reactions of ester enolates

h. Reduced by complex metal hydrides ($LiBH_4$, $LiAlH_4$, etc.); not generally susceptible to reduction by $NaBH_4$

i. Cleaved by Grignard reagents, alkyllithiums, etc.

j. Cleaved by bases, including tertiary amines; mechanism is E1cb

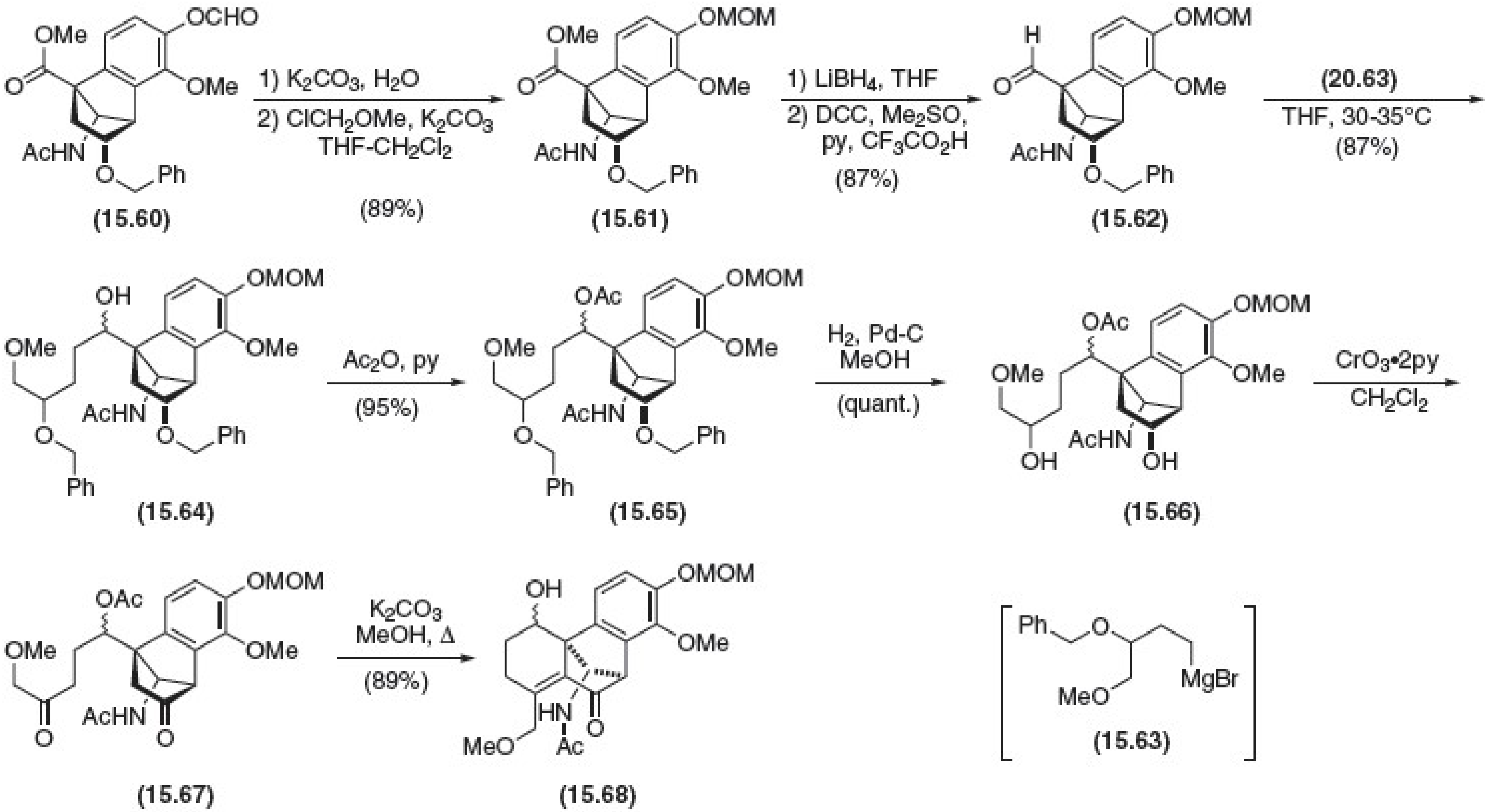
k. Isobutylene is formed in the E1 elimination of the *tert*-butyl group

l. Cleaved by alkyllithiums, but not by Grignard reagents

m. Ease of cleavage is slowed by increased steric bulk of the groups on silicon

n. Silyl fluoride and ethylene are formed in this fragmentation by the E1cb or E2 mechanism

Figure 15.18



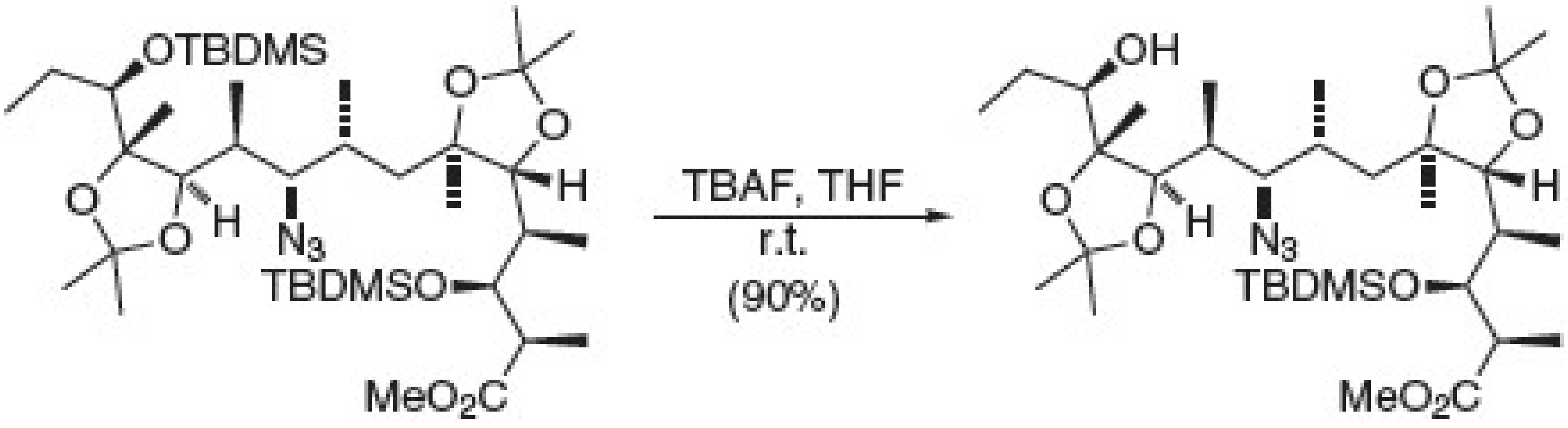
The use of protecting groups in steps of Wiesner's synthesis of 13-desoxydelphonine involving construction of the A ring

Table 15.9

Relative stabilities of silyl ether protecting groups

Silyl ether	Introduction	In Acid	In Base
RÑ $OSiMe_3$ (RÑ OTMS)	Me_3SiCl, imidazole, DMF	1	1
RÑ $OSiEt_3$ (RÑ OTES)	Et_3SiCl, imidazole, DMF	64	10-100
RÑ $OSiMe_2Bu^t$ RÑ OTBS	Bu^tSiMe_2Cl, imidazole, DMF Bu^tSiMe_2OTf, 2,6-lutidine, CH_2Cl_2	2×10^4	2×10^4
RÑ $OSi(Pr^i)_3$ RÑ OTIPS	$(i\text{-}Pr)_3SiCl$, imidazole, DMF $(i\text{-}Pr)_3SiOTf$, 2,6-lutidine, CH_2Cl_2	7×10^5	1×10^5
RÑ $OSi(Ph)_2Bu^t$ RÑ OTBDPS	$t\text{-}Bu(Ph)_2SiCl$, imidazole, DMF	2×10^4	5×10^6

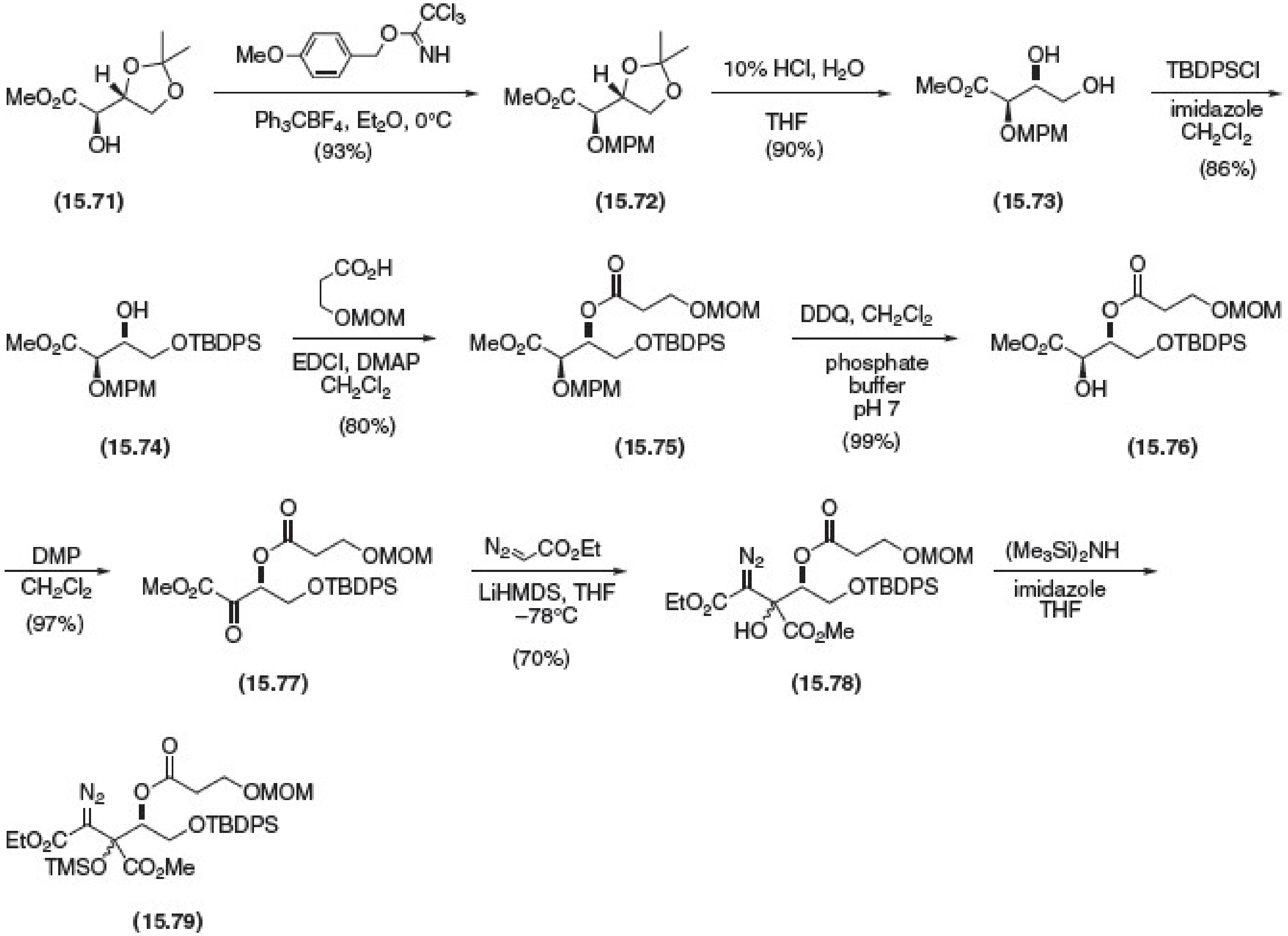
Deprotection of silyl ethers with fluoride



(15.69) (15.70)

tert-Butyldimethylsilyl (TBDMS) ethers resist hydrolysis, but can be cleaved with fluoride anion. TBDMS ethers of primary alcohols are cleaved most rapidly.

Figure 15.19



Sequence from Hashimoto's synthesis of the zaragozic acids

Reaction synopsis

Protection of Alcohols

Alkyl ethers
- formation: RX, base; R=Me, $PhCH_2$, p-$MeOC_6H_4CH_2$; etc.
- cleavage: BBr_3, CH_2Cl_2; H_2, Pd-C (allyl, benzyl); DDQ, CAN (PMB ethers); HCO_2H (trityl ethers)

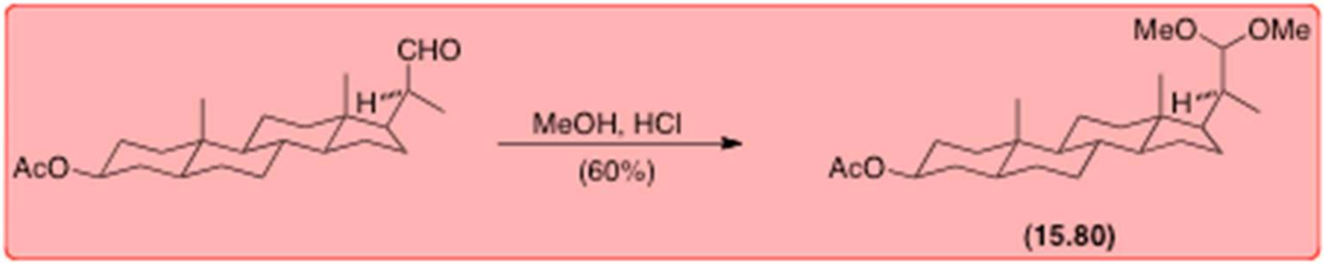
Silyl ethers
- formation: R_3SiX, EtN(i-Pr)$_2$; X=Cl, OTf
- cleavage: TBAF, THF; etc.

Acetals/ketals
- formation: $ROCH_2$-Cl, base; R=Me, $Me(OCH_2CH_2)_2$, DHP, TsOH; etc.
- cleavage: H_3O^+; $TiCl_4$, CH_2Cl_2, etc.

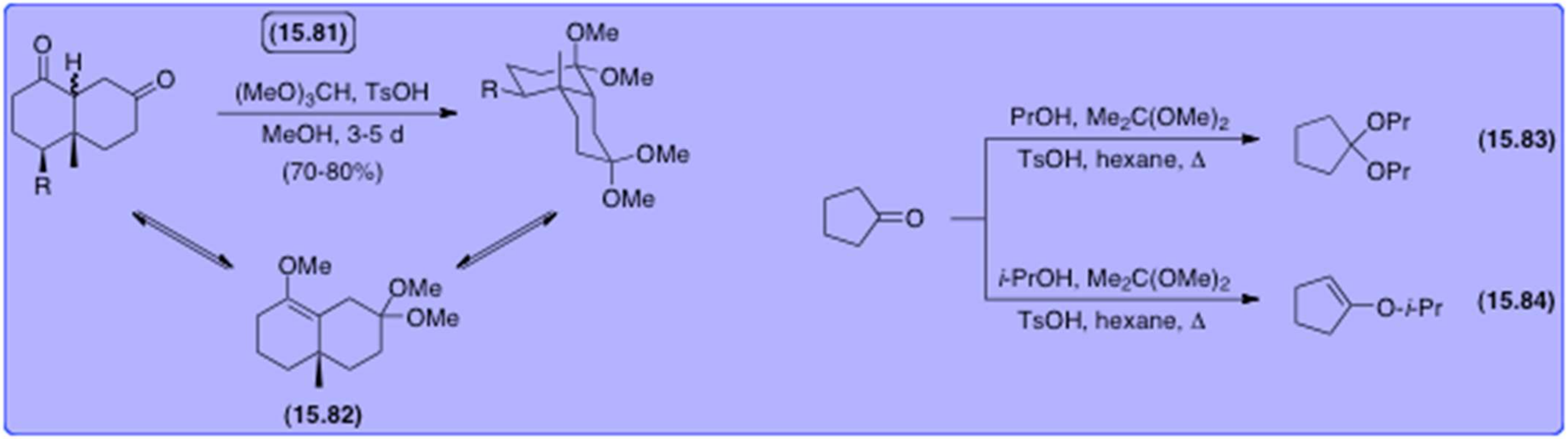
Carboxylic esters
- formation: Ac_2O, Py; Me_3COCl, py; PhCOCl, KOH, H_2O; etc.
- cleavage: K_2CO_3, MeOH; NaOH, H_2O, THF; NH_3, H_2O; etc. $LiBH_4$, Et_2O; $LiAlH_4$, Et_2O; etc.

Mixed carbonate esters
- formation: Boc_2O, Py; CbzCl, Py, etc.
- cleavage: TFA (Boc); H_2Pd-C (Cbz); etc.

Protection of aldehydes and ketones



(15.80)



(15.81)

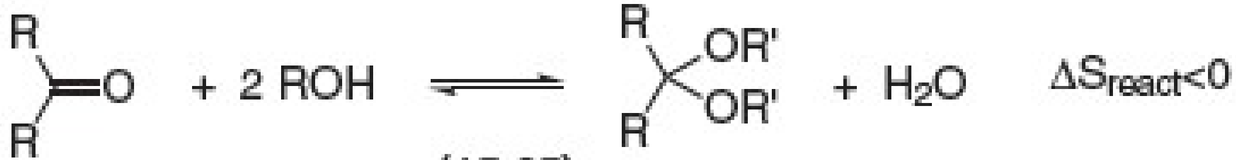
(15.82)

(15.83)

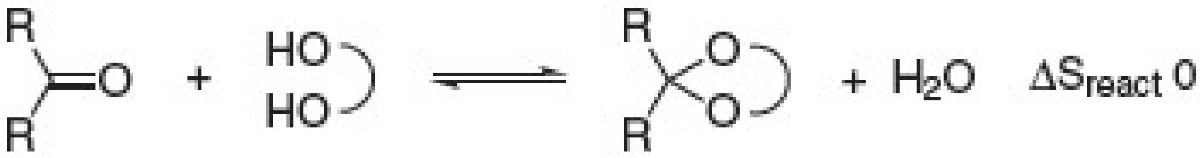
(15.84)

Formation of ketals is often complicated by formation of enol ethers

Entropic factors in ketal formation



(15.85)

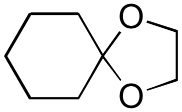
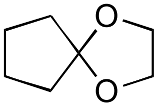
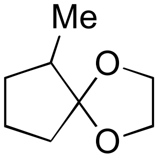
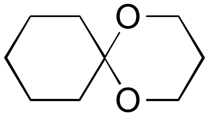
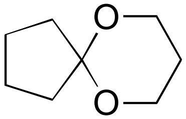
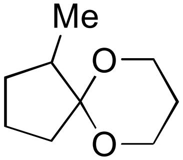
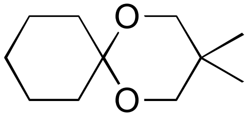
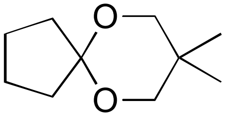
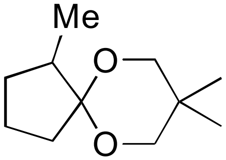
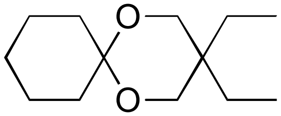
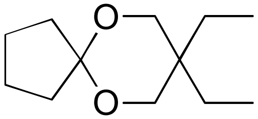
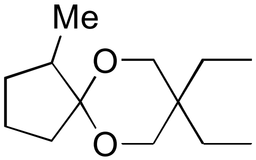
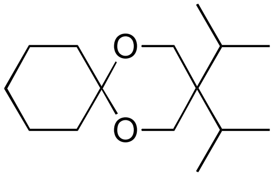
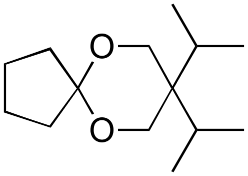
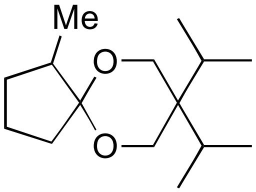


(15.86)

The ΔS_{react} for the formation of ketals from open-chain alcohols is negative; the ΔS_{react} with diols is approximately zero. Formation of cyclic ketals is entropy-favored over formation of open-chain ketals

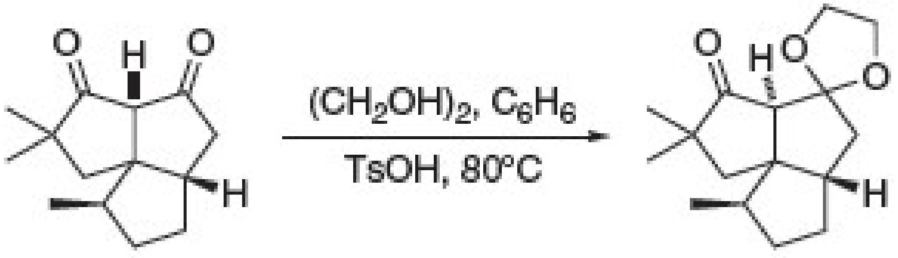
Table 15.10

Relative rates for hydrolysis of cyclic ketals by 0.003 *M* HCl in dioxane-water (70:30)

ketal	rate	ketal	rate	ketal	rate
	1		13.0		8.02
	30.6		172		259
	2.01		16.5		23.0
	0.888		7.65		11.3
	0.335		2.67		3.28

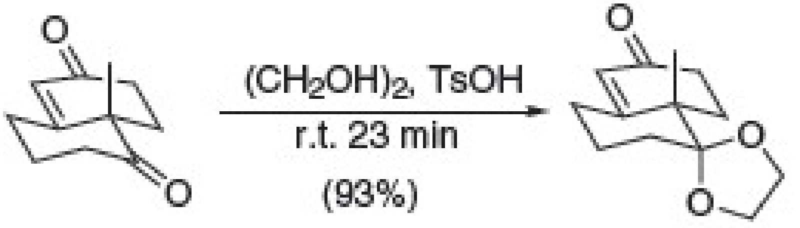
Ketal formation: relative rates

The least hindered ketone carbonyl group reacts first



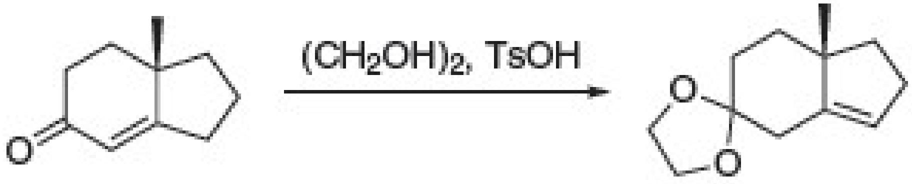
(15.87)

Saturated ketones react faster than α,β-unsaturated ketones



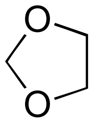
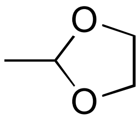
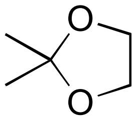
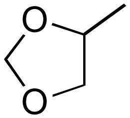
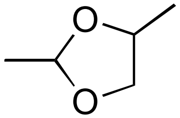
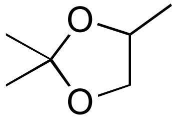
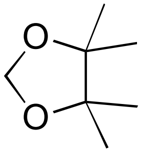
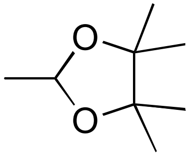
(15.88)

Ketal formation in α,β-unsaturated ketones is usually accompanied by double bond migration where possible



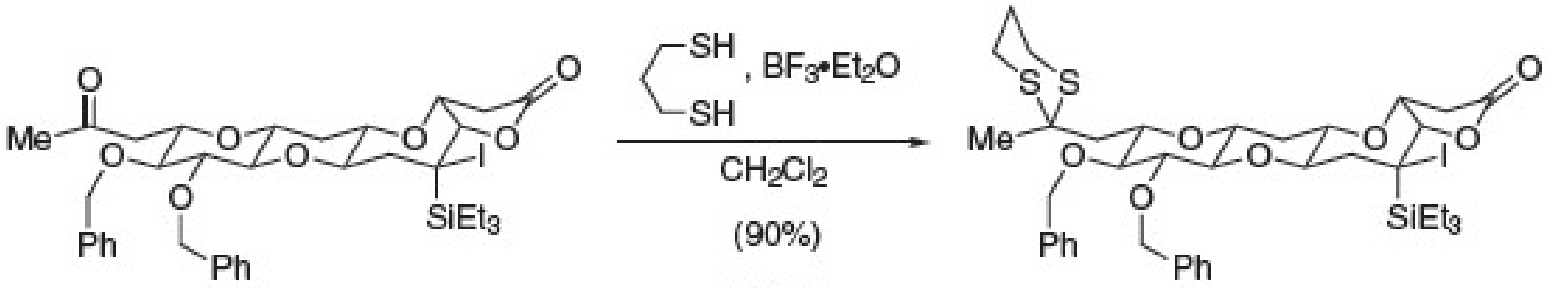
(15.89)

Table 15.11

dioxolane	*k*	dioxolane	*k*	dioxolane	*k*
	1		5130		54300
	1.52		7540[a] 1910[b]		55100
	0.223		713		

Relative rate constants (L mol^{-1} s^{-1}) for the acid-catalyzed hydrolysis of 1,3-dioxolane and its derivatives at 25°C

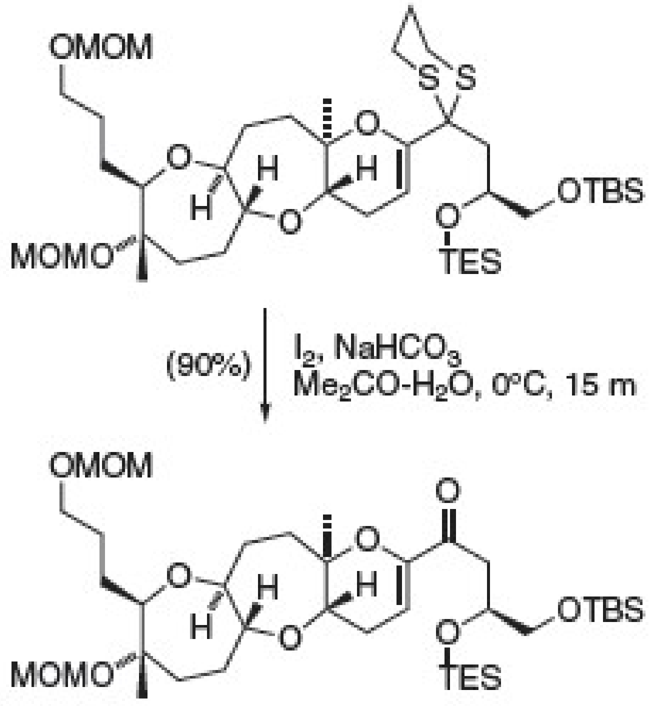
Dithioketals



(15.90)

Dithioketals are formed by Lewis acid-catalyzed condensation of thiols (or dithiols) with ketones

Hydrolysis of dithioketals can be accomplished with mercury halides, or by oxidation and subsequent hydrolysis



(15.92)

Reaction synopses: Protection of aldehydes and ketones

Acetals and ketals

- formation: MeOH, TsOH, PhH, Δ; $HO(CH_2)_2OH$, TsOH, PhH, Δ; etc.
- cleavage: H_2SO_4, H_2O, THF; $(CO_2H)_2$, H_2O; etc.

Dithioacetals and dithioketals

- formation: $HS(CH_2)_3SH$, BF_3; etc.
- cleavage: $HgCl_2$, $CaCO_3$; $HgCl_2$, $CdCO_3$; NBS, H_2O; MeI, $MeCN\text{-}H_2O$; etc.

Reaction synopses: Protection of carboxylic acids

Esters

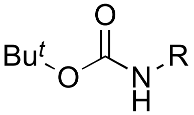
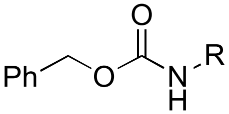
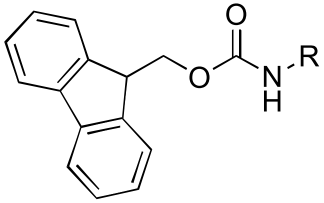
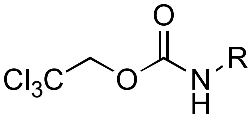
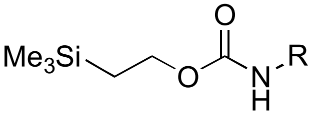
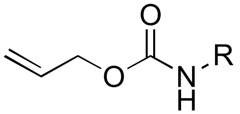
- formation: CH_2N_2, Et_2O (R'=Me); R'OH, DCC; $Me_2C{=}CH_2$, H_2SO_4 (R=Bu^t); etc.
- formation: MeOH, TsOH, PhH, Δ; $HO(CH_2)_2OH$, TsOH, PhH, Δ; etc.
- cleavage: H_2SO_4, H_2O, THF; $(CO_2H)_2$, H_2O; etc.
- cleavage: K_2CO_3, MeOH; TFA (R'=Bu^t); Et_2NH (R'=Fm); dimedone, $Pd(OAc)_2$ (R'=allyl); $LiAlH_4$, Et_2O; H_2, Pd-C (R'=allyl, benzyl); etc.

1,3-oxazolidines

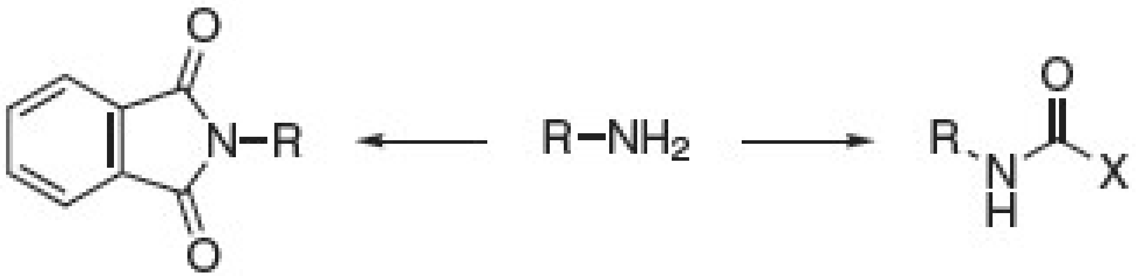
- formation: 1) $(COCl)_2$, CH_2Cl_2; 2) $HOCH_2CMe_2NH_2$; etc.
- cleavage: HCl, H_2O; etc.

Table 15.12

Carbamate protecting groups for amines

Protected amine	Acronym	Representative conditions for incorporation and removal
	Boc	*On:* $(Boc)_2O$, NaOH, H_2O, 25¡C *Off:* 3 *M* HCl, EtOAc; etc.
	Cbz, or Z	*On:* Cbz-Cl, Na_2CO_3, H_2O *Off:* H_2, Pd-C
	Fmoc	*On:* Fmoc-Cl, $NaHCO_3$, dioxane-H_2O *Off:*piperidine, DMF; etc.
	Troc	*On:* Troc-Cl, py *Off:* Zn, THF, H_2O (pH 4.2); etc.
	Teoc	*On:* Teoc-O-succinimide, $NaHCO_3$, dioxane-H_2O *Off:* TBAF, KF, MeCN
	Aloc	*On:* $H_2C{=}CHCH_2OCOCl$, py *Off:* $(Ph_3P)_4Pd$, dimedone, THF

Reaction synopses: Protection of amines



Amides

- formation: RCOCl, $(RCO)_2O$; etc.
- cleavage: HCl, H_2O, Δ; KOH, H_2O-EtOH, Δ; etc.; acylases, buffer

Carbamates

- formation: ROCOCl, base (R=*t*-Bu, $PhCH_2$, etc.)
- cleavage: HCl, H_2O; KOH, EtOH; etc.; TFA (R=*t*-Bu); H_2, Pd-C (R=$PhCH_2$); etc.

Phthalimides

- formation: phthalic anhydride, $CHCl_3$, Δ; etc.
- cleavage: H_2NNH_2, EtOH, 25°C; KOH, H_2O, EtOH, Δ; etc.

Protection of alkenes

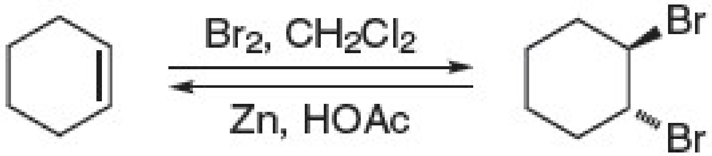
Protection by addition to the π bond, followed by deprotection by an elimination reaction

addition of bromine/reductive elimination

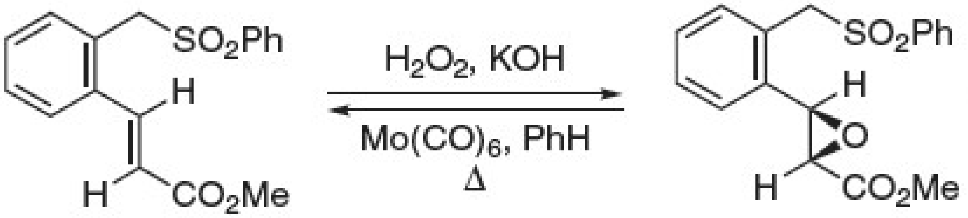
epoxidation/deoxygenation

hydroboration/dehydroboration

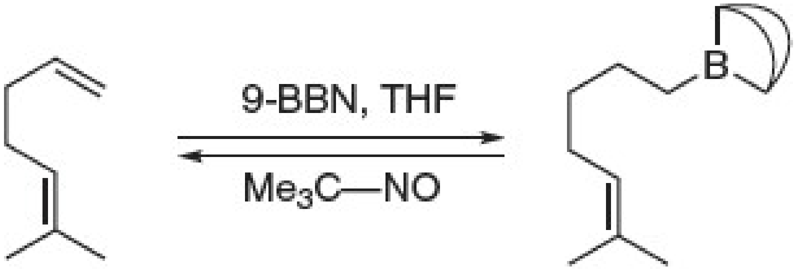
Diels-Alder cycloaddition/cycloreversion



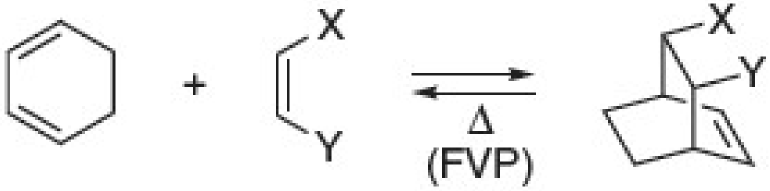
(15.100)



(15.102)

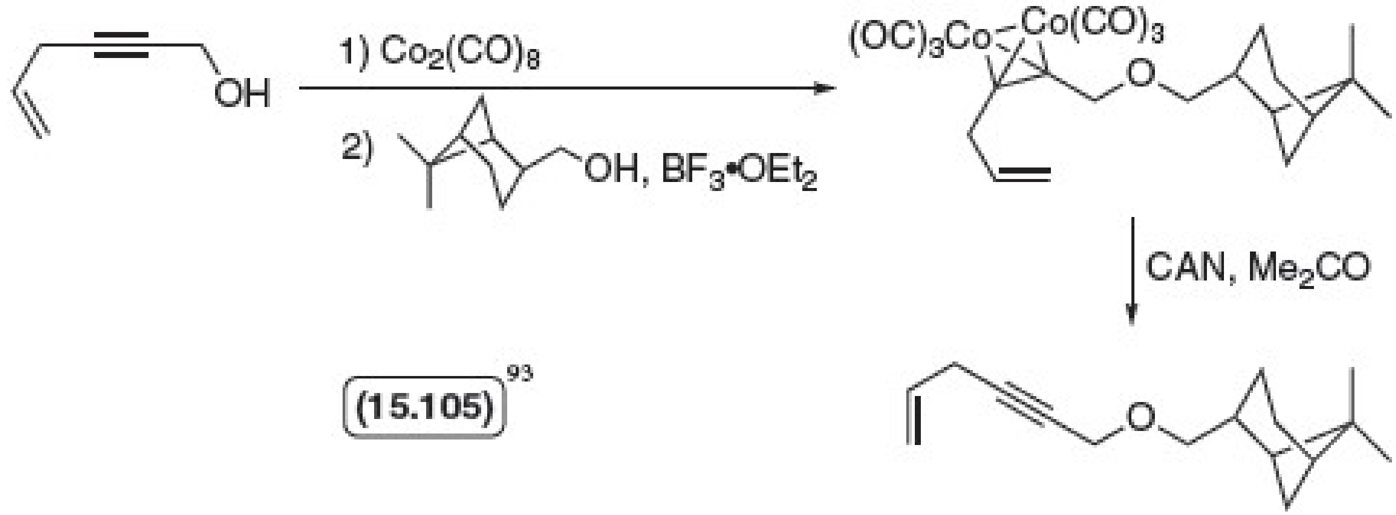


(15.103)



(15.104)

Protection of alkynes



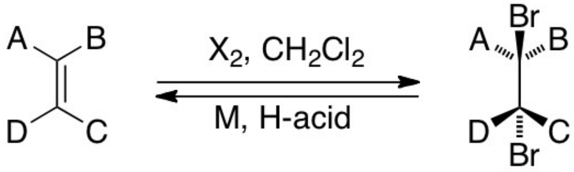
(15.105)[93]

Dicobalt octacarbonyl reacts with the alkyne to give an organometallic complex without the alkyne π bonds.

The alkyne is regenerated after the reaction by oxidation of the organometallic complex

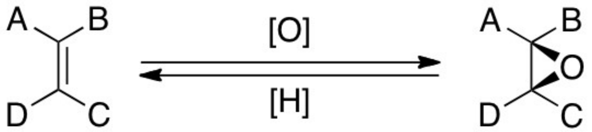
Reaction synopses: Protection of alkenes

Halogen and halogen-like adducts



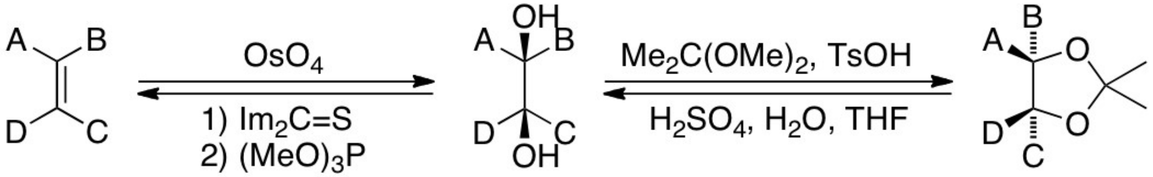
protection: Br_2, CH_2Cl_2; etc.
deprotection: Zn, HOAc; Mg, Et_2O; etc.

epoxides

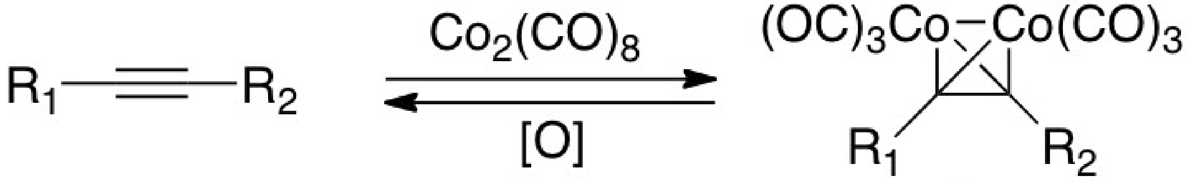


protection: *m*-CPBA (simple alkenes); or
H_2O_2, KOH (conjugated enones or esters
deprotection: $N_2{=}C(CO_2Me)_2$, $Rh_2(OAc)_4$, PhH, Δ; or
$Mo(CO)_6$, PhH, Δ; etc.

vicinal diols and acetonides



Reaction synopses: Protection of alkynes



protection: $Co_2(CO)_8$, CH_2Cl_2; etc.
deprotection: $K_3Fe(CN)_6$; or CAN; etc.