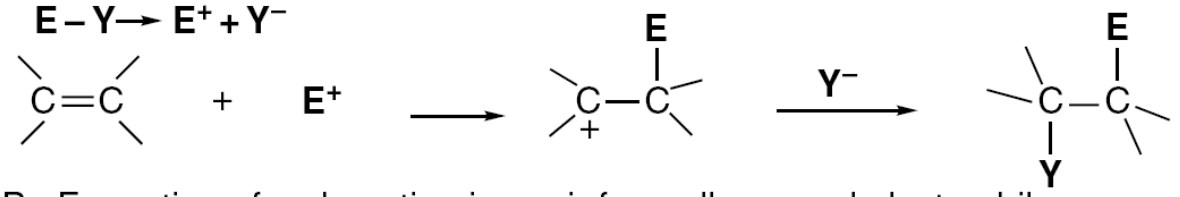
Electrophilic Additions to C-C Multiple Bonds

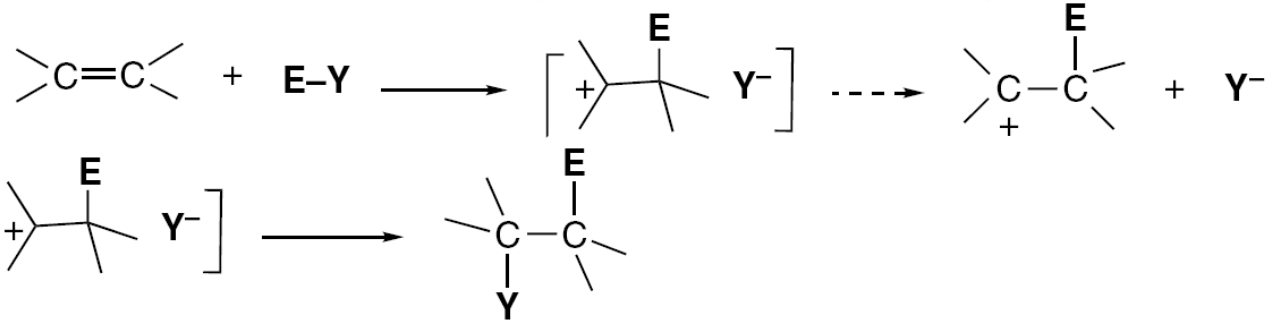
- electrophilic additions - chemistry of alkenes and alkynes
- polar additions – perpendicular attack
- several mechanisms:

Ad_E2

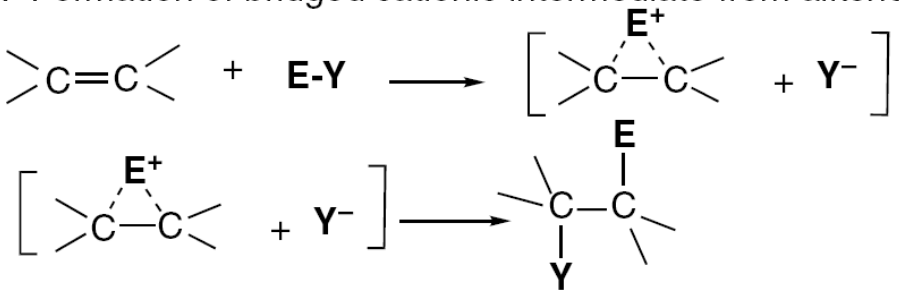
A. Prior dissociation of electrophile and formation of carbocation intermediate



B. Formation of carbocation ion pair from alkene and electrophile



C. Formation of bridged cationic intermediate from alkene and electrophile

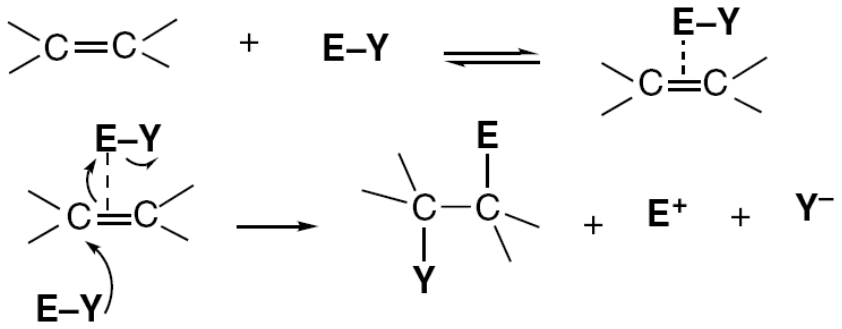


Electrophilic Additions to C-C Multiple Bonds

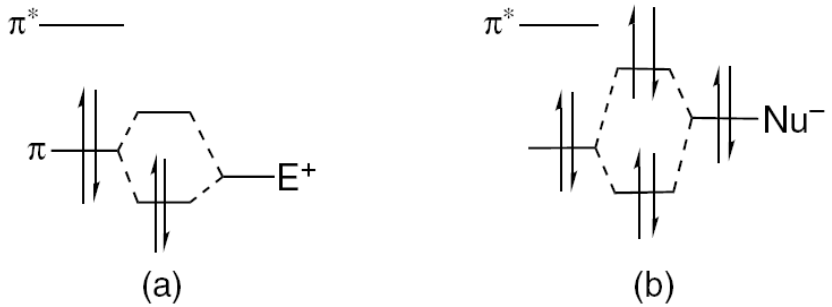
- several mechanisms:

Ad_E3

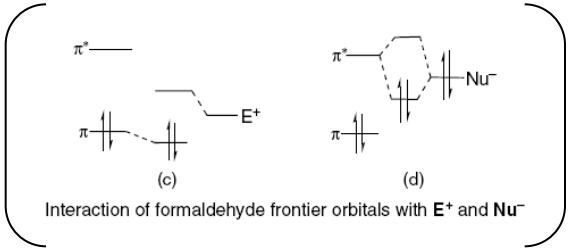
D. Concerted addition of electrophile and nucleophile in a termolecular reaction



- MO theory:



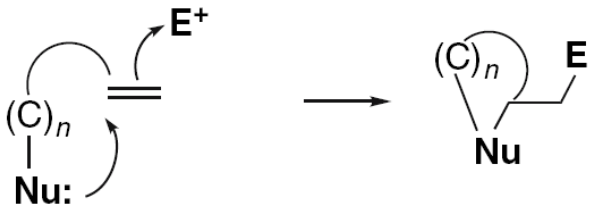
Interaction of ethene frontier orbitals with **E^+** and **Nu^-**



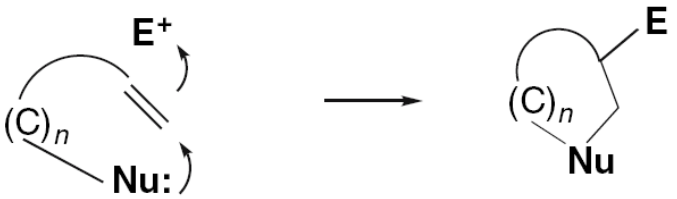
Interaction of formaldehyde frontier orbitals with **E^+** and **Nu^-**

Electrophilic Additions to C-C Multiple Bonds

- inter- x intramolecular:
  - synthesis of heterocycles



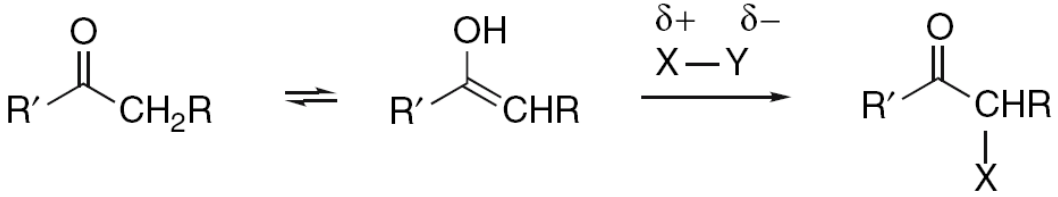
exo – cyclization



endo – cyclization

Watch out!

- carbonyl compounds:
- α-substitution

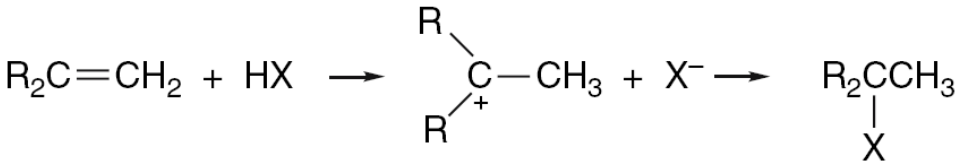


Electrophilic Additions to C-C Multiple Bonds

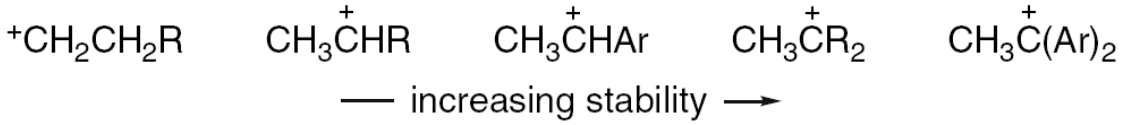
Electrophilic Addition to Alkenes

1. *Addition of Hydrogen Halides*

- regioslective
- *Markovnikov's rule*

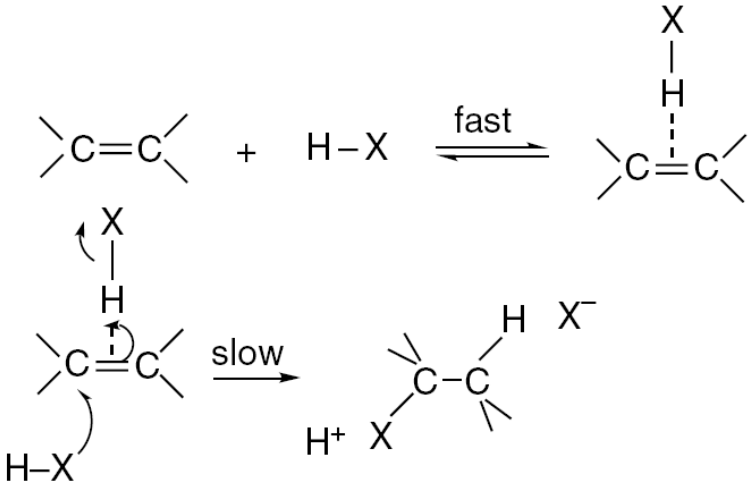


- stability of carbocations:



- *anti*-addition (*syn*-addition)
- Ad_E3

$$\text{Rate} = k[\text{alkene}][\text{HX}]^2$$



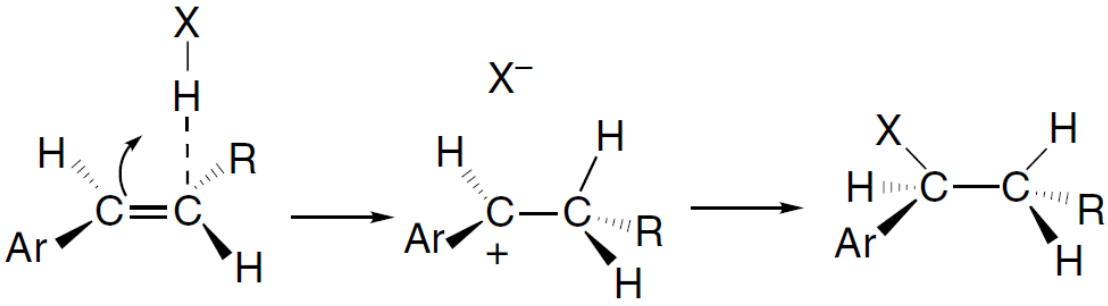
Electrophilic Additions to C-C Multiple Bonds

Electrophilic Addition to Alkenes

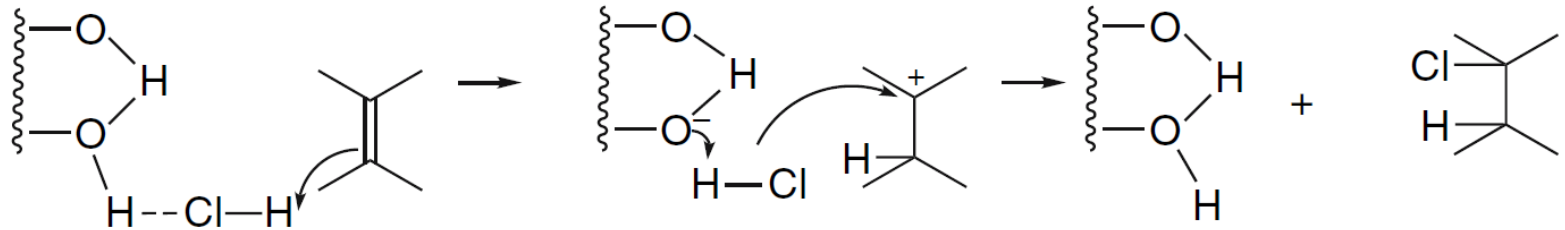
1. *Addition of Hydrogen Halides*

- Ad_E2

$$\text{Rate} = k[\text{alkene}][\text{HX}]$$



- the order of reactivity of the hydrogen halides: HI > HBr > HCl
- terminal and disubstituted internal alkenes (HCl - slow)
- presence of silica or alumina

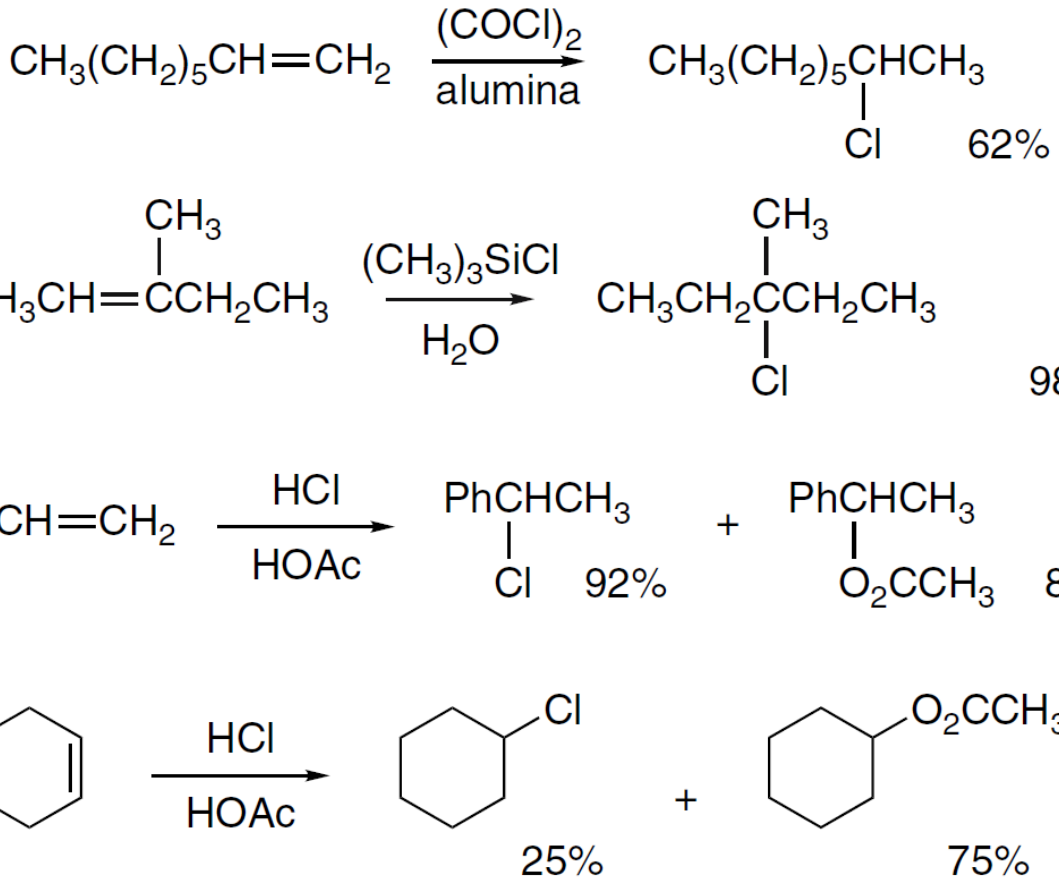


- HX generated *in situ* from $SOCl_2$, $(ClCO)_2$, $(CH_3)_3SiCl$, $(CH_3)_3SiBr$, $(CH_3)_3SiI$
- solvents: nonpolar (slower)
  polar (faster)

Electrophilic Addition to Alkenes

1. *Addition of Hydrogen Halides*

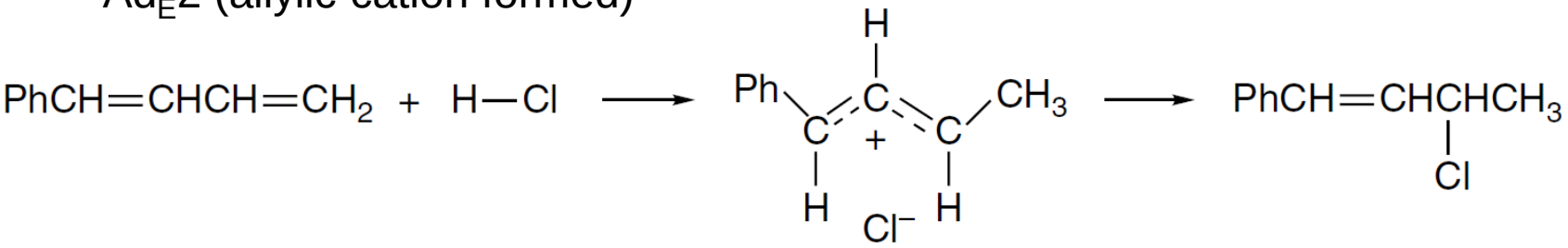
Examples



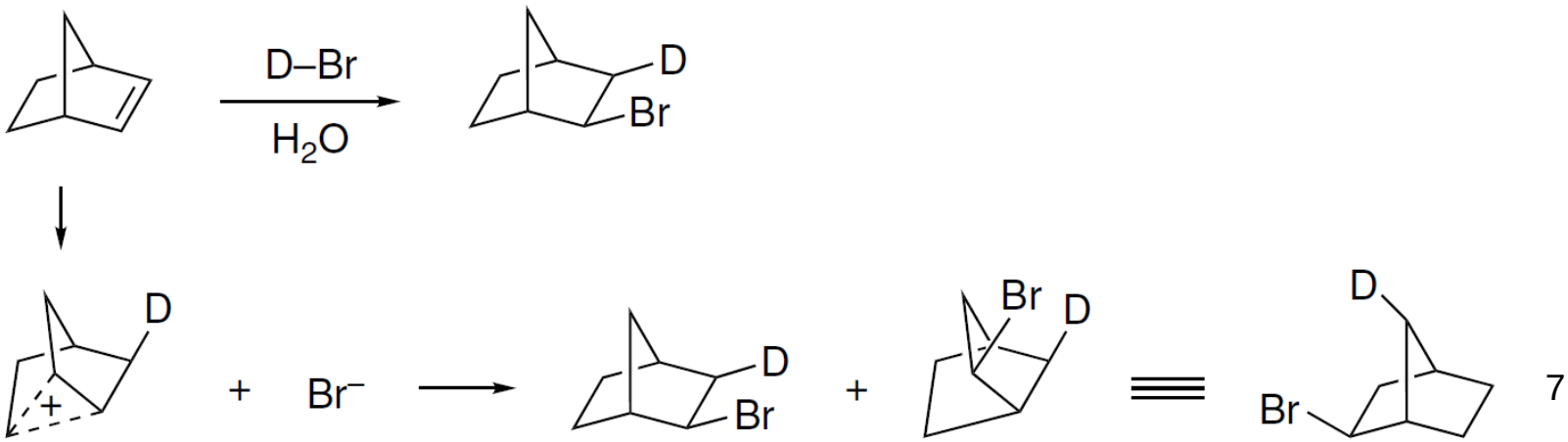
Electrophilic Addition to Alkenes

1. *Addition of Hydrogen Halides*

- conjugated dienes
  - Ad_E2 (allylic cation formed)



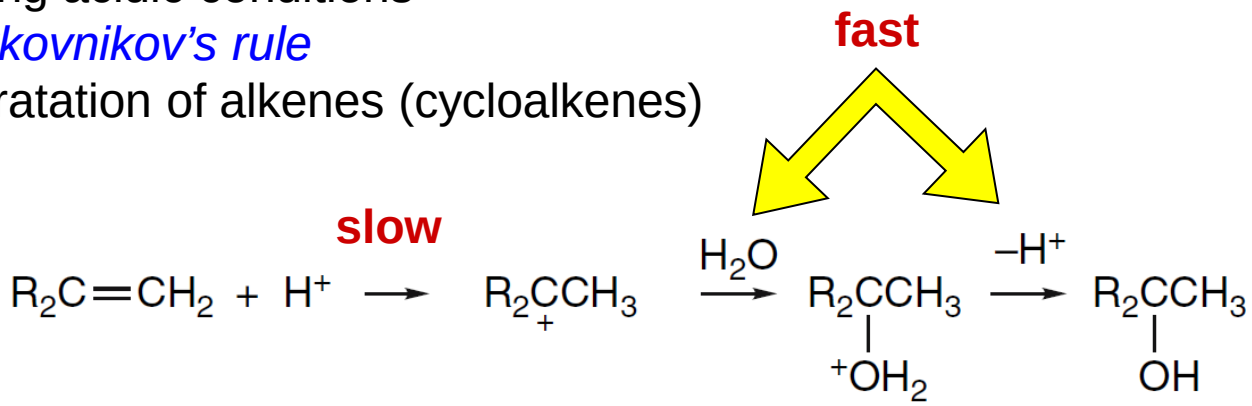
- norbornenes
  - *syn*-addition (*exo*-norbornyl halogenides)



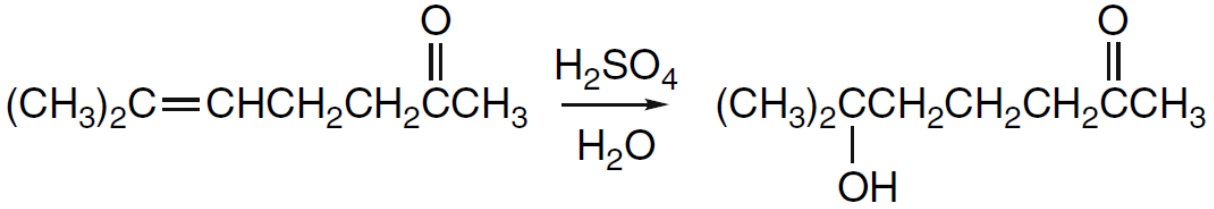
Electrophilic Addition to Alkenes

2. *Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles*

- oxygen nucleophiles (H_2O)
  - strong acidic conditions
  - *Markovnikov's rule*
  - hydratation of alkenes (cycloalkenes)



Example

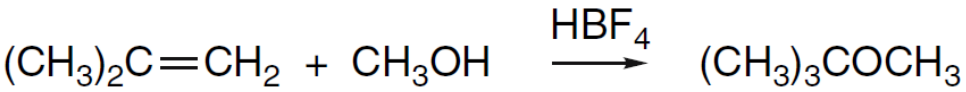


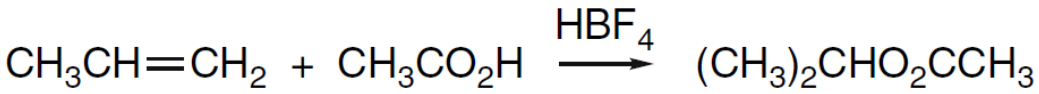
Electrophilic Addition to Alkenes

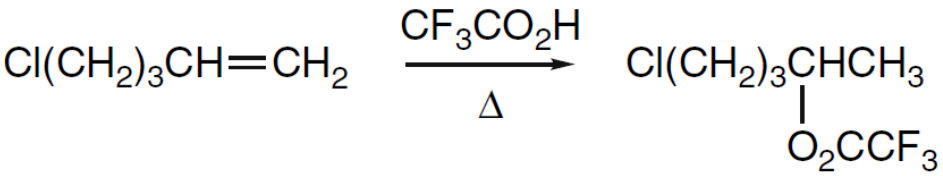
2. *Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles*

- other oxygen nucleophiles (ROH, RCOOH)
  - acidic conditions (HBF_4)

Examples



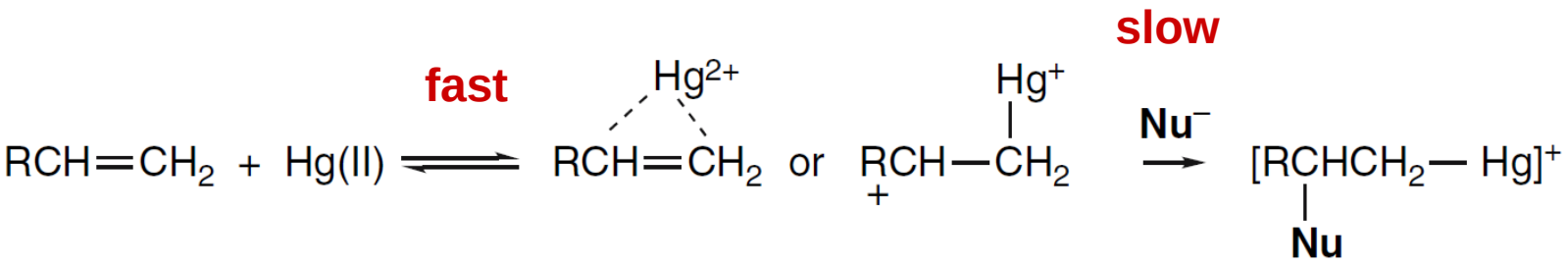




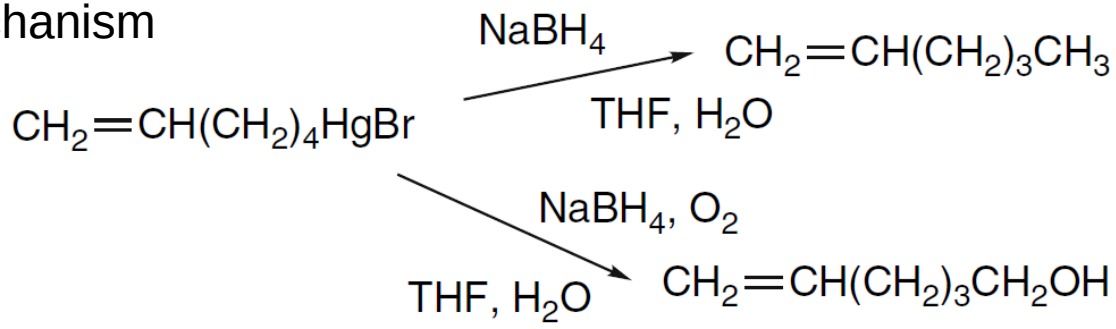
Electrophilic Addition to Alkenes

3. *Oxymercuration-Reduction*

- metal (Hg^{2+}) instead of H^+
- electrophilic reagent: Hg(OAc)2, $Hg(OOCCF_3)_2$, $Hg(OTf)_2$, $Hg(NO_3)_2$
- nucleophiles: H_2O, ROH, ROOH, RNH_2, $RCOO^-$
- *Markovnikov's rule*



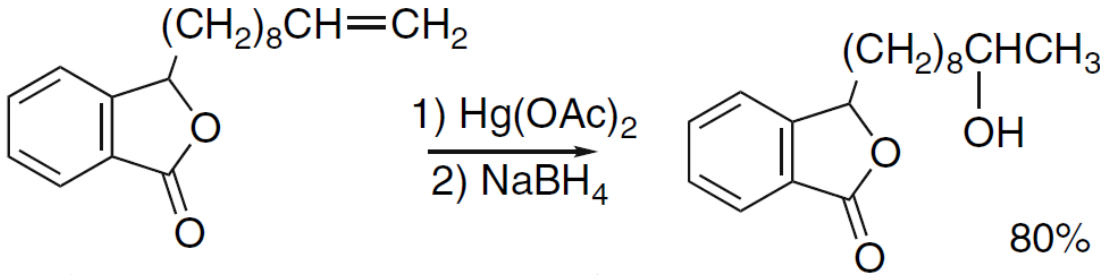
- *2nd step:* reduction ($NaBH_4$,Bu_3SnH, Na-Hg)
- radical mechanism



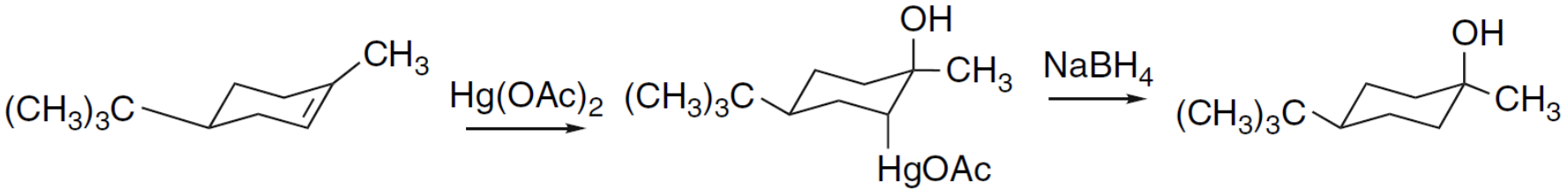
Electrophilic Addition to Alkenes

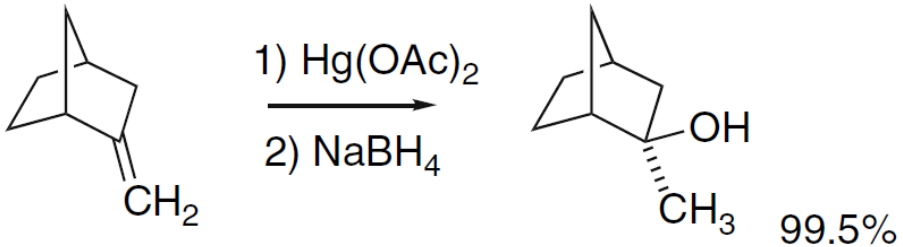
3. *Oxymercuration-Reduction*

Examples



- stereoselectivity





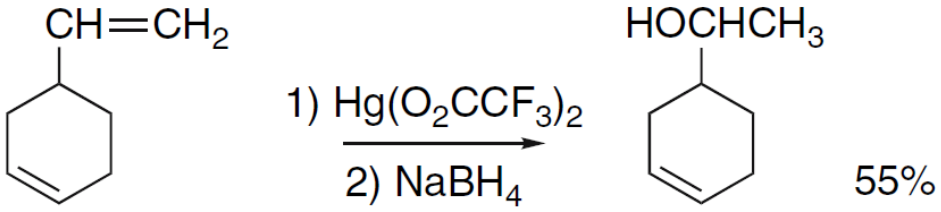
Electrophilic Additions to C-C Multiple Bonds

Electrophilic Addition to Alkenes

3. *Oxymercuration-Reduction*

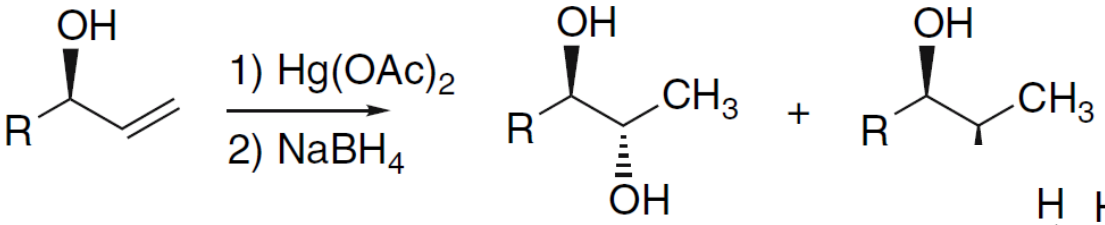
Examples

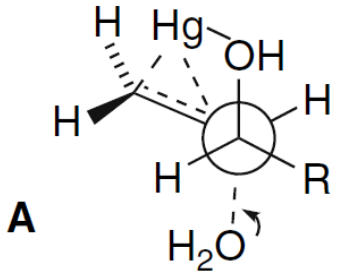
- regioselectivity



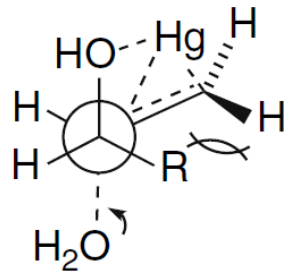
55%

- stereoselectivity





A

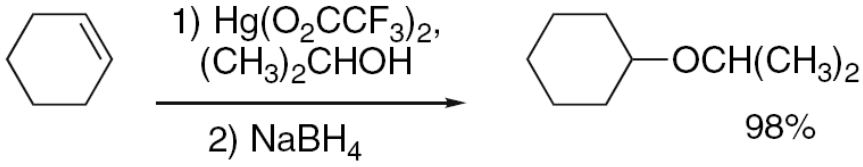


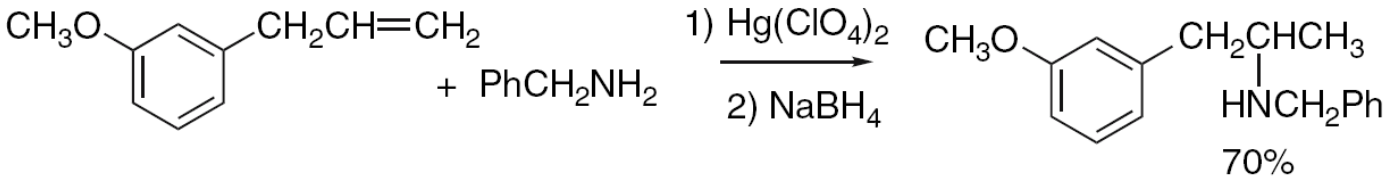
B

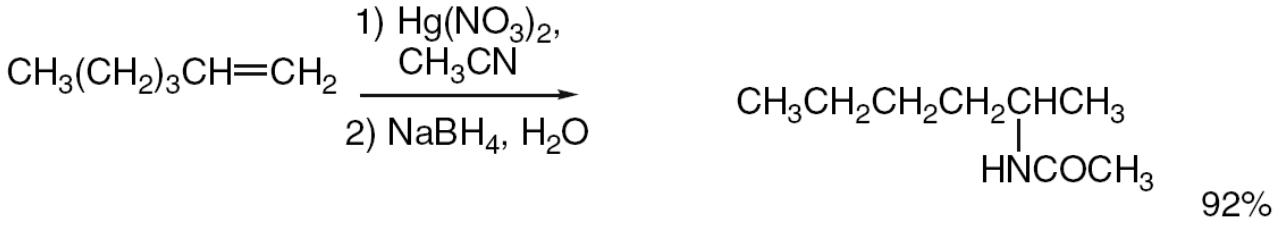
Electrophilic Addition to Alkenes

3. *Oxymercuration-Reduction*

Examples



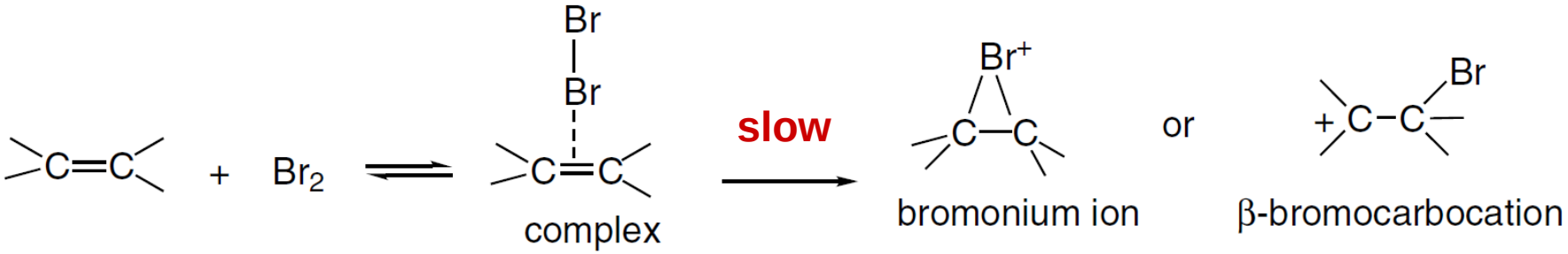




Electrophilic Addition to Alkenes

4. Addition of Halogens to Alkenes

- order of reactivity: $F_2 > Cl_2 > Br_2 > I_2$
- fluorination – strongly exothermic
- iodination – easily



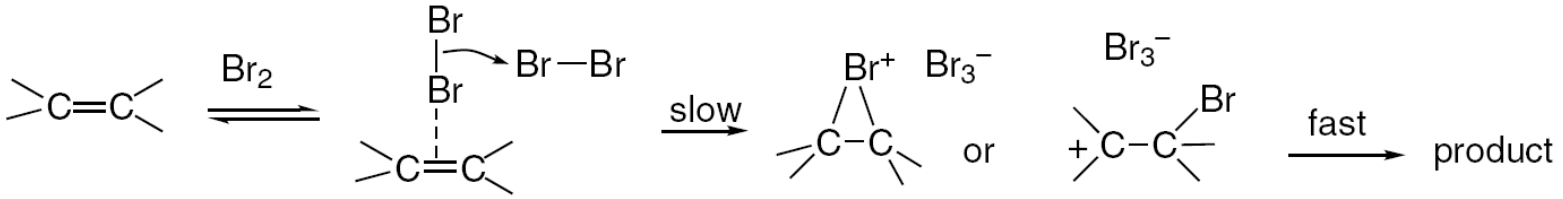
$$\text{Rate} = k_1[\text{alkene}][\text{Br}_2] + k_2[\text{alkene}][\text{Br}_2]^2 + k_3[\text{alkene}][\text{Br}_2][\text{Br}^-]$$

- polar solvents (MeOH) - 3. term (high [Br^-])
- non-polar solvents – 1. and 2. term

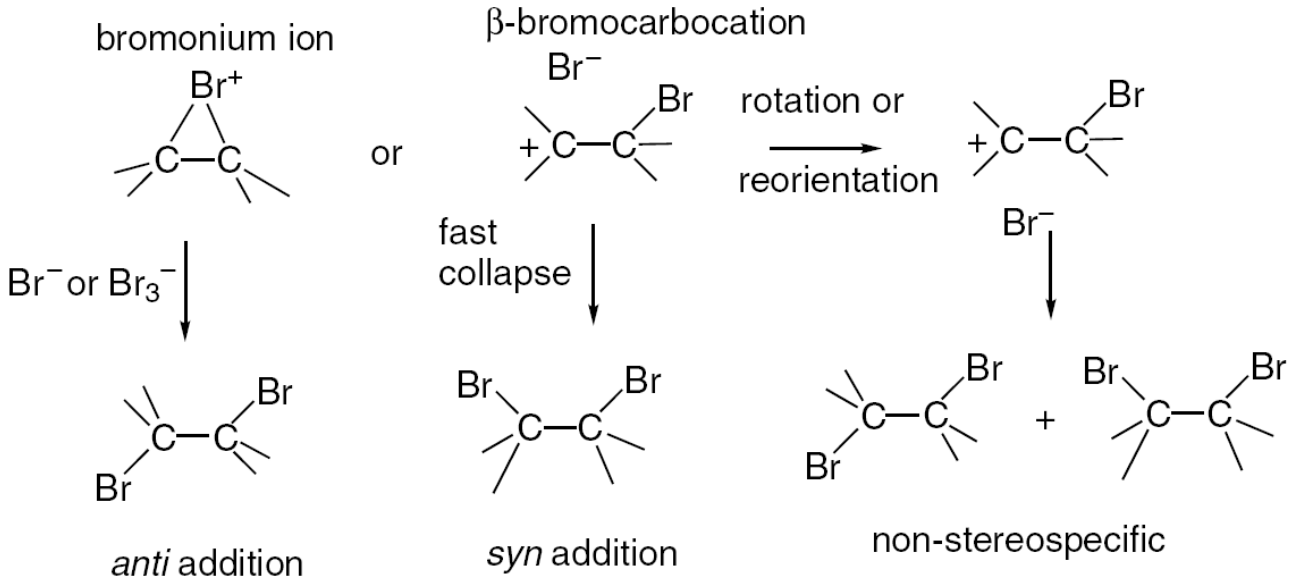
Electrophilic Additions to C-C Multiple Bonds

Electrophilic Addition to Alkenes

4. Addition of Halogens to Alkenes



- *anti*-addition (for the substituents non-stabilizing carbocation intermediate)
- conjugation, aromates - increase of *syn*-addition
- bromination > chlorination (stereospecificity)



Electrophilic Addition to Alkenes

4. *Additions of Halogens to Alkenes*

- relative reactivity of alkenes:

Alkene	Relative reactivity		
	Chlorination[a]	Bromination[b]	Bromination[c]
Ethene		0.01	0.0045
1-Butene	1.00	1.00	1.00
3,3-Dimethyl-1-butene	1.15	0.27	1.81
Z-2-Butene	63	27	173
E-2-Butene	50	17.5	159
2-Methylpropene	58	57	109
2-Methyl-2-butene	1.1×10^4	1.38×10^4	
2,3-Dimethyl-2-butene	4.3×10^5	19.0×10^4	

a. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965), in excess alkene.
b. J. E. Dubois and G. Mouvier, *Bull. Chim. Soc. Fr.*, 1426 (1968), in methanol.
c. A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.* **42**, 3673 (1977), in $ClCH_2CH_2Cl$.

Electrophilic Additions to C-C Multiple Bonds

Electrophilic Addition to Alkenes

4. Addition of Halogens to Alkenes

- solvent effects:
  anti-addition (non-polar solvents)
  syn-addition (polar solvents)

- *E/Z* isomer effects

Alkene	Solvent	Ratio *anti:syn*
A. Bromination		
Z-2-Butene[a]	CH_3CO_2H	> 100 : 1
E-2-Butene[a]	CH_3CO_2H	> 100 : 1
Cyclohexene[b]	CCl_4	Very large
Z-1-Phenylpropene[c]	CCl_4	83:17
E-1-Phenylpropene[c]	CCl_4	88:12
Z-2-Phenylbutene[a]	CH_3CO_2H	68:32
E-2-Phenylbutene[a]	CH_3CO_2H	63:37
cis-Stilbene[d]	CCl_4	> 10 : 1
	CH_3NO_2[d]	1:9

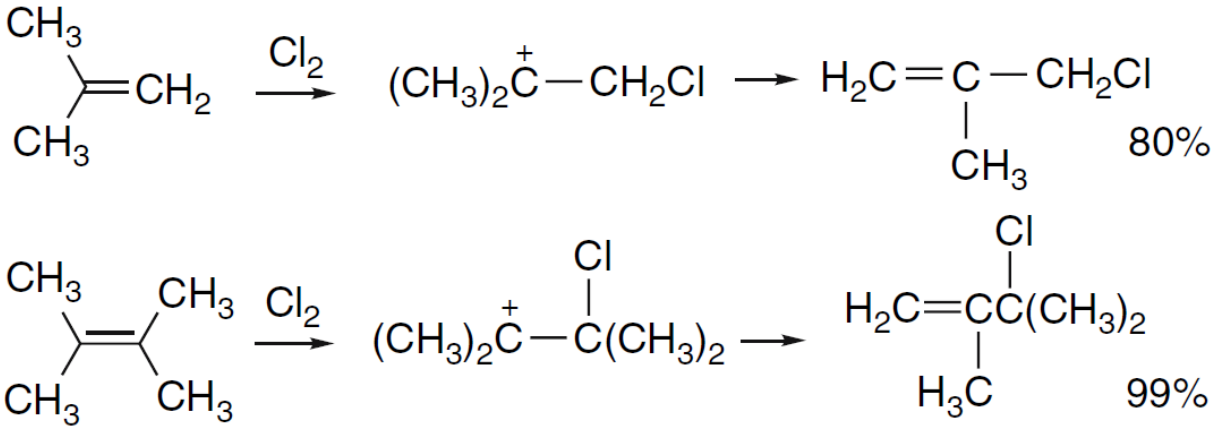
Alkene	Solvent	Ratio *anti:syn*
B. Chlorination		
Z-2-Butene[e]	None	> 100 : 1
	CH_3CO_2H[f]	> 100 : 1
E-2-Butene[e]	None	> 100 : 1
	CH_3CO_2H[f]	> 100 : 1
Cyclohexene[g]	None	> 100 : 1
E-1-Phenylpropene[f]	CCl_4	45:55
	CH_3CO_2H[f]	41:59
Z-1-Phenylpropene[f]	CCl_4	32:68
	CH_3CO_2H[f]	22:78
Cis-Stilbene[h]	$ClCH_2CH_2Cl$	8:92

Electrophilic Additions to C-C Multiple Bonds

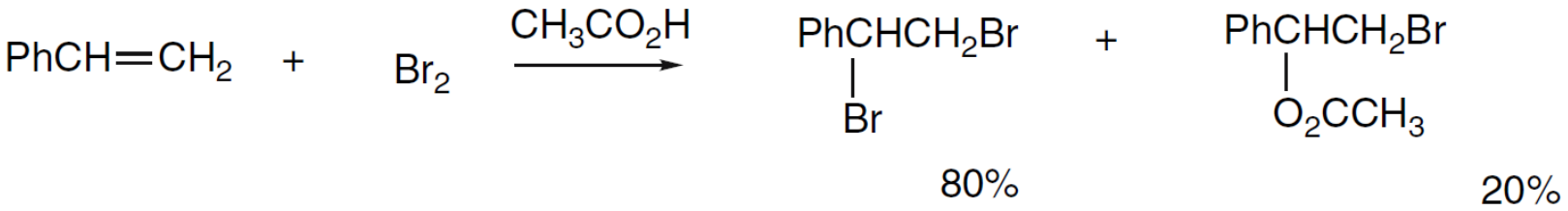
Electrophilic Addition to Alkenes

4. Additions of Halogens to Alkenes

- addition x elimination (branched alkenes)



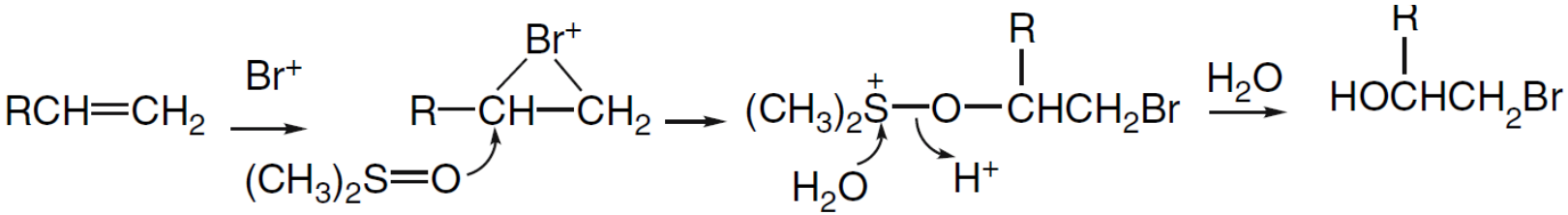
- side reactions (solvent as nucleophile)



Electrophilic Addition to Alkenes

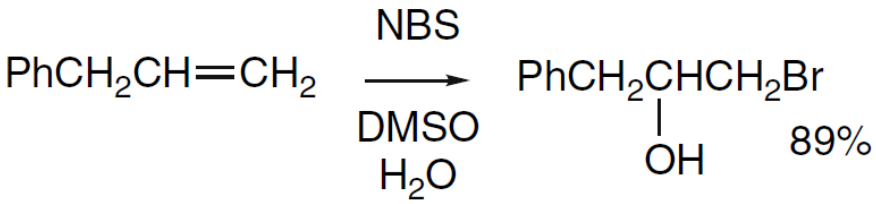
4. *Additions of Halogens to Alkenes*

- side reactions (solvent as nucleophile)
  H_2O ($NBS/DMSO/H_2O$)



- *anti*-addition

Example

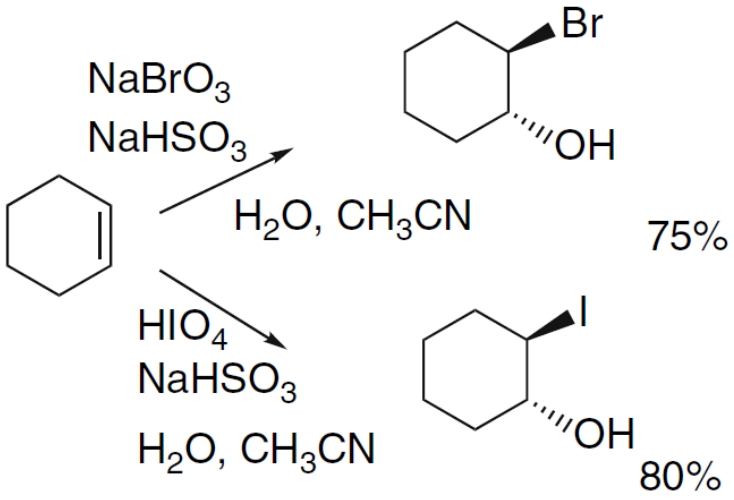


Electrophilic Addition to Alkenes

4. *Additions of Halogens to Alkenes*

- other systems for the preparation of *halohydrines* ($NaBrO_3$ or $NaIO_4/NaHSO_3/CH_3CN/H_2O$)
- „HOX“

Examples

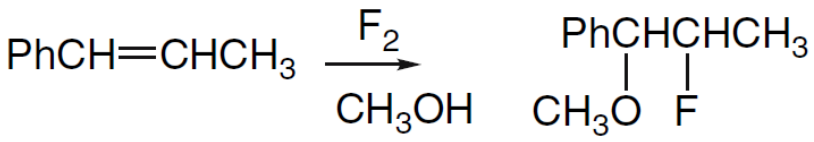


Electrophilic Addition to Alkenes

4. *Additions of Halogens to Alkenes*

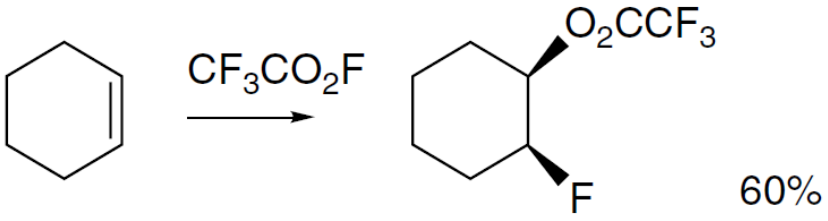
Fluorination

- F_2 (exothermic), *syn*-addition, low temperature, cleavage of C-C bonds
- XeF_2
- rapid formation and collapse of an ß-fluorocarbocationfluoride ion pair
- nucleophilic solvent reactions



- CH_3OF, CH_3COOF

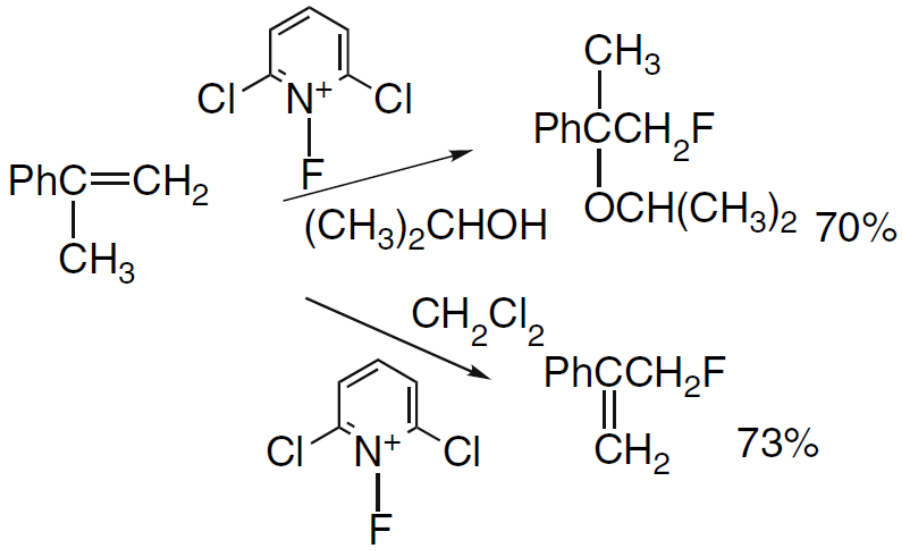
Example



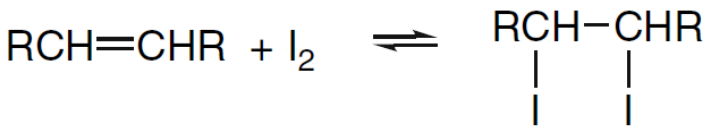
Electrophilic Addition to Alkenes

4. *Additions of Halogens to Alkenes*

Examples



Iodination



- diiodo compounds - seldom used
- other systems: $(py)_2I^+ BF_4^-$, $ICl/AgNO_3$, $I_2/(NCS)_2$

Electrophilic Addition to Alkenes

5. *Additions of Other Electrophilic Reagents to Alkenes*

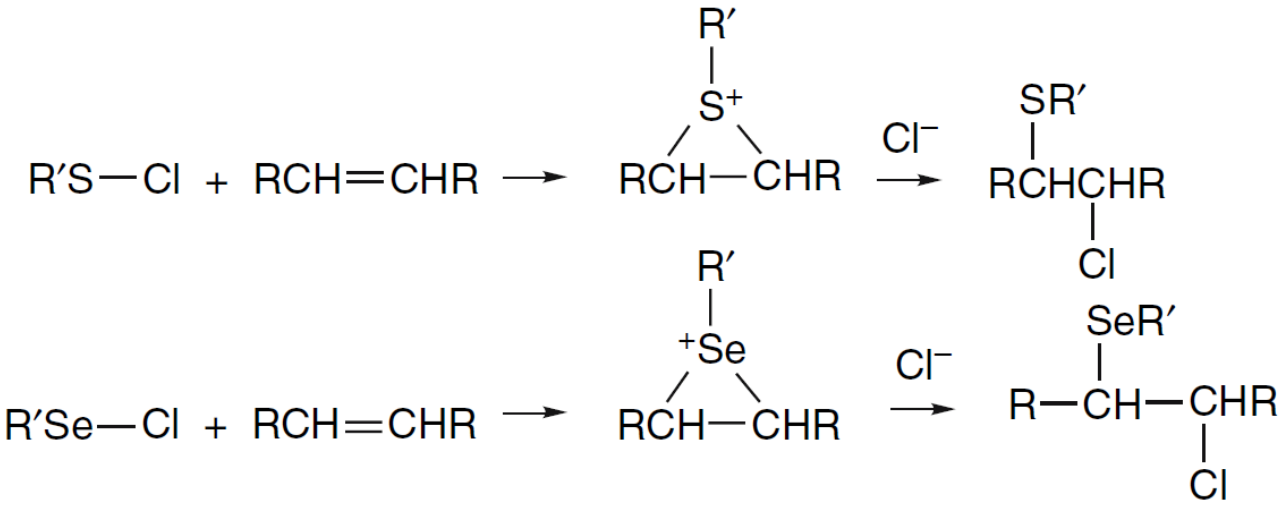
Reagent	Preparation	**Product**
I—N=C=O	$AgCNO$, I_2	RCH(I)—CH(NCO)R
Br—N=$\overset{+}{N}$=N^-	HN_3, Br_2	RCH(Br)—CH(N_3)R
I—N=$\overset{+}{N}$=N^-	NaN_3, ICl	RCH(I)—CH(N_3)R
I—S=C≡N	$(NCS)_2$, I_2	RCH(I)—CH(S—C≡N)R
I—ONO_2	$AgNO_3$, ICl	RCH(I)—CH(ONO_2)R
Cl—SCN	$Pb(SCN)_2$, Cl_2	RCH(Cl)—CH(SCN)R

Electrophilic Addition to Alkenes

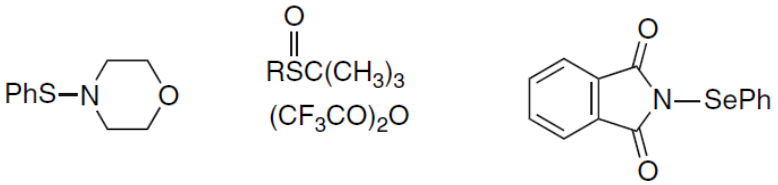
5. *Additions of Other Electrophilic Reagents to Alkenes*

Sulfur and Selenium Reagents

- divalent atoms
- subsequent elimination in sythetic application



-other reagents:

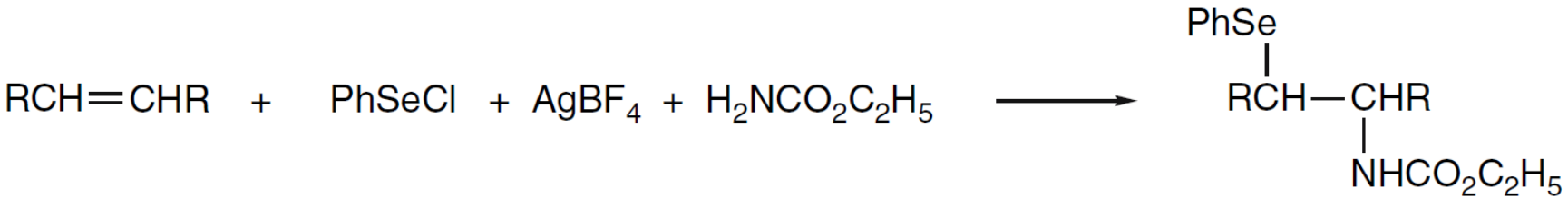


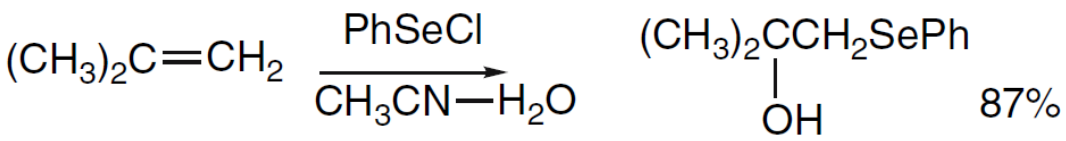
Electrophilic Addition to Alkenes

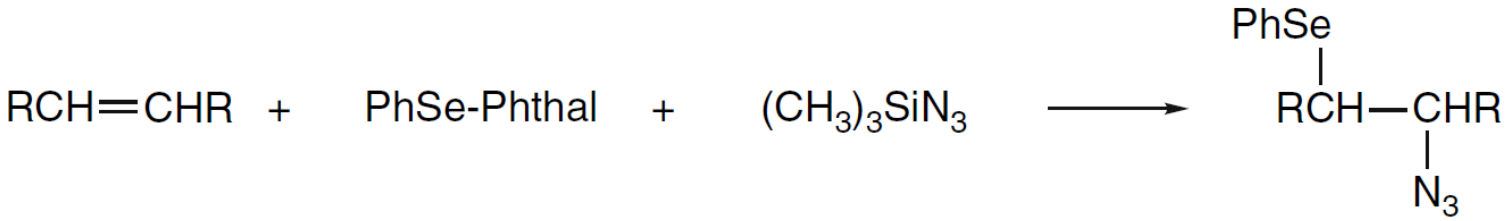
5. *Additions of Other Electrophilic Reagents to Alkenes*

Sulfur and Selenium Reagents

Examples



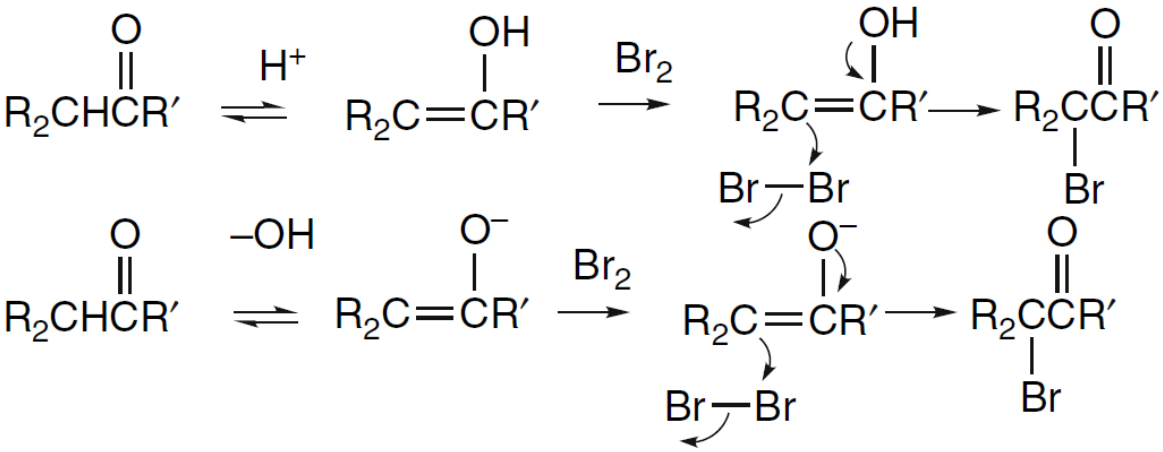


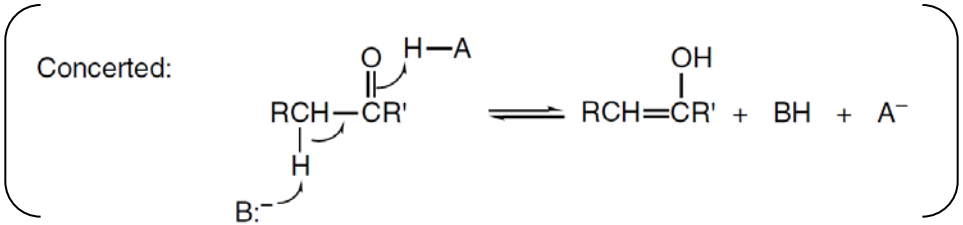


Electrophilic α-Substitution of Carbonyl Compounds

1. *α-Halogenation of Carbonyl Compounds*

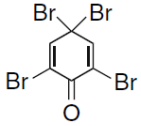
- closely related to electrophilic additions to alkenes
- nucleophile - enol, enolate or enolate equivalent
- electrophilic attack by the halogen
- restoration of the carbonyl group





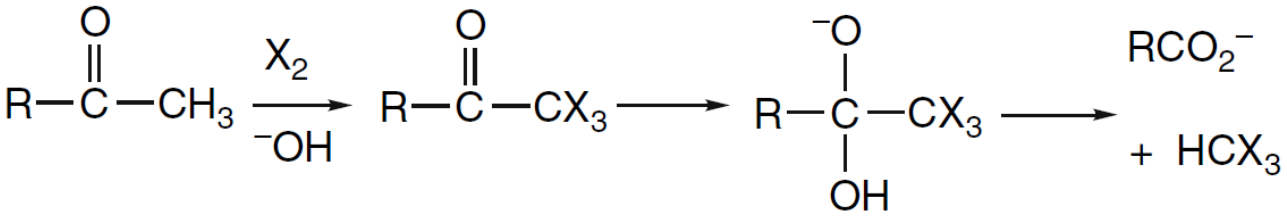
Electrophilic α-Substitution of Carbonyl Compounds

1. α-Halogenation of Carbonyl Compounds

- Br_2, Cl_2 – autocatalytic
- acid-sensitive compounds – NBS, 

- acid-catalyzed enolization – X substituents decrease the rate (mono-)
- base-catalyzed enolization – X substituents increase the rate (poly-)
- polar effect of X

- base-induced cleavage

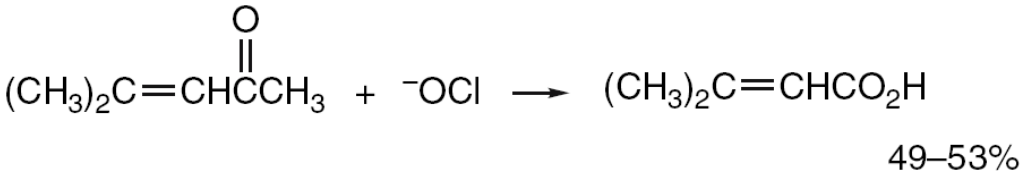


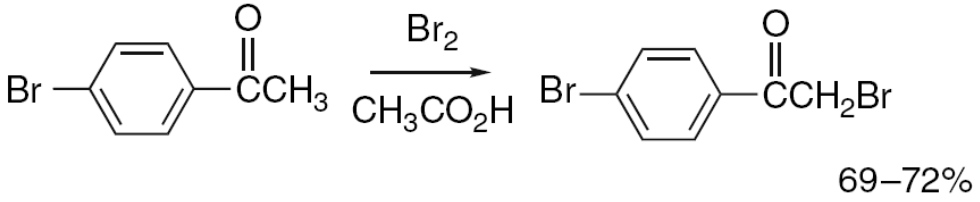
- oxidation with X_2 – 2-propanol (positive haloform reaction)

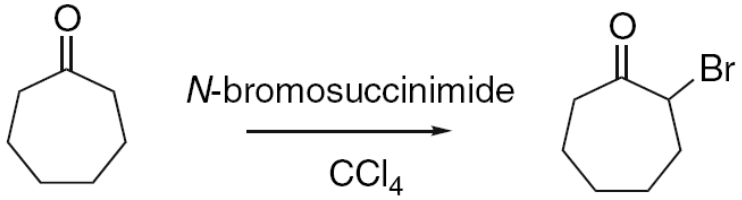
Electrophilic α-Substitution of Carbonyl Compounds

1. *α-Halogenation of Carbonyl Compounds*

Examples



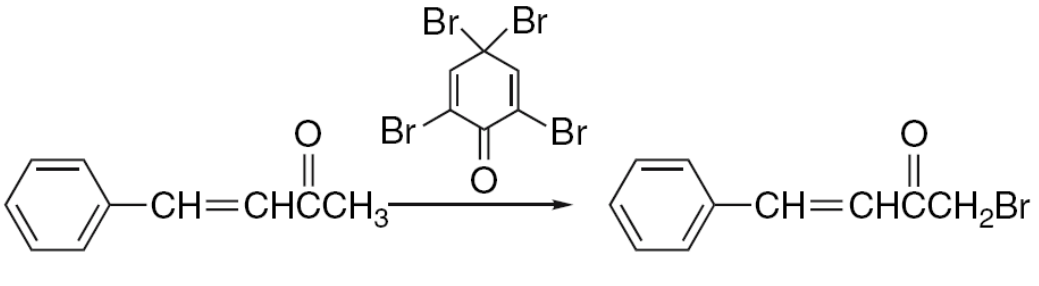


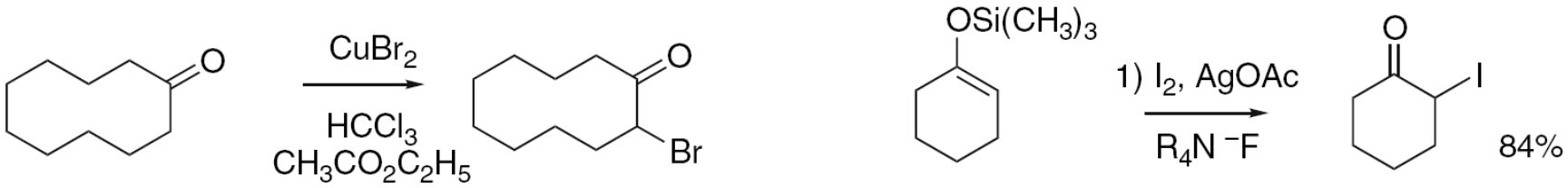


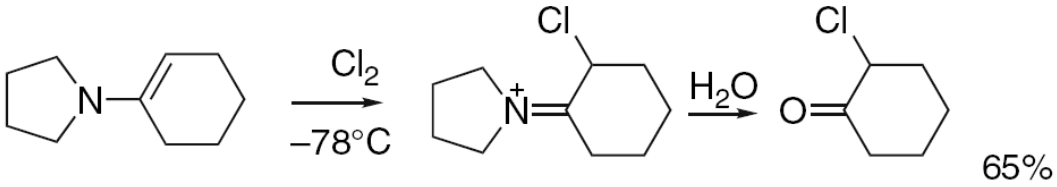
Electrophilic α-Substitution of Carbonyl Compounds

1. *α-Halogenation of Carbonyl Compounds*

Examples







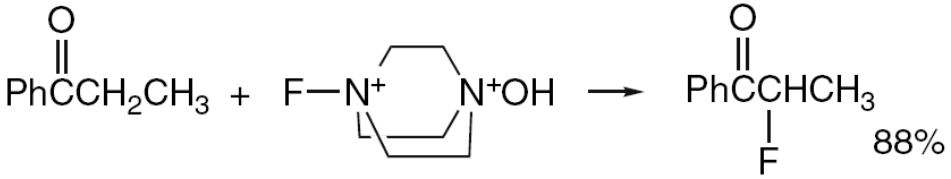
- LDA/Br_2, NCS, TfCl,etc.

Electrophilic α-Substitution of Carbonyl Compounds

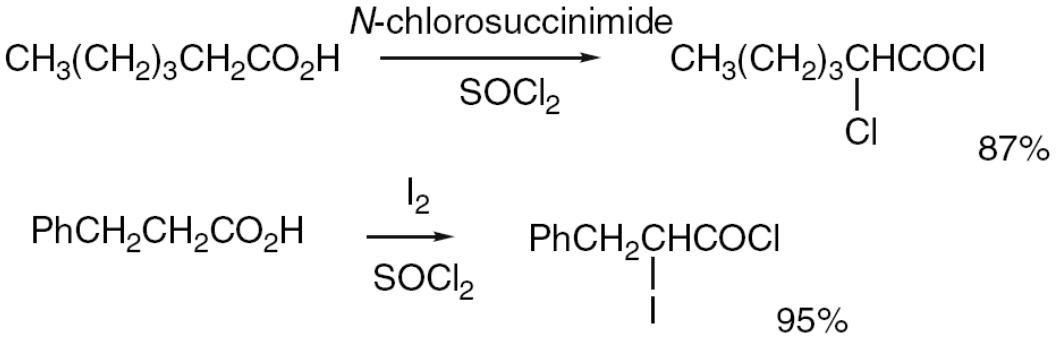
1. α-Halogenation of Carbonyl Compounds

α-fluoroketones

- preparation:
  - from silylenol ethers – F_2, XeF_2, CF_3OF
  - from ketones – *N*-fluoropyridinium salts or fluoro derivatives of 1,4-diaza-bicyclo[2.2.2]octane



acyl chlorides

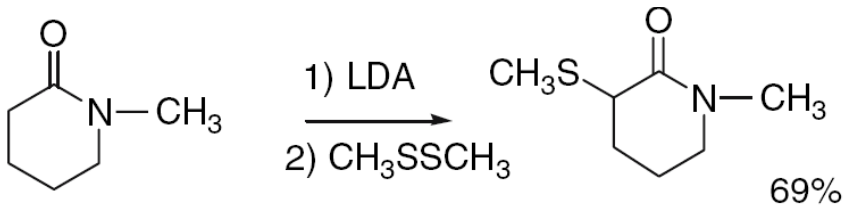


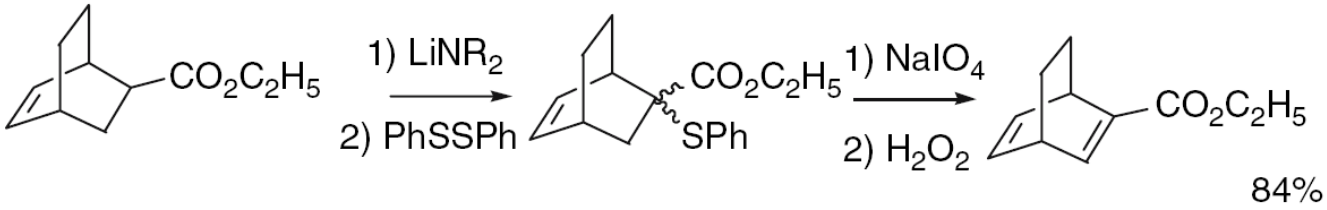
Electrophilic α-Substitution of Carbonyl Compounds

2. α-Sulfenylation and Selenylation of Carbonyl Compounds

- synthetically very important
- approach to unsaturated compounds
- preparation *via* enolates – regiospecific
- sulfenylation reagents – disulfides (RSSR)
- selenylation reagents – diselenides or selenenyl halides (RSeBr, RSeCl)

Examples

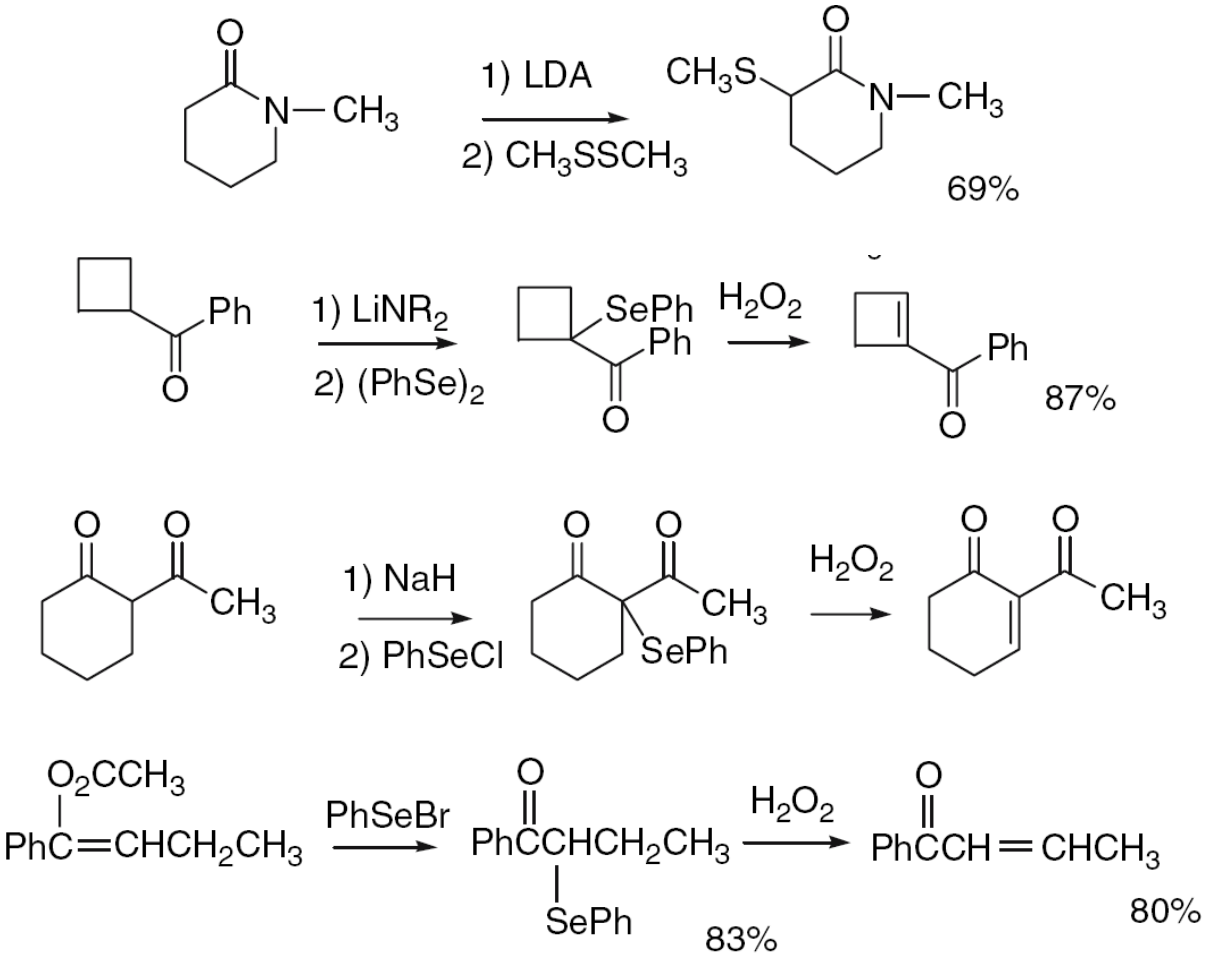




Electrophilic α-Substitution of Carbonyl Compounds

2. *α-Sulfenylation and Selenylation of Carbonyl Compounds*

Examples

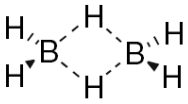


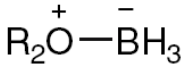
Electrophilic Additions to C-C Multiple Bonds

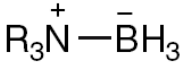
Addition at Double Bonds via Organoborane Intermediates

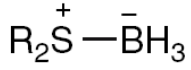
1. *Hydroboration*

- BH_3
- solvents (THF, Me_2S)

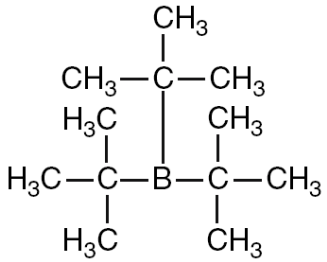




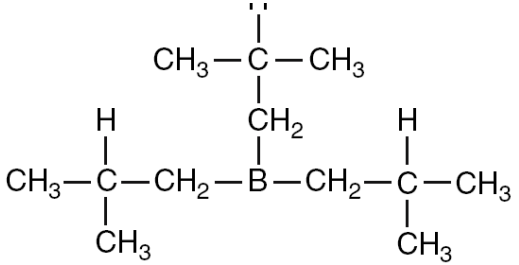




- regioselective – anti-Markovnikov
- trialkylboranes

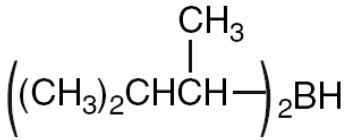


nonbonded repulsions

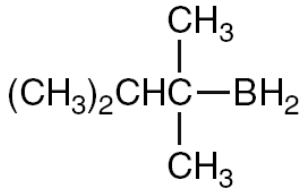


nonbonded repulsions reduced

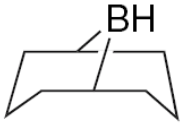
- higher regioslectivity:



disiamylborane
bis(1,2-dimethylpropyl) borane



thexylborane
1,1,2-trimethylpropylborane



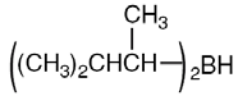
9-BBN
9-borabicyclo[3.3.1]nonane

Electrophilic Additions to C-C Multiple Bonds

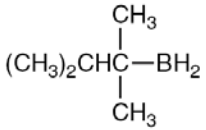
Addition at Double Bonds via Organoborane Intermediates

1. *Hydroboration*

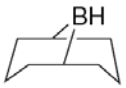
- regioslectivity:



disiamylborane



thexylborane



9-BBN

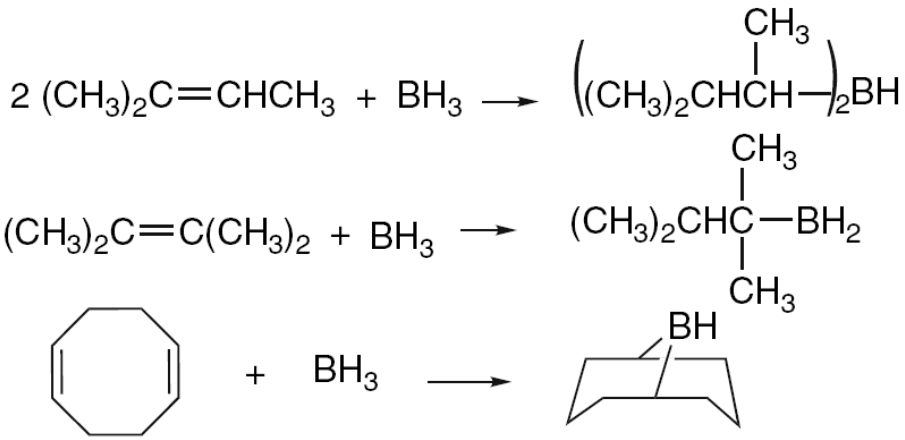
	Percent boron at less substituted carbon			
Hydroborating agent	1-Hexene	2-Methyl-1-butene	4-Methyl-2-pentene	Styrene
Diborane[a]	94	99	57	80
Chloroborane-dimethyl sulfide[b]	99	99.5	–	98
Disiamylborane[a]	99	–	97	98
Thexylborane-dimethyl sulfide[c]	94	–	66	95
Thexylchloroborane-dimethyl sulfide	99	99	97	99
9-Borabicyclo[3.3.1]borane	99.9	99.8[f]	99.3	98.5

Electrophilic Additions to C-C Multiple Bonds

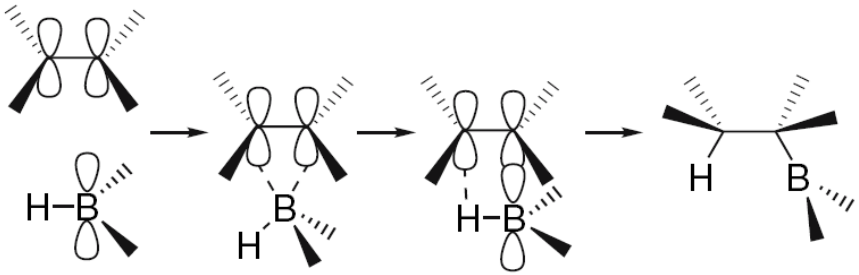
Addition at Double Bonds via Organoborane Intermediates

1. *Hydroboration*

- preparation:



- stereoselectivity – *syn*-addition
- four-center TS

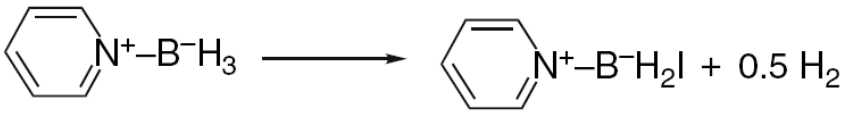


Electrophilic Additions to C-C Multiple Bonds

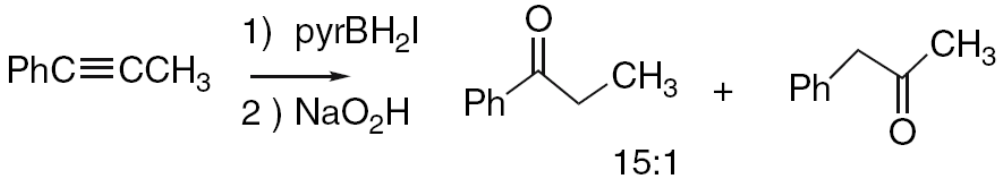
Addition at Double Bonds via Organoborane Intermediates

1. *Hydroboration*

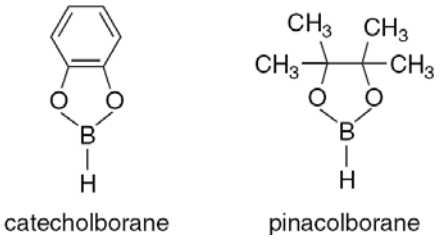
- haloboranes: BH_2Cl, BH_2Br, $BHCl_2$, $BHBr_2$
- higher reactivity (higher regioselectivity)

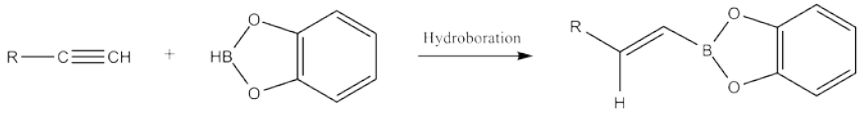


Example



- catecholborane, pinacolborane
- less reactive, synthetic application (Suzuki precursores, hydroboration *via* TM)



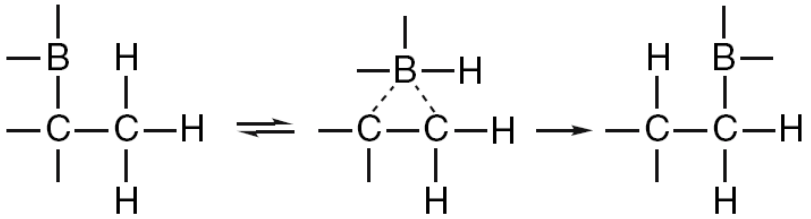


Electrophilic Additions to C-C Multiple Bonds

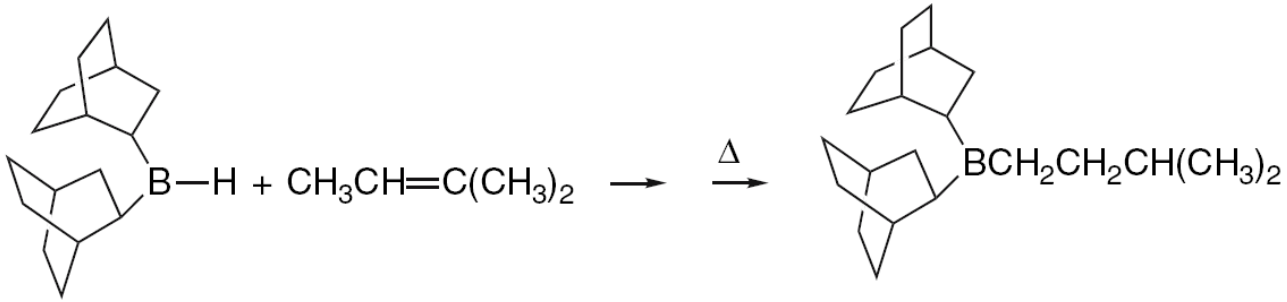
Addition at Double Bonds via Organoborane Intermediates

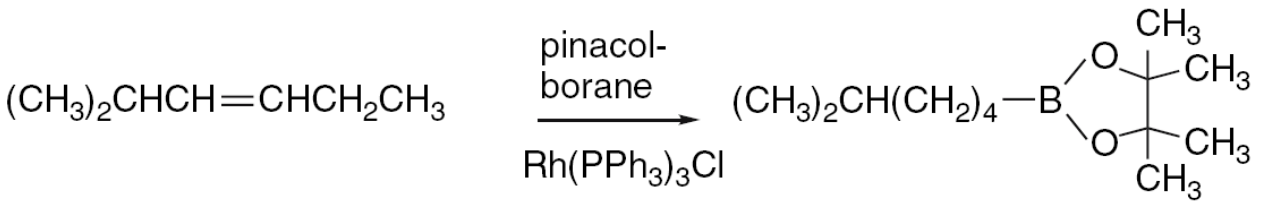
1. *Hydroboration*

- migration of boranes:



Examples





Electrophilic Additions to C-C Multiple Bonds

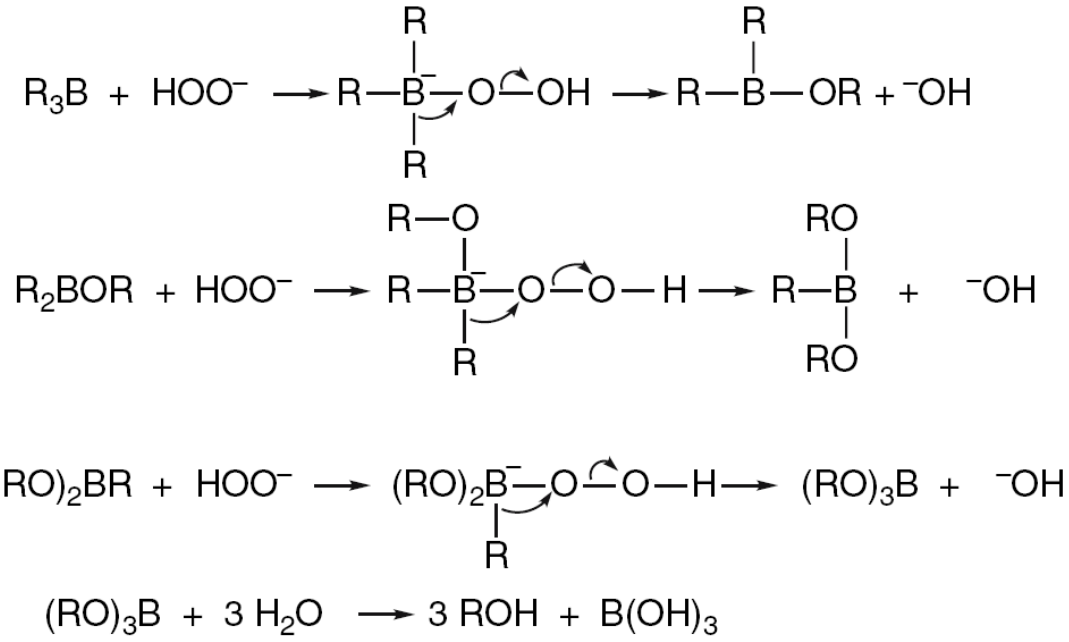
Addition at Double Bonds via Organoborane Intermediates

2. *Reaction of Organoboranes*

Oxidation to ROH

$(2K_2SO_5 \cdot KHSO_4 \cdot K_2SO_4)$

- oxidation reagents (H_2O_2/HO^-, HO_2^-, Oxone, O_2/perfluoralkanes)



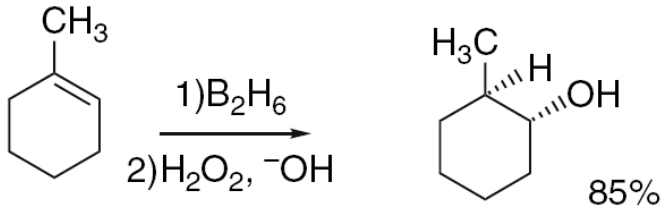
- replacement of C-B into C-O – retention of configuration

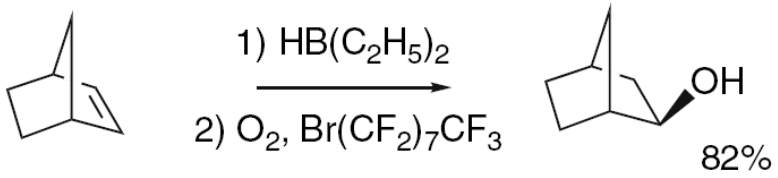
Addition at Double Bonds via Organoborane Intermediates

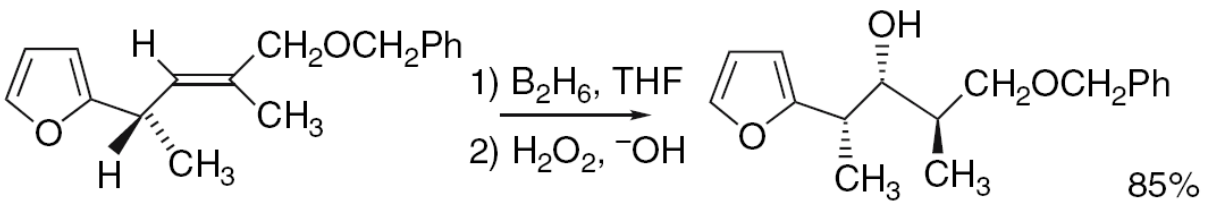
2. *Reaction of Organoboranes*

Oxidation to ROH

Examples







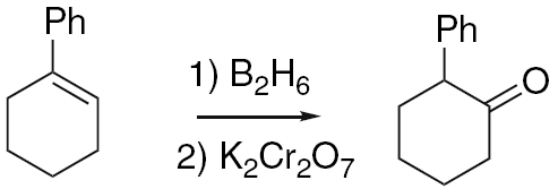
Addition at Double Bonds via Organoborane Intermediates

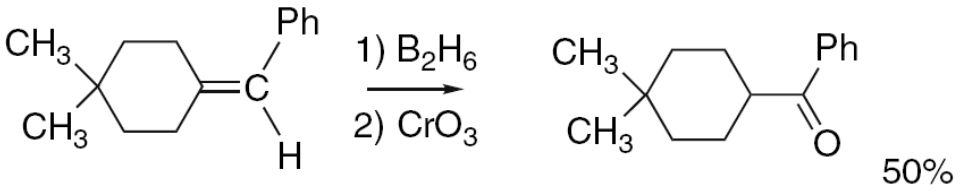
2. *Reaction of Organoboranes*

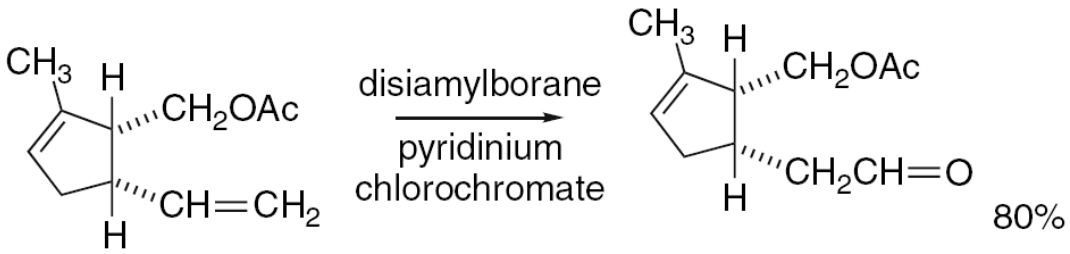
Oxidation to Aldehydes, Ketones and Carboxylic Acids

- oxidation reagents (PCC, $K_2Cr_2O_7$, Ru(VII))

Examples







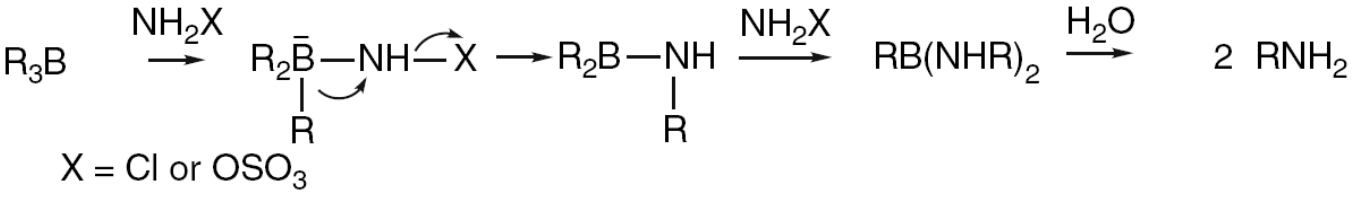
Electrophilic Additions to C-C Multiple Bonds

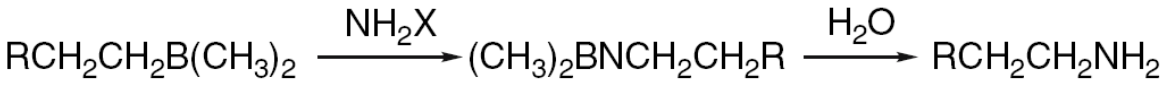
Addition at Double Bonds via Organoborane Intermediates

2. *Reaction of Organoboranes*

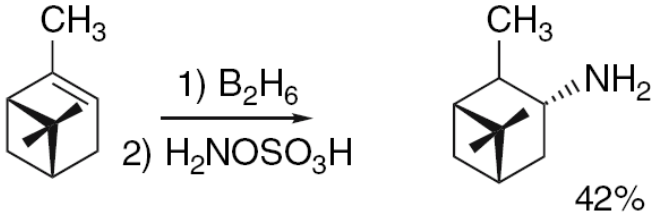
Amination

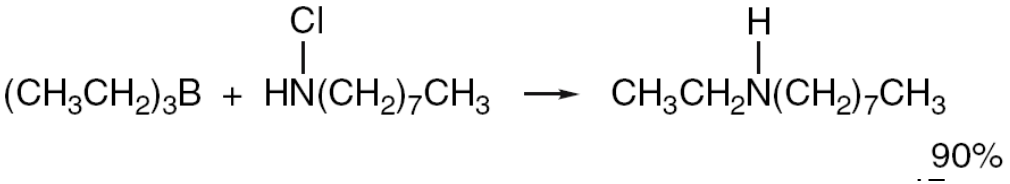
- amination reagents (chloramine, hydroxylamine-*O*-sulfonic acid)
- high efficient (Me_2BH, $BHCl_2$)





Examples





Addition at Double Bonds via Organoborane Intermediates

2. *Reaction of Organoboranes*

Halogenation

- hydroboration+halogenation – anti-Markovnikov
- halogenation reagents (I_2 or Br_2/base, ICl/NaOAc, etc.)

Examples