Emerge - Clayden Nucleophilic Substitution Reactions

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Ashish Mishra • Apr 14, 2022

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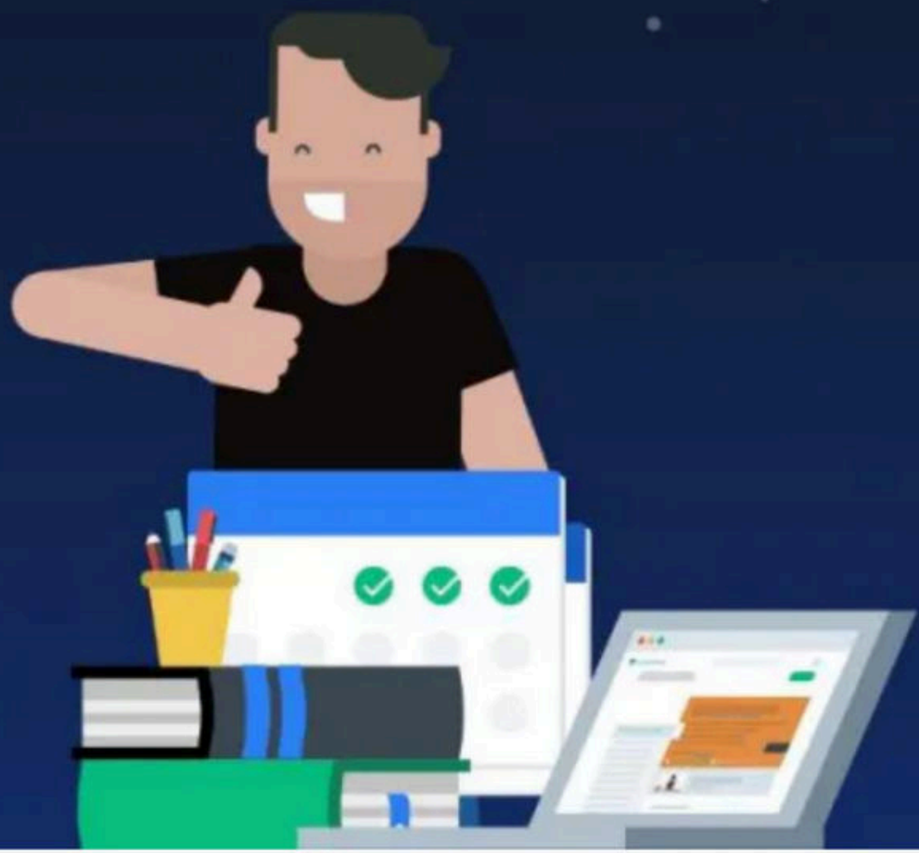

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30	15
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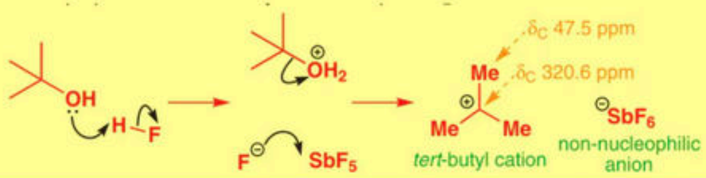
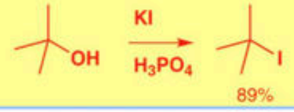
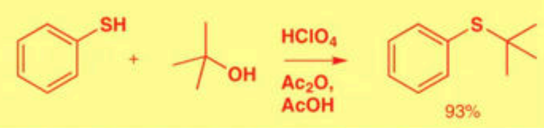
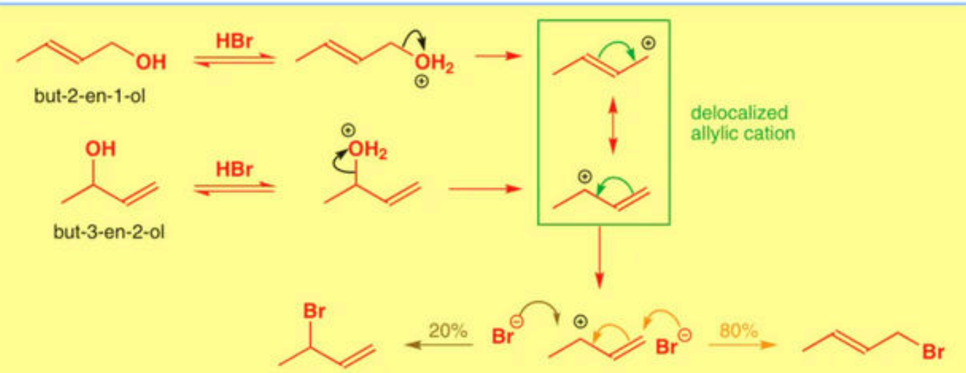
Clayden Nucleophilic substitutions

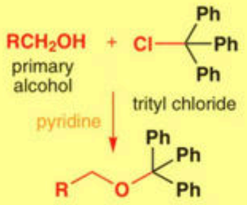
Nucleophilic substitution at saturated carbon

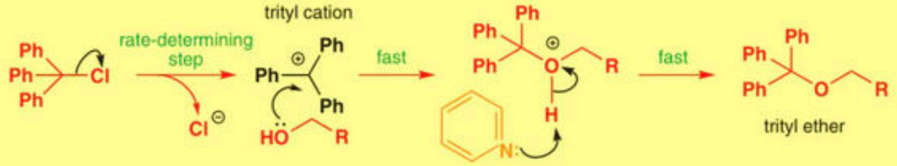


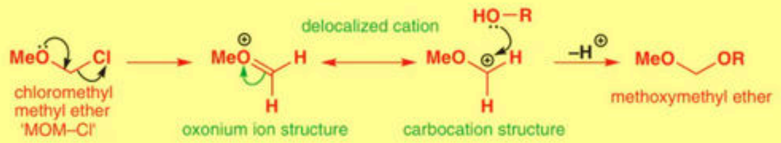





HBr
OH
but-2-en-1-ol
OH2
HBr
OH
but-3-en-2-ol
OH2
delocalized
allylic cation
Br
20%
Br
Br
80%
Br

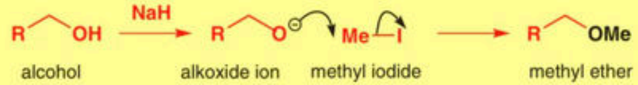

RCH2OH
primary
alcohol
+
Cl
Ph
Ph
Ph
trityl chloride
pyridine
R
O
Ph
Ph
Ph

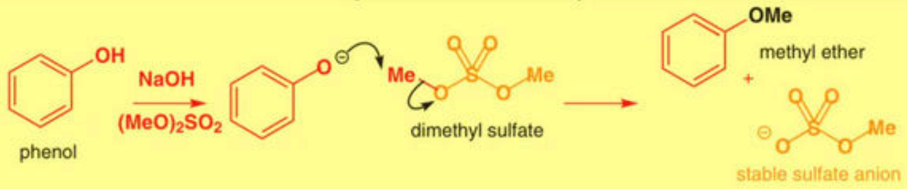

Ph
Ph
Ph
Cl
rate-determining
step
Cl
trityl cation
Ph
Ph
Ph
HO
R
fast
Ph
Ph
O
R
H
N:
fast
Ph
Ph
Ph
O
R
trityl ether

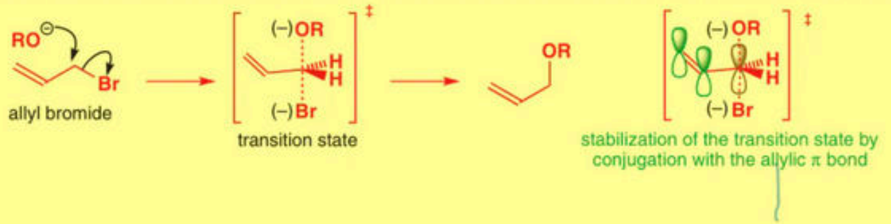

MeO
Cl
chloromethyl
methyl ether
'MOM–Cl'
MeO
H
H
oxonium ion structure
delocalized cation
HO—R
MeO
H
H
carbocation structure
–H
MeO
OR
methoxymethyl ether

Rates of solvolysis of alkyl chlorides in 50% aqueous ethanol at 44.6 °C

Compound	Relative rate	Comments
	0.07	primary chloride: probably all S_N2
	0.12	secondary chloride: can do S_N1 but not very well
	2100	tertiary chloride: very good at S_N1
	1.0	primary but allylic: S_N1 all right
	91	allylic cation is secondary at one end
	130000	allylic cation is tertiary at one end: compare with 2100 for simple tertiary
	7700	primary but allylic and benzylic

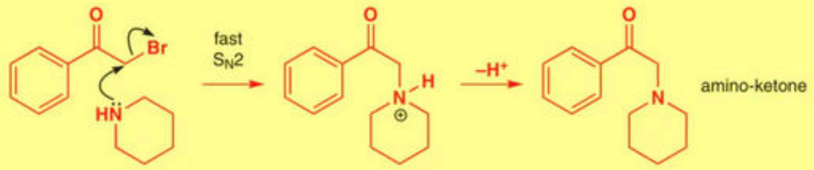






Among the fastest of all S_N2 reactions are those where the leaving group is adjacent to a carbonyl group. With α-bromo carbonyl compounds, two neighbouring carbon atoms are both powerfully electrophilic sites. Each has a low-energy empty orbital—π* from C=O and σ* from C–Br (this is what makes them electrophilic)—and these can combine to form a new LUMO (π* + σ*) lower in energy than either. Nucleophilic attack will occur easily where this new orbital has its largest coefficient, shown in orange on the diagram.

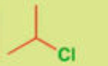
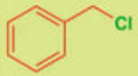
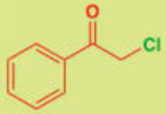
The effect of this interaction between antibonding orbitals is that each group becomes more electrophilic because of the presence of the other—the C=O group makes the C–Br bond more reactive and the Br makes the C=O group more reactive. In fact, it may well be that the nucleophile will attack the carbonyl group, but this will be reversible whereas displacement of bromide is irreversible.

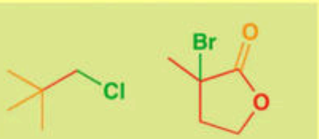


Quantifying structural effects on S_N2 reactions

Some actual data may help at this point. The rates of reaction of the following alkyl chlorides with KI in acetone at 50 °C broadly illustrate the patterns of S_N2 reactivity we have just analysed. These are relative rates with respect to *n*-BuCl as a 'typical primary halide'. You should not take too much notice of precise figures but rather observe the trends and notice that the variations are quite large—the full range from 0.02 to 100,000 is eight powers of ten.

Relative rates of substitution reactions of alkyl chlorides with the iodide ion

Alkyl chloride	Relative rate	Comments
	200	least hindered alkyl chloride
	0.02	secondary alkyl chloride; slow because of steric hindrance
	79	allyl chloride accelerated by π conjugation in transition state
	200	benzyl chloride a bit more reactive than allyl: benzene ring slightly better at π conjugation than isolated double bond
	920	conjugation with oxygen lone pair accelerates reaction (this is an S_N1 reaction)
	100,000	conjugation with carbonyl group much more effective than with simple alkene or benzene ring; these α-halo carbonyl compounds are the most reactive of all

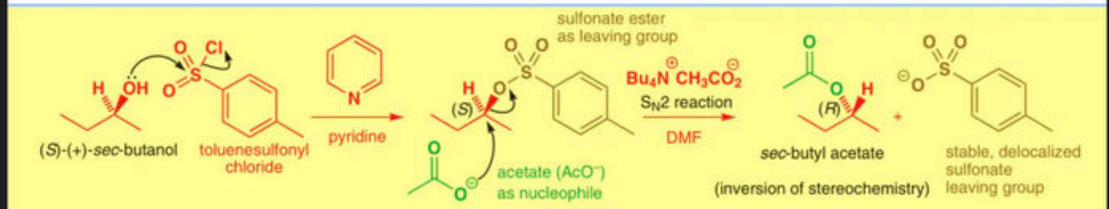


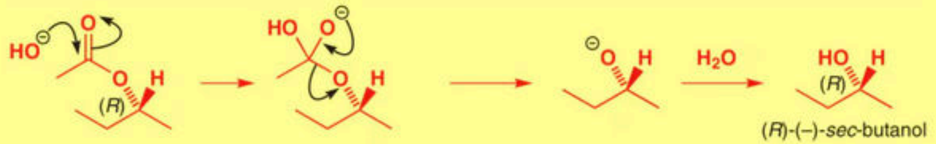
neopentyl chloride

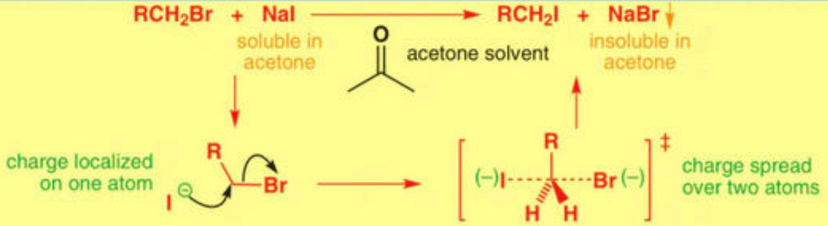
no S_N1; slow S_N2 due to hindrance

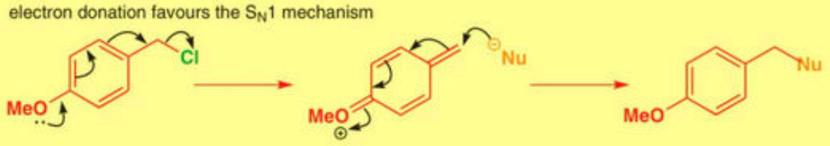
tertiary and adjacent to C=O

v. slow S_N1; reacts slowly by S_N2

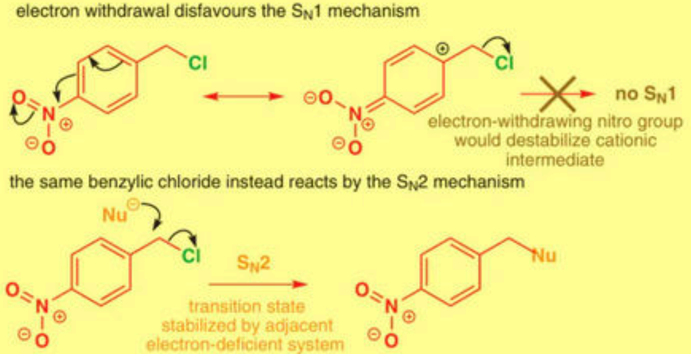


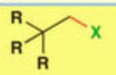


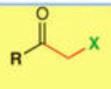
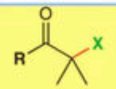




On the other hand, an electron-withdrawing group, such as a nitro group, within the benzylic compound will decrease the rate of the S_N1 reaction and allow the S_N2 mechanism to take over.

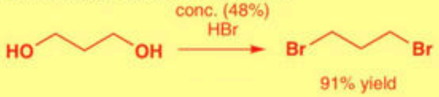


Electrophile	Me–X				
	methyl	primary	secondary	tertiary	'neopentyl'
S_N1 mechanism?	bad	bad	poor	excellent	bad
S_N2 mechanism?	excellent	good	poor	bad	bad

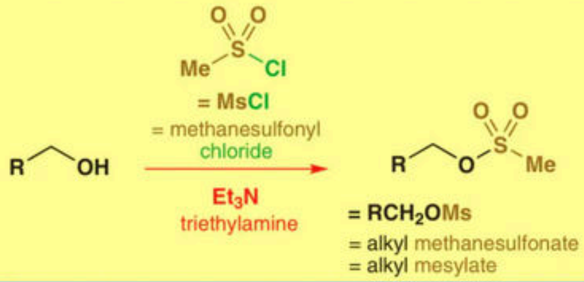
Electrophile					
	allylic	benzylic	α-alkoxy (adj. lone pair)	α-carbonyl	α-carbonyl and tertiary
S_N1 mechanism?	good	good	good	bad	bad
S_N2 mechanism?	good	good	okay but S_N1 better	excellent	possible

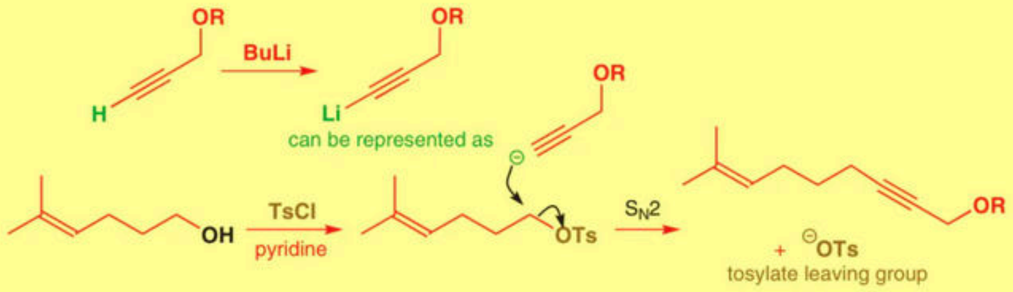
substituting a secondary alcohol in acid

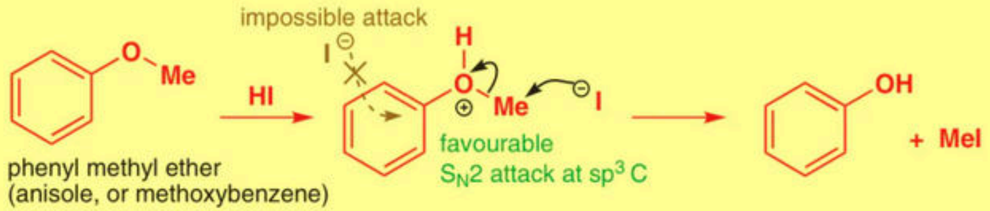
substituting a primary alcohol in acid



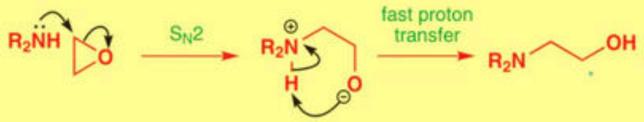

= TsCl
= p-toluenesulfonyl chloride
pyridine
= RCH2OTs
= alkyl p-toluenesulfonate
= alkyl tosylate

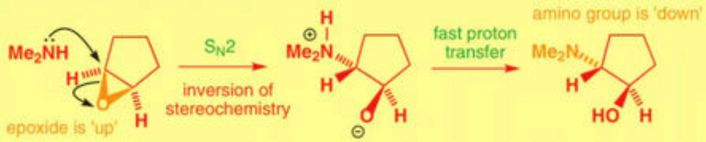

= MsCl
= methanesulfonyl chloride
Et3N
triethylamine
= RCH2OMs
= alkyl methanesulfonate
= alkyl mesylate

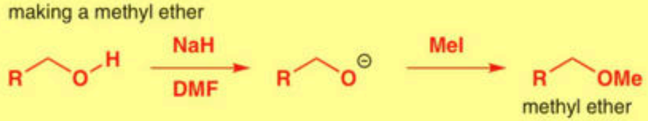

BuLi
can be represented as
TsCl
pyridine
SN2
+ OTs
tosylate leaving group


impossible attack
HI
favourable
SN2 attack at sp3 C
+ MeI
phenyl methyl ether
(anisole, or methoxybenzene)

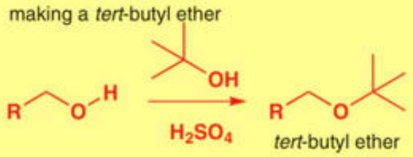

BBr_3 acts as a Lewis acid—empty p orbital accepts a lone pair of electrons
BBr_3
aryl alkyl ether
H_2O
OH


R_2NH
S_N2
fast proton transfer
OH


Me_2NH
epoxide is 'up'
S_N2
inversion of stereochemistry
fast proton transfer
amino group is 'down'

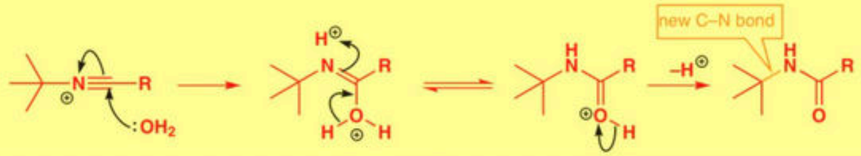

making a methyl ether
NaH
DMF
MeI
methyl ether

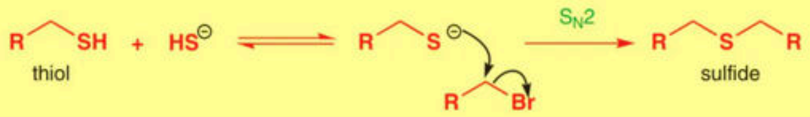

S_N2

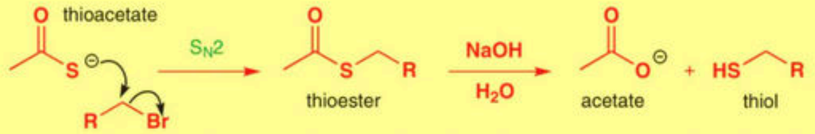

making a *tert*-butyl ether
OH
H_2SO_4
tert-butyl ether


S_N1
- H
t-butyl cation

The resulting cation is captured by the water molecule released in the first step and an exchange of protons leads to a secondary amide. The overall process is called the Ritter reaction and it is one of the few reliable ways to make a C–N bond to a tertiary centre.



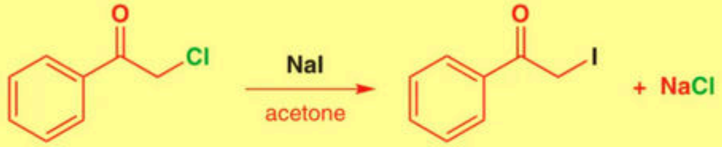




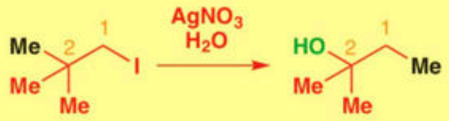
Nucleophiles in substitution reactions

Relative rates (water = 1) of reaction of nucleophiles with MeBr in EtOH

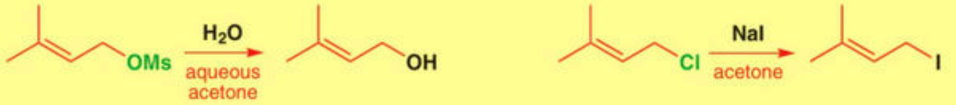
nucleophile	F^-	H_2O	Cl^-	Et_3N	Br^-	PhO^-	EtO^-	I^-	PhS^-
relative rate	0.0	1.0	1100	1400	5000	2.0×10^3	6×10^4	1.2×10^5	5.0×10^7

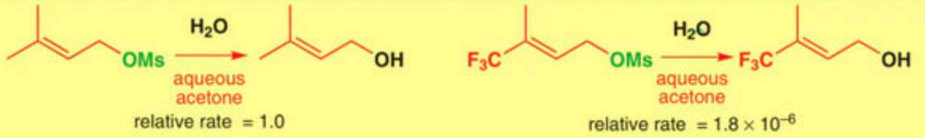


this reaction does not happen


Me
Me
Me
I
AgNO3
H2O
HO
Me
Me
Me


special arrow to show migration
Ag
Me
Ag
H
H
H
migration of Me to carbon 1
forms tertiary carbocation
H2O
HO
Me

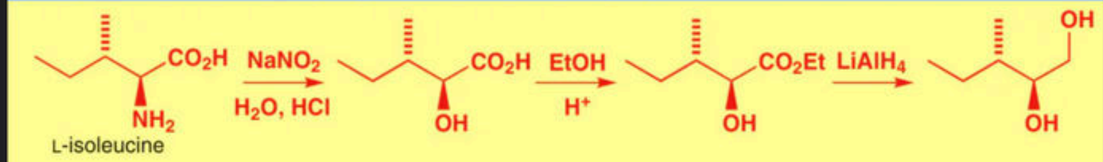

OMs
H2O
aqueous
acetone
OH
Cl
NaI
acetone
I

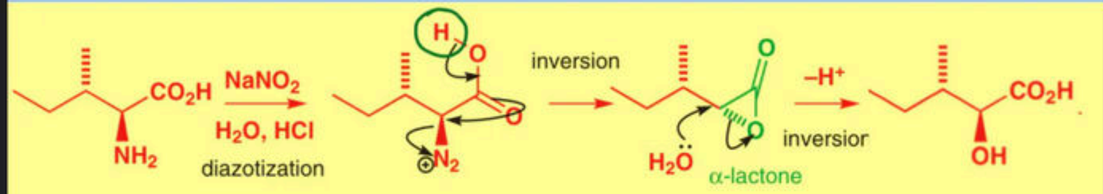

OMs
H2O
aqueous
acetone
OH
relative rate = 1.0
F3C
OMs
F3C
OH
relative rate = 1.8 × 10−6

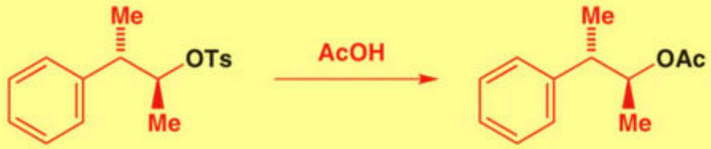

Cl
NaI
acetone
I
relative rate = 1.0
F3C
Cl
F3C
I
relative rate = 11.0

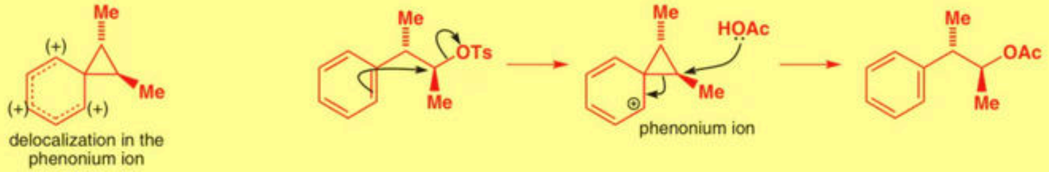

H
OTs
Bu4N
AcO
DMF
AcO
H
S
R
TsO
H
Bu4N
AcO
DMF
H
OAc
R
S

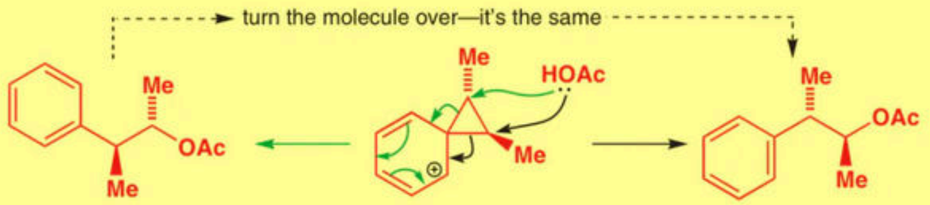
NGP


CO2H
NaNO2
H2O, HCl
CO2H
EtOH
H+
CO2Et
LiAlH4
OH
NH2
OH
OH
L-isoleucine

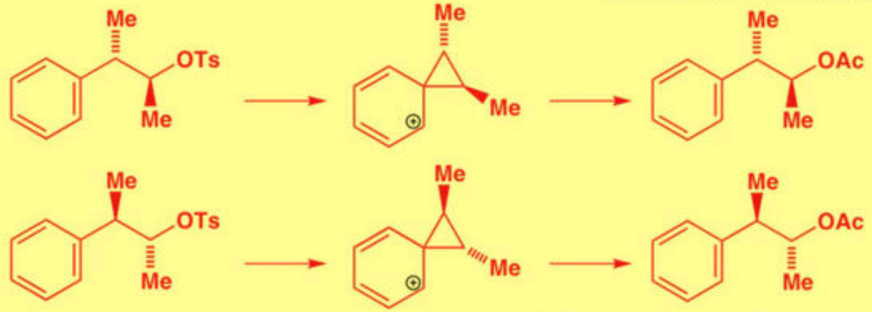

CO2H
NaNO2
H2O, HCl
diazotization
H
O
N2
inversion
O
O
H2O
α-lactone
–H+
inversior
CO2H
OH


Me
OTs
Me
AcOH
Me
OAc
Me

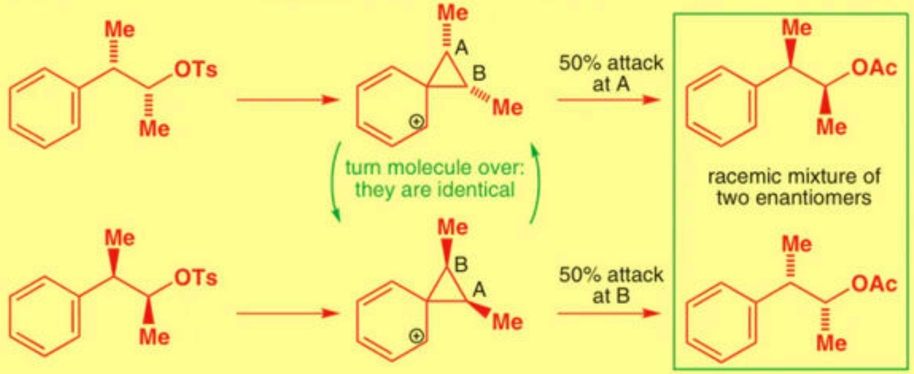

Me
(+)
Me
(+)
(+)
delocalization in the
phenonium ion
Me
OTs
Me
Me
HOAc
Me
phenonium ion
Me
OAc
Me

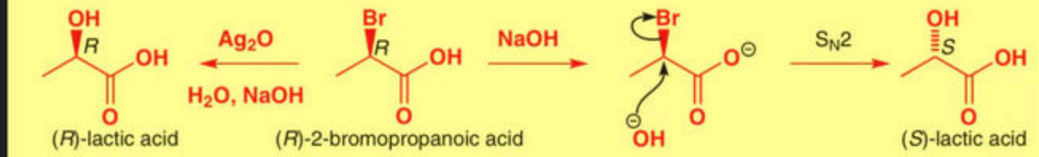


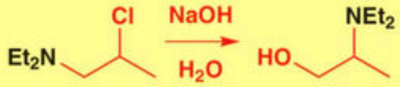
from this enantiomer of tosylate . . . we get this phenonium ion . . . and this enantiomer of product
whichever end the acid attacks

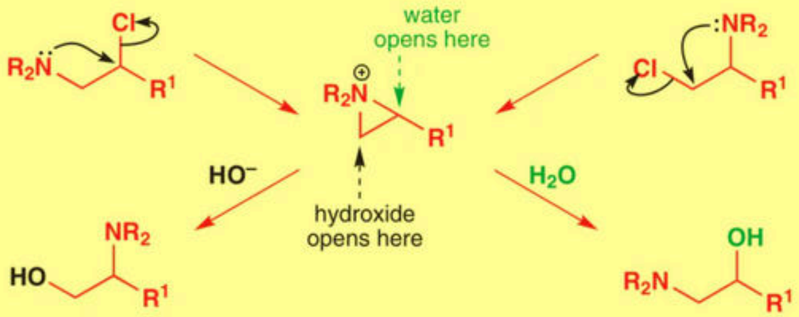


from either enantiomer . . . we get the same achiral phenonium ion . . . and therefore racemic product







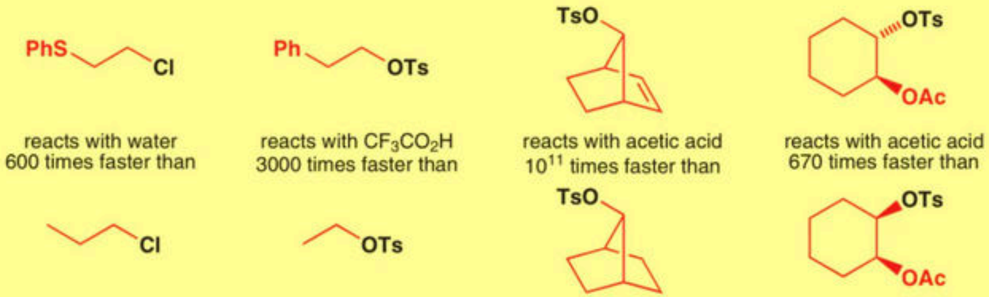


$CH_3CH_2CH_2CH_2Br < (CH_3)_2CHCH_2Br < CH_3CH_2CH(Br)CH_3 < (CH_3)_3CBr$ (S_N1)

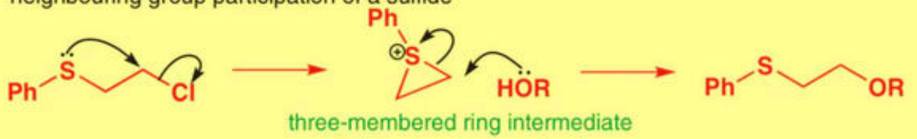
$CH_3CH_2CH_2CH_2Br > (CH_3)_2CHCH_2Br > CH_3CH_2CH(Br)CH_3 > (CH_3)_3CBr$ (S_N2)

$C_6H_5C(CH_3)(C_6H_5)Br > C_6H_5CH(C_6H_5)Br > C_6H_5CH(CH_3)Br > C_6H_5CH_2Br$ (S_N1)

$C_6H_5C(CH_3)(C_6H_5)Br < C_6H_5CH(C_6H_5)Br < C_6H_5CH(CH_3)Br < C_6H_5CH_2Br$ (S_N2)

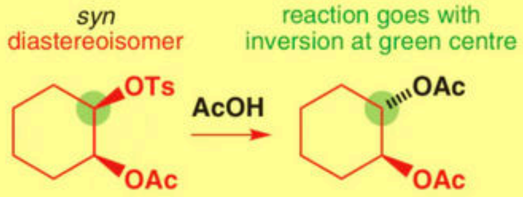


neighbouring group participation of a sulfide

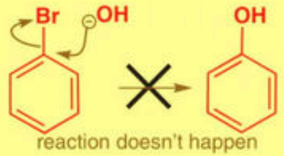


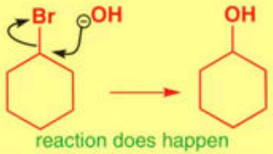
anti
diastereoisomer

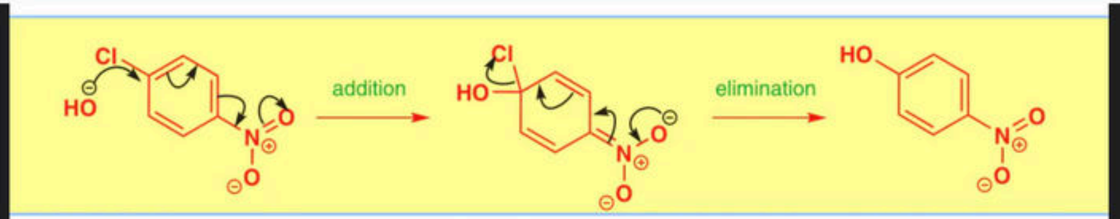
reaction goes with
retention at orange centre



Nucleophilic aromatic substitution

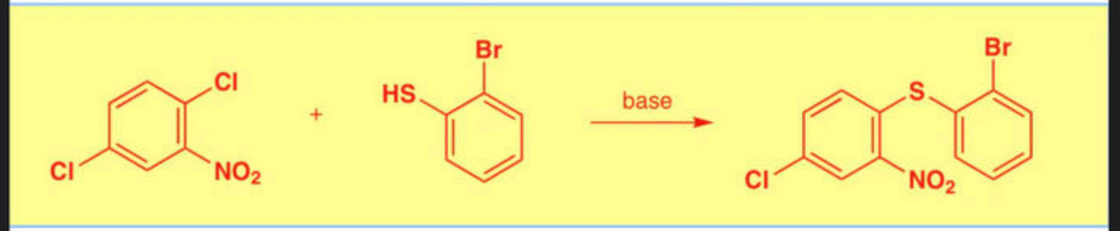


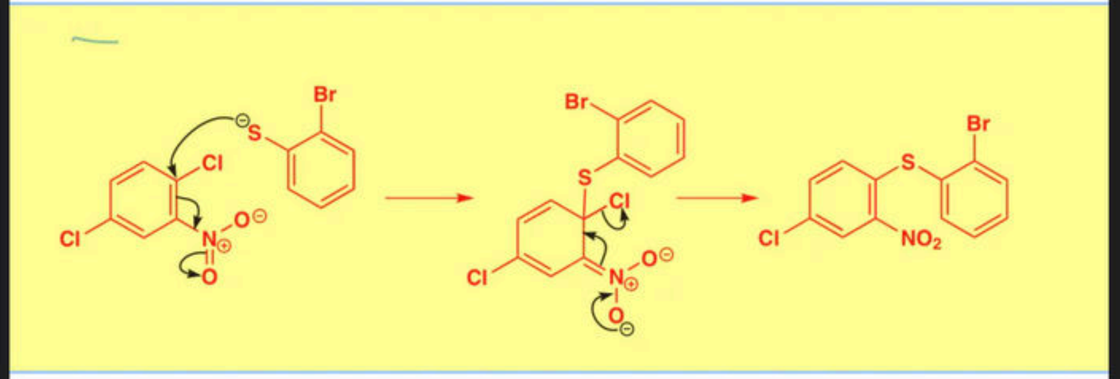



Cl
HO
addition
Cl
HO
elimination
HO


Br
R
HNO3
H2SO4
Br
R
NO2
CN
CN
R
NO2

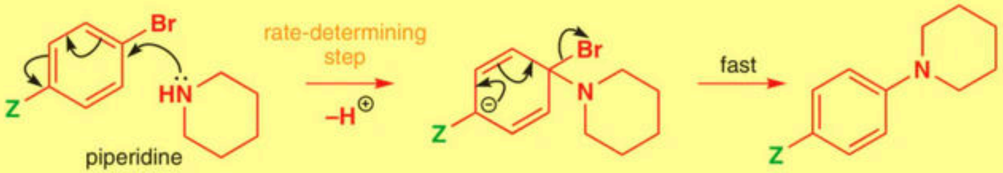

Cl
HNO3
H2SO4
Cl
NO2
NO2
H2N—NH2
hydrazine
H2N
NH
NO2
NO2
2,4-dinitrophenylhydrazine

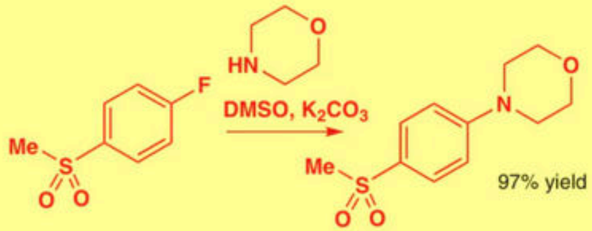

Cl
Cl
NO2
+
HS
Br
base
Br
S
Cl
NO2

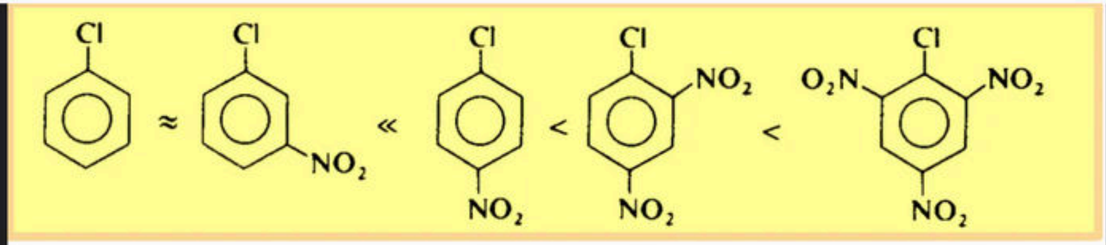

Br
S
Cl
Cl
N
O
O
Br
Br
S
Cl
Cl
N
O
O
Br
S
Cl
NO2

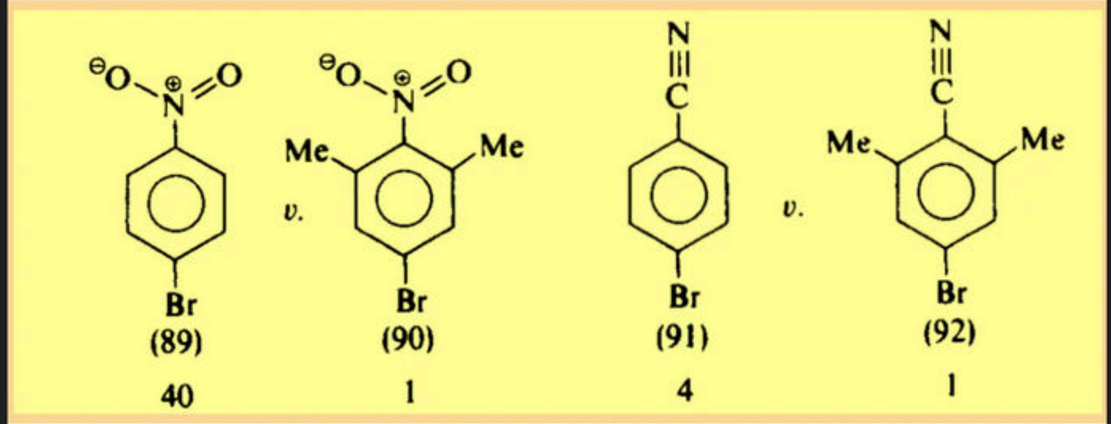

OMe
MeO⊖
MeOH
F
N
H
N

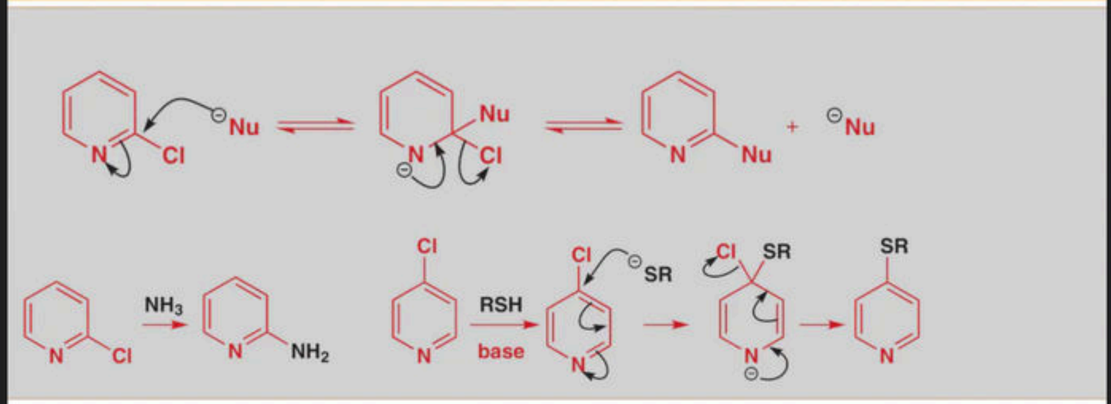

fluoride accelerates this step
because it is very electronegative
azide
addition
rate-
determining
step
elimination
F⊖

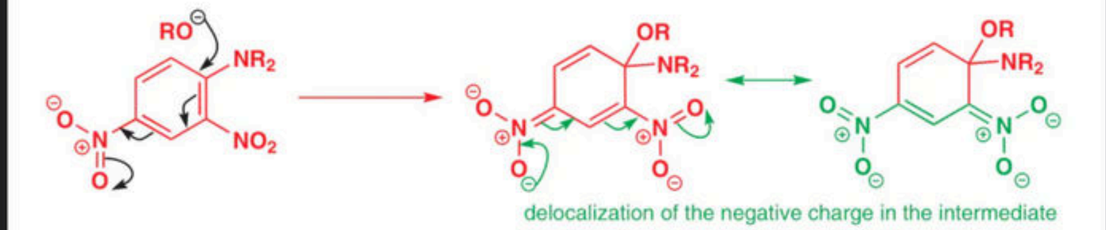

Br
HN
Z
piperidine
rate-determining
step
–H⊕
Br
N
Z
fast
N
Z


HN
O
F
DMSO, K2CO3
Me
S
O
O
N
O
Me
S
O
O
97% yield

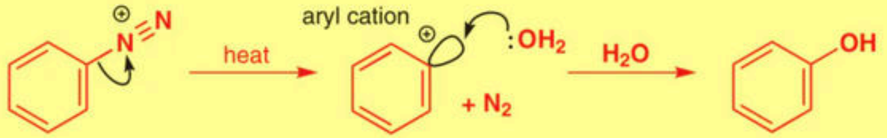

Cl
≈
Cl
NO2
≪
Cl
NO2
<
Cl
NO2
NO2
<
O2N
Cl
NO2
NO2

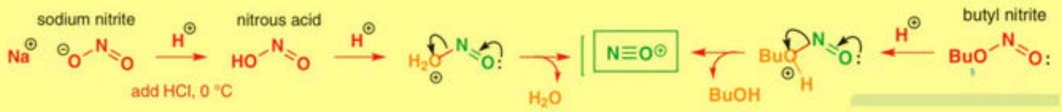

Br
(89)
40
v.
Me
Me
Br
(90)
1
N
C
Br
(91)
4
v.
N
C
Me
Me
Br
(92)
1

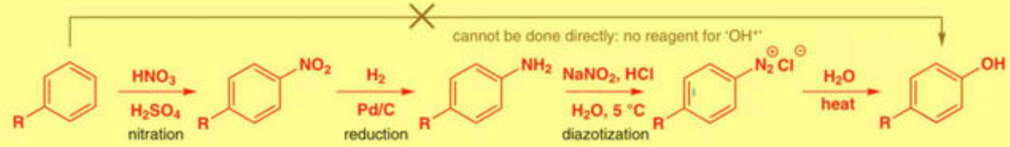

Nu
N
Cl
Nu
N
Cl
N
Nu
+
Nu
N
Cl
NH3
N
NH2
Cl
N
RSH
base
Cl
SR
N
Cl
SR
N
SR
N

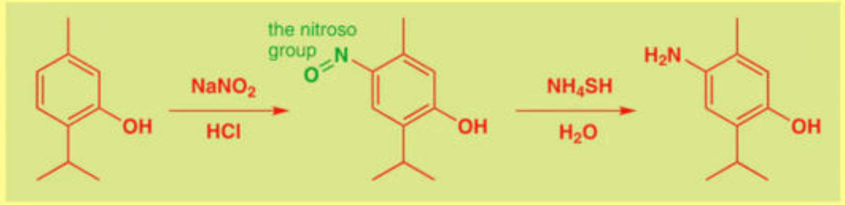

RO
NR2
NO2
OR
NR2
OR
NR2
delocalization of the negative charge in the intermediate

The S_N1 mechanism for nucleophilic aromatic substitution: diazonium compounds

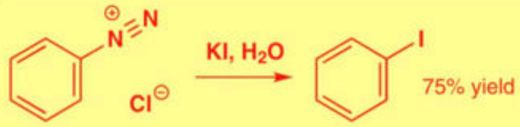


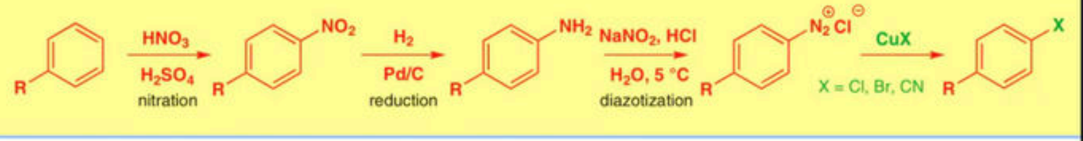


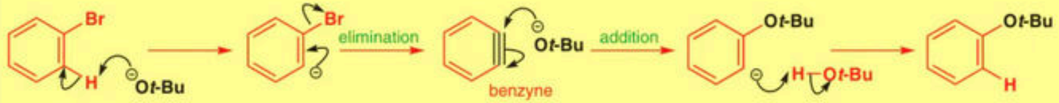



the nitroso group
NaNO2
HCl
NH4SH
H2O
OH
H2N


Ac2O
NaOEt
NMe2
Cl
OH

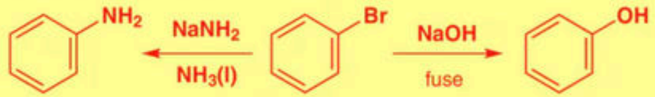

KI, H2O
75% yield

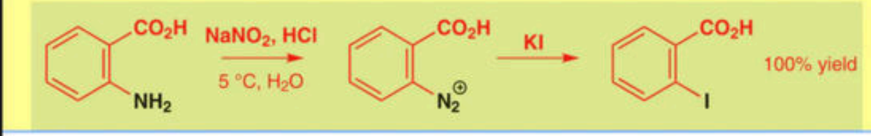

HNO3
H2SO4
nitration
H2
Pd/C
reduction
NaNO2, HCl
H2O, 5 °C
diazotization
CuX
X = Cl, Br, CN

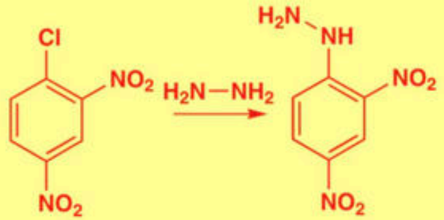

elimination
addition
benzyne


NaNH2
NH3 (l)

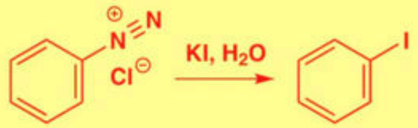
The benzyne mechanism





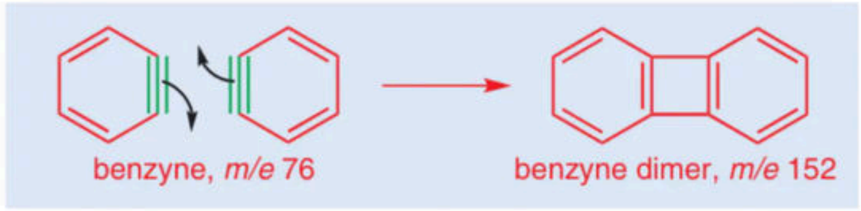


nucleophilic aromatic substitution: addition–elimination mechanism



nucleophilic aromatic substitution: S_N1 mechanism

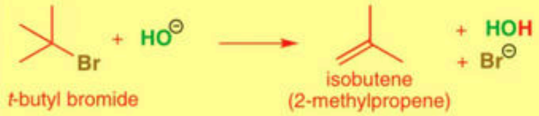
nucleophilic aromatic substitution: elimination–addition mechanism



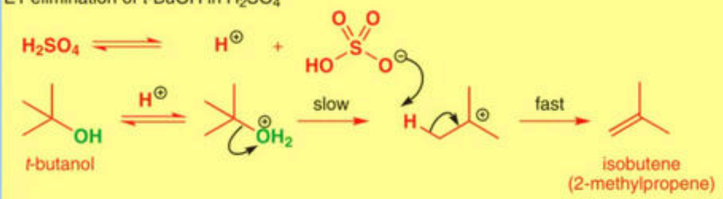
Elimination reactions

nucleophilic substitution reactions of *t*-BuBr

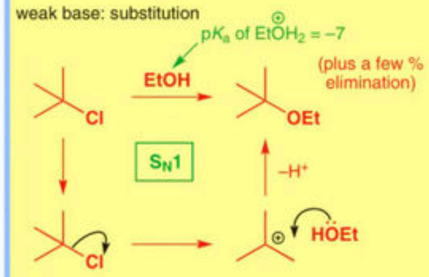
reaction of *t*-BuBr with concentrated solution of NaOH



E1 elimination of *t*-BuOH in H_2SO_4

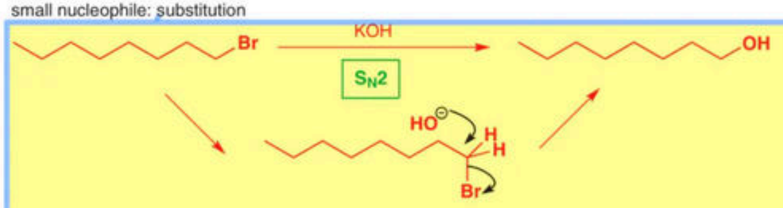


weak base: substitution

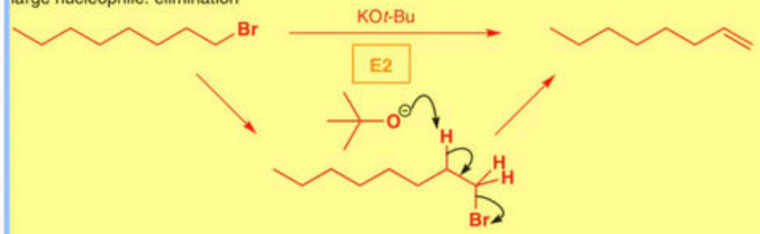


strong base: elimination

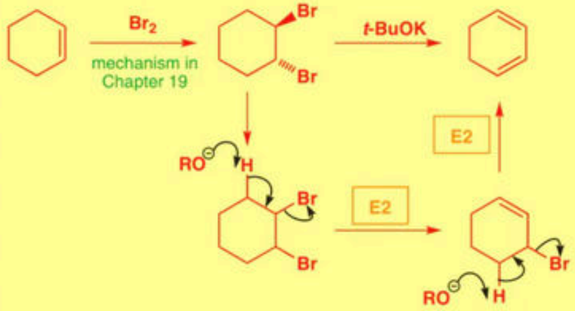
small nucleophile: substitution



large nucleophile: elimination



synthesis of a diene by a double E2 elimination



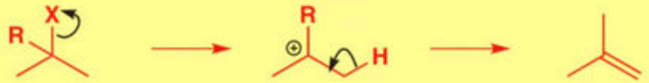
bromoacetaldehyde

'diethyl ketene acetal'

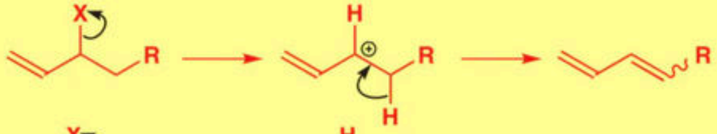
substrates that readily eliminate by E1

stabilized carbocations

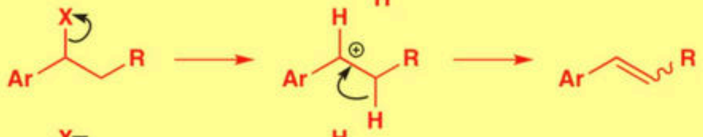
tertiary



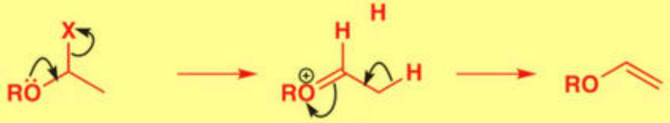
allylic



benzylic



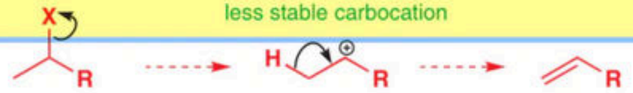
α-hetero substituted



may also eliminate by E2

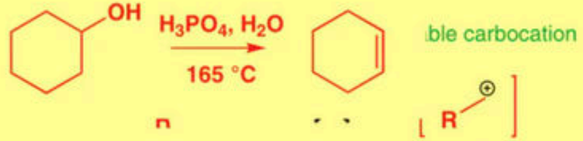
substrates that may eliminate by E1

secondary



less stable carbocation

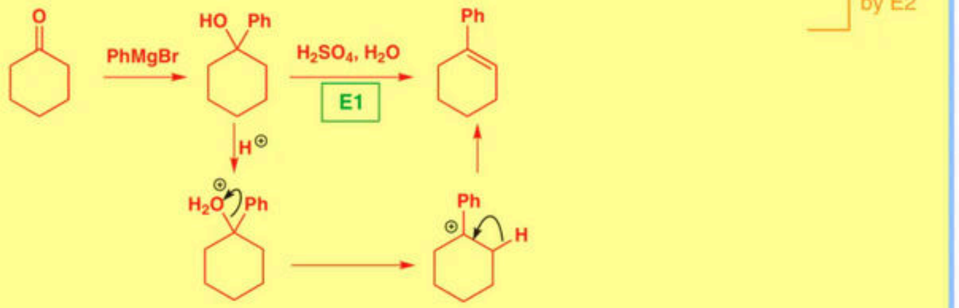
su



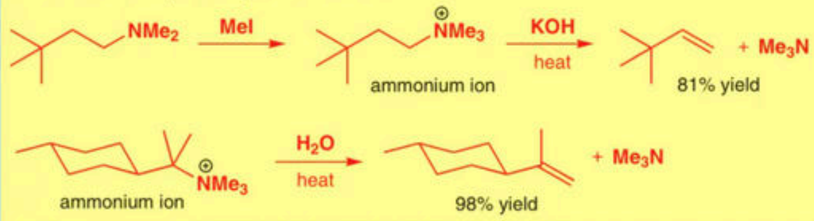
ble carbocation

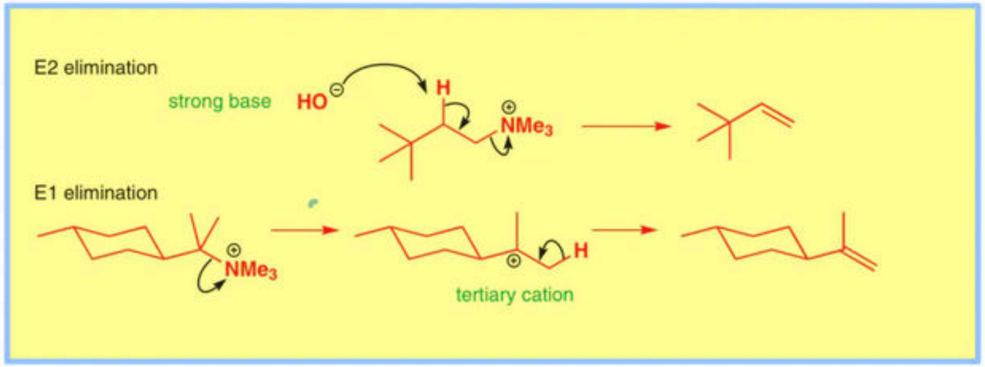
substrates that cannot eliminate by either mechanism—no appropriately placed hydrogens

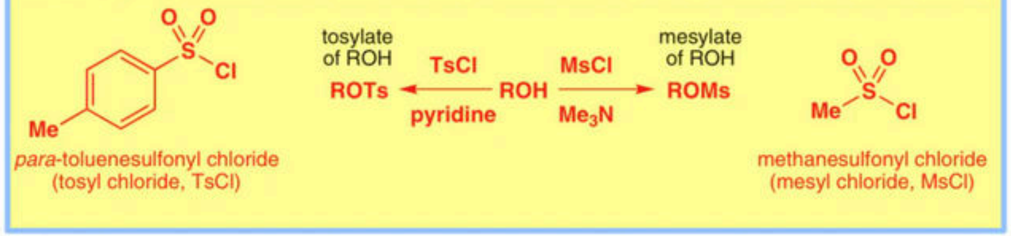
cannot eliminate by E2



eliminations from quaternary ammonium ions





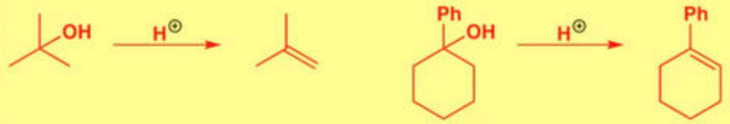


E2 eliminations of tosylates

DBU

1,8-diazabicyclo-
[5.4.0]undecene-7

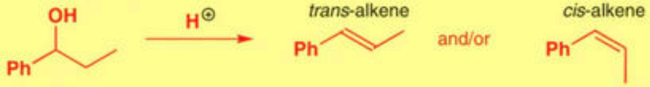
only one alkene possible



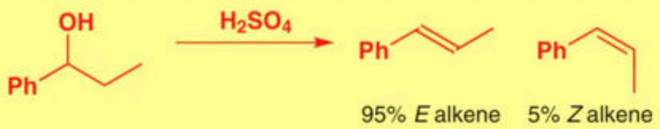
two regioisomeric alkenes possible

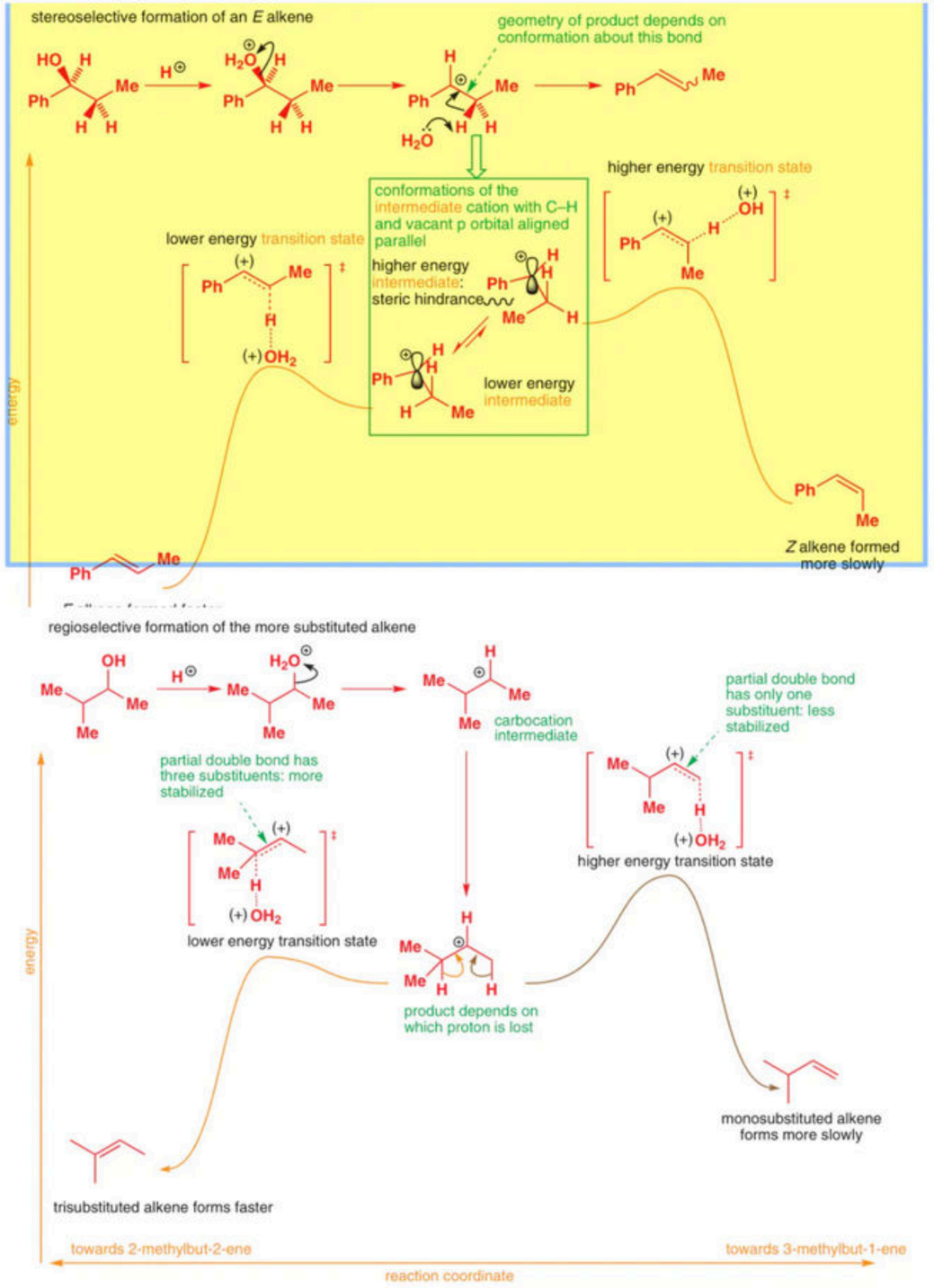
regioisomers

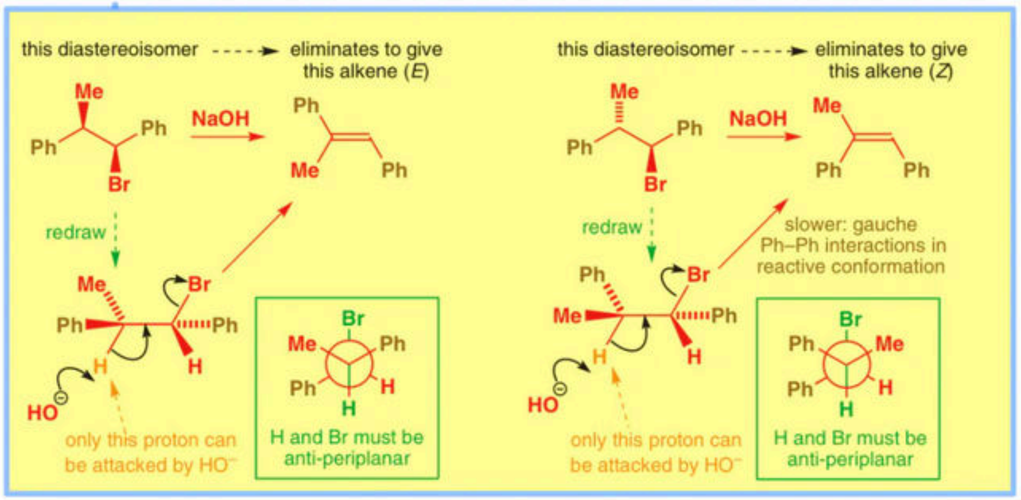
two stereoisomeric alkenes possible

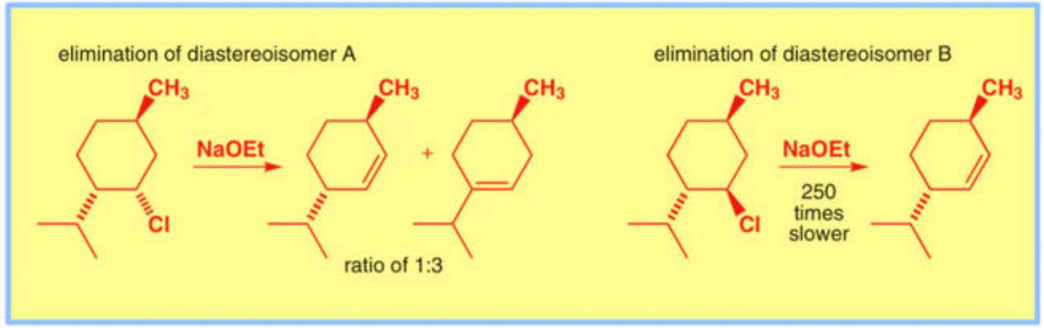


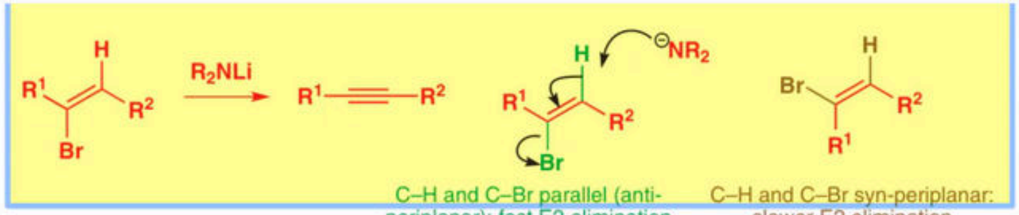
stereoisomers
(geometrical isomers)

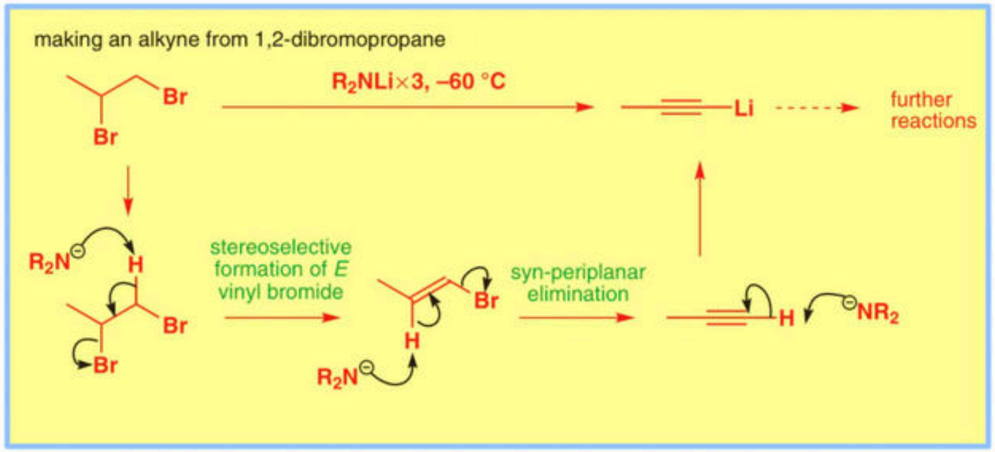

OH
Ph
H_2SO_4
Ph
Ph
95% *E* alkene
5% *Z* alkene

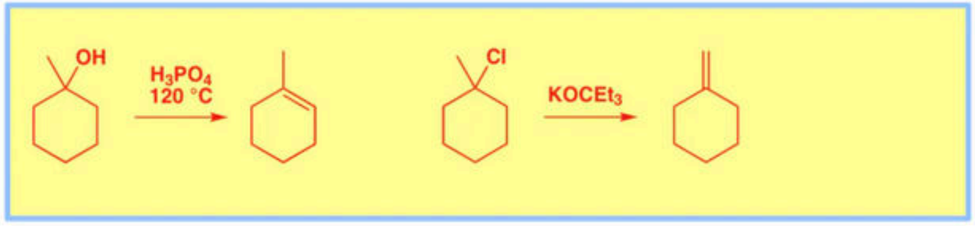

stereoselective formation of an E alkene
geometry of product depends on conformation about this bond
higher energy transition state
conformations of the intermediate cation with C–H and vacant p orbital aligned parallel
lower energy transition state
higher energy intermediate: steric hindrance
lower energy intermediate
energy
Z alkene formed more slowly
regioselective formation of the more substituted alkene
carbocation intermediate
partial double bond has only one substituent: less stabilized
partial double bond has three substituents: more stabilized
higher energy transition state
lower energy transition state
product depends on which proton is lost
monosubstituted alkene forms more slowly
trisubstituted alkene forms faster
towards 2-methylbut-2-ene
towards 3-methylbut-1-ene
reaction coordinate

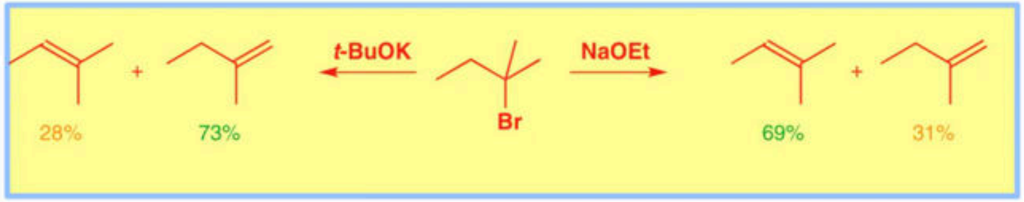

this diastereoisomer
eliminates to give this alkene (E)
NaOH
redraw
only this proton can be attacked by HO⁻
H and Br must be anti-periplanar
this diastereoisomer
eliminates to give this alkene (Z)
NaOH
redraw
slower: gauche Ph–Ph interactions in reactive conformation
only this proton can be attacked by HO⁻
H and Br must be anti-periplanar


elimination of diastereoisomer A
NaOEt
ratio of 1:3
elimination of diastereoisomer B
NaOEt
250 times slower

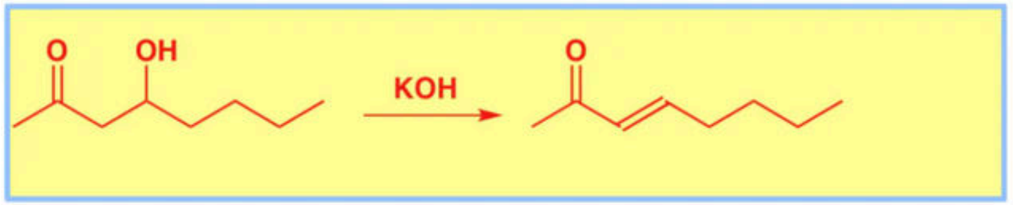

R2NLi
C–H and C–Br parallel (anti-periplanar): fast E2 elimination
C–H and C–Br syn-periplanar: slower E2 elimination

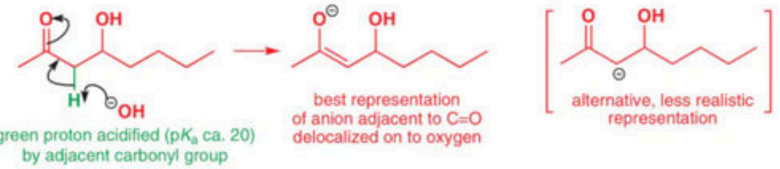

making an alkyne from 1,2-dibromopropane
R2NLi×3, –60 °C
further reactions
stereoselective formation of E vinyl bromide
syn-periplanar elimination

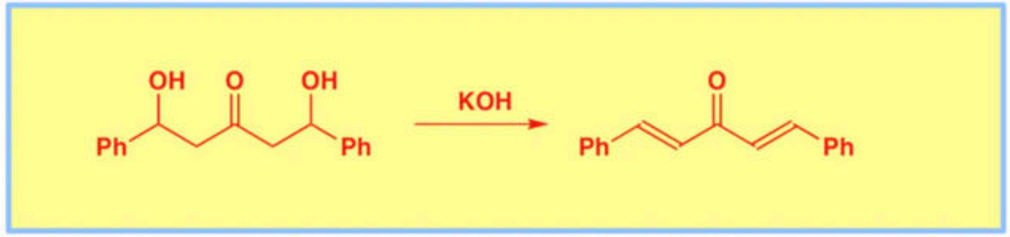

H3PO4
120 °C
KOCEt3

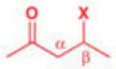

t-BuOK
NaOEt
28%
73%
69%
31%

-E1cB







		Poor nucleophile (e.g. H_2O, ROH)	Weakly basic nucleophile (e.g. I^-, RS^-)	Strongly basic, unhindered nucleophile (e.g. RO^-)	Strongly basic, hindered nucleophile (e.g. DBU, t-BuO^-)
methyl	H_3C-X	no reaction	S_N2	S_N2	S_N2
primary (unhindered)		no reaction	S_N2	S_N2	E2
primary (hindered)		no reaction	S_N2	E2	E2
secondary		S_N1, E1 (slow)	S_N2	E2	E2
tertiary		E1 or S_N1	S_N1, E1	E2	E2
β to anion-stabilizing group		E1cB	E1cB	E1cB	E1cB