



# Emerge - Clayden Nucleophilic Substitution Reactions

Special class

Ashish Mishra • Apr 14, 2022



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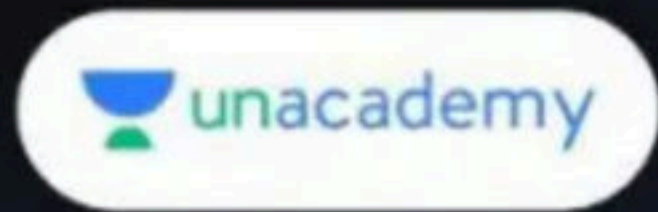
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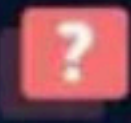
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Questions

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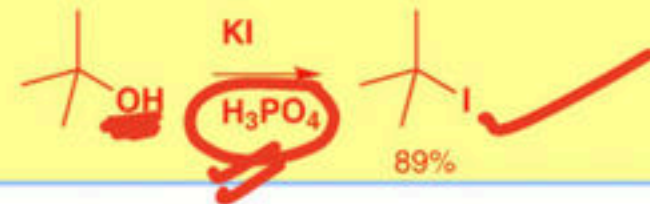
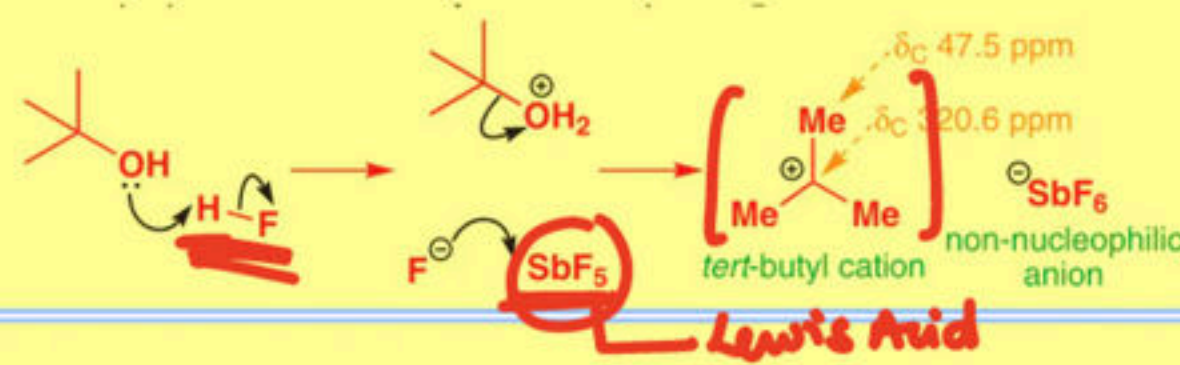
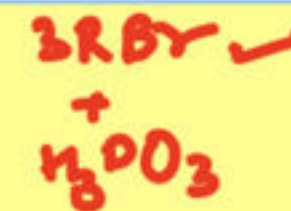
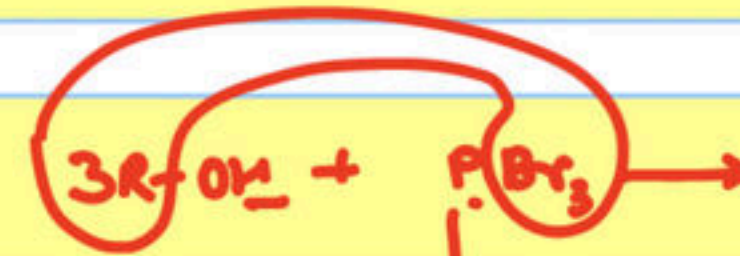


# Clayden Nucleophilic substitutions

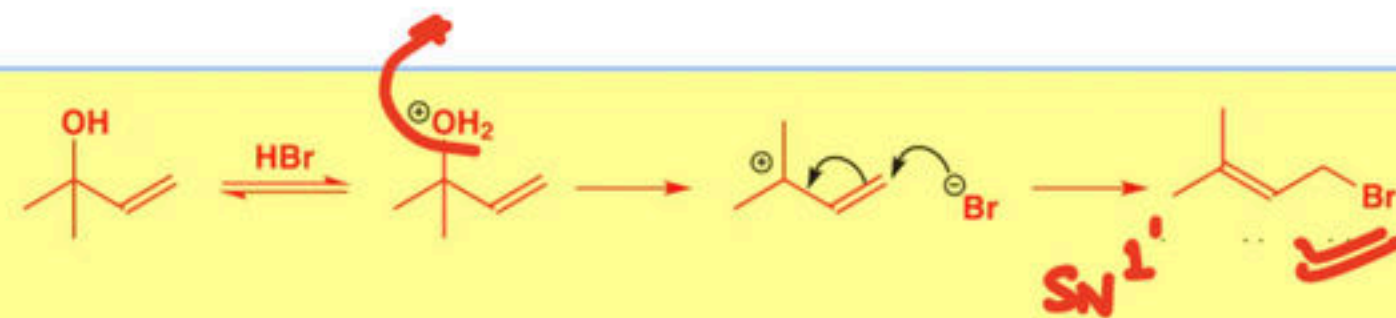
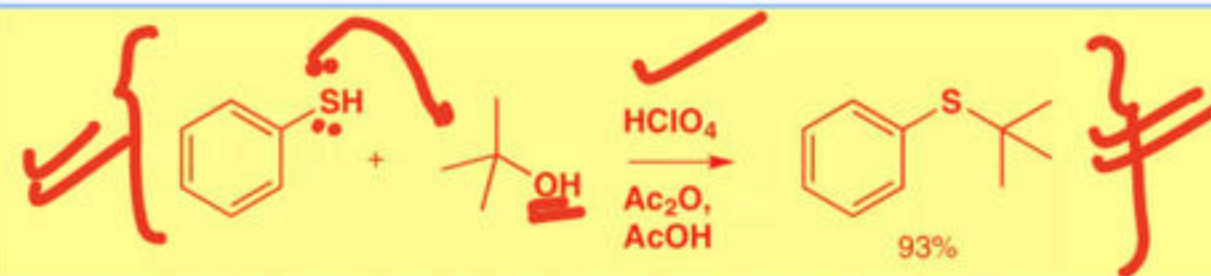
# Nucleophilic substitution at saturated carbon



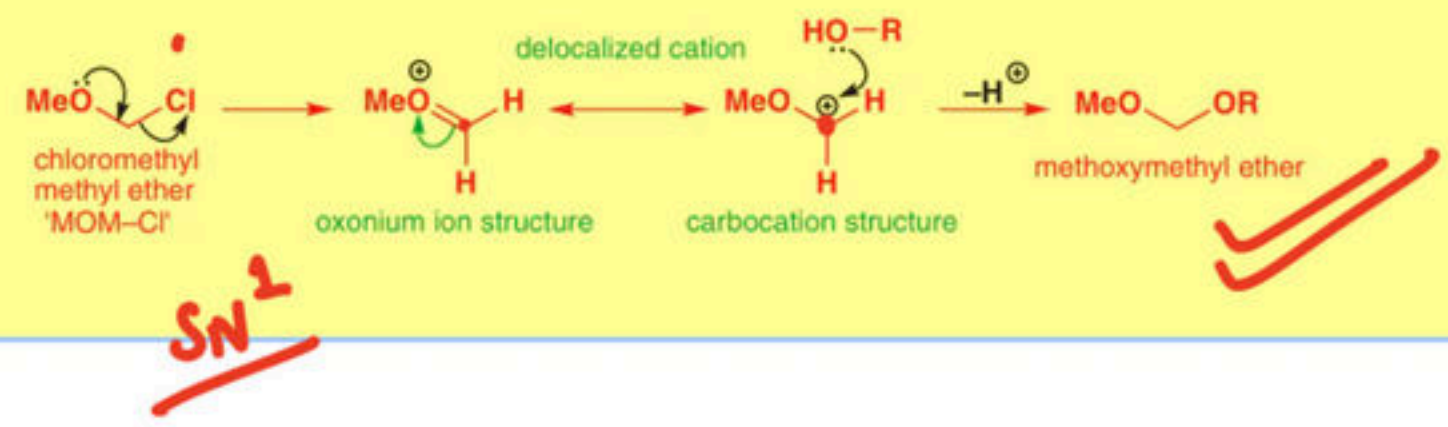
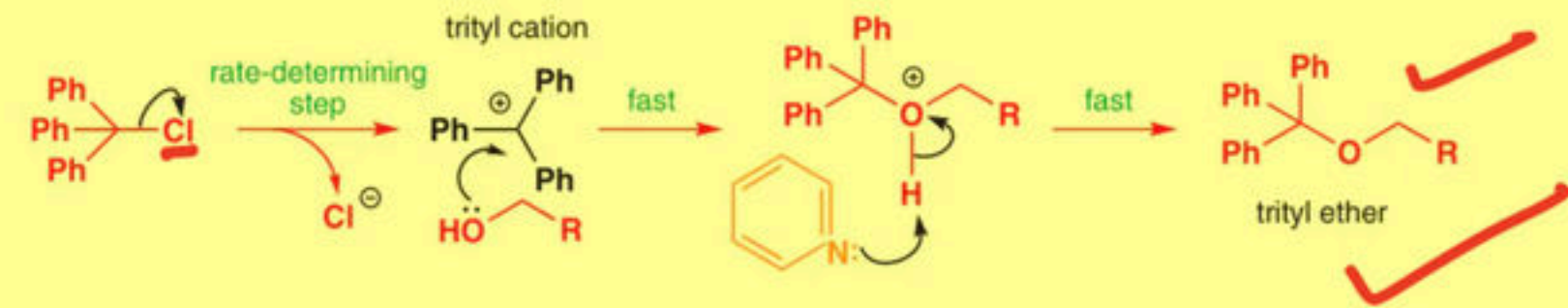
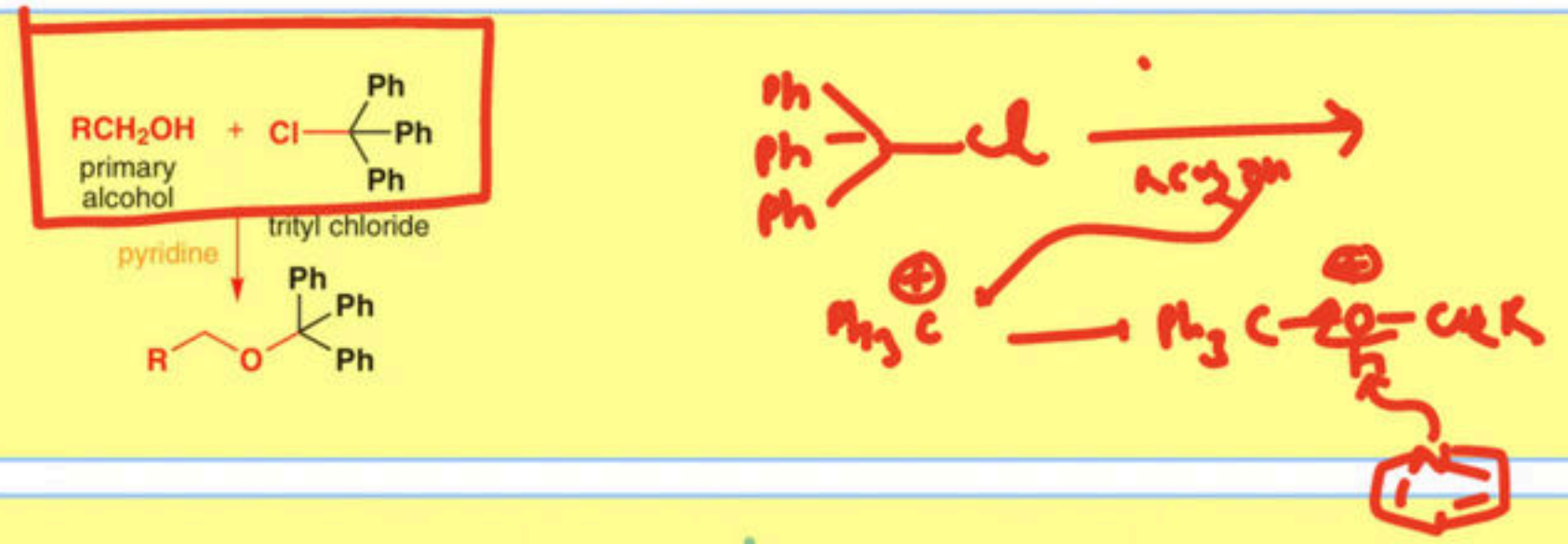
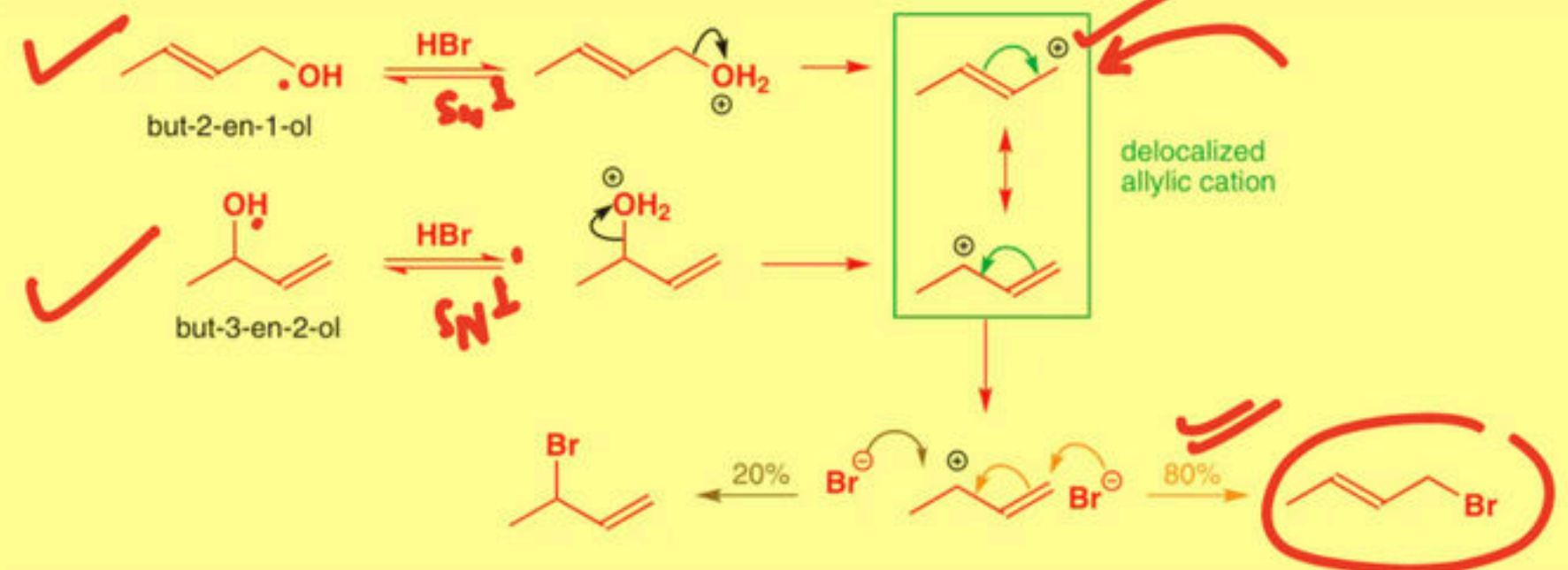
$\text{S}_{\text{N}}1$




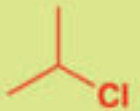



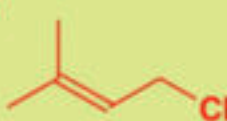

$\text{H}^{\ominus}$

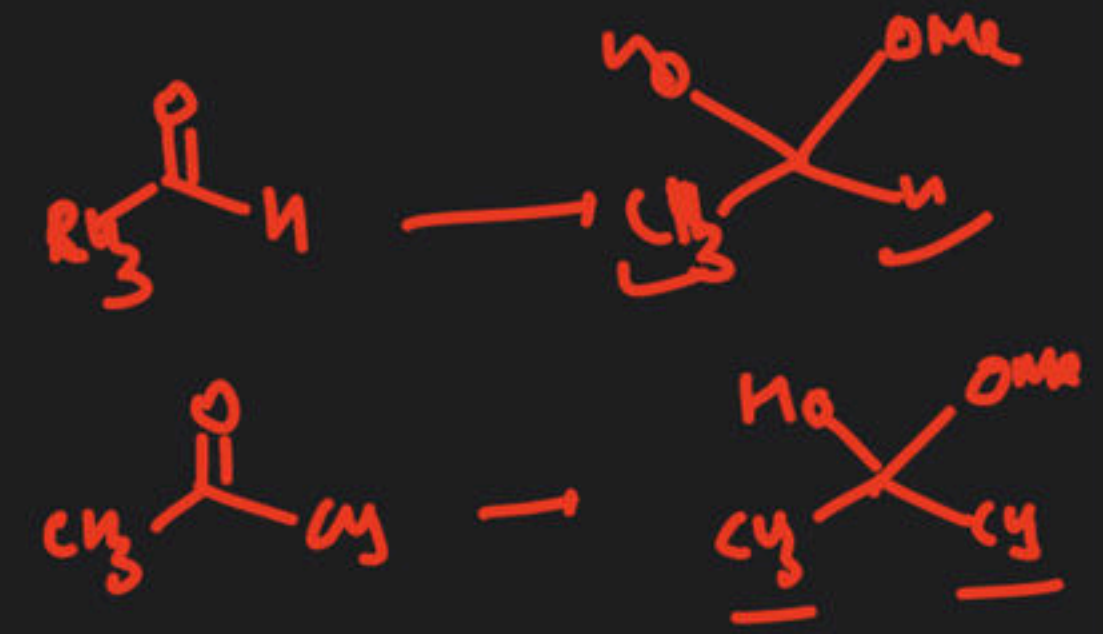
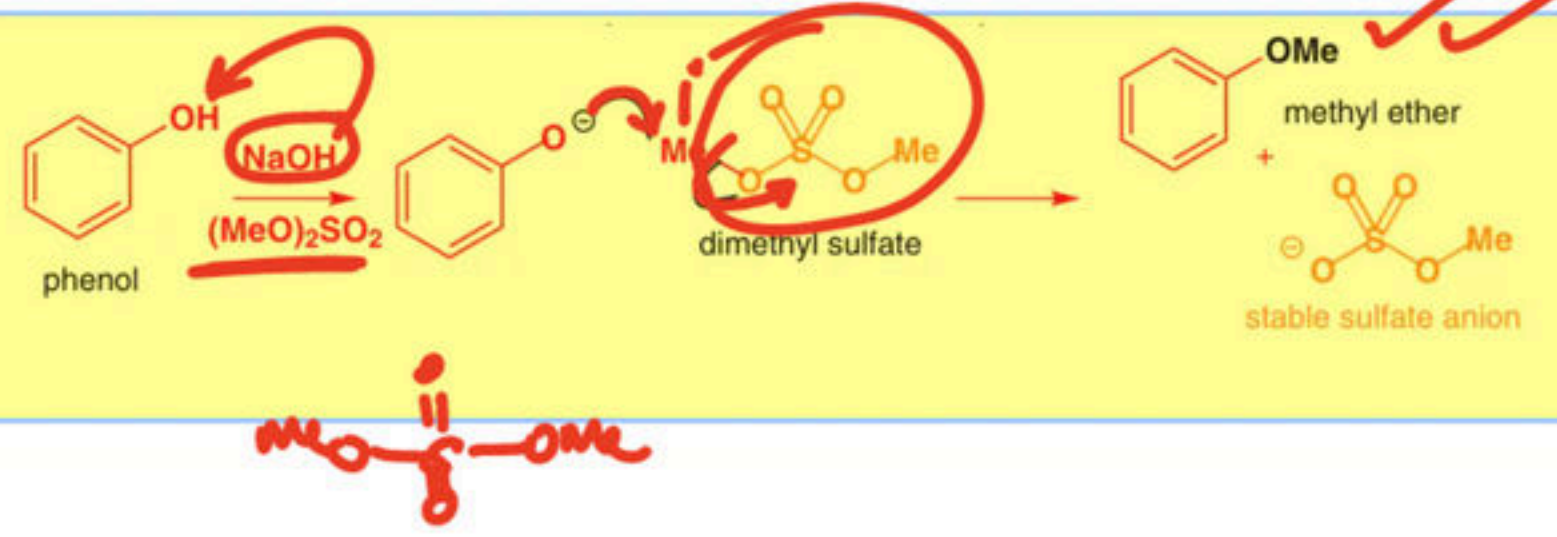
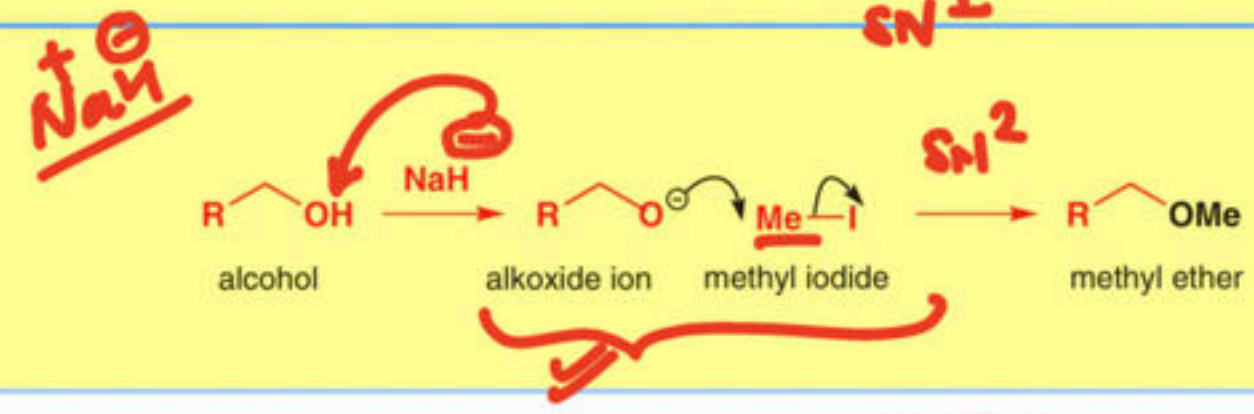
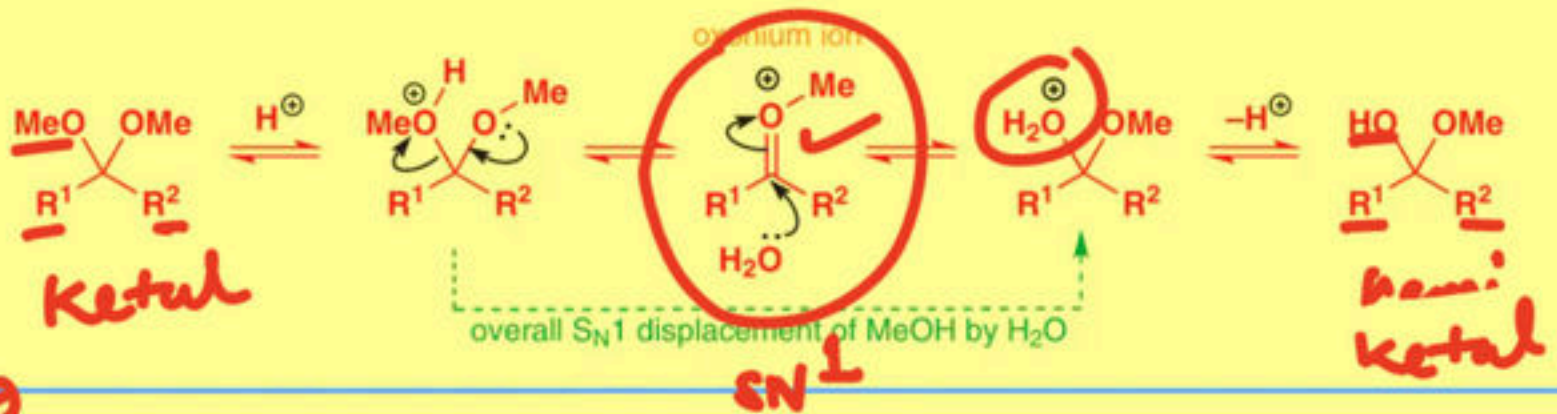


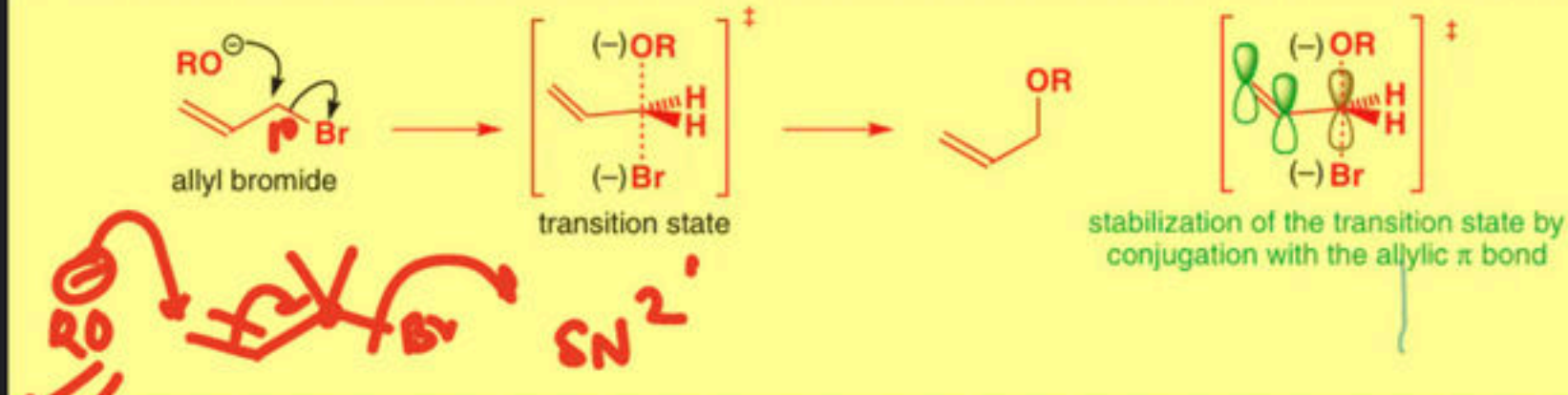
$\text{H}^{\ominus}$   
 $\text{HI}$   
 $(\text{p}K_{\text{a}} = -10)$



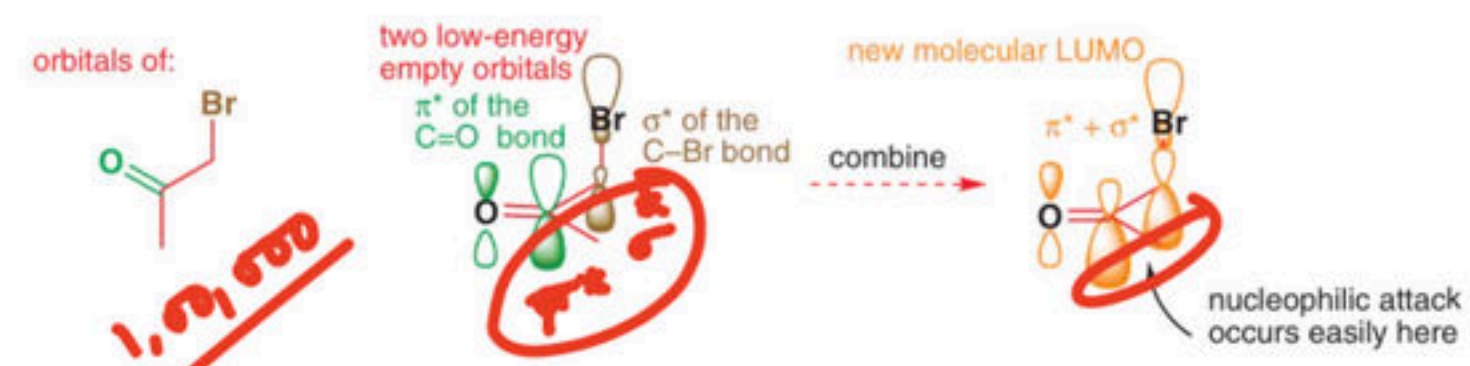
Rates of solvolysis of alkyl chlorides in 50% aqueous ethanol at 44.6 °C

Compound	Relative rate	Comments
	0.07	primary chloride: probably all S <sub>N</sub> 2
	0.12	secondary chloride: can do S <sub>N</sub> 1 but not very well
	2100	tertiary chloride: very good at S <sub>N</sub> 1
	1.0	primary but allylic: S <sub>N</sub> 1 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

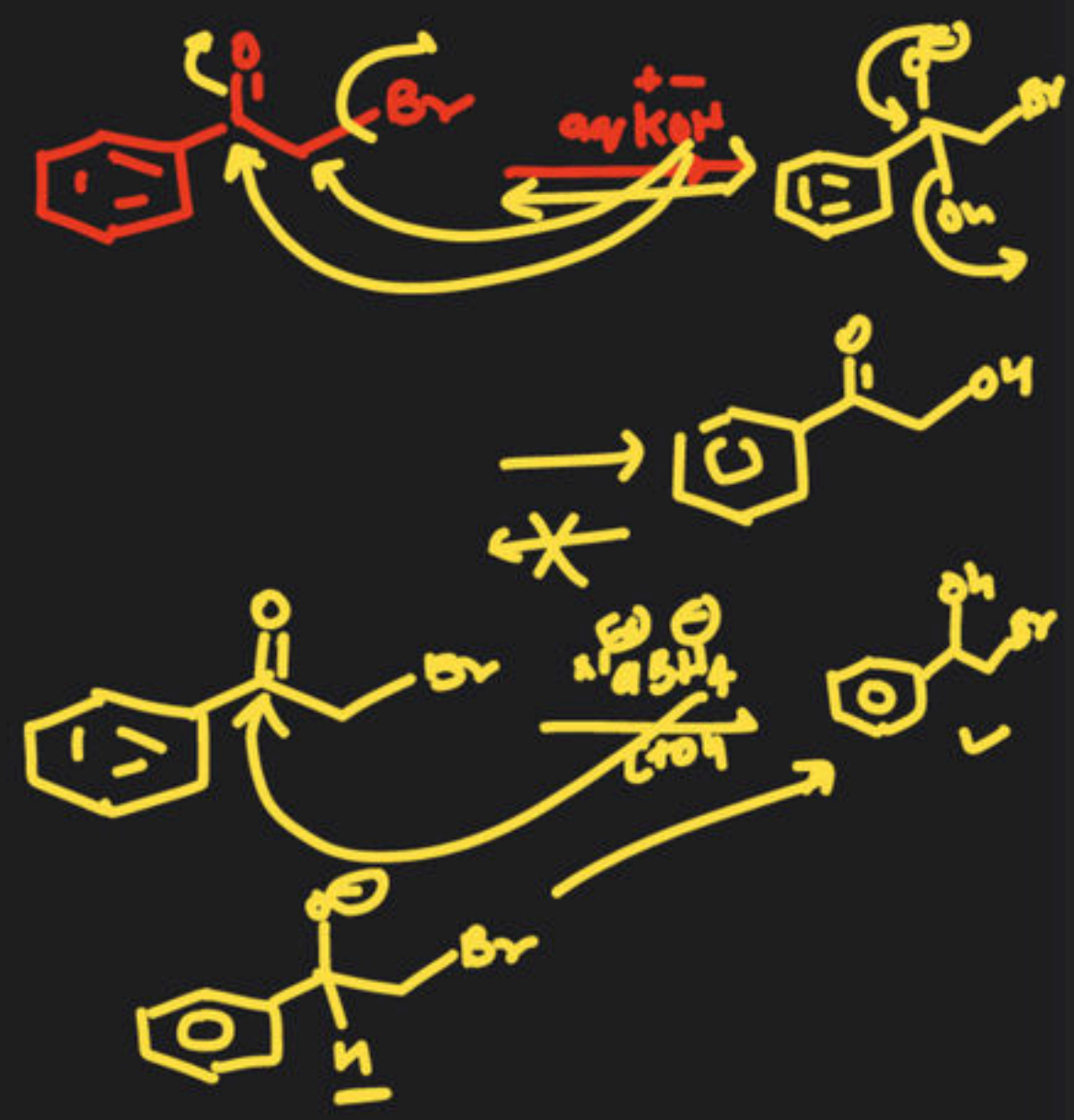
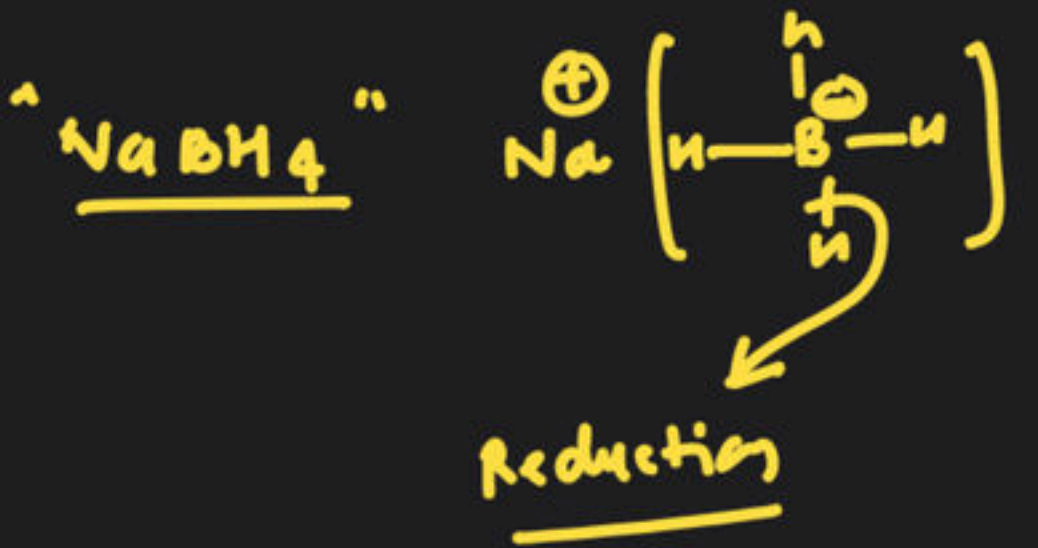
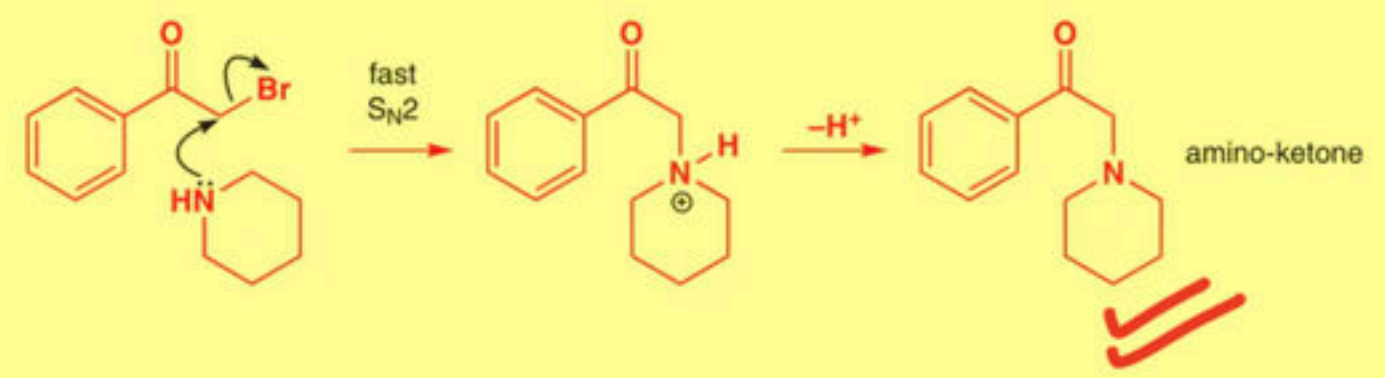




Among the fastest of all  $S_N2$  reactions are those where the leaving group is adjacent to a carbonyl group. With  $\alpha$ -bromo carbonyl compounds, two neighbouring carbon atoms are both powerfully electrophilic sites. Each has a low-energy empty orbital— $\pi^*$  from C=O and  $\sigma^*$  from C-Br (this is what makes them electrophilic)—and these can combine to form a new LUMO ( $\pi^* + \sigma^*$ ) 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.

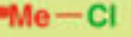


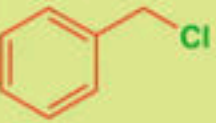

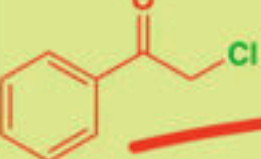


### Quantifying structural effects on S<sub>N</sub>2 reactions

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<sub>N</sub>2 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
 Me-Cl	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 <sub>N</sub> 1 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



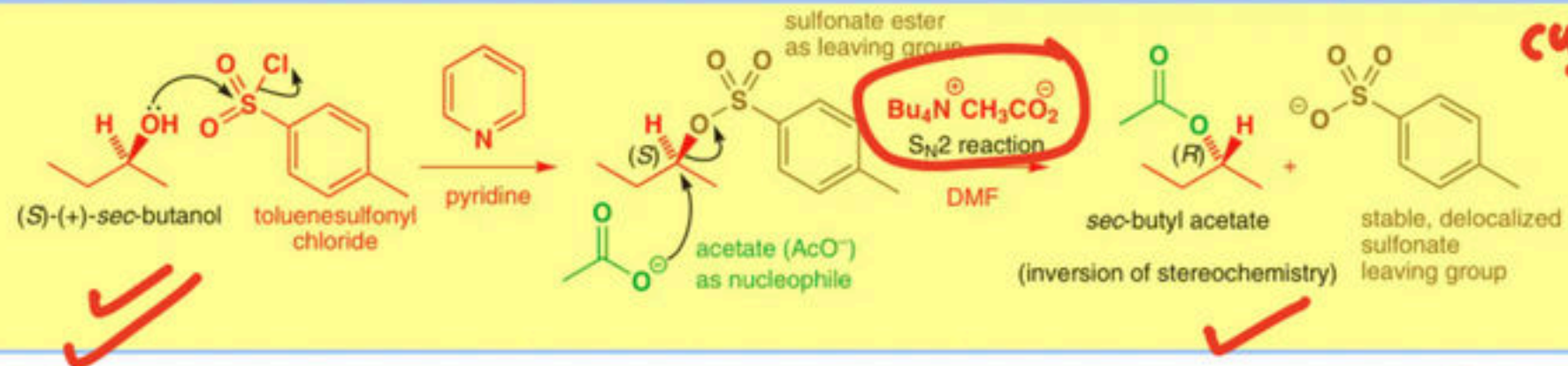
neopentyl chloride

no S<sub>N</sub>1;  
slow S<sub>N</sub>2  
due to hindrance

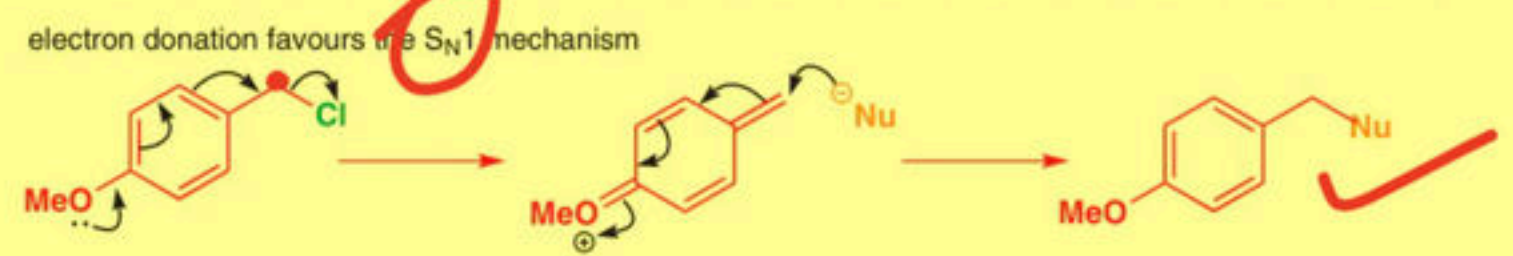
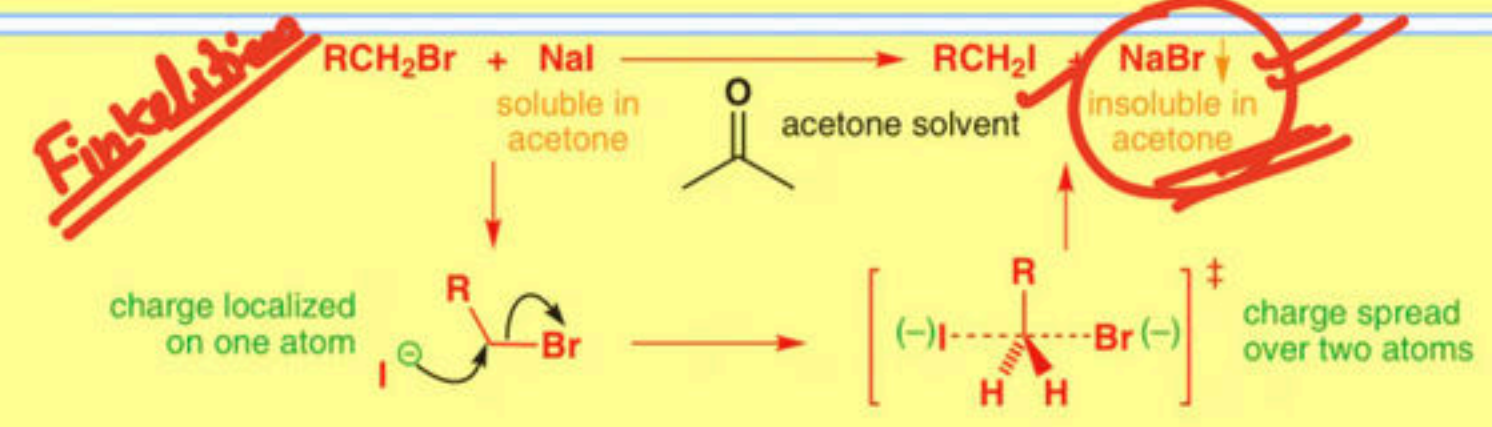
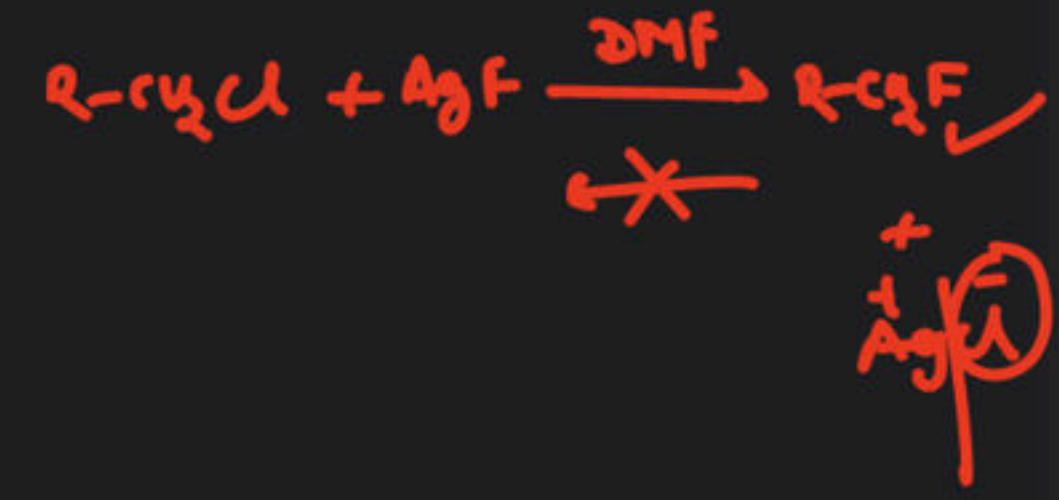
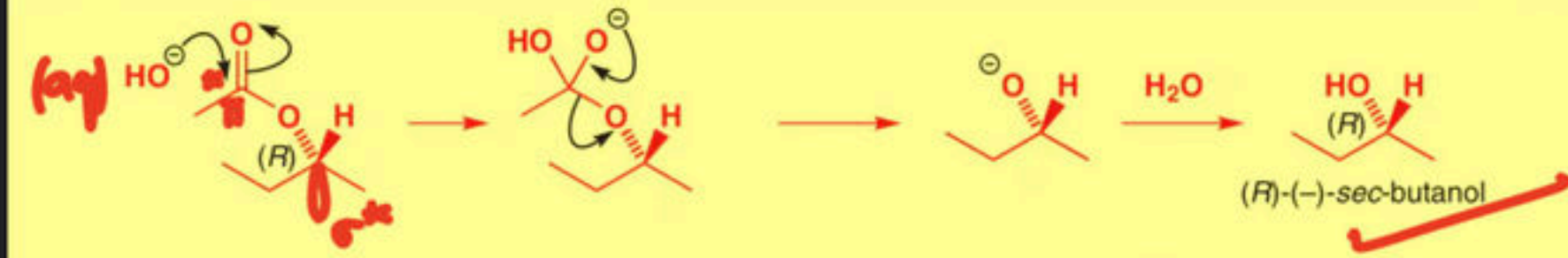


tertiary and adjacent to C=O

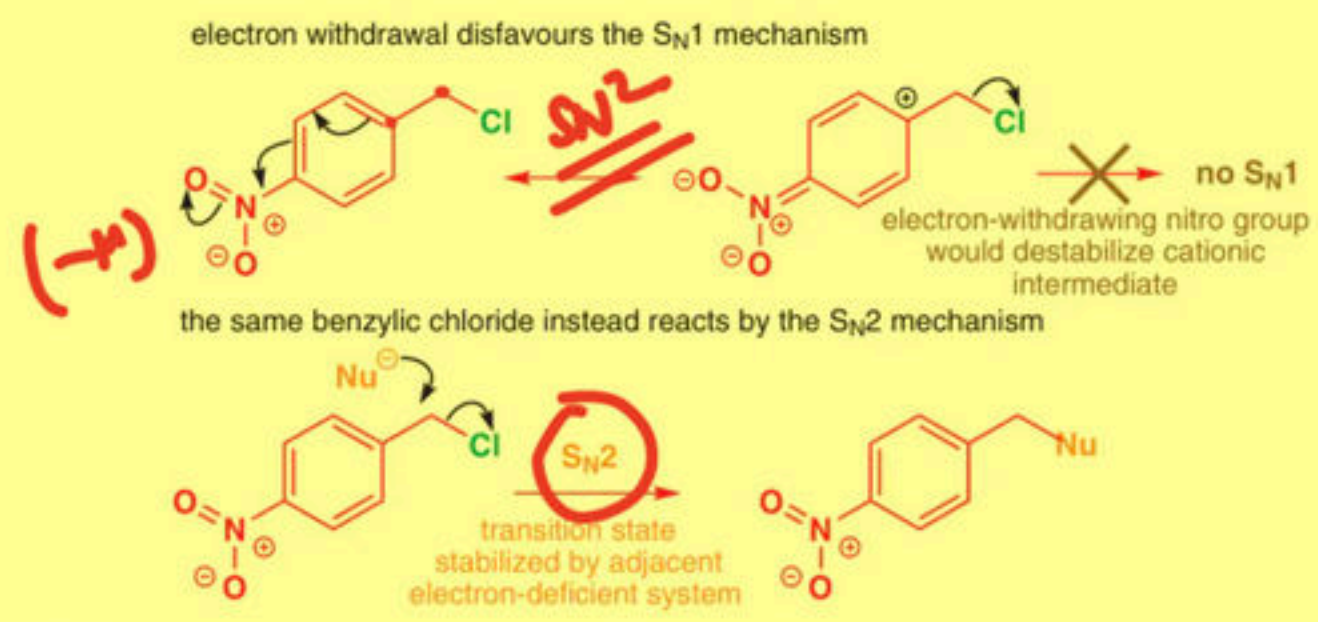
v. slow S<sub>N</sub>1;  
reacts slowly  
by S<sub>N</sub>2



cyano<sup>-</sup>



On the other hand, an electron-withdrawing group, such as a nitro group, within the benzylic compound will decrease the rate of the S<sub>N</sub>1 reaction and allow the S<sub>N</sub>2 mechanism to take over.

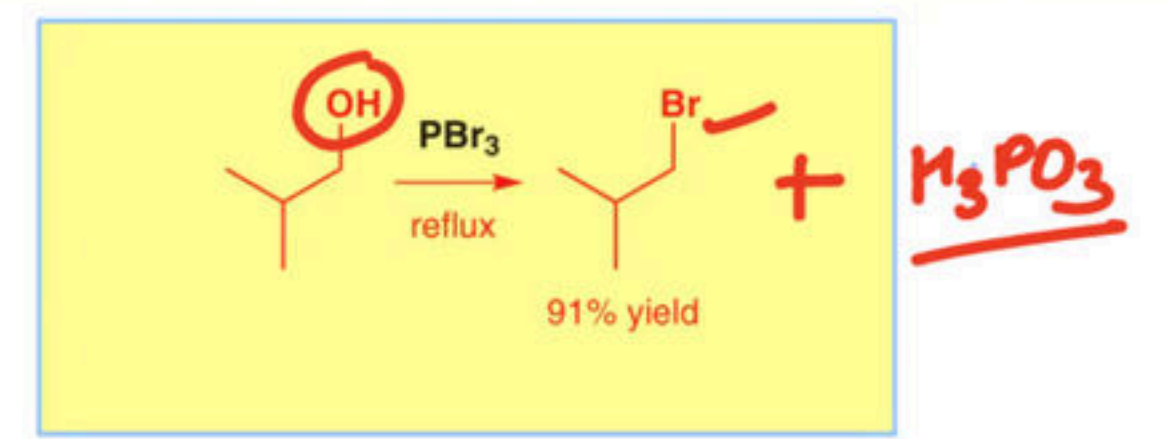
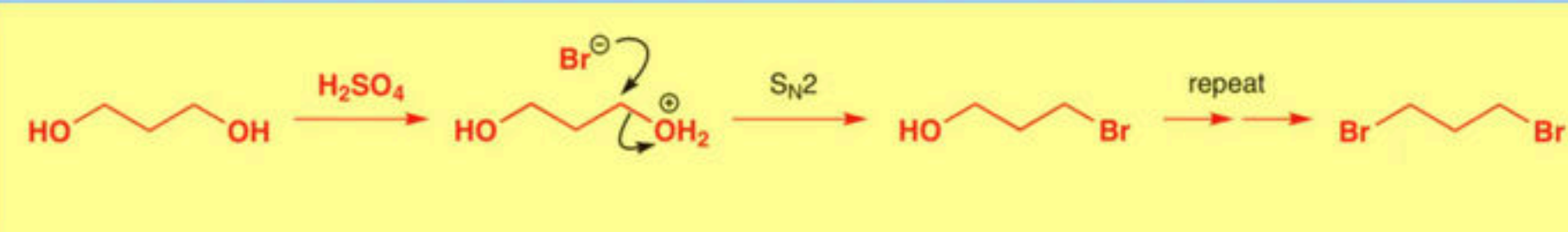


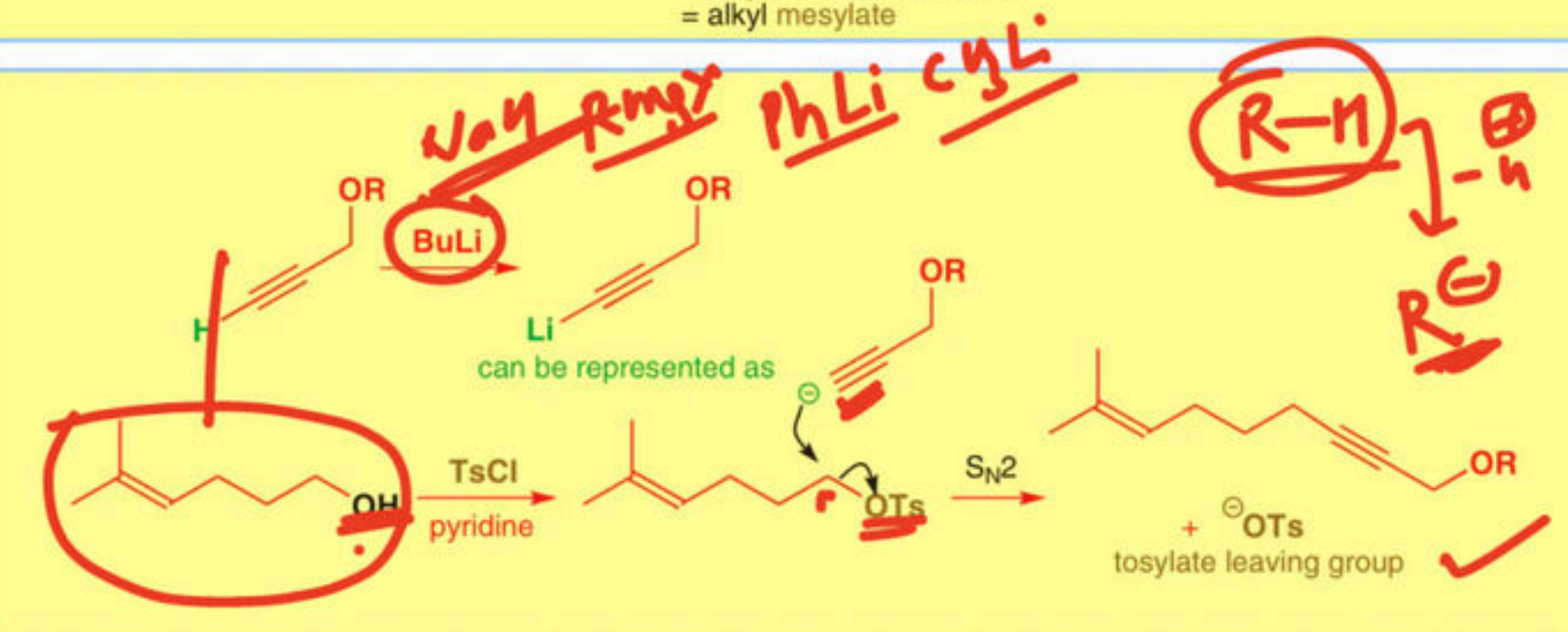
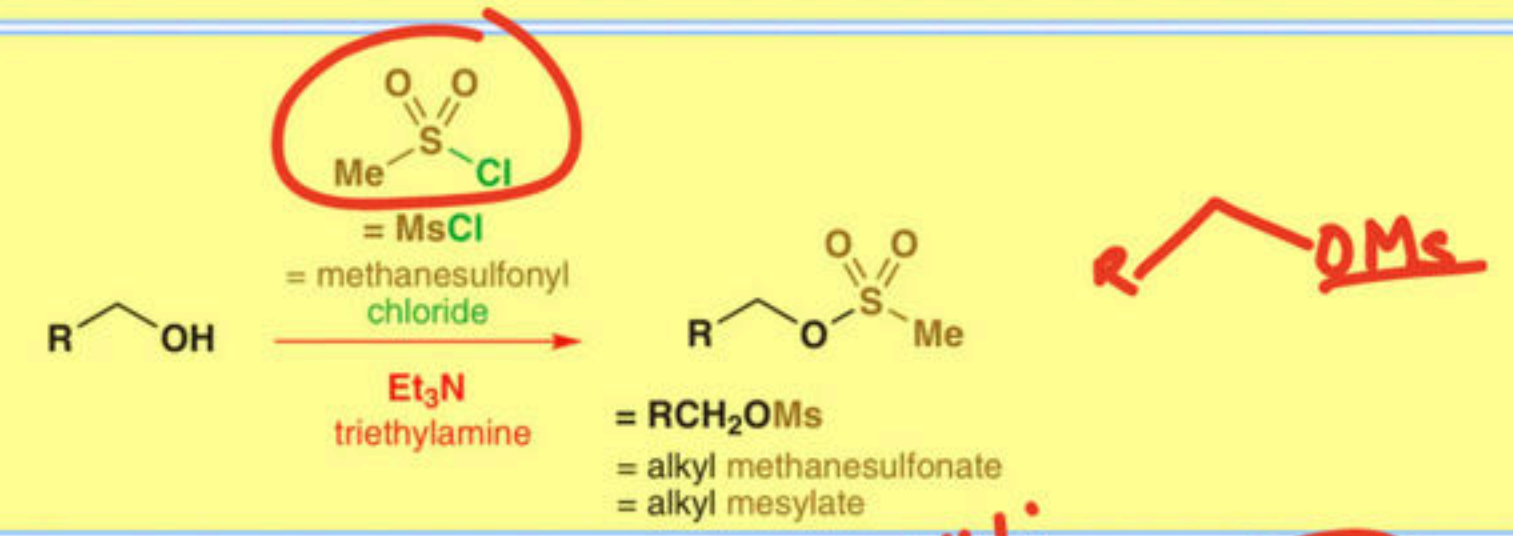
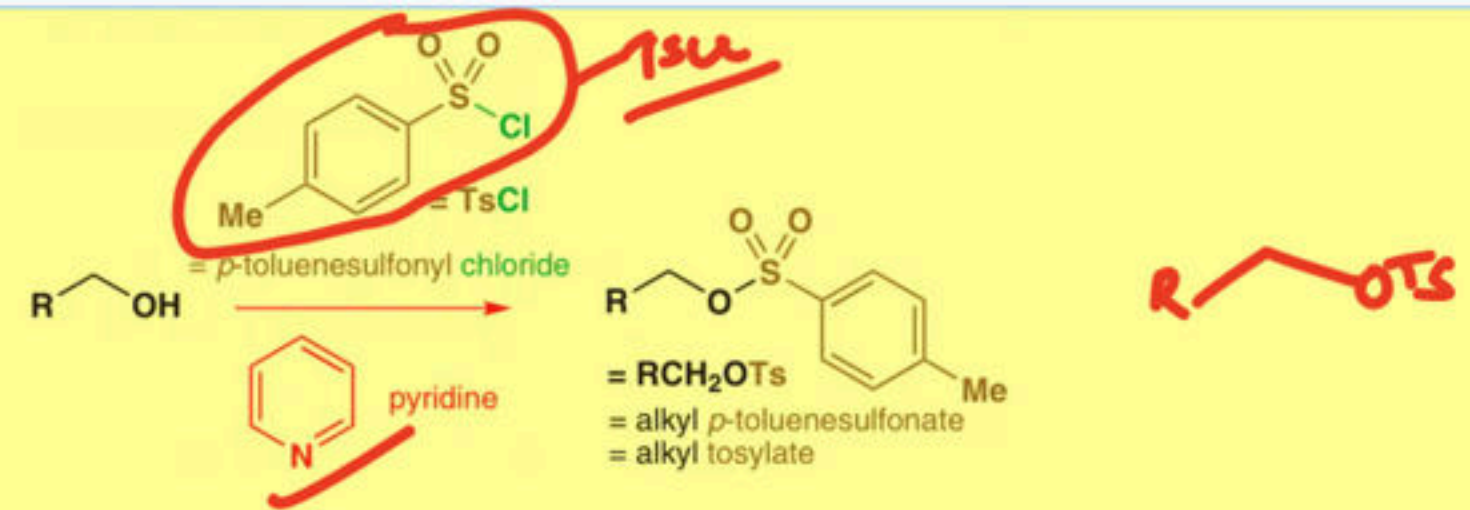


Electrophile	Me-X				
	methyl	primary	secondary	tertiary	'neopentyl'
- S <sub>N</sub> 1 mechanism?	bad	bad	poor	excellent	bad
- S <sub>N</sub> 2 mechanism?	excellent	good	poor	bad	bad

Electrophile					
	allylic	benzylic	α-alkoxy (adj. lone pair)	α-carbonyl	α-tertiary carbonyl and tertiary
S <sub>N</sub> 1 mechanism?	good	good	good	bad	bad
S <sub>N</sub> 2 mechanism?	good	good	okay but S <sub>N</sub> 1 better	excellent	possible

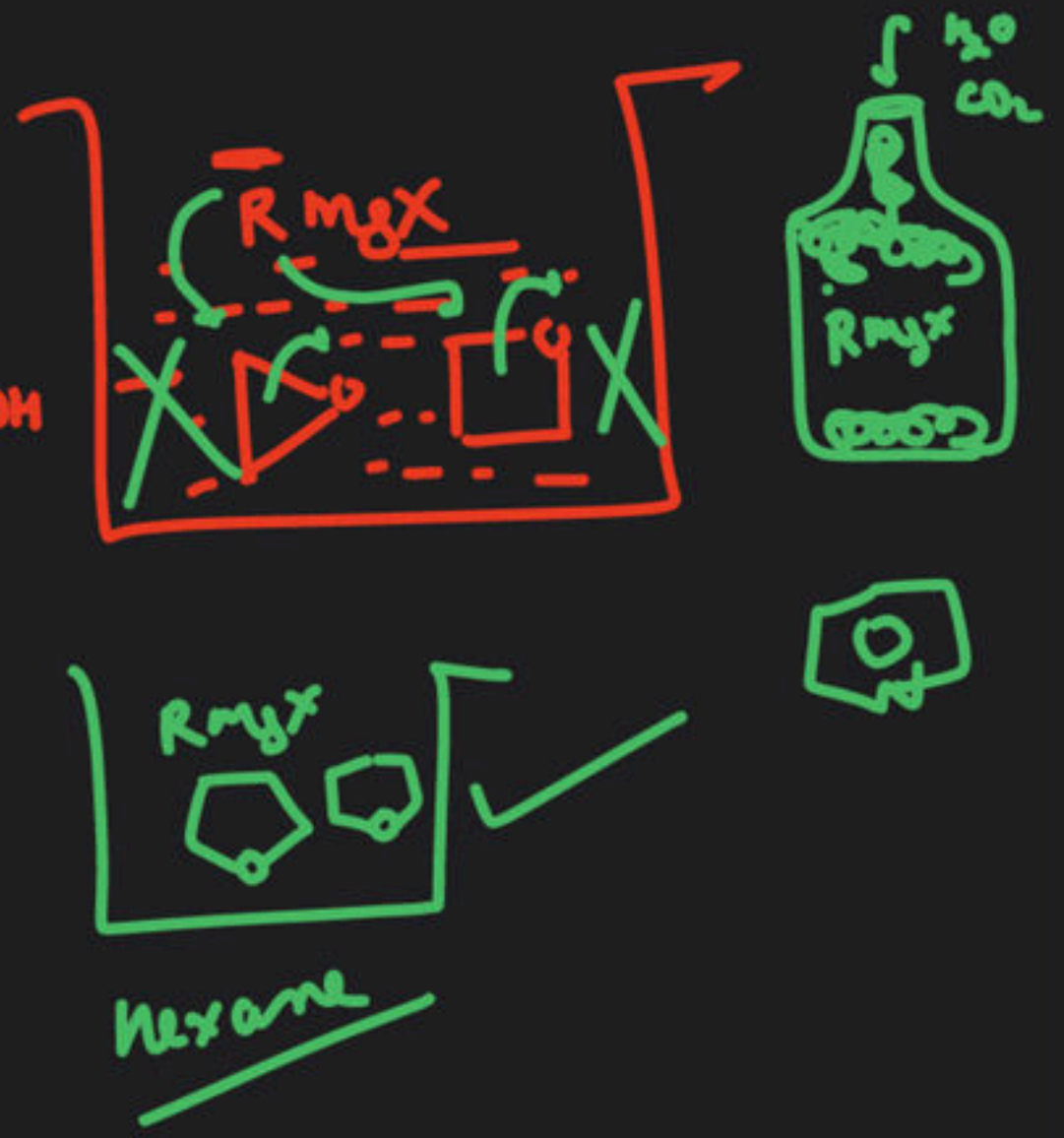
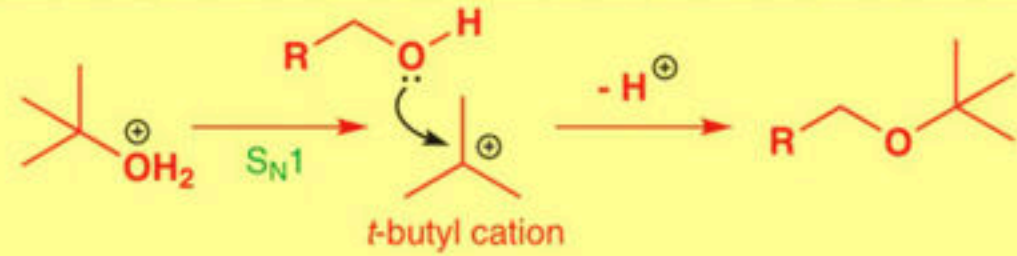
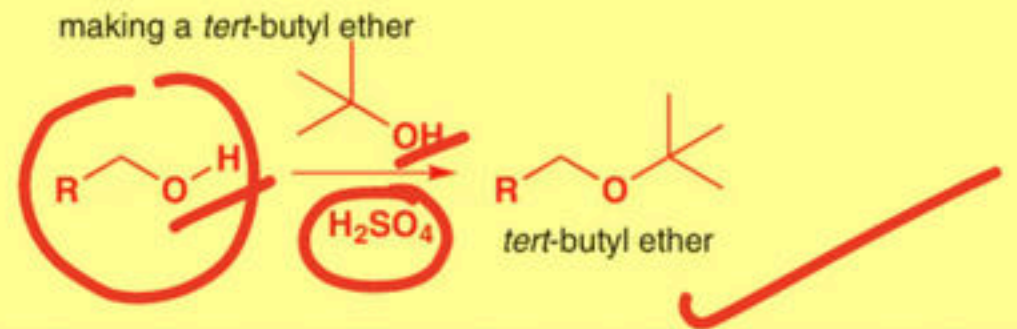
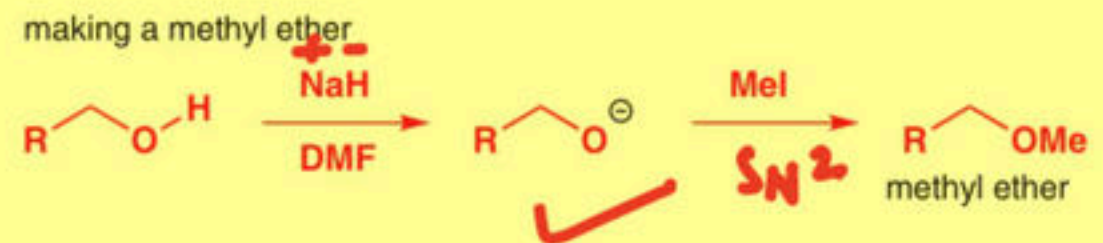
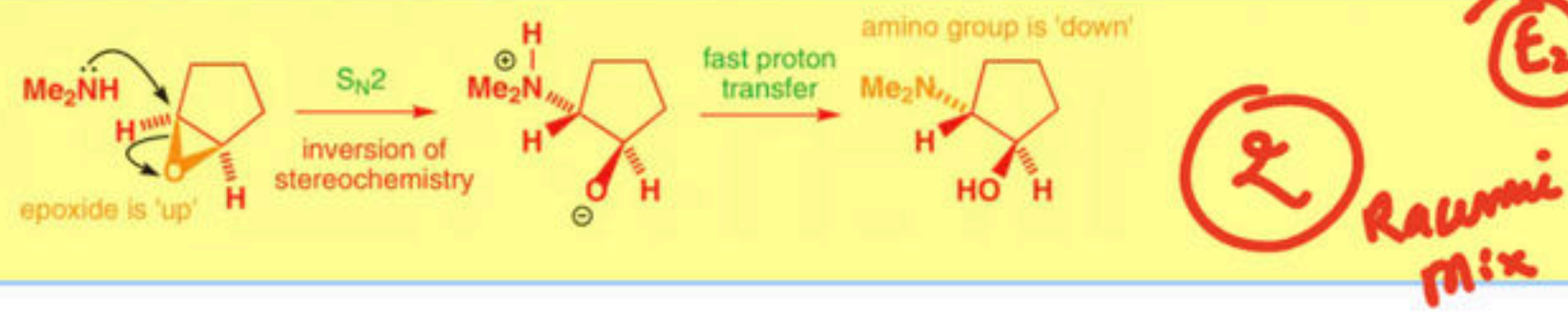
1, 2, 3, 4, 5, 6, 7, 8, 9, 10





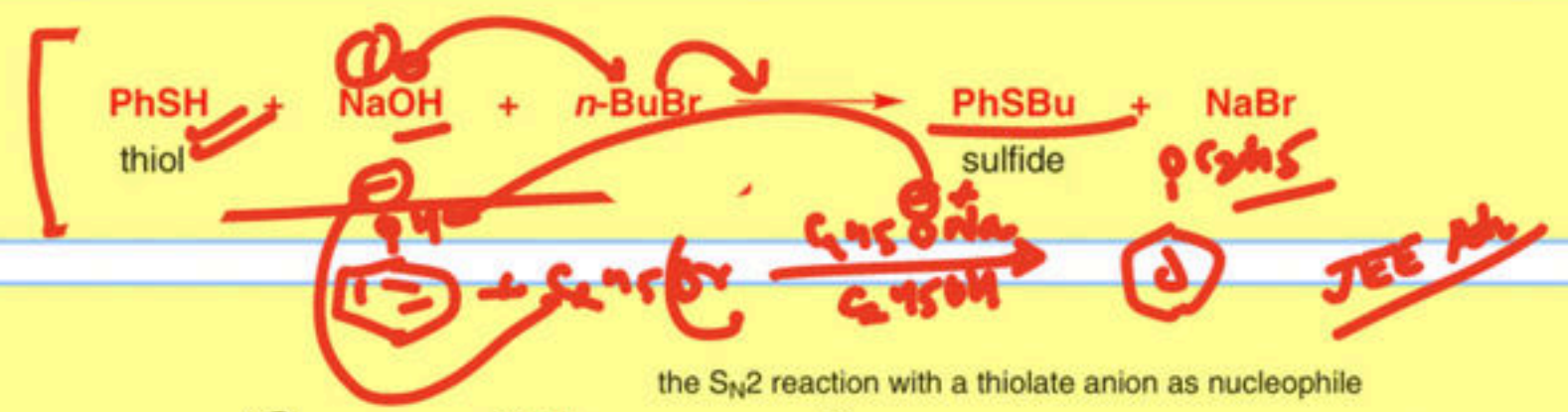
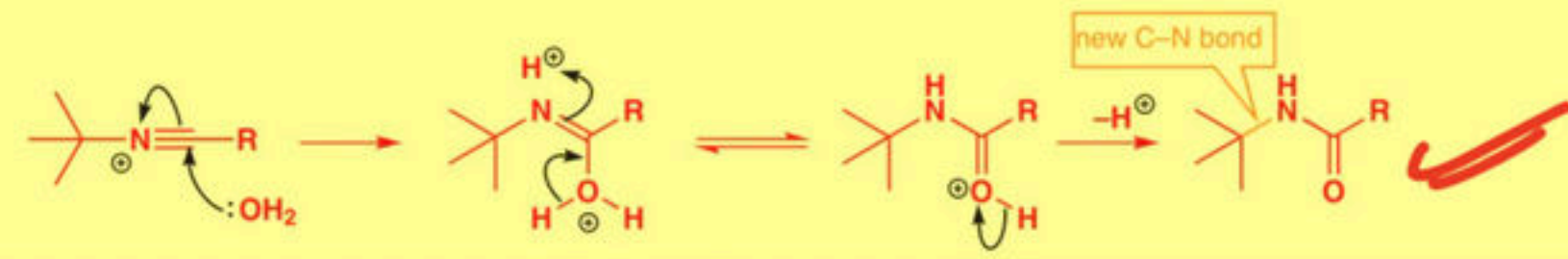
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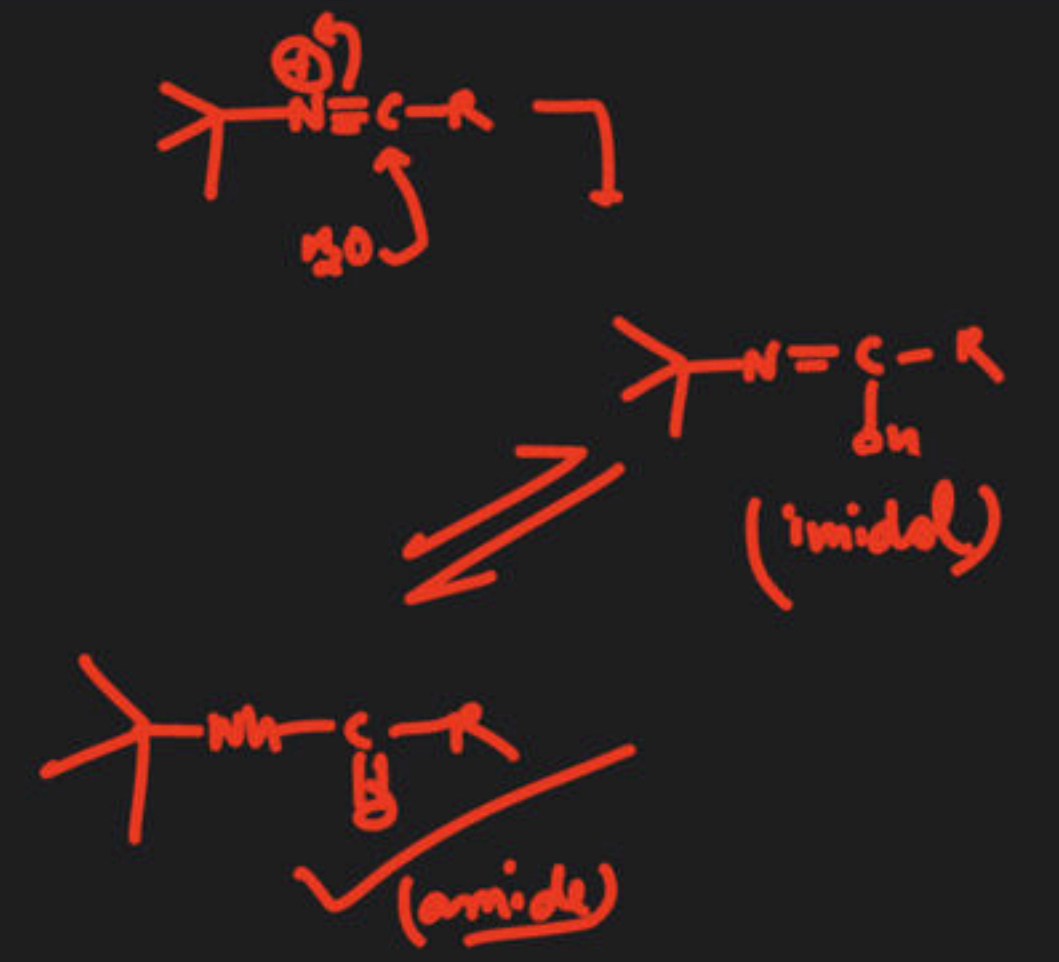
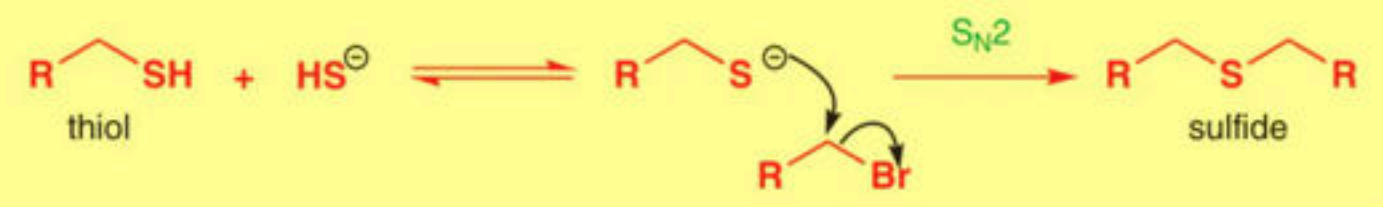




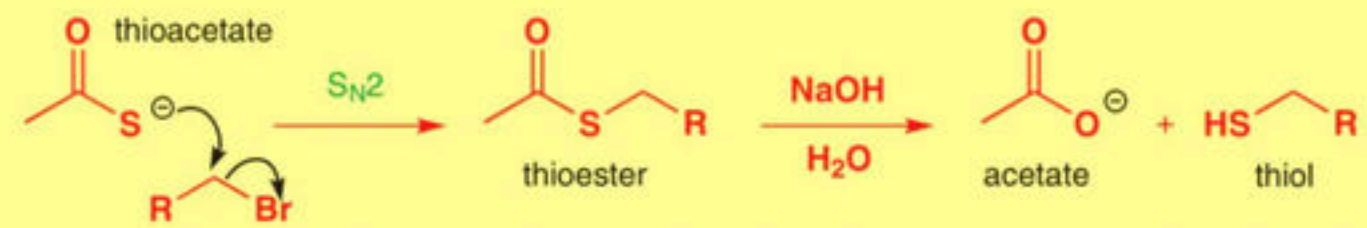
The resulting cation is captured by the water molecule released in the first step and an exchange of protons leads to a secondary amide. The overall process is called the Ritter reaction and it is one of the few reliable ways to make a C-N bond to a tertiary centre.



9:15 7:15







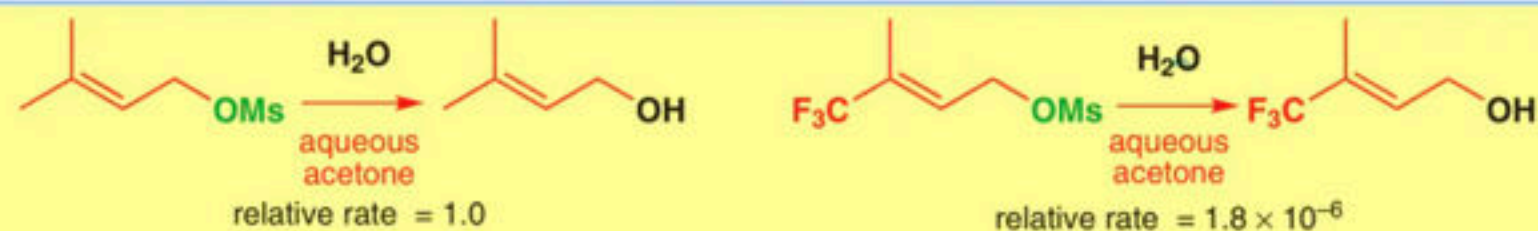
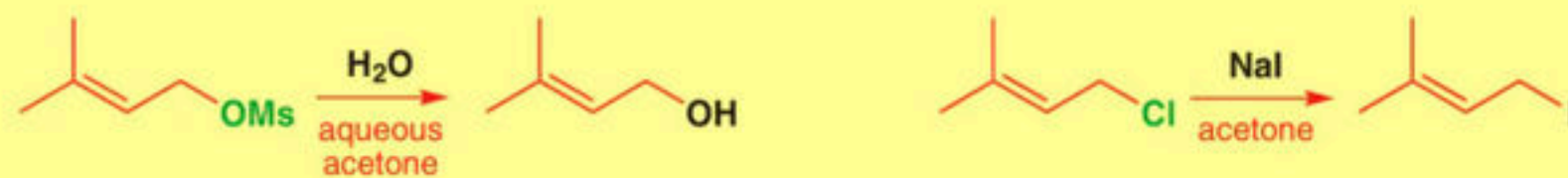
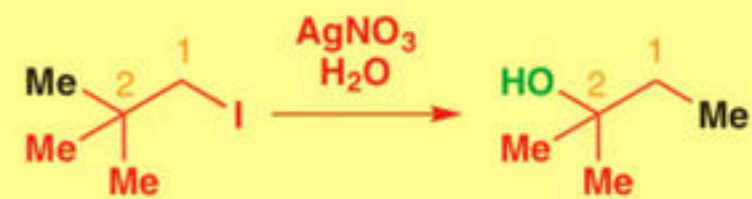
### Nucleophiles in substitution reactions

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

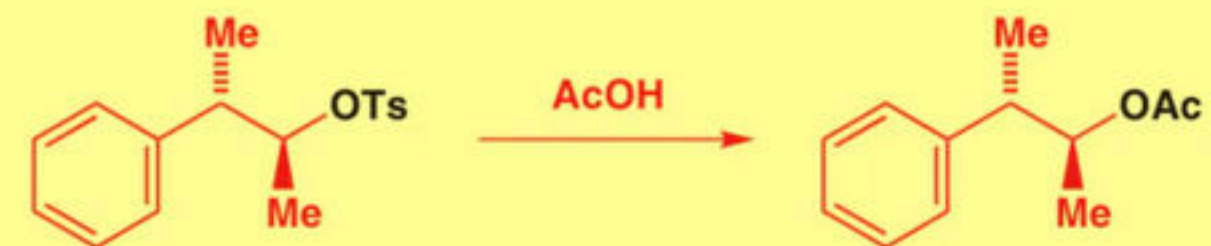
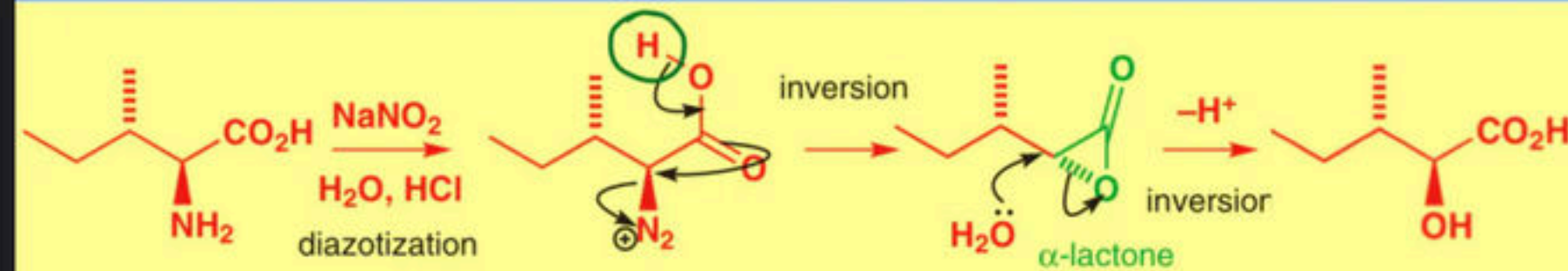
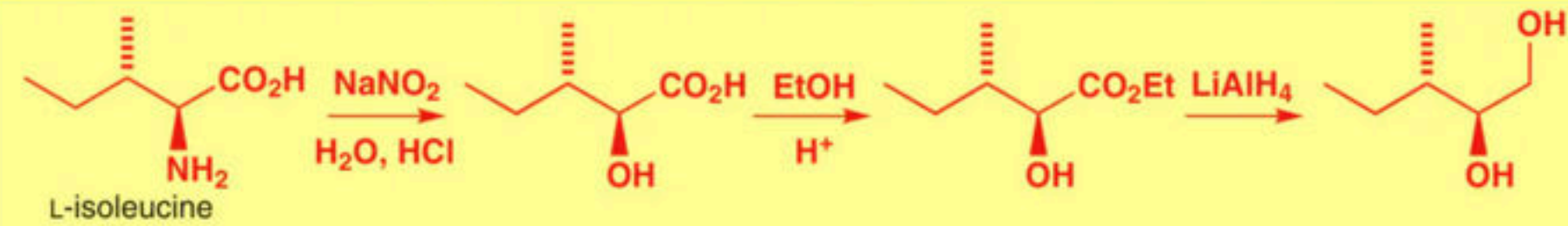
nucleophile	F <sup>-</sup>	H <sub>2</sub> O	Cl <sup>-</sup>	Et <sub>3</sub> N	Br <sup>-</sup>	PhO <sup>-</sup>	EtO <sup>-</sup>	I <sup>-</sup>	PhS <sup>-</sup>
relative rate	0.0	1.0	1100	1400	5000	2.0 × 10 <sup>3</sup>	6 × 10 <sup>4</sup>	1.2 × 10 <sup>5</sup>	5.0 × 10 <sup>7</sup>



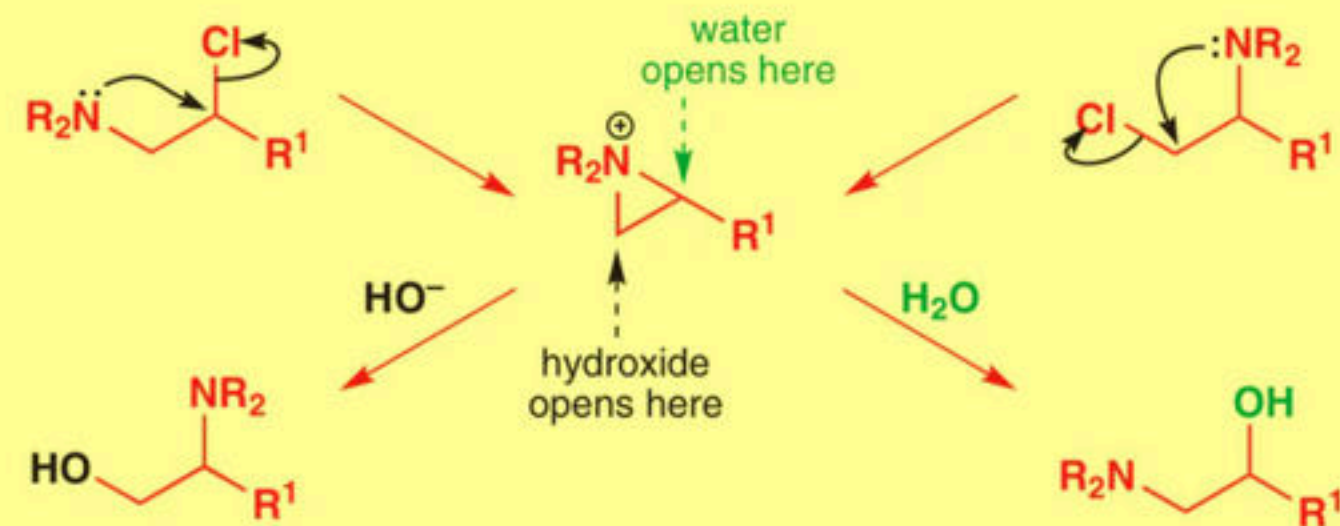
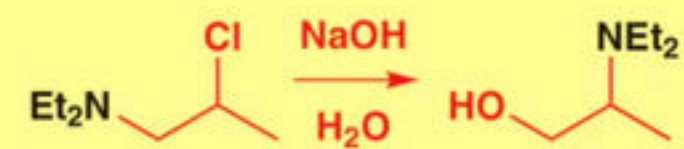
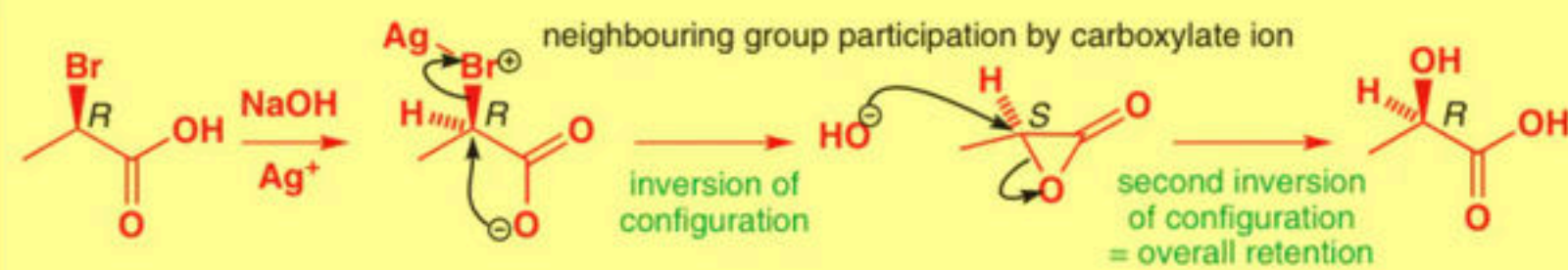
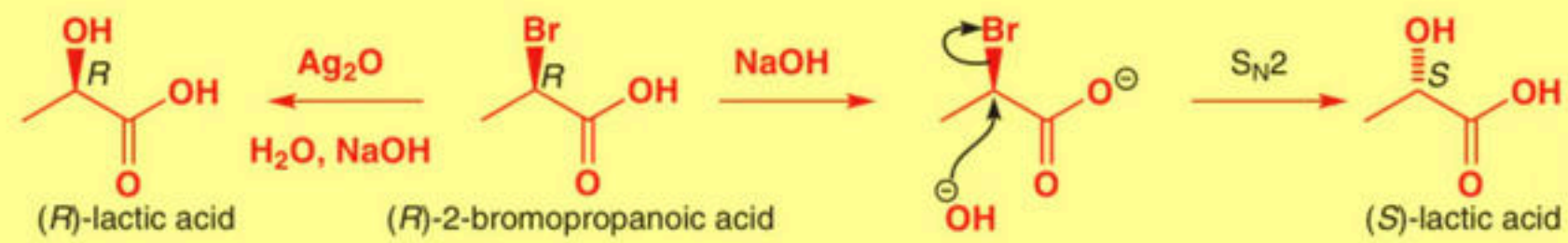
this reaction does not happen



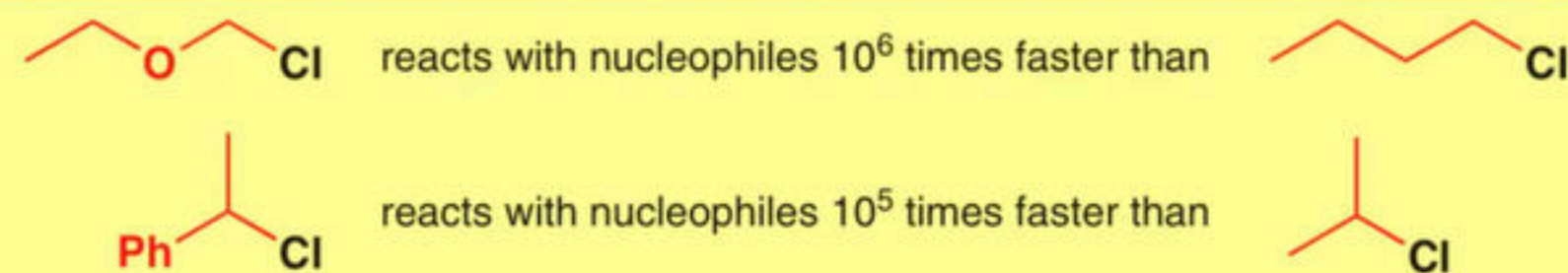
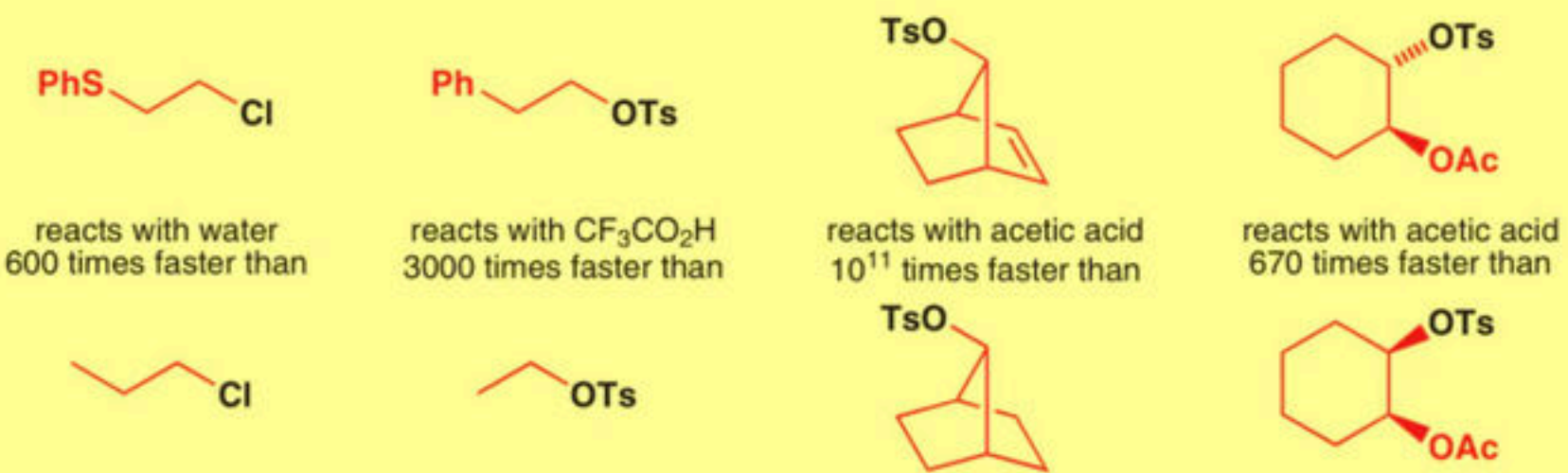
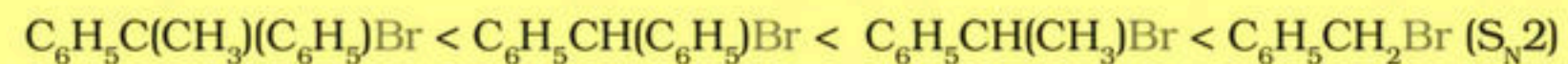
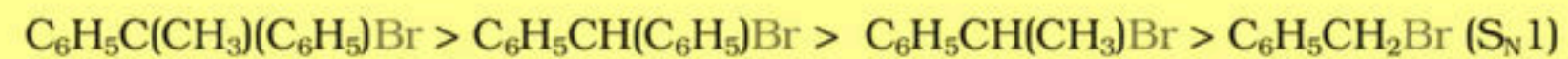
# NGP







$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} < (\text{CH}_3)_2\text{CHCH}_2\text{Br} < \text{CH}_3\text{CH}_2\text{CH}(\text{Br})\text{CH}_3 < (\text{CH}_3)_3\text{CBr} \text{ (S}_{\text{N}}1)$   
 $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} > (\text{CH}_3)_2\text{CHCH}_2\text{Br} > \text{CH}_3\text{CH}_2\text{CH}(\text{Br})\text{CH}_3 > (\text{CH}_3)_3\text{CBr} \text{ (S}_{\text{N}}2)$

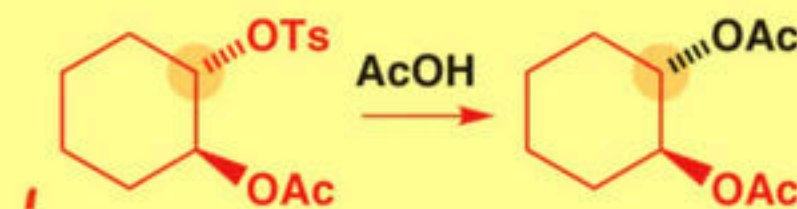


neighbouring group participation of a sulfide



*anti*  
diastereoisomer

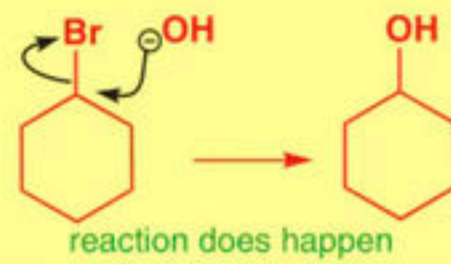
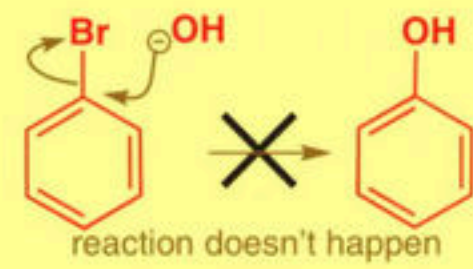
reaction goes with  
retention at orange centre

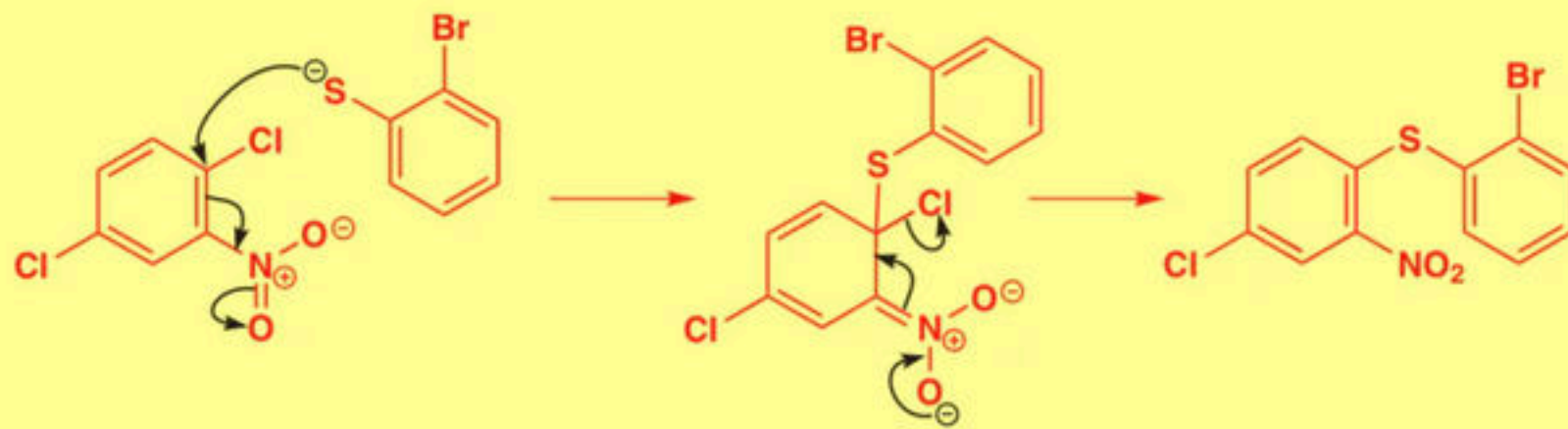
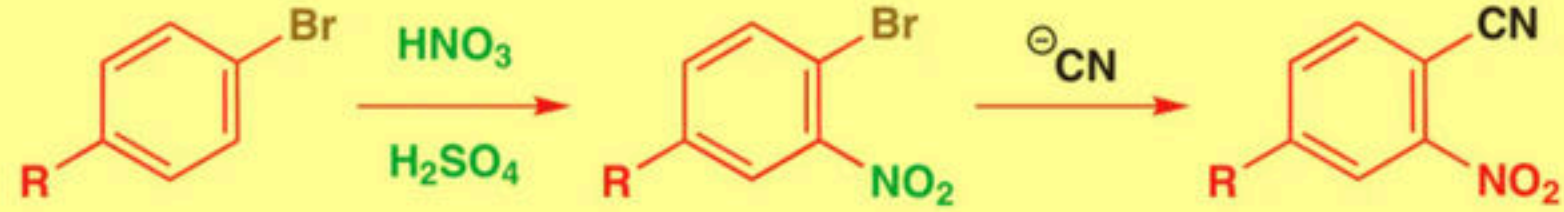
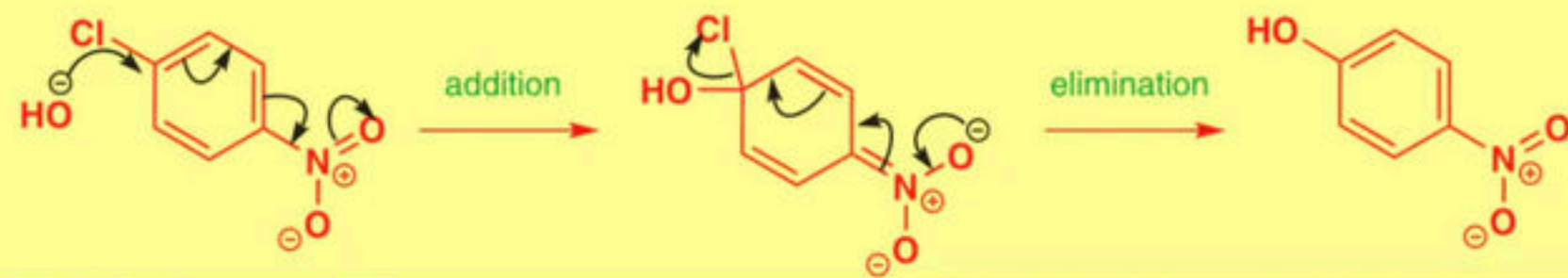


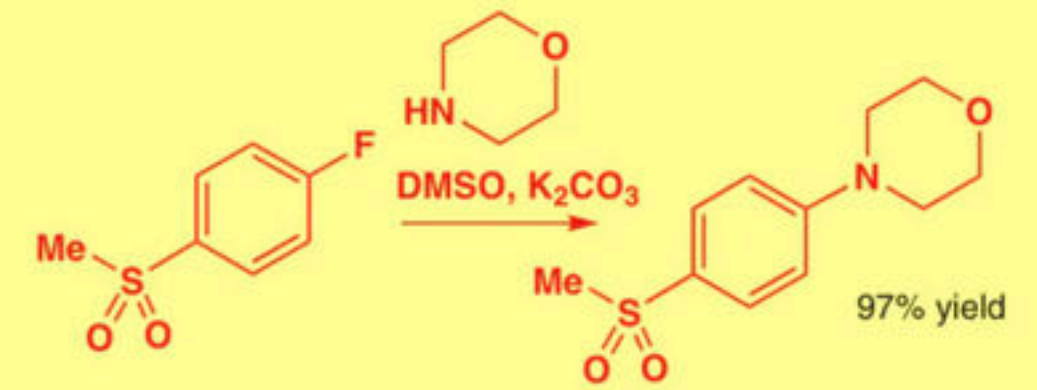
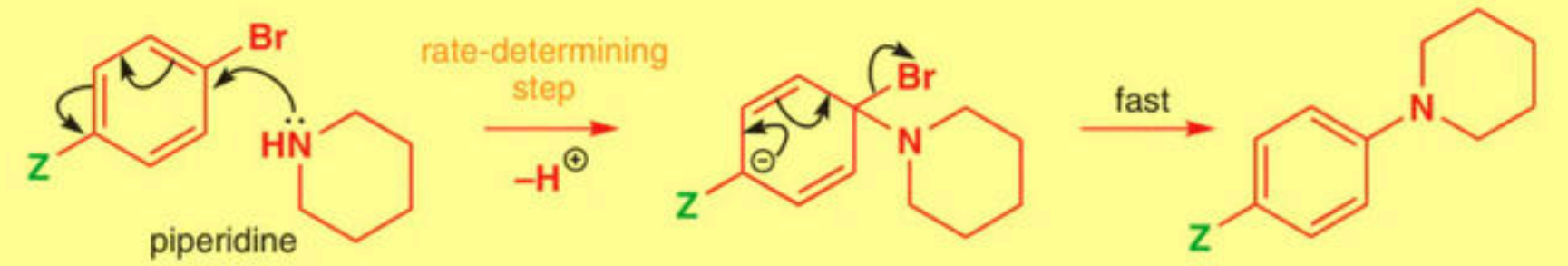
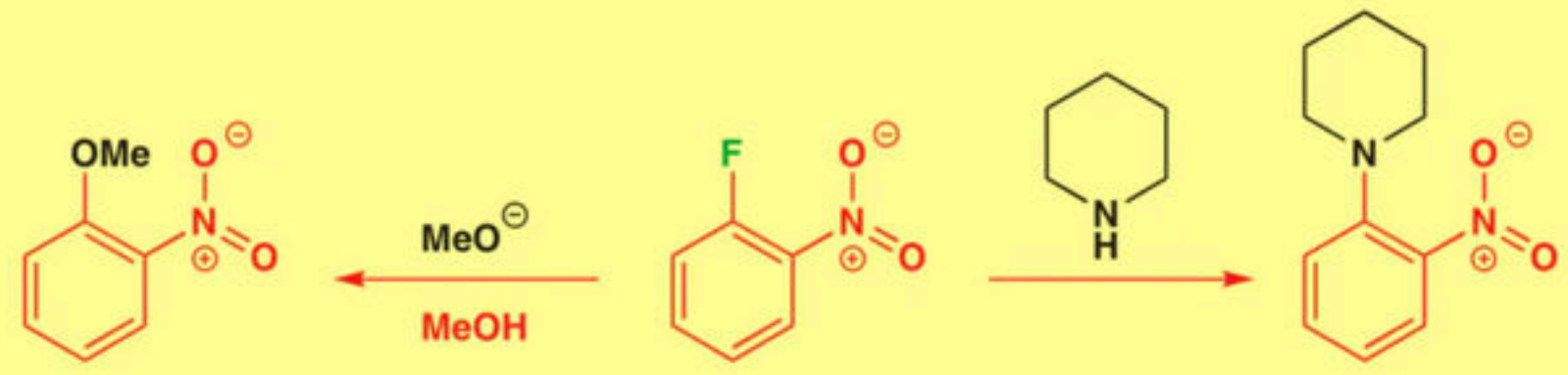
syn diastereoisomer      reaction goes with inversion at green centre

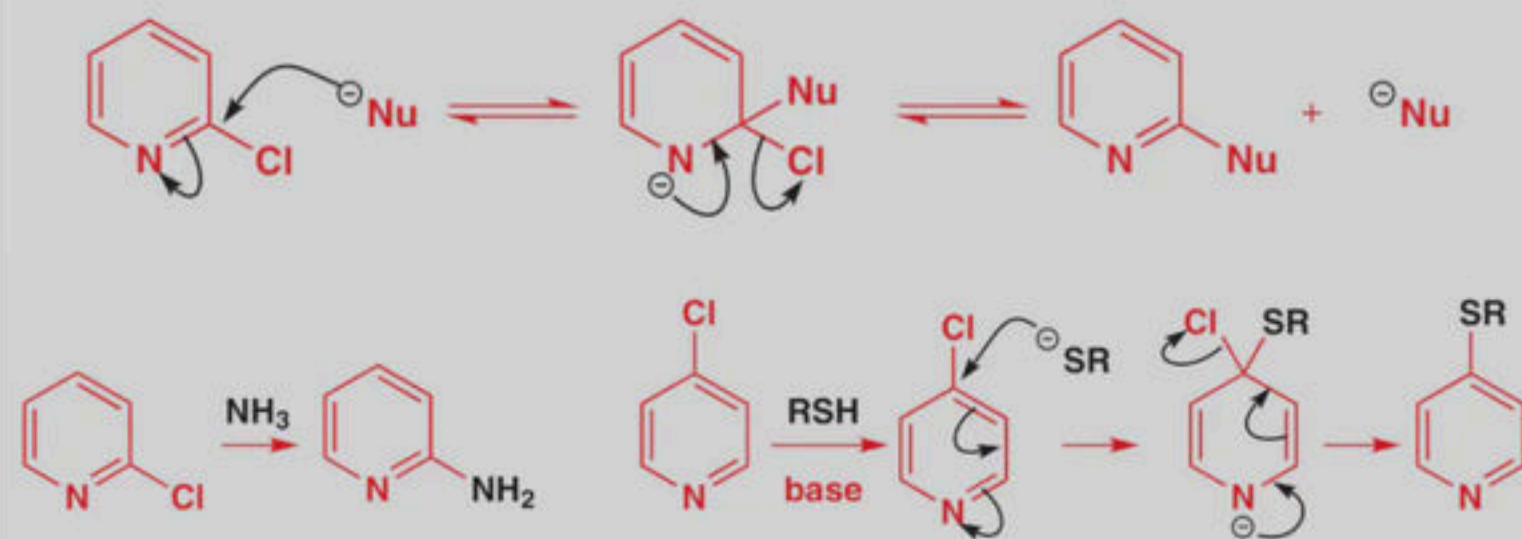
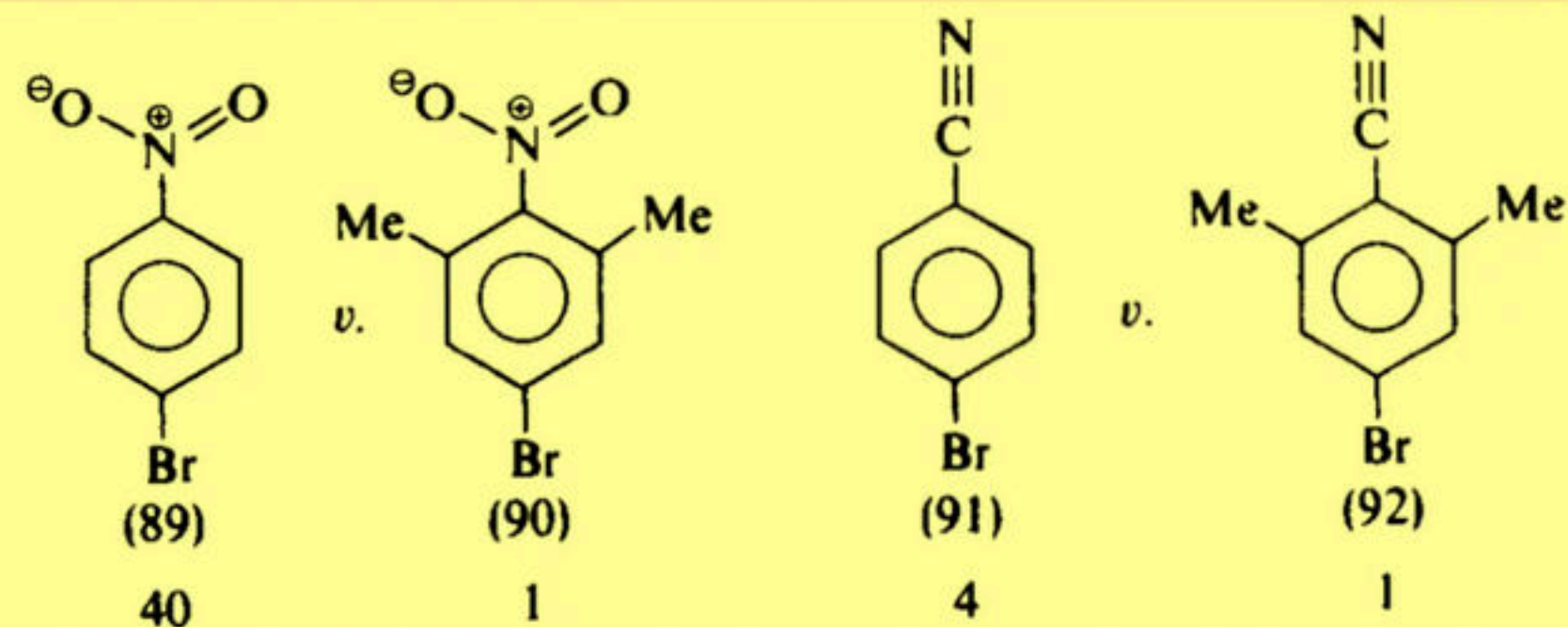
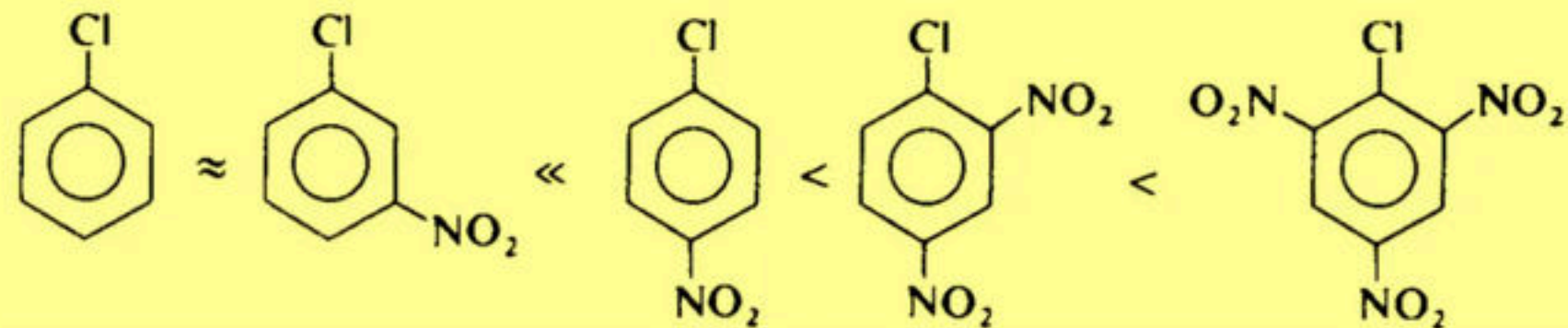


## Nucleophilic aromatic substitution



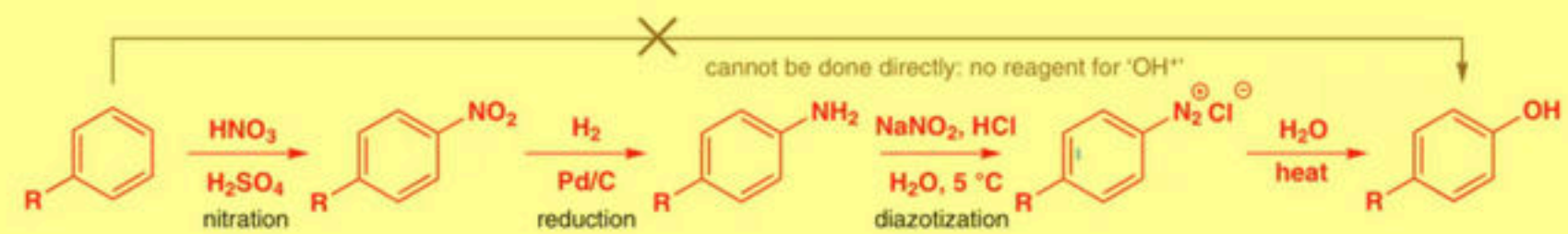
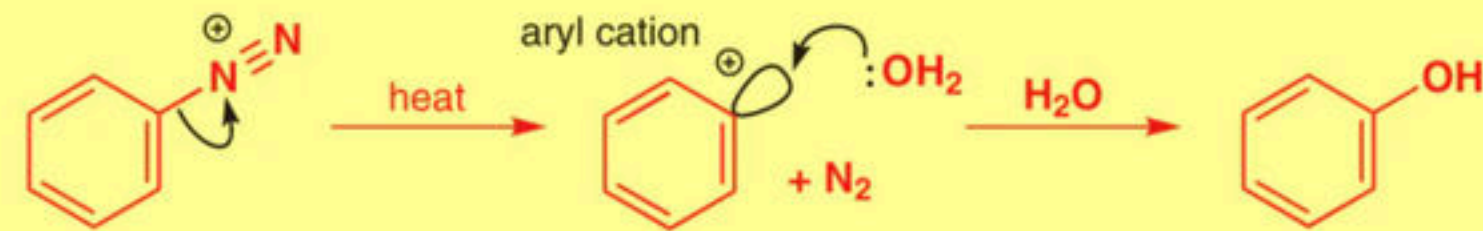


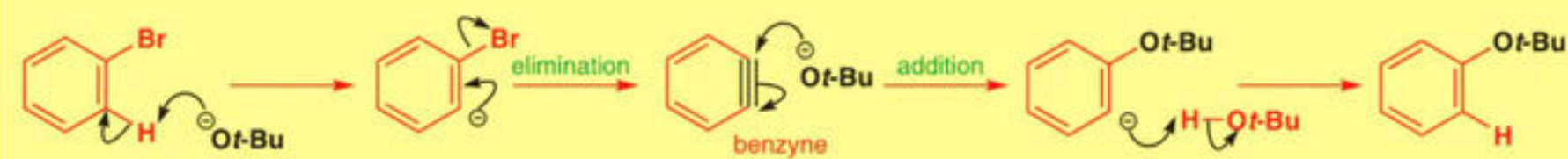
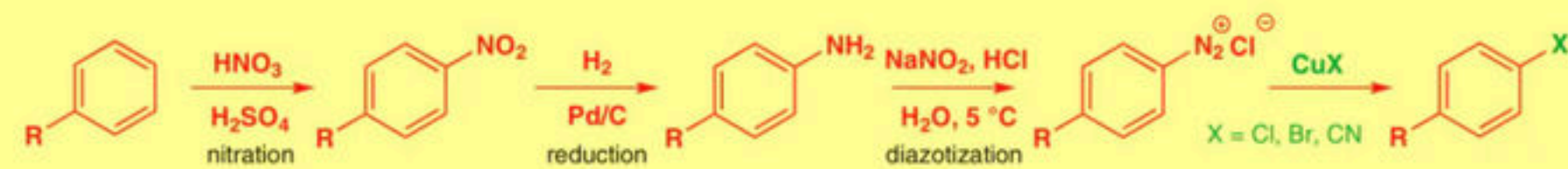
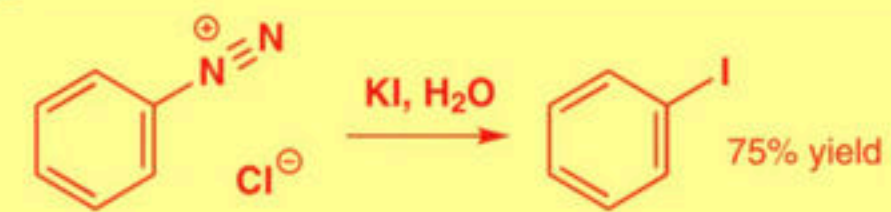
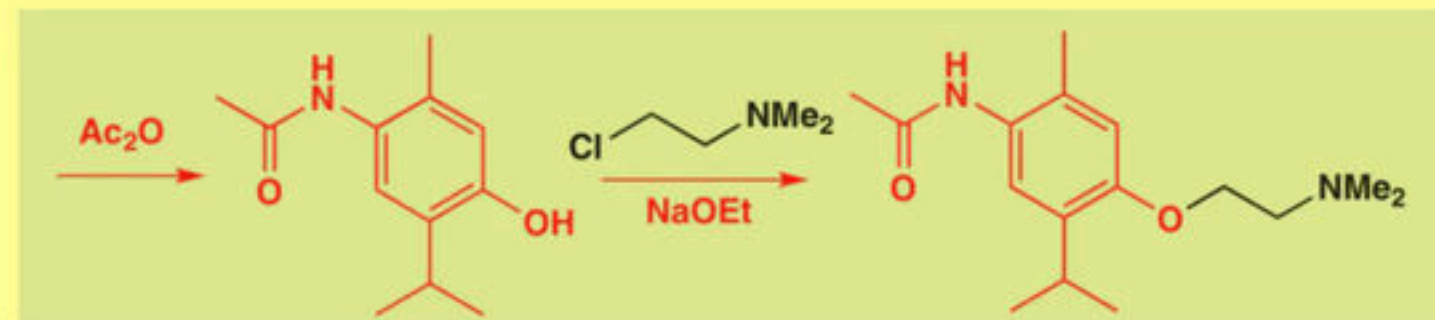
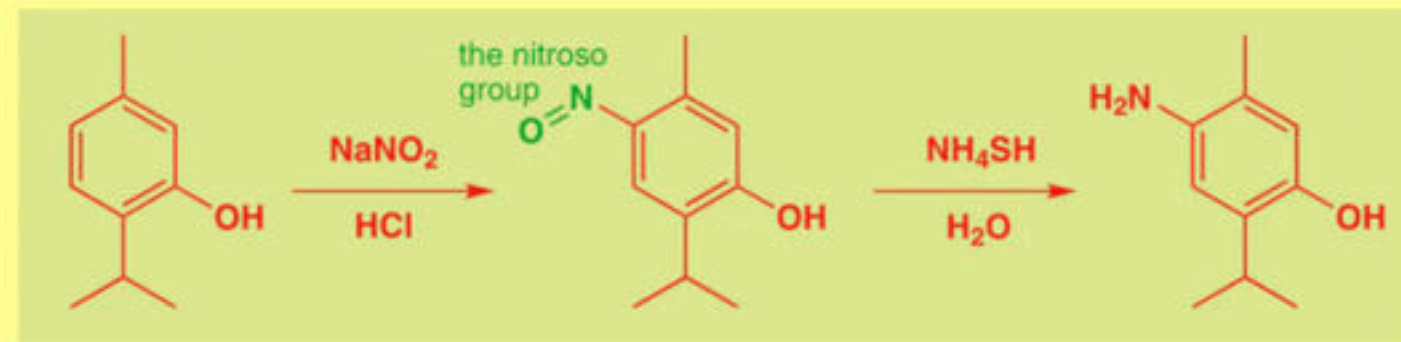


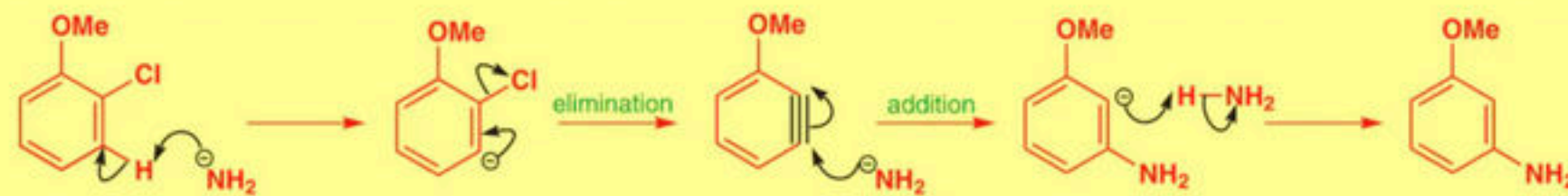




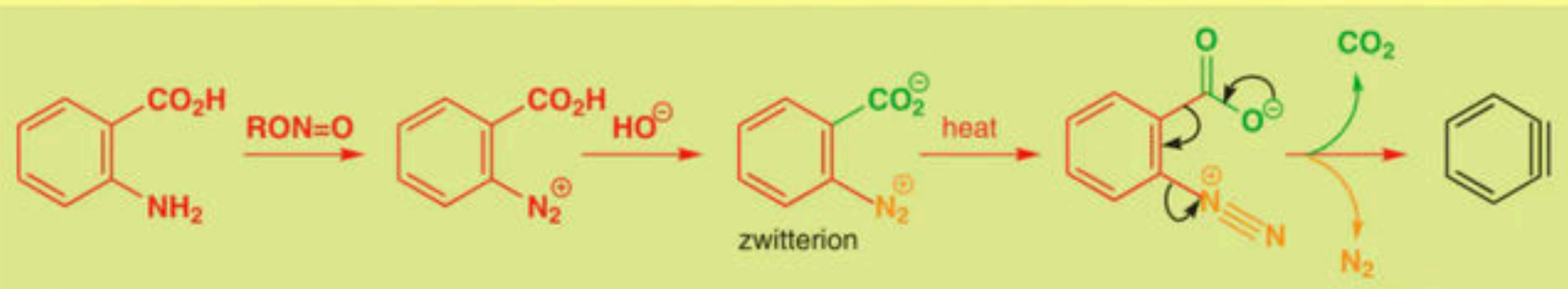
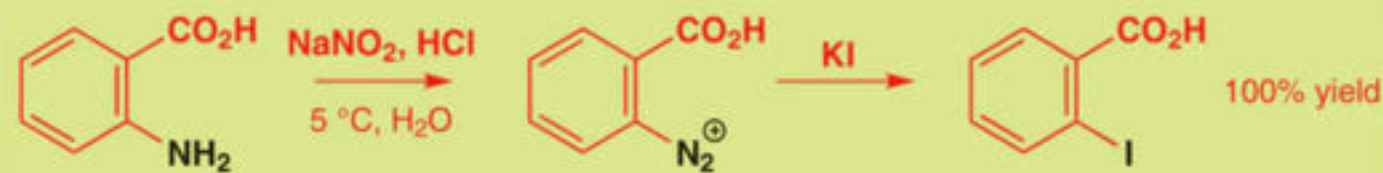
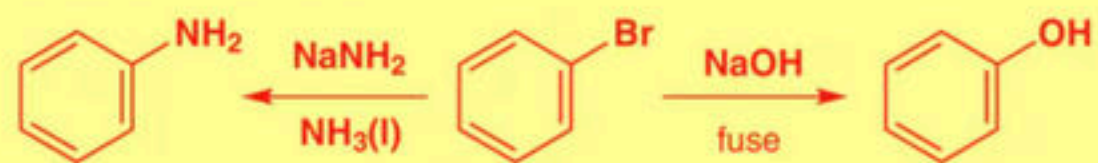
### The $S_N1$ mechanism for nucleophilic aromatic substitution: diazonium compounds





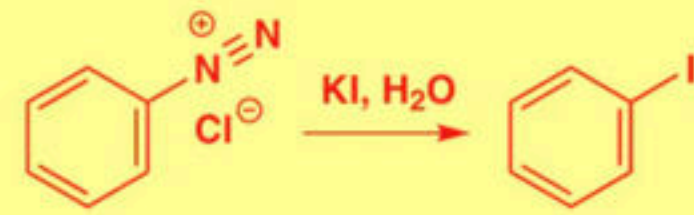


## The benzyne mechanism





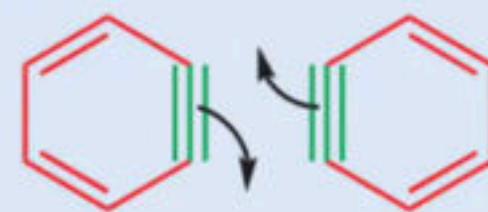
nucleophilic aromatic substitution:  
addition-elimination mechanism



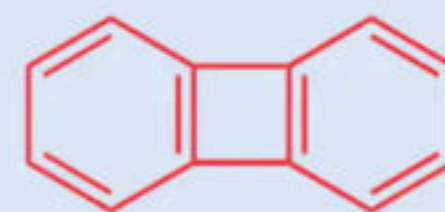
nucleophilic aromatic substitution:  
 $\text{S}_{\text{N}}1$  mechanism



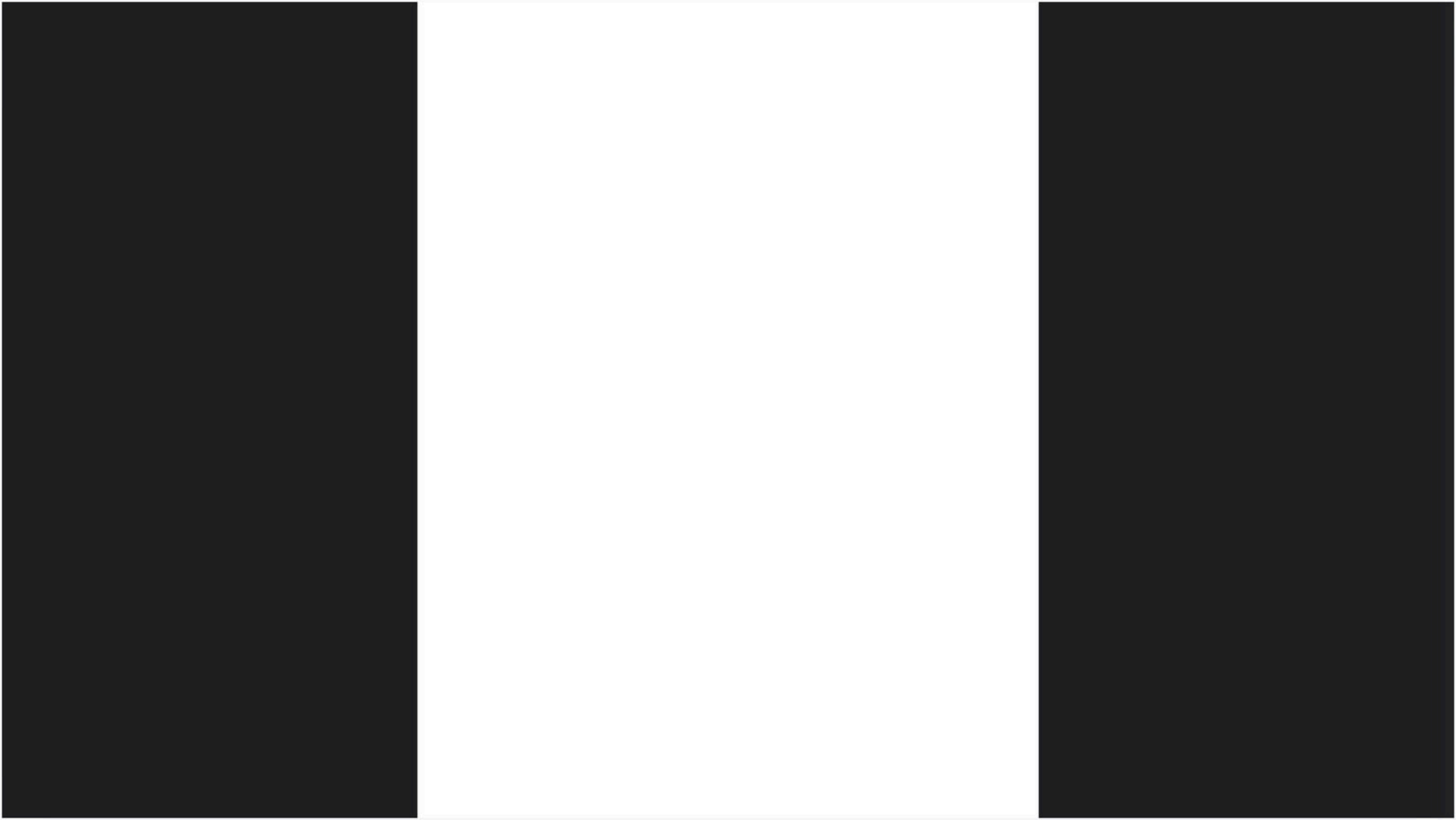
nucleophilic aromatic substitution:  
elimination-addition mechanism



benzyne,  $m/e$  76



benzyne dimer,  $m/e$  152

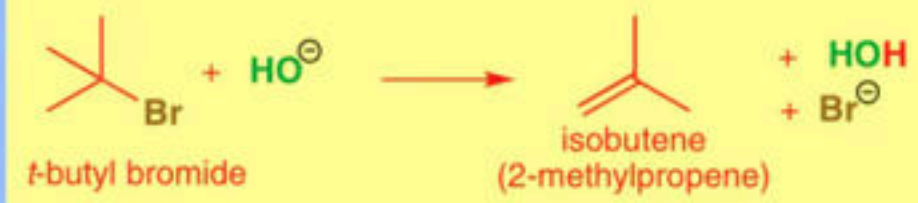


## Elimination reactions

nucleophilic substitution reactions of *t*-BuBr



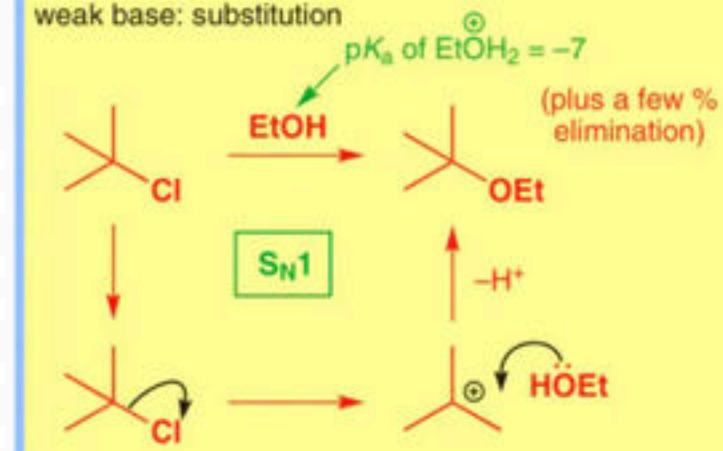
reaction of *t*-BuBr with concentrated solution of NaOH



E1 elimination of *t*-BuOH in  $\text{H}_2\text{SO}_4$



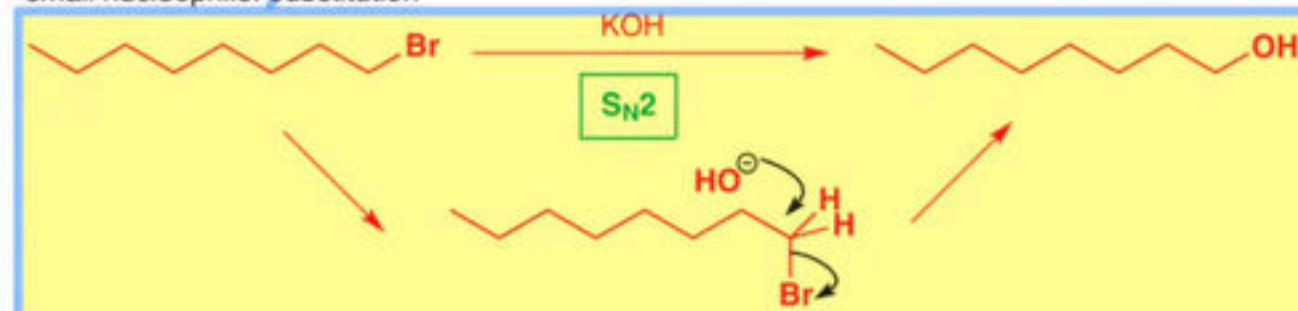
weak base: substitution



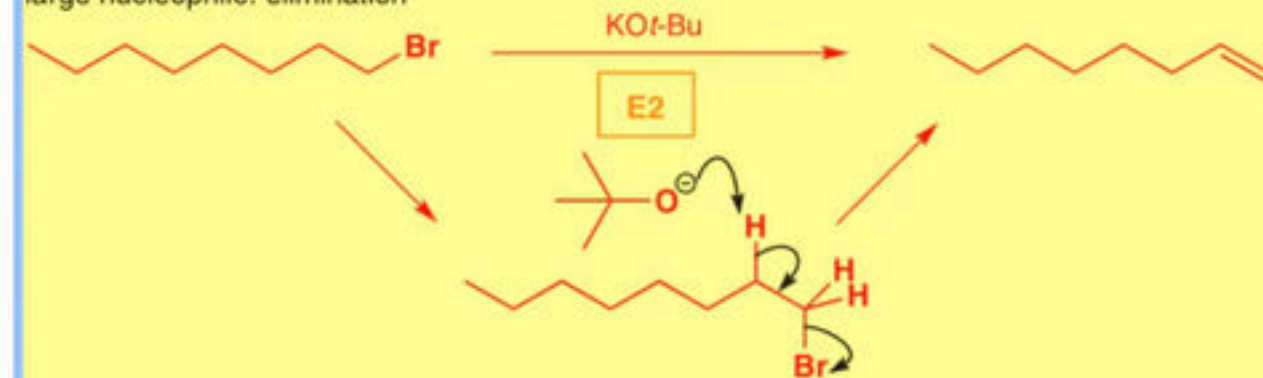
strong base: elimination



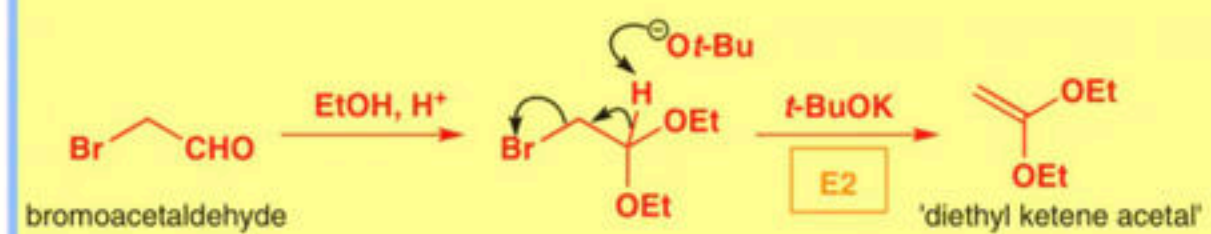
small nucleophile: substitution



large nucleophile: elimination

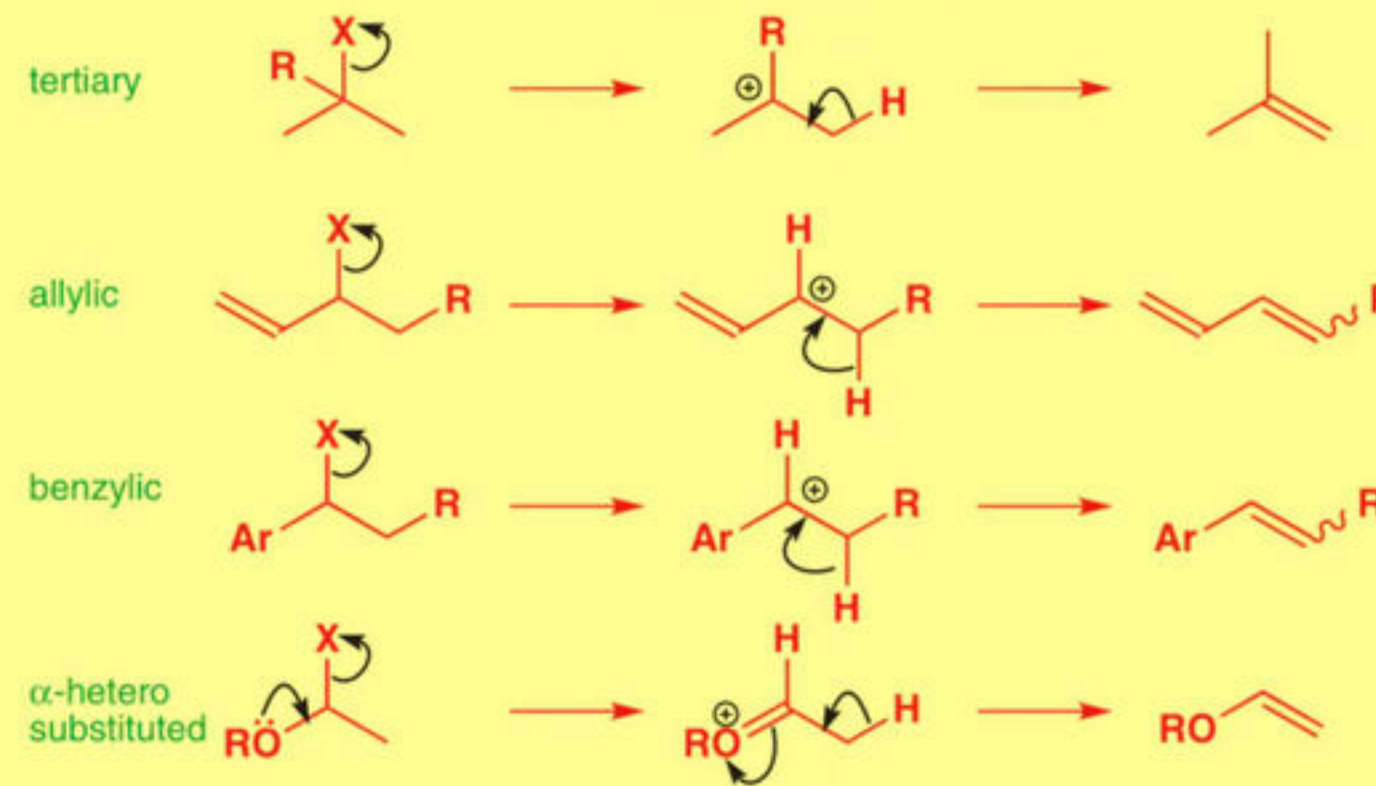


synthesis of a diene by a double E2 elimination



substrates that readily eliminate by E1

stabilized carbocations



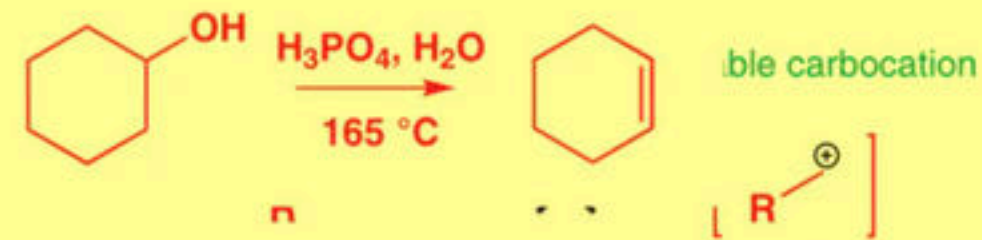
may also eliminate by E2

substrates that may eliminate by E1

less stable carbocation

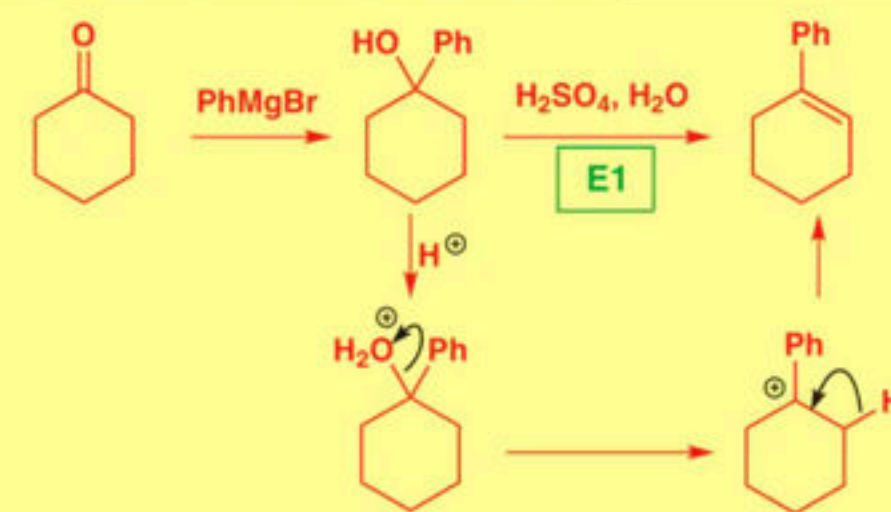


su

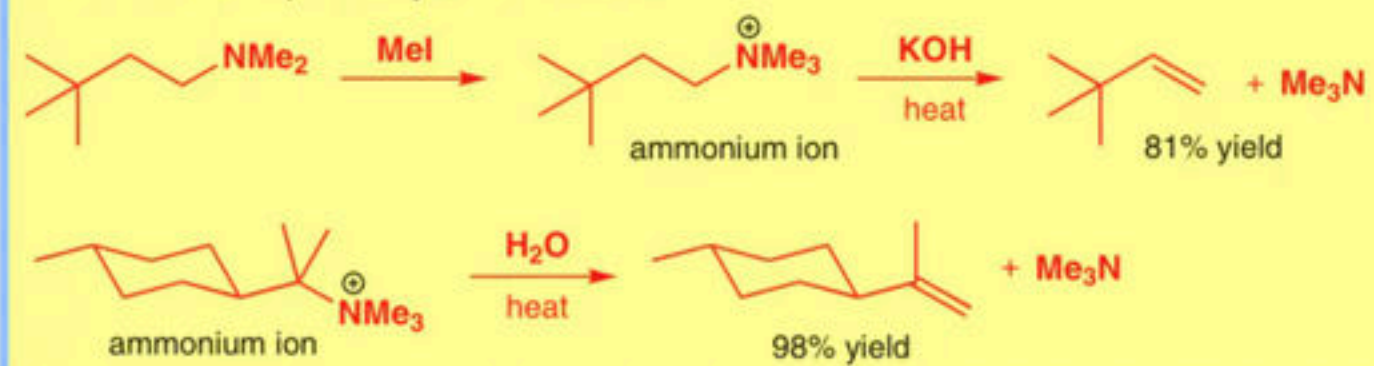


substrates that cannot eliminate by either mechanism—no appropriately placed hydrogens

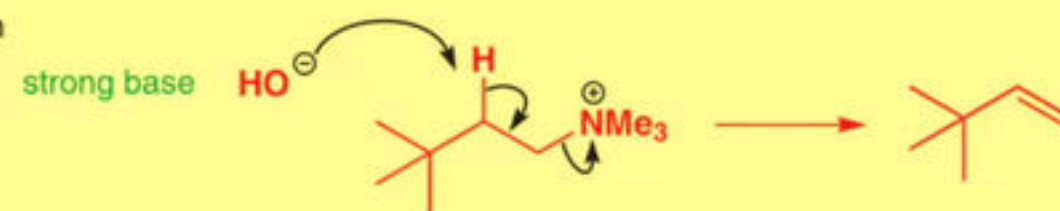
cannot eliminate by E2



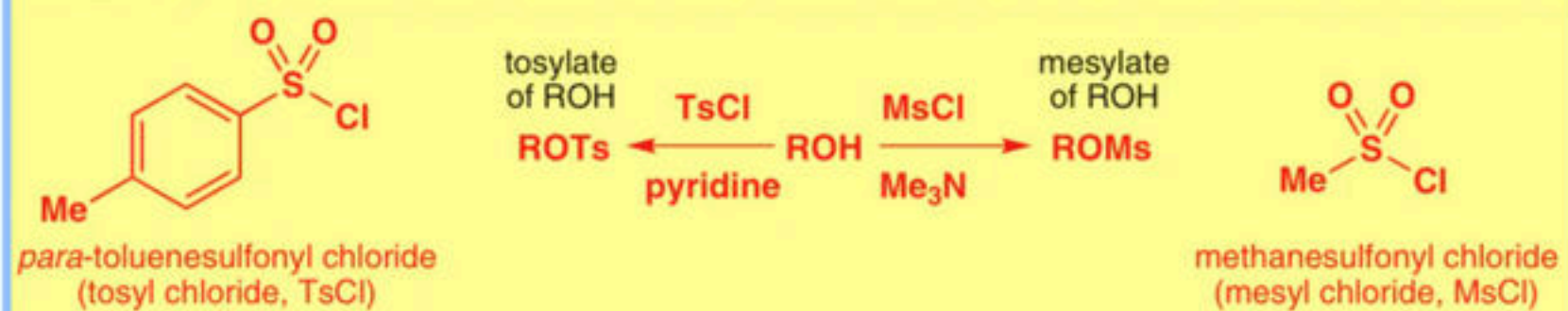
eliminations from quaternary ammonium ions



E2 elimination

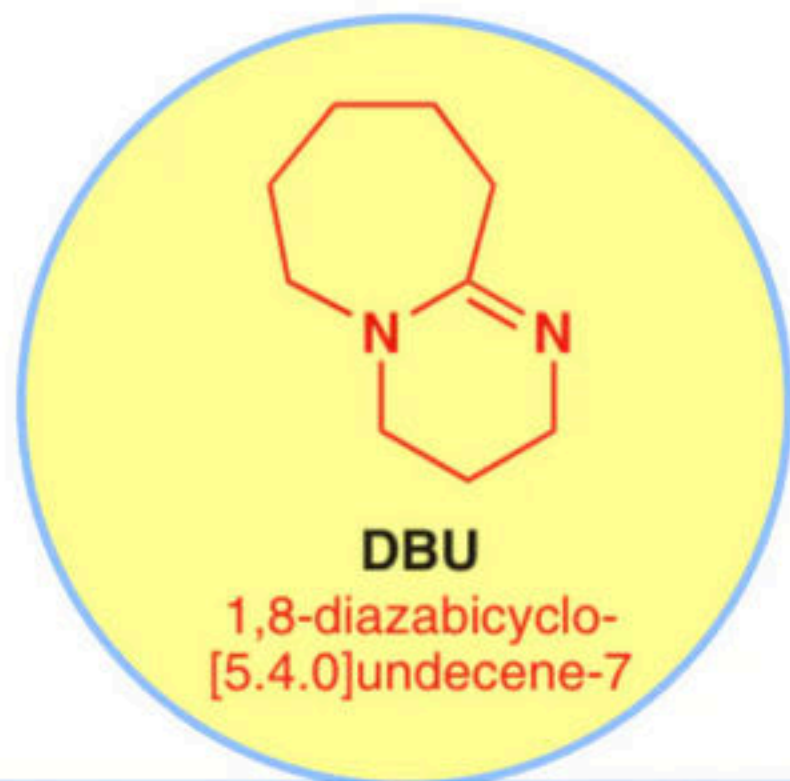


E1 elimination



E2 eliminations of tosylates





only one alkene possible

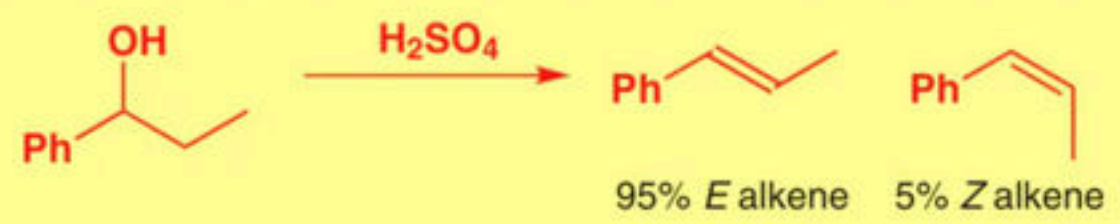


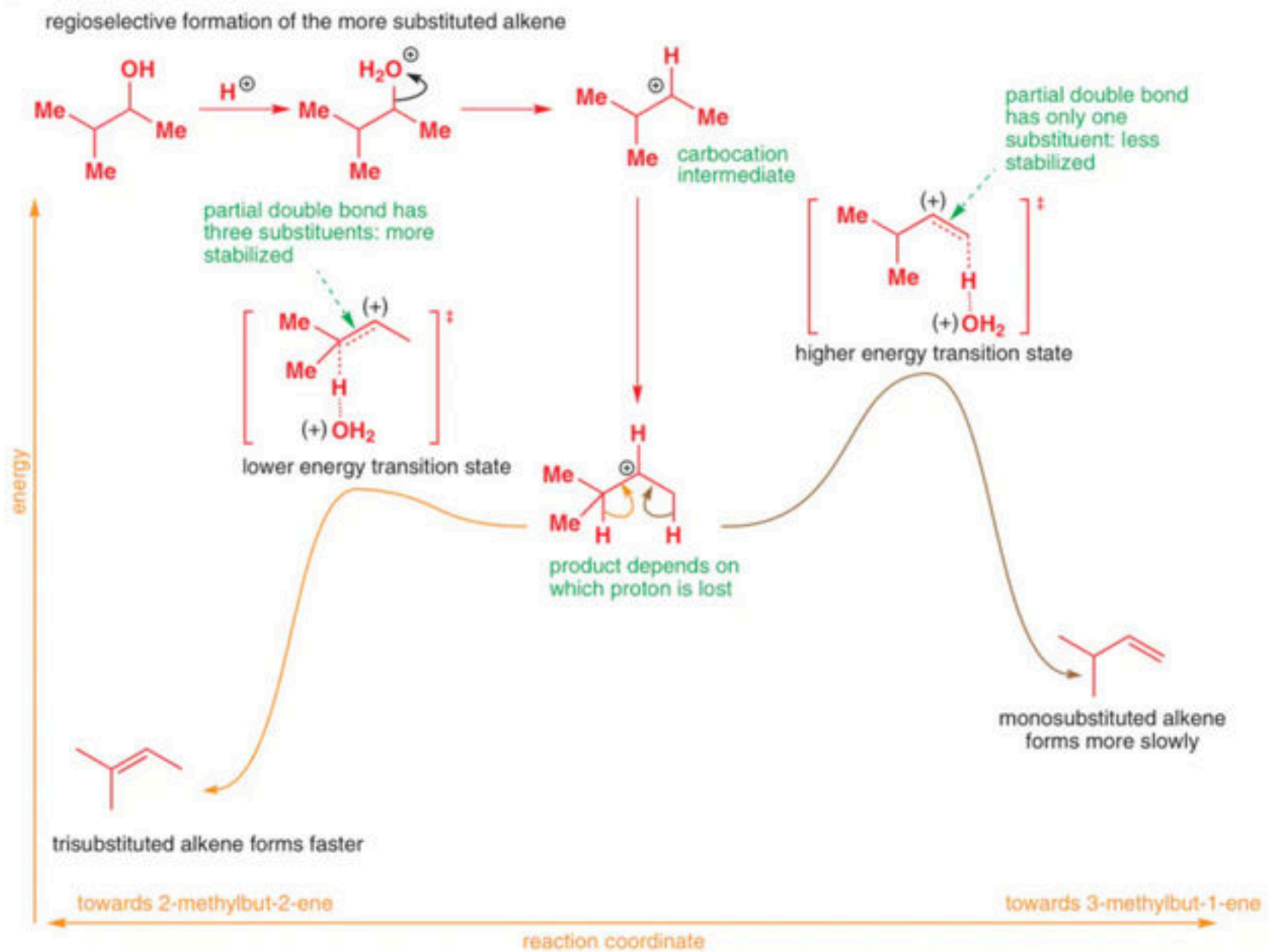
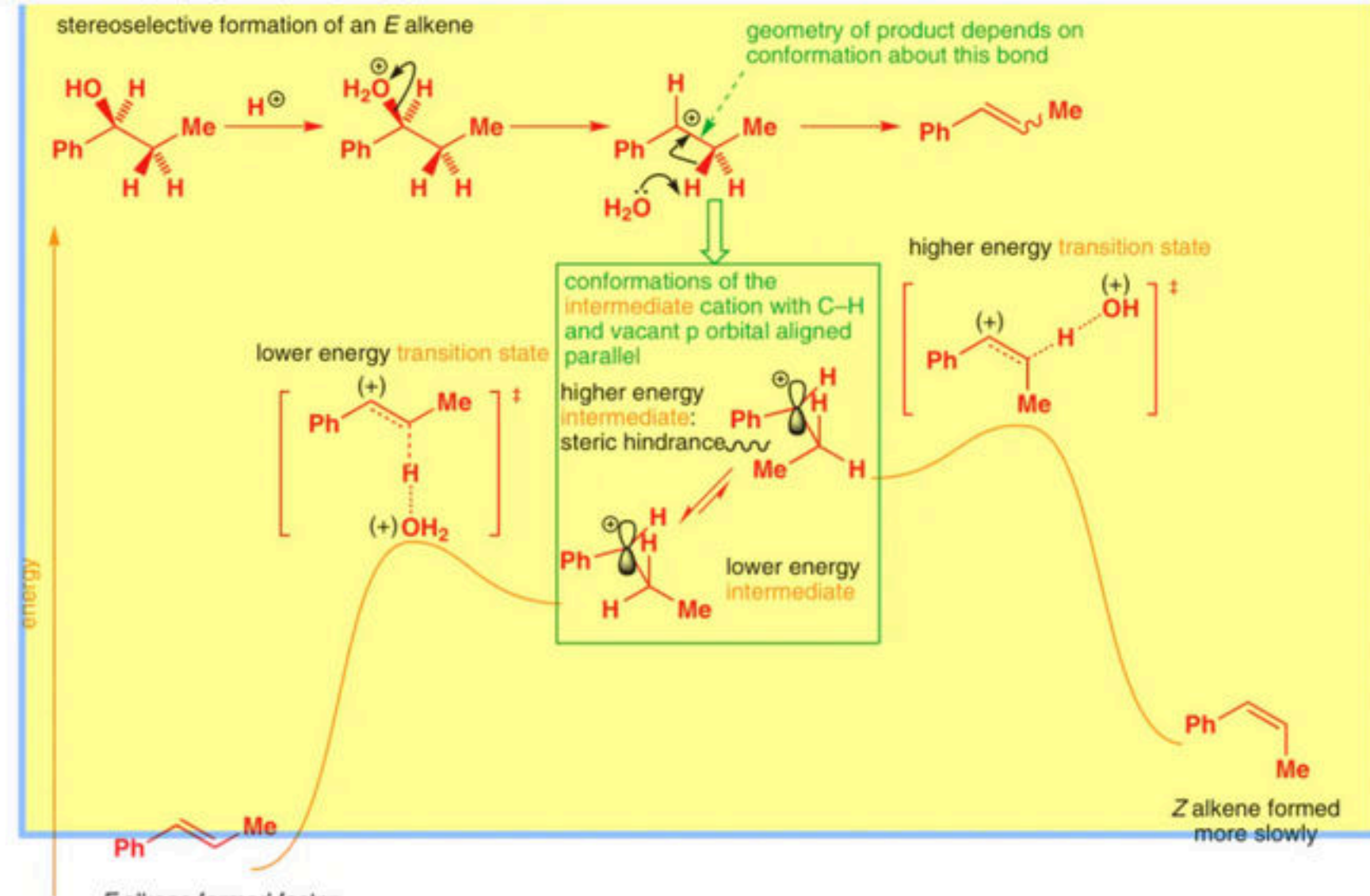
two regioisomeric alkenes possible

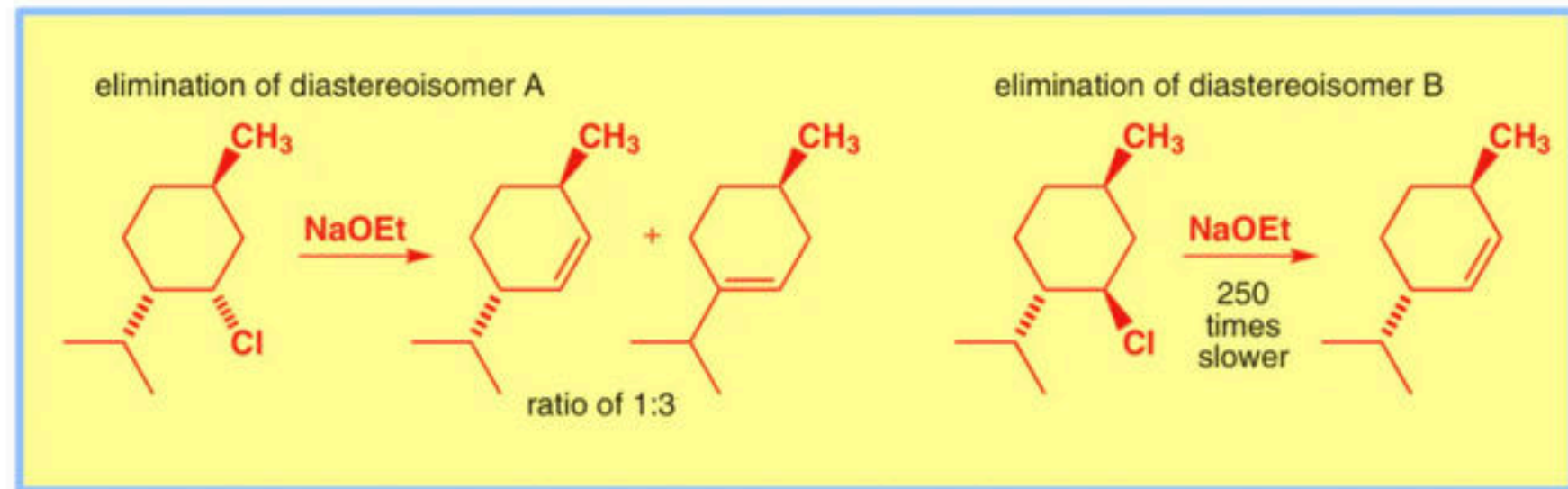
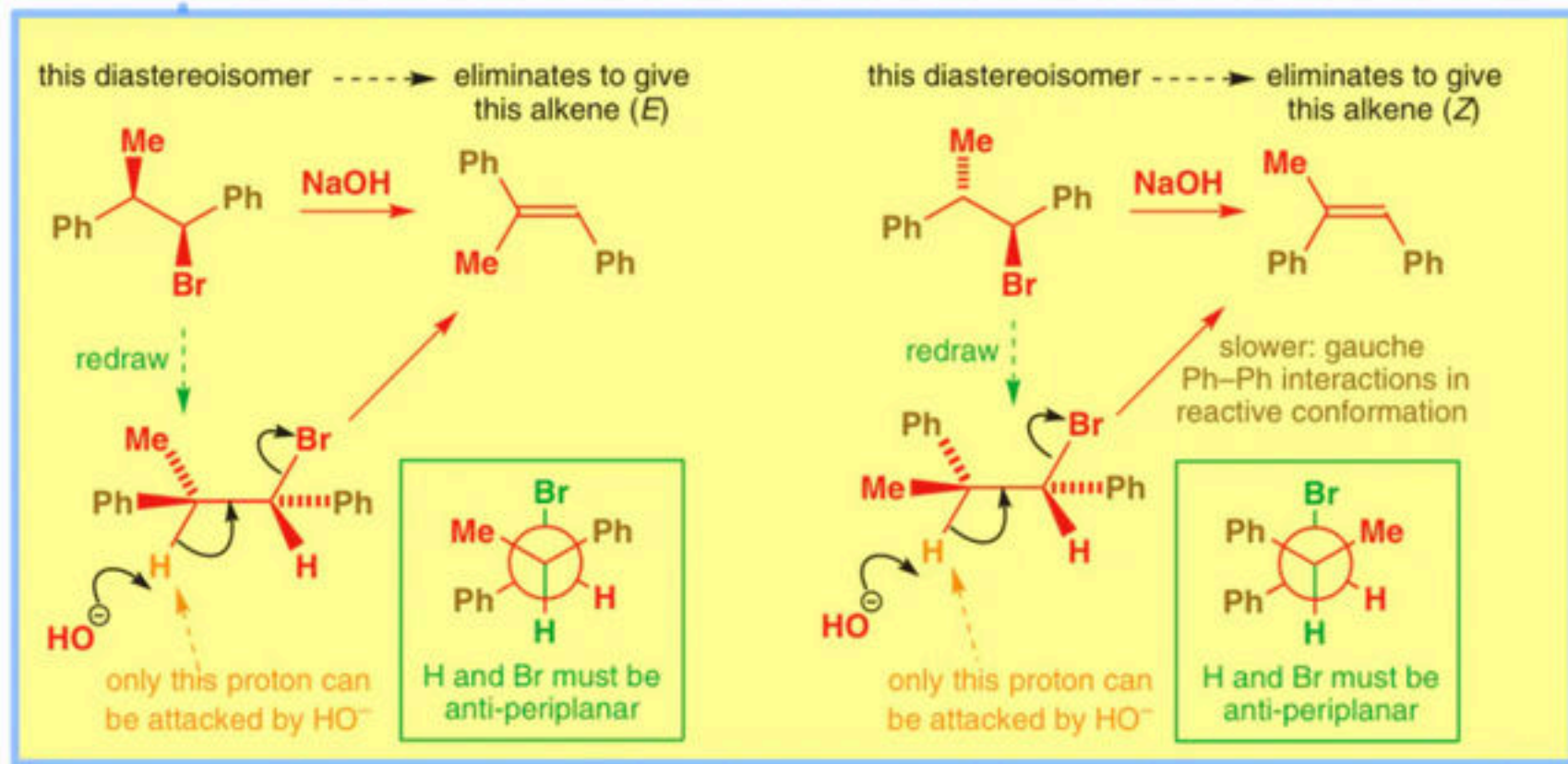


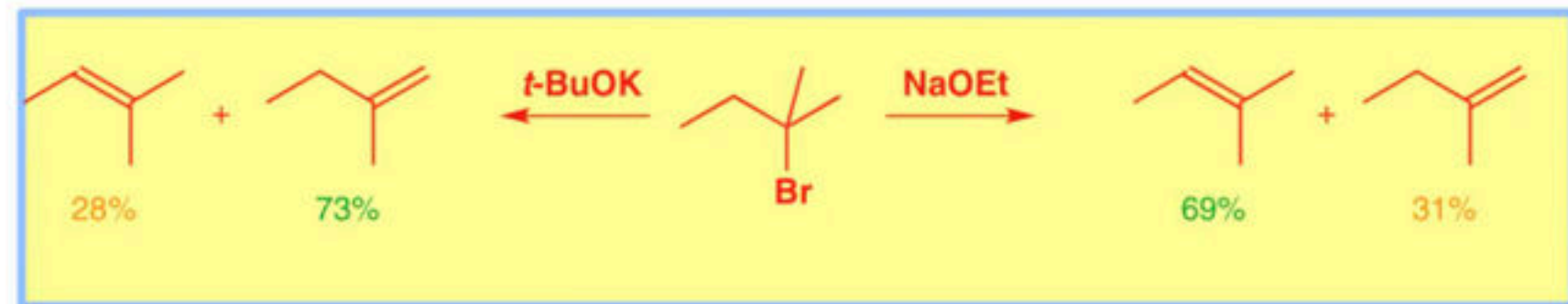
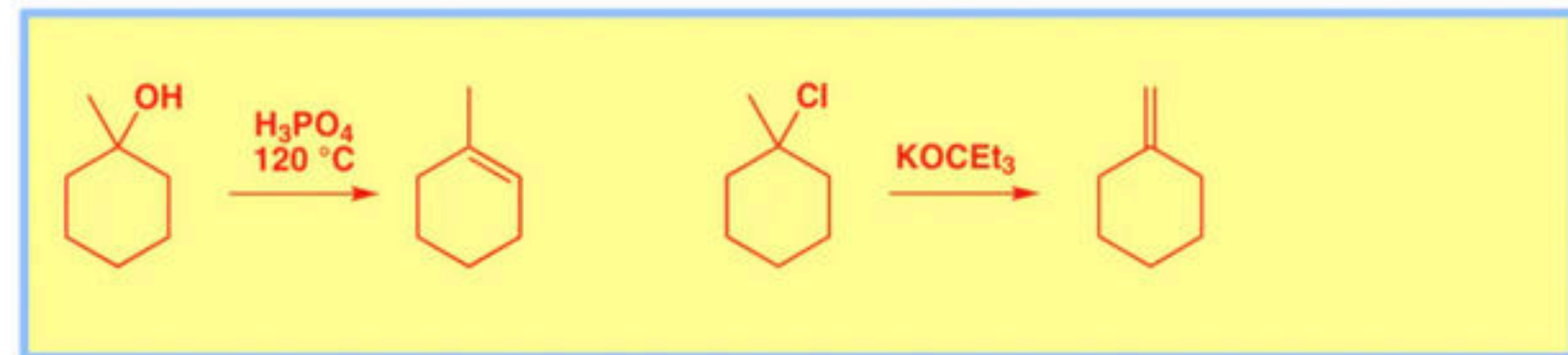
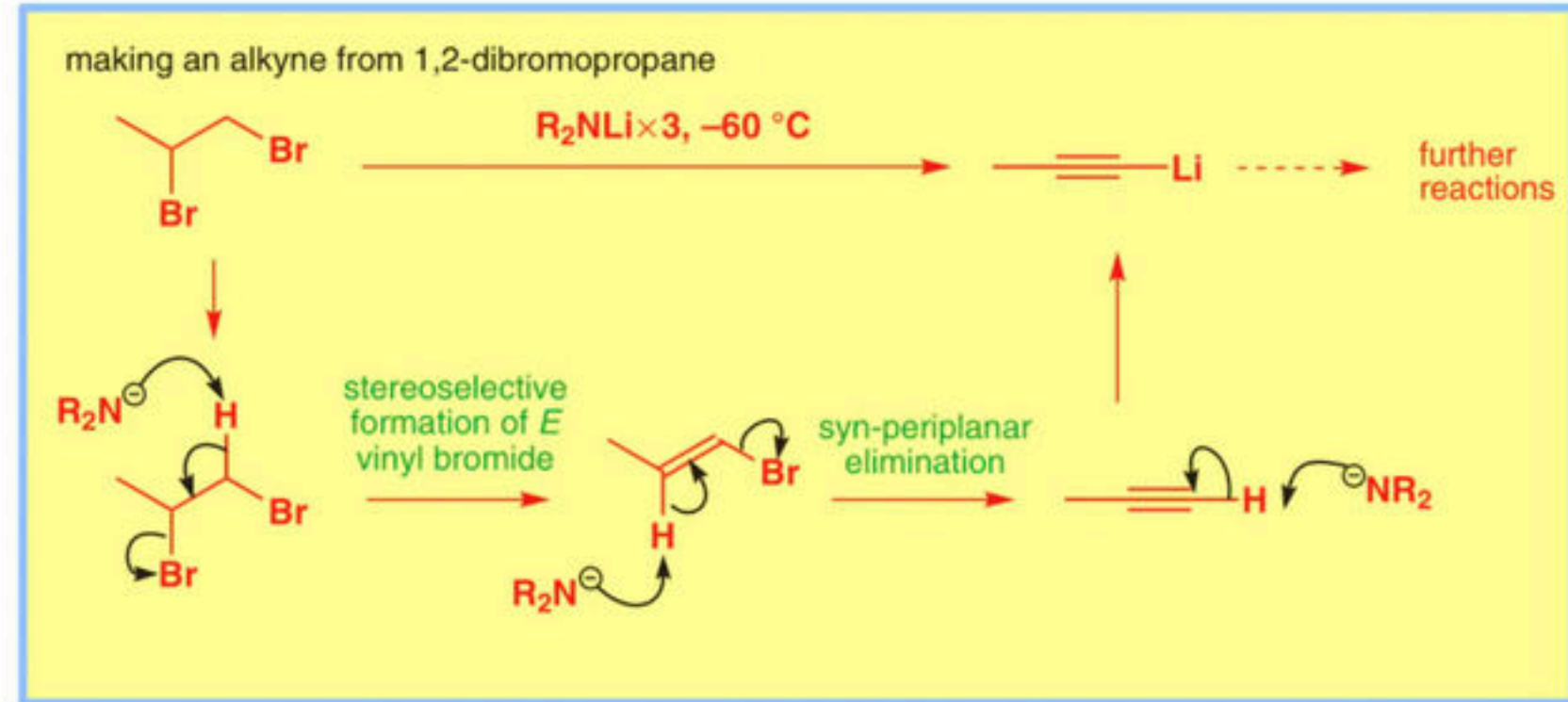
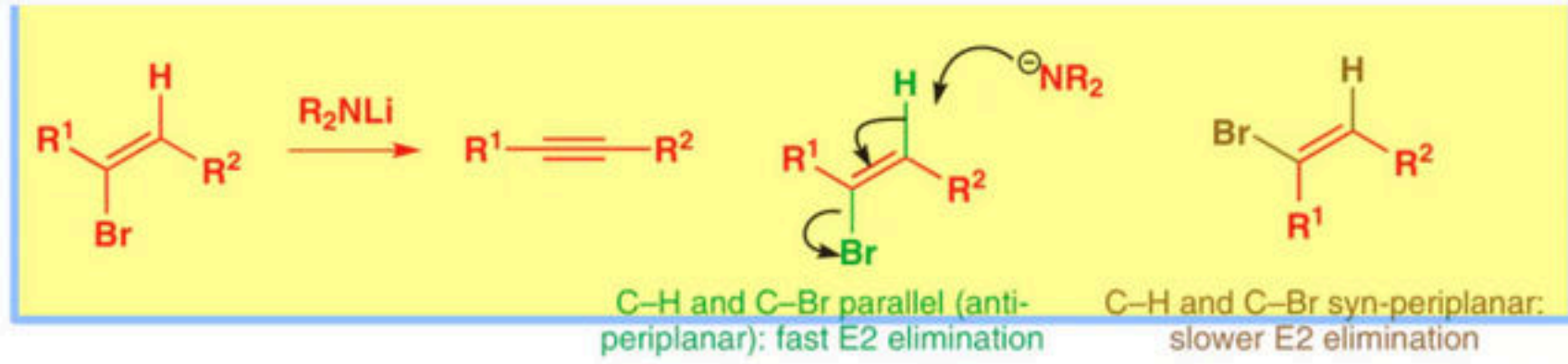
two stereoisomeric alkenes possible



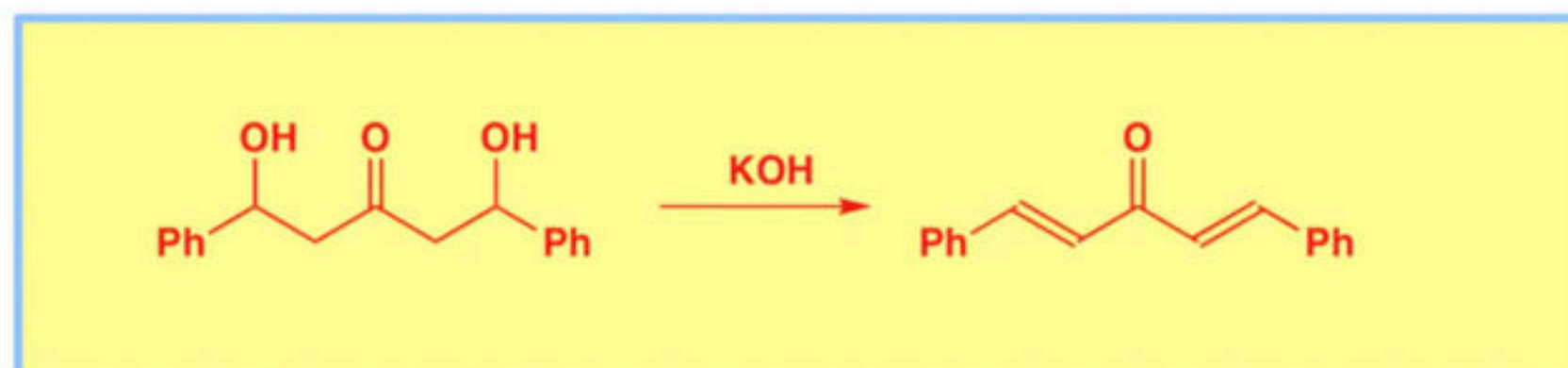
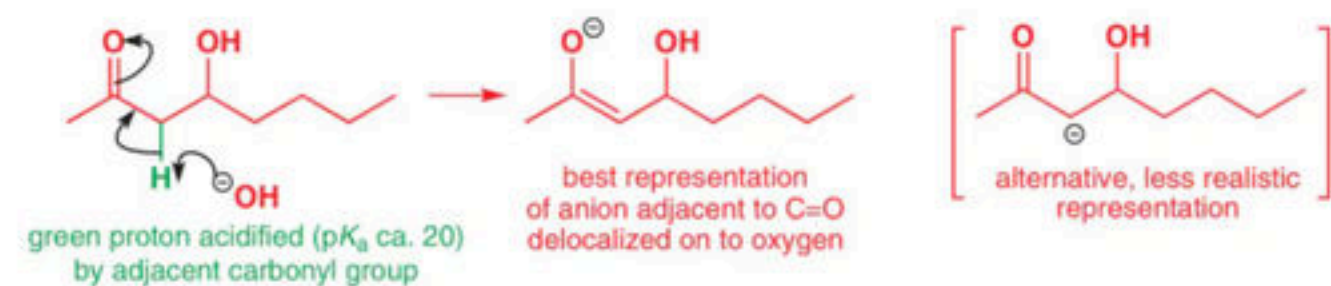
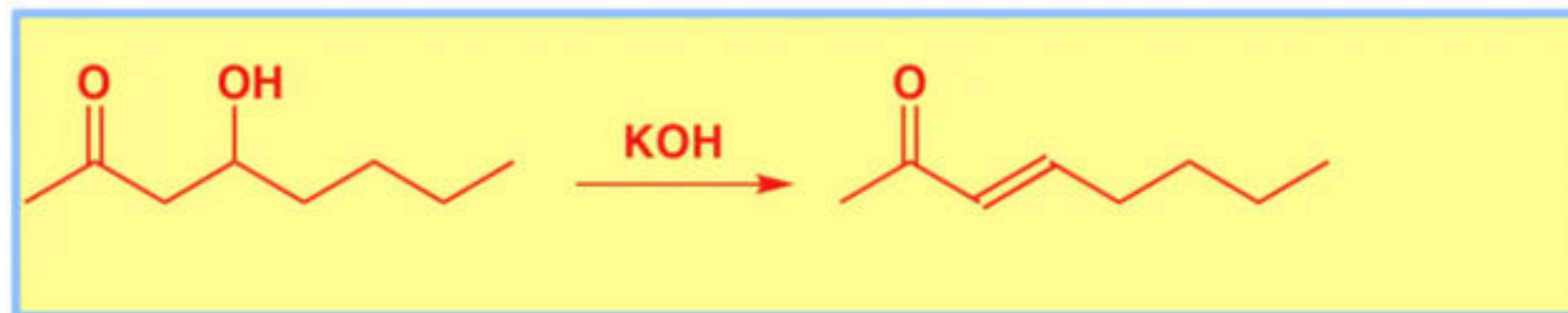








**-E1cB**



		Poor nucleophile (e.g. H <sub>2</sub> O, ROH)	Weakly basic nucleophile (e.g. I <sup>-</sup> , RS <sup>-</sup> )	Strongly basic, unhindered nucleophile (e.g. RO <sup>-</sup> )	Strongly basic, hindered nucleophile (e.g. DBU, t-BuO <sup>-</sup> )
methyl	$\text{H}_3\text{C}-\text{X}$	no reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
primary (unhindered)		no reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	E2
primary (hindered)		no reaction	S <sub>N</sub> 2	E2	E2
secondary		S <sub>N</sub> 1, E1 (slow)	S <sub>N</sub> 2	E2	E2
tertiary		E1 or S <sub>N</sub> 1	S <sub>N</sub> 1, E1	E2	E2
β to anion-stabilizing group		E1cB	E1cB	E1cB	E1cB