Today

Make Lab Announcements

Review Syllabus

Chap 10 Reactions of Alcohols…
Sections 10.1, 10.2
Substitution Reactions

Next Class

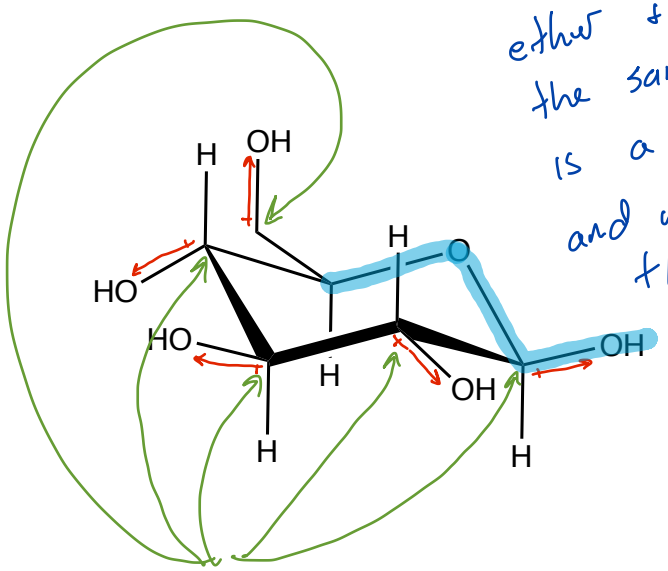
Chap 10 Reactions of Alcohols…

Sections 10.1, 10.2
Substitution Reactions

Section 10.3
Sulfonate Esters

Section 10.4
Elimination Reactions

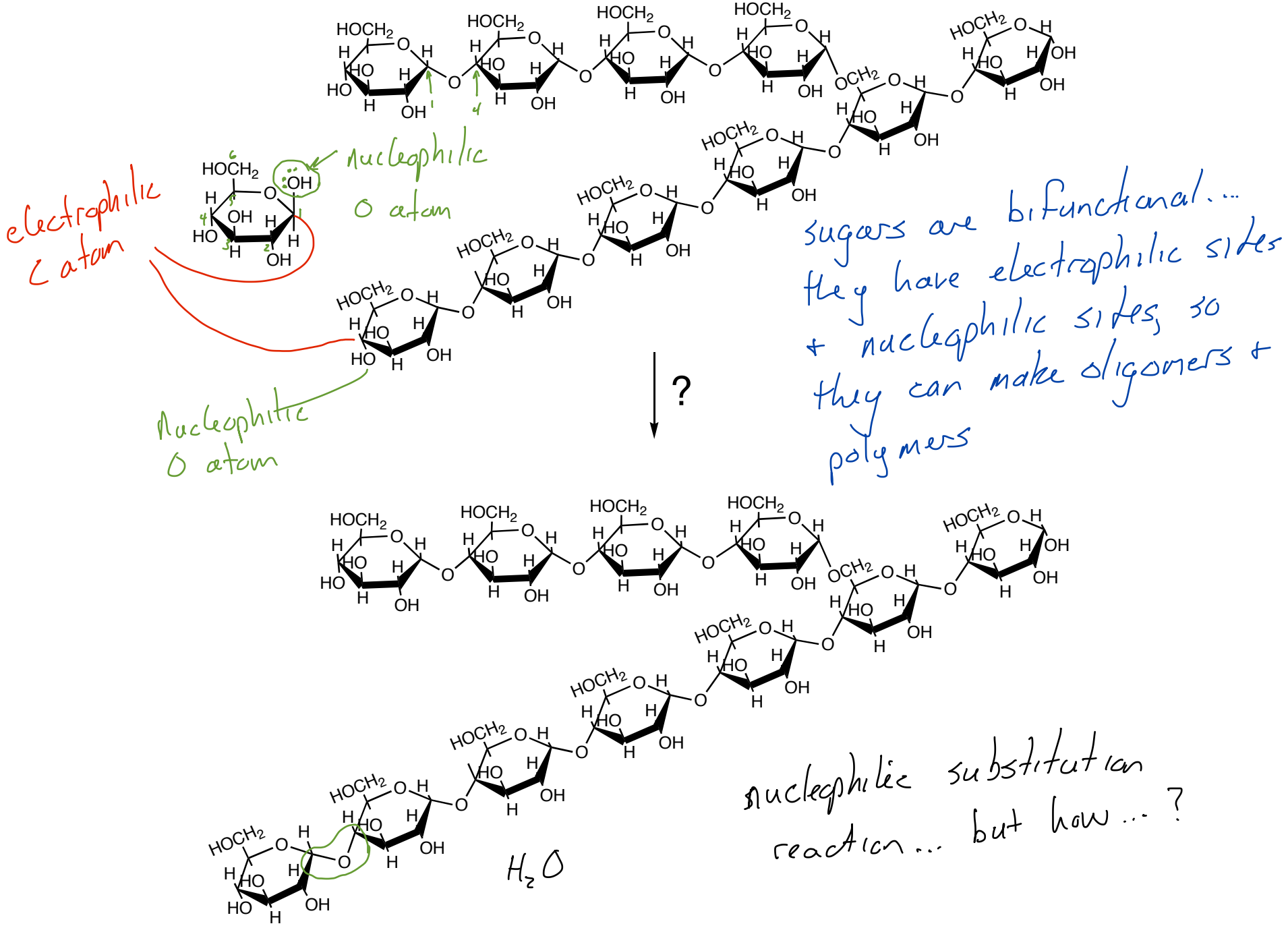
Reactions of Alcohols... Why?



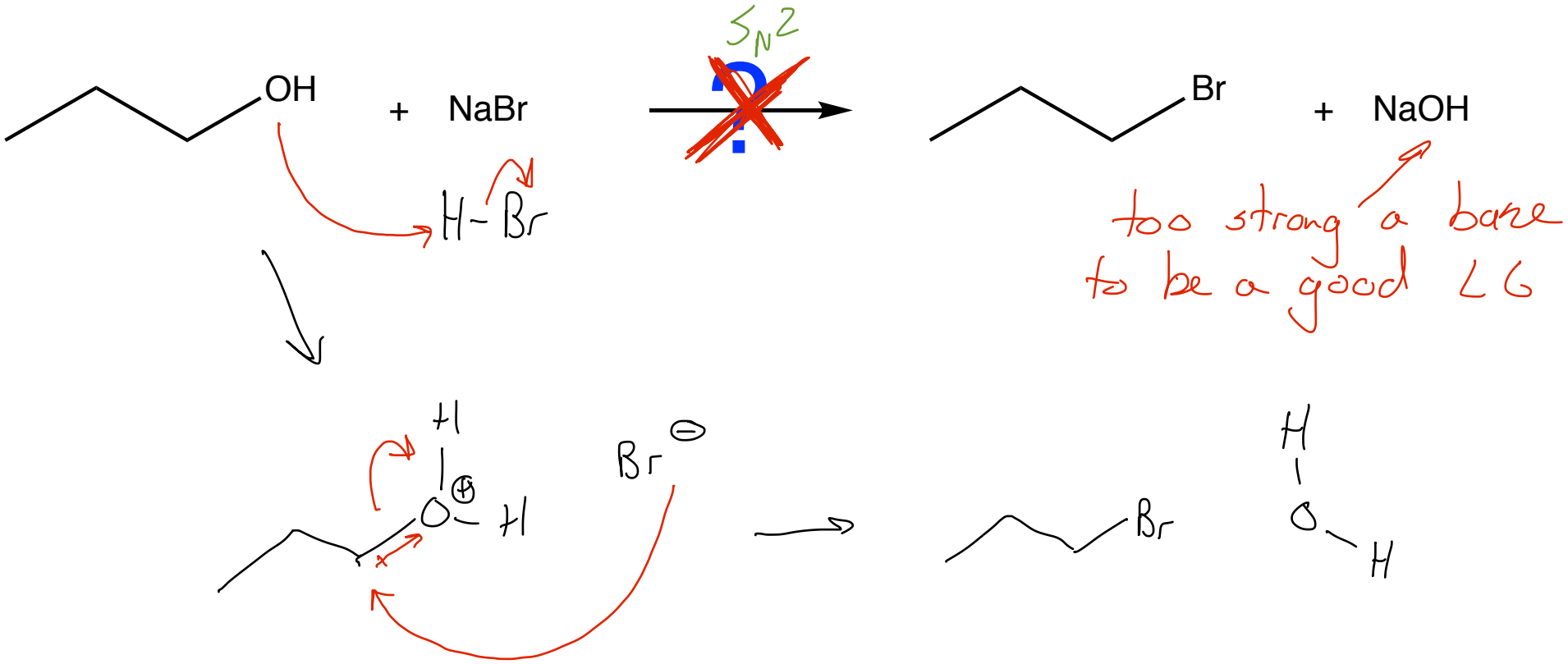
ether + alcohol on the same C atom is a hemiacetal... and we will look at those later

these C atoms are electrophilic... which means they are attractive to nucleophiles

Reactions of Alcohols... Why?

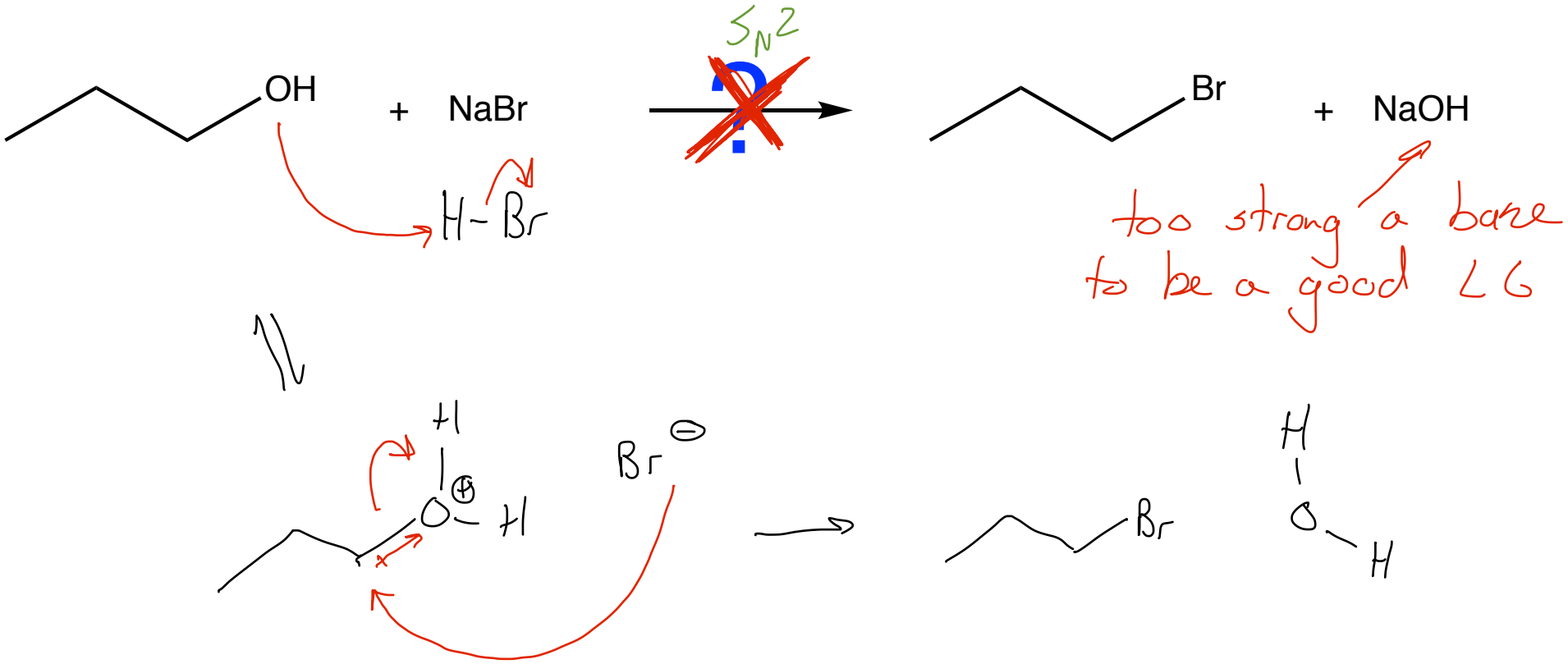


Hydroxide is **not** a good leaving group



React the alcohol with an acid to convert the bad $OH^{\ominus}$ LG to a good H_2O LG before the nucleophile attempts to push the LG off

Hydroxide is **not** a good leaving group



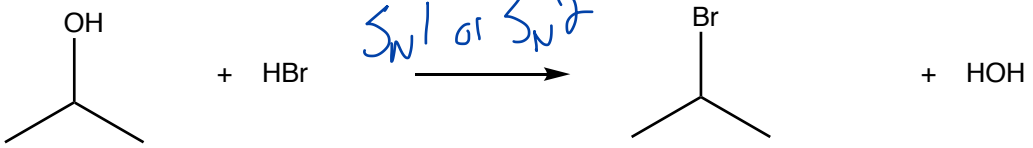
Mechanism?

Conditions are encouraging S_N1 chemistry which makes S_N2 chemistry difficult

Section 10.1

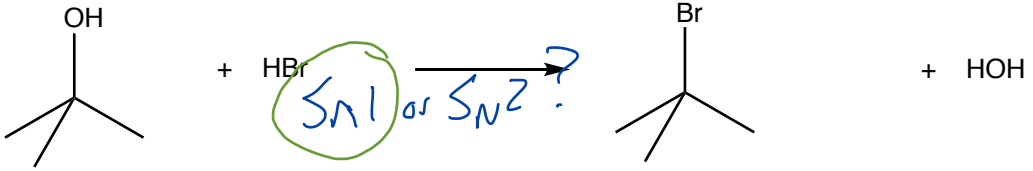
S_N1 or S_N2?

1° α-C — 1° α-C so C^+ not possible ... must do S_N2



S_N1 or S_N2?

2° α-C — 2° C^+ can form under these conditions, S_N2 is less likely due to the conditions of the rxn



S_N1 or S_N2?

3° α-C — 3° α-C too crowded for S_N2 too much steric hinderance

S_N2 needs a good Nucleophile

$Br^\ominus$ is OK

protic or aprotic

/

H-bond donor solvents

\

- tend to help LG's leave
- tend to make nucleophiles weaker
- tend to encourage S_N1 mechanisms

HF $K_a \approx 10^{-4}$

$CH_3OH \xrightarrow{HBr} CH_3Br + H_2O$

$CH_3OH \xrightarrow{HI} CH_3I + H_2O$

Strong acids

$CH_3OH + HF \rightarrow NR$ not strong enough

$CH_3OH + HCl \rightarrow NR$

$CH_3OH \quad H-Cl \rightarrow CH_3-\overset{\oplus}{O}(H)H + Cl^{\ominus} \rightarrow NR$

$CH_3OH \quad H-Br \rightarrow CH_3-\overset{\oplus}{O}(H)H + Br^{\ominus} \rightarrow CH_3-Br + H_2O \quad S_N2$ ✓

S_N2 reactions are favored at 1° & methyl α-C

are favored when good nucleophiles are used

are favored when aprotic solvents are used

protic solvents reduce the nucleophilicity of nucleophiles

$CH_3OH \quad H-F \rightleftharpoons CH_3-\overset{\oplus}{O}(H)H \cdots F^{\ominus} \cdots H-O-CH_3$

F^- too weak a Nu under these conditions

$CH_3OH \quad H-Cl \rightarrow CH_3-\overset{\oplus}{O}(H)H \cdots Cl^{\ominus} \cdots H-O-CH_3$

Cl^- too weak a Nu under these conditions

Today

Sections 10.1, 10.2
Substitution Reactions

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Sulfonate Esters

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Section 10.4
Elimination Reactions

Friday

Chap 13 Infrared

Spectroscopy

HF $K_a \approx 10^{-4}$

$CH_3OH \xrightarrow{HBr} CH_3Br + H_2O$

$CH_3OH \xrightarrow{HI} CH_3I + H_2O$

↑ strong acids

$CH_3OH + HF \rightarrow NR$ not strong enough

$CH_3OH + HCl \rightarrow NR$

$CH_3OH \quad H-Cl \rightarrow CH_3-\overset{\oplus}{O}(H)H + Cl^{\ominus} \rightarrow NR$

$CH_3OH \quad H-Br \rightarrow CH_3-\overset{\oplus}{O}(H)H + Br^{\ominus} \rightarrow CH_3-Br + H_2O \quad S_N2$ ✓

S_N2 reactions are favored at 1° & methyl α-C

are favored when good nucleophiles are used

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protic solvents reduce the nucleophilicity of nucleophiles

$CH_3OH \quad H-F \rightleftharpoons CH_3-\overset{\oplus}{O}(H)H \cdots F^{\ominus}$ (H-bonds: CH_3-O-H)

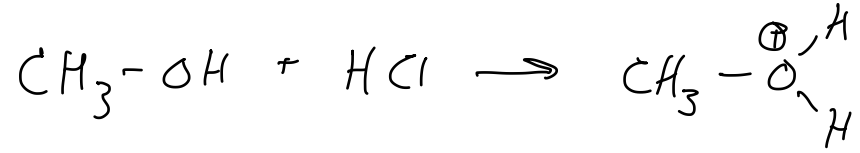
F^- too weak a Nu under these conditions

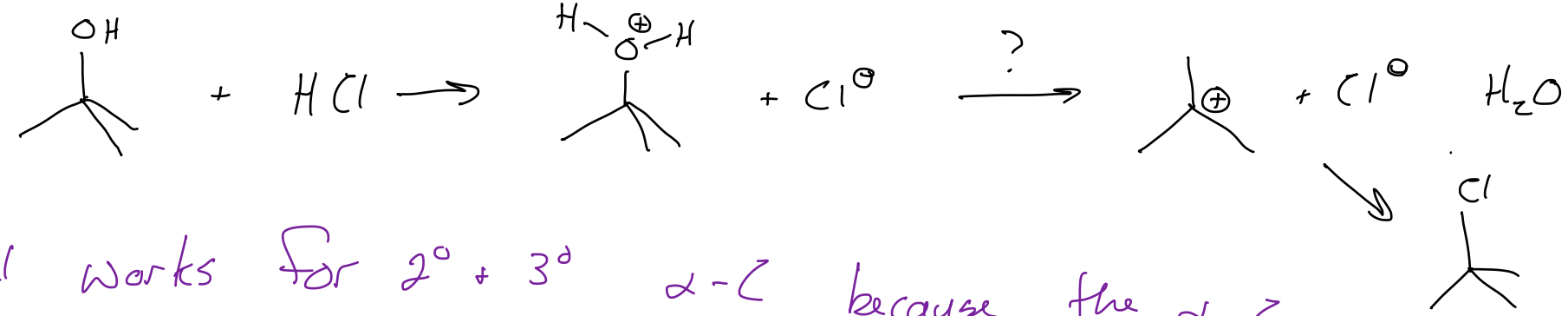
$CH_3OH \quad H-Cl \rightarrow CH_3-\overset{\oplus}{O}(H)H \cdots Cl^{\ominus}$ (H-bond-like interaction: CH_3-O-H)

Cl^- too weak a Nu under these conditions

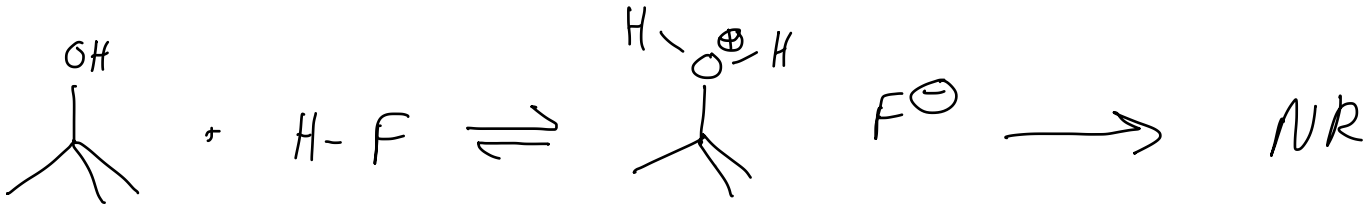
$Br^{\ominus}$ & $I^{\ominus}$ are large enough that H-bonding isn't an issue.

Limitations of using H^+ to convert hydroxyl group to a good leaving group

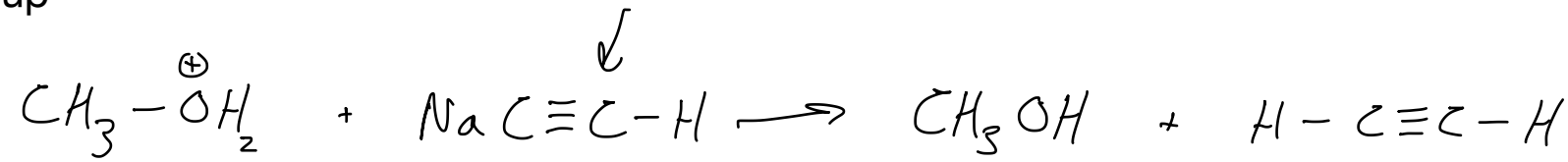




HCl works for 2° + 3° α-C because the α-C can do S_N1 chemistry



Because H-F is a weak acid the more likely reaction is for the protonated alcohol to lose the $H^\oplus$ back to the $F^\ominus$ and go back to the beginning instead of forming a $C^\oplus$



$Na^{\oplus}\ {}^{\ominus}C{\equiv}CH$

very e^- rich, no steric hindrance, great nucleophile

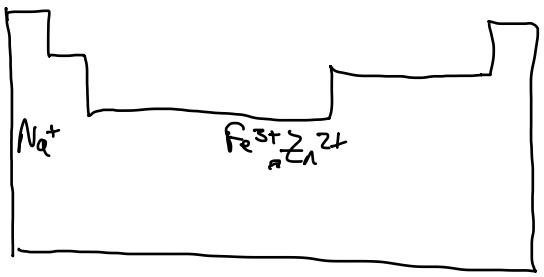
Very small window of nucleophiles that can work with protonated alcohols Nu must be nucleophilic enough to react with the α-C, not small enough to be significantly distracted by or e^- rich enough to act as a base and react with the H^+

What is the solution if one wants to use nucleophiles like $Cl^{\ominus}$ or ${}^{\ominus}C{\equiv}C-H$? Don't use H^+

But what can we use to "soak up" the OH^- e^-'s?

What about a Lewis acid? Sure... why not

Other ways to convert hydroxyl group to a good LG and use Cl^- as a Nucleophile?



Na^+ is not ⊕ enough to be a strong Lewis acid

M^{2+} or M^{3+} these are good Lewis acids

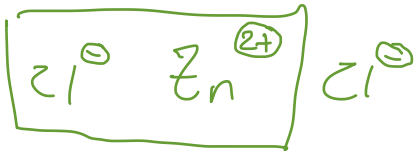
$$AlCl_3 + 3H_2O \rightarrow Al(OH)_3 + 3HCl$$

Al^{3+} is a very strong Lewis acid

Zinc works well for our purposes

$$CH_3OH + ZnCl_2 \rightarrow CH_3-\overset{\oplus}{O}(H)-ZnCl \xrightarrow{Cl^\ominus} CH_3Cl + HOZnCl$$

alcohol acts as solvent



$H^\oplus$ $Cl^\ominus$

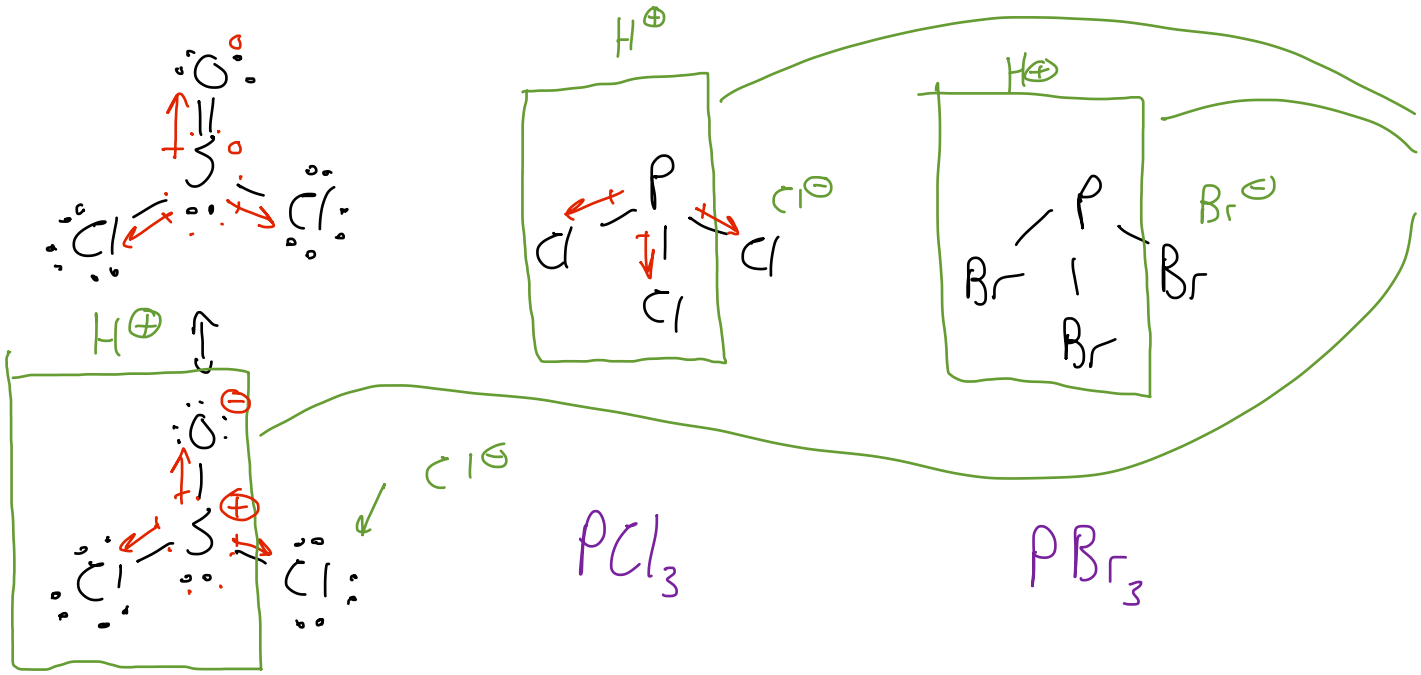
no OH^- LG

Zn^{2+} is the metal in the active site of alcohol dehydrogenase

Other ways to convert hydroxyl group to a good LG and use Cl^- as a Nucleophile?

Section 10.2

Non-metal Lewis acids can do the reaction too...



this part plays the role of the $H^\oplus$

PCl_3

PBr_3

$OSCl_2$ (or $SOCl_2$)

The sulfur is a Lewis acid because the O + Cl's draw e^- density away. The S reacts with the alcohol's O atom

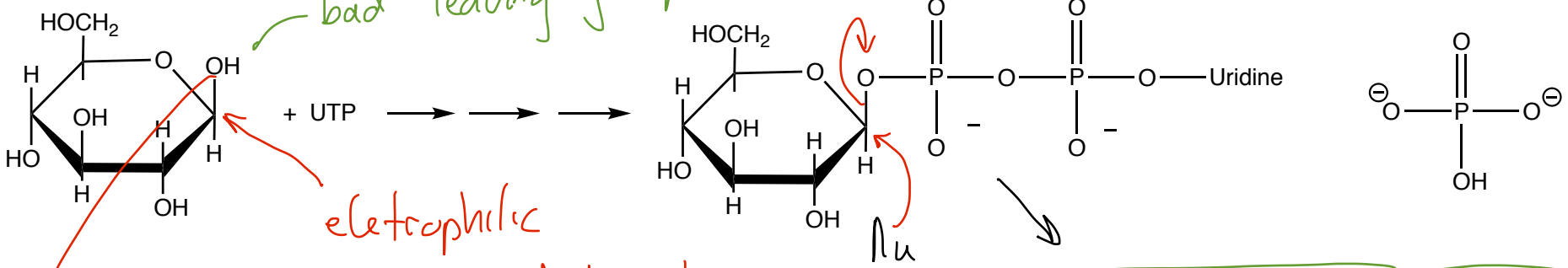
S_N2 chemistry CH_3 + 1° α-C will work

2° α-C will work but not as well

3° α-C? NO

How about just making good leaving groups?

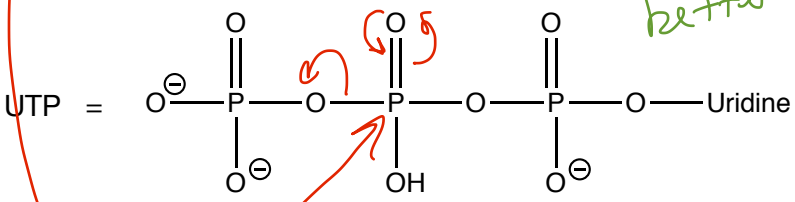
Biochemical Conversion of a Bad Hydroxyl Leaving Group to a Good Phosphate Leaving Group



bad leaving group

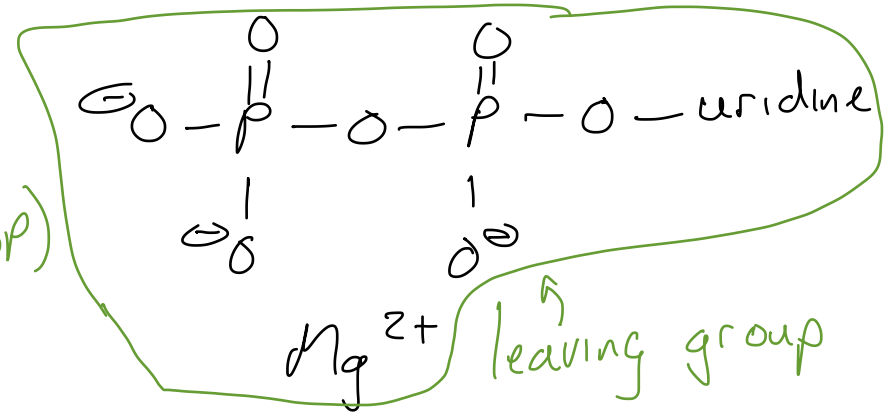
electrophilic

α-C good target for nucleophilic attack



use UTP to convert bad $OH^{\ominus}$ LG into a better phosphate (UDP) leaving group

this is actually a multi step mechanism



leaving group

this is a much weaker base than OH^-

Today

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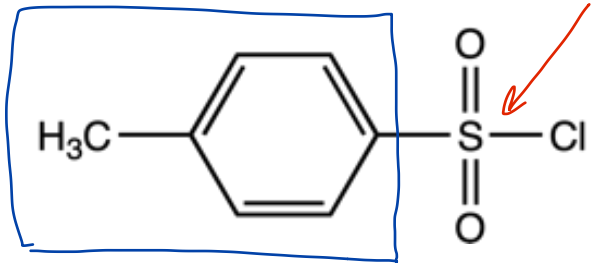
Elimination Reactions

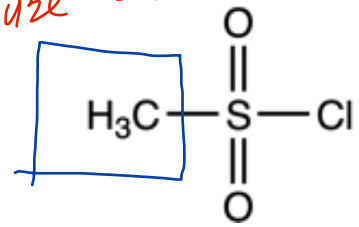
Friday

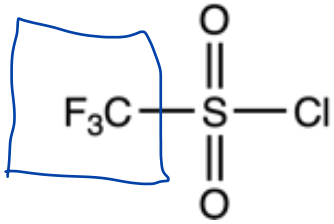
Section 13.1 Introduction to Mass Spectrometry

p-toluenesulfonylchloride	methanesulfonyl chloride	trifluoromethanesulfonyl chloride



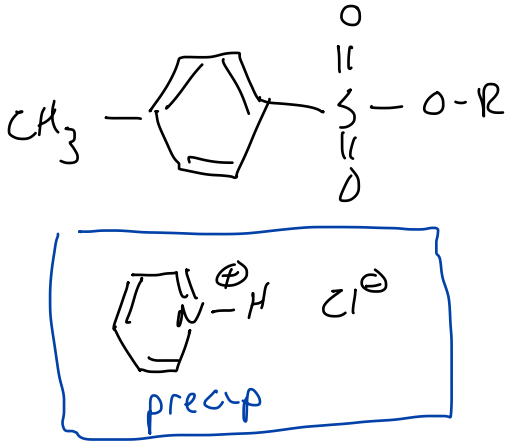
electron deficient S atom because all the eneg atoms attached

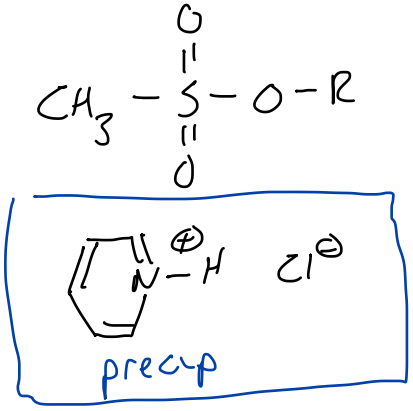


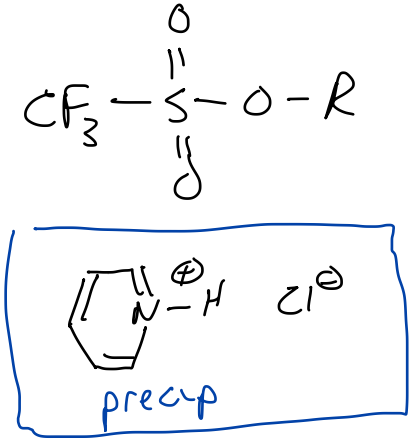


p-toluenesulfonyl chloride a.k.a. toscyl chloride	methanesulfonyl chloride	trifluoromethanesulfonyl chloride a.k.a. triflyl chloride

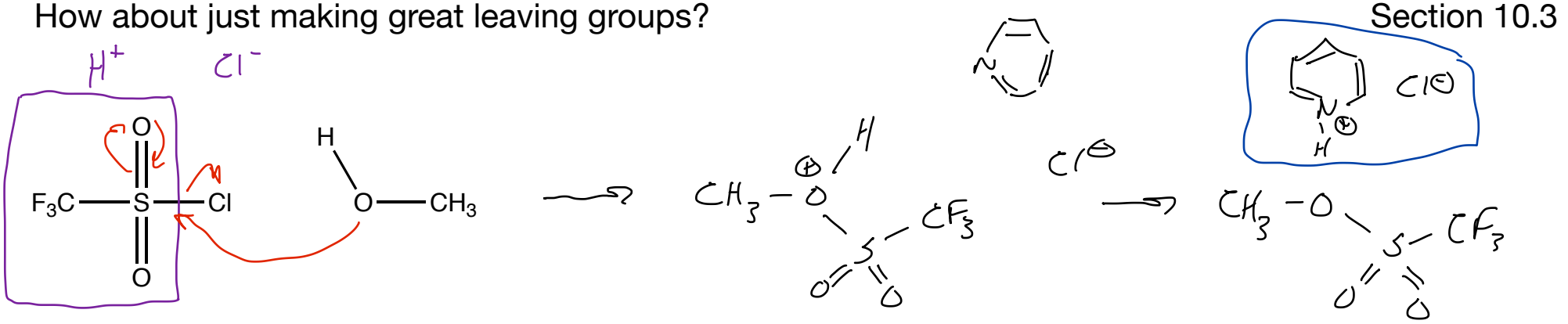
+ ROH in pyridine

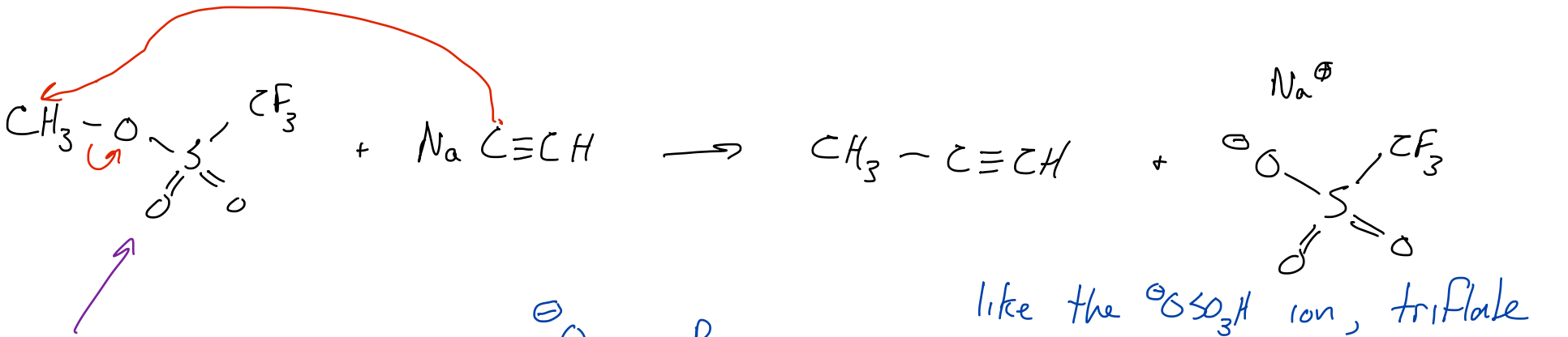






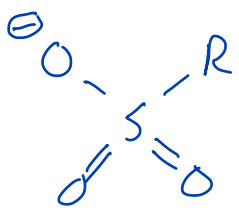
How about just making great leaving groups?



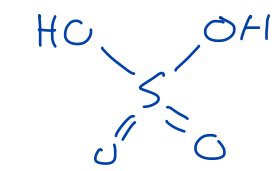


trifluoromethylsulfonate LG

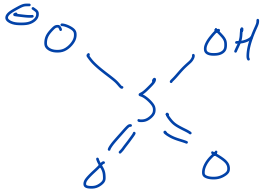
triflate LG



Kinda, sorta looks like



strong

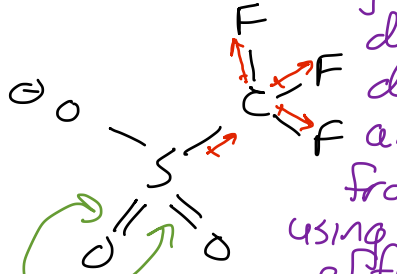


weak base

this is the conjugate base of H_2SO_4

H^+

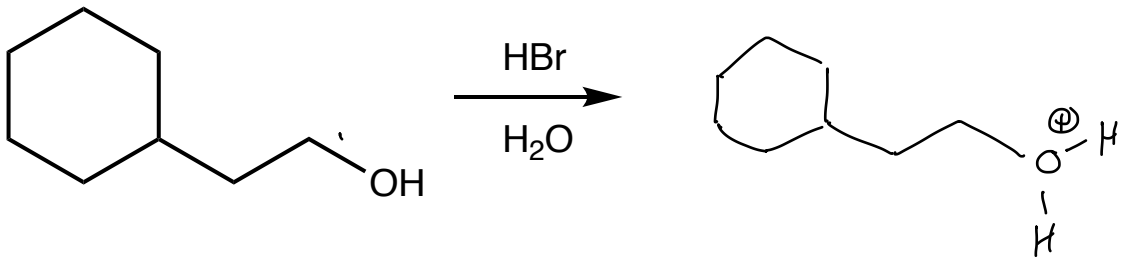
like the $^{\ominus}OSO_3H$ ion, triflate is a weak base, so it is a good LG



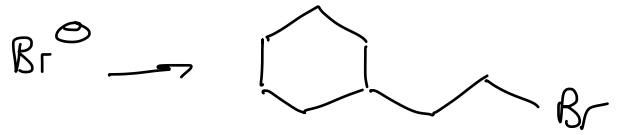
eneg F's draw e⁻ density away from O using inductive effect

resonance stabilization over 3 O atoms

Reactions



good Nu, can do S_N2 or S_N1 with protons present

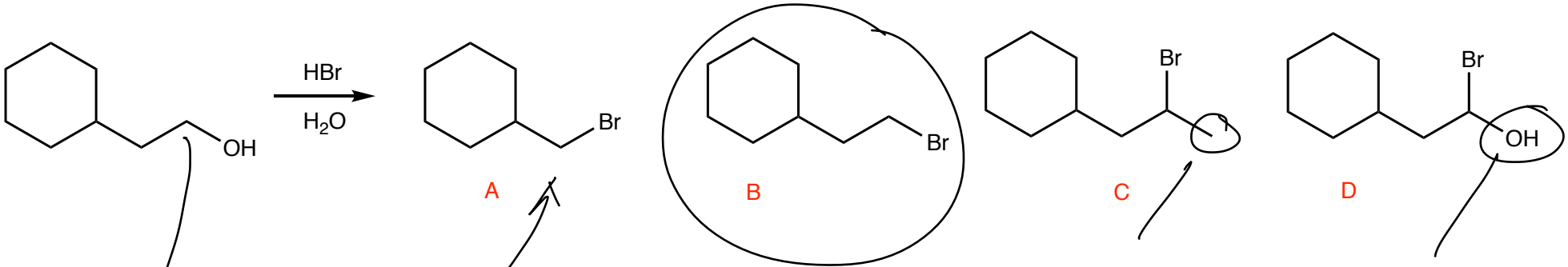


2-cyclohexyl-1-ethanol

H_2O

(2-bromoethyl)cyclohexane

Reactions



lost a C

remember to add the bond to connect to the new atom don't just erase the old bond

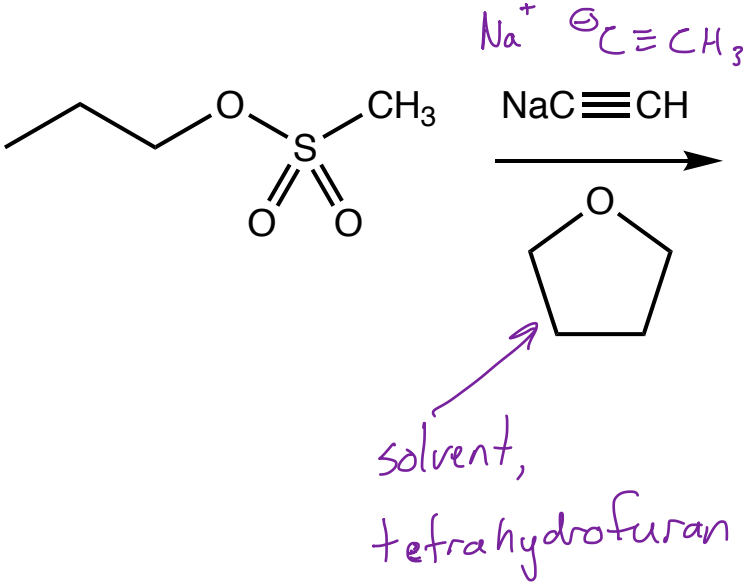
too many C atoms

leaving group has to leave

S_N2 'cuz 1° α-C ... work with HCl ? NO

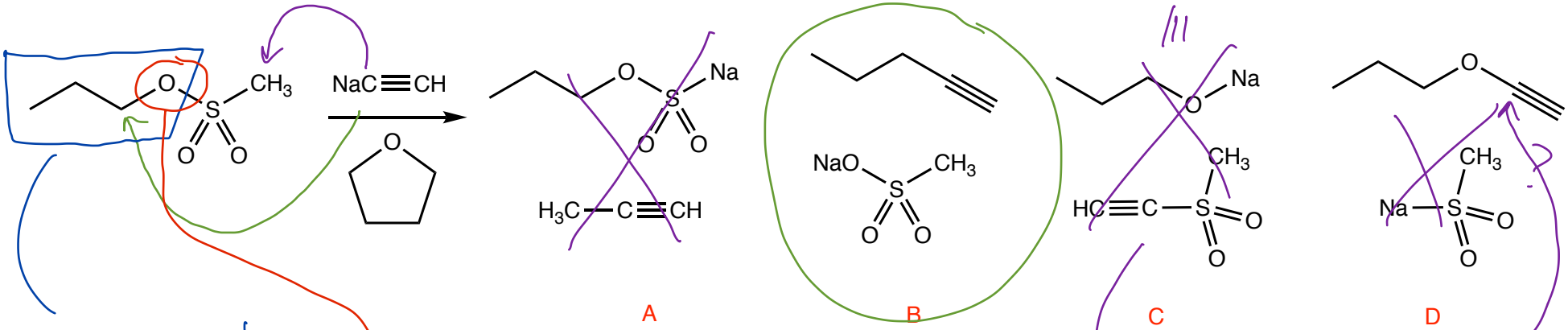
HCl only works with 2° + 3°

Reactions



Reactions

too strong a base to be a LG



this was the alcohol we started with

this is the O of the OH that we were converting into a good LG

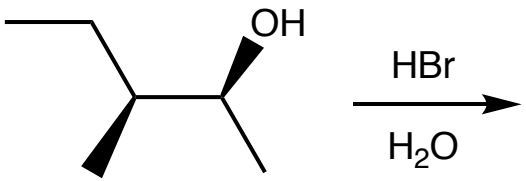
and this C is going to be more attractive to the nucleophile because of the oneg O atom banded to it

HC≡CΘ would attack S

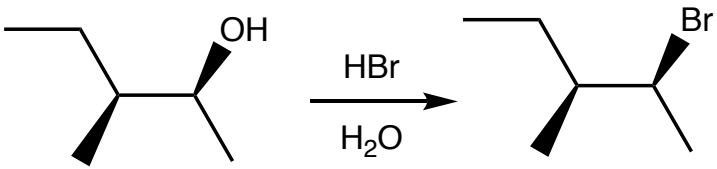
this e⁻ rich C atom would be repelled by the e⁻ rich O atom

the C with the C to O bond is our target for nucleophilic substitution

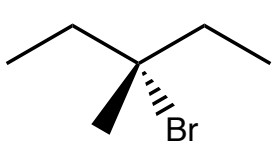
Reactions



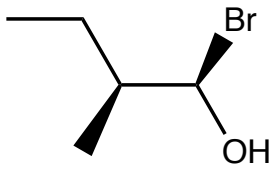
Reactions



A



B



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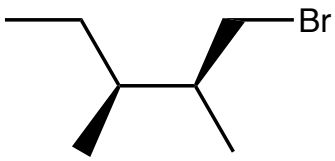
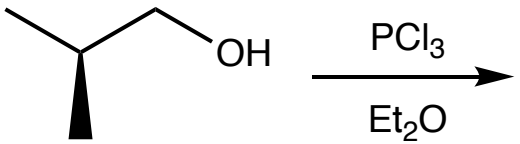
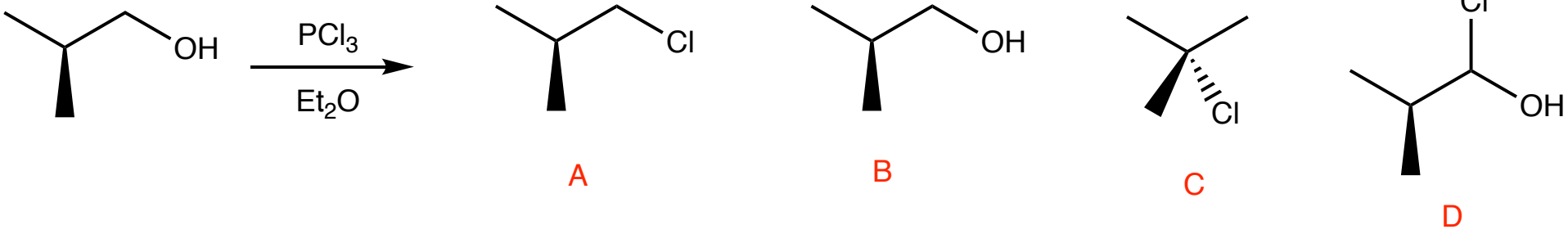


D

Reactions



Reactions



A B C D

Strong mineral acids acids convert bad hydroxyl LGs to good water LGs.

Sufficiently nucleophilic counter ions will react with all alcohols.

$X^{\ominus} = Br^{\ominus}$ & $I^{\ominus}$ works for 1°, 2°, & 3° aliphatic alcohols (alkanes)

$X^{\ominus} = Cl^{\ominus}$ works for 2° & 3°

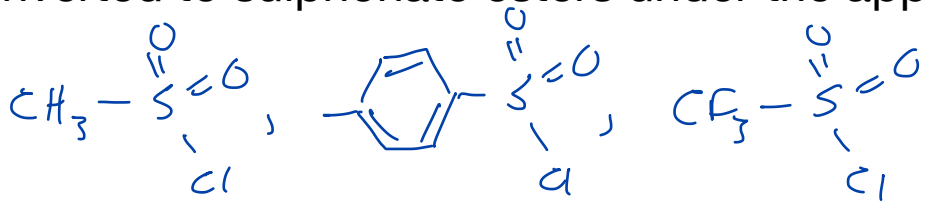
$ZnCl_2$ converts the hydroxyl to a better LG so the Cl^- will react

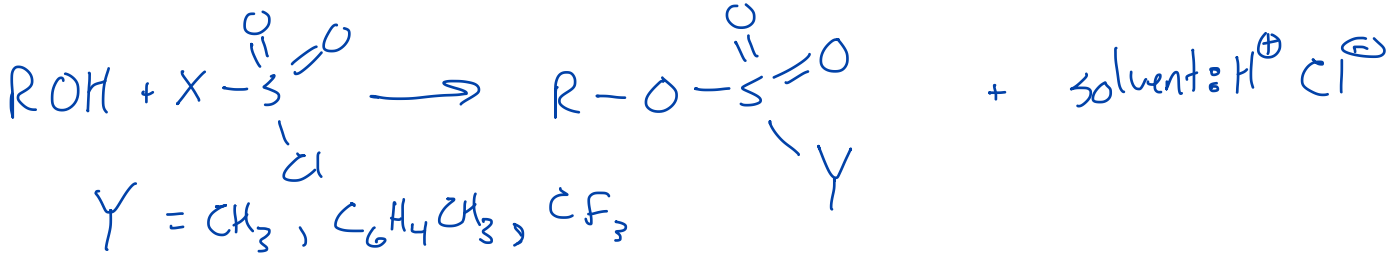
Zinc Lewis acid makes a better LG .... 1°, 2°, 3° α-C ok

Aprotic Lewis acids that release nucleophilic ions will react with alcohols via an S_N2 mechanism

$OSCl_2$ PCl_3 PBr_3 1°, 2° α-C no 3° α-C

Alcohols can be converted to sulphonate esters under the appropriate appropriate conditions.





What happens when hydroxyl groups are converted to good leaving groups and no nucleophile is added?