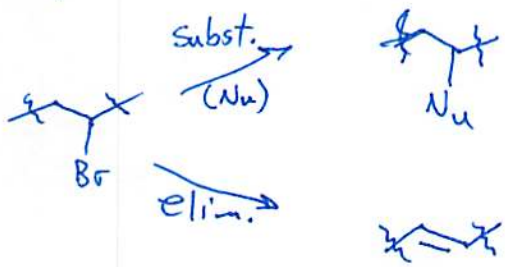
# Alkyl Halides - Synthesis

By now, we have looked at reactions of R-X (alkyl halides) along with a few ways to synthesize them. These compounds can be very useful in organic synthesis.

In general, consider:

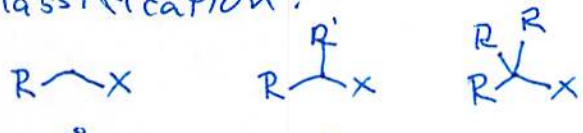



In our bodies, the "Nu" can be DNA. Its alkylation can lead to lots of diseases. Similarly, alkylating DNA of cancer cells can be used in chemotherapy.

Alkyl Halides can be toxic, but not all of them are bad.

Nomenclature: ON YOUR OWN!

Classification:



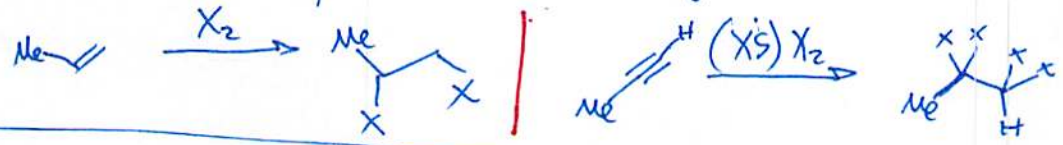

Physical properties:
- Polar (no H-bonding)
- Moderate boiling / melting point
- Water insoluble (generally)

# Synthesis of Alkyl Halides (R–X)

## ① Halogenation of Alkanes (free-radical halogenation)

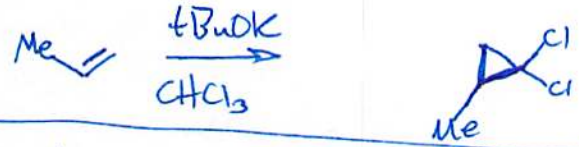

X = Cl, Br

## ② Halogenation of Alkenes & Alkynes (Ionic Electrophilic Addition) IEA




## ③ Addition of HX to Alkenes & Alkynes (IEA)

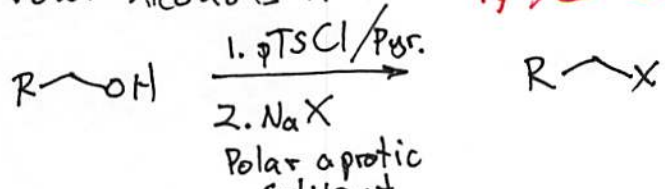

## ④ Addition of :CCl2 to alkenes




## ⑤ Allylic Bromination

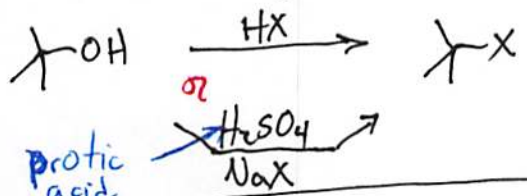

## ⑥ From Alcohols via Ts

1°, & 2° only, via $S_N2$



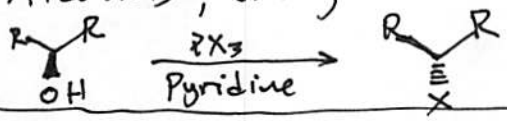

## ⑦ From Alcohols by protonation

3°, Allylic, Benzylic ; via $S_N1$



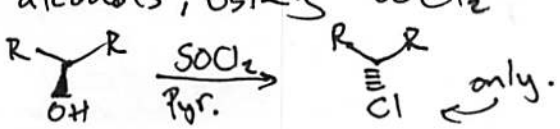

## ⑧ From Alcohols, using $PX_3$

via $S_N2$, works for 1°, 2° only




## ⑨ From alcohols, using $SOCl_2$

via $S_N2$ / 1°, 2°



# Reaction 6: 1° or 2° R-OH to R-X

Strategy: ① Convert -OH into a better, non-ionizable leaving group (LG)

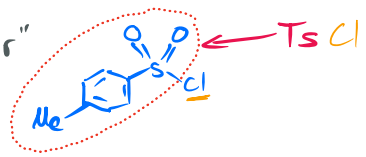
② Displace with NaX, where X = Cl, Br, I

Net Rxn: R-OH $\xrightarrow[\text{2) NaX, DMF}]{\text{1) TsCl, Pyridine}}$ R-Br (SN2)

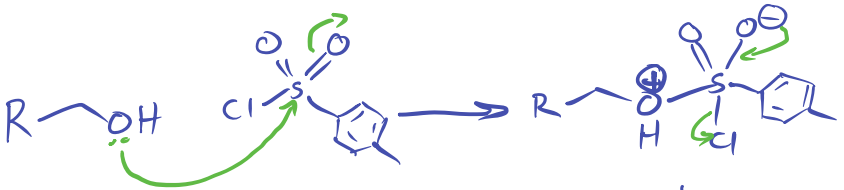
Polar Aprotic solvent

TsCl = Tosyl Chloride

Pyridine "Pyr" — Base



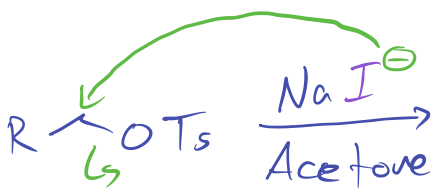

Mechanism: Rxn 1



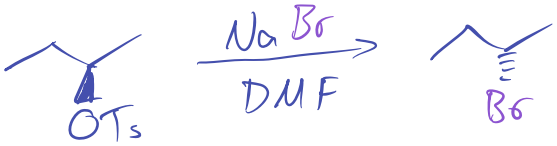
Stable, can be isolated

R-OTs ≡ end of step 1

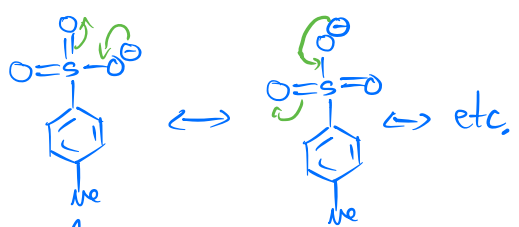

Rxn 2:




For 2° ROH




SN2 Rxn results in Net inversion of stereochemistry.




- Excellent LG
- Non-Nucleophilic
- Does not ionize on its own

why? - Resonance!

## Rxn 7 | ROH to RX using HX

strategy: Protonate –OH to turn it into a better LG

Net Rxn 

Mechanism – $S_N1$

Works best for: 3°, Allylic, or Benzylic halides

Disadvantages:
- Competitive elimination products
- Rearrangements can occur
- lose chirality

Advantage: Best way to make 3° halides from ROH.

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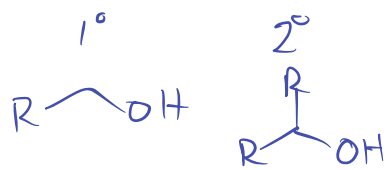
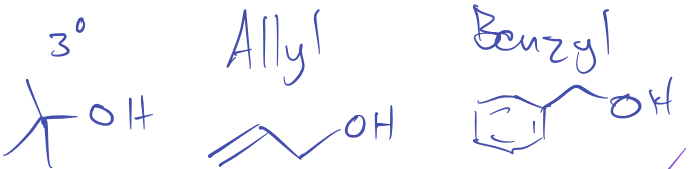
Summary:



- Convert to tosylate
- Displace with $X^{\ominus}$



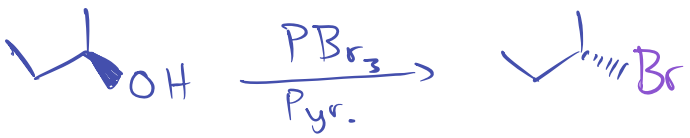
- Protonate OH
- Nucleophilic attack to ⊕C by $X^{\ominus}$
- Rearrangements possible

# Reaction 8| ROH to RX using $PX_3$

Phosphorous Trihalides

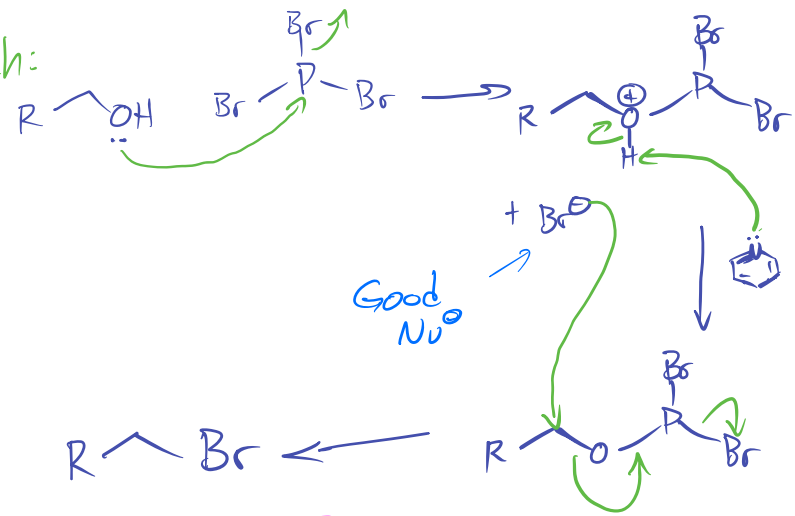
- $PX_3$ = $PCl_3$, $PBr_3$, $P + I_2 \equiv$ "$PI_3$"
- ROH = $-CH_3$, 1°, 2° (in order of reactivity)
- No Rearrangements!

ex. 



- Polar aprotic solvent
- Via $S_N2$-type process
- Net inversion of stereochemistry

Mech:




$S_N2$

+ $Br{=}P{=}O$
& $Br^{\ominus}$

- Not isolable (too reactive)

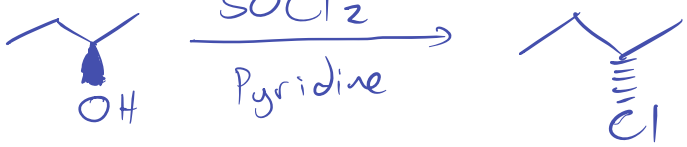
- If chiral center, results in net inversion of stereochemistry.

# Rxn 9 | R-OH to R-Cl using thionyl chloride ($SOCl_2$)

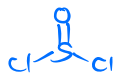
only

not RBr or RI

Net Rxn:

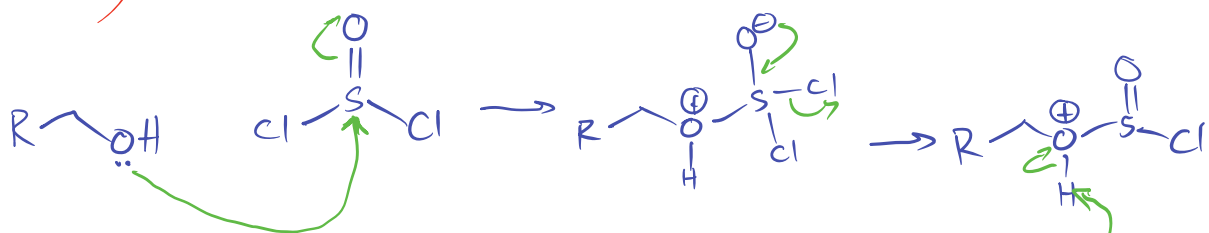



$SOCl_2$ =



- Net $S_N2$
- Works with 1° or 2°

## Mechanism (WoW)



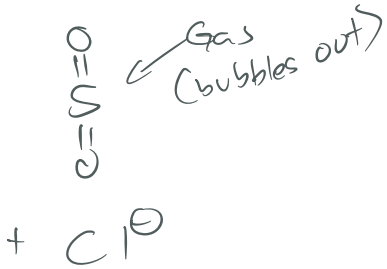




Activated LG

$S_N2$

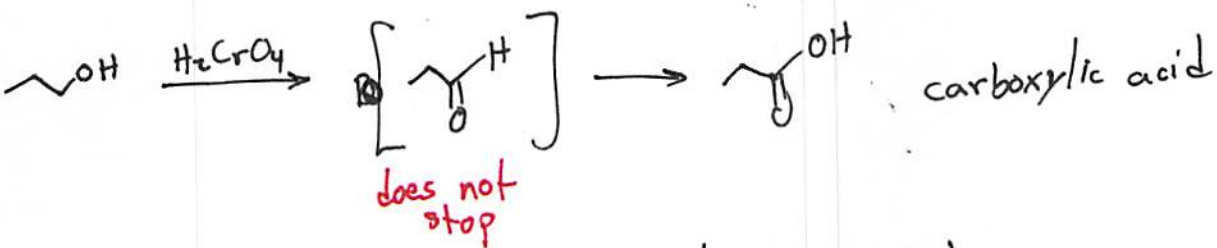


# Oxidation of Alcohols

## ① Vigorous Oxidation – using chromic acid

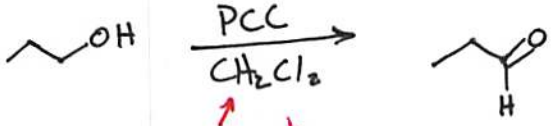
2° –OH  Ketone

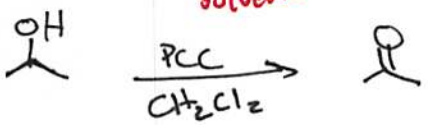
1° –OH 

carboxylic acid

3° –OH does not oxidize to carbonyl compound.

## ② Mild Oxidation – Using PCC or HOCl

1° –OH  aldehyde!

2° –OH  Ketone!

3° –OH No oxidation.

PCC =  $CrOCl^{\ominus}$

Pyridinium chlorachromate

OR

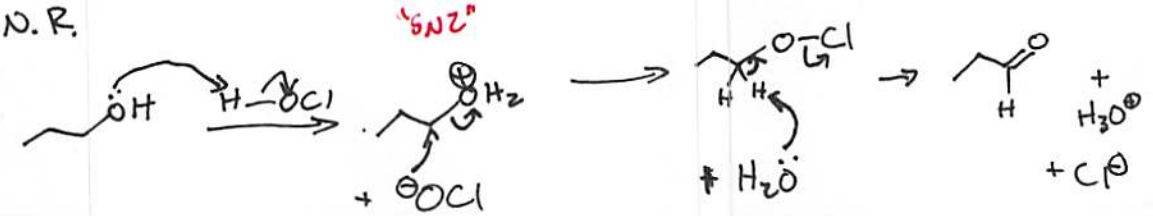
1° –OH  aldehyde!

2° –OH  Ketone

3° –OH N.R.

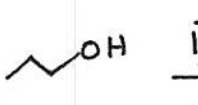
HOCl formed by:

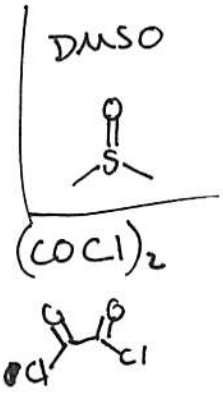
NaOCl, AcOH, @ 0°C > Reagents

Mechanism: 

# Swern Oxidation (Mild) - 2 step Rxn.

oxyallyl chloride

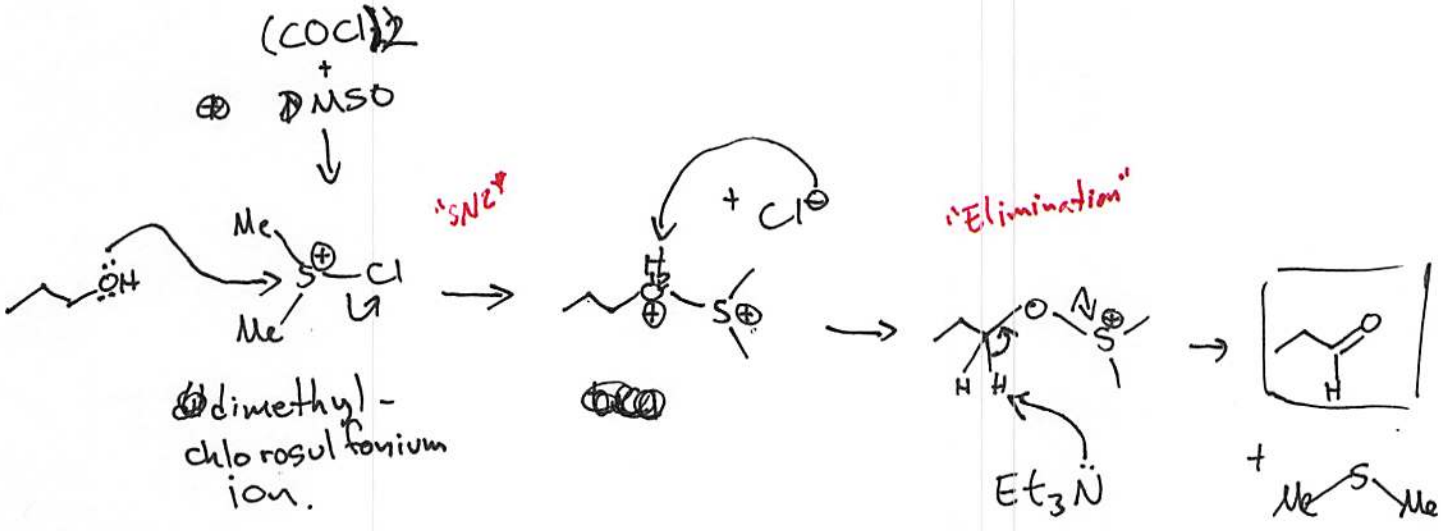
1° -OH  1) DMSO/(COCl)2 2) $Et_3N$  aldehyde




2° -OH  "Swern"  Ketone

3° -OH N.R.

Mechanism:




dimethyl-chlorosulfonium ion.