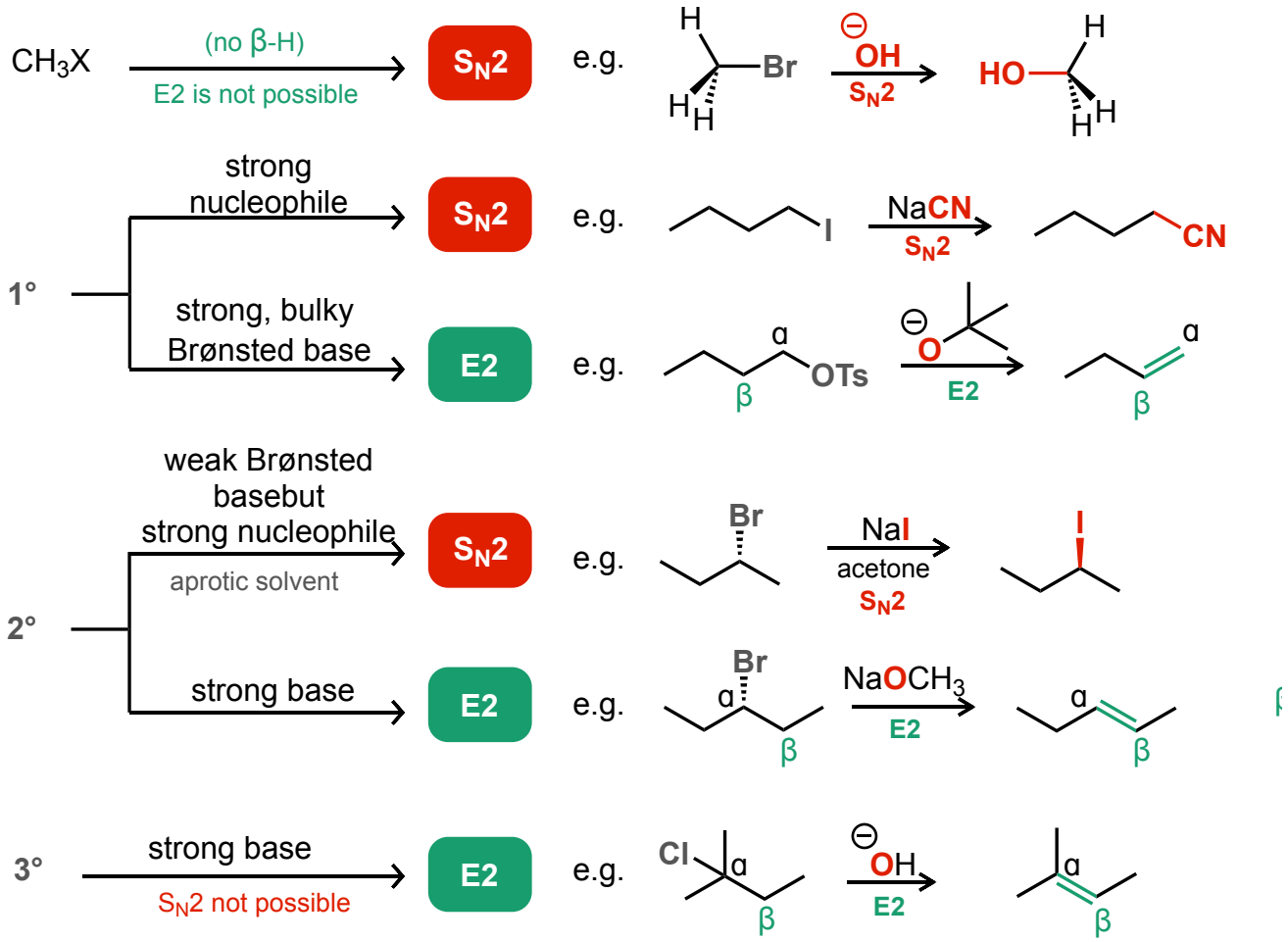
Substitution and Elimination Reactions with R—X

The flow chart shown below can be used to identify which reaction mechanism (S_N2 or E2) is likely, given your specific reactants and reaction conditions.

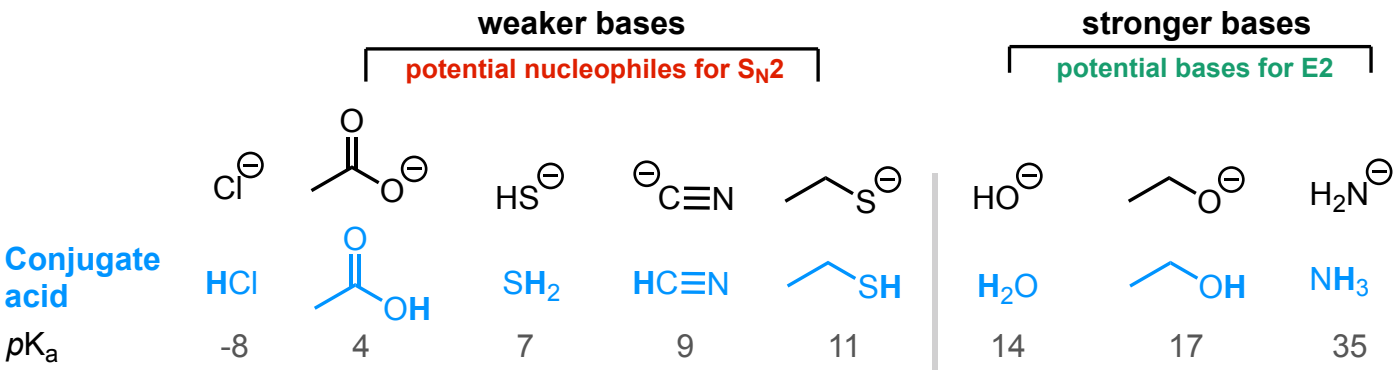
Flow Chart use only with R—X or R—OTs *read from left to right*

1) **Designate the degree of substitution** of the **carbon bearing the leaving group**
2) Assess the **strength and sterics of the Lewis base**
3) If necessary, determine if the solvent is protic (common for E2) or aprotic



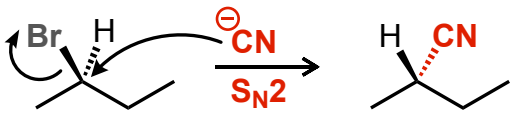
Scope of Lewis Base Strength in Bimolecular Reactions

If the **base** has a **conjugate acid** with a pK_a value higher than H_2O (14), then the Brønsted base is strong enough to initiate an E2 reaction



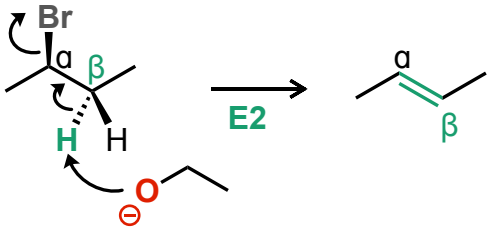
Curved Arrow Mechanisms for Bimolecular Substitution and Elimination

Curved-arrow mechanisms for ***concerted*** (*i.e.,* occur in a single step) substitution reactions (S_N2) and elimination reactions (E2):



Cyanide nucleophile attacks from the opposite face of the leaving group

Note: inversion of stereochemistry only [Br on wedge, CN on hash]



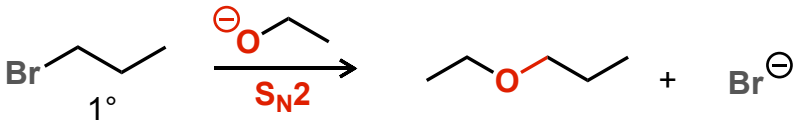
Reaction typically forms the most substituted, *E* alkene between antiperiplanar β-H and leaving group

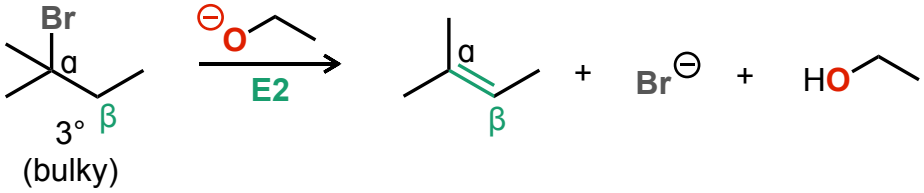
[Br on wedge, H on hash]

The alkene will always form between α and β

Impact of the Sterics of the Electrophile on S_N2 and E2

As shown in the chart above, **as the degree of substitution of the electrophile increases**, **E2 reactions are more likely to occur**

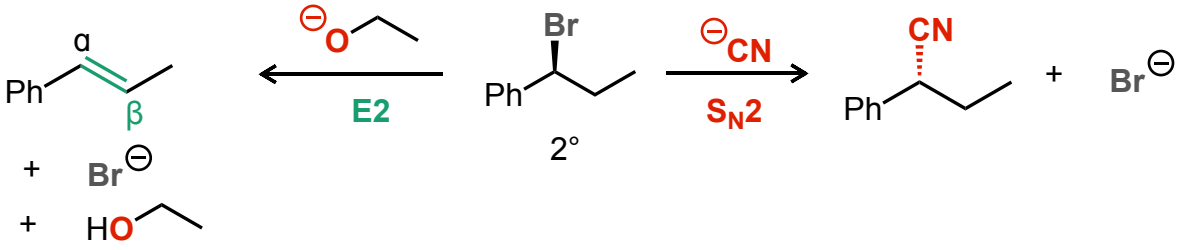




Given that ethoxide is mildly basic (pK_a of ethanol ~ 17), it can participate in S_N2 or E2 reactions, depending on the substitution of the electrophile

Impact of Base Strength on S_N2 and E2

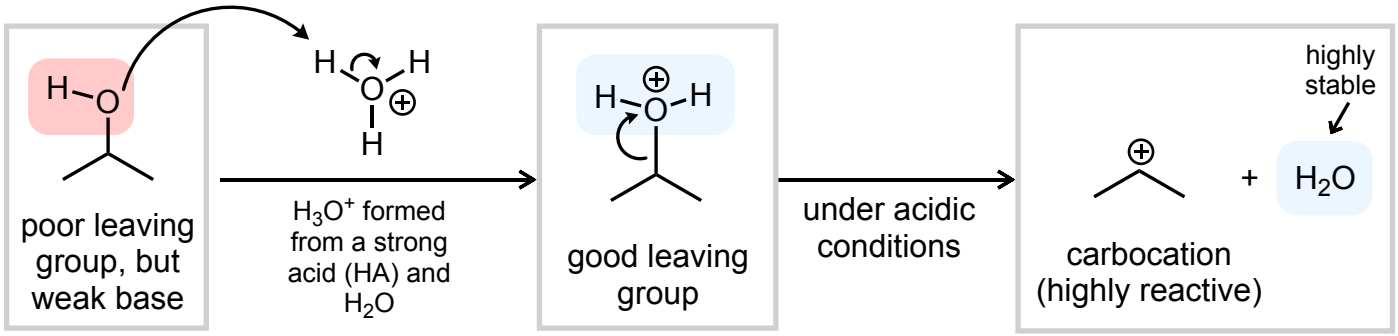
In general, **weak bases, like cyanide, are nucleophiles for S_N2 reactions** whereas **stronger bases like ethoxide or t-butoxide are bases in E2 reactions**. This trend is especially impactful at 2° R—X electrophiles.



Substitution and Elimination Reactions with Alcohols (R—OH)

Although the -OH group of an alcohol is a poor leaving group, **alcohols can still undergo stepwise substitution (S_N1) and elimination reactions (E1) in the presence of strong acids**.

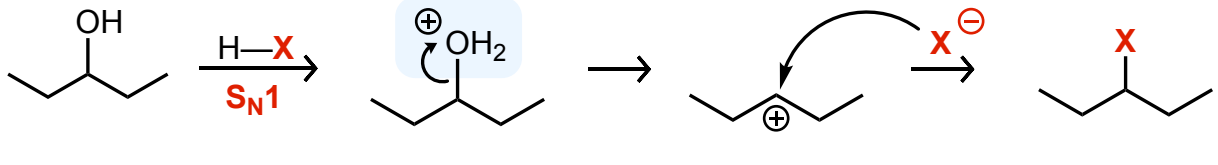
Why Strong Acid?



Curved Arrow Mechanisms for Unimolecular Substitution and Elimination

Curved-arrow mechanisms for ***step-wise*** (*i.e.,* occur over multiple steps) substitution reactions (S_N1) and elimination reactions (E1):

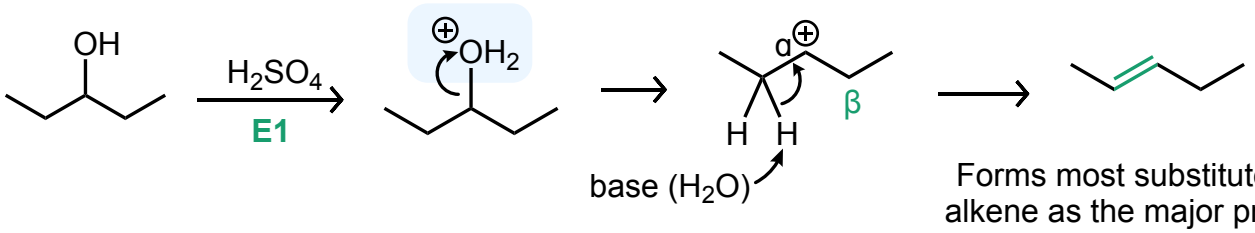
In both reactions, the first step involves protonation of the alcohol to "activate" it as a leaving group. Then, "water" leaves and a carbocation is formed.



$\ominus$X is nucleophilic enough to promote an S_N1 reaction

forms both stereoisomers if a chiral center is made (racemic mixture)

Note: carbocation shifts possible



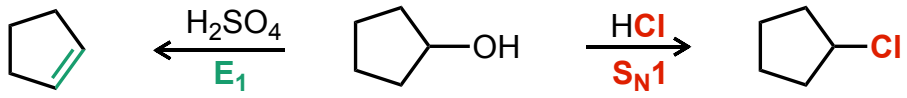
Forms most substituted, E alkene as the major product

Alkene will always form between the carbocation carbon and the β-carbon

No antiperiplanar requirement between β—H and leaving group because final step to form the alkene occurs from the carbocation intermediate

How to Decide Between S_N1 and E1?

In general, this is determined by the conjugate base of the strong acid that was used. Remember that strong acids completely dissociate in H_2O.

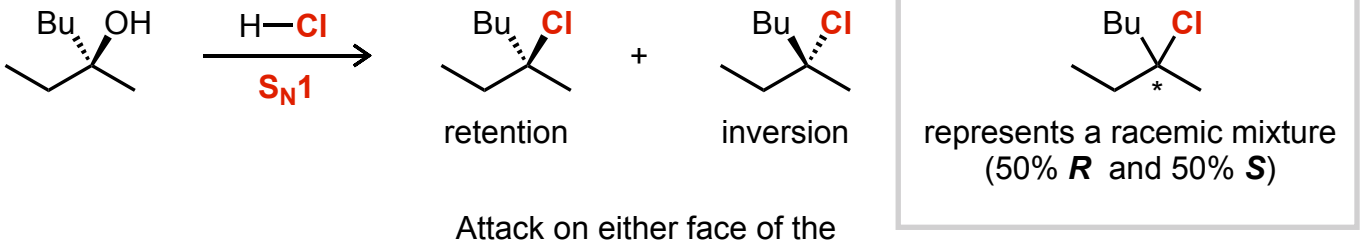


HSO_4 is not nucleophilic so E1 occurs

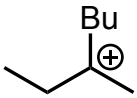
$Cl^{\ominus}$ is nucleophilic enough to promote an S_N1 reaction

Products in Substitution Reactions

In S_N1 reactions, there is always racemization of stereochemistry at the chiral center involved in the reaction

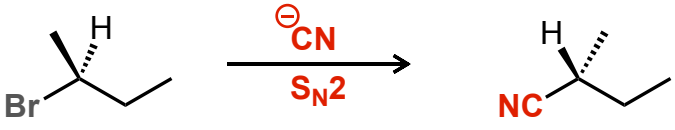


via:



Attack on either face of the carbocation results in stereoisomers if the reaction forms a chiral center

Recall that in S_N2 reactions, there is always complete inversion of stereochemistry, resulting in the formation of a single stereoisomer



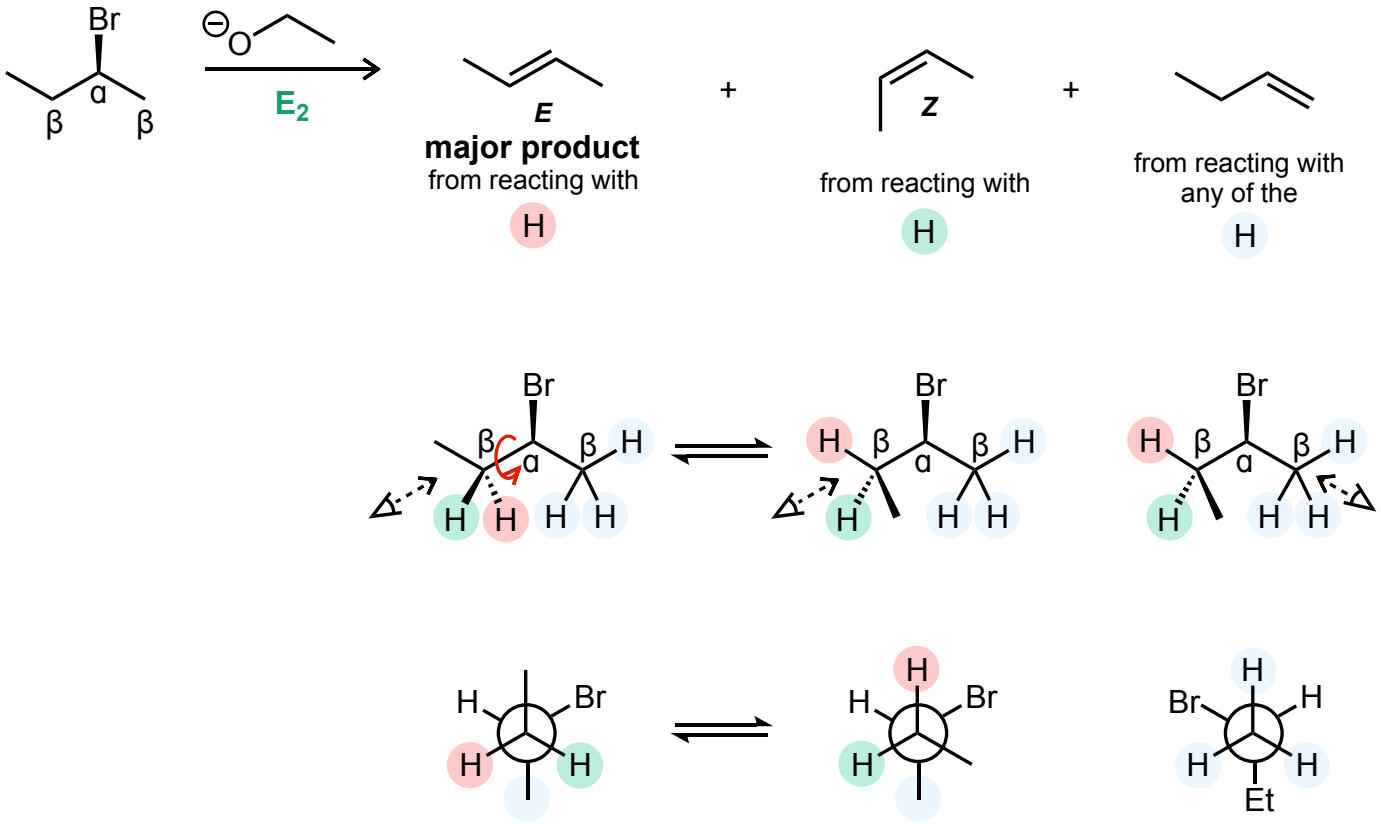
inversion only

Products in Elimination Reactions

In both **E1** and **E2** reactions, **both regioisomers and stereoisomers can form**. However, the reactions both typically favor the most substituted, ***E*** alkene as the major product

Multiple β-sites can react, producing alkenes at different positions in the molecule (regioisomers). In some cases, having two β-H's on a single site will generate two stereoisomers.

E2 reactions with multiple reactive β carbons



The reacting β-H must be antiperiplanar to the leaving group

E1 reactions with multiple reactive β carbons

Since carbocations are planar, deprotonation to form the alkene results in both ***E*** and ***Z*** isomers being formed (stereoisomers) for any and all β-sites with atleast one H atom