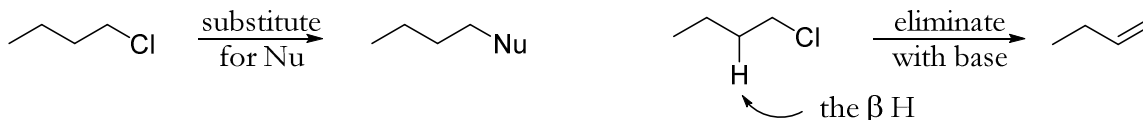


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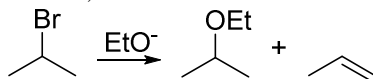
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Chapter 9 covers reactions you can do with alkyl halides. For the most part, these break down into two categories: substitution and elimination. Substitution results in replacing the halogen with some other group. Elimination results in removing the halogen, along with a hydrogen on a neighboring atom (the β H), to create a new double bond.



There are several terms that are useful to know here:

- The **substrate** is the molecule having this reaction performed on it.
- The **leaving group** or LG is the group that dissociates from the substrate. In this chapter, all the leaving groups are halogens.
- The **base/nucleophile** is the molecule that attacks the substrate. If it performs substitution, then it's acting as a nucleophile (because it's attacking a C atom); if it performs elimination then it's acting as a base (because it's attacking an H atom). Often it can do a mixture of both jobs:



Reaction Kinetics

The reactions we'll see can be subdivided based on kinetics (how fast the reaction occurs, or the reaction rate). Reaction rate is defined as:

$$\text{rate} = \frac{\text{change in product concentration}}{\text{time}}$$

The rate is often set by the concentrations of one or more reactants; concentrations are usually given in square brackets. For a reaction like $A + B \rightarrow C$, the rate can be measured at various concentrations of each reactant. For example, if double the concentration of A or the concentration of B doubles the rate, then the rate law would be $\text{rate} = k [A][B]$. For a different reaction, perhaps doubling the concentration of A quadruples the rate but doubling the concentration of B has no effect. In this case the rate law would be $\text{rate} = k [A]^2$. **Overall kinetic order** is the sum of the powers in the rate law for a reaction. For $\text{rate} = k [A][B]$, it's second-order overall (first-order in A, and first-order in B). For $\text{rate} = k [A]^2$, it would also be second-order overall (second-order in A, and zeroth-order in B). The order is determined by how many molecules are involved in the rate-determining step. First-order reactions involve only one molecule and are unimolecular, second-order reactions involve two and are bimolecular, and third-order reactions involve three and are termolecular. k , the rate constant, varies from reaction to reaction. A bigger k gives a faster reaction. It's controlled by the activation energy, ΔG^\ddagger - a smaller activation energy gives bigger k . It's also controlled by temperature - higher temperature gives a bigger k .

The substitution and elimination reactions in this chapter each have one unimolecular and one bimolecular option. They are:

S_N1 : First-order substitution	E1: First-order elimination
S_N2 : Second-order substitution	E2: Second-order elimination

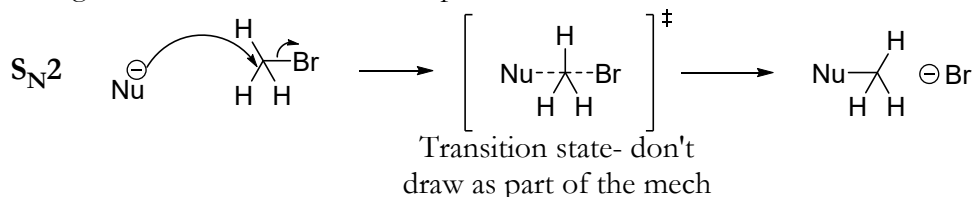
Looking at the mechanism for each one will explain why it behaves the way it does.

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S_N2

The attacking nucleophile forms a bond to the substrate at the same time the leaving group is dissociating. This is a concerted, one-step reaction.

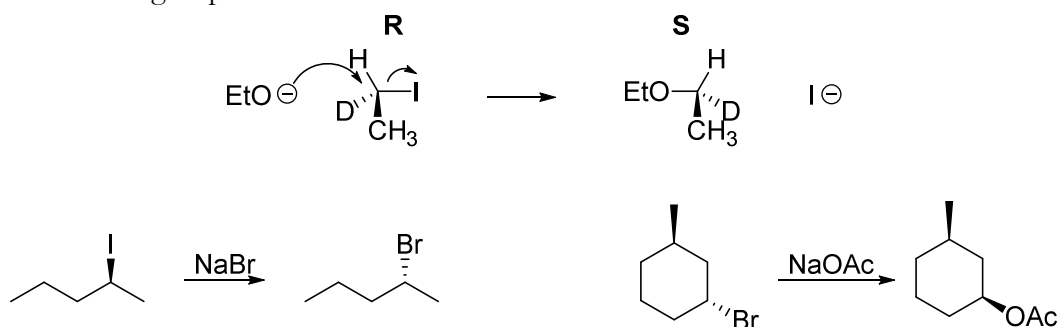


Since both the substrate and the nucleophile are involved in the RDS, the reaction is second-order. This reaction has several interesting characteristics, as a result of its mechanism being what it is.

- Since the carbon has bonds or partial bonds to five atoms at once during the transition state, space is at a premium. The fewer R groups and the more Hs there are on the central carbon (in other words, the less sterically hindered the carbon is), the faster this reaction will go. The trend is Me > 1° > 2° > 3°. Some examples of relative S_N2 rates are given below – these are just examples under a very specific set of conditions, but the same general trends hold for all S_N2 reactions.

Substrate	Relative Rate	This list has increasing substitution at the α carbon - it goes from Me, to 1°, to 2°, to 3° alkyl halides. S _N 2 is good on Me and 1°, mediocre on 2°, and NR (no reaction) on 3°.	Substrate	Relative Rate	This list has increasing substitution at the β carbon, although they're all Me or 1°. The last compound, commonly named neopentyl bromide, is so slow at S _N 2 that it's also NR. This is called the neopentyl effect.
	145			145	
	1			0.82	
	0.0078			0.036	
	0.0005			0.000012	

- Since the nucleophile attacks from the side opposite to the leaving group, **inversion of stereochemistry** occurs. We've seen this before in the opening of bromonium rings – it's similar to an umbrella turning inside-out. If the leaving group had a bold bond before, then the new group will have a dashed bond or vice-versa.



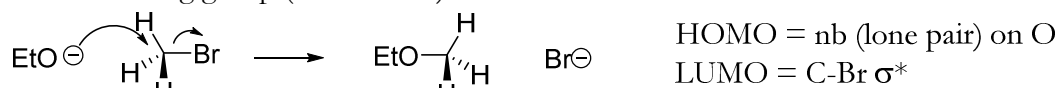
This also means that as long as the leaving group and the incoming group have the same priority ranking in CIP rules, the molecule will convert from R to S or vice-versa at the attacked carbon.

Why does S_N2 happen this way? It has to do with the shapes of the frontier molecular orbitals involved. The HOMO is the lone pair on the nucleophilic atom (the O in EtO⁻

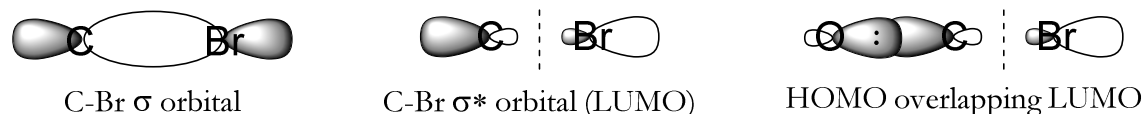
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in this example) and the LUMO is the bond that is about to break between the carbon and the leaving group (the C-Br σ^*).



For the reaction to occur, these orbitals must overlap each other. The shapes of the C-Br σ and σ^* orbitals are shown here:

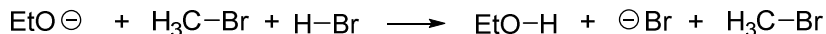


The largest lobe of the σ^* orbital is on C, pointing in the opposite direction from the Br. For the lone pair on the nucleophile to overlap with this, it must perform backside attack from about 180° away from the leaving group. This is why backside attack on carbon is required – it's the only way for the orbitals to overlap properly.

- The S_N2 mechanism looks very similar to an acid-base reaction:



The only difference is that an alkyl group is getting transferred, instead of a proton. The rates for these reactions, though, are very different. Acid-base occurs almost instantaneously, while S_N2 takes minutes to hours. This means that if both reactions are a possibility (as determined by relative pK_a values, like we saw in Ch. 3), acid-base will happen faster.

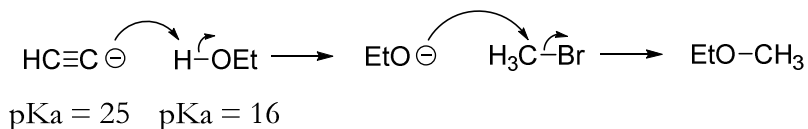


If all reagents are present in equal amounts,
no S_N2 occurs - only acid-base

However, the product of the acid-base reaction can often go on to do its own S_N2 reaction on the substrate, giving an unexpected side product.



Instead, the base/Nu does acid-base reaction with EtOH
first, creating EtO⁻. This goes on to perform S_N2 on CH_3Br



- Nucleophilicity vs. Basicity: Basicity is how good something is at forming new bonds to H, and nucleophilicity is how good something is at forming new bonds to something other than H (in this case, C). We can use pK_a values to compare basicity. There's not a single number that describes nucleophilicity, but we can get an estimate of it by comparing S_N2 rates under the same conditions. It turns out that nucleophilicity follows different trends in protic vs. aprotic solvents. In **protic solvents**:
 - If the charge-bearing atoms are within the same row of the periodic table, more basic = more nucleophilic.

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- If the charge-bearing atoms are within the same column of the periodic table, more basic = less nucleophilic.

Here are some examples within the same row. The S_N2 rate constants are all for a reaction with CH_3I in CH_3OH .

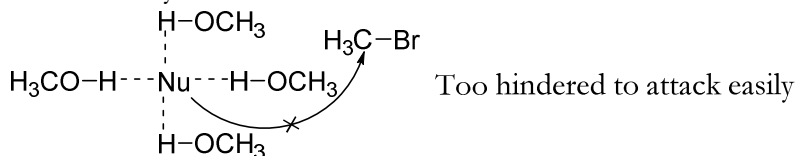
Base/Nu	pKa	S_N2 rate
CH_3O^-	15.1	2.5×10^{-4}
PhO^-	10	7.9×10^{-5}
AcO^-	4.76	2.7×10^{-6}
F^-	3.2	5.0×10^{-8}

Note that even though three of these have the same charge-bearing atom, they all have different pKa values and therefore different nucleophilicities.

Here are some examples within the same column. The S_N2 rates are all for the same reaction again.

Base/Nu	pKa	S_N2 rate
I^-	-10	3.4×10^{-3}
Br^-	-8	8.0×10^{-5}
Cl^-	-6	3.0×10^{-6}
F^-	3.2	5.0×10^{-8}

So iodide (I^-) is a weak base but a really good nucleophile in protic solvents. Why is this? It has to do with hydrogen-bonding to protic solvents. Small atoms are the best at hydrogen bonds, especially when they're stronger bases. Unfortunately, this means they're so wrapped up in H-bonds to the solvent molecules that they're not able to attack the substrate as effectively.



However, switching to an aprotic solvent reverses this trend! In **aprotic solvents**:

- More basic = more nucleophilic, for both directions in periodic table

Here are some rates again, for S_N2 in two different solvents: CH_3OH (protic) and DMF (aprotic).

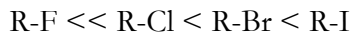
Base/Nu	pKa	S_N2 rate in CH_3OH	S_N2 rate in DMF
I^-	-10	3.4×10^{-3}	0.4
Br^-	-8	8.0×10^{-5}	1.3
Cl^-	-6	3.0×10^{-6}	2.5
F^-	3.2	5.0×10^{-8}	>3

By taking away the option of H-bonding to solvent, not only are we speeding up the rates of all S_N2 reactions, but we're also reversing the trend within a column of the periodic table. In general, aprotic solvents are the best choice for fast S_N2 reactions, but for practical reasons (solubility, boiling point, etc.) protic solvents are sometime used.

- Leaving group ability: since the C-LG bond breaks during the rate-determining step, it can really slow down the reaction if it's a difficult bond to break. This is based on bond strength for the C-LG bond, which is largely set by how stable the LG is with a negative charge after it leaves. Based on pKa values for HX acids, F^- is the strongest base, so it's least stable with a negative charge, so it forms the strongest bond to C, so it's the worst leaving group. So for S_N2 rates on alkyl halides,

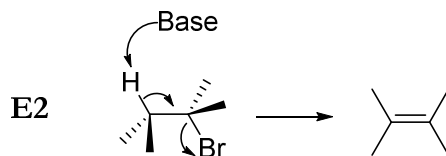
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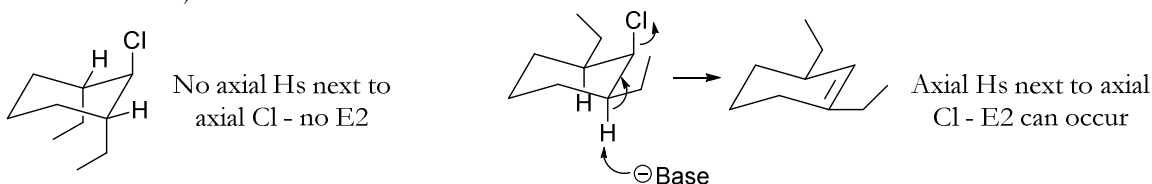
E2

This is another second-order reaction, but an elimination instead of a substitution. The base removes the H at the same time the LG dissociates.

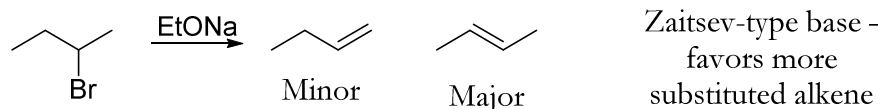


Like S_N2 , this is a concerted reaction – everything happens at once.

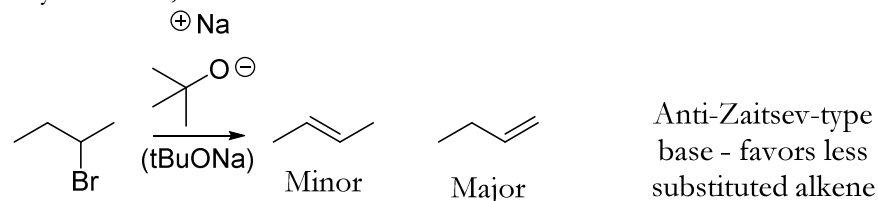
- Since everything is happening at once, geometry is important here just like it is for S_N2 . You need antiplanar (also called antiperiplanar) geometry: the four atoms (H, C, C, and the leaving group) are all in the same plane, with the H and the leaving group pointing opposite directions. If you can't get antiplanar geometry, E2 can't happen. This comes up most often on rings, which are rotationally constrained more than linear chains. For E2 to happen on a cyclohexane, the leaving group and the H must be up axial or down axial on adjacent carbons.



- Regiochemistry: often, there are multiple different protons that could be pulled off during an elimination, to form different alkenes. **Zaitsev's Rule** says that the more stable, substituted alkene will be formed as the major product.



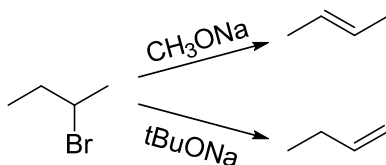
Almost all bases obey Zaitsev's Rule, with one major exception: bases which are large and sterically hindered, like *t*-butoxide.



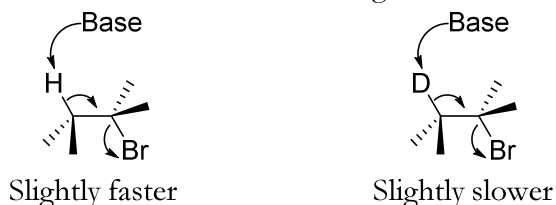
This is because, being large and hindered, it takes too much energy to squeeze them up against the substrate to pick off the proton that would give the best product. Instead, they go for the short-term of a lower activation energy and take the easiest proton to access – the one that gives the less substituted alkene. For both these cases (Zaitsev and anti-Zaitsev bases) there's usually not an overwhelming majority in favor of one product or another. Product ratios are usually 2 or 3 to 1. However, this is still enough that we can more-or-less target the desired product by choosing the right base.

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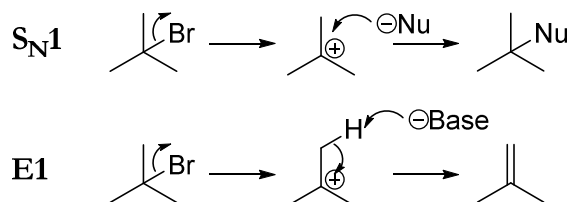


- Leaving-groups effects: the same as for S_N2 . RF is the slowest, RI is the fastest.
- Kinetic isotope effect (KIE): For reasons based on lowest-state vibrational energy, C-H bonds are just slightly weaker than C-D bonds. This means that if a C-H bond gets broken during the RDS of a reaction, the reaction will happen slightly slower if we replace the H with a D. This is called the “primary deuterium isotope effect”, and can be used to prove that the E2 mechanism involves losing an H/D in the RDS.



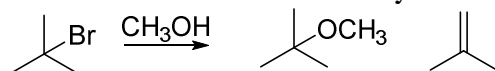
$S_N1/E1$

These two reactions are covered together since they have so much in common. In both reactions, the leaving group dissociates first and leaves a carbocation behind, then the Base/Nu comes in to attack either C or H. Since the RDS involves only the alkyl halide, it's first-order.



For both of these reactions, the overall arrows are exactly the same as for S_N2 or E2, but they're broken into multiple steps instead of all simultaneous. This means it's a stepwise reaction, rather than concerted.

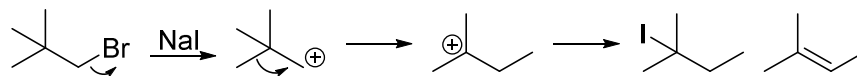
- Most of the behavior of these reactions is determined by the fact that they go through carbocations. More substituted carbocations are more stable, so the reaction rates are the opposite of S_N2 : $Me < 1^\circ < 2^\circ < 3^\circ$.
- Leaving-groups effects: the same as for S_N2 . RF is the slowest, RI is the fastest.
- E1 & S_N1 have the same rate-determining step, but different product-determining steps. Anything that speeds up E1 will also speed up S_N1 , so these two reactions usually occur together and give a mixture of products.
- E1 & S_N1 are fastest in polar protic solvents. This is because the carbocation benefits from being stabilized by the solvent. If there's nothing more nucleophilic around, the solvent itself can react with the substrate – this is **solvolysis**.



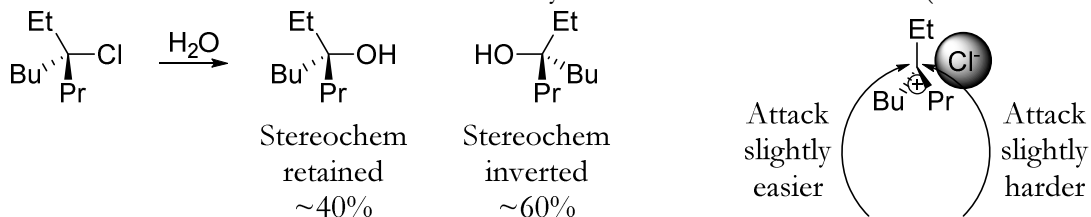
- E1 obeys Zaitsev's rule. However, like we've seen for carbocations previously, rearrangements are possible! (And for S_N1 as well).

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- S_N1 : The substrate goes through a carbocation intermediate, so you'd expect completely scrambled stereochemistry like for the carbocation reactions in Ch. 7. However, this is not quite accurate! The inverted product is favored by a slight margin. This is because the leaving group dissociates, but it is still nearby, partially blocking access to one face of the carbocation. If the carbocation existed for a long time this wouldn't happen, because the leaving group would have time to drift away. The fact that it still has an effect on the outcome means that the carbocation is only in existence for a short time ($\sim 10^{-8}$ seconds).



Predicting Reaction Outcomes

How can we predict which one of these four reactions will actually happen? We need to look at the three molecules involved: substrate, solvent, and Base/Nu.

1. Classify substrate as Me, 1° , 2° , or 3° . Check for neopentyl effect ($3^\circ \beta$ C).
2. Classify solvent as protic or aprotic. Protic solvents are generally things like ROH, RCO_2H , or H_2O . Aprotic solvents are generally the ones that go by acronyms: DMSO, DMF, THF, DCM, chloroform, and acetone. In general, polar protic solvents favor $E1$ and S_N1 reactions, while polar aprotic solvents favor $E2$ and S_N2 reactions. Usually this preference is not strong enough to control the choice of reaction, but check for acid-base reactions with the Base/Nu.
3. Classify base/nucleophile as strong or weak base, good or poor nucleophile.

	Strong Bases (usually in aprotic solvents)	Weak Bases (usually in protic solvents)
Good Nucleophiles	HO^- , RO^- (if R isn't bulky), $\text{RC}\equiv\text{C}^-$	I^- , Br^- , HS^- , RS^- , CN^- , N_3^-
Poor Nucleophiles	 (tBuO^-) (LDA)	Cl^- , F^- , RCO_2^- , H_2O , ROH , RCO_2H

Strong bases are technically anything with a pK_a greater than about 15. In general, anything with a negative charge on C, N, or O is strong, unless there's additional stabilization coming from somewhere (resonance, etc.). If it's a strong base then it's assumed to be a good nucleophile, unless it's very bulky like tBuO^- .

Weak bases are anything with a pK_a below 15. Weak base/good nucleophiles fall into two categories: those at the stronger end of the weak base categories like N_3^- (pK_a of 9.4) and CN^- (pK_a of 4.7), and those with a minus charge on large atoms (I, Br or S). Weak base/poor nucleophiles are anything outside of this category, including molecules with no negative charge at all.

4. Use this information to select which mechanism(s) will occur.

If you have a strong base: You must do S_N2 or $E2$ only! Carbocations (from $E1$ or S_N1) can't exist in the presence of strong bases. $E2$ is the default, unless both the

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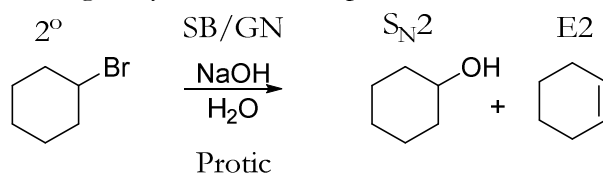
substrate and the base/nucleophile are unhindered. However, if S_N2 turns out to be the predicted mechanism, it can still be blocked by the neopentyl effect, giving NR.

- Strong base/good nucleophile:
 - S_N2 on Me and 1°
 - $S_N2/E2$ on 2°
 - E2 on 3°
- Strong base/poor nucleophile:
 - S_N2 on Me
 - E2 on $1^\circ, 2^\circ, 3^\circ$

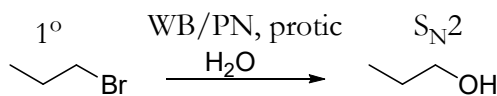
If you have a weak base: E1/ S_N1 mix is the default, but S_N2 can happen under the right circumstances.

- Weak base/good nucleophile:
 - S_N2 on Me, $1^\circ, 2^\circ$
 - $S_N1/E1$ on 3°
- Weak base/poor nucleophile:
 - S_N2 on Me, 1°
 - $S_N1/E1$ on $2^\circ, 3^\circ$

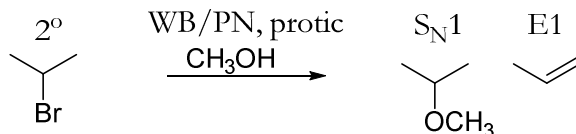
5. Apply this mechanism to the substrate. In example below, the substrate is 2° , the solvent is protic, and the Base/Nu is a strong base/good nucleophile. This combination gives you a mixture of E2 and S_N2 as the favored outcome. Using S_N2 gives you the first product shown, and E2 gives you the second product.



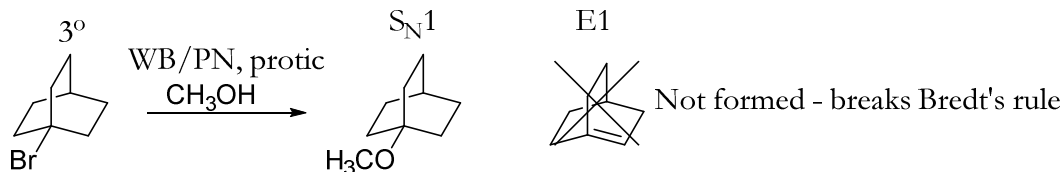
Here, the solvent is also working as the base/nucleophile. This is an example of solvolysis. You have a 1° substrate, protic solvent, and weak base/poor nucleophile, giving you an S_N2 outcome.



Here, you have a 2° substrate, protic solvent, and weak base/poor nucleophile, giving you an $S_N1/E1$ outcome.



Sometimes a predicted outcome will be blocked by other reasons. Even though an $S_N1/E1$ mix is predicted here, the E1 product isn't formed because it violates Bredt's rule.

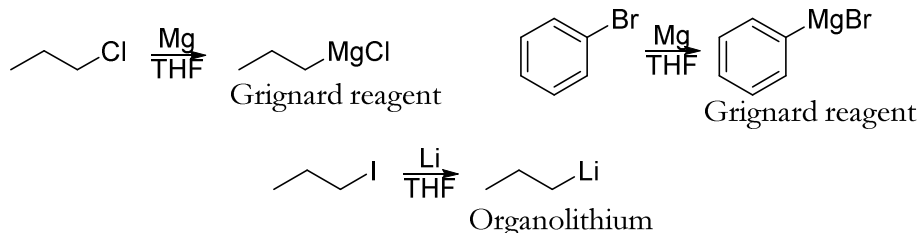


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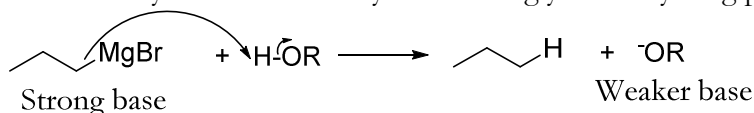
Organometallics

Anything with a bond between a carbon atom and a metal atom is an organometallic compound. Two useful types are Grignard and organolithiums, which are both made from alkyl halides. The mechanism for this goes by a complicated single-electron-transfer mechanism that we won't cover.

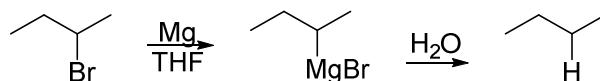


For Grignards, you must have some kind of ether solvent (usually THF or diethyl ether). For organolithiums, ethers or alkane solvents like hexanes will work.

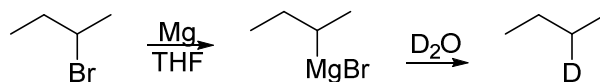
The organometallic that's formed has a big delta negative charge on carbon, which makes it act like a very, very strong base – in fact, it can be drawn as an ionic compound or a covalent compound, since it's midway in between. They react strongly with anything protic:



This can be used as a way to turn alkyl halides into alkanes, in two steps. This is the first example we'll see of a multistep synthesis: using the product of one reaction as a starting material for the next.

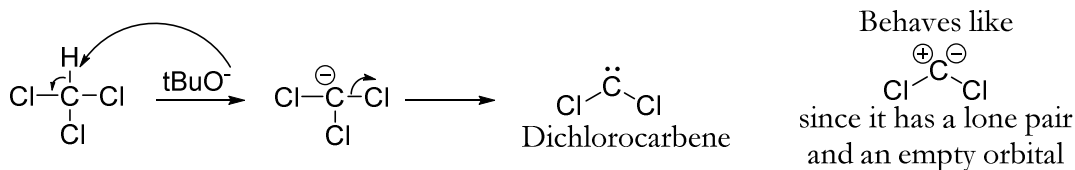


We can also use this to label molecules with deuterium in selected places, by using D_2O instead of H_2O .



Carbenes and Carbenoids

Both the eliminations we looked at were β eliminations- you lose an H and an LG from adjacent carbons. It's also possible to do an α elimination, where you lose an H and an LG from the same carbon. These only happen under specific circumstances. To make this happen, you need a substrate that's good at stabilizing a minus charge, and a strong, bulky base. This creates a carbene, which has an unfilled octet. It behaves like a carbon with a negative charge and a positive charge at the same time, although you shouldn't draw it this way.

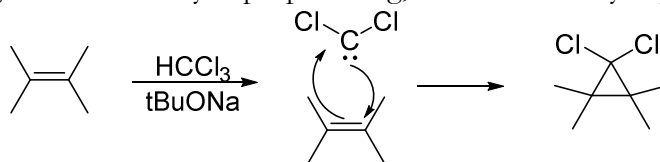


It's a neutral carbon with both an empty orbital (so it's a great electrophile) and a lone pair (so it's a great nucleophile). The one reaction that we'll see it doing involves both behaviors at the same time. This is the same mechanism as that simultaneous attack/back-attack thing

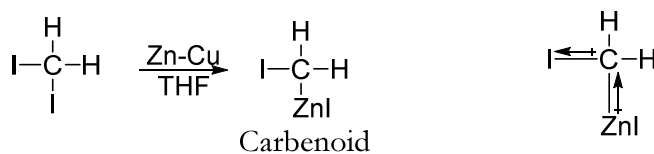
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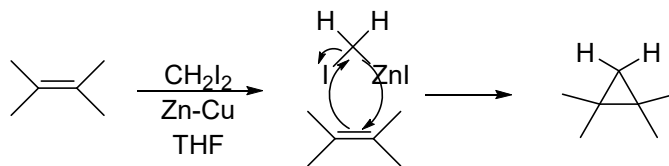
we used to make bromonium ions, only the three-membered ring it makes is permanent. Since we're making an all-carbon cyclopropane ring, this is called a cyclopropanation.



This particular reaction creates a ring with two halogens attached to one corner, but what if we don't want those halogens? In that case, we can use Simmonds-Smith cyclopropanation instead. Combining diiodomethane with zinc-copper couple creates something that's very similar to a Grignard, but with Zn instead of Mg. It's not a true carbene - it doesn't have a full positive and negative charge, but it does have sizeable delta positive (due to the bond to iodine) and delta negative (due to the bond to zinc) charges. For this reason, it behaves like a milder carbene, and is called a carbenoid.



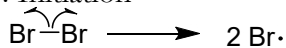
Again, it does the same attack and back-attack to make a three-membered ring.



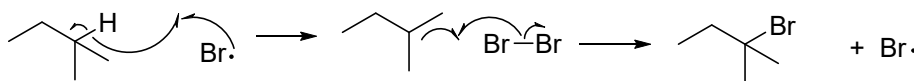
Radical halogenations of alkanes

This is a way to create alkyl halides from alkanes (not from alkenes, which we saw in Ch. 4 & 5). Here, instead of adding an H and a Br to a double bond, we're pulling an H off the molecule and replacing it with a halogen. No radical initiator is needed – the dihalogen will split into radicals on its own, as long as you use UV light (written as $h\nu$), or heat (written as Δ).

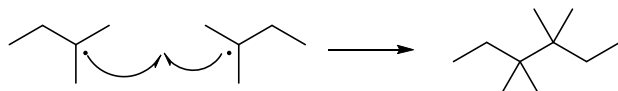
1. Initiation



2. Propagation



3. Termination: any step that involves 2 radicals getting together, for example:

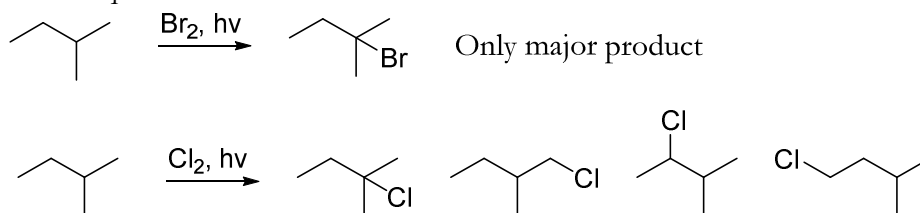


This works best for chlorine and bromine. For iodine it's too endothermic and reacts too slowly, and for fluorine it's too exothermic and goes out-of-control until most Hs are replaced. Bromine is significantly endothermic, so it's slow and energy-poor. For this reason, bromine will carefully select which H to pull off so that only the most stable radicals are formed. The net result is that radical halogenations with Br_2 only adds a Br at the most

Loudon Chapter 9 Review: Reactions of Alkyl Halides

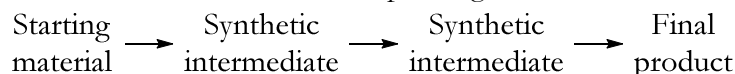
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substituted carbons. Chlorine, on the other hand, is much less endothermic and can afford to create radicals anywhere. It's a lot less predictable and basically useless unless every H on the molecule is equivalent.

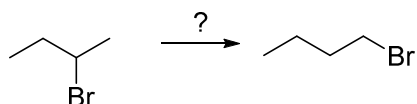


Multistep Synthesis

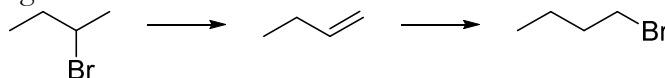
Synthesis involves stringing together multiple reactions to get from a **starting material** to a **target molecule** or **final product**, via one or more **synthetic intermediates**. We only care about showing overall reactions here, no arrow-pushing mechanisms.



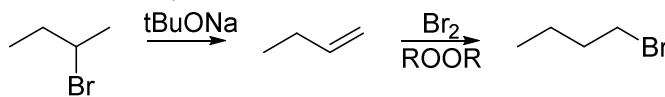
Now that we've covered reactions that create alkyl halides (in Ch. 4 & 5) and reactions that use them, we can start putting them together for synthesis. A common case is where we have a functional group on one carbon, and we want to end up with a functional group on a neighboring carbon instead.



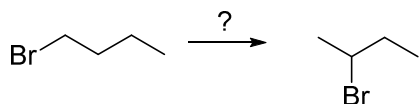
The only way we know of (at present) to gain some kind of functional group handle on the rightmost carbon is by forming an alkene between the two carbons by doing an elimination, and then adding things back to the alkene:



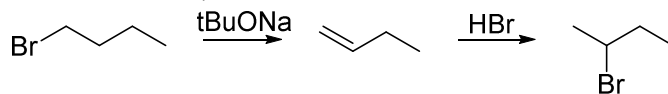
Now we can choose between Zaitsev/anti-Zaitsev eliminations, and Markovnikov/anti-Markovnikov additions, to control the regiochemistry of both reactions. The elimination in this case needs to be anti-Zaitsev, and the addition needs to be anti-Markovnikov.



What about this synthesis?



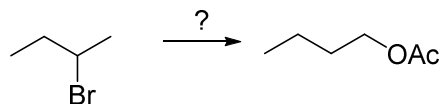
The elimination is neither Zaitsev nor anti-Zaitsev, since there's only one choice. However, we need to be careful – this is a 1° alkyl halide and will undergo $\text{S}_\text{N}2$ if we use a strong base that's not hindered. For this reason, we still use tBuONa.



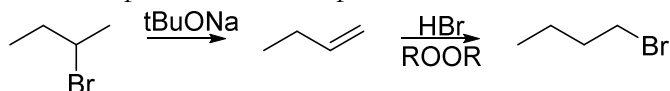
How about this one?

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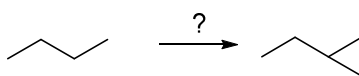
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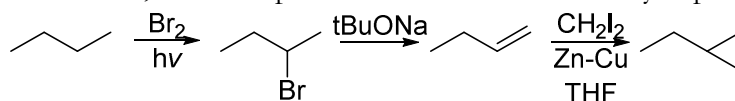
We need to add a group anti-Markovnikov as the last step, but we haven't covered any ways to add an OAc group. Instead, we can add a bromine in the correct location first, and then replace it later by an S_N2 reaction. Bromine is a very convenient placeholder atom, since we have control over where it adds to the alkene (it's the only halogen where we can choose Markovnikov or anti-Markovnikov), and it's also easy to replace afterwards (since it's such a good LG). We can use some protic solvent to promote S_N2 .



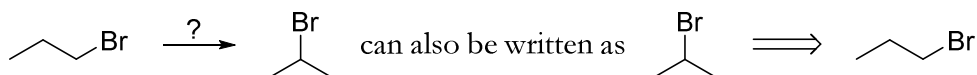
One more synthesis:



We only know one reaction that can do anything with alkanes: radical halogenation. Our first step will be to add a bromine atom to the most substituted carbon. From there, we can eliminate to make an alkene, and then perform a Simmonds-Smith cyclopropanation.



Sometimes it's easiest to work backwards from the target – this is called **retrosynthetic analysis**. Often this is shown with a two-line retrosynthetic arrow, which basically means “is synthesized from” and can also be shown by a regular arrow pointing in the opposite direction.



Something that's very helpful for synthesis is keeping track of all the functional group interconversions. Appendix V in Loudon has a good listing of which reactions we can use to get to and from a given functional group – this is a good place to review the methods we've covered so far. Finally, one more convention: the “cut here” or “disconnect” line – shown as either a slightly wavy line or a straight line with a knob at each end. This can be used in either the forward or the backwards direction.

