Chapter 9 covers reactions of alkyl halides. Most of 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 to create a new double bond. The carbon where a functional group is attached is called the α carbon, the next carbon along the chain is the β carbon, and so forth. Any protons on the β carbon are called β Hs. What we’ll see in most of this chapter are β eliminations.

- The **substrate** is the molecule having this reaction performed on it (the alkyl halide).
- 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:

Note that this molecule might be written as a bare anion (like EtO⁻ above), or it might be listed with a counterion (like EtONa or EtOK). In this case, remember that any metal listed as part of the compound is bonded ionically, so it behaves as a spectator ion while the anion does the reaction.

### Reaction Kinetics

The reactions we’ll see can be subdivided based on kinetics (how fast the reaction occurs, or the reaction rate). 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 effect of \([A]\) and \([B]\) vs. rate can be measured. Reaction rate is given by this formula:

\[
\text{rate} = \frac{\text{change in product concentration}}{\text{time}} = k [A]^m [B]^n
\]

Here are some examples of possible rate laws for this reaction:

<table>
<thead>
<tr>
<th>Rxn</th>
<th>If doubling [A]…</th>
<th>If doubling [B]…</th>
<th>Rate law</th>
<th>Order in A ((m))</th>
<th>Order in B ((m))</th>
<th>Overall order</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>doubles rate</td>
<td>has no effect</td>
<td>(k [A])</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Unimolecular</td>
</tr>
<tr>
<td>2</td>
<td>doubles rate</td>
<td>doubles rate</td>
<td>(k [A][B])</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Bimolecular</td>
</tr>
<tr>
<td>3</td>
<td>quadruples rate</td>
<td>has no effect</td>
<td>(k [A]^2)</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Bimolecular</td>
</tr>
<tr>
<td>4</td>
<td>quadruples rate</td>
<td>doubles rate</td>
<td>(k [A]^2[B])</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>Termolecular</td>
</tr>
</tbody>
</table>

The overall order is determined by how many molecules are involved in the rate-determining step. Unimolecular reactions involve only one molecule at the RDS, for example. 

\(k\), the rate constant, varies depending on the exact conditions. A bigger \(k\) gives a faster reaction. It's controlled by the activation energy, \(\Delta G^\ddagger\) - 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:

- **\(S_n2\): Bimolecular substitution**
- **E2: Bimolecular elimination**
- **\(S_n1\): Unimolecular substitution**
- **E1: Unimolecular elimination**
S<sub>n</sub>2: Bimolecular Substitution
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 with this mechanism:

\[
\text{S}_\text{N}2 \quad \text{Nu} \quad \text{H} \quad \text{X} \quad \xrightarrow{\text{Transition state- don't draw as part of the mech}} \quad \text{Nu} \quad \text{H} \quad \Theta \quad \text{X}
\]

Since both the substrate and the nucleophile are involved in the RDS, the reaction is second-order. Let’s look at the three groups that are involved in the reaction (the R alkyl group, the X leaving group, and the Nu) and see how each one influences the rate.

- **R group vs. rate:** Since the α carbon has bonds or partial bonds to five atoms at once during the transition state (it’s briefly pentavalent), space is at a premium. The less branching there is on the α carbon - in other words, the less sterically hindered it is - the faster this reaction will go. In addition, more branching at the β carbon will also slow S<sub>n</sub>2 down. In general, if the α carbon is 3° or the β carbon is 4°, it’s considered no reaction (NR). Some examples of relative S<sub>n</sub>2 rates are given below.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Rate</th>
<th>This list has increasing substitution at the α carbon. S&lt;sub&gt;n&lt;/sub&gt;2 is good on Me and 1°, mediocre on 2°, and NR (no reaction) on 3°.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeBr</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>t-Br</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2°Br</td>
<td>0.0078</td>
<td></td>
</tr>
<tr>
<td>3°Br</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>t°Br</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **X group vs. rate:** 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<sup>-</sup> 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<sub>n</sub>2 rates on alkyl halides,

R-F << R-Cl < R-Br < R-I

- **Nu group vs. rate:** This gets into the topic of 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 pKa values to compare basicity. There’s not a single number that describes nucleophilicity, but we can get an estimate of it by comparing S<sub>n</sub>2 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.
  - In protic solvents: If the charge-bearing atoms are within the same column of the periodic table, more basic = less nucleophilic.
  - In aprotic solvents: More basic = more nucleophilic, at all times.
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Here are some examples of relative rates for S_n2 with CH_3I in CH_3OH (protic) or DMF (aprotic). Note that even though three of these have the same charge-bearing atom, they all have different pKa values and therefore different nucleophilicities.

<table>
<thead>
<tr>
<th>Base/Nu</th>
<th>pKa</th>
<th>Rate in CH_3OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3O</td>
<td>15.1</td>
<td>5000</td>
</tr>
<tr>
<td>PhO</td>
<td>10</td>
<td>1580</td>
</tr>
<tr>
<td>AcO</td>
<td>4.76</td>
<td>54</td>
</tr>
<tr>
<td>F</td>
<td>3.2</td>
<td>1</td>
</tr>
</tbody>
</table>

So fluoride is a relatively strong base but a poor nucleophile in protic solvents. Why is this? It has to do with hydrogen-bonding. 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.

If we swap to an aprotic solvent instead, we take away the option of H-bonding to solvent, which speeds up the rates of all S_n2 reactions and also reverses 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 protic solvents are sometime used.

- **Stereochemistry:** 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 (usually they’re each priority #1), 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` 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:
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The largest lobe of the $\sigma^*$ 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.

- **$S_{N2}$ vs acid-base reactions:** These two mechanisms look very similar.

\[
\begin{align*}
&\text{S}_{N2} \text{ reaction} \\
\text{EtO} &\quad \text{H}_3\text{C}-\text{Br} \quad \text{EtO-CH}_3 \\
\text{EtO} &\quad \text{H}_3\text{C}-\text{Br} \quad \text{EtO-} \\
\end{align*}
\]

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 the acid-base is favorable (as determined by relative pKa values, like in Ch. 3), it will happen faster.

\[
\text{EtO} + \text{H}_3\text{C}-\text{Br} + \text{H}-\text{Br} \rightarrow \text{EtO-H} + \text{Br} + \text{H}_3\text{C}-\text{Br}
\]

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.

\[
\begin{align*}
\text{EtO} &\quad \text{H}_3\text{C}-\text{Br} \quad \text{EtOH} \\
\text{EtO} &\quad \text{H}_3\text{C}-\text{Br} \\
\end{align*}
\]

In fact, this can even happen with protic groups elsewhere on the substrate:

\[
\begin{align*}
\text{HO} &\quad \text{Br} \quad \text{NaNH}_2 \\
\text{HO} &\quad \text{Br} \\
\end{align*}
\]

This is one example of an intramolecular $S_{N2}$ reaction.

**E2: Bimolecular Elimination**

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.

- **R group vs. rate:** Since no carbon is pentavalent, crowding is not such an issue here. E2 can happen about equally well regardless of sterics, so long as there is a $\beta$ H.
- **X group vs. rate:** the same as for $S_{N2}$: RF is the slowest, RI is the fastest.
- **Base vs. rate:** Since the base/nucleophile is acting as a base here, higher pKa will mean a faster reaction.
- **Stereochemistry:** 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. This means that for alkenes with E/Z forms, you might need to use Newman projections to determine the product. When the elimination happens, the remaining four groups flatten out into the same plane.

If antiplanar geometry isn’t possible, E2 can’t happen. This comes up most often on rings, which are rotationally constrained. 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. These

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.

---

**S_{1}E_{1}: Unimolecular Substitution & Elimination**

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.
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For both of these reactions, the overall arrows are the same as for SN2 or E2, but they’re broken into multiple steps instead of all simultaneous. This means it’s a stepwise reaction, rather than concerted. E1 & SN1 have the same rate-determining step, but different product-determining steps. Anything that speeds up E1 will also speed up SN1, so these two reactions usually occur together and give a mixture of products.

- **R group vs. rate:** 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 SN2: Me < 1° < 2° < 3°.
- **X group vs. rate:** the same as for SN2: RF is the slowest, RI is the fastest.
- **Solvent vs. rate:** E1 & SN1 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 **solvolyis**.

- **SN1 stereochemistry:** 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 (~10⁻⁴ seconds).

- **Regiochemistry:** E1 always obeys Zaitsev’s rule. However, like we’ve seen for carbocations previously, rearrangements are possible, for both E1 and SN1.

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. **Check for acid/base reaction** with solvent or protic group on substrate. This might change the Base/Nu that is used for the following steps. Protic solvents are generally...
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things like ROH, RCO₂H, or H₂O. Aprotic solvents are generally the ones that go by acronyms: DMSO, DMF, THF, DCM, chloroform, and acetone.

2. **Classify substrate** as Me, 1°, 2°, or 3°. Check for neopentyl effect (4° β C) – this blocks Sₐn₂, so if Sₐn₂ ends up being the favored reaction then there might be no reaction at all.

3. **Classify base/nucleophile** as strong or weak base, good or poor nucleophile.

<table>
<thead>
<tr>
<th>Good Nucleophiles (GN)</th>
<th>Strong Bases (SB) - usually in aprotic solvents</th>
<th>Weak Bases (WB) - usually in protic solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO⁻, RO⁻ (if R isn’t bulky), RC≡C</td>
<td>I, Br, HS⁻, RS⁻, CN⁻, N₃⁻</td>
<td>Cl⁻, F⁻, RCO₂⁻, H₂O, ROH, RCO₂H</td>
</tr>
<tr>
<td>Poor Nucleophiles (PN)</td>
<td>(tBuO⁻)</td>
<td></td>
</tr>
<tr>
<td>N⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Strong bases** are technically anything with a pKa 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 pKa below 15. Weak base/good nucleophiles fall into two categories: those at the stronger end of the weak base categories like N₃⁻ (pKa of 9.4) and CN⁻ (pKa of 4.7), and those with a negative 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. **Select which mechanism(s) will occur.**

**Strong bases**: Must do Sₐn₂ or E₂ only! Carbocations can’t exist in the presence of strong base. Sₐn₂ if steric aren’t too bad, otherwise Sₐn₂/E₂ mix or just E₂.

**Weak bases**: Sₐn₂ if steric aren’t too bad, otherwise E₁/Sₐn₁ mix.

<table>
<thead>
<tr>
<th></th>
<th>SB/ZN (Zaitsev)</th>
<th>SB/PN (anti-Zaitsev)</th>
<th>WB/ZN (Zaitsev)</th>
<th>WB/PN (Zaitsev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Sₐn₂</td>
<td>Sₐn₂</td>
<td>Sₐn₂</td>
<td>Sₐn₂</td>
</tr>
<tr>
<td>1°</td>
<td>Sₐn₂</td>
<td>Sₐn₂/E₂</td>
<td>Sₐn₂</td>
<td>Sₐn₂</td>
</tr>
<tr>
<td>2°</td>
<td>Sₐn₂/E₂</td>
<td>E₂</td>
<td>Sₐn₂</td>
<td>Sₐn₁/E₁</td>
</tr>
<tr>
<td>3°</td>
<td>E₂</td>
<td>E₂</td>
<td>Sₐn₁/E₁</td>
<td>Sₐn₁/E₁</td>
</tr>
</tbody>
</table>

If **Sₐn₂**: Check for neopentyl effect (4° β C) – this will block Sₐn₂.
If **E₂**: Check for antiplanar geometry. If there’s no H that can get antiplanar to LG, then E₂ is blocked. SB/ZN prefers Zaitsev and SB/PN prefers anti-Zaitsev, but only if the H in that location can get antiplanar – if not, they’ll take whichever H is available.
If **Sₐn₁/E₁**: Check for carbocation rearrangements.
If **mixed outcome (Sₐn₂/E₂ or Sₐn₁/E₁)**: lower temperature favors substitution and higher temperature, otherwise written as Δ (capital delta) or “heat”, favors elimination. This is because elimination gives one additional product molecule, which creates more entropy, which becomes the dominant term at higher temperatures (if you remember the equation ΔG = ΔH – TΔS from general chemistry, that’s the equation dictating the outcome). If no temperature is listed, show both products.
5. **Apply this mechanism** to the substrate. In example below, you have a 2° substrate and SB/GN. This combination gives you a mixture of E2 and Sn2. Using Sn2 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. A 1° substrate and WB/PN gives you Sn2.

Here’s an example of the neopentyl effect. You have a 1° substrate and WB/GN. This combination should give Sn2, but Sn2 is blocked, so we’d call this NR.

Here’s an example of regiochemistry being dependent on which H is available to eliminate. The reagent prefers to go Zaitsev, but there’s no antiplanar H there, so it’s forced to go anti-Zaitsev.

**Organometallics**

Anything with a bond between a carbon atom and a metal atom is an organometallic compound. Two commonly used types are organolithium reagents, which have a C-Li bond, and Grignard reagents, which have a C-Mg bond. Because carbon is more electronegative than Mg or Li, these both have a big delta negative charge on carbon, which makes them 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.

Grignard reagents:  
\[
\text{MgBr} \quad \text{covalent form} \quad \ominus \text{MgBr} \quad \text{ionic form}
\]

Organolithium reagents:  
\[
\text{Li} \quad \text{covalent form} \quad \ominus \text{Li} \quad \text{ionic form}
\]

You can view the ionic form as a deprotonated hydrocarbon, which is a very strong base – pKa values are usually around 45-60 depending on structure. They react strongly with anything that has a lower pKa (which is most things). You can show either the covalent or the ionic form for these reactions.

Both Grignards and organolithiums are made from alkyl halides (Cl, Br or I). The mechanism for this goes by a single-electron-transfer mechanism that we won’t cover.
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For Grignards, you must have some kind of ether solvent (usually THF or diethyl ether). For organolithiums, ether, THF, or alkane solvents like hexanes will work.

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.

\[ \text{Br} \xrightarrow{\text{Mg, THF}} \text{MgBr} \xrightarrow{\text{H}_2\text{O}} \text{H} \]

We can also use this to label molecules with deuterium in selected places, by using D\(_2\)O instead of H\(_2\)O.

\[ \text{Br} \xrightarrow{\text{Mg, THF}} \text{MgBr} \xrightarrow{\text{D}_2\text{O}} \text{D} \]

**Carbenes and Carbenoids**

Both the eliminations we looked at were \( \beta \) eliminations- you lose an H and an LG from adjacent carbons. It’s also possible to do an \( \alpha \) 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, but don’t draw it this way.

![Carbene](image)

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 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.

![Cyclopropanation](image)

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.

![Carbenoid](image)

Again, it does the same attack and back-attack to make a three-membered ring.
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\[
\text{CH}_2\text{I}_2 \xrightarrow{\text{Zn-Cu}} \text{THF} \rightarrow \text{H}_\text{ZnI} \xrightarrow{\text{H}} \text{H}_2
\]

**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 (hv), or heat (Δ).

1. **Initiation**
   \[
   \text{Br} \rightarrow \text{Br} \rightarrow 2 \text{Br}.
   \]

2. **Propagation**
   \[
   \text{H} \rightarrow \text{Br} \rightarrow \text{Br} \rightarrow \text{H} + \text{Br}.
   \]

3. **Termination**: any step that involves 2 radicals getting together, for example:
   \[
   \text{H} \rightarrow \text{H}.
   \]

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 Br₂ only adds a Br at the most 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.

\[
\text{Br}_2, \text{hv} \rightarrow \text{Br} \quad \text{Only major product}
\]

\[
\text{Cl}_2, \text{hv} \rightarrow \text{Cl} \rightarrow \text{Cl} \rightarrow \text{Cl} \rightarrow \text{Cl}
\]

**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.

```
Starting material → Synthetic intermediate → Synthetic intermediate → Final product
```

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. We have to “walk” it over by one carbon atom.
Loudon Chapter 9 Review: Reactions of Alkyl Halides
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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 $S_2$ if we use a strong base that’s not hindered. For this reason, we still use tBuONa. High temperatures will favor E2 over $S_2$ out of the expected $S_2$/E2 mix.

How about this one?

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. We then need to add a group anti-Markovnikov, 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 $S_2$ 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 protic solvent to promote $S_2$.

One more synthesis:

This involves moving an alkene around rather than a halogen, but it’s still the same idea. Once the anti-Zaitsev alkene is formed, we can perform 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.

\[
\text{Br} \quad \xrightarrow{?} \quad \text{Br} \quad \text{can also be written as} \quad \text{Br} \quad \xrightarrow{\quad} \quad \text{Br}
\]

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. You can also make charts of all the ways to get to, or from, a particular functional group.

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{Br} & \xrightarrow{1) \text{BH}_3} \text{CH}_2\text{CH}_2\text{OH} \\
& \xrightarrow{2) \text{H}_2\text{O}_2, \text{H}_2\text{O}, \text{OH}} \text{CH}_2\text{CH}_2\text{OH} \\
& \xrightarrow{\text{NaOH}} \text{CH}_2\text{CH}_2\text{X} \\
\text{CH}_2\text{CH}_2\text{X} & \xrightarrow{1) \text{Hg}([\text{OAc}_2], \text{H}_2\text{O}, \text{THF}} \text{CH}_2\text{CH}_2\text{OH} \\
& \xrightarrow{2) \text{NaBH}_4, \text{OH}} \text{CH}_2\text{CH}_2\text{OH}
\end{align*}
\]

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.

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\quad} \quad \text{CH}_2\text{CH}_2\text{OH} \\
\quad & \quad \xrightarrow{\quad} \quad \text{HOOCCH}_2\text{CH}_2\text{COOH}
\end{align*}
\]

The more reactions we cover, the more options there will be to perform a synthesis. In general, if all the steps work, then you’ll get full points, but try not to make your synthetic route too long. If it’s more than twice as many steps as the shortest route, you might be penalized a little for inefficiency.