

Unit 7

Radicals

7.38 Radicals - 1

- 12/9:
- Grade cutoffs on Exam 4.
 - A: 75-100.
 - B: 60-74.
 - C: 50-59.
 - < C: < 50.
 - Speak with your TF first (then Prof. Buchwald) if you didn't do as well as you would like.
 - Announcements.
 - The final exam is the last possible final exam: Friday, 12/20, 1:30 PM, 50-340.
 - Syllabus update: Instead of rushing through two topics, Prof. Buchwald decided to focus more intently on one topic (radicals) for the last two lectures.
 - Lecture outline.
 - A. Introduction.
 - Definition.
 - Structure.
 - Stability and stabilization.
 - Generation.
 - B. Reactions of radicals.
 - 1) Termination steps.
 - a) Radical-radical coupling.
 - b) Disproportionation.
 - 2) Propagation steps.
 - a) Abstraction.
 - b) Addition to double and triple bonds.
 - c) Fragmentation.
 - d) Rearrangement.
 - 3) Radical chain reactions.

- We'll begin with Topic A: Introduction.
- **Radical:** A neutral, carbon-centered (for the sake of this class) species that can be characterized by electron spin resonance (ESR).

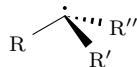


Figure 7.1: A radical.

- ESR is also beyond the scope of this class; it is analogous to NMR if you are curious.
 - Reading: Chapter 37 of Clayden et al. (2012).
 - Structure of radicals.
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- Figure 7.2: Radical structure.
- The carbon center is sp^2 -hybridized.
 - It is approximately planar (aka a “shallow pyramid,” but we don’t have to worry about that).
 - It is subject to stereochemical “umbrella-ing”: When sp^3 -hybridized, radicals rapidly invert, like an umbrella in a windstorm.
 - Thus, for our purposes, there are no enantiomerically enriched radicals.
 - Aside: It is a trend in modern research to take things that are unstable and stabilize them, e.g., via binding to a transition metal.
 - People are designing molecules that can selectively bond to one face of a radical over another.
 - All of this is way beyond the scope of this class.
 - Stability of radicals.
 - Radicals are electron-deficient, so methods of donating electron density into the partially filled orbital are typically the most useful at stabilizing them.
 - Hyperconjugative stabilization.
- $3^\circ > 2^\circ > 1^\circ > \text{Me}$
- It’s about a 3 kcal/mol difference between 3° and 2° , and between 2° and 1° .
 - However, it’s about a 6 kcal/mol difference between 1° and methyl.
 - These differences roughly correlate with the number of hyperconjugative, no-bond resonance structures.
 - 9 such structures for 3° , 6 for 2° , 3 for 1° , and 0 for methyl.
 - Analogously to Figure 2.3a, each methyl group adjacent to the radical adds three C–H bonds that can donate into the partially filled radical *p*-orbital.
 - Heteroatom destabilization.
- $\text{R}_3\text{C}\cdot > \text{R}_2\text{N}\cdot > \text{RO}\cdot$
- Note that since radicals are electron deficient, carbon-centered radicals are also more stable than radicals centered on more electronegative elements.

- Resonance stabilization.

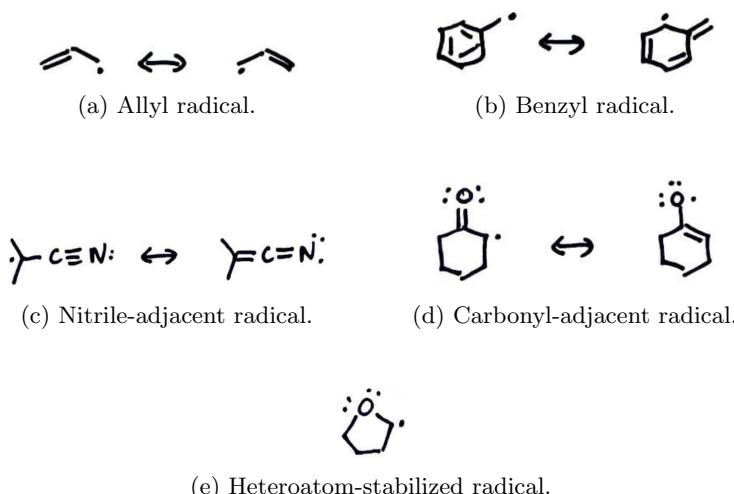


Figure 7.3: Resonance-stabilized radicals.

- Allyl (Figure 7.3a) and benzyl (Figure 7.3b) radicals are also significantly stabilized, due to resonance.
 - The allyl radical is 9 kcal/mol more stable than the propyl radical; 9 kcal/mol amounts to hundreds of times increased stability since each 1.4 kcal/mol is a 10-fold increase in stability.
- Unlike many other electron-deficient species, electron-withdrawing groups actually stabilize radicals as well (Figures 7.3c & 7.3d)!
 - This is because of resonance.
- Lastly, radicals are also stabilized by lone pairs.
 - This yields 2-centered, 3-electron bonding.
 - Implication: Radicals α to an ether are stabilized. Here's why this is important.
 - \triangleright When you work in the lab (at MIT or elsewhere) and you buy an ether, the two most common ones to buy are tetrahydrofuran (THF) and diethyl ether (Et_2O).
 - \triangleright Once you open the container, you need to date it and then check it every six months for peroxides. These can form spontaneously in air, and then are dangerous because they're explosive!
 - An analogy to this is the stabilization of carbocations by resonance (see Figure 6.3a).

- Unstable radicals.

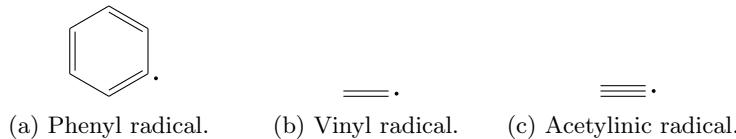


Figure 7.4: Unstable radicals.

- What these all have in common is that they must be generated by cleaving (in a homolytic sense) relatively strong C–H bonds.
- In contrast, many of the radicals in Figure 7.3 derive from relative weaker C–H bonds (in a homolytic sense).

- Generation of radicals.
- Peroxides.

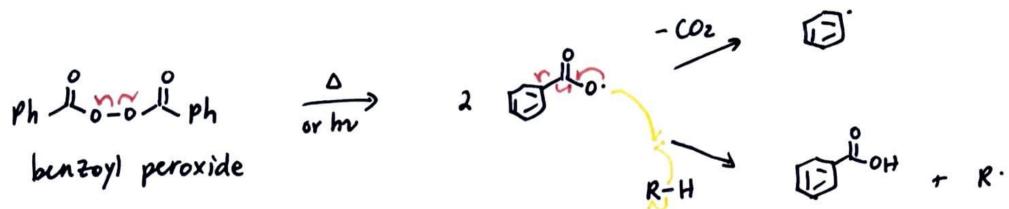


Figure 7.5: Generating radicals from peroxides.

- Many old acne medications contained benzoyl peroxide.
- The center O–O bond is very weak: Its bond dissociation energy is only about 30 kcal/mol.
- Thus, under heat or light, the O–O bond can break in two (we draw this using *single-headed curved arrows*) to yield an intermediate.
- This intermediate will then either quickly do decarboxylation to form CO₂ and a phenyl radical, or quickly grab hydrogen from a nearby R–H to form benzoic acid and a R· radical.
- Either process kills the bacteria in acne!

- Initiators.

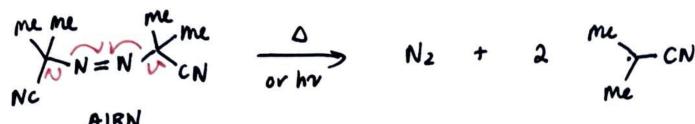


Figure 7.6: Generating radicals from AIBN.

- AIBN (azoisobutyronitrile) — under light or heat — forms nitrogen gas and two equivalents of a tertiary, resonance-stabilized radical (see Figure 7.3d).
- We now move onto Topic B: Reactions of radicals.
- Radicals often participate in **radical chain reactions**.
 - These are used in the synthesis of polymers, they're in our body, and we put things in our food to prevent them because food spoils via radical chain reactions.
- We now discuss Topic B.1: Termination steps.
- **Termination** (step): A process that consumes radicals via mutual annihilation.
- We'll now cover Topic B.1.a: Radical-radical coupling.



Figure 7.7: Radical-radical coupling.

- We now move onto Topic B.1.b: Disproportionation.



Figure 7.8: Disproportionation.

- We now move onto Topic B.2: Propagation steps.
- More specifically, we'll cover Topic B.2.a: Abstraction.

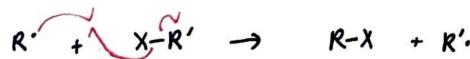


Figure 7.9: Radical abstraction.

- Also called S_H2 (substitution, homolytic, bimolecular).
- This step continues the radical chain because we put one radical in and get one radical out.
- We now move onto Topic B.2.b: Addition to double and triple bonds.

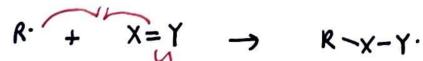


Figure 7.10: Radical addition to multiple bonds.

- We attack an X=Y bond, attach to one atom (say X), and form a Y-centered radical.
- We now move onto Topic B.2.c: Fragmentation.
- This is typified by the decarboxylation reaction in Figure 7.5.
- We now move onto Topic B.2.d: Rearrangement.

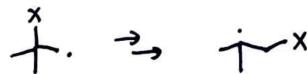


Figure 7.11: Radical rearrangement.

- This allows us to get to a more stable radical, e.g., 1° → 3°.
- Radical fragmentation and rearrangement, in particular, are usually *very fast* processes.
- We now move onto Topic B.3: Radical chain reactions.
- These have three steps: Initiation, propagation, and termination.
- Example radical chain reaction: Radical reduction.

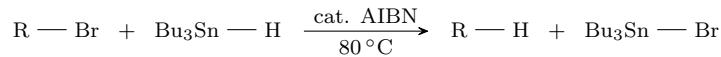
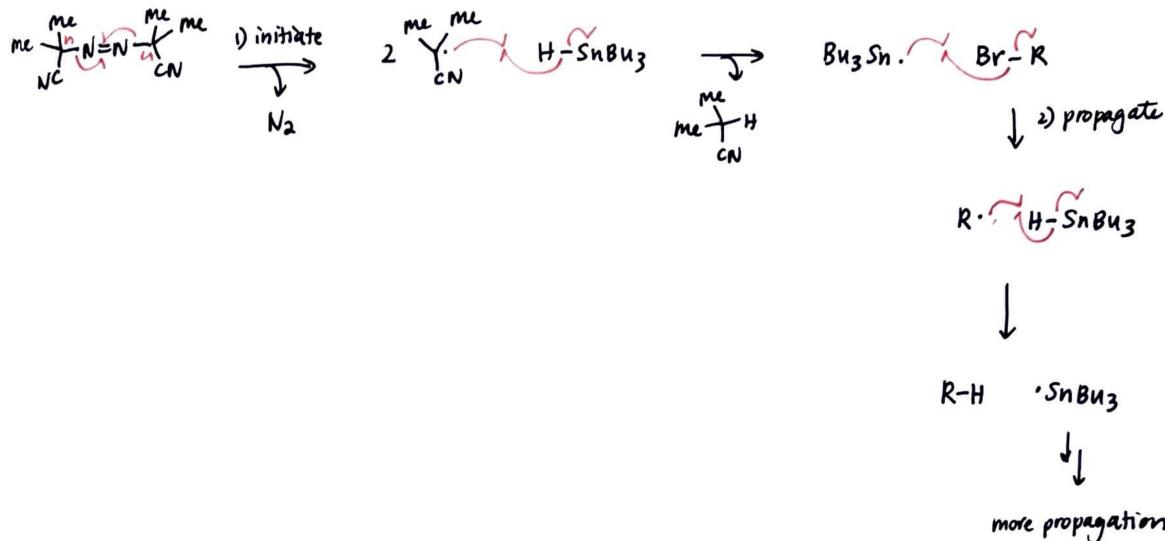


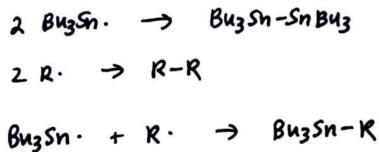
Figure 7.12: Radical reduction of alkyl halides.

- Combine R-Br and Bu₃Sn-H with a catalytic amount of AIBN at 80 °C.
 - Every butyl group is *n*-butyl, but Prof. Buchwald won't write out all the n's.
- This reduces the alkyl halide to an alkyl group!
- Energetic analysis.
 - Bond dissociation energies (BDEs).
 - The R-Br bond has a BDE of about 70 kcal/mol.
 - The Bu₃Sn-H bond has a BDE of about 74 kcal/mol.
 - The R-H bond in the product has a BDE of about 95 kcal/mol.
 - The Bu₃Sn-Br bond in the product has a BDE of about 85 kcal/mol.

- Thus, via Hess's law, this reaction is thermodynamically favorable overall by 36 kcal/mol!
- However, if we just mix the reactants, nothing happens because of the *kinetic* barrier.
 - This is why we add a catalytic amount of AIBN.
 - Note that we do mean “catalytic amount” and not “catalyst”: AIBN is consumed in the reaction and not regenerated (per Figure 7.6), so it is not technically a catalyst.
- Let's now discuss the mechanism of the above reaction.



(a) Initiation and propagation steps.



(b) Possible termination steps.

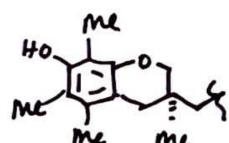
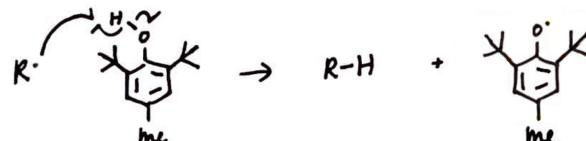
Figure 7.13: Radical reduction mechanism.

- First, AIBN will undergo its initiation reaction (see Figure 7.6).
- The radicals generated by this initiation step go after the weak Bu_3Sn-H bond, generated a tributylstannyl ($Bu_3Sn\cdot$) radical.
- These tin radicals then like to go after halogens because Sn–X bonds are *strong*.
 - Thus, this step is favorable by about 15 kcal/mol!
- Then the $R\cdot$ radical can go after the next molecule of Bu_3Sn-H to regenerate $Bu_3Sn\cdot$ (to react further) as well as a molecule of the $R-H$ product.
 - This step is favorable by about 21 kcal/mol.
- Adding up the propagation steps both thermodynamically and molecule-by-molecule gives our net reaction and $\Delta H = -36$ kcal/mol.
- Termination steps.
 - Radical-radical coupling (see Figure 7.7) of $Bu_3Sn\cdot$ radicals, $R\cdot$ radicals, and $Bu_3Sn\cdot + R\cdot$.
 - For a radical chain process to be efficient, we want propagation to occur around a hundred times before termination occurs.

7.39 Radicals - 2

12/11:

- Announcements.
 - The final exam counts for $\frac{4}{3}$ the credit of a typical 1-hour exam.
 - They made an exam that is 200 points, and they will then scale everyone's score down to 133. $\bar{3}$ points.
 - The exam's difficulty parallels the previous exams and practice exams.
 - It is comprehensive: You should remember the things you learned during the first half of the course.
 - Some of today's material may appear on the final.
 - Lecture 38 recap.
 - Radicals: Neutral, often carbon-centered, seven electrons.
 - Stabilization.
 - Order of stability: $3^\circ > 2^\circ > 1^\circ > \text{Me}$.
 - Can also be stabilized through resonance (e.g., allyl and benzyl radicals).
 - Other stabilized radicals (Figure 7.3).
 - Lecture outline.
- B. Reactions of radicals.
- Radical abstraction (revisited).
 - Radical addition (revisited).
 - Allylic bromination.
 - Tributylstannyll reactions.
 - Radical rearrangements (revisited).
- Radical abstraction ($\text{S}_{\text{H}}2$).
 - See Figure 7.9.
 - This process could be part of a propagation scheme because there's no **annihilation** of radicals (indeed, you have one radical in the starting materials, and one radical in the products).
 - X can be hydrogen or a halogen. It is *never* an sp^3 -hybridized alkyl group.
 - H-atom abstraction.



(c) Vitamin E.

Figure 7.14: Hydrogen-atom abstraction.

- Radical processes like the one in Figure 7.14a can cause all kinds of spoilage and damage in food, so we add in butylated hydroxytoluene (BHT).
 - See the discussion below Figure 6.12 for more on BHT.
- BHT can receive a reactive, damaging radical and form a stabilized, relatively unreactive radical (Figure 7.14b).
 - This slows down the process of spoilage!
- Besides BHT, Vitamin E is nature's radical scavenger (Figure 7.14c).
 - BHT is just a suped-up form of Vitamin E.
- Radical additions.

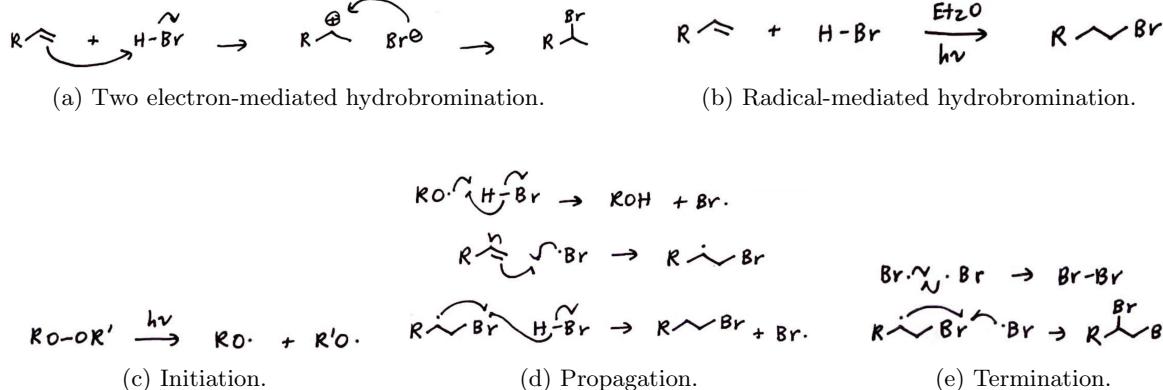
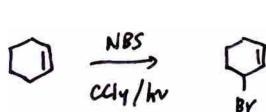


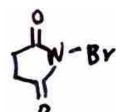
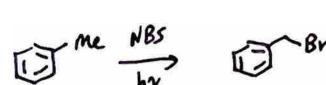
Figure 7.15: Radical addition.

- See Figure 7.10.
 - You've also seen this in 5.12, but it's worth reviewing now.
- You should remember hydrohalogenation reactions from 5.12 (Figure 7.15a).
 - It gives the Markovnikov product.
 - This is because the secondary carbocation is far more stable than the primary carbocation.
- However, if we do this reaction in diethyl ether (also known as just "ether") on a sunny day, we get the anti-Markovnikov product as well (Figure 7.15b)!
- Let's see how this happens (Figures 7.15c-7.15e).
 - Organic peroxides (formed in ether as discussed last class) react with light in an initiation step.
 - Then propagation proceeds through a secondary radical that is more stable than a primary radical.
 - Sometime down the line, we can annihilate our radicals in termination steps. For example, two bromine radicals could recombine into Br₂.

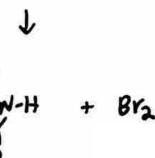
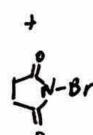
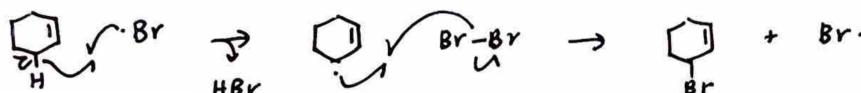
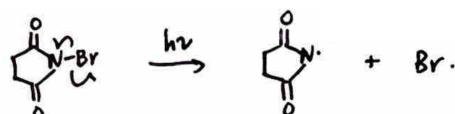
- Allylic bromination.



(a) Allylic bromination.

(b) $N\text{-bromosuccinimide}.$ 

(c) Benzylic bromination.



(d) Allylic bromination mechanism.

Figure 7.16: Allylic and benzylic radical bromination via $N\text{-bromosuccinimide}.$

- In addition to $N\text{-bromosuccinimide}$ (NBS), $N\text{-chlorosuccinimide}$ (NCS) and $N\text{-iodosuccinimide}$ (NIS) are a thing!
- In an initiation step, we cleave the $\text{N}-\text{Br}$ bond to form a succinimidyl radical that is doubly stabilized by resonance with the two adjacent carbonyls, even though its nitrogen-centered.
- Then the bromine radical ($\text{Br}\cdot$) abstracts an allylic hydrogen.
 - It doesn't go after the vinyl or alkyl hydrogens because they don't have resonance stabilization, like the allylic positions do.
- This gives HBr as a byproduct.
 - HBr then reacts with NBS to form a *very small* amount of Br_2 .
 - It is important that only a very small amount of Br_2 is formed, because we don't want Br_2 to dibrominate the olefin (as you studied in 5.12).
- The allylic radical now comes in and brominates itself using Br_2 .
 - This regenerates $\text{Br}\cdot$, and the propagation steps continue.
- This mechanism is somewhat surprising to Prof. Buchwald, because it seems like the allylic radical could just react with NBS directly in a propagation step. However, it was proven that this is *not* the case, and the drawn mechanism is correct.

- How does HBr react with NBS to form Br₂ and succinimide?

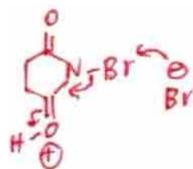
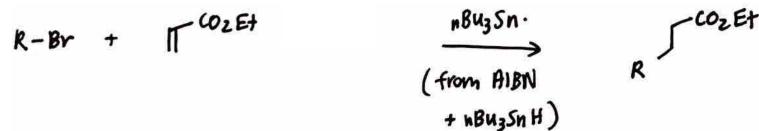
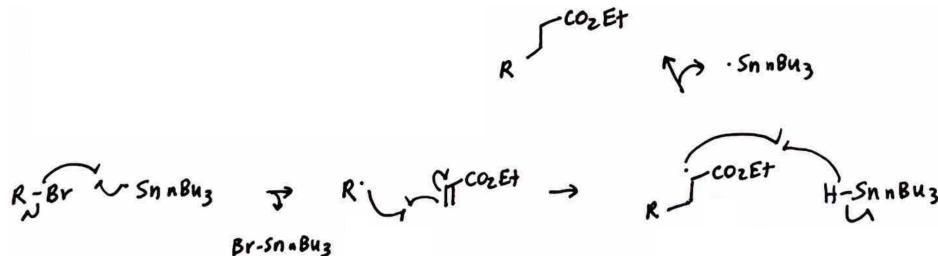


Figure 7.17: Bromine formation from NBS and HBr.

- HBr (a strong acid) protonates the NBS carbonyl, and then Br⁻ attacks the protonated NBS's Br atom.
- Then we get an **amide-iminol tautomerization**.
- This is not content you have to worry about.
- Alkylating α, β -unsaturated electron-withdrawing groups.



(a) The reaction.



(b) The mechanism.

Figure 7.18: Radical alkylation of α, β -unsaturated systems.

- This is similar to using Gilman's reagent for 1,4-addition (see Figure 5.51)!
- The tributylstannyl radical is once again useful for abstracting bromine from an alkyl halide, and we generate it using AIBN + HSnBu₃.
- Note that the R· radical is not too electron deficient.
- Additionally, the α, β -unsaturated system reacts more slowly with electron-deficient olefins.
- We preferentially form the more electron deficient radical that is in resonance with the EWG.
- Intramolecular radical ring closure.

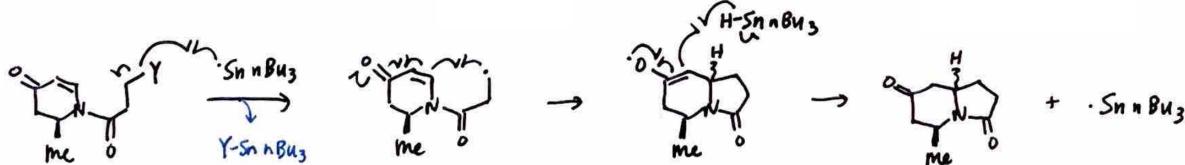


Figure 7.19: Intramolecular radical alkylation.

- This is a variant on the chemistry we just discussed in Figure 7.18.
 - Now we've gone from a system with one ring to a system with two rings.
 - Radical rearrangements.
 - In the literature, there's a series of common rearrangements called **radical clocks**.

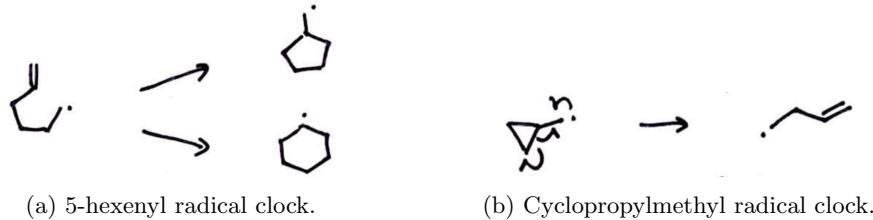


Figure 7.20: Radical clocks.

- One common reactant is called a 5-hexenyl radical.
 - The rate of reaction is $k = 10^5 \text{ s}^{-1}$, which is pretty fast!
 - Note that formation of the top product proceeds 50 times faster than the formation of the bottom product.
 - Another common reactant is a cyclopropylmethyl radical.
 - The rate of reaction is $k = 10^8 \text{ s}^{-1}$, which is *extremely* fast!
 - We're still forming a primary radical as a byproduct (which isn't super stable), but we're gifted 25 kcal/mol by the cyclopropane ring opening.
 - 1,2-shifts of aryl groups.

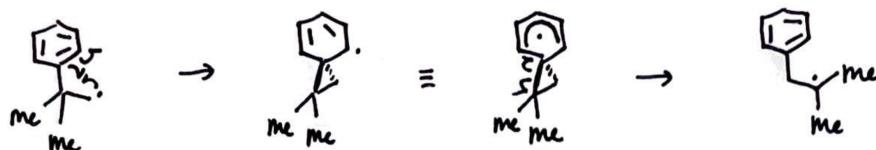


Figure 7.21: Radical rearrangements of aryl groups.

- The driving force is going from a primary radical to a more stable tertiary radical.
 - Once we form the unstable (because we've broken aromaticity) intermediate, it can either react backwards or proceed on to the product.

● γ -(acyloxy)alkyl rearrangement

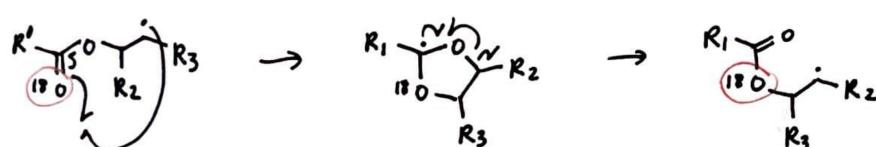


Figure 7.22: γ -(acyloxy)alkyl rearrangement.

- The mechanism has been elucidated using ^{18}O isotopic labeling, as in Figure 4.43.