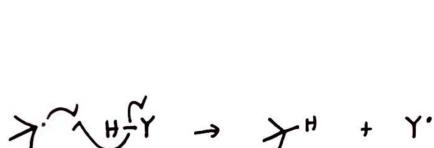


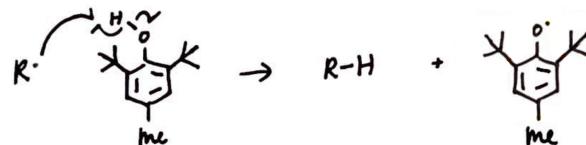
## 7.39 Radicals - 2

12/11:

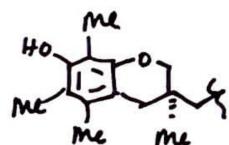
- Announcements.
    - The final exam counts for  $\frac{4}{3}$  the credit of a typical 1-hour exam.
    - They made an exam that is 200 points, and they will then scale everyone's score down to 133. $\bar{3}$  points.
    - The exam's difficulty parallels the previous exams and practice exams.
    - 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.



(a) The reaction.



(b) Butylated hydroxytoluene.



(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.

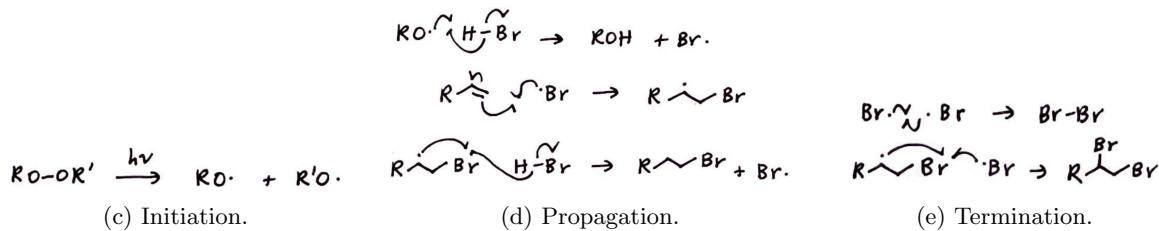
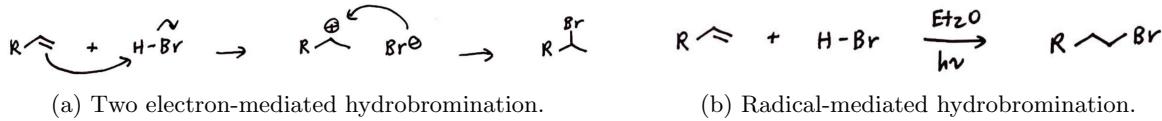
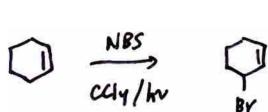


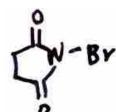
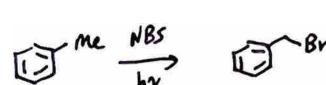
Figure 7.15: Radical addition.

- 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 Br<sub>2</sub>.

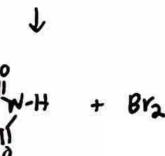
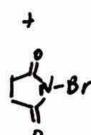
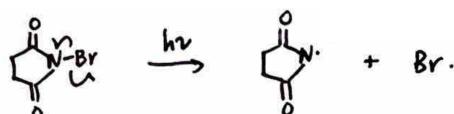
- Allylic bromination.



(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 N–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  $\text{Br}_2$ .
  - It is important that only a very small amount of  $\text{Br}_2$  is formed, because we don't want  $\text{Br}_2$  to dibrominate the olefin (as you studied in 5.12).
- The allylic radical now comes in and brominates itself using  $\text{Br}_2$ .
  - 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 Br<sub>2</sub> and succinimide?

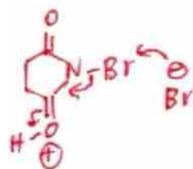
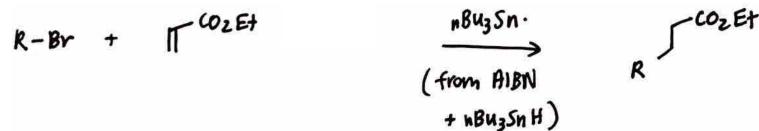
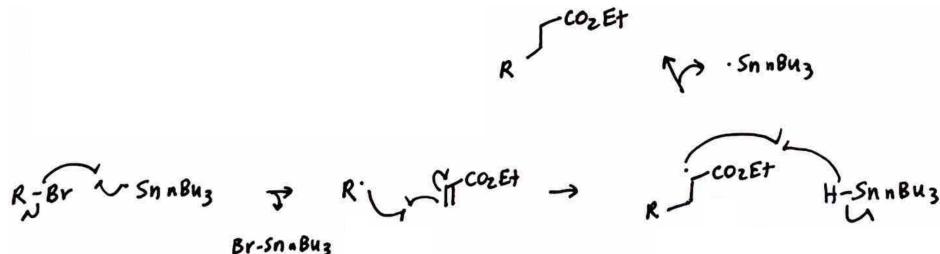


Figure 7.17: Bromine formation from NBS and HBr.

- HBr (a strong acid) protonates the NBS carbonyl, and then Br<sup>-</sup> attacks the protonated NBS's Br atom.
- Then we get an **amide-iminol tautomerization**.
- This is not content you have to worry about.
- Alkylating  $\alpha, \beta$ -unsaturated electron-withdrawing groups.



(a) The reaction.



(b) The mechanism.

Figure 7.18: Radical alkylation of  $\alpha, \beta$ -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 + HSnBu<sub>3</sub>.
- Note that the R· radical is not too electron deficient.
- Additionally, the  $\alpha, \beta$ -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.

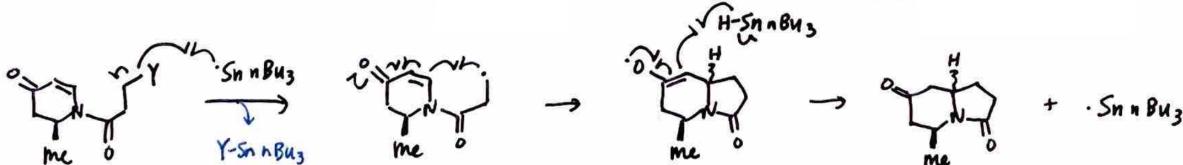


Figure 7.19: Intramolecular radical alkylation.

- 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**.

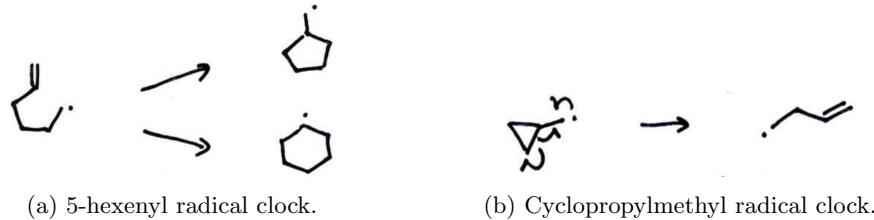


Figure 7.20: Radical clocks.

- 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.

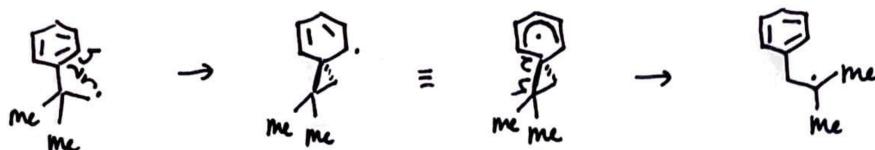


Figure 7.21: Radical rearrangements of aryl groups.

- 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.

•  $\gamma$ -(acyloxy)alkyl rearrangement.

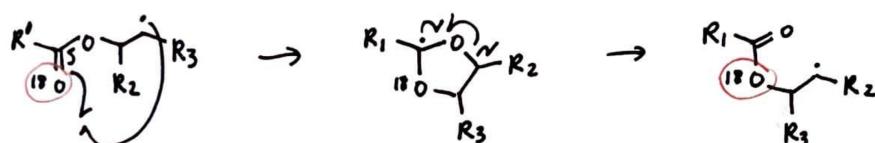


Figure 7.22:  $\gamma$ -(acyloxy)alkyl rearrangement.

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