Week 5

Misc. Reactive Intermediates

5.1 Radicals

• Lecture 7 recap.

- Anion formation: $R-H \rightleftharpoons R^- + H^+$.
- pK_a's are a measure of anion stability.
- Anions are stabilized by...
  - Electronegative substituents (that withdraw electron density);
  - More s-character (to hold the negative charge closer to the positive nucleus);
  - Delocalization/resonance (to spread out the negative charge);
  - Orbital overlap with adjacent atoms (along the lines of reverse hyperconjugation, e.g., in the case of ylides).
- Anions are pyramids with low inversion barriers, and hence are effectively planar.

• Today: Radicals.

• Lecture outline.

- Structure of radicals.
- Stability of radicals (thermodynamic and kinetic).
- Bond dissociation energy.
- Synthesis of radicals.
- Radical reactions.
- Probing radical mechanisms: Radical clocks, traps, and cages.
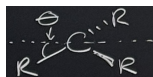- Radical ions.

• Structure of radicals.

Figure 5.1: Angle of deviation from planarity.

- Most radicals are shallow pyramids with small inversion barriers (< 5 kcal/mol).
  - The methyl radical ($\cdot CH_3$) is planar by ~ 10 kcal/mol.
  - Recall the discussion of its QMOT diagram (Figure 2.5)!

  – As with anions, electronegative substituents raise the inversion barrier.

  ■ For example, the trifluoromethyl radical ($\cdot\,CF_3$) is pyramidal.

  – Increasing sterics favor pyramidalization (more p-character)?? Wouldn't bulky groups push apart?

  – Consider the angle of deviation θ from planarity.

  ■ The ethyl radical (1°) has $\theta = 11.9°$.
  ■ The isopropyl radical (2°) has $\theta = 18.6°$.
  ■ The isobutyl radical (3°) has $\theta = 24.1°$.

- Thermodynamic stability of radicals.

  – Delocalization stabilizes radicals.

  ■ Delocalization with neighboring heteroatoms is especially stabilizing!

  – Hyperconjugation stabilizes radicals.

  ■ Thus, in terms of decreasing stability, 3° > 2° > 1°.
  ■ This is analogous to cations.

  – More p-character stabilizes radicals.

  ■ Thus, in terms of decreasing stability, $p > sp^3 > sp^2 > sp > s$.
  ■ This is because radicals are inherently electron deficient, so they want to be further from the δ^+ nucleus.
  ■ This is the opposite of anions!
  ■ Alternatively: The more s-character, the stronger the bond, and hence the less stable the radical formed by homolytic bond cleavage.
      ➢ We'll formalize this notion with **BDEs** in just a moment.

  – More electronegative atoms destabilize the radical center.

  ■ Thus, in terms of decreasing stability, $\cdot\,C > \cdot\,N > \cdot\,O$.

  – Larger atomic size stabilizes radicals.

  ■ Thus, in terms of decreasing stability, $\cdot\,S > \cdot\,O$.
  ■ This is because larger atoms are more polarizable.

- Kinetic stability of radicals.

  – Consider a relatively stable radical, such as one that has some resonance stabilization. Suppose we add some steric blocking to it. This yields a **persistent radical**.

- **Persistent radical**: A kinetically stable radical that may even be shelf-stable.

  – These are not thermodynamically stable: It's still a radical, so it doesn't want to exist. But it just won't react with anything.
  – Classic example: **TEMPO**.
  – Persistent radicals are useful for radical traps and other experiments discussed later this lecture.

- **(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl**: A common persistent radical. *Also known as* **TEMPO**. *Structure*
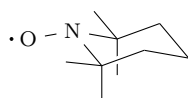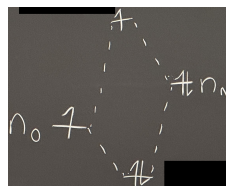

(a) Structure.   (b) $N-O\,\cdot$ molecular orbitals.

Figure 5.2: TEMPO.

  - Formed by oxidizing 2,2,6,6-tetramethylpiperidine (TMP), a sterically hindered organic base, with H_2O_2 in the presence of the tungstate anion ($WO_4{}^{2-}$).
  - Check: TEMPO *does* have both resonance stabilization (with the adjacent nitrogen heteroatom) and steric blocking (from the adjacent quaternary carbons).
  - The MO diagram (Figure 5.2b) reveals that the $N-O\cdot$ bond is an example of a 2c-3e bond.
  - The **spin density map** shows that the radical is evenly dispersed on O and N: 50% radical density on O and 50% on N.
  - Takeaway: If you want to design your own persistent radical, take something with some resonance, add some steric blockers, and you're good to go!

- **Bond dissociation energy**: The energy it takes to symmetrically break a chemical bond. *Also known as* **BDE**. *Given by*
$$X-Y \rightleftharpoons X\cdot + Y\cdot \qquad\qquad \Delta H^\circ = BDE$$

  - Observe that this definition is analogous to those of HIA and pK_a from the past two lectures!
  - X and Y can be organic groups, hydrogen, heteroatoms, etc.
  - The above reaction denotes **homolytic** bond cleavage, as opposed to **heterolytic**.
  - BDE is an extremely useful measure of "bond strength." It's probably one of the top three key concepts we should take away from Phys Orgo to use in the rest of our careers.

    ■ Guideline: A weak bond yields a more stable radical.

  - BDE is useful for predicting if a reaction is endothermic or exothermic.
  - One big factor that affects BDE is bond polarity.

    ■ In general, more polar bonds are stronger.
      ➢ This contrasts with heterolytic cleavage, where polar bonds are easier to cleave.
      ➢ Essentially, acidic bonds are "stronger" even if it's easier to take off the acidic proton with your own "hands" (reagents) in lab.
    ■ See Table 5.1 for more.
    ■ Key point: When we talk about "strong bonds," just remember that we're talking about the BDE.

- **Homolytic** (bond cleavage): The breaking of a chemical bond in such a way that an *equal* amount of electron density is left on both products.

- **Heterolytic** (bond cleavage): The breaking of a chemical bond in such a way that an *unequal* amount of electron density is left on both products.

- Let's look at some example comparisons between pK_a's and BDE's to see the aforementioned inverse relationship.

	H_3C-H	H_2N-H	$HO-H$	$F-H$
pK_a (H_2O)	48	38	15.7	3.2
BDE (kcal/mol)	105	107	119	135

Table 5.1: BDEs and pK_a's are inversely related.

  - As we go to the right, it becomes easier to remove H^+.
  - As we go to the left, it become easier to remove $H\cdot$.

- Some BDEs to know. (Memorize these!! They will likely come up in your Quals!)

    - The effect of bond polarity.
        - ■ C–C: ~ 81 kcal/mol.
        - ■ C–H: ~ 98 kcal/mol.
        - ■ O–H: ~ 105 kcal/mol.

    - The effect of hyperconjugation.
        - ■ Me–H: ~ 105 kcal/mol.
        - ■ Et–H: ~ 100.5 kcal/mol.
        - ■ ^{i}Pr–H: ~ 98.1 kcal/mol.
        - ■ ^{t}Bu–H: ~ 95.7 kcal/mol.

    - The effect of hybridization.
        - ■ $RC\equiv C$–H: ~ 132.8 kcal/mol.
        - ■ $R_2C{=}CH$–H: ~ 111.2 kcal/mol.
        - ■ Ph–H: ~ 112.9 kcal/mol.

    - The effect of resonance.
        - ■ All–H: ~ 88.2 kcal/mol.
        - ■ Bn–H: ~ 88.5 kcal/mol.
        - ■ Note that allyl bonds are broken more easily than benzyl ones because resonance stabilizing the product radical doesn't force you to break aromaticity; indeed, breaking aromaticity is a little less fun than moving a π-bond around.

    - The effect of atomic size and polarizability.
        - ■ Me–I: ~ 57.1 kcal/mol.
        - ■ Me–Br: ~ 70.3 kcal/mol.
        - ■ Me–Cl: ~ 83.7 kcal/mol.
        - ■ Me–F: ~ 110.0 kcal/mol.

    - Peroxides.
        - ■ HO–H: ~ 119 kcal/mol.
        - ■ HO–OH: ~ 51 kcal/mol.
        - ■ ^{t}BuOO–H: ~ 88 kcal/mol.
        - ■ ^{t}BuO–OH: ~ 44 kcal/mol.
        - ■ ^{t}BuO–H: ~ 106 kcal/mol.

- Polar effects on radicals.

(a) Unmixed radical energy.   (b) Radical near EDG.   (c) Radical near EWG.
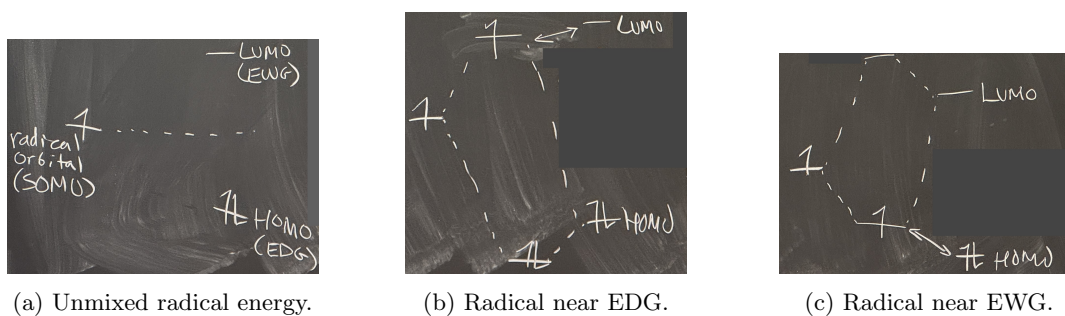
Figure 5.3: Radicals near EDGs and EWGs.

– Both EDGs *and* EWGs can stabilize radicals, despite the fact that radicals are electron deficient.

– Example: A radical α to a carbonyl (e.g., homolytically cleave one of acetone's C−H bonds).

  ■ The carbonyl *will* destabilize the radical inductively.

  ■ However, it will also *stabilize* the radical through resonance.

  ■ The second effect (resonance) is stronger.

– Let's now justify these stabilizing effects using MO theory.

  ■ Before mixing (Figure 5.3a), a typical radical has energy intermediate between the HOMO of an EDG and the LUMO of an EWG.

  ■ When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), *two* electrons get stabilized and *one* gets destabilized. It follows that there is a net stabilization of the molecule, as expected.

  ■ When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), the sole electron present in the system gets stabilized. It follows that there is *still* a net stabilization of the molecule, even here!

– These molecular orbital diagrams reveal two additional attributes of polarized radicals, as well.

  1. EDGs make radicals more nucleophilic.

     ■ When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), a new radical SOMO (the antibonding orbital) is created.

     ■ This new SOMO is a better energy match with LUMOs, so the radical electron is more likely to mix with a LUMO since this will lead to greater thermodynamic stabilization of the product than before.

     ■ In other words, the radical is now more nucleophilic.

  2. EWGs make radicals more electrophilic.

     ■ When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), a new radical SOMO is once again created, but it is the stabilized bonding orbital this time.

     ■ This new SOMO is a better energy match with HOMOs, so the radical electron is more likely to mix with a HOMO since this will lead to greater thermodynamic stabilization of the product than before.

     ■ In other words, the radical is now more electrophilic.

• Synthesis of radicals.

  – Also known as **initiation**, if we're doing a radical chain reaction.

  – Most common way to make a radical: Homolytic cleavage of a weak bond.

    ■ We'll often use light or heat to give a little burst of energy and break this bond.

  – Commonly used radical initiators.

    ■ Peroxides are easily broken by light and heat, so we often use them.

      ➢ Example: Organic peroxides react like RO−OR $\xrightarrow[\Delta]{h\nu}$ RO ·

    ■ **AIBN**.

    ■ Br_2.

      ➢ Bromine reacts like Br−Br $\xrightarrow[\Delta]{h\nu}$ Br ·

    ■ Paramagnetic metals, i.e., metals with 1 unpaired electron.

      ➢ Example: $\mathbf{Cp_2Ti^{III}Cl}$.

    ■ Single-electron transfer (SET) or energy transfer (ET).

      ➢ Often done with metals, electrochemistry, or photochemistry.

      ➢ These are increasingly common ways to cycle one-electron oxidation states.

  – Essentially, if we ever need to make a radical, we can choose old-school or new-school based on what we have on hand!

- **Azobisisobutyronitrile**: A common thermal radical initiator. *Also known as* **AIBN**.

Figure 5.4: AIBN as a thermal radical initiator.

  – This radical has a very cool design: Under heat or shock, you cleave the $N-C$ bonds to form tertiary radicals that are additionally stabilized by their proximity to a π-system, and release N_2.
  – You commonly see AIBN used with $HSnBu_3$ in radical cyclizations.

- **Titanocene monochloride**: An increasingly popular SET agent. *Denoted by* $\mathbf{Cp_2Ti^{III}Cl}$.
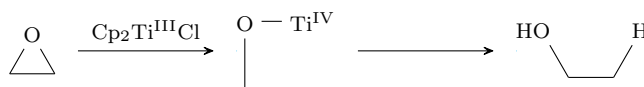
Figure 5.5: $Cp_2Ti^{III}Cl$ as an SET radical initiator.

  – For example, $Cp_2Ti^{III}Cl$ can be used for radical-mediated epoxide openings, as shown above.
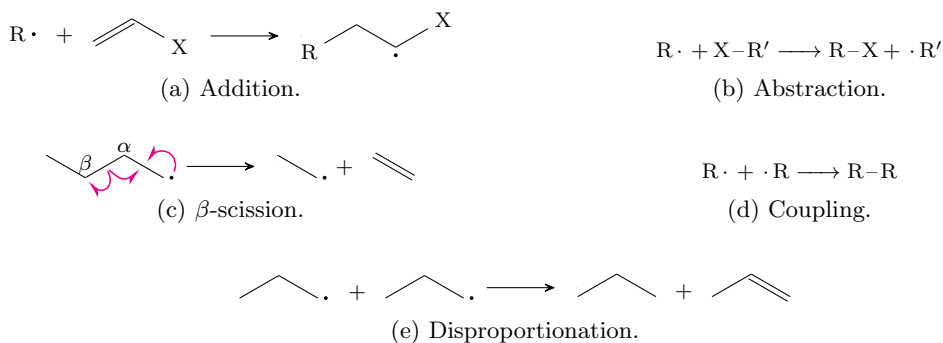
- Radical reactions.

(a) Addition.

$$R\cdot + X-R' \longrightarrow R-X + \cdot R'$$

(b) Abstraction.

(c) β-scission.

$$R\cdot + \cdot R \longrightarrow R-R$$

(d) Coupling.

(e) Disproportionation.

Figure 5.6: Radical reactions.

  – Addition to multiple bonds (Figure 5.6a).
      ■ This can lead to cyclization, quenching, propagation, etc.
      ■ If it's a cyclization, we follow **Baldwin's rules**.[1]
  – Abstraction (Figure 5.6b).
      ■ X is a halogen or hydrogen.
  – β-scission and fragmentation.
      ■ In general, β-scission refers to breaking the chemical bond between the carbons α and β to the radical.
      ■ Fragmentation can be interpreted more broadly.
      ■ Example: The second step in the cleavage of benzoyl peroxide would count as fragmentation. Formally, this is called **radical decarboxylation**.
  – Radical chain propagation.
      ■ This occurs by one of the above mechanisms.

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[1]These rules are not covered in this course, but basically, they tell us which radical cyclizations are allowed.

– Polymerization.

■ If this is our goal, great! Radical chain reactions are great for making polymers.

■ If this is not our goal, it's a common side reaction for which we need to watch out.

– Radical coupling/dimerization, i.e., a **termination** step.

■ Two radicals form a bond.

■ ΔH is always negative (from an enthalpic point of view), but sterics can prevent this as with persistent radicals.

– Disproportionation.

■ A reaction in which two radicals form two nonradical products.

■ This is another possible termination step.

– **Barton deoxygenation**.

• **Radical decarboxylation**.
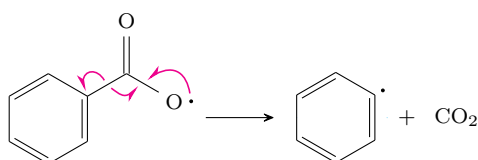
Figure 5.7: Radical decarboxylation.

– Radical decarboxylation can help us generate unstable radicals.

– For example, Ph· isn't too stable normally, but we will form it under radical decarboxylation conditions regardless because CO_2 is a really good leaving group. Basically, CO_2 helps the thermodynamics work out.

• **Barton deoxygenation**. A method of deleting hydroxyl groups. *Also known as* **Barton-McCombie deoxygenation**.
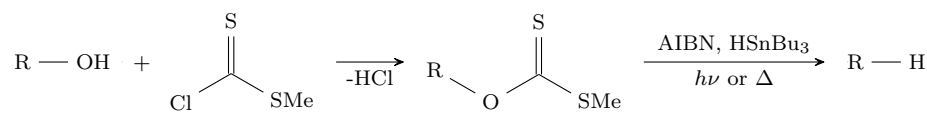

Figure 5.8: Barton-McCombie deoxygenation.

– Masha wanted to include this one named reaction, even though named reactions are not our focus in this class.

– Essentially, we react an alcohol to form a xanthate ester and then cleave it off with radicals.[2]

• David: Why would you ever choose to use a thermal initiator over a photochemical one?

– Practically speaking, chemical initiators can be a bit easier to work with in lab because with photochemical, you have to find the exact right wavelength that will activate our initiator and do nothing else in our reaction.

• Radical **clocks** and **traps**.

– This is the first of many mechanistic experiments we'll cover in this class, so take note of it in case you want to use it in your final project (the mechanistic proposal)!!

– Radical clocks and traps both test for the presence of radical intermediates.

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[2]See 5.47 notes for a mechanism.

- **Radical trap**: A species (often a persistent radical) that can quickly sequester a radical intermediate.

  - Example: If we add TEMPO ($R_2N-O\cdot$) to our reaction mixture, any radical intermediate $R\cdot$ that is formed in solution is likely to react with TEMPO to form a **TEMPO adduct** as follows.

  $$R\cdot + R_2N-O\cdot \longrightarrow R-O-NR_2$$
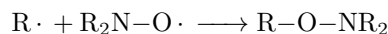
  - Example: Per MO theory, O_2 is a ground-state triplet diradical, so it can interact with $R\cdot$ and form the peroxide as follows.

  $$R\cdot + \cdot\ddot{O}-\ddot{O}\cdot \longrightarrow R-\ddot{O}-\ddot{O}\cdot$$
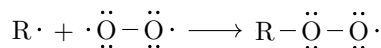
  - Interpret the results of a radical trap experiment with caution — they can't be the basis of our whole argument that something is a radical mechanism; they are just a good first piece of evidence.

- **Radical clock**: A reaction with a known (fast) rate that is used to benchmark a radical reaction of interest.

(a) 5-hexenyl clock.   (b) Cyclopropylmethyl clock.
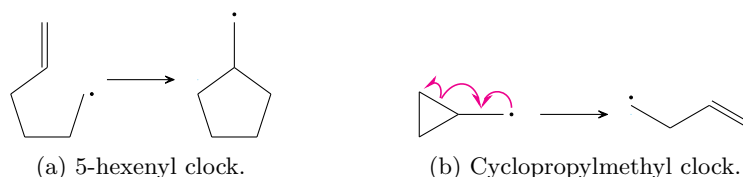
Figure 5.9: Radical clock reactions.

  - Method: Synthesize an analogue of your substrate with a certain functional group attached such that if a radical is formed at a certain site, it will react with your new functional group instead of doing the designed reactivity.

  - Example: Enable the formation of a 5-hexenyl radical so that it can do a **5-exo-trig cyclization**.[3]

    - The rate of this reaction is $k = 2.3 \times 10^5 \, \text{s}^{-1}$.

  - Example: Enable the formation of a cyclopropylmethyl radical so that it can do a radical ring opening and form an olefin.

    - The rate of this reaction is even quicker: $k = 9.4 \times 10^7 \, \text{s}^{-1}$.
    - This is gold standard for a mechanistic experiment to prove radical mechanisms.

  - These are very common kinetic probes for mechanisms!

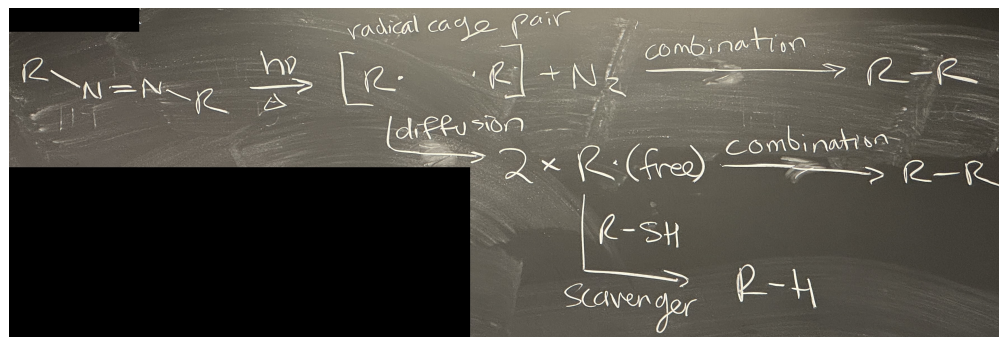- Another mechanistic experiment: The **radical cage effect**.

Figure 5.10: Radical cage effect.

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[3]This is a type of radical cyclization allowed by Baldwin's rules.

- Consider a radical initiator of the form R–N=N–R.
- When it decomposes — either thermally or photochemically — it will form two radicals that are in very close proximity to each other in solution.
  - We call these two radicals a **radical cage pair**, where the "cage" is the surrounding solvent molecules.
- These radicals can easily recombine within the cage in a radical coupling/dimerization reaction to form R–R.
- However, they can also diffuse out of the cage, drifting apart to yield 2 R · in solution.
  - These "free" radicals can then combine again to form R–R.
  - Or, alternatively, they can interact with a radical scavenger (such as a thiol[4]) in solution.
- Notes on the cage effect.
  - A more viscous solvent makes it harder to escape the cage.
  - A scavenger can differentiate pathways.
  - Stereoretentive radical reactions can occur within a radical cage, because combination within the cage can outcompete stereoinversion.
    - ➢ However, if you diffuse out of the cage, forget it.
    - ➢ Takeaway: Cages can have stereochemical consequences, such as retention.
- I need to do more reading on this and figure out exactly what I'm responsible for here!!
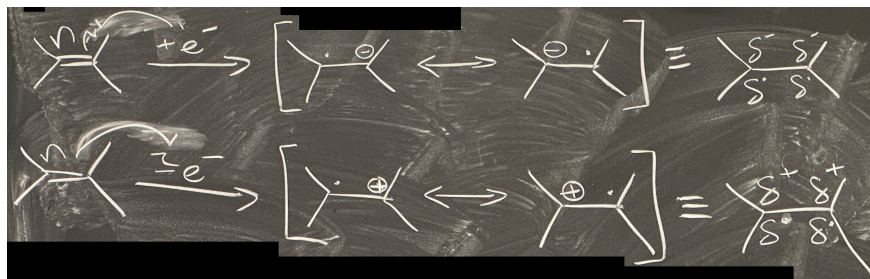
- Radical anions and cations.

Figure 5.11: Radical ion formation and structure.

- Start with a π-system.
- When we add an electron to the π-system or subtract one from it, we form a radical ion.
- These radical ions exist in resonance with each other, giving us partial radical and ion character at both sides of the π-system.
- Example of radical cations: Mass spec.
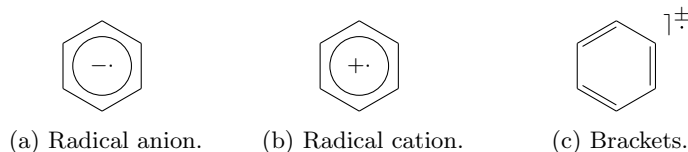
- Radical ions are common in aromatic rings.

(a) Radical anion. (b) Radical cation. (c) Brackets.

Figure 5.12: Aromatic radical ion notation.

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[4] Alison Wendlandt uses thiols (such as adamantane thiol, AdSH) as HAD sources in her research!

- – As such, we have a special notation for them.
  - ■ Use a circle for the π-system, and then write "$\pm\cdot$" in the center.
  - ■ Alternatively, we can write the "$\pm$" and "$\cdot$" on top of each other outside a bracket surrounding the species.
- – Example of aromatic radical anions: The Birch reduction. See Labalme (2024).

- • Radical ions can undergo **mesolytic cleavage** to generate a radical plus an ion.

$$R{-}X^{\rceil\pm}_{\cdot} \longrightarrow R\cdot + X^{\pm}$$

- – This is what happens in mass spec!
- – It's actually a common phenomenon, even though we often don't think of it in that much detail.

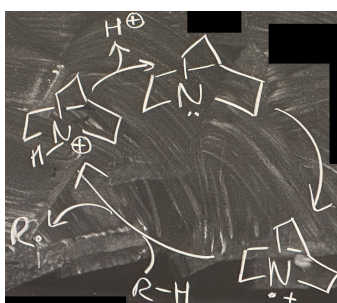- • Example of radical ions: A plug for using these species in catalysis.

Figure 5.13: Catalysis with radical ions.

- – Quinuclidine forms a radical cation, reacts with $R{-}H$ to form $R\cdot$ and quinuclidinium via an H-atom abstraction (HAA) pathway, and then can reform quinuclidine by loss of a proton. The $R\cdot$ then goes on to do cool stuff.
- – Here, quinuclidine is used as a catalytic initiator!
- – Reference: Le et al. (2017).