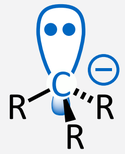
4.8 Radical Reactions (S_R, A_R)

Carbon-Centered Reactive Intermediates



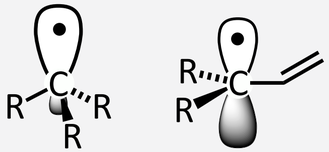
carbanion

5 electrons
negative formal charge

teatrahedral

sp^3

3 bonds, 1 electron pair
octet rule fulfilled



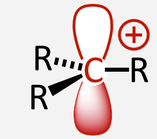
radical

4 electrons
neutral

in between

sp^3 or sp^2 or mixed

open shell



carbenium cation

3 electrons
positive formal charge

trigonal planar

sp^2

3 bonds
electron sextet (deficient)

- **formal charges** are determined by **homolytic bond cleavage** and counting electrons

Radical Reaction Mechanisms

- **radical reaction mechanisms involve molecules with unpaired electrons (•) as reactive intermediates**
- "radicals" are obtained by homolytic bond cleavage (electron pair is equally split between atoms)

- **simple radical reactions occur between two (same or different) radicals**

  - reaction sequence ends finally by "combination" of the unpaired electrons (•) to from new bond
  - bond formation hence requires electrons to have opposite spin (represented by half arrows)
  - however, many steps can happen in between

Bond Energies

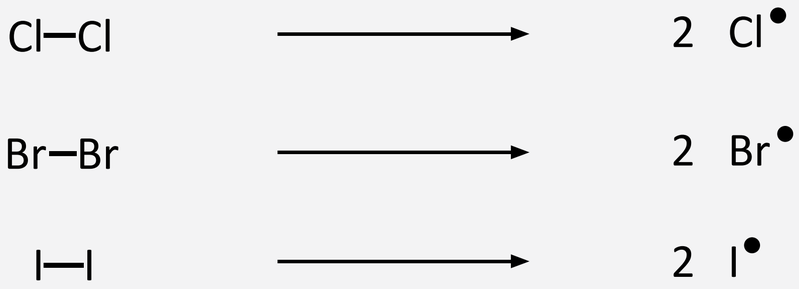
	ΔG / kJ mol^{-1}		ΔG / kJ mol^{-1}		ΔG / kJ mol^{-1}
H–OH	498	H_3C–OH	383	HO–OH	213
H–CH_3	435	H_3C–CH_3	368	MeO–OMe	151
H–Cl	431	H_3C–Cl	349	Cl–Cl	243
H–Br	366	H_3C–Br	293	Br–Br	192
H–I	298	H_3C–I	234	I–I	151

- **homolytic bond cleavage can be achieved by thermal activation or light as an energy source**
  - all bonds can undergo homolytic cleavage at elevated temperatures (typically ≥ 200 °C)
  - just a matter of kinetics because molecules show a Boltzmann distribution of thermal energies
  - light can serve as an energy source (e.g. blue of UV, ≤ 400 nm, ≥ 300 kJ/mol)

Generation of Radicals by Homolytic Bond Cleavage

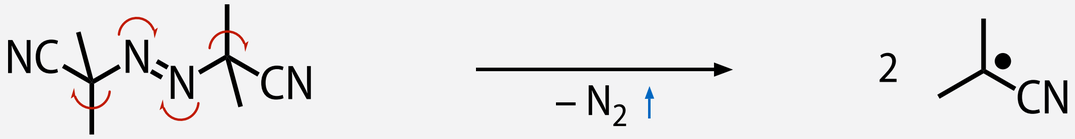
- radicals are formed by homolytic bond cleavage of weak covalent bonds by heat (Δ) or light (hν)

- dihalogens



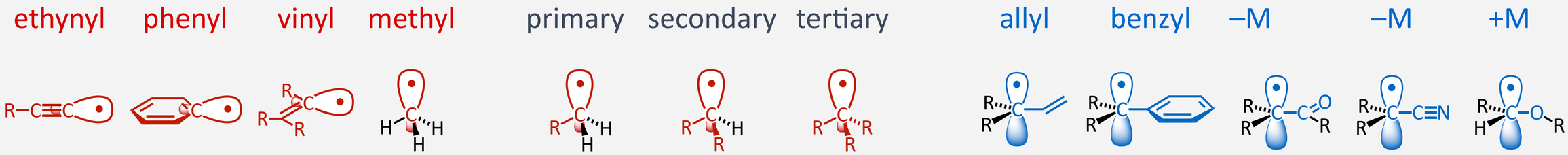
- peroxides

- azo compounds



Stability of Carbon Radical Centers

- radicals are often pyramidal, unpaired electron in sp^3 orbital carbon center
- radicals with π-conjugated substituents are planar, unpaired electron in p orbital
- (values are covalent R–H bond energies in kJ/mol, energy required to generate the radical)

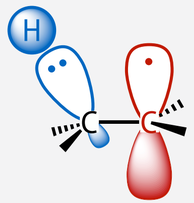


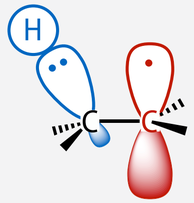
increasing stability

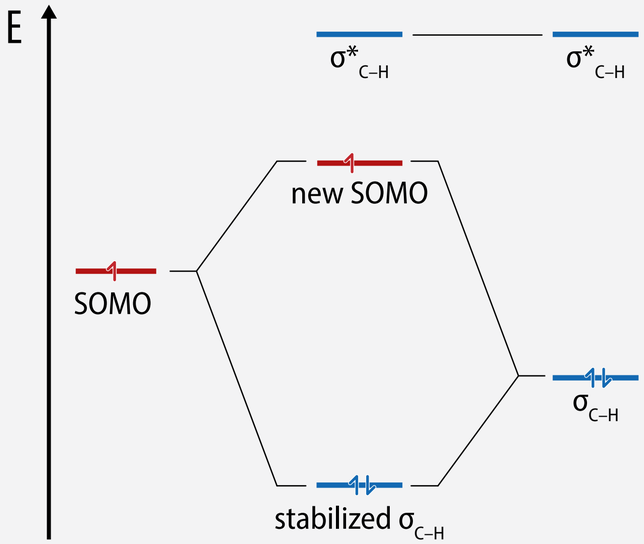
- **all radicals are reactive intermediates, have short lifetimes, and cannot be isolated**
- **free radical reactions are fast single-step reactions, but many side-reactions occur**
- **free radicals are electron-deficient carbon centers, (almost) same rules for stability as carbocations**
- **notably, however, stabilization by both +M and –M substutents**

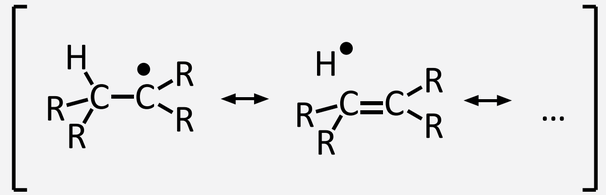
Stabilization by Hyperconjugation

- alkyl substituents on the radical carbon center stabilize the radical by “hyperconjugation”





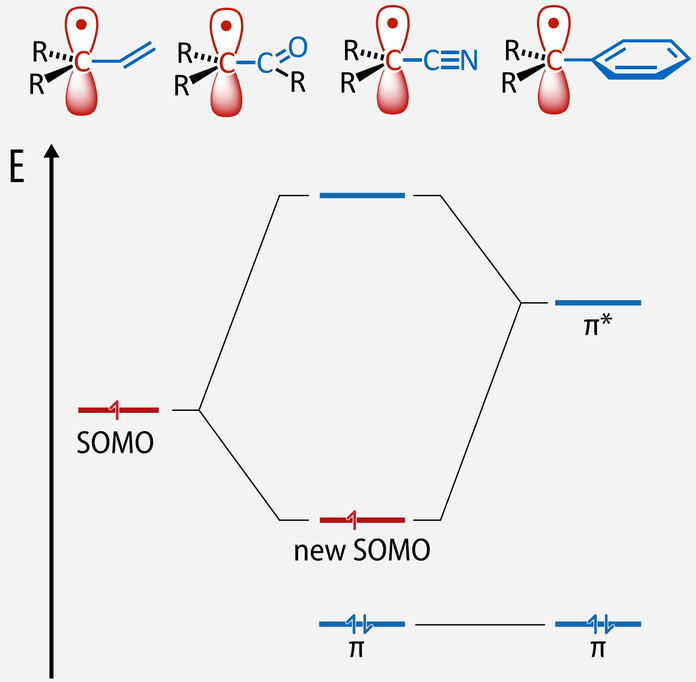




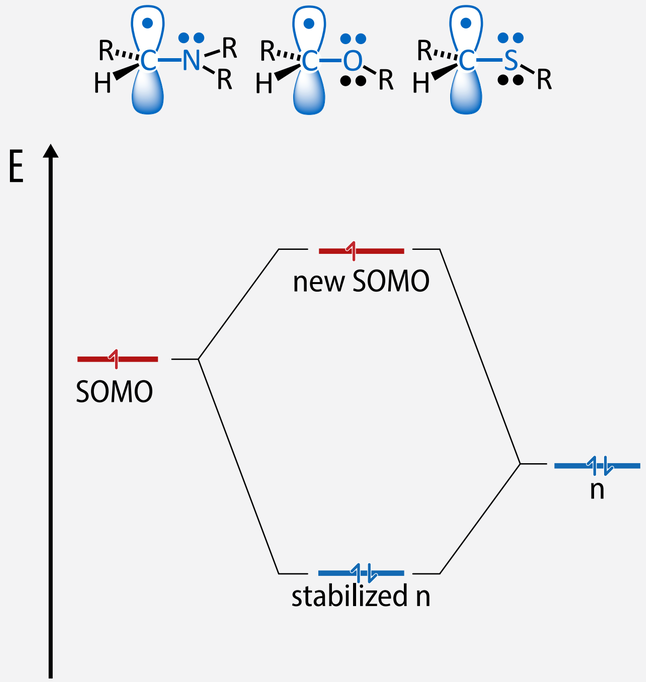
- **three-center three-electron bond partially delocalizes the C–H bond towards electron center**
- **hydrogens on the substituent are rendered more labile for abstraction (by another radical)**

Stabilization by +M and –M Substituents

- stabilization by –M substituents works for radicals and carbanions, but not for carbocations
- stabilization by +M substituents works for radicals and carbocations, but not for carbanions



π conjugated & –M substituents

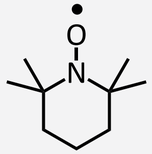


+M substituents

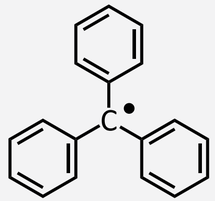
- **stabilization by –M substituents *facilitates* radical *generation*, yields less reactive radical**
- **stabilization by +M substituents *facilitates* radical *generation*, but yields more reactive radical**

Persistent Radicals

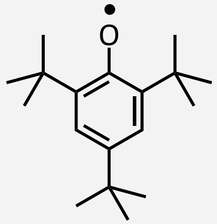
- persistent radicals are stable molecular compounds with unpaired electrons, can be isolated



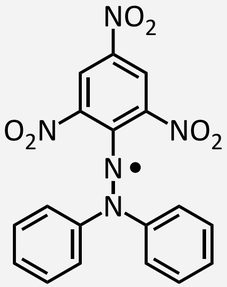
teramethylpiperdineoxide
(TEMPO)



triphenylmethyl
(trityl)



2,4,6-tri(*tert.*-butyl)phenoxyl

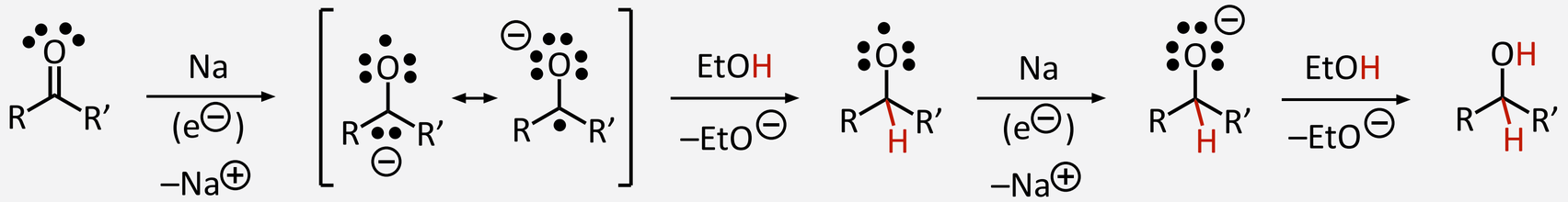


2,2-diphenyl-1-picrylhydrazyl
(DPPH)

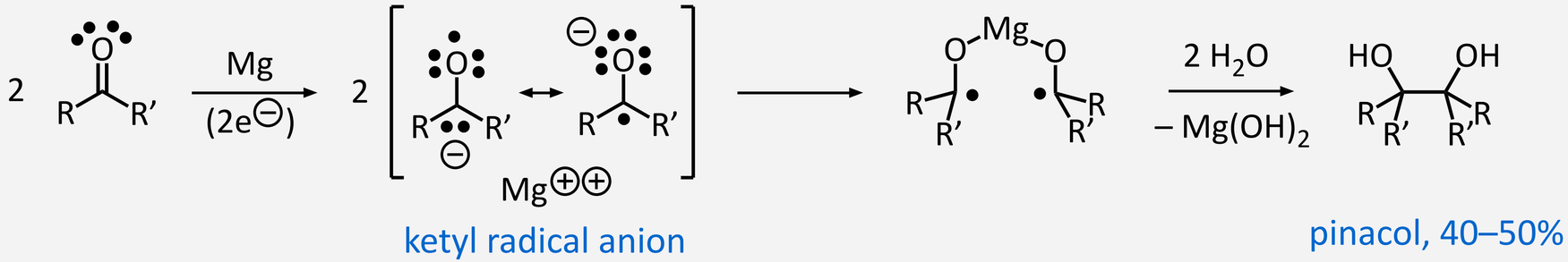
- **persistent radicals stabilized by electronic effects and steric hindrance shielding the radical center**

Radical-Radical Dimerization Reactions

- alkaline or earth alkaline metals transfer electrons, reduce ketones to alcohols in protic solvents



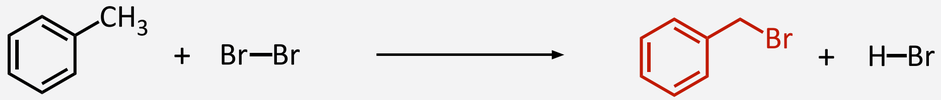
- **earth alkaline metals in aprotic solvents result in radical combination, yielding a diol (pinacol reaction)**



- **electrostatic repulsion of ketyl radical anions requires complexation with earth alkaline cation**

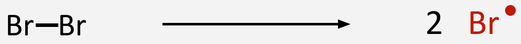
Alkyl Halogenation by Radical Substitution (S_R)

net reaction



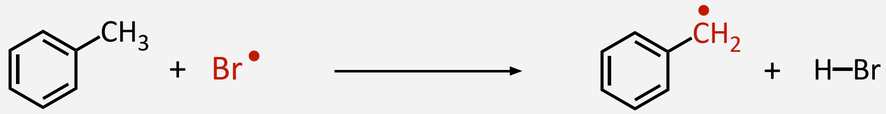
alkyl halogenation

initiation



bond homolysis

propagation (up to 10^6 times)

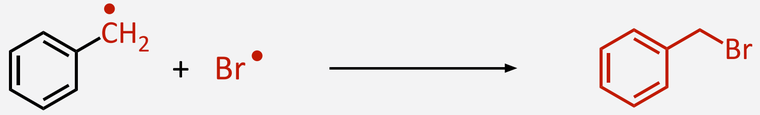


hydrogen abstraction

halogen abstraction, main product

termination reactions

not productive



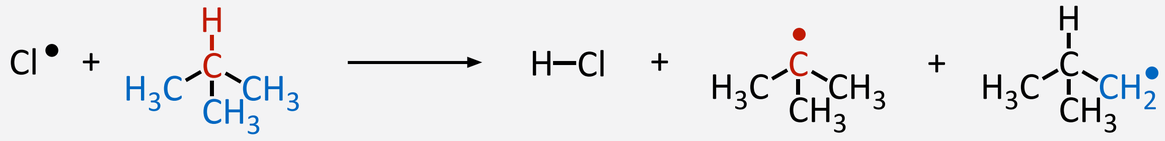
main product

side product

- radical substitution reactions are **chain reactions**
- conditions chosen to achieve **“steady state” of equal initiation and termination reaction rates**

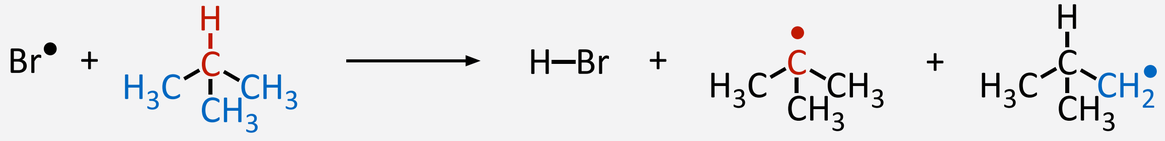
Regioselectivity of Radical Substitutions

- regioselectivity of radical substituion reactions is decided in the hydrogen abstraction step
- radicals are highly reactive, all hydrogens compete, product mixtures are always obtained
- outcome is superposition of statistics and stabilization of new radical (C–H bond strength)



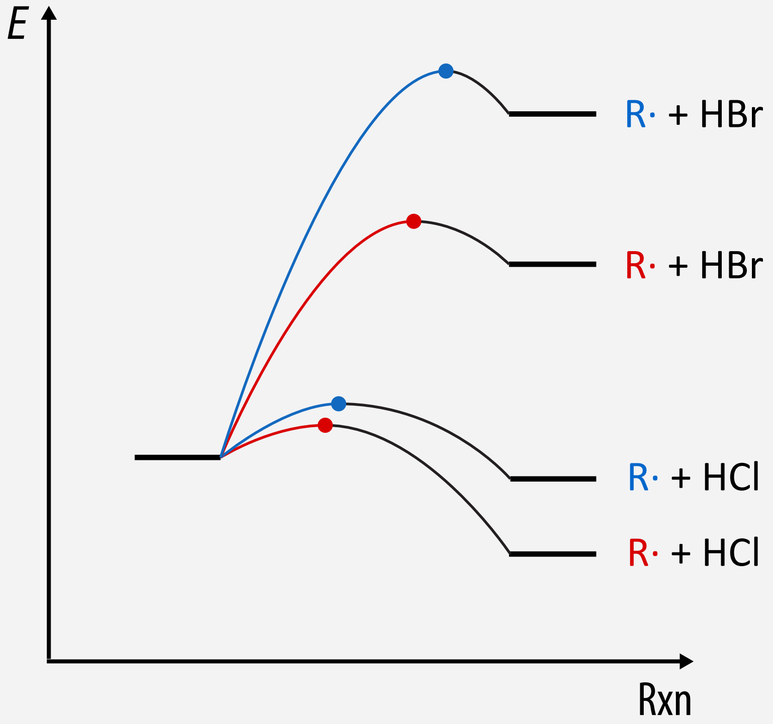
1 H +397 kJ/mol –431 kJ/mol 37% 63%

9 H +423 kJ/mol reactivity ratio = 37/63 · 9/1 ≈ 5/1



1 H +397 kJ/mol –366 kJ/mol 99% 1%

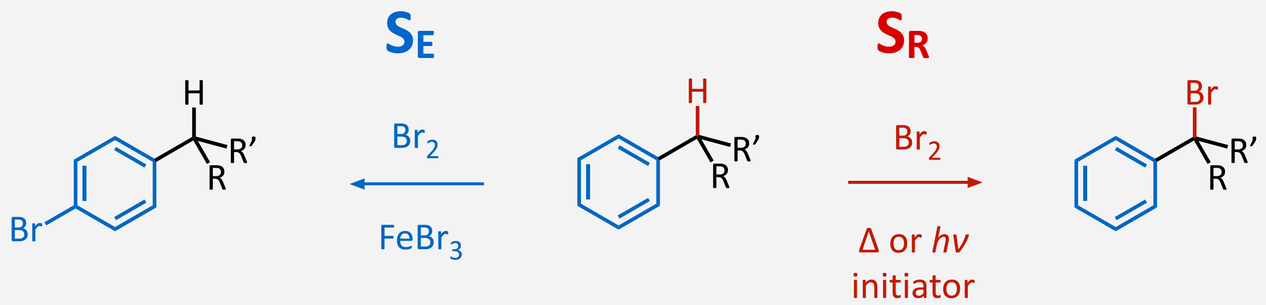
9 H +423 kJ/mol reactivity ratio = 99/1 · 9/1 ≈ 891/1



- **reactivity chlorine > bromine > iodine (H–Hal bond is weaker)**
- **C–H bond abstraction becomes less favorable (or even endergonic)**
- **selectivity chlorine < bromine < iodine radicals (“later” transition states differentiate better)**

Electrophilic Substitution versus Radical Substitution with Dihalogens

- on alkylarenes, dihalogens can be used to affect electrophilic or radical substitution reactions



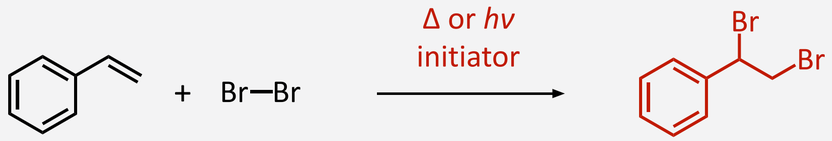
"cold, catalyst, core"

"sun, side chain"

- **halogenation of the arene (core) requires a Lewis acid catalyst, polar solvent, cooling**
- **halogenation of the side chain requires heat or light, an initator, apolar solvent**

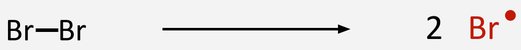
Dihalogenation of Double Bonds by Radical Addition (A_R)

net reaction

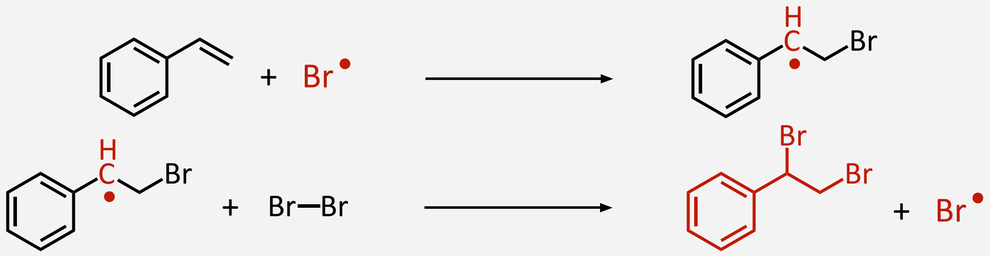


double bond dihalogenation

initiation



propagation (up to 10^6 times)



radical addition to double bond

halogen abstraction, main product

termination reactions

not productive

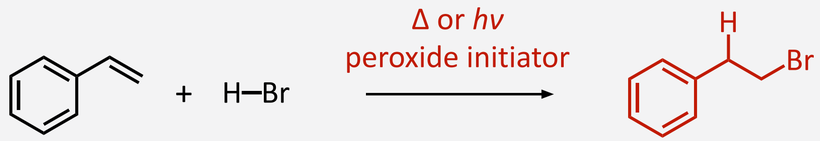
main product

side product

- **radical addition reactions are chain reactions, strongly preferred over radical substitutions**
- **conditions chosen to achieve "steady state" of equal initiation and termination reaction rates**

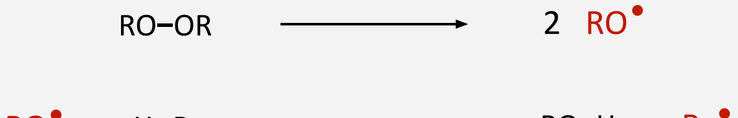
Hydrohalogenation of Double Bonds by Radical Addition (A_R)

net reaction



double bond hydrohalogenation
anti-Markovnikov

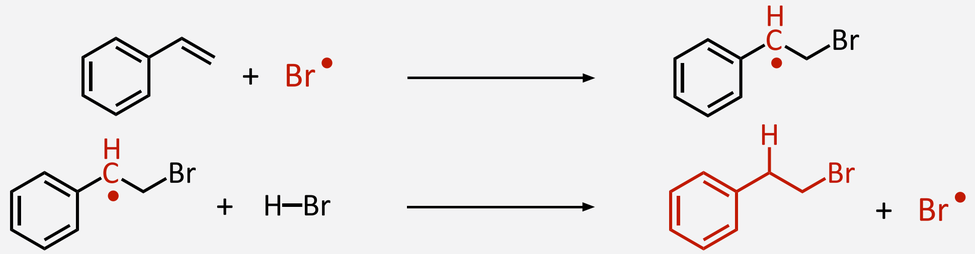
initiation



bond homolysis (peroxide)

hydrogen abstraction (peroxyl)

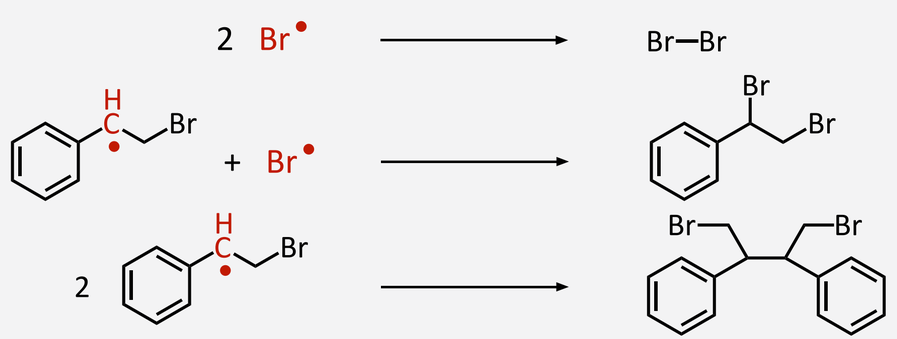
propagation (up to 10^6 times)



radical addition to double bond

hydrogen abstraction, main product

termination reactions



not productive

side product

side product

- **anti-Markovnikov product is formed because initial radical addition prefers more stable radical**