

Thiyl Radicals in Organic Synthesis



When burned, sulfur melts to a blood-red liquid and emits a blue flame that is best observed in the dark.

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MacMillan Group Meeting
November 6, 2014

I. Generalities

II. Thiyl-Mediated Hydrogen Atom Transfer

III. Addition of Thiols to C=C bonds

IV. Fragmentation of β -Sulfanyl Radicals

V. Addition of Thiols to Alkynes

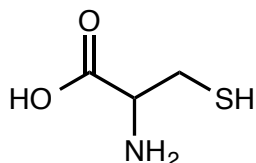
VI. Addition of Thiols to Isonitriles

VII. Addition of Thiols to C=S bonds

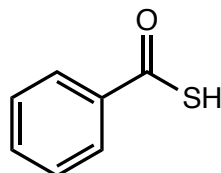
I. Generalities

■ S-H Bond Dissociation Energies in Thiols

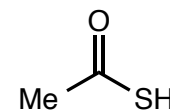
- Alkanethiols: similar S-H BDEs around 87 kcal mol⁻¹ regardless of the structure of the alkyl residue



86 kcal mol⁻¹

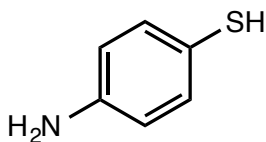


87 kcal mol⁻¹

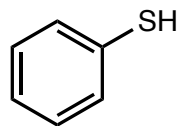


88 kcal mol⁻¹

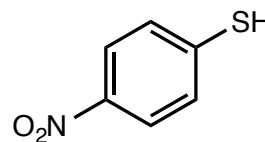
- Thiophenols: weaker S-H BDEs due to the stabilization by resonance of the corresponding arenethiyl radical



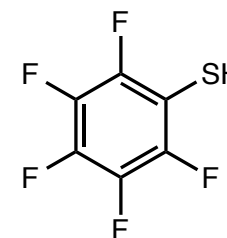
70 kcal mol⁻¹



79 kcal mol⁻¹



82 kcal mol⁻¹



84 kcal mol⁻¹

■ S-S Bond Dissociation Energies in Disulfides

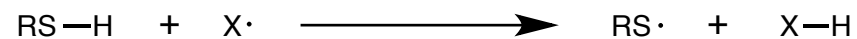
- Dialkyldisulfides: around 65 kcal mol⁻¹

- Diaryldisulfides: around 50 kcal mol⁻¹

I. Generalities

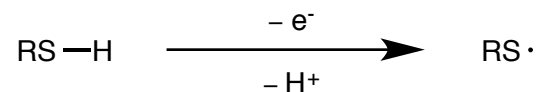
■ Generation of Thiyl Radicals

- Hydrogen atom abstraction by the other radicals having a corresponding higher X-H BDEs

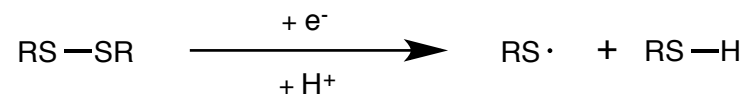


Initiator: AIBN, $(\text{PhCO}_2)_2$, $(t\text{-BuO})_2$, $\text{Et}_3\text{B}/\text{O}_2$

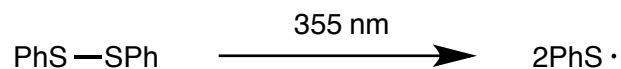
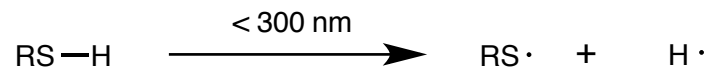
- One-electron oxidation by $\text{Mn}(\text{OAc})_3$, O_2



- One-electron reduction of disulfides



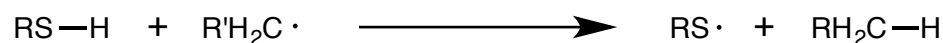
- Homolytic cleavage by radiolysis or light irradiation



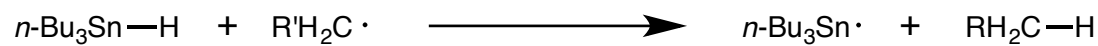
II. Thiol-Mediated Hydrogen Atom Transfer

■ Rate of Hydrogen Atom Transfer

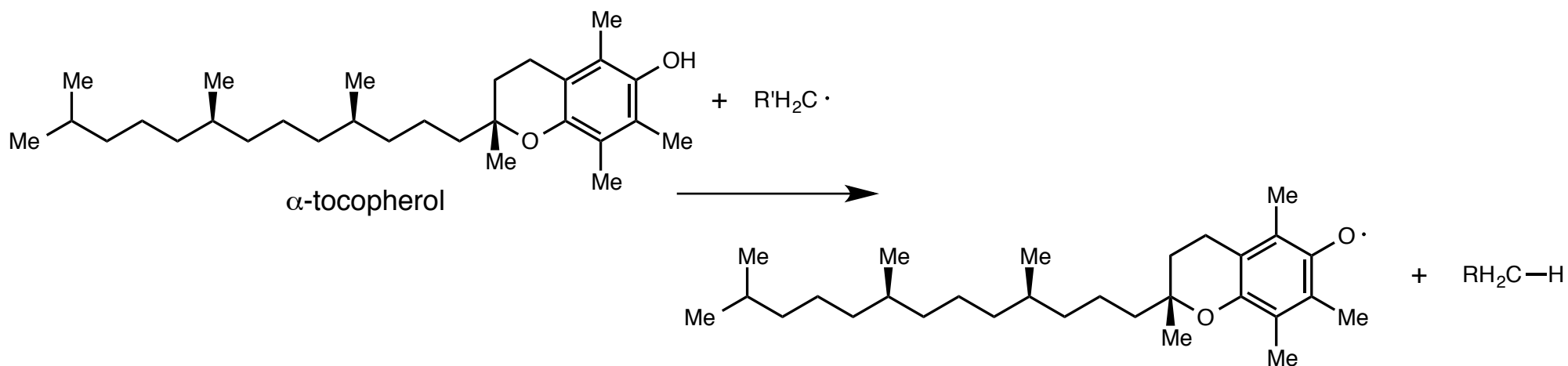
- The reactivity of a class of radicals toward a given hydrogen atom donor is well described by two parameters: the activation energy of the thermoneutral reaction (E_{e0}) and the enthalpy of the reaction of interest (ΔH_e)
- Different interactions in the transition state such as polar effects, antibonding (triplet repulsion), or neighboring π -electrons may influence E_{e0} , which is particularly low for the reactions of alkyl radicals with thiols



$$\text{S-H BDE} = 87 \text{ kcal mol}^{-1} \quad k_{298\text{K}} = 2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$$



$$\text{Sn-H BDE} = 79 \text{ kcal mol}^{-1} \quad k_{298\text{K}} = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$$

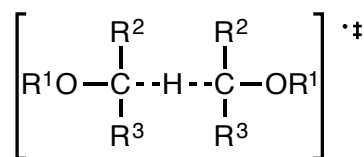


$$\text{O-H BDE} = 77 \text{ kcal mol}^{-1} \quad k_{298\text{K}} = 6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$$

II. Thiol-Mediated Hydrogen Atom Transfer

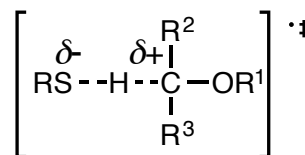
■ Polar Effect in Hydrogen Atom Transfer

■ In hydrogen atom transfers between two radicals of different electronegativity, charge transfer configurations may contribute to the character of the transition state, such polar effects resulting in a lowering of the activation barrier



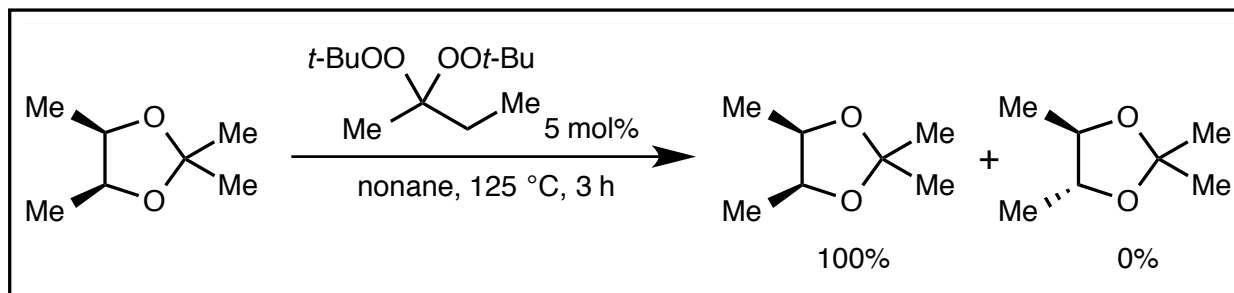
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the absence of charge-transfer stabilization of the symmetrical transition state, in which the incoming and outgoing α -alkoxyalkyl radicals have the same electronegativity

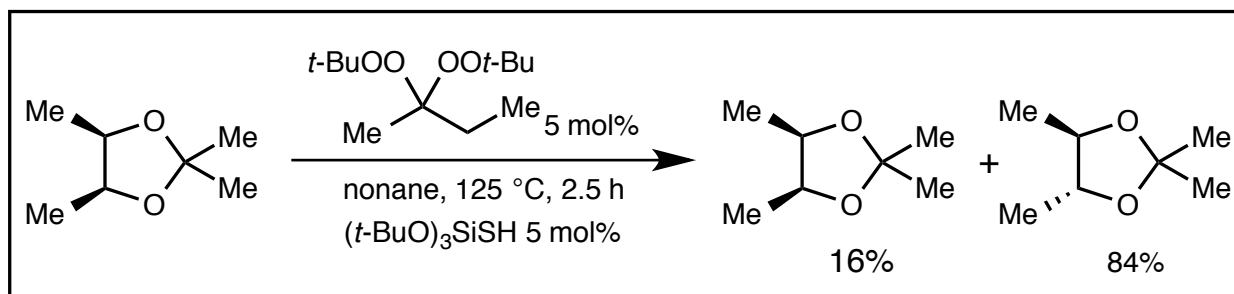


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benefits from charge-transfer stabilization because the electronegativities of the nucleophilic α -alkoxyalkyl radical and the electrophilic thiyl radical are significantly different



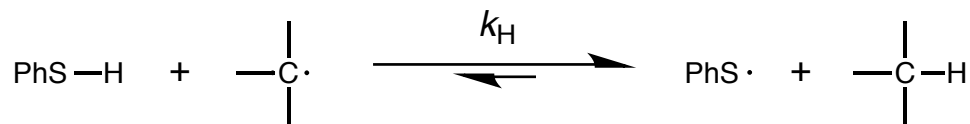
high activation energy



thermodynamic equilibrium

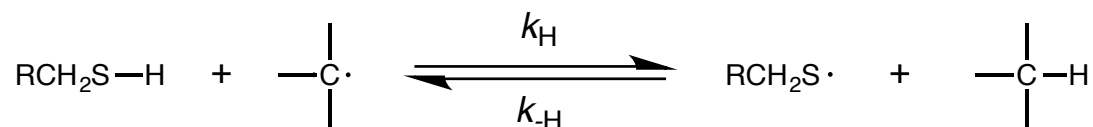
II. Thiyl-Mediated Hydrogen Atom Transfer

■ Rate Constants for the Reduction of Various Alkyl Radicals by Thiophenol



entry	radical	$k_H/[\text{M}^{-1} \text{s}^{-1}] (T/\text{K})$	$\Delta H/[\text{kcal mol}^{-1}]$
1	$n\text{-C}_3\text{H}_7\text{-CH}_2\cdot$	$1.3 \times 10^8 (298)$	-17
2	$(\text{CH}_3)_2\text{CH}\cdot$	$1.0 \times 10^8 (298)$	-15
3	$(\text{CH}_3)_3\text{C}\cdot$	$1.4 \times 10^8 (298)$	-12
4	$n\text{-C}_6\text{F}_{13}\text{-CF}_2\cdot$	$2.8 \times 10^5 (303)$	-20
5	$\text{ROCH}_2\text{CH}_2\cdot$	$7.6 \times 10^7 (353)$	-18
6	$\text{PhCH}_2\cdot$	$3.0 \times 10^5 (298)$	-5

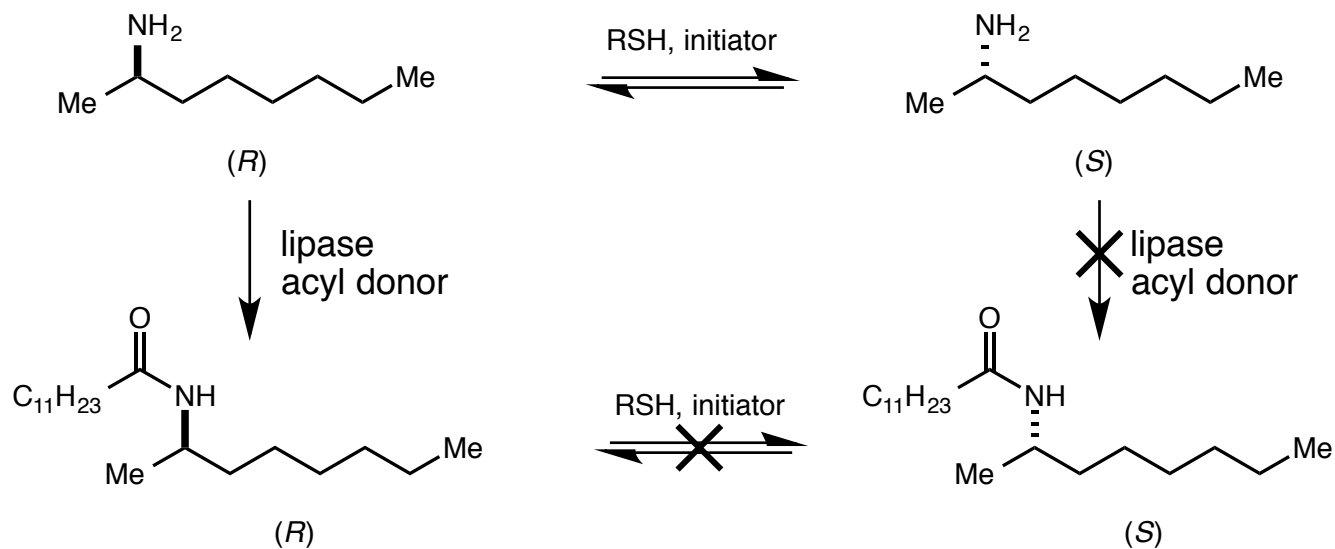
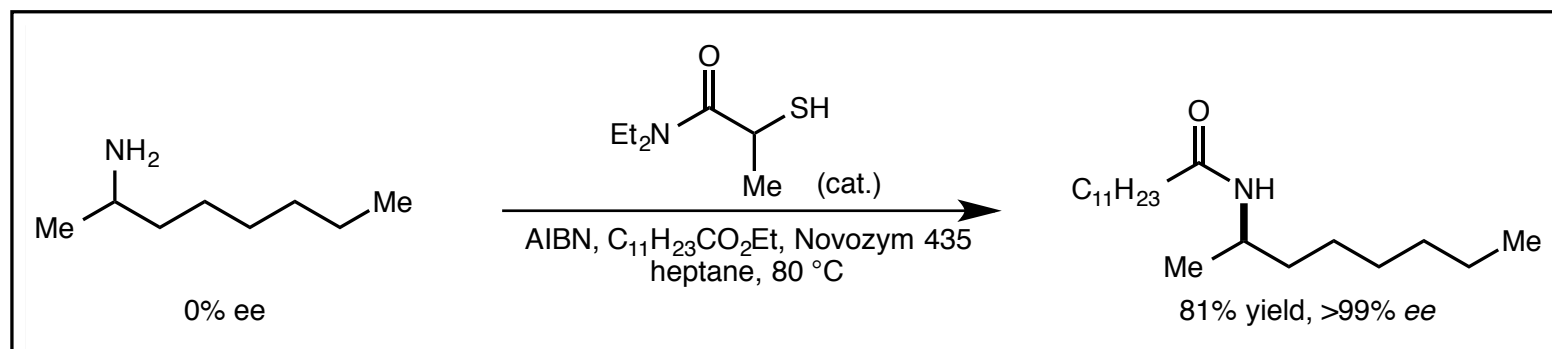
■ Rate Constants for the Reduction of Various Alkyl Radicals by Alkanethiol



entry	radical	$k_H/[\text{M}^{-1} \text{s}^{-1}] (T/\text{K})$	$k_{-H}/[\text{M}^{-1} \text{s}^{-1}] (T/\text{K})$	$\Delta H/[\text{kcal mol}^{-1}]$
1	$\text{R-CH}_2\cdot$	$2 \times 10^7 (298)$		-13
2	$\text{R}_3\text{C}\cdot$	$4 \times 10^6 (303)$	$2 \times 10^4 (353)$	-8
3	$\text{R-CH(OMe)}\cdot$	$2 \times 10^7 (298)$		-4
4	$\text{R-C(=O)}\cdot$	$7 \times 10^6 (353)$		-1
5	$\text{Ph-CHR}\cdot$	$7 \times 10^2 (333)$	$1 \times 10^6 (353)$	+2
6	$\text{Ph-CH(OMe)}\cdot$		$2 \times 10^7 (353)$	+2

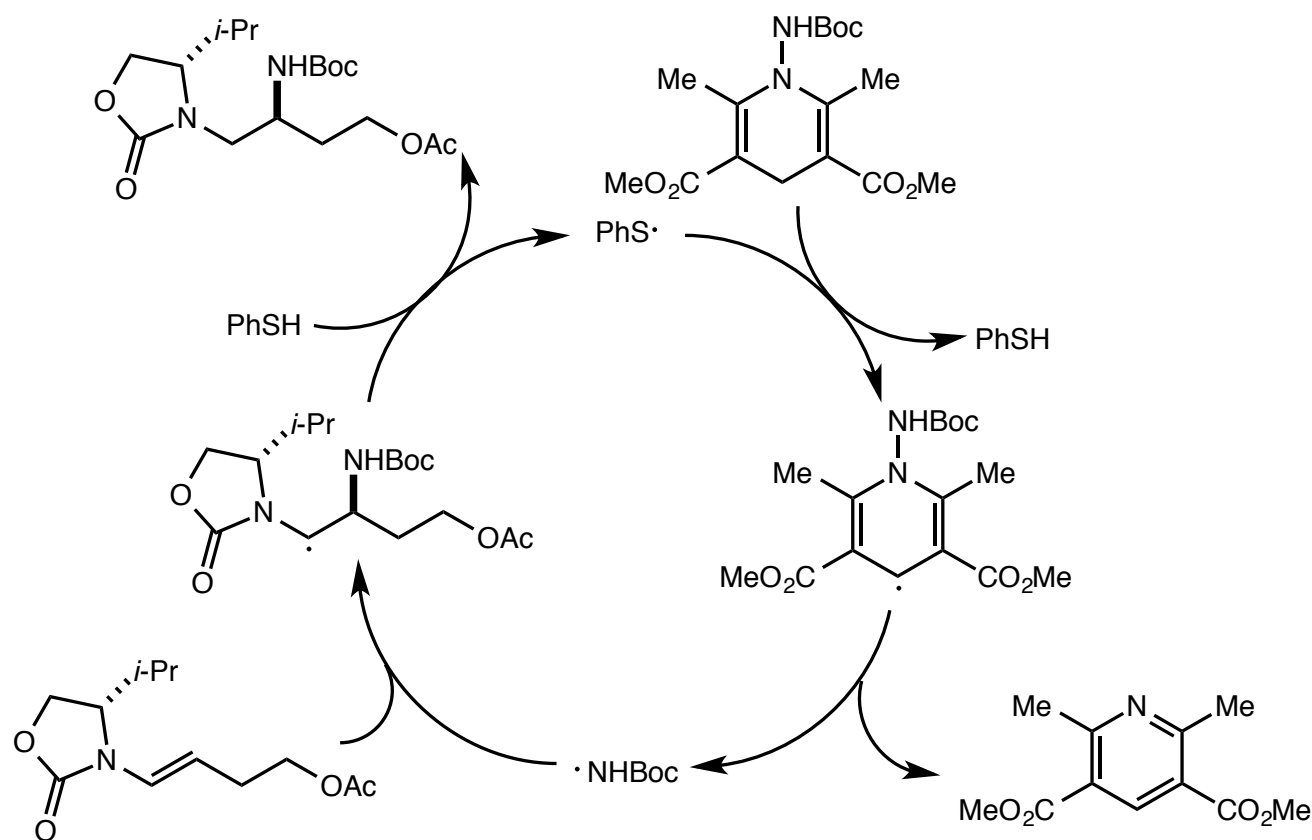
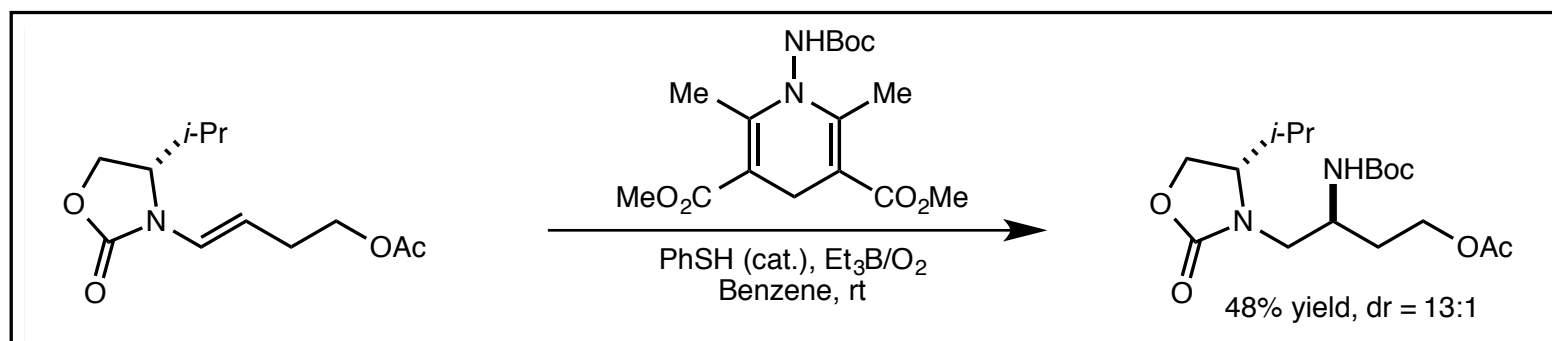
II. Thiol-Mediated Hydrogen Atom Transfer

■ Dynamic Kinetic Resolution of α -Chiral Amines



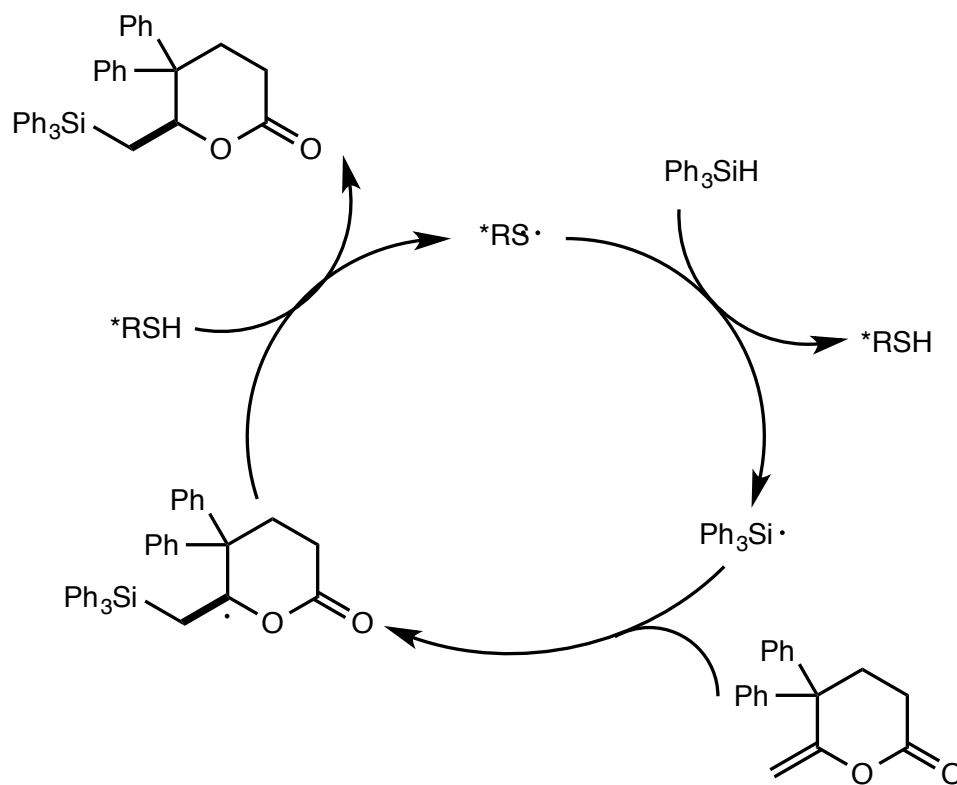
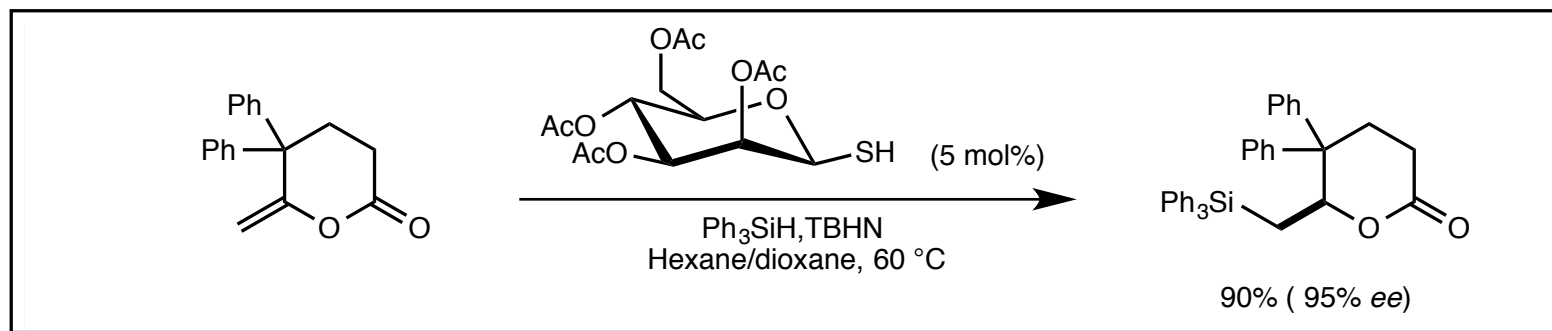
II. Thiyl-Mediated Hydrogen Atom Transfer

■ Hydrogen Abstraction from Benzylic Positions



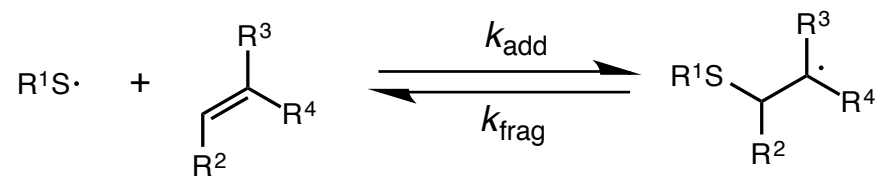
II. Thiyl-Mediated Hydrogen Atom Transfer

■ Hydrogen Abstraction from Silane

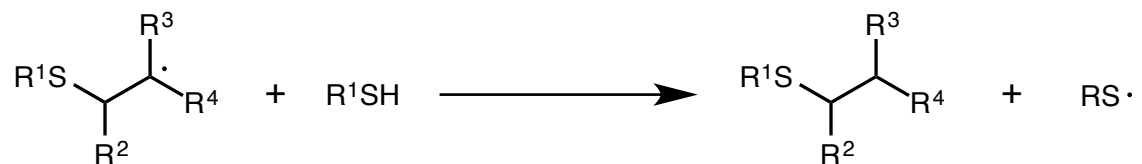


III. Addition of Thiols to C=C bonds

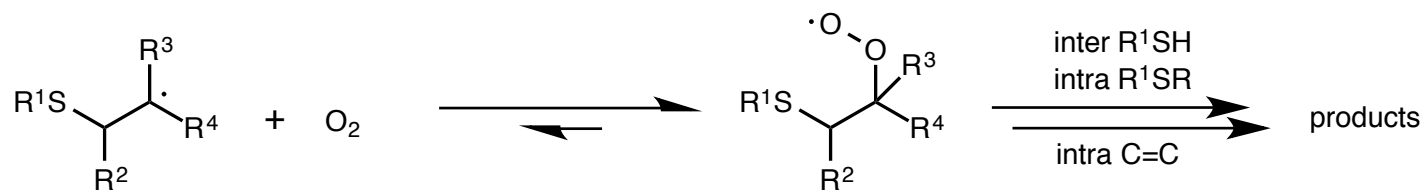
■ anti-Markovnikov Addition of Thiyl Radicals to Olefins



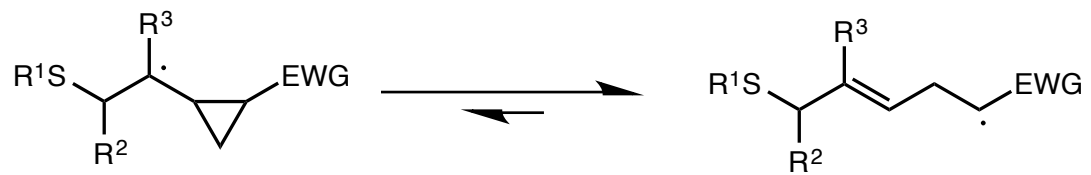
■ Thiol-Ene Coupling (TEC)



■ Thiol-Olefine Cooxidation (TOCO)

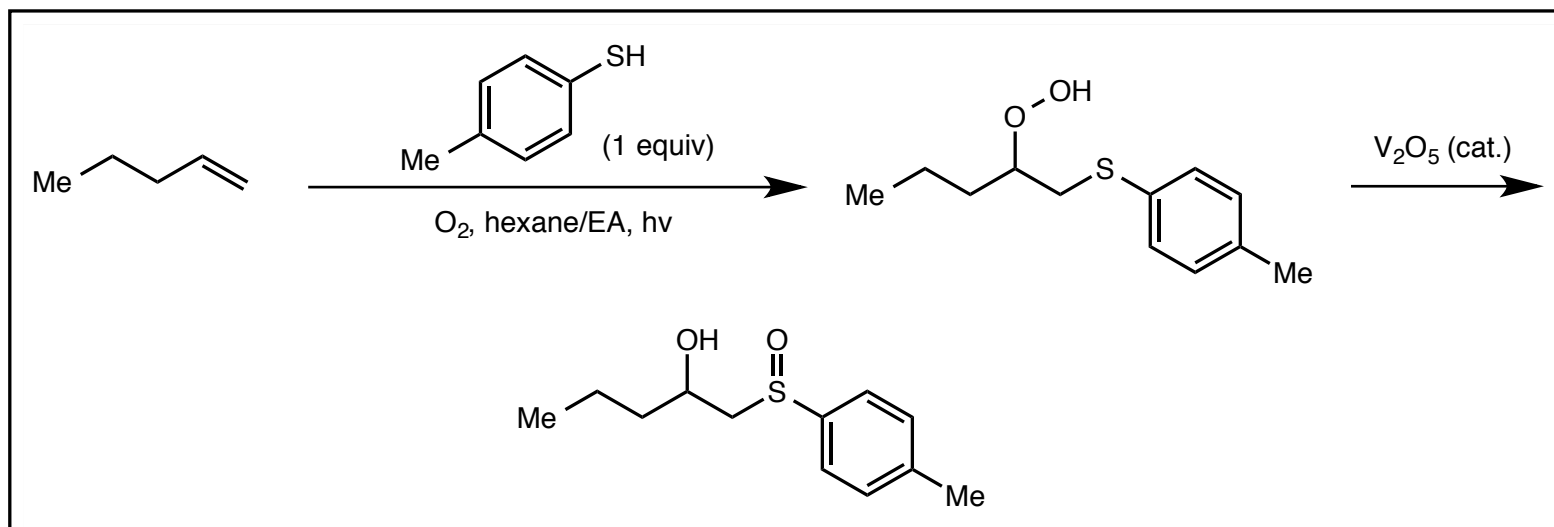
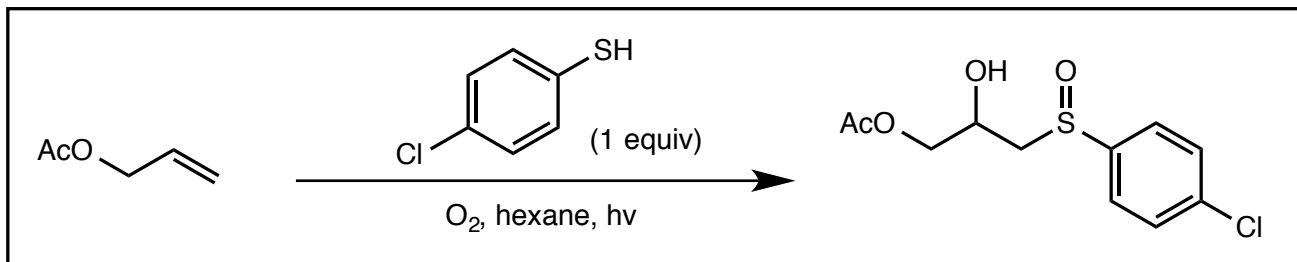


■ Ring-Opening of Vinyl Cyclopropane



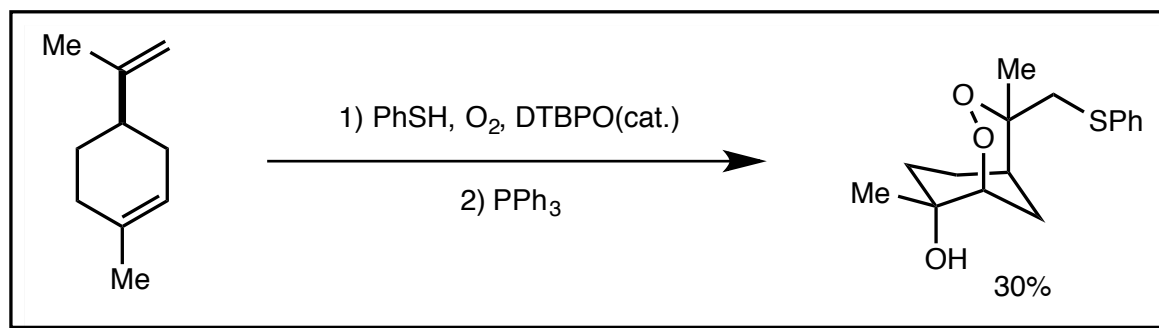
III. Addition of Thiols to C=C bonds

■ Thiol-Olefine Cooxidation (TOCO)

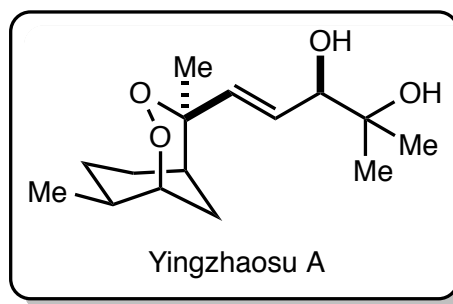
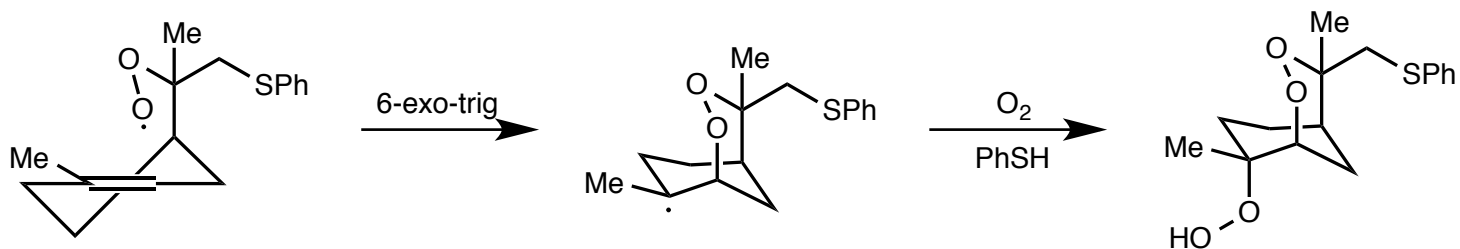


III. Addition of Thiols to C=C bonds

■ Thiol-Olefin Cooxidation (TOCO)

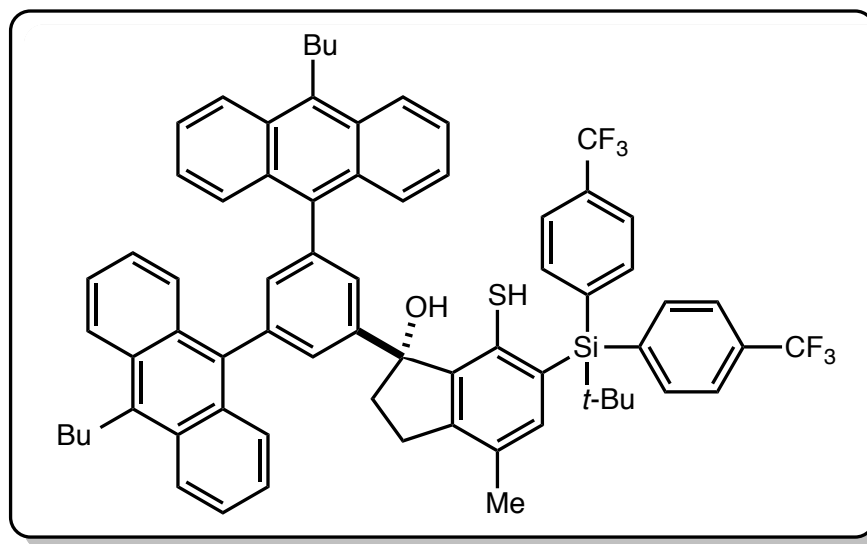
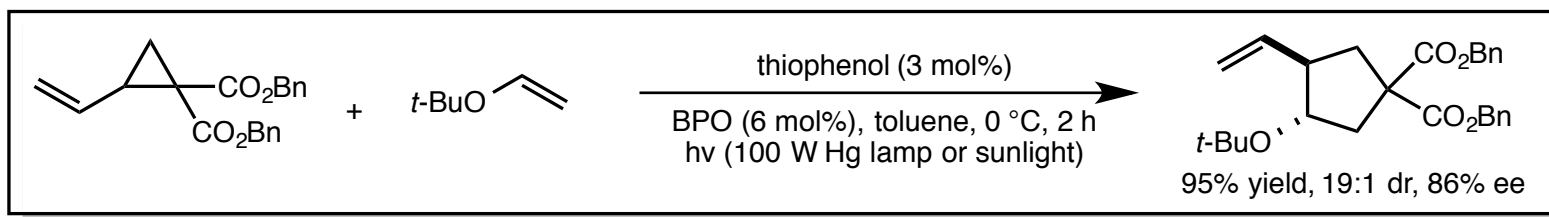


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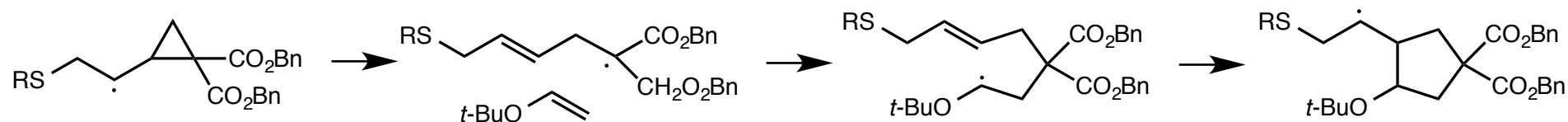


III. Addition of Thiols to C=C bonds

■ Ring-Opening of Vinyl Cyclopropane

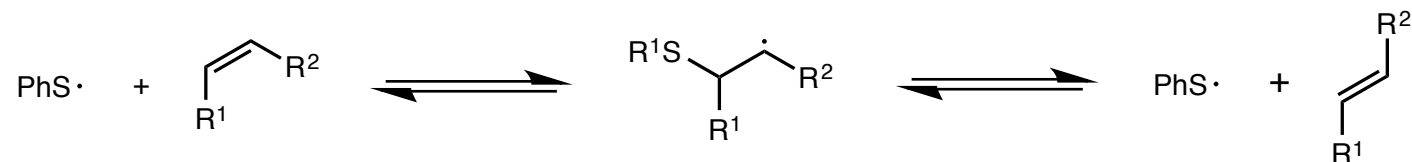


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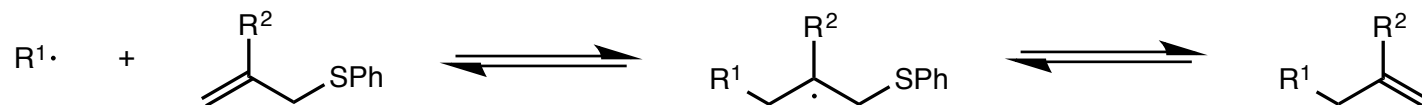


IV. Fragmentation of β -Sulfanyl Radicals

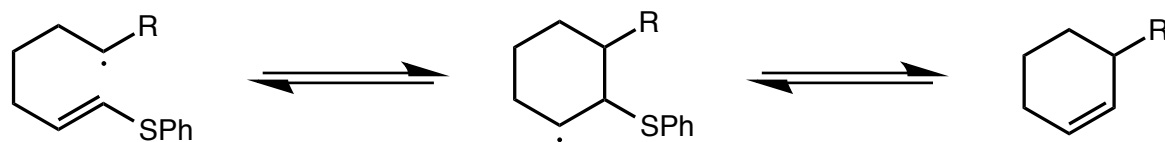
■ Isomerization of Alkenes



■ Fragmentation of Allyl Sulfides

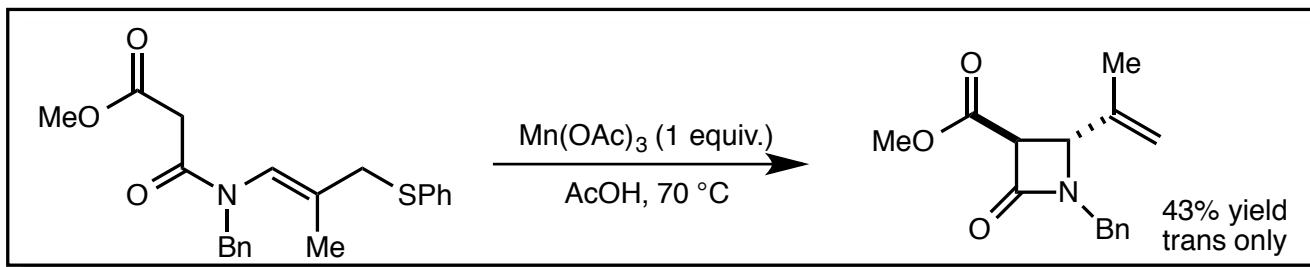


■ Fragmentation of Vinyl Sulfides

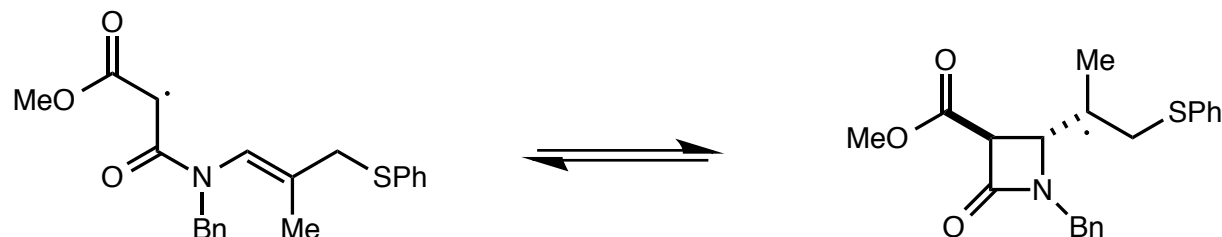


IV. Fragmentation of β -Sulfanyl Radicals

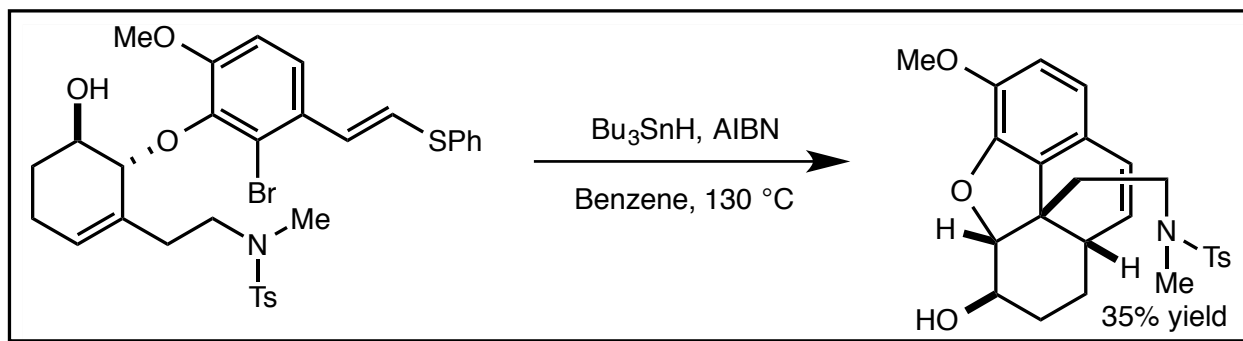
■ Fragmentation of Allyl Sulfides



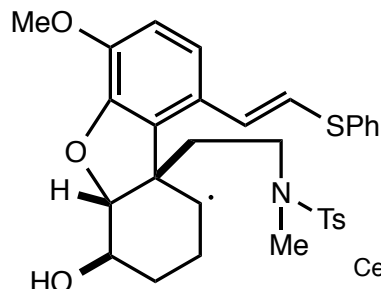
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■ Fragmentation of Vinyl Sulfides

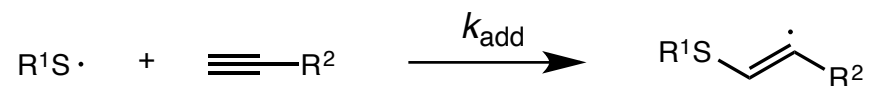


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V. Addition of Thiols to Alkynes

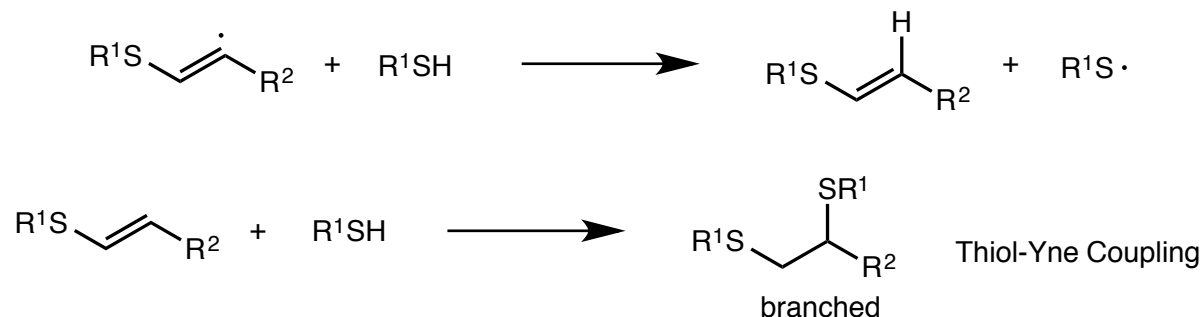
■ Addition of Thiyl Radical to Alkynes



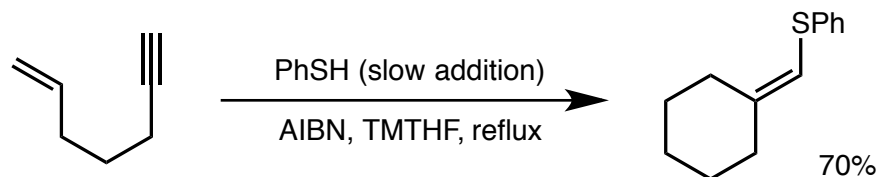
■ Addition to alkynes is more exothermic than to alkenes as replacing a very weak π -bond by a stronger $\text{C}^{\text{sp}2}\text{-S}$ σ -bond compensates for the energetic cost of generating a vinyl radical

■ The reverse reaction that releases the triple bond is rather slow, and fragmentation of the thiyl radical is generally not observed due to the rapid decay of the resulting highly reactive vinyl radical

■ Very few intermolecular trappings of β -sulfanylalkenyl radicals in a new C–C bond-forming reaction have been reported because it's very hard to compete with the hydrogen atom abstraction from thiols

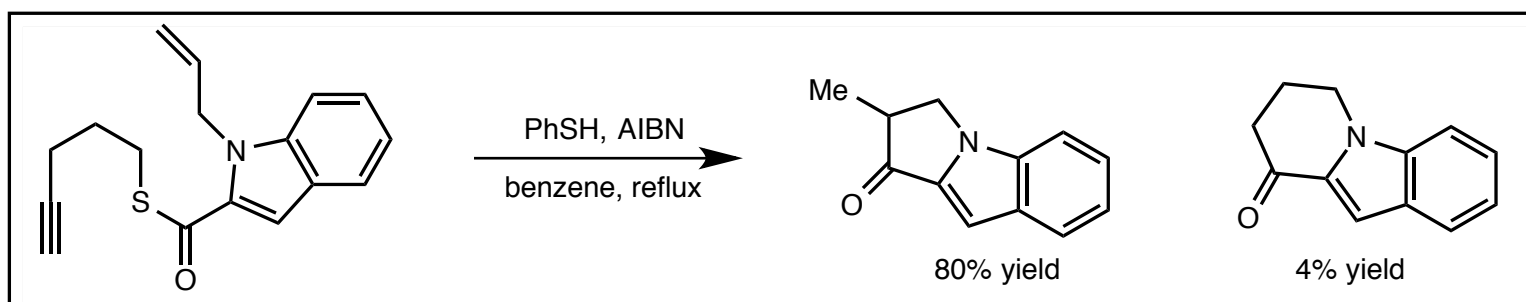
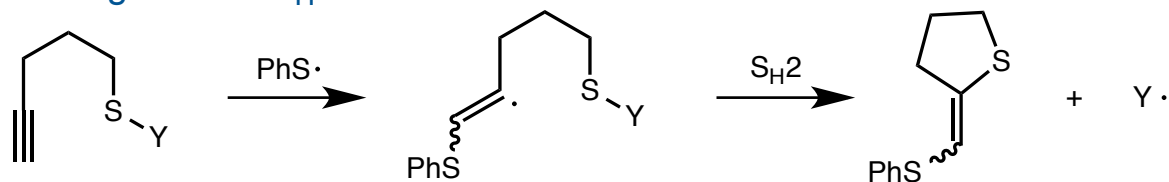


■ Intramolecular trapping by C=C, C=N bonds

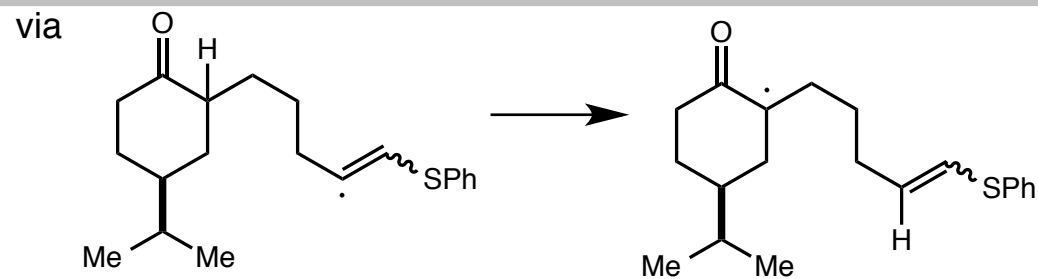
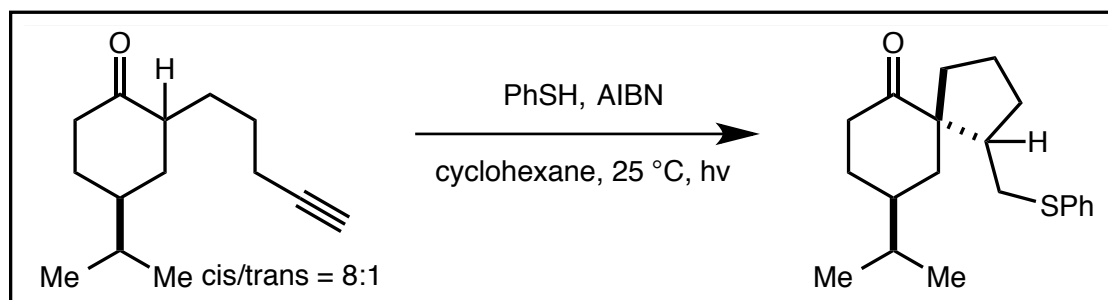


V. Addition of Thiols to Alkynes

■ Intramolecular Chalcogenation: S_H2 at Sulfur

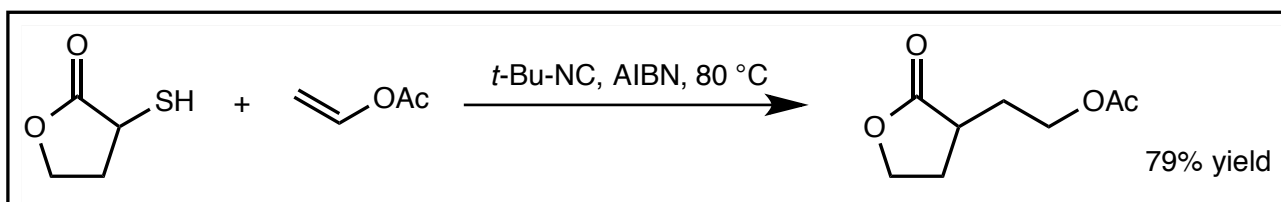
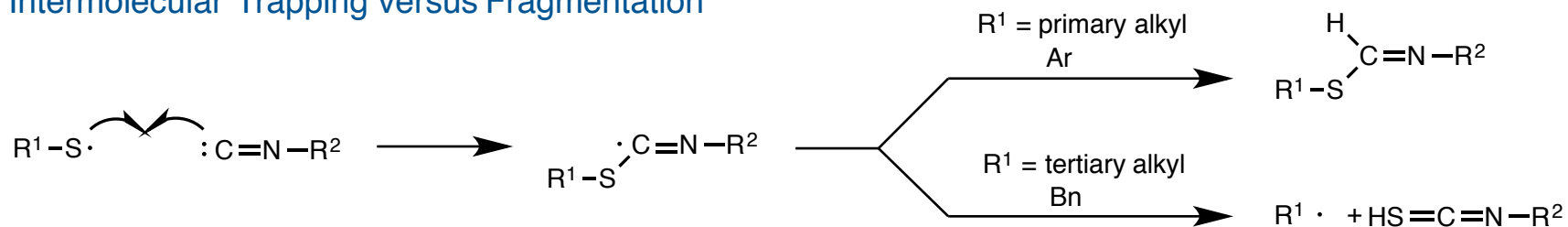


■ Translocation Reactions: 1,n-Hydrogen Transfer

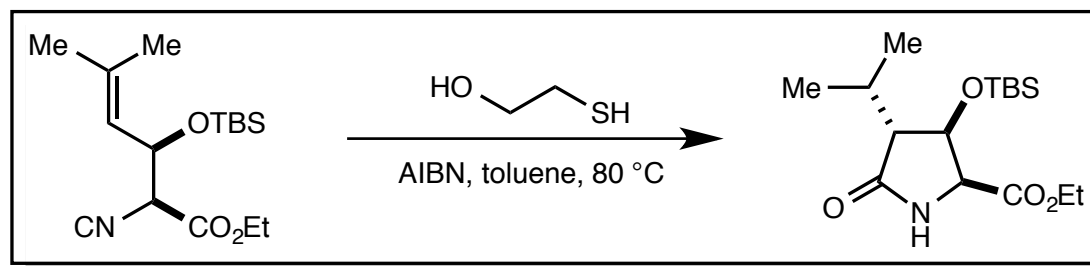


VI. Addition of Thiols to Isonitriles

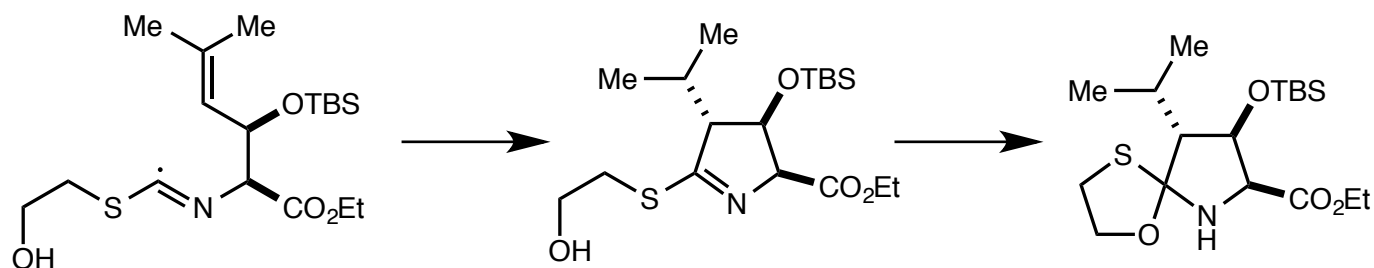
■ Intermolecular Trapping versus Fragmentation



■ Intramolecular Trapping by Alkenes or Alkynes

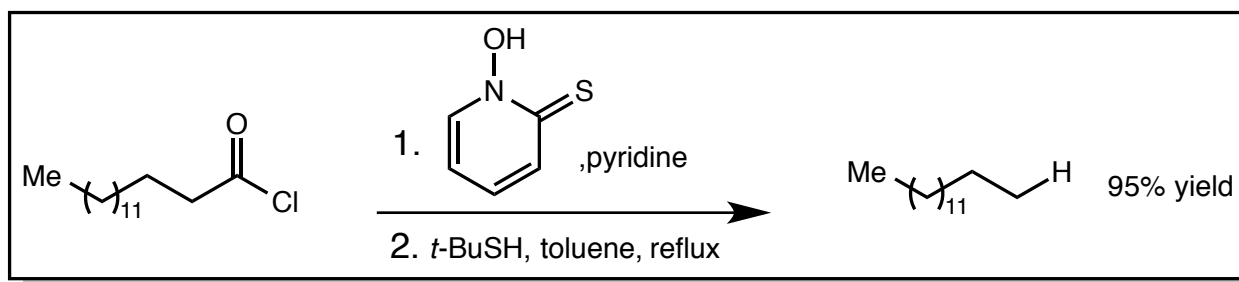
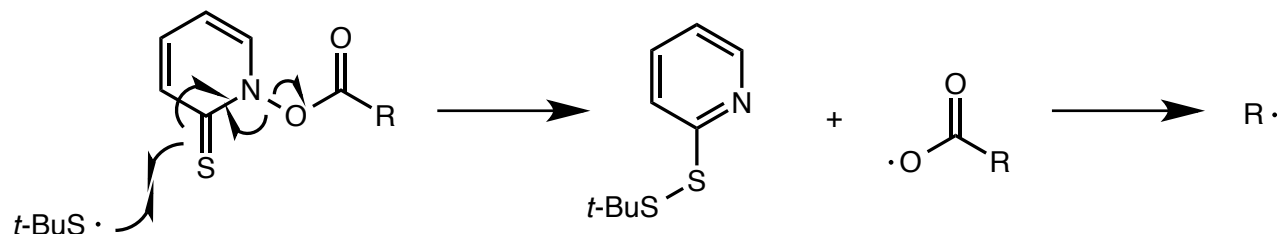


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VII. Addition of Thiols to C=S bonds

■ Barton Reductive Decarboxylation



■ Barton Reductive Deoxygenation of Tertiary Alcohols

