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Mechanistic Aspects and Synthetic Applications of Radical Additions to Allenes

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Abstract

More than 50 years have passed since Haszeldine reported the first addition of a trifluoromethyl radical to an allene; in the intervening years, both the chemistry of allenes and the reactivity of single-electron species have become topics of intense interest. In this Review, we provide an overview of the fundamentals of radical additions to allenes and highlight the emergence of theoretical and experimental evidence that reveals unique reactivity patterns for radical additions to allenes as compared with other unsaturated compounds. Factors capable of exerting control over the chemo-, regio-, and stereoselectivities of the attack of carbon- and heteroatom-based radicals at each of the three potential reactive sites in an allene substrate are described. These include reaction conditions, the nature of the attacking radical, the substitution pattern of the allene, and the length of the linker between the radical center and the proximal allene carbon in the substrate.

Cycloaddition reactions between allenes and partners containing π -bonds, which are likely to proceed through radical pathways, are presented to highlight their ability to rapidly access complex polycyclic scaffolds. Finally, the synthetic utility of the products arising from these chemistries is described, including their applications to the construction of complex molecules.

Graphical Abstract

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1. INTRODUCTION

Since the first synthesis of an allene by Burton and Pechmann in 1887,¹ significant efforts have been devoted to studying the reactivities of this unique type of unsaturated compound.^{2–16} More than 50 years have passed since Haszeldine reported the first addition of a trifluoromethyl radical to an allene,¹⁷ yet there continues to be great interest in both the mechanistic aspects and the synthetic applications of radical reactions involving allenes.¹⁸ This is due in part to the expanding diversity and ease of new methods to synthesize increasingly complex allenes^{19–24} as well as ongoing reports of applications that harness the unique reactivity of allenes as compared to alkenes and alkynes.^{9,10,13,14} Because of their structural differences and unique bonding properties, the reactivities of allenes toward different types of radicals is less predictable than the trends observed in reactions with alkenes and alkynes.²⁵ In the intervening decades since Haszeldine's report, a handful of reviews dedicated specifically to radical reactions of allenes have appeared,^{6,7} most notably a pair of reviews by Ma et al.⁷ and Hartung and Kofp,²⁵ both published in 2004. More recently, and during the preparation of this manuscript, Wu and coworkers published a short review on the functionalization of allenes via radical processes.¹⁸ The goal of this Review is to present a comprehensive picture of the development of radical additions to allenes since 1950 to the present day, even if aspects have been previously covered. This is key to enabling the reader to directly compare and contrast reactivity patterns in the additions of diverse radicals to allenes, as well as gaining a more complete picture of the mechanistic aspects and broad synthetic applications of radical reactions of allenes. A section

highlighting the power of radical additions to allenes for the preparation of complex molecular scaffolds present in bioactive natural products is also presented in the hope that it will inspire continuing investigation into this fascinating research topic.

Allenes contain two cumulated π -bonds, with the double bonds located in mutually perpendicular planes (Figure 1). The C1 and C3 carbons of an allene are sp^2 -hybridized, whereas the central C2 carbon is sp -hybridized. To simplify discussions throughout this Review, the positions and π -bonds have been labeled as illustrated in Figure 1.

The ability to achieve radical attack on an allene in a selective manner can be both challenging and synthetically powerful. This is illustrated in Schemes 1 and 2, where the intermolecular addition of a radical to an unsymmetrically substituted allene can occur at three potential sites: terminal attack at either C1 or C3 or central attack at C2.

Attack at the C1 or C3 of allene **1** results in a pair of rapidly interconverting, nonlinear radical intermediates **3a,b** and **5a,b**,²⁵ where the attack is reversible under certain circumstances^{26–30} (Scheme 1). The initial vinyl radical intermediate **2** or **4** first adopts a π -type configuration, which then isomerizes to the more energetically favored σ -type radicals **3a,b** and **5a,b**. The isomerization of the *E/Z* vinyl radicals has a low activation barrier,^{31–34} with the ratio of *E/Z* products largely affected by steric effects; these are covered in more detail in section 2.

Attack on the C2 of allene **1** initially results in a π -type alkyl radical **6** or **8**, which rotates around the C2–C3 bond of **6** or the C1–C2 bond of **8** to assume the appropriate geometry for resonance-stabilized allylic radical **7a** or **7b** (Scheme 2). Multiple research groups have demonstrated that the activation barrier for this rotation is negligible.^{28,29,35,36}

In general, reactions of radicals with an unsubstituted allene (propadiene) typically occur at the α carbon, irrespective of the type and polarity of the radical intermediate (Scheme 1). In contrast, substituted allenes are generally attacked at the central (β) carbon to give allylic radical intermediates (Scheme 2); indeed, selectivity can often be determined by assessing the relative stabilities of these intermediates. Thus, thermodynamics largely controls the selectivity in radical additions to allenes, as opposed to the use of frontier molecular orbital (FMO) theory to explain the selectivities of radical additions to alkenes and aromatic π -systems. However, further studies are needed to better understand the factors that contribute to the differences between alkenes and allenes in terms of their behavior toward radicals. Such investigations will undoubtedly expand the synthetic utility of these reactions and enable tunable control over site-selectivity.

2. INTERMOLECULAR ADDITIONS OF RADICALS TO ALLENES

2.1. Halogen Radicals

2.1.1. Chlorine Radicals.—Reactions of chlorine radicals with allenes have only recently been studied by a handful of research groups. A greater understanding of the processes involved in the chlorination of low-molecular-weight hydrocarbons, including allenes, may facilitate better methods for the synthesis of chlorinated compounds, efficient

biomass combustion, and the incineration of hazardous waste. Two possible pathways were proposed for the reaction between a chlorine radical and propadiene³⁷ (Scheme 3): (1) H-atom abstraction of the allenic proton to form an allenic radical **9** and (2) chlorine addition to C2 of propadiene to form an allylic radical **11**, which could undergo the elimination of HCl to form the propargyl radical **10**.

Mixtures of propadiene and Cl₂ were photolyzed at 355 nm, and the absolute rate coefficients of these reactions were measured over a temperature range of 292 to 850 K and a pressure range of 4–10 Torr. These results led Farrell et al. to the discovery that the addition of the chlorine radical to propadiene constitutes an important pathway up to $T \approx 800$ K.³⁷ On the basis of ab initio calculations, the 2-chloroallyl radical **11** was suggested to be the major product. These calculations were carried out at the G2 level of theory, indicating that the chlorine radical attack on the C2 of propadiene is 20 kcal/mol lower in enthalpy than the attack on C1 or C3. Nonetheless, the possibility of an initial bond formation between the chlorine and C1 or C3, followed by isomerization to the more stable allylic radical via a 1,2-Cl shift could not be ruled out.

As the temperature of the reaction of propadiene and Cl₂ is increased to >800 K, HCl formation is the major pathway. The larger pre-exponential factor extracted from the Arrhenius plot, compared with those of other exothermic hydrogen abstraction reactions between chlorine radicals and hydrocarbons, indicates that an addition–elimination mechanism might be the major pathway at higher temperatures.

By irradiating mixtures, under an inert atmosphere, of Cl₂ and propadiene at 351 nm, Atkinson et al. provided further spectral evidence that a C₃H₄Cl radical was produced upon irradiation.³⁸ This study was also briefly discussed in a previous review by Hartung and Kopf.²⁵ Ab initio calculations supported the proposal that the addition of a chlorine radical to propadiene should readily occur at room temperature. The addition of a chlorine radical to both the C2 and C1/C3 of propadiene would form incipient ensembles of 2-chloroallyl and 3-chloro-1-propene-2-yl radicals **11** and **12** (Scheme 4), with the internal energy of each radical enabling isomerization to establish an equilibrium mixture of radicals. However, the allylic radical **11** was proposed as the dominant species in the reaction due to its stability.

Studies by Hudgens et al. showed results consistent with previous experimental and computational studies. Ab initio calculations supported a higher barrier for H-atom abstraction compared with the exothermicity of chlorine radical addition to propadiene. An equilibrium between **11** and **12** is established by the rapid transfer of a chlorine atom between the C1/C3 and C2 atoms.³⁶ The possibility of the isomerization of **11** and **12** via hydrogen and chlorine atom transfers was deemed irrelevant at ambient temperature based on ab initio calculations. For a discussion on this study in a previous review, see the review by Hartung and Kopf.²⁵

Zhao and Murphy carried out the chlorination of allenes using the hypervalent iodine reagent 1-chloro-1,2-benziodoxol-3-one. The regioselective and chemoselective dichlorination of various aryl-substituted allenes **13**³⁹ furnished the corresponding 2,3-dichlorides **14** in moderate to good yield, with the *Z* isomer as the major isomer (Scheme

5a). The reaction was proposed to proceed via a radical mechanism, which was supported by the inhibition of the reaction in the presence of 1.5 equiv of TEMPO (Scheme 5b). The homolytic cleavage of the I–Cl bond in 1-chloro-1,2-benziodoxol-3-one provides a chlorine radical, which attacks the C2 of allene **13**. When R = alkyl in **13**, the 1,3-diene **15** is proposed to form from the same allylic radical intermediate **16** by a competing hydrogen atom abstraction step (Scheme 5c).

2.1.2. Bromine Radicals.—An early report of the homolytic addition of HBr to an allene was published by Kovachic et al. in 1961⁴⁰ and was previously discussed in the review by Griesbaum.² Mixtures of HBr or DBr were irradiated with deuterated or nondeuterated propadienes **17** to synthesize deuterated propenes (Scheme 6). The major products **18** and **19** were brominated on the central carbon and hydrogenated/deuterated on the terminal carbon. Only a small amount of 3-bromopropene was observed.

In 1964, Griesbaum et al. published a study on the free-radical addition of HBr to propadiene, where several reaction parameters were varied, including the HBr/propadiene ratio, the reaction temperature, the reaction phase, the reaction medium, and other conditions.²⁶ When the reaction was carried out in the gas phase under UV irradiation at room temperature, an equimolar mixture of HBr and propadiene generated 2-bromopropene **20a** as the major product in 85% yield, with trace amounts of 1,2-dibromopropane **21** and 2,2-dibromopropane **22** (Scheme 7).

By lowering the reaction temperature to –40 °C and changing to the liquid phase, Griesbaum found that the same adducts were formed, but in varying ratios (Scheme 8). As the temperature was decreased, the amount of terminal addition product increased, along with a concomitant decrease in the extent of central addition product. Increased amounts of the dibromo adducts **21** and **23** were also noted.

The use of AIBN as the initiator decreased the reaction time by a factor of three; however, the amount of **20b** and **23** also increased (Scheme 8). When the reaction was carried out in a 1 M solution of propane, the amount of terminal addition product resulting from the attack of the radical on the terminal allene carbon was increased by 10%. In the presence of 10 equiv of HBr, the major products were various dibrominated adducts, including **23** (43%), **21** (34%), and **20b** (23%). When excess propadiene was utilized, the amount of the terminal addition product **20b** decreased, leading to **20a** as the major product (Scheme 9).

On the basis of the above experimental data, Griesbaum proposed the reaction pathway illustrated in Scheme 10. The regioselectivity of bromine radical addition to propadiene was strongly dependent on the reaction temperature and reactant ratio; lowered temperatures and excess HBr favored the formation of a terminal attack product. Griesbaum stated that the experimental results described above do not reflect the initial regioselectivity of bromine attack on the central versus the terminal allene carbon. This was proposed to be due to the ability of allenes to form bridged radical intermediates, followed by fast rearrangement to yield the corresponding allylic or vinylic radical intermediates (Scheme 10).⁴¹ For a discussion on this study in previous reviews, see refs 2, 3, and 25.

In 1964, Abell et al. published studies on the gas-phase addition of HBr to propadiene, in which several reaction parameters were varied, including the reaction temperature (from 50 to 150 °C), the reactant ratio (propadiene/HBr from 10:1 to 1:10), and the pressure (from 10 to 80 mm).^{3,4,25,30} The major product was 2-bromopropene **20a**, in accordance with the findings of Kovachic and Griesbaum. The reaction was first-order in HBr concentration but independent of propadiene concentration, with a positive activation energy (~4.5 kcal/mol). By utilizing the available experimental data and making approximations using a group contribution method, it was deduced that the addition of bromine radical to propadiene was exothermic. The authors proposed that the initial point of attack of the bromine atom was on the C1/C3 of the allene, followed by rearrangement to the more stable 2-bromoallyl radical due to the small reaction barrier. Reviews by Griesbaum² and Taylor³ also discuss this study.

In 1966, Heiba et al. published studies on the kinetics of the free-radical addition of HBr to propadiene, which provided an explanation for the observed ratios of terminal versus central attack on the allene, as well as the effects of the reaction temperature and HBr/propadiene ratio on the product distribution.³⁵ A mechanism was proposed that was consistent with these results (Scheme 11) based on the observation that the ratio of terminal:central addition products **20b:20a** was constant when the HBr concentration was high but dropped when the HBr concentration was low. The dependence of the product ratio on the HBr concentration ruled out the mechanism initially proposed by Abell.²⁷

Kinetic studies also carried out by Heiba showed that the ratio of rate constants k_1/k_2 in Scheme 11 is equal to 2. Bromine addition to both the terminal and central carbons is exothermic; however, the addition to the terminal carbon is reversible, even at -78 °C, whereas the addition to the central allene carbon is irreversible. The observation that more **20a** is produced as the temperature increases was explained by the higher activation energy of the reverse reaction of the Br radical addition (k_{-1}) as compared with the hydrogen-transfer reaction rate k_3 . At constant temperature, the ratio **20b:20a** depends only on the HBr concentration.

In 1969, Tien and Abell studied the relative energetics and the stereochemical outcome of free-radical additions of HBr to various methyl-substituted allenes in the gas phase.^{4,25,27} By varying the concentration of either the allene or HBr, a first-order rate dependence on HBr concentration was established. Activation energies were obtained for the free-radical HBr addition to the allenes in Scheme 12 by studying the reaction kinetics at temperatures of 40–120 °C. The tetramethyl-substituted allene **25** gave the lowest values, and propadiene **17c** gave the highest values, albeit with <1 kcal/mol difference in energy. Competition experiments of allenes with limited amounts of HBr were conducted to compare the relative reactivities of allenes in Scheme 12. The relative reactivities were found to be 1:1.36:1.31:1.56:1.65 (**17c/26/24/27/25**) at 60 °C (the same trend holds at higher temperatures), with **25** displaying the fastest rate. The increased reactivity with increased methyl substitution was proposed to result from the additional stabilization of the 2-bromoallyl radical intermediates due to increased hyperconjugation. The major product for each allene has Br attached to the central allene carbon.

There has been a recent surge in studies directed toward the synthetic applications of the addition of bromine radicals to allenes. Forty years after Moorthy and Devaprabhakara's initial studies, the Ryu group reported their findings on the regioselective radical bromoallylation of allenes **28** for the synthesis of 2-bromosubstituted 1,5-dienes **30**.⁴² By employing AIBN as the initiator and an electron-deficient allyl bromide **29** as the radical acceptor, regioselective radical bromination and new carbon–carbon bond formation were achieved in one pot (Scheme 13). This method tolerated monosubstituted, 1,1-disubstituted, and 1,3-disubstituted allenes, as well as functional groups that include OTIPS, NPhth, and CO₂Et. Interestingly, allenes containing Cl CO₂Et substituents exclusively gave the *E* alkene. Both 2-(bromomethyl)acrylate and 2-(bromomethyl)-acrylonitrile gave excellent yields.

The Ryu group proposed these reactions proceed via a radical chain mechanism involving generation of 2-bromoallyl radical **31a,b**, followed by an S_H2' reaction (S_H = homolytic substitution) to yield the addition product and regenerate the bromine radical (Scheme 14). The *E* selectivity was explained by the steric repulsion between the R group and Br in the allyl radical precursor **31b** required for formation of the *Z* product.

In 2014, the Ryu group published a three-component coupling strategy to synthesize 2-bromo-1,7-dienes by adding an electron-deficient alkene coupling partner to a mixture of allene and allyl bromide⁴³ (Scheme 15a). This one-pot method involves the initial attack of a bromine radical on the allene central carbon to form a 2-bromoallyl radical intermediate; this nucleophilic species selectively attacks the electron-deficient alkene to form an electrophilic alkyl radical. The alkyl radical then attacks the allyl bromide to furnish the product and a Br radical. Interestingly, when the alkylidenecyclopropane **32** was subjected to the reaction conditions, two products were isolated, the coupling product **34** and a methylenecyclopentane **35**. The two products have a common precursor, **33**, that can either attack the allyl bromide to form the major product **34** or undergo 5-*exo* cyclization, followed by β -fission, to form the minor product **35** (Scheme 15b).

In summary, the regioselectivity in the addition of halogen radicals (Cl, Br) to allenes strongly depends on the reaction conditions and the allene substitution pattern. In general, reactions of Cl and Br radicals with allenes yield the product resulting from the addition to the central carbon of the allene. In the case of both Cl and Br radicals, the temperature has been shown to affect both the reaction pathway and the regioselectivity. After the initial formation of a 2-chlorinated allylic radical, temperatures >800 K lead to the elimination of HCl (Scheme 3, *vide infra*). Decreasing the reaction temperature of the free-radical HBr addition to propadiene increases the amount of addition to the terminal carbon and decreases the addition to the central allene carbon. The identity of the radical initiator and a decreased concentration can also increase the amount of terminal addition product. In contrast, a higher allene/HBr ratio favors the central addition product. Multiple research groups also noted that the final product distribution does not reflect the initial regioselectivity in the addition of halogen radicals to the allene. Computational analysis on the addition of a Cl radical to propadiene at room temperature indicate that it can occur at both the C2 and the C1/C3 of the allene to give a mixture of radicals that interconvert via 1,2-halogen transfer. The radical

addition of a Br radical to any carbon of an allene is exothermic; however, addition to the terminal allene carbon is reversible, whereas the addition to the central carbon is irreversible.

Recent studies have shifted focus from understanding the physical organic chemistry of the addition of halogen-based radicals to allenes to broadening the synthetic applications of these types of reactions. More complex allenes have been converted to motifs that include 1,2-dichlorides, 1,5-dienes, and 1,7-dienes under mild conditions, showcasing the great potential of the regioselective addition of halogen radicals to allenes to furnish stereodefined vinyl halides containing additional synthetic handles for further transformations.

2.2. Carbon-Centered Radicals

2.2.1. Perfluoroalkyl Radicals.—Haszeldine et al. reported the first addition of a carbon-centered radical to an allene in 1954.¹⁷ By irradiating a mixture of propadiene and CF₃I with UV light, a high yield of a compound with the formula CF₃(C₃H₄)I **36** was obtained. The spectral (UV and IR) and chemical evidence supported the CF₃ radical addition to the C1/C3 carbons of propadiene (Scheme 16). The abstraction of the allenic hydrogen was not deemed to be a major pathway because only trace amounts of trifluoromethane were detected. Reviews by Griesbaum² and Taylor³ also discuss this study.

Szwarc et al. utilized the photolysis of hexafluoroazomethane to study the kinetics of the CF₃ radical addition to olefins or allenes, as previously discussed in other reviews.^{3,25,44} In Scheme 17, k_2 denotes the rate of CF₃ radical addition to either olefins or allenes, whereas k_1 is the rate of hydrogen abstraction of the *iso*-octane solvent by the CF₃ radical. Higher ratios of k_2/k_1 indicate the higher reactivity of the CF₃ radical toward the substrate. Because the k_2/k_1 of penta-2,3-diene (1,3-dimethylallene) was higher than that of, it was surmised that penta-2,3-diene is more reactive than propadiene toward the electrophilic CF₃ radical due to the increased electron density on the terminal allene carbons induced by the additional methyl groups.

Abell and Meunier studied the kinetics of the photoaddition of CF₃I to propadiene by irradiating propadiene and CF₃I at different ratios, reaction temperatures, total pressures, and light intensities.^{3,25,45} The sole product was **36**, resulting from the addition of the CF₃ radical to the terminal allene carbon, consistent with previous reports.^{46,47} On the basis of kinetic data and studies showing that the reaction rate is inversely dependent on temperature, the mechanism in Scheme 18 was proposed.

To the best of our knowledge, after Abell's 1967 report, no published studies on the intermolecular addition of carbon-centered radicals to allenes appeared in the literature until after 2000. In 2001, Ogawa and Hirao^{46,47} described a photoinduced, regioselective radical addition of perfluoroalkyl iodides to various substituted allenes **38** to form monoadducts of the form **39**. The perfluoroalkyl radical added to the terminal carbon of the allene to form a vinylic radical, which abstracts an iodine atom from the perfluoroalkyl iodide (Scheme 19). Trace amounts of products formed from the attack of the perfluoroalkyl radical on the central allene carbon were also observed for 1,3- and 1,1-disubstituted allenes. Nonpolar solvents, including toluene or halogen-containing solvents (C₆F₆, PhCF₃, and CHCl₃), are

the most effective for this iodoperfluoroalkylation protocol. The *E/Z* ratios are likely controlled by the A^{1,3}-strain present in the intermediate vinylic radical.

The Ma group described a Na₂S₂O₄-initiated free-radical addition of perfluoroalkyl iodides to monosubstituted allenes **40** to form adducts **41** (Scheme 20).^{48,49} The regioselectivities mirror those in Scheme 19, with the perfluoroalkyl radical adding to the least-substituted terminal carbon and the iodine atom adding to the central carbon of the allene. Compared with the photoinduced formation of perfluoroalkyl radicals, the major isomer was *Z*, albeit with low selectivity.

Liu et al. also described the use of Na₂S₂O₄ to initiate a stereo- and regioselective radical coupling between perfluoroalkyl iodides and electron-deficient allenes **42** substituted with phosphine oxide, phosphonate, or ester groups⁵⁰ (Scheme 21). Vinyl iodides of the *E* configuration **43** were exclusively obtained; however, when the allene was substituted with an alkyl group, mixtures of *E/Z* isomers were observed. The excellent stereoselectivity in some products was proposed to arise from the disfavored interaction between the vinyl radical electron and the lone pairs on the double-bonded oxygen in the intermediate alkene substituents P(O)Ph₂, P(O)(OEt)₂, and CO₂Et (Scheme 21).

In 2011, the Ma group described a similar protocol⁵¹ using Na₂S₂O₄/Na₂CO₃ as the initiator for the radical addition of perfluoroalkyl iodides to allenes. The scope was expanded from their previous work⁴⁸ (Scheme 22) to encompass 2,3-allenols of the form **44**. In general, this protocol gives 3-iodo-4-perfluoroalkyl-substituted allylic alcohols **45** in moderate to good yields with moderate to good stereoselectivity. The 1,1-disubstituted allenes gave lower yields as compared with the monosubstituted allenes (Scheme 22), whereas tri- and tetrasubstituted allenols gave complicated mixtures and no evidence of the desired products.

In 2013, the Ma group described a Cu(I)-catalyzed synthesis of β-trifluoromethyl butenolides **47** via the oxytrifluoromethylation of 2,3-allenoic acids **46** in the presence of the Togni Reagent II (Scheme 23).⁵² In contrast with the previous examples described in this section, the CF₃ radical is ultimately installed on the central carbon of the original allene carbon. The reaction required the presence of at least one aromatic group at C1 of **46**; however, further alkyl and aryl substitution was tolerated at C1 and C3.

To better understand the mechanism leading to this reversal in regioselectivity, the Ma group carried out the experiments described in Scheme 24. The addition of TEMPO to the reaction mixture (Scheme 24a) resulted in no butenolide product formation; only the TEMPO–CF₃ adduct **49** was observed. In a second experiment, employing an enantioenriched allene **50** as the starting material yielded only the racemic product (Scheme 24b). Finally, when the carboxylic acid functionality was replaced with an ester, none of the desired product was produced, and 82% of the precursor **52** was recovered (Scheme 24c). The same observation was made when the phenyl substituent on the allene **52** was replaced with an *n*-hexyl group; the lack of reaction suggests that benzylic stabilization is key for the successful addition of the CF₃ radical to the allene.

On the basis of these experimental results, Ma proposed two possible mechanisms for Cu(II)-catalyzed radical cyclizations of 2,3-allenoic acids (Scheme 25). In Pathway I, the

activated catalyst **53** and the Togni Reagent II react to form the radical intermediate **54**, which releases a CF₃ radical and **55**. The CF₃ radical attacks the central carbon of the allene **46** to form an allylic radical intermediate, which is then oxidized by **55** to generate **56**. The subsequent cyclization of **56** forms the product **47** and 2-iodobenzoic acid. The alternative Pathway II involves the coordination of **46** and **55** to form a complex **57**, which is then attacked by the CF₃ radical to form **58**. The reductive elimination of **58** furnishes the final product.

Liu et al. developed a Cu(I)-catalyzed, intermolecular, regioselective oxytrifluoromethylation of allenes **59** that also employs the Togni Reagent II⁵³ as the source of a trifluoromethyl radical (Scheme 26). The majority of the substrates are monosubstituted allenes, which give moderate to high yield of **60**; similar to Ma's work, the trifluoromethyl group is installed at the central C2 carbon of the allene precursor. In contrast, a more sterically hindered 1,3-disubstituted allene gave only 14% yield.

To probe the mechanism of this transformation, TEMPO was added to the reaction mixture, resulting in the formation of 46% yield of a TEMPO–CF₃ adduct. The addition of BHT (butylated hydroxytoluene) as the radical scavenger inhibited the reaction and decreased the overall yield by 20%. On the basis of these experimental results, which suggest the intermediacy of radical species, two reaction pathways were proposed (Scheme 27). In Pathway I, an interaction between Togni II and CuCl generates a CF₃ radical, which attacks the central carbon of allene **59** to form the allylic radical intermediate **62**. Intermediate **63**, formed from **62**, undergoes reductive elimination to give the desired product **60**. Alternatively, Pathway II involves the cationic species **64**, generated from Togni II and CuCl. This is proposed to react with allene **59** to give an iodine(III) intermediate **65**. The attack of the carbonyl oxygen on the terminal allene carbon in the more stable allyl cation **66** eventually affords the desired product **60**. In both mechanisms, the heteroatom linkage (O, N, S) on the allene **59** is important for the effective stabilization of proposed intermediates in pathway I (**62**) and pathway II (**66**).

The Wang and Liu groups reported Cu(I)-catalyzed syntheses of CF₃-containing allyl azides and thiocyanates from 1,1-disubstituted aryl allenes **67** in the presence of Togni's Reagent.⁵⁴ This method afforded the trifluoromethylazidation products **68** with excellent regioselectivity. In these examples, the CF₃ also exclusively adds to the central allene carbon and furnishes good stereoselectivity for the *E* isomer. However, substrates containing bulky R groups or ortho-substituted aryl rings gave lower *E/Z* selectivities, indicating that the chemistry is sensitive to steric hindrance. The scope was also limited because monosubstituted, 1,3-disubstituted, and 1,1-dialkyl substituted allenes result in low yield and with poor regioselectivity (Scheme 28).

The trifluoromethylazidation protocol was extended to trifluoromethylthiocyanation (Scheme 29) to provide the desired products **70** in good to excellent yield. The *E/Z* selectivity was lower as compared to trifluoromethylazidation, although the major isomer was also of the *E* configuration.

On the basis of the experimental results, a mechanism was proposed for the trifluoromethylthiocyanation (Scheme 30). The CF₃ radical is generated from **71**, which itself forms from the attack of Togni's reagent by TMSNu. The addition of the CF₃ radical to allene **67/69** affords allylic radical **72**, which is proposed to be more stable than its *Z* isomer due to the steric hindrance between the aryl group and the adjacent CF₃ group. A nucleophilic radical, produced from the reduction of the corresponding anionic species by Cu(II), is proposed to couple to the allyl radical to form the desired product **68/70**. Pathway II involves generation of the Cu(III) intermediate **73** from a combination of **72**, Cu(II), and the nucleophilic anion. The reductive elimination of **73** affords the final product.

In 2017, the Ma group reported a Cu(II)-catalyzed formation of CF₃-substituted vinylic cyclopropanes **75** from 2,3-butadienyl malonates **74** in the presence of Togni's reagent II (Scheme 31).⁵⁵ The CF₃ radical, generated in situ, selectively attacks the central carbon of the allene. High regioselectivity was achieved by employing 1,1,3-trisubstituted allenes to prevent CF₃ radical attack on the terminal carbons of the allene.

Radical scavengers, including 1,4-dinitrobenzene and benzoquinone, either suppressed or completely shut down the reaction. TEMPO–CF₃ and BHT–CF₃ adducts were formed when TEMPO or BHT was added to the reaction mixture, supporting the presence of CF₃ radicals. Additionally, 31% of byproduct **76** was isolated. Control experiments showed that **76** does not form in the absence of the Cu(II) catalyst. On the basis of the experimental results, the Ma group proposed the mechanism in Scheme 32. The key step includes the production of a CF₃ radical by release from the radical intermediate **77** (generated from the reaction between active catalyst **78** and Togni Reagent II).

In 2017, the Akita group⁵⁶ described a Ru(II)-catalyzed oxytrifluoromethylation of allenes **79** to form 2-CF₃-substituted allyl acetates **80** in the presence of the Umemoto reagent, which functions as an electrophilic source of CF₃. Under irradiation with blue LED, CF₃-containing allyl acetates are synthesized in a regioselective and stereoselective manner from 1,1-di-, 1,3-di-, and 1,1,3-trisubstituted allenes (Scheme 33). Monosubstituted allenes give low regio- and stereoselectivities, whereas tetrasubstituted allenes are not compatible under the reaction conditions. Alkyl-substituted allenes (such as cyclohexylallene) give unidentifiable mixtures of products.

On the basis of the experimental results, a mechanism was proposed (Scheme 34). Upon irradiation, the ground-state Ru(II) catalyst is promoted to the excited state, which reduces the Umemoto reagent and generates a CF₃ radical. The addition of the radical to the allene furnishes allylic radical **81**, which is oxidized by Ru(III) to regenerate Ru(II) and form allyl cation **82**. The thermodynamically more stable conformation of **82** avoids the steric clashing between CF₃ and aryl groups. Nucleophilic attack of AcOH on **82** yields the product **80**.

The synthesis of α -CF₃ acroleins **84** from the Ag(I)-catalyzed regioselective trifluoromethylation of allenes **83** in the presence of the Langlois reagent was described by Zanoni and Maiti in 2018 (Scheme 35).⁵⁷

Three key experiments helped to show the importance of air for a successful reaction, which requires the presence of a CF₃ radical intermediate. First, the addition of TEMPO to the reaction mixture completely inhibits the reaction, with a TEMPO–CF₃ adduct detected by GC–MS. When the reaction is conducted under N₂, dimer **85** is isolated in 90% yield; however, when the reaction is carried out under O₂, the oxidation of the aryl allene to the corresponding aryl aldehyde **86** (R = H) is observed (Scheme 36a), leading to the proposed mechanism shown in Scheme 36b. Ag(I) is reduced by persulfate to Ag(0), which reduces the Langlois reagent to generate the CF₃ radical. The addition of the CF₃ radical to the allene forms an allylic radical intermediate **87**; oxidation at C3 furnishes the carbonyl product. The authors propose that the spin density of the allene carbons in the allylic radical intermediate determines the stability and reactivity of the corresponding radical, with a lower spin density equating to a more reactive radical species. Benzylic conjugation on C1 increases the spin density, whereas computational analysis determined that C3 always displays a lower spin density, regardless of the identity of the aryl group, leading to the observed oxidation at this site.

In conclusion, both the source of the perfluoroalkyl radical and the substitution pattern of the allenes greatly affect the regioselectivity and chemoselectivity of the R_F radical addition to the allene precursor. Using perfluoroalkyl iodides (R_FI) as the radical source favors the addition of the R_F radical to the terminal allene carbon. (See Schemes 16 and 19–22.) In addition, the addition of R_FI is generally site-selective, with R_FI added to the less substituted allene double bond, regardless of the allene substitution pattern. (See Schemes 19–22.) Stereoselectivity in these reactions, irrespective of the R_F radical source, has been shown to be affected by the presence of carbonyl-containing substituents on the allene, giving the *E* isomer as the only product. (See Schemes 21 and 35.)

Recently, the transition-metal-catalyzed incorporation of CF₃ groups into allene substrates has attracted significant attention from multiple research groups. In these trifluoromethylation reactions, transition metals that include Cu(I), Cu(II), Ag(I), and Ru(II) have been used in conjunction with common trifluoromethylation reagents such as Togni's Reagent, the Togni Reagent II, the Umemoto reagent, and the Langlois reagent. In contrast with the use of perfluoroalkyl iodides as the radical source, these reactions showed a drastic change in regioselectivity, with the CF₃ radical exclusively adding to the central allene carbon. However, this regioselectivity could be achieved only via substrate control. For example, the reaction of Cu(I)/Togni II and allenes proceeded regioselectively only with aryl or heteroatom-substituted allenes. Trifluoromethylation carried out with Umemoto/Ru(II) or Langlois/Ag(I) proceeded regioselectively only with aryl allene substrates. This unique regioselectivity was largely attributed to the stabilization of the allylic radical or cationic intermediate enabled by the presence of either an aryl group or a heteroatom substituent; alternatively, the CF₃ radical attack on the terminal allene carbon could be blocked by increasing the steric hindrance through the installation of alkyl substituents. Future work in this area should focus on methods to achieve catalyst control over the regioselectivity of CF₃ radical addition to allenes without having to rely solely on substrate control.

2.2.2. Other Carbon-Centered Radicals.—Szwarc et al. studied the relative reactivities of methyl radicals in addition to isolated, conjugated, and cumulated dienes at

various temperatures.⁵⁸ In the presence of decomposing acetyl peroxide, the ratio of k_2/k_1 was measured, where k_2 denotes the rate of a CH_3 radical addition to the diene and k_1 denotes the rate of hydrogen abstraction of the solvent molecule (*iso*-octane) (Scheme 37). A larger ratio of k_2/k_1 indicates a higher rate of radical addition under the same reaction conditions.

Selected values of k_2/k_1 for the addition of a CH_3 radical to five allenes are presented in Scheme 38. Compared with k_2/k_1 values for the corresponding isomers of isolated dienes or conjugated dienes (e.g., 1,4-pentadiene = 60; *trans*-1,3-pentadiene $\approx$ 840 at 65 °C), the reactivity of allenes toward methyl radicals is decreased. Additionally, alkyl or phenyl substitution on the C1 and C3 of the allene precursors did not affect the reactivity, in contrast with the “steric blocking effect” present in noncumulated dienes. These observations led Szwarc to propose that the initial site of attack for the CH_3 radical is on C2. Interestingly, the presence of phenyl groups in **89** does not obstruct the attack of the CH_3 radical and increases the reactivity three-fold, as compared with propadiene **17c**. In considering the reported attack of CF_3 radicals on the terminal carbons of allenes,⁵⁸ Szwarc reasoned that the electrophilic CF_3 radical should attack the more electron-rich C1 and C3 allene carbons, whereas the nucleophilic methyl radical should favor attack at C2 due to the better matching of the electronics of the allene and the radical. By comparing the frequency factor A and the activation energies of reactions between CH_3 radicals and allenes as well as noncumulated dienes, the decreased reactivity of allenes was proposed to arise from a low A factor, as opposed to a higher activation energy.

Experimental evidence⁴⁵ that a CH_3 radical adds to the terminal carbon of propadiene was presented by the Abell group in 1967. After irradiating a mixture of CH_3I and propadiene in the gas phase at 35 and 75 °C, **90** was isolated as the only product (Scheme 39). This result refuted previous predictions that a methyl radical would only attack the central allene carbon, indicating that the polar effects of the radicals do not play a role in determining the regioselectivity of the reaction.

In 1972, Caserio and coworkers investigated the factors governing the regioselectivity of the free-radical addition of methane derivatives, as briefly described in a previous review by Hartung and Kopf,^{25,29} to penta-2,3-diene **27**, 2-methyl-penta-2,3-diene **91**, and cyclonona-1,2-diene **101**. The methane derivatives studied included CF_3I , CH_3I , and CCl_3Br . The yields were not provided, but the ratios of the isolated adducts and identifiable byproducts are given in Scheme 40.

Scheme 40a,b shows that the ground-state electron distribution of the allenes does not dictate the regioselectivity of the attacking radicals, as a more electrophilic CF_3 radical does not show a stronger preference for terminal attack when compared with the nucleophilic CH_3 radical (Scheme 40a). Steric factors, on the contrary, are thought to play a role in regioselectivity, as the larger CCl_3 radical favors attack at the central carbon in allenes that are more heavily substituted (such as **96** as compared with **27**) (Schemes 40b,c). The irreversible addition of a CCl_3 radical to an allene is shown by the recovery of the enantiomerically enriched (*S*)-(+)-**27**. A small net rotation is observed in **94** and **95**,

indicating that the addition of the CCl_3 radical is not stereospecific. The reaction of cyclic allene **101** with CCl_3Br proceeds in a regiospecific fashion, with only **102** being observed.

In 1981, the Boldt group published their findings^{25,59} on the free-radical addition of bromomalonitrile to allenes with alkyl substitution. They envisioned two pathways to the addition product, where the attack of the malonitrile radical occurs at C2 or at C1/C3 of the allene precursor (Scheme 41). Selected experimental results in Scheme 41 show that allenes with more alkyl substituents (such as **24** and **96**) favor the attack of the malonitrile radical at the central allene carbon.

In 2003, Reissig and coworkers reported a SmI_2 -induced ketyl-allene coupling reaction to yield 4-hydroxy-1-enol ethers **104** (Scheme 42).⁶⁰ Various carbonyl compounds **103**, including cyclic and acyclic ketones, as well as aldehydes, were coupled to methoxyallene to furnish **104** in moderate to good yield. The key intermediate in this reaction is proposed to be the ketyl radical anion **105**, which is generated by electron transfer between SmI_2 and the carbonyl group. The regioselective addition of the ketyl species to the terminal allene carbon furnishes the vinyl radical intermediate **106**. This regioselectivity is attributed to the match between the more electrophilic character of the distal allene double bond and the nucleophilic samarium ketyl.^{61,62}

In 2007, the Huang group developed a $\text{Mn}(\text{OAc})_3$ -mediated oxidative free-radical addition of dimethyl malonate or ethyl cyanoacetate to allenes **107** to furnish furan-2(5*H*)-ones or dimethyl 2-(2-oxoethylidene)malonates **108** (Scheme 43) as the major products.⁶³

In the presence of 4.5 equiv of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, as opposed to 2.5 equiv, the allene **109** was converted to the noncyclized product **110** (Scheme 44).

On the basis of experimental results and previous literature reports, a mechanism for the Mn-mediated cyclization was proposed, as shown in Scheme 45. $\text{Mn}(\text{OAc})_3$ oxidizes dimethyl malonate or cyanoacetate to the corresponding alkyl radical **111**. The intermediate **111** adds the allene at C2 to form resonance-stabilized **112**, which upon oxidation by Mn(III) forms a resonance-stabilized carbocation **113**. When R = alkyl, the cyclization is followed by the reaction with H_2O and a 1,3-H shift to furnish the product **108**. However, when R = H, H_2O attacks the benzylic carbocation to form **114**, which is oxidized by Mn(III) to the corresponding carbonyl group. A final 1,3-H shift of the carbonyl yields the product **110**.

In 2013, Yoshida et al. developed a regio- and stereoselective synthesis of functionalized hydroxyhexa-hydrocyclopenta[*b*]-furancarboxylates from alkenes.⁶⁴ The method was extended to a single example of an aryl-substituted allene **115** (Scheme 46). The diastereoselectivity was proposed to result from the steric hindrance between the aryl and ester group.

In 2015, the Xu and Li groups reported a photo-redoxcatalyzed addition of an α -aminoalkyl radical to 2,3-allenoates **116**.⁶⁵ In the presence of a catalytic amount of $\text{Ru}(\text{bpy})_3(\text{BF}_4)_2$, the α -aminoalkyl radical is regioselectively added to the central carbon of the 2,3-allenoate to produce unsaturated γ -aminobutyric ester derivatives in moderate yield (Scheme 47). The

electron-deficient nature of 2,3-allenoates enables them to function as efficient coupling partners in reactions with nucleophilic α -aminoalkyl radicals. It is worth noting that only **117** is obtained when at least one substituent is present on the C1 of the allene. The reported yields are low (<35%) for 1,1-disubstituted-2,3-allenoates, likely due to steric effects. On the basis of experimental results and literature precedent, a mechanism was proposed for the radical coupling (Scheme 48). The excited Ru(II) catalyst oxidizes the amine to the corresponding radical cation **119**, which is deprotonated by $\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$ to form an α -aminoalkyl radical **120**. The addition of **120** to the central allene carbon generates an allylic radical **121**, which is reduced by Ru(I) to the corresponding allylic anion **122**. The protonation of the anion affords the final products **123** and **124**.

Overall, general rules to predict the regio-, chemo-, and stereoselectivities of additions of carbon-centered radicals to allenes are difficult to ascertain due to the greater diversity of carbon versus halogen radicals and the relatively limited scope of allenes that have been studied. However, some conclusions can be drawn as to the regioselectivity in certain cases. First, the sterics of the attacking radical play an important role in directing the regioselectivity. With the same methylated allene substrate, the larger CCl_3 radical favors attack on C2, whereas a smaller CF_3 radical prefers to attack at C1/C3. In addition, allene sterics also affect the regioselectivity in the attack on a malonitrile radical. Allenes containing more methyl substituents divert the regioselectivity of malonitrile radical to the less hindered C2 of the highly substituted allene. Future efforts should focus on examining these reactivity patterns with a larger range of carbon-centered radicals and allenes to provide a more comprehensive picture of the selectivity trends that will improve the synthetic utility of this chemistry.

2.3. Nitrogen-, Phosphorus-, Oxygen-, and Sulfur-Centered Radicals

2.3.1. Nitrogen Radicals.—Research on the addition of nitrogen-centered radicals to allenes has been explored with aminium, nitro, and *N*-sulfonimide radicals. Among these, the nitro radical has been the most heavily studied due to its facile conversion to other functional groups and its potential to access useful building blocks such as nitroolefins, which are widely used in a biological or pharmaceutical context.^{66–68} These reactions proceed in a regioselective fashion to attack at C2 of allenes that contain alkyl, aryl, or silyl substitution.

In 1967, Neale published a study on the free-radical addition of dialkyl *N*-chloramines to unsaturated hydrocarbons, including 1,3-dienes, terminal olefins, acetylenes, and allenes.⁶⁹ The irradiation or addition of a Fe(II) catalyst to a mixture of dialkyl *N*-chloramine and allene **125** in sulfuric and acetic acids generated the corresponding 1:1 chloramine adducts **126** via a free-radical chain mechanism (Scheme 49). The major product was formed from the initial attack of an aminium radical on the terminal allene carbon.

Almost 50 years after Neale's publication on the intermolecular aminium radical attack on allenes, the Lee group developed a regioselective synthesis of α -nitro- α,β -unsaturated silyl oximes **128** by employing NaNO_2 and AcOH as a nitrogen dioxide radical source and silyl allenes **127** as radical acceptors⁷⁰ (Scheme 50). After testing various 1,1,3-trisubstituted silyl allenes, it was determined that the size of the silyl group did not affect the yields or *E/Z*

ratios of **128**. However, replacing a silyl with a *tert*-butyl group gave decomposition, indicating the importance of the silyl group to the success of the reaction. Unsaturated functionalities, including alkenes or aromatic rings, were compatible with the method, suggesting that the silyl allenyl moiety is more reactive toward the NO₂ radical. No reaction was noted with 1,3-disubstituted silyl allenes, possibly due to the formation of an unstable secondary carbon-centered radical **130** (R¹ = H). The treatment of nitroalkene derivatives **128** with TBAF initiates 5-*endo-dig* cyclization onto the alkene carbon; the subsequent Nef reaction^{71,72} gives isooxazolidinones **129** in moderate yield.

In addition to the protocol in Scheme 50, the Lee group also described the chloronitration of allenes **131** employing Fe(NO₃)₃ as a nitrite source (Scheme 51). It is noteworthy that allene **131b**, which lacks a silyl substituent, is also a viable substrate for Fe(NO₃)₃ nitration; however, silyl allenes do give better regioselectivity, with **132** noted as the major regioisomer.

On the basis of experimental results, the Lee group proposed the mechanism shown in Scheme 52. The nitrogen dioxygen radical is generated from heating a mixture of NaNO₂ and AcOH or by combining Fe(NO₃)₃ and FeCl₃. The addition of the NO₂ radical to allene **127** gives the allylic radical intermediate **134**, which is either trapped by the nitroso radical to form **135** or reacts with FeCl₃ via electron transfer to form the regioisomers **132** and **133**. The subsequent tautomerization of **135** gives **128**.

In 2014, Ma reported a regio- and stereoselective nitrooxoamination of allenes **137** with AgNO₂ and TEMPO.⁷³ Various monosubstituted allenes gave nitroalkenes of the form **138**, with the *E* configuration as the major product (Scheme 53). In general, allenes substituted with aryl and heterocyclic groups gave higher yields compared with alkyl substitution. This chemistry shows mechanistic similarities to Lee's method (Scheme 52), where a nitrogen dioxygen radical adds to the central allene carbon to form an allylic radical intermediate.

In 2015, Zhang published a regioselective synthesis of allenamides and fluorinated tetrasubstituted alkenes from allenes and NFSI or its derivatives.⁷⁴ A Cu(I) catalyst supported by a neocuproine (NC) ligand furnished allenamides from 1,1- and 1,3-disubstituted aryl allenes (Scheme 54a). However, 1-aryl-substituted and 1,1-dialkyl-substituted allenes were not viable substrates. Various aryl-substituted N-F reagents were also well-tolerated in this protocol.

A mechanism was proposed (Scheme 54b) based on the experimental results and previous literature.^{75–77} The initial oxidation of the Cu(I) catalyst by **140** generates a Cu(III) species **142'**, which is in equilibrium with a Cu(II)-stabilized nitrogen radical species **142** through redox isomerization. The addition of **142** to allene **139** affords a vinyl radical intermediate that yields the allenamide product **141** and regenerates the Cu(I) catalyst following β -hydride elimination.

In the presence of an Ag(I) catalyst, a mixture of allene **144** and the N-F reagent **140** yields fluorinated tetrasubstituted alkenes **145** via a radical aminofluorination process (Scheme 55). In general, 1,1-disubstituted and monosubstituted allenes give the corresponding fluorinated

alkenes in moderate to excellent yield. Electron-deficient allenes with an ester group at C3 do not react, even at 100 °C. The stereoselectivity of the alkene products is strongly affected by the sterics of the alkyl substituent on the allene, with bulky groups giving higher stereoselectivity in favor of the *E* isomer. The fluorinated alkene product was proposed to form from fluorine atom transfer to the vinyl radical intermediate **143'**.

2.3.2. Phosphorus Radicals.—In 1965, Goldwhite reported the first example of the free-radical addition of phosphine to an allene by irradiating an equimolar mixture of phosphine and propadiene under UV light.^{2,3,78} The product mixture included a trace amount of a 1:1 adduct, plus large amounts of polymeric materials. The adduct was characterized as isopropenylphosphine (Scheme 56).

In 1991, Mitchell published a synthesis of vinyl phosphines by the free-radical addition of diphenylphosphine to allenes and alkynes.⁷⁹ The major products were generally vinyl phosphines **147** (Scheme 57), generated from diphenylphosphine radical attack on the central allene carbon, regardless of the substituents on the allene precursor. In most cases, allyl phosphines **149**, which are formed from phosphine radical attack on the terminal allene carbon, are observed in small amounts.

2.3.3. Oxygen Radicals.—Studies of oxygen-centered radical attack on allenes are rare, with the majority of interest centering on atmospheric chemistry. For example, reactions of allenes with hydroxyl radicals has been extensively studied^{80,81} because the hydroxyl radical is an important reactive intermediate in combustion processes. It is also present in the atmosphere of a few planets and the interstellar medium.⁸² However, because these studies were not directed toward synthetic applications of radical additions to allenes, they are not discussed here.

2.3.4. Sulfur Radicals.—In 2014, the Renaud group published a review article describing the regio- and stereoselectivities of thiyl radical attack on allenes.⁸³ Therefore, this Review will cover only sulfonyl radical and other sulfur-centered radical additions to allenes; the reader is referred to the Renaud review for further details.

2.3.4.1. Sulfonyl Radicals. Free-radical reactions of aryl/alkyl sulfonyl halides and allenes have been studied since the late 1960s. Recently, a surge in difunctionalization of allene double bonds (with one of the functionalities being the sulfonyl group) has attracted the attention of multiple research groups due to the synthetic versatility of sulfonyl groups as well as the abundance of biological molecules containing a vinyl sulfone moiety.^{84–86} In general, a sulfonyl radical adds regioselectively to allenes, with terminal attack giving rise to the major product in reactions with propadiene; however, for more hindered allenes, the sulfonyl radical tends to attack the central carbon. Other sulfur-centered radicals, such as the SCF₃ radical, also favor attack on central allene carbon.

Truce and Wolf published studies on the free-radical addition of sulfonyl iodides to allenes in the late 1960s and early 1970s.^{87,88} The irradiation of mixtures of alkyl or aryl sulfonyl iodides and various allenes yielded 1:1 adducts in moderate to good yield (Scheme 58a). The regioselectivity and stereoselectivity depended on the substituents present on the allenes as

well as the identity of the sulfonyl iodides. The use of propadiene gave mixtures of products, irrespective of the sulfonyl iodide employed in the reaction. The four products **151–154** were proposed to arise from the mechanistic pathways depicted in Scheme 58b. Irradiation initiates the homolytic cleavage of the S–I bond to generate the corresponding sulfonyl radical and an iodine atom. The addition of the sulfonyl radical to either the central or terminal allene carbon gives the corresponding allyl or vinyl radical intermediates; these undergo iodine abstraction with sulfonyl iodide to generate products **152** and **151**, respectively.

As shown in Scheme 59, **156–158** were the only products observed when allenes **24**, **27**, and **155** were subjected to the same reaction conditions described in Scheme 58. Any substitution on the allene strongly favored the attack of the sulfonyl radical on the central allene carbon due to the lower activation energy to yield a stable allylic radical intermediate. In the case of phenyl allene **155**, sulfonyl radical attack favored the formation of the product with the iodine attached to C3. The preference of iodine abstraction by the C3 radical was attributed to less steric hindrance at C3 compared with C1 as well as the increased stability of the intermediate resulting from conjugation with the styrene (Scheme 59). The *trans* stereoselectivity in the addition of sulfonyl iodide to phenyl allene **155** was rationalized by the relief of the steric strain between the relatively large sulfonyl and phenyl groups in the allylic radical intermediate.²⁵

The Caserio group studied the regio- and stereoselectivities of tosyl iodide addition to various allenes, including optically active examples.²⁹ Similar to the experimental results obtained by Truce and Wolf, the tosyl radical preferentially attacked the terminal carbon of propadiene but preferred to attack the central carbon of methyl-substituted allenes **24** and **26** (Scheme 60) and 1,2-cyclononadiene (Scheme 61). Iodine abstraction furnished the most substituted alkene, with the exception of 2-methyl-2,3-pentadiene **96**, which delivered **163**.

When optically active allenes (*S*)-(+)-**27** and (*S*)-(–)-1,2-**101** were irradiated in the presence of tosyl iodide, the allylic iodide product **164** was found to be racemic (Scheme 61). The loss of optical activity indicated that the reaction proceeds through a planar, delocalized allylic radical intermediate, as opposed to a nonplanar, localized radical. Racemization also suggested that 90° rotation about the C2–C3 bond is faster than iodine abstraction. The recovered 2,3-pentadiene (*S*)-(+)-**27** retained its optical activity, implying that the tosyl radical adds to the central carbon of 2,3-pentadiene in an irreversible fashion. However, in the case of 1,2-cyclononadiene (*S*)-(–)-1,2-**101**, the addition of the tosyl radical to the central carbon proved reversible. The intermediate radical was proposed to be nonplanar, favoring a conformation that relieves torsional strain and nonbonded interactions in the nine-membered carbocycle. The lack of allylic resonance stabilization promoted reversibility in this thermoneutral process, as described in a previous review.²⁵

In 2001, Kang et al. achieved regio- and stereospecific radical additions of *p*-TsBr or *p*-TsI to allenic alcohols in the presence of catalytic amounts of AIBN⁸⁹ (Scheme 62). The *p*-Ts radical was found to attack the central carbon of the allene, with the (*E*)-alkene observed as the sole product for allene **166a**. Depending on the length of the tether bearing the hydroxy

group, products can arise from radical addition only (**168**, **172**) or radical addition, followed by cyclization (**168–170**).

When allenic sulfonamides **173** were subjected to the same conditions using *p*-TsBr as the radical source, the Br was installed at the less substituted terminal double bond of the allene. The corresponding cyclization products **175** and **176** were obtained by subjecting the initial addition products **174** to K₂CO₃ in DMF (Scheme 63).

Kang also published a similar study on the regio- and stereospecific syntheses of (*E*)-*p*-Ts-substituted allylic bromides using the same protocol⁹⁰ (Scheme 64). By subjecting the allylic bromide product **177** to different nucleophiles, the regioselective synthesis of α,β -unsaturated sulfone derivatives **178** was achieved in good to excellent yield.

The same group employed α -allenic alcohols to accomplish regio- and stereospecific syntheses of β -sulfonyl- α,β -unsaturated ketones **179** via *p*-TsBr radical addition to allenes, followed by base-promoted 1,4-elimination⁹¹ (Scheme 65).

In 2018, Lu et al. published a regio- and stereoselective synthesis of (*E*)- α -halomethyl vinylsulfones **181** and **183** via a Cu(I)-catalyzed difunctionalization of allenes **180** and **182**.⁹² A 1.5:1 mixture of allene and sulfonyl iodide was subjected to a catalytic amount of CuI and 1,10-phenanthroline in dichloro-methane at room temperature to produce various 1:1 adducts in moderate to excellent yield (Scheme 66).

TEMPO and galvinoxyl radical trapping experiments gave reduced yields, suggesting the presence of radical intermediates. On the basis of previous literature and their experimental results, Lu et al. proposed the mechanism in Scheme 66. The oxidation of Cu(I) to Cu(II) by the sulfonyl iodide reagent gives a sulfonyl radical **184** and iodide. The attack of the sulfonyl radical on the central carbon of the allene affords the corresponding allylic radical **185**, which was oxidized to the allylic cation **186** by Cu(II) to regenerate Cu(I). The regioselective attack of the iodide on C3 furnished the final product. Density functional theory (DFT) computational analysis was used to rationalize the regioselectivity of the iodide attack; the analysis showed a higher NPA charge on C3 than C1, indicating a higher electrophilicity at C3.⁹³

Recently, Wu described a Cu(II)-catalyzed cyclic arylsulfonylation of 2,3-allenoic acids **187** to afford 4-sulfonylated furan-2(5*H*)-ones **188** in moderate to good yield (Scheme 67).⁹⁴ The aryldiazonium tetrafluoroborate likely reacts with DABCO-(SO₂)₂ to form an aryl sulfonyl radical, which regioselectively attacks C2 of the 2,3-allenoic acid. Na₂S₂O₅ could also be used as a SO₂ source but gives lower yields of **188** than DABCO-(SO₂)₂. Electron-rich and electron-deficient aryl groups are tolerated by both methods.

The addition of 2 equiv of TEMPO completely inhibited the reaction, indicating the presence of radical intermediates. Wu proposed the mechanism in Scheme 67. In Path A, the aryl sulfonyl radical resulting from the addition of SO₂ to the aryl radical is generated from single electron transfer between Cu(I) and ArN₂BF₄. In Path B, the aryl sulfonyl radical is formed from DABCO-(SO₂)₂ and ArN₂BF₄. The addition of the aryl sulfonyl radical to the central allene carbon gives the allylic radical intermediate **189**, which is oxidized by Cu(II)

to the corresponding carbocation **190**. The cyclization of the carboxylate yields the final product **188**.

2.3.4.2. Other Sulfur-Centered Radicals.: In 2016, Lei and coworkers described a highly regio- and stereoselective oxysulfonylation of monosubstituted allenes **191** to form 2-sulfonyl allylic alcohols **192** in moderate to good yield.⁹⁵ Various arylsulfinic acids were examined, with electron-rich arylsulfinic acids giving higher yields than electron-deficient ones. A 1,1-diphenyl allene gave an inferior yield compared with monosubstituted allenes (Scheme 68). Allenes substituted with ester groups **193** furnish olefinic sulfonyl compounds **194** as the major products.

The addition of TEMPO and BHT inhibited the reaction, suggesting a mechanism involving radical intermediates. The use of $^{18}\text{O}_2$ in place of air results in 86% of isotope incorporation into **192**, indicating the participation of O_2 in the reaction (Scheme 69a). On the basis of these experimental data, Lei proposed the mechanism in Scheme 69b. The initial deprotonation of phenyl sulfinic acid gives **195**, which undergoes oxidation to form the conjugated sulfonyl radicals **196** and **197**.⁹⁶ The regioselective addition of the sulfonyl radical to the allene produces allylic radical **198**, which is trapped by O_2 to yield **199**. The subsequent reduction by **195**, protonation by the pyridinium ion, and a final reduction give the product **200**.

In 2017, the Qing group published a Cu(I)-catalyzed cyclic oxytrifluoromethylthiolation and Cu(II)-catalyzed bis-trifluorothiolation of 2,3-allenoic acids.⁹⁷ Various 1-, 1,1-di-, and 1,3-substituted allenoic acids were heated with CuCN, $(\text{NH}_4)_2\text{S}_2\text{O}_8$, and AgSCF_3 to afford trifluoromethylthiolated butenolides **202** (Scheme 70). Most 2-alkyl-4-arylbuta-2,3-allenoic acids **201** gave moderate to good yield, with the exception of **202e'**, which gave only trace amounts of bis-trifluoromethylthiolated byproduct. Product **202** could be transformed to trifluoromethylthiolated furan derivatives by employing either LDA/ Ac_2O or NaHDMS/ CIP(O)(OPh)_2 .

In the same paper, Qing described a catalytic Cu(OAc)_2 -mediated bis-trifluoromethylthiolation of 2,3-allenoic acids **205**. The corresponding ditrifluoromethylthiolated carboxylic acids **206** were obtained in moderate yield in most cases (Scheme 71).

To probe the mechanism of the reaction, Qing and coworkers added radical scavengers to the reaction, including BHT or 1,4-benzoquinone, and found only trace amounts of **202**. In addition, replacing carboxylic acid in **205** with an ethyl ester gave only trace amounts of desired bis-trifluoromethylthiolation products. Qing proposed the mechanism shown in Scheme 70, where the oxidation of AgSCF_3 by peroxydisulfate anion forms the Ag(II)SCF_3 species that serves as the source of either the SCF_3 radical or $(\text{SCF}_3)_2$. The regioselective addition of the SCF_3 radical to the central allene carbon gives the allylic radical intermediate **203**. The oxidation of **203** by Cu(II) or S_2O_8^- yields the corresponding allylic cation **204**, which eventually cyclizes to the desired product **202**. For similar work that employs $\text{Cu(OAc)}_2/\text{S}_2\text{O}_8^-$ to accomplish the sulfenylation, sulfonylation, and selenylation of 2,3-allenoic acids with disulfides or diselenides, see ref 98.

2.4. Other Metal-Centered Radicals (Sn, Ge, Se, Te, In)

2.4.1. Sn and Ge Radicals.—In 1965, Fish et al. published the first study^{99,100} on AIBN-catalyzed Me₃SnH addition to allenes **17c**, **14**, **26**, **27**, and **96**. In all cases, an excess of allene was used. The reaction proceeds via a free-radical chain mechanism to yield 1:1 adducts from trimethyltin radical attack on either the central or terminal allene carbon (Scheme 72). Theoretically, two types of products can be formed from attack of the trimethyltin radical on either the central or the terminal carbon of the allene. When the allene is unsymmetrical, four potential products (**207–210**) are possible.

Fish et al. compared the amounts of products resulting from attack of the central allene carbon on an ethanethiyl radical versus the attack of a nucleophilic trimethyltin radical on an allene substrate. Products resulting from the reaction at the central carbon of the allene increased with increasing methyl substitution on the substrate (Scheme 73). Thus it was concluded that the regioselectivities of ethanethiyl and trimethyltin radical additions to allenes are not determined by polarity but rather by the favored formation of an allylic radical intermediate as the methyl substitution increases on the allene. This was ascribed to the increased steric hindrance in the approach of the trimethyltin radical and the increased stability of the resulting radical intermediate due to hyperconjugation.

The product distribution for allene **96** by considering the stability of allylic radicals **211** and **211'** leads to the formation of **207–96** and **208–96** (Scheme 74). Both allylic radical intermediates **211** and **211'** display strain resulting from steric interactions between the SnMe₃ and vicinal methyl group(s) or 1,3-dimethyl interactions. Rotation around the C1–C2 or C2–C3 bond minimizes strain while also maintaining maximum π -orbital overlap. Rotation around the C1–C2 bond in both **211** and **211'** is more favorable than rotation around the C2–C3 bond due to the preference for a vinyl-substituted tertiary radical over a secondary radical. Therefore, hydrogen abstraction occurs preferentially at C1 as opposed to C3 to furnish **207–96** as the major product.

There is a preference for the formation of **208-26-(E)** over **208-26-(Z)** for allene **26** by considering the stability of radical intermediates **212** and **212'**, as shown in Scheme 75. Both **212** and **212'** were formed from the attack of the SnMe₃ radical on the C2 of allene **26**. It was reasoned that **212** was produced as the major isomer due to the absence of the strain between C1-Me and C2-SnMe₃ that is present in **212'**.

Fish proposed that the predominant formation of **207-27-(Z)** over **207-27-(E)** can be explained as described in Scheme 76. The allylic radical intermediate has two isomeric forms, represented by **213** and **213'**. Isomer **213'** is expected to be the major form of the radical because the interaction between C2-SnMe₃ and C3-Me in **213'** is estimated to be lower in energy than the corresponding interaction between C1-Me and C3-Me in **213**. The latter interaction in **213** is estimated to be 5.4 kcal, similar to values for 1,3-diaxial interactions between methyl groups in cyclohexane. However, the interaction energy between C2-SnMe₃ and C3-Me in **213'** is estimated to be <4.3 kcal (the computed value for the cis interaction between Me and ^tBu attached to ethylene).¹⁰¹ The longer C–Sn bond in **213'**, as compared with the C–C bond of a ^tBu group (2.17 vs 1.54 Å for the C–C bond), is largely responsible for a lower interaction energy between the SnMe₃ and its proximal

groups. Similar arguments may be applied to explain the regio- and stereoselectivities for the addition of Me₃SnH to **26** under radical conditions.

In 1988, Oshima et al. described a BEt₃-induced radical addition of Ph₃SnH and Ph₃GeH to allenes to access vinylic triphenylstannanes (Scheme 77) and vinylic triphenylgermanes¹⁰² (Scheme 78). For the unsubstituted allene **17c**, the Ph₃Sn radical attacks both the terminal and central allene carbons, favoring the formation of allyltin **215** but also producing significant amounts of the vinyltin **216**. For mono or 1,3-disubstituted allenes **214a–c** and **101**, the Ph₃Sn radical attacks the central carbon in a regioselective manner to give predominantly the vinyltin products **216** and **217**.

In general, allylic germanes were formed as the major product in Scheme 78. Because no *E/Z* ratio was provided by the authors, the stereoselectivity of this hydrogermylation method has not been established. The Ph₃Ge radical is less reactive than the Ph₃Sn radical, as exemplified by its reluctance to react with 6,7-tridecadiene and 1,2-cyclononadiene.

In 1991, Mitchell et al. studied the radical addition of Me₃SnH to allenes, demonstrating an expanded substrate scope compared with the work of Fish et al. (Scheme 79).¹⁰³ Two conditions were employed, where the reaction was initiated by either AIBN or light. Overall, the results showed that these two different modes of initiation furnish different ratios of products yet still display the same preference for attack at either the central or the terminal carbon if the same allene precursor is employed.

In 2007, Shibata and Baba accomplished a regio- and stereoselective hydrostannation of allenes by using dibutyltin hydride generated in situ.¹⁰⁴ A mixture of Bu₂SnH₂ and Bu₂SnI₂, in combination with monosubstituted or disubstituted allenes, predominantly delivered the (*E*)-vinyl tin products at room temperature in moderate to good yield (Scheme 80). Substituting Me₃SnH (Scheme 79) with Bu₂SnIH increased the regioselectivity by predominantly favoring attack at the central carbon, with little product observed from attack at the terminal carbon. It is noteworthy that the stereoselectivity was improved with a bulky R substituent on the allene (e.g., compare **222a** with **222b**). Allenes with oxygen substituents (**222c,d**) yielded *Z* alkenes preferentially, in contrast with allenes bearing alkyl substituents. The reaction was completely suppressed in the presence of the radical scavenger galvinoxyl.

The reaction was proposed to proceed through a free-radical chain mechanism (Scheme 81). The redistribution of Bu₂SnI₂ and Bu₂SnH₂ generates the Bu₂ISn radical, which attacks the central allene carbon to form the allylic radical intermediate **224**. Because of the steric repulsion between the alkyl and the tin substituents, the *E* alkene **225**-(*E*) is the major product following hydrogen abstraction by Bu₂SnIH on the less substituted allene carbon. When an alkoxy substituent was present on the allene, the coordination between the oxygen and the iodotin center favored the formation of the *Z* alkene product **226**-(*Z*).

In summary, the addition of Sn-based radicals to allenes is sensitive to the sterics of the substituents present on the precursor. For both SnPh₃ and SnMe₃ radicals, the addition to the terminal carbon is favored if the reactant allene is propadiene; however, for methylated

allenes, a preference to add to the central carbon was observed. In general, regardless of the source of the Sn radical, the hydrostannation is chemoselective, with the less substituted double bond of the allene undergoing reaction. Ge radicals, on the contrary, favor addition to the terminal allene carbon. However, hydrogermylation displays the same chemoselectivity as radical hydrostannation, with the less substituted allene double bond undergoing the preferential reaction.

2.4.2. Se and Te Radicals.—Interest in introducing Se into an allene carbon primarily originated from the known synthetic applications of vinylselenides.¹⁰⁵ Reports on the intermolecular addition of Se, Te, and In radicals to allenes have demonstrated that the addition proceeds in a regioselective fashion, with a new bond formed between the heteroatoms and C2 of the allene. In addition, the radical hydroselenation of allenes is chemoselective, with the less substituted allene double bond undergoing the preferential reaction.

Sonoda et al. developed a regioselective hydroselenation of mono- and disubstituted allenes **227** to afford vinyl selenides **228** in good to excellent yield using benzene selenol as the selenium source.¹⁰⁶ The reaction was proposed to occur via a radical chain mechanism with O₂ as the initiator. The selenyl radical selectively attacks the central allene carbon to yield 1:1 to 2:1 *E/Z* mixtures of vinyl selenides (Scheme 82). Selenyl radical addition to allenes is more regioselective than its sulfur counterpart, as a phenyl thiyl radical was reported to afford a 3:1 mixture of products from the attack at the central and terminal allene carbons, respectively.^{25,107}

In 1990, Ogawa published a study on photoinduced radical additions of Ph₂Se₂ to allenes.¹⁰⁸ Various mono-, 1,1-di-, and 1,3-disubstituted allenes **229** were converted to 1-(phenylselenomethyl)vinyl selenides **230** in moderate to excellent yield and with moderate to excellent *E/Z* ratio (Scheme 83). The phenylselenenyl radical, generated from the homolytic dissociation of (PhSe)₂, regioselectively adds to the central allene carbon to form an allylic radical **231**, which is trapped by a phenylseleno group by the approach of (PhSe)₂ from the less substituted terminal allene carbon.

Interestingly, replacing Ph₂Se₂ with Ph₂S₂ gave a complex mixture of products, presumably due to the inferior ability of Ph₂S₂ to capture carbon radicals as compared with diselenide. For comparison, the rate constant for homolytic substitution between diphenyl disulfide and a primary carbon radical is $7.6 \times 10^4 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ in benzene at 80 °C compared with $1.2 \times 10^7 \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ for diphenyl diselenide under the same conditions.¹⁰⁹ In 1993, Ito published a kinetic study on the addition of arylthiyl and phenylselenenyl radicals to allenes using flash photolysis (Scheme 84).^{25,110} Both ArS and PhSe radicals add to olefins, acetylenes, and dienes in a reversible fashion. By studying the decay profile of ArS and PhSe radicals in aerated and degassed cyclohexane solutions of 3-methyl-1,2-butadiene and 2,4-dimethyl-2,3-hexadiene, Ito concluded that these radicals add to the central allene carbon in an irreversible manner. The rate of ArS and PhSe radical addition to the central allene carbon was not affected by increasing the methyl substitution on the allene. In general, the PhSe radical is less reactive than the ArS radical toward 1,3-diene, styrene, and phenylacetylene. However, this trend is reversed in reactivities toward allenes, as the PhSe

radical was 1.3 to 1.8 times more reactive than the PhS radical. This suggests an increase in the rate of addition to the central carbon as the orbital size of the unpaired electron on the attacking radical increases.

In 1998, Ogawa published a photoinduced regioselective thioselenation of allenes **232** using a (PhS)₂–(PhSe)₂ binary system.¹¹¹ Upon irradiation at wavelengths >300 nm, β -selenoallylic sulfides **233** were afforded in moderate to excellent yield (Scheme 84). ¹H NMR monitoring of the reaction showed the initial formation of diselenide **234**, followed by the slow conversion of **234** to **233**. In addition, subjecting **234** to (PhS)₂ under the same photoinduced conditions generated the thioselenation product **233** over time, suggesting the mechanism illustrated in Scheme 84. At $\lambda > 300$ nm, the homolysis of (PhSe)₂ was favored over (PhS)₂ because the absorption maximum of (PhS)₂ is 250 and 330 nm for (PhSe)₂. The PhSe radical regioselectively adds to the central carbon of allene to form an allylic radical intermediate, which is in equilibrium with the diselenide adduct **234**. Meanwhile, the allylic radical is also converted to the more stable thioselenation product **233** upon reaction with PhSSePh.

The dithiolation of allenes was also accomplished by Ogawa by employing a (PhS)₂–(PhTe)₂ binary system. Interestingly, when 4,4-dimethylpenta-1,2-diene **146g** (Scheme 85) was subjected to an equimolar amount of (PhS)₂ in an attempt to obtain the dithiolation product, a complex mixture of products was formed instead, likely due to allene oligomerization. This result was attributed to the inferior ability of (PhS)₂, as compared with (PhSe)₂ and (PhTe)₂, to capture the carbon-centered radical intermediate. However, the addition of (PhS)₂ and (PhTe)₂ to 4,4-dimethylpenta-1,2-diene did not afford the expected thiotelluration product and instead gave the dithiolation product **235** in good yield and with good stereoselectivity. Ogawa proposed that the presence of (PhTe)₂ prevented competing oligomerization.

Ogawa also developed regioselective selenophosphinations of allenes and alkynes to introduce diphenylphosphino and phenylseleno groups simultaneously to the double or triple bond of allenes or alkynes, respectively.¹¹² The irradiation of an equimolar mixture of allene **236**, (Ph₂P)₂, and (PhSe)₂ in degassed CDCl₃ in a sealed NMR tube afforded the selenophosphination product **237** in good to excellent yield with a moderate *E/Z* ratio (Scheme 86). Upon oxidation by air during workup, the corresponding phosphine oxide products **238** were generated in moderate yield. Seleno and phosphino groups were found to add to the less substituted double bond of the allene, with the seleno group ultimately attached to the central allene carbon. Mono- and 1,1-disubstituted allenes were tolerated in this protocol; however, cyclononadiene gave no selenophosphination product.

A control experiment run in the dark gave trace amounts of the addition product, suggesting a radical mechanism (Scheme 87). At wavelengths >350 nm, only the (PhSe)₂ was homolytically cleaved to generate the phenylselenenyl radical. In situ formed Ph₂PSePh could also be employed as another source of the phenylselenenyl radical, which regioselectively attacks the central allene carbon to form an allylic radical intermediate **239**. Subsequent trapping by Ph₂PSePh (S_H2 homolytic substitution) gives the final product.

In 2016, Kumaraswamy et al. described visible-light-induced regio- and stereoselective chalcogenyl oxyfunctionalizations of mono-, 1,1-di-, and 1,3-disubstituted allenes **240**, **242**, and **244**.¹¹³ In the presence of a diphenyl dichalcogen reagent and LiCl, allenes were converted to Z-substituted α,β -unsaturated aldehydes or ketones as the major product in good to excellent yield (Scheme 88b). When (PhTe)₂ was used in place of (PhSe)₂, the corresponding vinyl tellurium product **241b** was obtained in good yield and with good stereoselectivity. However, no reaction occurred when (PhS)₂ was used (Scheme 88a). For allenes **244**, the oxidation stopped in the alcohol stage to furnish the allylic alcohol products (Scheme 88c).

It is noteworthy that the phenoxy allene **244a** and the allenyl *N*-tosylbenzenamide **244b** gave phenol and aniline sulfonamide as the only products (Scheme 89). This was attributed to captodative stabilization^{114–116} or the stabilization of the radical cation **246** by the allene functioning as an adjacent π -acceptor. The resulting highly stabilized neutral radical **247** gives the corresponding phenol and aniline sulfonamide **248** or **249** upon hydrogen abstraction.

Kumaraswamy et al. proposed the mechanism as shown in Scheme 90 based on the experimental results and previous literature.^{117,118} Upon irradiation, (PhSe)₂ is promoted to the singlet excited state, which is then reduced by the ground-state allene via a single electron transfer to form exciplex **250**. LiCl and exciplex **250** yield the solvent-separated ions **251** and **252**. The attack of the radical anion **251** on the radical cation **252** gives the allylic radical intermediate **253**, which, upon trapping of O₂, forms the peroxy radical **254**. The disproportionation of **254** gave the aldehyde, ketone, or allylic alcohol product depending on the starting allene.

2.4.3. In Radicals.—Baba and Shibata published the first regioselective hydroindation of allenes **255** in 2008 by using HInCl₂ generated in situ as an indium radical source.¹¹⁹ Sequential protonation converted the vinylindium product **256** and **257** to the corresponding olefins **258** and **259** in moderate to good yield (Scheme 91). The regioselectivity of the indium radical attack was confirmed by adding iodine to the hydroindation products **256** and **257**. The isolation of the vinyl iodide product confirmed the preference for the indium radical to attack the central allene carbon. The addition of the radical inhibitor galvinoxyl completely suppressed the reaction, suggesting a radical mechanism. The intermediacy of an indium radical in similar reactions has been described.^{120–124}

3. INTRAMOLECULAR RADICAL ADDITIONS TO ALLENES

3.1. Carbon-Centered Radicals

3.1.1. Ketyl Radical Anions.—In 1983, the Pattenden group developed a reductive cyclization of allenic ketones via electrolysis to furnish functionalized fused bicyclic ring systems (Scheme 92).¹²⁵ The cyclization introduces both unsaturation and a bridgehead hydroxyl group into the product, a motif common in marine terpenoids.¹²⁶ Allenes examined in the annulation reaction all favored *exo*-cyclization to form five-membered rings. Allene **262** produced **263**, with the vinyl group located *trans* to the hydroxyl group and hydrogen atom.

A detailed discussion of the reaction results was provided in 1985.¹²⁶ Two results are particularly noteworthy: First, when a tethered cyclohexanone (**260b** in Scheme 92) was employed, changing the reaction condition from electrolysis to sodium naphthalenide changed the cyclization mode from 5-*exo-dig* to 5-*endo-dig* (compare **261b** with **266**); however, in the case of the tethered cyclopentanone **260a**, altering the reaction conditions did not affect the cyclization mode. The Pattenden group reasoned that efficient orbital overlap between the singly occupied molecular orbital (SOMO) of the ketyl radical and the lowest unoccupied molecular orbital (LUMO) of the central allene carbon, which is influenced by the size of the ketone ring, was an important consideration (Scheme 93). The ketyl radical **267** overlaps efficiently with only one LUMO on the central sp-hybridized carbon, forming the 5-*exo-dig* product **261a** with both sets of reaction conditions. However, in **268**, the closer proximity between the radical center and the central allene carbon enables a sufficient overlap between the SOMO and both LUMOs of the central allene carbon. In addition, the difference in potentials between the sodium naphthalenide anion and the electrode (−3.09 vs −2.43 V (vs Ag/Ag(I))) proved important. The electrochemically generated ketyl radical is of lower energy and cannot overcome the activation energy barrier to form the thermodynamic *endo* product. Pattenden reasoned that this is due to the greater potential of the sodium naphthalenide radical anion (−3.09 V vs Ag/Ag(I)) as compared with the electrode potential of −2.43 V under the experimental conditions. The *trans* relationship between the hydroxyl and vinyl groups results from the minimization of the repulsion between the electron density on the oxyanion and the vinyl radical in the transition state.

In 1986, the Crandall group described an alternative to Pattenden's strategy for the reductive radical cyclization of allenic ketones, where the ketyl radical is generated from a dissolving metal reduction (Scheme 94).¹²⁷ For allene **269**, cyclization onto the central carbon was the major pathway, resulting in the same regioselectivity as the cyclopentanone analogue **260** in Scheme 92 and its carbon-centered radical analogue **313a** in Scheme 103. When $n = 2$, cyclization gave the five-membered ring as the major product, resulting from the regioselective radical attack on the proximal allene carbon. Compared with its analogue **313b** in Scheme 103, the regioselectivity of the ketyl radical anion is improved.

Cyclization is the major pathway for allenyl ketones of the form **269**, regardless of the reaction conditions. However, ketone **270** seems to be less competitive in cyclization, as it does not cyclize under Birch reduction conditions. In contrast, the reduction with sodium naphthalenide gave stereoselective cyclization to five-membered rings. Compared with **270**, the analogous aldehyde **271** favored the reduction to the acyclic alcohols **276–278** over cyclization under sodium naphthalenide reduction conditions.

Cossy et al. published their findings on the intramolecular additions of ketyl radical anions to unsaturated systems, including alkenes, alkynes, allenes, and nitriles via photochemically induced electron transfer.¹²⁸ Electron donors utilized in the reaction include HMPA and Et₃N (Scheme 95). Compared with electroreductive cyclizations of allenic ketones (Scheme 92), the overall yield is higher; however, products resulted from both 5-*endo*- and 5-*exo-dig* cyclization modes.

In 1993, Gillmann described a regioselective reductive cyclization of ester-substituted allenic aldehydes mediated by SmI, ¹²⁹ 2 where the regioselectivity parallels previous results under similar conditions¹²⁷ (Scheme 96). The high **284/285** diastereoselectivity for allene **280** could be explained by the chelation of the samarium to both the ester and ketyl radical oxygen atoms. Replacing SmI₂ with *n*-Bu₃SnH and AIBN lowered the yield to **37%** and the *dr* to 5:1. For allene **281**, the competing reduction of either the aldehyde or the allene double bond could not be suppressed.

In 2005, the Molander group described a SmI₂-mediated regioselective reductive cyclization of allenic ketones and aldehydes to afford carbocycles and heterocycles (Scheme 97).¹³⁰ For allenes bearing a cyclic ketone substituent, [3.3.0], [3.4.0], and [4.4.0] ring systems were obtained in low to good yield. Uncyclized alcohol resulting from ketone reduction was an unavoidable byproduct in some cases. The lower cyclization yields and increased reduction products using β -keto esters, as compared with their ketone counterparts, were attributed to the lower energy of the SOMO in the ketyl radical anion of the former, leading to a larger SOMO–LUMO gap and retarding the rate-determining cyclization step. Heteroatoms, including nitrogen, were tolerated in the tether, resulting in moderate to excellent yield of the cyclized products.

In 2012, the Procter group described reductive radical cyclizations and cyclization cascades of unsaturated allenyl lactones in the presence of SmI₂–H₂O to afford fused [5.3.0] bicycles (Scheme 98).¹³¹ When allenyl lactones were treated with **8** equiv of SmI₂–H₂O at room temperature, cycloheptan-1,4-diols containing three new stereocenters were produced with excellent *dr* and in moderate to excellent yield. The use of 4 equiv of SmI₂–H₂O furnished the corresponding hemiketal products in modest to good yield and with high *dr*. Allenyllactones gave greater diastereoselectivity than their alkenyl and alkynyl counterparts; the higher *dr* and preference for the formation of the cycloheptanol and hemiketal products are explained further in Scheme 99.

The reduction of the ester group in lactone **294** or **296** by SmI₂–H₂O affords a ketyl radical anion **298**, where the radical resides in the axial position, due to the stabilization by the anomeric effect. A 5-*exo-dig* cyclization, reduction, and protonation affords hemiketal **299**, which ring-opens to enone **300**. Another single-electron reduction of **300** yields the ketyl radical anion **301**. The diastereoselective protonation and reduction of **301** furnish enone **302**, which undergoes diastereoselective protonation to deliver **303**. In the presence of excess SmI₂–H₂O, **303** is converted to a cycloheptan-1,4-diol; otherwise, the process stops at the hemiketal **299**. Alkenyllactones result in a lower *dr*, as the diastereoselectivity is established during the formation of the seven-membered ring, as opposed to “post-cyclization”.

The Procter group further demonstrated reductive cyclization cascades of lactones that bear appropriately positioned allenes and alkenes to afford [5.3.0]- and [4.2.1]-bicyclic ring systems (Scheme 100). The [5.3.0] bicycles, containing four new stereocenters, were obtained in good to excellent yield and with moderate to excellent *dr*, whereas the [4.2.1] bicycles were obtained in moderate yield and with moderate *dr*.

3.1.2. Other Carbon-Centered Radicals.—The Crandall group extensively studied the intramolecular addition of carbon-centered radicals to allenes during the 1980s and early 1990s. In 1982, they reported their first study of the reactivity of homoallenyl radicals generated from homoallenyl iodides in the presence of *n*-Bu₃SnH.¹³² Theoretically, four products **305–308** could be generated, as illustrated in Scheme 101.

In most cases, reactions of homoallenyl iodides with *n*-Bu₃SnH predominantly gave the corresponding acyclic allene from hydrogen abstraction. Only vinyl cyclopropanes result from cyclization; no **307** or **308** was observed. For allenes studied by Crandall, the preference for 3-*exo-trig* cyclization is higher than that for the analogous olefinic counterpart (cyclopropylcarbinyl radical), which tends to rearrange to the corresponding cyclopropyl radical. (See Scheme 102.) For allene **304c**, the cyclization proved more facile when compared with allenes that lack substituent branching. The ring-opening process was readily reversible, as evidenced by small amounts of unbranched acyclic allenes formed from the isomerization of cyclopropyl vinyl radical intermediates.

The reversibility of the 3-*exo-trig* cyclization of a homoallenyl radical was tested by subjecting deuterated allene **309** to *n*-Bu₃SnH in mineral oil at room temperature. More than 95% of the deuterium was retained at the homoallenyl position, suggesting that the cyclization is irreversible.

The cyclic vinyl iodide **310** was subjected to different reaction conditions to study the interconversion between the homoallenyl and the vinyl cyclopropane radical. On the basis of the product ratios, it was proposed that ring opening is slower than H-atom abstraction at room temperature. When the temperature was increased to 80 °C, the amount of ring-opened product **311** increased, indicating a large activation barrier for isomerization between the two radicals. In contrast, the interconversion between the cyclopropylcarbinyl radical and the homoallylic radical is fast; no *n*-Bu₃SnH-trapped cyclopropane product was observed.^{133,134}

In 1984, the Crandall group used allenic bromides and iodides **313a–d** as precursors to generate carbon-centered radicals.¹³⁵ The tether length between the halide atom and the proximal allene carbon was altered to determine the impact on the cyclizations of these reactive intermediates (Scheme 103). Four products were isolated, where **314** and **315** result from the cyclization of an allylic radical generated from the initial attack of the carbon radical on the central allene carbon. The cyclization product **317** is formed from the vinyl radical intermediate resulting from the attack on the proximal allene carbon. Finally, **316** forms from the competing reduction of the homoallenyl radical by *n*-Bu₃SnH.

As shown in Scheme 103, the regioselectivity and cyclization efficiencies were strongly dependent on the tether length and the size of the resulting ring. As expected, as the chain length increases, the cyclization efficiencies decrease. The regioselectivity was not dependent on the stability of the radical intermediate, similar to previous reports on the intermolecular radical attack of allenes.¹³⁶

When *n* = 1 (**313a**), cyclization was faster than H-atom abstraction, giving a low yield of **316** under neat conditions. Crandall suggested an early transition state for the cyclization, where

conformational features dictate whether the radical attacks the central or the proximal allene carbon. The absence of bond angle distortions in the transition state when attack occurs at the central allene carbene favors the formation of **314** and **315** over **316**.

When $n = 2$ in **313b**, the carbon radical cyclizes slowly as compared with **313a**; this was confirmed by the generation of **316**, even in dilute solution. The formation of **317** was 1.6 times faster than the formation of **314** and **315** based on the product ratio. The preference for the formation of the smaller ring was rationalized using the same arguments proposed by Beckwith for the cyclization of 5-hexenyl radicals.¹³⁷

Increasing the tether to $n = 3$ (allene **313c**) resulted in faster rates of hydrogen abstraction. Cyclization favored the formation of **317** over **314** and **315**; the 1,5-hydrogen transfer in the acyclic allenic radical accounted for the minor product 2-methyl-2,4-nonadiene. When $n = 4$ (allene substrate **313d**), hydrogen abstraction was the dominant pathway, with minor products observed from acid-catalyzed isomerization of the allene.

In 1991, the Crandall group published another study on the reduction of allenyl iodides with $n\text{-Bu}_3\text{SnH}$.¹³⁸ In contrast with the precursors utilized in their previous study,¹³⁵ these substrates contained radical stabilizing groups attached to the proximal allene carbon, including $\text{P}(\text{O})\text{Ph}_2$, $\text{S}(\text{O})\text{Ph}$, and SO_2Ph . The introduction of radical stabilizing groups had a significant impact on the regioselectivity and the cyclization rate. As shown in Scheme 104, four products could potentially be formed from the allenyl radical: attack at the central allene carbon to afford **321** and **322**, on the proximal carbon to yield **324**, and hydrogen abstraction to give **323**.

When $n = 1$ (allene **320a**), the product distribution parallels that of analogues **304a** and **304b** (Scheme 101); the major product was **323**. Any observed cyclization products resulted from a 3-*exo-trig* cyclization mode. When substrates with $n = 2$ (allene **318a**, **319a**, and **320b**) were compared with analogue **313a** (Scheme 103), a preference to attack the central allene carbon was maintained, but allenes substituted with electron-withdrawing *Z* groups (Scheme 104) preferred 5-*exo-dig* over the 5-*endo-dig* cyclization mode. The cyclization rate was increased, and no H-atom abstraction product **323** was observed. When $n = 3$, the radical formed in the analogue **313b** attacked both the central and proximal allene carbons, whereas *Z*-substituted allenes **318b**, **319b**, and **320c** gave products resulting only from attack at the central allene carbon. The ratio of cyclization was increased, and no H-atom abstraction product **323** was observed.

When $n = 4$, the analogue **313c** mainly gave the hydrogen abstraction product **316**. Attack on the proximal allene carbon was favored to furnish cyclization product **317**. Again, the addition of an electron-withdrawing *Z* substituent (allenes **319c**, **320d**) completely altered the regioselectivity to favor attack on the central allene carbon to form a seven-membered ring in **321**. When $n = 5$ (allene **320e**), cyclization did not occur, and the major product was the acyclic allene **323** from hydrogen atom abstraction.

In 1994, Balasubramanian et al. reported a regioselective synthesis of 3-ethenyl-2,3-dihydrobenzofurans and 3-ethenyl-2,3-dihydroindoles from *o*-haloaryl allenyl methyl ethers

and amines.¹³⁹ In the presence of *n*-Bu₃SnH, aryl halides readily undergo 5-*exo-trig* cyclization at the proximal carbon of the allene **325** to afford the corresponding products **326** in good yield (Scheme 105). For allenyl ether substrates, <10% of products formed from 6-*exo-dig* cyclization were detected. In all cases, no reduction products were observed.

In 1998, Renaud and coworkers developed a diastereoselective Ueno–Stork-type radical cyclization of bromoacetals, where diastereoselectivity is controlled by the acetal center.^{25,140} The protocol is applicable to both alkene- and allene-tethered bromoacetals, with an allene example illustrated in Scheme 106. The chemistry is initiated by tributyltin hydride and triethylborane-oxygen to generate a carbon-centered radical, which subsequently undergoes 5-*exo-trig* cyclization. The *cis* diastereoselectivity is best explained by intermediate **328**, in which the alkoxy group preferentially occupies the axial position. Employing the (1*R*,2*S*)-2-phenyl-cyclohexyl group as a chiral auxiliary enabled the enantiomerically and diastereomerically pure allene **327** to be converted to the enantiomerically pure lactone **328** in 50% overall yield in a cyclization/hydrolysis/oxidation sequence.

In 2004, Sha published a photoinduced regioselective radical cyclization of α -iodocycloalkanones **330** bearing an allenic substituent, to give spirocyclic rings **331** in moderate to good yield¹⁴¹ (Scheme 107a). The addition of (Bu₃Sn)₂ to the reaction affords the same products, albeit in lower yield for allenes **332b–d**. Extending the scope to the formation of [3.3.0]- and [4.3.0]-bicyclic ring systems of the form **333** and **334** gave products in moderate yield and with moderate *dr* (Scheme 107b). A 1,5-H transfer in vinyl radical **336**, formed from the 5-*exo-trig* cyclization of **335**, was proposed as a key step in the formation of the allylic iodide isomer (Scheme 107c).

In 2005, the Hsung group developed a highly regioselective radical cyclization of allenamides mediated by *n*-Bu₃SnH.¹⁴² Aryl iodides were employed as radical precursors to synthesize derivatives of isoquinoline, indane, naphthalene, and isoindole scaffolds (Scheme 108). The intermediate aryl radical selectively attacks the central carbon of the allene in all cases. However, when a carbonyl group was inserted adjacent to the nitrogen, as in **337** and **340**, attack at the proximal allene carbon was favored, albeit with moderate selectivity and yield (Scheme 108). Hsung proposed that this change results from the ability of the carbonyl group to alter the trajectory of attack via structural constraints. It is worth noting that the introduction of a chiral auxiliary into allene **340** furnished only one diastereomer as the product.

In 2007, Guo et al. published the first computational study describing the factors that control the regiochemistry in radical cyclizations of allenes.¹⁴³ The ONIOM(QCISD(T)/6–311+G-(2df,2p)UB3LYP/6–311+G-(2df,2p)) method was utilized and gave computational results consistent with experimental results (Schemes 101 and 103). The reliability of using this computational method to handle radical cyclization reactions was demonstrated in their previous work.¹⁴⁴ In all cases, distal attack on C1 was neither kinetically nor thermodynamically favored. On the basis of the data presented in Scheme 109, when X = CH₂ and *n* = 2 (allene **343b**), the product **347** that results from the attack on the central carbon C2 was predicted to be both thermodynamically and kinetically preferred. When *n* =

3 (allene **343c**), the small difference ($11.6 - 10.7 = 0.7$ kcal/mol) in $G^\ddagger$ between **346** and **347** indicated the potential to form a mixture of **346** and **347** despite the fact that G is lower for the formation of **347**. For allene **343a**, the case was further complicated by the fact that **346** is kinetically favored, whereas **347** is thermodynamically favored. However, the calculated free energies of activation for the hydrogen abstraction of Me_3SnH with allene **343a** and cyclopropyl radical **348** (13.8 and 11.6 kcal/mol) were both lower than the $G^\ddagger$ value of **347** (17.9 kcal/mol), suggesting a preference for proximal attack, which is consistent with the experimental results. (See Scheme 101.)

When $n = 2$ in the allenes **344a** and **345a**, attack at the central C2 carbon to form **347** is kinetically and thermodynamically favored for both nitrogen- and oxygen-centered radicals. For allenes **344b** and **345b** with $n = 3$, both proximal and central attack products were expected for nitrogen- and oxygen-centered radicals, as computations predicted $G^\ddagger$ of <1.6 kcal/mol in both cases.

Intrinsic and thermodynamic energy barriers were calculated from activation energy barriers using the Marcus theory.^{145–147} The regioselectivity was predicted by balancing intrinsic and thermodynamic barriers (Scheme 110). Guo et al. discovered that $G_{\text{intrinsic}}$ values were always lower for the formation of **346** as compared with **347**, whereas a lower G_{therm} term predicts a preference to proceed through allylic radical intermediate **347**.

Lastly, Guo et al. calculated $G^\ddagger$ values for the radical cyclizations of allenes **343b** and **343c** to model the effects on the regioselectivity in the presence of various substituents on C1 or C3, including Ph, OMe, Cl, CN, and C(O)Me. When $n = 2$ (allene **343b**), substitution on C1 or C3 did not affect the regioselectivity of the preferred radical attack on the central allene carbon. However, when $n = 3$ (allene **343c**), certain substituents at either C1 or C3 were able to reverse the regioselectivity. The substitution of CN or C(O)Me at C1 reversed the preference for vinyl radical formation to favor the formation of the allylic radical. For C3 substitution, all of the groups examined reversed the regioselectivity to favor attack of the central carbon, providing computational support for the results obtained from Crandall's 1991 paper. (See Scheme 104.)

In 2007, Alcaide and Almendros described a regioselective radical cyclization of enantiopure and racemic 2-azetidinones tethered to bromovinyl and haloaryl allenes to afford fused bi- and tricyclic β -lactams in moderate to good yield¹⁴⁸ (Scheme 111). The vinyl and aryl radicals selectively attacked the central allene carbon to form nonconventional β -lactams.

In 2008, Huang et al. reported Ti(III)-induced intramolecular radical cyclizations of epoxyallene ethers and amines for the synthesis of tetrahydrofuran and pyrrolidine derivatives.¹⁴⁹ Various monosubstituted allenes **349** and **351** were converted to the desired products **350** and **352** in good yield. The epoxide C–O bond was homolytically cleaved to form an alkyl radical **353**, which regioselectively adds to the proximal allene carbon to form the five-membered ring (Scheme 112).

In 2014 and 2015, Yamashita et al. described a regioselective radical cyclization of allenylanilines **354**¹⁵⁰ and allenyl aryl iodides **356** to afford indole and dihydroindole derivatives in moderate to good yield.¹⁵¹ A mixture of the single-electron reductant SmI₂ and an aryl iodide generated the corresponding aryl radical, which cyclized in a regioselective fashion at either the central or the proximal carbon, depending on the length of the tether between the proximal allene carbon and the aryl iodide (Scheme 113). The regioselectivity was consistent with previously reported literature examples (see Scheme 108), albeit displaying a different radical initiation pathway. Yamashita et al. also developed an oxidation protocol employing DDQ, which converts the dihydroindole derivatives **357** to the corresponding hydroindoles **358** in modest to good yield.

3.2. Nitrogen- and Oxygen-Centered Radicals

Compared with intramolecular radical cyclizations of allenes induced by carbon-centered radicals, instances of reactions initiated by nitrogen-centered radicals are scarce. Nonetheless, two examples have been reported by Hatem, one of which¹⁵² is discussed in more detail in section 4.3. In this report, the chemoselectivity of an in-situ-generated stannyl radical was complicated by attack at both the central allene carbon and the oxime benzoyl group. In 2001, Hatem described a method to improve the chemoselectivity of the stannyl attack by employing a more stannophilic dithiosemicarbazide precursor, resulting in successful syntheses of 3*H*-pyrroles and alkylidenepyrrolines¹⁵³ (Scheme 114a). Refluxing a mixture of allenyl dithiosemicarbazide **359**, *n*-Bu₃SnH, and AIBN in cyclohexane afforded the unsaturated five-membered rings **360** and **361** in good yield. Because of the instability of certain products on silica gel and poor separations, a one-pot cyclization/reduction/protection protocol was developed to convert allenes **362** directly to pyrrolidine derivatives **363** (Scheme 114b). Hatem proposed that the unpaired electron on the iminyl nitrogen occupies a 2p orbital orthogonal to the C–N double bond; this predicts that 5-*exo* cyclization should be favored over the 5-*endo* mode due to the better overlap of the unpaired electron orbital with the π^* orbital of the distal allene double bond.

In 2010, Cramer and coworkers developed a heteroatom-induced Grob-type fragmentation of vinyl triflates to form allenes containing a terminal carbonyl functionality;¹⁵⁴ one example is illustrated in Scheme 115a. Cramer applied this fragmentation method to **364** to form the hydroxamic acid **366** in good yield. Subjecting **366** to intramolecular oxidative radical cyclization conditions induced a 6-*exo-trig* cyclization to form the vinyl radical intermediate **368**, which was trapped by molecular oxygen to form the hydroperoxide **369**. The rearrangement of **369** gave the α -hydroxy ketone **367** in moderate yield (Scheme 115b).

In 2015, Liu et al. developed a one-pot synthesis of α -O-, S-, and N-substituted 4-methylquinoline derivatives via a Cu(I)-catalyzed aerobic oxidative radical cyclization of *N*-hydroxyaminoallenes **370** in the presence of various nucleophiles (Scheme 116).¹⁵⁵ The first step of the synthesis proceeds through a radical cyclization pathway to afford tautomer **371** or **372** (or, in some cases, tautomeric mixtures of **371** and **372**), which then cyclizes to the corresponding 4-methylquinolines **373** in moderate to good yield upon the treatment with polyphosphoric acid (PPA) in hot toluene.

Selected mechanistic studies, as shown in Scheme 117, indicate a radical-type pathway for this chemistry. In the presence of 10 mol % TEMPO under a N₂ atmosphere, *N*-hydroxyaminoallene **374** gave a mixture of tautomers **375** and **376** in 80% yield, together with 4% of the TEMPO-trapped product. Liu proposed that the amidoxy radical **378** was produced from a Cu(I)/O₂ oxidation of **374**. The oxygen-centered radical of **378** attacks the central allene carbon to form an allylic radical intermediate **379**, which abstracts a hydrogen atom from **374** to yield **380**. The Cu(I)/O₂ oxidation of **380** gives **381**, which upon nucleophilic attack generates **382**; a final 1,2-H shift of **382** gives the ring-opened product.

Overall, the regio-, site-, and stereoselectivities of the intramolecular addition of carbon-, nitrogen-, and oxygen-centered radicals to allenes depend on the specific substrates and radical precursors. Nonetheless, the regioselectivity typically responds to the tether length between the attacking radical and the allene carbon. A general rule of thumb for predicting the regioselectivity is summarized in Scheme 118. When $n = 1$, the C-, N-, and O-centered radicals add to the C2 of allene to favor the formation of a five-membered ring. When $n = 1$, addition to C3 become the major pathway, with the only exception being shown in Scheme 108; in this case, $n = 2$, but products formed from C2 addition are reported as the major product. To reverse the addition of C-centered radicals from C3 to C2 ($n = 2, 3, 4$), radical stabilizing groups are required at C3, including P(O)Ph₂, S(O)Ph, and SO₂Ph (see Scheme 104).

4. TANDEM RADICAL CYCLIZATION REACTIONS

This section reviews tandem radical cyclization reactions of allenes, which typically display more complicated chemo-, regio-, and stereoselectivities due to the presence of extra sites of unsaturation tethered to the allene functionality. Typical substrates employed for such tandem reactions include allene-enes, allene-ynes, bis(allenes), aryl allenes, and their derivatives. Tandem reactions of allenes can be broadly divided into two types. In the first type (Type 1, Scheme 119), the radical adds either to the allene double bond (path a) or to the unsaturated functionality tethered to the allene (path b) to form a carbon-centered radical intermediate; the radical then attacks the unsaturated functionality of the allene tether or the allene itself, respectively. In the second type (Type 2), initiation first generates a radical in the allene tether; this intermediate radical species then either adds to unsaturated functionality in the allene tether (path a) or to the allene itself (path b); the resultant carbon radical then adds to any remaining unsaturated functionality.

4.1. Tandem Radical Cyclizations Initiated by Carbon-Centered Radicals

In 2005, the Hsung group explored tandem radical cyclizations with allenamides **383** and **389** (see Scheme 108;¹⁴² Scheme 120). Products of the tandem radical cyclization of **383** include **386** and **388**, whereas allenamide **389** did not undergo tandem cyclization, furnishing **390** instead. The aryl radical generated from **389** regioselectively attacks C2; 6-*exo-dig* cyclization establishes the 1,2-dihydroisoquinoline core in **390**.

Treatment of the aryl iodide **383** with *n*-Bu₃SnH and AIBN produced the corresponding aryl radical **384**, which attacks the proximal C1 of the allene to afford **385**. The vinyl radical **385** either undergoes 5-*exo-trig* cyclization or hydrogen abstraction to yield **386** or **387**,

respectively. Alternatively, rotamer **384'** may undergo 7-*exo-trig* cyclization onto the pendant alkene to form **391**. This intermediate is responsible for the formation of the bridged heterocycle **388** via attack at C2 of the allene (Scheme 121). Hsung reasoned that the allenamide **389** does not participate in tandem cyclization due to faster hydrogen abstraction by the stable allylic radical **392**.

In 2012, the Ma group developed a tandem radical addition/cyclization reaction of allene-*enes*.¹⁵⁶ Traditionally, radicals add in a chemoselective fashion to an allene over a competing alkene group, proceeding in an “allene-to-alkene” fashion.^{119,157} In contrast, Ma reported that a perfluoroalkyl radical, generated from perfluoroalkyl iodide, chemoselectively attacks the alkene moiety of **393**; the subsequent 5-*exo-trig* cyclization of the resulting alkyl radical occurs at C1 of the proximal allene (Scheme 122) to give vinyl iodides of the form **394**, which undergo dehydroiodination with TBAF to form the corresponding allenes **395**.

Wang et al. reported the synthesis of functionalized phenanthrenes **398** via the oxidative cyclization of 2-allenyl-1,1'-biphenyls **396** with α -carbonyl alkyl bromides **397** in the presence of catalytic amounts of CuCl and excess Ag₂CO₃.¹⁵⁸ Various alkyl bromides bearing α -ester, amide, and ketone groups were tested, resulting in moderate yield of the corresponding phenanthrene products. Allenes and 1'-phenyl rings substituted with a variety of groups were also examined to showcase the functional group compatibility (Scheme 123).

In the presence of stoichiometric amounts of TEMPO or BHT, only trace amounts of the desired phenanthrenes were obtained. Products derived from the trapping of **397** with TEMPO or BHT were observed by GC-MS. On the basis of previous literature precedent and experimental evidence, Wang proposed the mechanism shown in Scheme 124. The reduction of **399** by Cu(I) and Ag(I) yields radical species **400**, which attacks the less substituted terminal allene carbon in a regioselective fashion to afford vinyl radical **401**. The cyclization of **401** assembles the phenanthrene scaffold of **402**, which is subsequently oxidized to **403** by Cu(II) and Ag(II). The deprotonation of **403** gives the final product **404**.

4.2. Tandem Reactions Initiated by Sulfonyl Radicals

In 1995, Hatem described the chemoselective radical addition of tosyl bromide to allene-*enes* of the form **405** to afford vinyl sulfones **406**.¹⁵⁷ The tosyl radical selectively adds to C2 to yield an allylic radical, which adds to the alkene moiety in a 5-*exo-trig* fashion in the majority of the allenes that were examined (Scheme 125).

In the case of allene **407**, an alternative pathway involves the dehydrobromination of the addition/cyclization product to yield the alkene **408**. For allene **409**, 6-*endo-trig* cyclization competes with the 5-*exo-trig* pathway to deliver products **411** and **412** (Scheme 126).

In 1999, Hatem described radical addition/cyclization of tosyl bromide to β -allenyl ketoximebenzoates of the form **413**.¹⁵⁹ (Scheme 127). The allenes examined in the reaction furnished products **414–417** through the mechanisms proposed in Scheme 128. The addition of the in-situ-generated tosyl radical to the allene occurred in the same manner as described in previous reports (see Scheme 125), involving the chemoselective addition to the central

allene carbon to form the allylic radical **418**. Depending on the substitution pattern of the β -allenyl ketoximebenzoates, differing reaction pathways give rise to the cyclization products **415–417**. It is noteworthy to point out that **417** is produced via the 6-*endo-trig* cyclization of **418**, where the regioselectivity is attributed to steric factors that disfavor attack by the C1 radical on the oxime carbon.

Kang et al. reported tandem radical addition/cyclizations of bis(allenes) **419** initiated by *p*-tosyl radicals to afford the more stable trans-fused cyclopentanes **420** bearing vinyl sulfone, bromide, or selenide substitution¹⁶⁰ (Scheme 129). The reaction presumably proceeds in a manner similar to that of previous reports (see Scheme 61), with regioselective attack of the *p*-tosyl radical occurring on one of the central allene carbons to yield an allylic radical intermediate, which then attacks the proximal carbon of the remaining allene.

In 2017, Li et al. reported a diastereoselective synthesis of polycyclopentanoids, including diquinanes and triquinanes, that proceeds via tandem radical addition/cyclization of allenes bearing electron-deficient olefins; these reactions are initiated by thiyl radicals¹⁶¹ (Scheme 130). A catalytic amount of ABVN (2,2'-azobis(2,4 dimethylvaleronitrile)) generates a phenyl thiyl radical, which attacks the central allene carbon in a chemo- and regioselective manner to form a stabilized carbon-centered radical **421**. Intermediate **421** undergoes a tandem 5-*exo-trig*/5-*endo-trig* cyclization to establish the diquinane scaffold. Two quaternary bridgehead stereogenic centers are installed in a single step.

Various 1,1-disubstituted allenes, bearing aldehyde or ester groups on the olefin, were tested to afford diquinanes **423** in moderate to good yield and with good to excellent *dr* (Scheme 131a). Aryl thiols bearing various electron-donating and electron-withdrawing groups (EDGs and EWGs) were also examined to test the effect of electronics on the reaction (Scheme 131a). Triquinanes **425** and **427** were prepared in a similar fashion by employing cyclo-alkyl-substituted allenes **424** and the enantiomerically enriched allene **426** (Scheme 131b).

4.3. Tandem Reactions Initiated by Sn Radicals

In 1992, the Hatem group described a tandem addition/cyclization of β -allenyl *O*-methyloximes **428** initiated by a tributyltin radical. The resultant products were cyclopentenes of the form **429**, bearing an amine substituent and a vinyl stannyl functionality.^{162,163} A HCl-facilitated destannylation transforms **429** to **430** (Scheme 132). A limited scope of alkyl-substituted allenes was examined; however, in these cases, the tributyltin radical regioselectively attacks the central allene carbon to form an allylic radical, which then cyclizes onto the oxime carbon to establish the cyclopentene backbone.

In 1994, the Hatem group described a similar tandem addition/cyclization initiated by a tributyltin radical using *N,N*-dimethyl β -allenyl hydrazones **431** as radical acceptors^{152,163} (Scheme 133a). Hydrostannylation was observed in most cases to give **432** as the major product. The triene **433**, arising from tributyltin radical addition to C3 of **431**, followed by 4-*exo-trig* cyclization and fragmentation, was noted in some instances. Hatem also explored the potential for intramolecular stereo-control by installing a SAMP chiral auxiliary on the

hydrazone. In this case, subjecting **434** to the same conditions gave **435** in a *de* of 50% (Scheme 133b).

In 1997, the Hatem group presented two additional examples of the tandem addition/cyclization of allene-tethered *O*-benzyl oximes **436a,b** initiated by tributyl tin radicals.¹⁶³ Increasing the length of the tether between C3 of the allene and oxime by one carbon (Scheme 134) in **436** showed that the regioselectivity of the initial *n*-Bu₃Sn radical attack still favors the less substituted allene C1. However, minor amounts of product arising from the attack of the *n*-Bu₃Sn radical at C2 of the allene were noted. The authors reasoned that the exclusive C1 attack in allenes with *n* = 1 was due to the disfavored 4-*exo* or 6-*exo* modes of the cyclization of intermediate **442** as compared with the favored 5-*exo* cyclization of **441**. In addition, the attack of the *n*-Bu₃Sn radical on the sp-hybridized central allene carbon leads to more electron repulsion as compared with the attack on the sp²-hybridized carbon.

In 2000, Hatem subjected β -allenylbenzoyloximes **443** to *n*-Bu₃SnH under radical conditions and found that the product distribution depended strongly on the allene substitution pattern. Both steric and polar effects influenced the reaction pathway.¹⁵² For example, when R³ = H in **443**, cyclopentene **444** was isolated exclusively, suggesting that the major pathway involved the chemo- and regioselective addition of the tin radical to the central allene carbon, followed by 5-*exo-trig* cyclization (Scheme 135a). When *n*-Bu₃SnH was employed, the yield of **444** decreased when C1 of **443** was sterically hindered; when R³ = Me, the cyclopentene was produced in good yield in some cases (Scheme 135b). When R³ = Ph or P(O)(OEt)₂, the 6-*endo-trig* cyclization product **446** dominates with allenes, where C1 is sterically hindered. Chemoselectivity is an issue, as indicated by the competitive formation of the iminyl radical intermediate **447**, which furnishes **448** and **449** (Scheme 135c,d). Notably, for allenes bearing an EWG (phenyl and phosphonate groups) on the oxime carbon, the 6-*endo* process outcompetes the 5-*exo* ring closure. Hatem attributed this change in regioselectivity to a β -substituent effect; that is, a nucleophilic radical preferentially attacks the carbon that is not substituted with the EWG.¹⁶⁴

In 2001, Hatem reported a *n*Bu₃Sn-radical-initiated tandem addition/cyclization of allene-tethered hydrazones and oximes using identical reaction conditions to previous reports.¹⁶⁵ As discussed in Scheme 136, the five-membered ring of **451** arises from attack of the tin radical at C2, followed by 5-*exo* cyclization of the attack of the resulting nucleophilic carbon radical on the oxime carbon. In contrast, the formation of **452** occurs via the initial attack of the Sn radical at C3, followed by 4-*exo* cyclization onto the oxime carbon. The attack of the Sn radical on C2 is followed by the nucleophilic attack of a carbon radical on the oxime nitrogen to deliver **453**. Regioselectivity in the carbon-based radical cyclization was rationalized by the steric and electronic effects of the R groups as well as the electron-withdrawing power of the Y group. (When $\sigma > 0$, Y is electron-withdrawing.)

A comparison of the σ values of the three Y groups (Scheme 136) indicates that the C=N of the oxime is most activated for attack by a nucleophilic radical when Y = OBz and most deactivated when Y = N(Me)₂. In precursors of the form **450** that bear the same Y group, increasing the sterics of R disfavors the 5-*exo* mode of cyclization. When the sterics of the R groups are similar (e.g., *i*-Pr vs CF₃), polar effects play a bigger role in determining the

regioselectivity; for example, a C=N bond that is more polarized by virtue of being attached to a polar group favors 5-*exo* cyclization. When Y = OBz, the favored 5-*exo* cyclization to the activated C=N is less sensitive to polar effects exerted by less hindered R groups, such as H, Me, and CF₃.

In 2003, Alcaide and coworkers described a tandem reaction of 2-azetidinone-tethered allenynes **454** and **456**. The reaction features an initial attack of a triphenyltin radical on an alkyne, followed by the attack of the resulting vinyl radical on the central allene carbon (Scheme 137).¹⁶⁶ Both racemic and enantiopure allenynes were subjected to Ph₃SnH, furnishing bicyclic β -lactams in moderate yield and with excellent stereoselectivity. Compounds **455** and **457** were proposed to form via the initial addition of a triphenyltin radical to the terminal alkyne carbon to give a vinyl radical intermediate, which subsequently cyclizes at C2 of the allene.

In 2007, Alcaide and coworkers extended their previous reports of triphenyltin-radical-promoted cyclizations of 2-azetidinone-tethered allenynes to bromovinyl and halo-aryl allenynes **458–464**, providing unusual bi- and tricyclic β -lactams **465–471** in a regio- and stereoselective fashion.¹⁴⁸ Subjecting **458–464** to Ph₃SnH and catalytic AIBN converts them to the corresponding vinyl or aryl radicals, which regioselectively attack the central allene carbon to form fused seven-membered rings (Scheme 138).

In contrast with previous substrates that contained no olefin tethered to the allene, Hayashi subjected the allene-ene **472** to a tin radical;¹¹⁹ **473** was obtained in moderate yield, resulting from the regio- and chemoselective addition of a dibutyltin radical to the central allene carbon (Scheme 139).

4.4. Tandem Reactions Initiated by Other Metal and Nonmetal Radicals

4.4.1. Silyl Radicals.—The Pattenden group developed a tris(trimethylsilyl)silyl-radical-promoted cyclization of alkenyl allenecyclopropanes **475** and **476** to produce [5.6.0]- and [6.6.0]-1,3-dienes **480** and **481**, which are desilylated by TBAF to form **482** and **483**, respectively.¹⁶⁷ The reaction pathway was proposed as shown in Scheme 140. The regioselective addition of the silyl radical to the terminal alkene carbon gave the alkyl radical **477**, which cyclized at C1 of the allene to form vinyl radical **479**. Fragmentation and radical ring opening of the cyclopropane ultimately furnished allene **479** in good yield. Interestingly, when *n* = 1, a prolonged reaction time converted **479** to its isomer **480/481**. Alternatively, heating pure **479** in the presence of AIBN gives **480/481** in similar yield. An allenecyclopropane fused with a cyclohexane (*n* = 2) was also compatible with the reaction conditions, giving **480/481** and **482/483** in moderate yields.

The Pattenden group studied the effect of the tether length between C1 of the allene and the internal alkene carbon (Scheme 141). When *n* = 3, no formation of seven-membered ring was observed; rather, **485** was isolated in 80% yield. When *n* = 1, only **486** was recovered; the lack of product formation was attributed to the steric demand of the bulky tris(trimethylsilyl) group. To study the chemistry of the system when *n* = 1, a similar primary alkyl radical was generated from iodide **487**. Instead of undergoing unfavorable 4-

exo cyclization, the radical intermediate engages in 1,4-H transfer and cyclopropane ring opening to give **490** in 43% yield.

4.4.2. Indium Radicals.—In 2008, Hayashi et al. described an indium-radical-initiated hydroindation of allene-enes **491** to produce cyclic **492** bearing a vinyl indium functionality.¹¹⁹ Subsequent protonation of **492** yields the corresponding alkene **493–497** in good-to-excellent yield and with moderate-to-good *dr* (Scheme 142a). The reaction was proposed to proceed through the initial addition of the indium radical to C2 of allene **491** to form the allylic radical **500**, which then undergoes a 5-*exo-trig* cyclization. Hydrogen abstraction of **501** by HInCl₂ regenerates the indium radical and furnishes the product **492**.

5. ALLENE CYCLIZATION INVOLVING POTENTIAL DIRADICAL INTERMEDIATES

Whereas sections 1–4 discuss the addition of carbon- and heteroatom-based radicals to allenes, there are other reactions of allenes that are likely to involve radical intermediates. As methods for the preparation of allenes continue to be reported on a regular basis, there is a high likelihood that these compounds will be of significant interest as key building blocks for the construction of complex polycyclic scaffolds, explorations of new chemical space, and the development of new reaction methodologies. Thus section 5 is focused on methods involving the generation of presumed diradical intermediates with allenes in reactions that include [2 + 2] cycloadditions, enyne–allene reactions, and several others. Reactions and mechanistic experiments supporting a stepwise diradical mechanism will be discussed, along with challenges and opportunities in improving the regio- and stereochemical control in these potentially powerful transformations.

5.1. [2 + 2] Cycloadditions

Methods that employ two alkenes in formal or concerted [2 + 2] cycloadditions are well-established, with several excellent reviews available that focus on reactions involving diradical mechanisms.^{168–170} In contrast, methods that couple an allene, alkene, or alkyne to an allene in a [2 + 2] fashion are less common but have been recently gaining attention because the methylenecyclobutane derivatives can be employed as useful precursors to natural products and other complex molecules.¹⁶⁹ Known [2 + 2] reactions involving an allene and another π -system are readily categorized by subdividing these transformations into three categories: thermal cyclizations, photo-cyclizations, and metal-catalyzed cyclizations. The next section focuses on aspects of thermal [2 + 2] cycloadditions; whereas the bulk of the reactions are proposed to proceed through a diradical mechanism, an improved understanding of this chemistry through additional mechanistic studies is desirable. Nonetheless, useful insight into reactivity patterns does emerge from a discussion of how the substrate structure influences the regio-, chemo-, and stereoselectivities of the [2 + 2] reaction as well as isomerization of the precursor allenes, competing dimerization, and other side reactions.

5.1.1. With Allenes.—Allene [2 + 2] cycloadditions have been demonstrated under thermal conditions. However, recent reports are scarce, likely due to the harsh temperatures

and further reactions of the initial products, as discussed in more detail later. Despite these limitations, the mechanisms of allene–allene [2 + 2] reactions remain a topic of debate that may be resolved by further experimental investigations. Two mechanistic possibilities include a concerted [$\pi^2_s + \pi^2_a$] cycloaddition or a stepwise diradical [2 + 2] cycloaddition. Evidence disfavoring the concerted pathway, as discussed in section 5.2, arises from experimental results showing that the regioselectivity of the observed products aligns better with a diradical mechanism. The high level of stereospecificity can be rationalized by either the fast ring closure of the diradical intermediate or the generation of such species via individual stereospecific steps.¹⁷¹ This section focuses on the rationale for diradical mechanisms involving allene dimerization reactions.

Lebedev was the first to report the products of allene dimerization in the early 20th century (Scheme 143).^{172,173} Depending on the reaction conditions, dimers **502** and **503**, trimers **504–507**, or oligomers from reactions of **504–507** with **17c**, were observed. Yields of **503–507** are reduced when the thermally induced dimerization is carried out in dilute solutions of benzene, giving **502** in excellent yield.¹⁷⁴

Analogous to thermal [2 + 2] reactions of allenes and alkenes with alkynes, allene–allene cycloadditions are proposed to proceed via stepwise diradical pathways, as opposed to concerted [$\pi^2_s + \pi^2_a$] mechanisms, through plausible intermediates highlighted in Scheme 144. Center–center attack (C2–C2) involving **17c** results in a perpendicular, freely rotating diradical **508** that contains two stabilized allylic radicals. Minimization of steric interactions in the transition state suggests that the process occurs through a “cross-like configuration”, eventually resulting in a perpendicular arrangement of the allyl radicals in **508**. Radical recombination results in ring closure to **502**. An alternative pathway to **502** involves the terminal–terminal attack (C3–C3) of **17c** to give a bisvinyl diradical intermediate **509**. A minor byproduct, 1,3-dimethylenecyclobutane **503**, is often observed under thermal conditions and is proposed to arise from a C2–C3 attack of **17c** to give **510**, followed by ring closure.

Support for a diradical pathway and investigation into the plausibility of intermediates **508–510** has been demonstrated both computationally and experimentally. Johnson has carried out computational analysis at the CCSD(T)/6–311+G(d,p)//B3LYP/6–311+G(d,p) level and identified two possible transition states for **508** (Scheme 144) that differ in the geometry of the approach of the allenes.¹⁷⁵ Furthermore, a concerted transition state was not located. The energetically lower transition state to form **508** results from an orthogonal arrangement of the reacting allene (calculated energy barrier of 34.5 kcal/mol); the alternative transition state arises from the “side-on” reaction of the two allenes, resulting in a steric clash of the hydrogens in **17c** and a higher energy barrier (40.3 kcal/mol). The barrier for the formation of diradical **510** was calculated to be 41.5 kcal/mol, much greater than C2–C2 attack. The higher energy barrier is attributed to the instability of the vinyl radical in **510**. Presumably, the presence of two vinyl radicals imparts an even higher energy barrier to **509** as compared with **510**; therefore, **502** is assumed to arise solely from **508**.

Experimental evidence of stepwise diradical pathways has been provided by several groups.^{176,177} Kiefer compared the ratio of products obtained from the thermal dimerization of 2-

methyl-2,3-butadiene **24** and the thermolysis of 4,5-dimethylene-3,3,6,6-tetramethyl-3,4,5,6-tetrahydropyridazine **511** (Scheme 145). The dimerization of **24** yields regioisomers **512**–**514**, with **512** as the major component. To investigate if the thermal dimerization of allenes proceeds through a bisallylic diradical intermediate, **511** was subjected to either thermal or photochemical conditions. Under thermal conditions, the product ratios obtained with **511** were identical to those obtained using **24**, indicating that the bisallylic diradical **508** (Scheme 144) is a likely intermediate.

Other molecules have been used to probe the involvement of diradicals in a [2 + 2] reaction of allenes (Scheme 146). For example, Gajewski demonstrated that the pyrolysis of 1,2-bis(dideuteriomethylene)cyclobutane **515** results in a skeletal rearrangement to **518** and **519**, potentially via **516**.^{178,179} Four fates for **516** were proposed; at low conversions, the ratio of **518/519** was close to 2:1, indicating the internal rotation about the central bond of **516**. The pyrolysis of a 1:1 mixture of **515** and 1,2-bis(methylene)cyclobutane **502** gave little to no dideuterated material, indicating that the ring closure of **516** is faster than cleavage, as no **517** was observed.

To investigate the potential for diradical pathways in intramolecular allene [2 + 2] cycloadditions, Becher et al. utilized meso and racemic bisallenes **520**–**521** (Scheme 147).¹⁸⁰ Central–central attack in both **520** and **521** gives **522** and **523**, respectively. These intermediates undergo ring cleavage to furnish **526** and **529** from **522** and **523**, respectively. In addition, **522** and **523** can interconvert to **524** and **525** to establish planarity and increase alkene conjugation. Whereas **524** and **525** undergo ring closure to **527** and **528**, ring strain and high reaction temperatures can trigger ring opening back to the diradicals. The observation of **524**–**529** in the thermolysis of **520** and **521** indicates that bond rotation is competitive with ring closure as well as cleavage of the 1,2-dimethylenecyclobutane. This is supported by noting that estimates of the energetics of reaction/activation energies for ring closure and bond rotation give similar values (12–14 kcal/mol rotation barrier for allylic radicals and 10 kcal/mol for ring closure of 1,2-dimethylenecyclobutane).

5.1.2. With Alkenes.—In contrast with allene–allene [2 + 2] cycloadditions, thermal alkene–allene reactions have been extensively studied. Competing allene–allene dimerization is prevented by performing these reactions under dilute conditions or by using an excess of the alkene. As discussed later, regiocontrol in the addition has been demonstrated intramolecularly to form polycyclic scaffolds. However, intermolecular reactions suffer from poor regioselectivity and are ideal for investigating the mechanistic aspects of this chemistry.

Analogous to allene dimerization, [2 + 2] allene–alkene cycloaddition may proceed through either a concerted or a stepwise pathway (Scheme 148).^{181,182} Concerted reactions likely involve transition states **537** → **540**, including a [$\pi 2_s + \pi 2_a$] arrangement to yield a stereospecific cyclization. However, it is postulated that the transition states **537** and **538** of a [$\pi 2_s + \pi 2_a$] process will significantly differ in their respective heats of formation, leading to different energetic barriers for the formation of **532** and **533**, respectively. Variable temperature experiments show similar **532/533** ratios across a range of temperatures, indicating that a concerted pathway is not likely involved. Furthermore, the expected

chemoselectivity for a $[\pi 2_s + \pi 2_a]$ process does not match the experimental outcome, where an electron-deficient alkene reacts with the more electron-rich olefin of the allene and vice versa.

A concerted $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ process (**539** and **540**, Scheme 148) was also considered,¹⁸³ where the alkene interacts with the allene in a six-electron transition state. The expected and observed chemoselectivities are congruent, as the cyclobutane formation occurs at the less hindered site of an alkyl-containing allene. However, other factors, including reaction rates, kinetic isotope effect (KIE) experiments, and product ratios, weaken the support for a concerted pathway in favor of a stepwise diradical process. Furthermore, concerted $[\pi 2_s + \pi 2_s]$ processes are forbidden according to the Woodward–Hoffmann rules.¹⁸⁴

Two stepwise pathways are typically considered for $[2 + 2]$ alkene–allene cycloadditions, diradical and ionic, with an ionic mechanism favored in metal-catalyzed reactions.¹⁸⁰ Potential intermediates are highlighted in Scheme 148, where a new σ -bond forms at the central carbon of **530** to give **534** (via C2) or at one of the terminal allene carbons to furnish **535** (via C1) or **536** (via C3). Diradical **534** is proposed as the sole intermediate because this mimics the reactivity of carbon-based free-radical additions to allenes, which predominantly react at the central carbon (C2).¹⁸⁵

Taylor et al. published reports^{181,182} using fluorinated alkenes to provide evidence of a stepwise diradical mechanism in addition to 1,3-dienes (Scheme 149). The reactions of fluorinated alkene **542** and 1,3-diene **541** are proposed to yield diradical intermediates **543** and **544** to ultimately deliver 1,2- and 1,4-addition products **545** and **546**, respectively.¹⁸⁶ Compound **547** would be expected if the reaction was concerted; however, no **547** was noted. Taylor further employed symmetric and unsymmetric fluorinated alkenes to evaluate the plausibility of diradicals in thermal allene–alkene $[2 + 2]$ cycloadditions (Scheme 150). The reaction of **24** with **548a–b** and **542** results in four cyclobutanes (**550a–c**, **551a–c**, **553a–c**, and **554a–c**) via **549** and **552**. Presumably, **549** arises from the formation of a σ -bond between the alkene and the central allene carbon. The preferred geometry for **549** orients the allene and alkene perpendicular to one another, where the rotation of the alkene toward the substituted side of the allene results in the radical recombination to **551a–c** and rotation toward the least-substituted carbon gives **550a–c**. Vinyl cyclobutane derivatives **553a–c** and **554a–c** result from **552** via a 1,3-rearrangement of the starting allene **24**.

Variable-temperature experiments¹⁸¹ reveal key distinctions between concerted and stepwise pathways in terms of their respective potential energy surfaces. The concerted reaction of **24** and **548a** (Scheme 150) would entail two significantly different reaction barriers to furnish **550a** and **551a**; thus changing the temperature would likely influence the **550a/551a** ratio. In contrast, a stepwise pathway involves rate-limiting diradical formation, followed by relatively small barriers for ring closure of **549**. Thus changing the temperature would not be expected to alter the ratio of **550a/551a** if the reaction is stepwise. Experimentally, only small variations in the **550/551** ratios are observed, which is more consistent with a diradical, stepwise path.

Pasto and coworkers showed that reactions of monoalkylallenes **26** and **555a,b** with **542** (Scheme 151)¹⁸⁷ delivered *E/Z* stereoisomers **559** and **560**. In theory, either a concerted or diradical mechanism could be inferred from ratios of **559/560**. A concerted [$\pi 2_s + (\pi 2_s + \pi 2_s)$] process predicts **559** as the major product (even as R increases in size) due to steric effects and the preferred direction of the bond rotation about the terminal-substituted allene carbon. Experimentally, it was found that increasing the steric bulk in **26** and **555a,b** gives **560** as the major product. The reaction pathway (Scheme 151), supported by KIE experiments, suggests that **542** reacts with the more substituted olefin of **26** and **555a,b** to give transition state **556**. Pathway A rotates the large substituent in **556** toward the incoming alkene, resulting in a steric clash. However, pathway B rotates the large substituent away from the incoming alkene, minimizing steric interactions to give diradical **558**. This explains the observed product ratios, where increased steric interactions in **556** increase the formation of **560** at the expense of **559**. Ring closure is favored at the less hindered C3 of the allene, yielding higher ratios of **559** and **560**, as compared with competing closure at C1 to give **561**.

The above results and reasoning in Scheme 151 are used to infer if radicals are present in other [2 + 2] allene-alkene cycloadditions.¹⁸⁷ For example, *N*-phenylmaleimide **563** (Scheme 152), an electron-poor (LUMO controlled) reagent, could be envisaged to undergo a concerted reaction with the electron-rich olefin of allene **562**. The reaction of **563** with allenes (**24**, **562a,b**, R = CH₃, CH₂CH₃, C(CH₃)₃) under thermal conditions¹⁸³ showed chemoselectivity consistent with either a concerted [$\pi 2_s + (\pi 2_s + \pi 2_s)$] or a stepwise diradical process. A [$\pi 2_s + \pi 2_a$] pathway was ruled out because an electron-deficient alkene should react with the more electron-rich olefin. Compound **568**, a 1:2 adduct, presumably arises from the 1,5-hydrogen atom transfer (1,5-HAT) of the alkyl radical in the diradical intermediate, followed by radical recombination to form the alkene. The resulting diene would then presumably undergo a [4 + 2] cycloaddition to result in the Diels-Alder product **568**.

Pasto performed follow-up experiments on previous work carried out by the Kiefer group.¹⁸⁸ Diethyl fumarate and diethyl maleate were heated with dimethylallene to give methylenecyclobutanes. High stereospecificity (up to 99%) was observed and used to support a concerted mechanism. However, in this instance and other similar cases, the argument could be made that a high stereospecificity in radical cyclizations can be obtained if the bond formation/ring closure is faster than the bond rotation or competing processes that would give the expected lower stereospecificity. In the reaction outlined in Scheme 153, a proposed diradical intermediate would be at an energy minimum, as represented by **576**–**579**, when the new C–C is marginally shifted from a perpendicular arrangement. This “tilting” toward the allyl radical allows for a better orbital overlap in the ring closure. Of the four possible diradical intermediates, **576** and **578** are expected to be lower in energy because they minimize pseudo-1,3-diaxial interactions in the transition state. This proposal agrees with the experiment in terms of the relative ratios of products **571**–**575**. The alkyne **575** results from the reaction of the alkene at the less substituted carbon of **26**, **569**, and **146g**.

To better understand the nature of diradical intermediates involved in this chemistry, Pasto and coworkers studied reactions of **570** with dimethyl allene **24** and diethyl maleate **583** with **24** (Scheme 154).¹⁸⁹ The reaction of **24** with **570** led to *trans* diesters **580** and **581**, arising from a [2 + 2] cycloaddition, plus a cyclohexene **582** that results from the [1,3]-sigmatropic rearrangement of **24** and the subsequent [4 + 2] cyclization. In contrast, the reaction of **24** with **583** gives the expected *cis* diesters **584–586**; however, **580–582** are also observed. The presence of **580–582** is attributed to an internal rotation in diradical intermediates **587** and **589** to minimize steric interactions caused by eclipsing ester groups. In addition to the presence of *trans* ester products, a significant isomerization of **583** to **570** is observed, with ratios up to 5:1 (**583/570**) with **24**. Control experiments without **24** show no isomerization, suggesting that **24** is required for this process. Thus it was postulated that **570** arises from the cleavage of diradical intermediates **588** and **590**. The internal rotation and cleavage events are rationalized by an increase in energy of intermediates **587** and **589** due to increased steric interactions as compared with **588** and **590**. This gives a smaller energy barrier for rotation and cleavage in the reaction of **24** and **583**. The ring closure event itself is unaffected; therefore, competition between internal rotation, cleavage (from **588** to give **24** and **570**), and ring closure is dictated by the relative energies of diradical intermediates. Increased strain in either the allylic or aliphatic radical (for example, when *tert*-butylallene is used instead of **24**) results in increased internal rotation and cleavage, as compared with desired ring closure. The stabilization of diradical intermediates (for example, using methoxyallene instead of 1,1-dimethylallene **24**) leads to increased rates of ring closure relative to internal rotation and cleavage.

As shown in the examples discussed above, 1:1 adducts are often the major products if alkyl allenes are employed; however, functional groups other than alkyls can result in additional adducts from cyclodimerization processes or increased reactivity.¹⁸¹ Using a methoxy-substituted allene **146e** (Scheme 155a), Pasto noted that 1:1 adducts **591**, **592**, and **593** comprise the majority of the product mixture.¹⁹⁰ The remainder is composed of 1:2 adduct **594** and 2:1 adducts resulting from the allene dimerization of **595** or **596**. Chloro-substituted allene **597** (Scheme 155b) allows for the formation of additional adducts as compared with **146e**. This includes the formation of the 2:2 adduct **601**, 2:1 adducts **600a,b**, presumably arising from **599a,b**, and the 2:0 adduct **599c**. Analogous to reactions of **146e**, the reaction of **597** also results in 1:1 adducts **598a–c** and the 1:2 adduct **594**.

As already mentioned, intermolecular [2 + 2] allene–alkene cycloadditions suffer from poor regioselectivity (proximal vs distal π -bond of the allene) and side reactions. On the contrary, intramolecular reactions display higher regioselectivity and are tunable to some extent. Padwa reported that the terminal C1–C2 olefin of (phenylsulfonyl)allene **602** (Scheme 156) undergoes a [2 + 2] cycloaddition with a tethered alkene despite the presence of a more activated internal C2–C3 olefin of the allene.¹⁹¹ This stereospecificity was unexpected, as C2–C3 was thought to be more reactive than C1–C2; regioselectivity was attributed to the stability of radical intermediate **603** or **605**. When R³ = H (**602**), the reaction proceeds through diradical **603** to furnish **604**. The preference for 6-*exo-trig*, as opposed to 7-*endo-trig*, cyclization is consistent with previous work involving the intramolecular addition to an alkene via a carbon radical.¹⁹² A switch in regioselectivity was achieved by replacing the H

at R³ with Me or Br (**602**). The nonallylic radical in **605** is tertiary (when R³ = Me) and gains extra stability from hyperconjugation and kinetic stability from steric hindrance. In this case, the two radicals in **605** form a fused cyclopentane–cyclobutane, as exemplified by **606**. A further investigation of substitution on the alkene (**602**, R³ = H) showed that faster reaction rates are achieved with alkyl substitution at R¹ and R², presumably due to the higher stability of the nonallylic radical.

The nature of the tether in **602** (Scheme 156) could be altered at C5 to give bicyclic rings of different functionalities. The introduction of an oxygen at position five in **607** (Scheme 157) led to the formation of bicyclic pyran derivative **609** in 74% yield. A 60% yield of **612** is obtained when the oxygen of **607** is replaced by a methylene bridge in **610**. The placement of a bis(phenylsulfonyl)methane group at position five results in a good yield (69%) and a faster reaction rate, consistent with the Thorpe–Ingold effect. Increasing the allene tether by one methylene group (**616**) led to an unexpected product, where a nonallylic radical **617** undergoes a 1,5-HAT (hydrogen atom transfer) to result in a radical situated β to the SO₂Ph group, which combines with the allylic radical to deliver *trans*-diene **618**.

Alcaide and coworkers demonstrated an intramolecular allene–alkene [2 + 2] cycloaddition with excellent positional selectivity (Scheme 158).¹⁹³ Utilizing 2-azetidinone-tethered enallenes **619a–c** under thermal conditions results in **621a–c** as the sole product. Intermediate **620** arises from formation of a new σ -bond between the allene central carbon and the internal alkene carbon. Radical recombination of the diradical **620** furnishes the tricyclic β -lactam **621**, which has utility as a potential antibacterial agent. However, **623** was the authors' expected outcome based on the likelihood of forming a more stable secondary alkyl radical in **622**; however, this leads to a larger ring in **622** as compared with intermediate **620**, which is apparently unfavorable.

5.1.3. With Alkynes.—Alkynes, similar to alkenes and allenes, undergo thermal [2 + 2] cycloadditions with allenes. The products are methylenecyclobutenes, which are utilized in materials chemistry as dyes¹⁹⁴ and organic semiconductors.¹⁹⁵ Whereas the mechanisms of allene–alkene [2 + 2] reactions have been well studied, investigations involving alkynes as coupling partners have not received much attention. Reactions suffer from poor control of regio- and stereoselectivities, high reaction temperatures, and the formation of undesired byproducts. Scattered reports that address these issues and provide some mechanistic insights are discussed in this section.

The product of the [2 + 2] cycloaddition between **624** (R' = H) and allene **625** (R = H) gives methylene cyclobutene **626** (Scheme 159). Regio- and stereoisomers **627** and **628** are obtained with **625** (R = Me). Additional methylene cyclobutene products **629–632** arise when the substitution is increased on the allene **625** (R = Me) and alkyne **624** (R' = Me). Analogous to alkenes, the product ratios and reactivity of alkyne–allene [2 + 2] cycloadditions best reflect a diradical mechanism, as opposed to a concerted mechanism involving **633–636**. Diradical intermediates **637–640** result from formation of a new σ -bond at the central carbon or at the terminal carbon to give bisvinyl radicals **641–644**. Presumably the [2 + 2] cycloaddition proceeds through the allylic biradical intermediate due to energetic

considerations; both inter- and intramolecular variants have been explored experimentally and computationally, as described in more detail later.

Pasto investigated relative reactivities of alkene **646** versus alkyne **645** with allene **24** through an intermolecular competition experiment (Scheme 160).¹⁹⁶ Under thermal conditions, the alkyne reacts faster than the alkene, and no observable reaction with **646** was detected. Four products are observed: two 1:1 adducts (**647–648**) resulting from [2 + 2] cycloaddition and trace amounts of 2:1 (alkyne/allene) adducts **649–650**.¹⁹⁷ This observed reactivity is opposite that expected for free-radical additions, as alkenes typically react faster than alkynes. It is postulated that the reaction proceeds through a late transition state that depends on the relative stabilization of the radical by attached functional groups. The diradical resulting from the reaction of **24** and **645** is stabilized by functional groups on the allene and alkyne and is considered an endothermic process. A closer look at the energetics to generate two new radical centers and a new C–C bond, while cleaving a C–C π -bond, agrees with this classification. The greater reactivity was proposed to result from a decrease in the heat of formation of the diradical from the alkyne. The heats of formation of acetylene and ethene are 54.2 and 12.5 kcal/mol, respectively, and thus a lower barrier exists for the formation of a diradical intermediate from the alkyne.

In 2010, Brummond and Tantillo reported a mechanistic study of the thermal intramolecular [2 + 2] reaction of allenynes (Scheme 161).¹⁹⁸ A concerted process would entail a [$\pi 2_s + \pi 2_a$] arrangement in the transition state; this was ruled out based on geometric restrictions. Two diradical pathways (**a**) and (**b**) were considered, differing in the size of the initial ring formation. The pathway forming the small ring (**a**) has a lower barrier for cyclization than the competing pathway (**b**) due to the formation of a stabilized allyl and vinyl radical **652** when compared with bisvinyl radical **654**. In agreement with experimental results, the barrier for the formation of the diradical via the distal π -bond of the allene is lower than for the proximal π -bond. Thus regioselectivity is governed by the stability of diradical intermediates (allyl vs vinyl); the initial σ -bond formation occurs at the central allene carbon, analogous to [2 + 2] cycloadditions involving a π -bond and an allene.

Different alkyne substituents affect the outcome of intramolecular reactions from both experimental and computational standpoints.¹⁹⁸ Aromatic substituents are often attached to the alkyne, as the resulting benzylic radical is stabilized by delocalization into the aromatic ring. Computational analysis shows that the intermediate radical is almost linear in nature, contributing to a more planar π -system and a lower energy intermediate. In contrast, carbonyl groups α to the alkyne have only a small stabilizing effect. Experiments involving the use of cyclopropyl groups on the alkyne have been carried out by Brummond and Tantillo (Scheme 162).¹⁹⁹ Three alkynyl cyclopropyl derivatives **655a–c** were used to probe the presence of diradical intermediates. Compound **655a** underwent a [2 + 2] cycloaddition with no observed ring opening; however, **655b** furnished ring-opened **657–658**, supporting the hypothesis that radical intermediates are involved.¹⁹⁹ Performing the reaction with **655c** also supported the likelihood of radical over cation intermediates. Electrostatic potential maps suggested that diradical pathways are more likely than zwitterionic pathways²⁰⁰ due to the small difference in charge build-up in the intermediates for the conversion of **655a** to **656** and **655c** to **659–660**.

In addition to their work in [2 + 2] intramolecular alkene/allene cycloadditions, Aragoncillo and coworkers reported an alkyne variant that furnishes **665a–e** (Scheme 163).²⁰¹ Subjecting **661** to thermal conditions gave a new σ -bond between the proximal alkynyl carbon and the central allene carbon to yield allylic/vinyl radical **664**. Whereas the distal alkynyl carbon could potentially form a new σ -bond with the central allene carbon, a higher energy barrier for the formation of **662** relative to **664** is likely; this, coupled to a lack of stabilization in the resulting vinyl radical, disfavors this process. Thus **663a–e** are not observed in the reaction.

The use of the diyne–diallene **666** allows for a double [2 + 2] cycloaddition, presumably via a tetraradical intermediate **667** (Scheme 164). Stopping the reaction prematurely results in the recovery of starting material and the bis(β -lactam-allenynes) **668**, indicating that both cyclizations may occur concurrently.

In summary, allenes have been utilized in thermal [2 + 2] reactions with molecules containing π -bonds, including other allenes, alkenes, and alkynes; however, the intermolecular control of regioselectivity in these reactions is usually poor. In contrast, intramolecular variants often display excellent selectivity, depending on the substituents installed on the allene, and are synthetically useful. Whereas the field of allene [2 + 2] cycloaddition has been largely dominated by thermal processes, focus has more recently shifted to metal-catalyzed [2 + 2] cycloaddition reactions, which are not thought to proceed through diradical mechanisms. Despite their limitations, non-metal-catalyzed [2 + 2] cycloadditions are still of great interest due to their functional group tolerance, the retention of unsaturation in the product for further functionalizations, the “green” aspects of this approach, and the general interest in the mechanistic details. In addition, diradical intermediates have been implicated in the cleavage of double-stranded deoxyribonucleic acid (DNA) to influence disease pathways and thus continue to be pertinent to the medicinal chemistry community.¹⁴⁷ Future opportunities include the development of useful intermolecular cycloaddition reactions of allenes with improved selectivities and yields, advancing the photochemical variants of this chemistry and the applications of electrochemical variants. To the best of our knowledge, the addition of electrochemically generated radicals to allenes has not been developed, but such variants could further the general understanding of the mechanism and provide insight into other similar systems.

5.2. Enyne–Allene Radical Cyclizations

Since the initial report of the Bergman cyclization, diradical intermediates have been of great interest due to their antitumor activities and their ability to engage in cascade reactions.²⁰² In the Bergman cyclization, a diphenyl radical intermediate is proposed to result from a corresponding enediyne under thermal conditions. A benzene ring results upon trapping with hydrogen. Antibiotics such as esperamicin and calicheamicin can be synthesized via this method, with the enediyne core furnishing the diradical intermediate in situ under thermal conditions. These diradical intermediates are indicated in the cleavage of double-stranded DNA and remain of great interest to medicinal chemists. In most cases, the Bergman cyclization of acyclic enediynes requires high reaction temperatures (>130 °C); however, the analogous reaction of cyclic enediynes can occur at much lower temperatures (37 °C) due to increased ring strain and are more applicable to drug design.

Following Bergman's seminal report, variations on this chemistry have been explored, including reactions of enyne-allenes, such as the Myers–Saito and Schmittel cyclizations (Scheme 165). The Schmittel cyclization involves the formation of a new bond between C2 and C6, resulting in a fulvenyl diradical intermediate. On the contrary, the Myers–Saito cyclization involves the reaction of the central allene carbon C2 and the terminal C7 carbon of the alkyne to form an intermediate α ,3-tolyl diradical. There are several excellent sources for interested readers to seek further information on the Myers–Saito and Schmittel cyclizations.^{203–206}

5.2.1. Myers–Saito Cyclization.—The Myers–Saito cyclization was independently reported by Myers and Saito in the late 20th century (Scheme 165).^{204,205} Saito postulated that the Bergman cyclization requires high temperatures due to the bonding distance between the two carbons that form the initial C–C σ -bond. It was predicted that utilizing enyne-allenes would lower the activation barrier for the reaction due to a decrease in the bonding distance between C2 and C7. Accordingly, mild reaction temperatures can be utilized with acyclic enyne-allenes (R = H, alkyl) to furnish α ,3-didehydrotoluene derivatives. Studies describing the applications of this useful transformation are discussed in the following sections.

5.2.1.1. Mechanism of the Myers–Saito Cyclization. The mechanism of the Myers–Saito cyclization has been studied both experimentally and computationally. Saito showed that performing the reaction in cyclohexadiene (1,4-CHD) led to **672**, along with **673** and dimer **674** (Scheme 166).²⁰⁴ DNA cleavage studies indicate that enyne-allenes react similarly to enediynes and proceed through diradical intermediates. However, the nature of the intermediate of the Myers–Saito reaction is solvent-dependent.²⁰⁵ In protic solvents, diradical **671** displays ionic character and is best represented by **670**. In nonpolar solvents, such as 1,4-CHD, **671** possesses more diradical character and participates in a stepwise pathway. Overall, the intermediate of the Myers–Saito cyclization is best described by the resonance structures **670** and **671** and is dependent on solvation effects, with polar protic solvents stabilizing charged intermediates. Finn published a comprehensive report on various functional groups that favor **670** or **671**.²⁰⁷

Utilizing **675** in methanol or 1,4-CHD results in different ring-opened products, **677** (via **676**) and **679** (via **678**), respectively (Scheme 167). Shibuya reported ionic character could be minimized by introducing electron-withdrawing groups on the ring, resulting in more cleavage of double-stranded DNA via diradical intermediates.²⁰⁸ Computational analysis was used to further investigate why the Myers–Saito proceeds at much lower temperature than the Bergman cyclization. Morokuma reported the lower activation energy of the Myers–Saito (21–23 kcal/mol) versus the Bergman (32 kcal/mol) cyclization is due to smaller four-electron repulsion and smaller overlap between the two in-plane π -bonds.²⁰⁹ In addition, as the C–H bonds are out-of-plane in the transition state, the methylene radical is perpendicular to aromatic π -system, suggesting conjugation does not contribute to the observed lower activation energy.

5.2.1.2. Generation of Enyne–Allenenes and Substituent Effects on Myers–Saito

Cyclization.: The enyne–allene core **682** is accessed via [2,3]- and [3,3]-sigmatropic rearrangements of **681**.²¹⁰ Saito showed that a [2,3]-sigmatropic rearrangement of **681a** generates allenylphosphine **682a** (Scheme 168); **682a** can be trapped with 1,4-CHD to give **684a**. Saito later expanded the scope of the [2,3]-sigmatropic rearrangement to include the sulfoxide **681b** and vinyl ether **681d**.²¹¹

Other allene substitution patterns have been investigated (Scheme 169). Grissom utilized aromatic enyne–allenenes with various substituents at C3 in **685** ($R = P(O)Ph_2$) and observed no cyclization under thermal conditions, presumably due to the $A^{1,3}$ -strain between the C3 substituent and the ortho substituent of the aromatic ring. In addition, Grissom also investigated substitution at C1 in **686**, including a phosphine and a phenylsulfoxide group.

As mentioned previously, Finn summarized the effects of different substituents on the outcome of the Myers–Saito cyclization.²⁰⁷ Early work by Saito indicated that decreasing the distance between the reactive centers is critical to achieving increased rates relative to Bergman cyclization.²⁰⁴ Substituent effects support this hypothesis: Large bulky groups on the alkyne, such as *t*-butyl (Scheme 169), dramatically decrease the rate due to the increase in distance between the reactive centers (3.25–3.3 Å). However, if the reactive centers in the enyne–allene are too close (3.18–3.19 Å), then the compounds are unstable. Substituents at the alkyne terminus show little electronic effects on the cyclization rates, based on observations using substrates with electronically differentiated *para*-substituted aromatic rings on the alkyne. Electronically differentiated groups on the allene terminus of **685** also have little effect on the rate of cyclization. These results provide support for an early transition state, where the nascent benzylic radical or cation is not in conjugation with the aromatic system but resides orthogonal to it.

5.2.1.3. Cascade Reactions.: Diradical intermediates in the Myers–Saito reaction can be intercepted with a variety of radical trapping groups or acceptors (Scheme 170). Wang and coworkers developed several cascade reactions using this $\alpha,3$ -didehydro-toluene diradical intermediate.^{213,214} For example, the intermediate **690** that results from reaction of **689** can undergo a 5-*exo-trig* cyclization involving the phenyl radical. The resultant alkyl radical undergoes 1,5-HAT to give **692**, which engages in a 6-*endo-trig* cyclization and radical recombination to deliver **693**. The Myers–Saito cyclization of enyne–allene **697** results in **698**; a 6-*exo-dig* cyclization, followed by trapping of the benzylic radical in **699** results in **700**. Grissom demonstrated the 5-*exo-trig* cyclization of **695** (from enyne–allene **694**) to gain access to substituted bicyclic scaffolds **696**,^{215–217} whereas Moore engaged $\alpha,3$ -didehydrotoluene diradical intermediates in polymerization reactions.²¹⁸

The Myers–Saito cyclization provides a mild strategy for the formation of $\alpha,3$ -didehydrotoluene diradicals that have found uses in synthetic, materials, and medicinal chemistry. The diradical may undergo either inter- and intramolecular reactions to furnish polycyclic scaffolds that can be subjected to additional functionalizations. The generation of this type of diradical intermediate through either photochemical or electrochemical means

could unlock other useful application of this chemistry, whereas the reduction or oxidation of the benzyl radical can be envisaged as an alternative pathway for further reactivity.

5.2.2. Schmittel Cyclization.—The Schmittel cyclization involves the formation of a new bond between C2 and C6 in **701** and is the predominant pathway when the alkyne is substituted with a large bulky group, such as a *tert*-butyl or trialkylsilyl group (Scheme 171).²¹⁹ In addition, computational analysis suggests that the Schmittel cyclization occurs via orbital interactions between vertical and side π -orbitals, whereas the Myers–Saito reaction occurs via vertical–vertical and side–side π -orbital interactions.²²⁰ In a classical physical organic sense, either a concerted or stepwise pathway is possible from **703** (Scheme 172). A concerted pathway involves either inter- or intramolecular H-atom transfer in **704** via a six-membered transition state, whereas a stepwise pathway involves the formation of diradical **705**, followed by H-atom abstraction to furnish **706**. Whereas many of these types of cyclizations are defined by classical views, the Schmittel cyclization is more complicated. Theoretical studies, radical trapping experiments,²²¹ and DNA cleavage studies have all provided compelling evidence of a diradical intermediate. However, as described in the following section, recent mechanistic studies indicate that dynamic effects need to be considered and incorporated into mechanistic explanations for these cyclizations.

5.2.2.1. Dynamic Trajectories and KIE Experiments.: Singleton and coworkers have explored the mechanism of the Schmittel cyclization through computations and KIE experiments.²²² They postulated that both concerted and stepwise pathways result from the same initial transition state due to their inability to identify a transition state for the diradical intermediate and computed geometric similarities in the initial stages of the reaction. To explain the concerted nature of the reaction, Carpenter’s views on dynamic effects were incorporated.²²³ Carpenter has discussed multiple examples where a mechanism appears to be concerted but is actually stepwise in nature. In these cases, the barrier of the second step is overcome by an excess of kinetic energy generated by the formation of the intermediate, leading directly to the product. In addition, Engels has found via computational analysis that stepwise and concerted mechanisms have approximately the same free energy of activation.²²⁴

Schmittel reported a comprehensive mechanistic study involving a detailed examination of the reactivity in cyclizations where various substituents have been installed at different positions in the enyne–allenes **707a–c** (Scheme 173).²²⁵ When radical stabilizing groups are present at the allene or alkyne terminus (or both), the stepwise/dynamic mechanism is favored, as evidenced by an observed KIE near unity with **707a,b**. This can also be explained by Carpenter’s dynamic model, where the intermediate overcomes the reaction barrier of the second step by an excess buildup of kinetic energy in the first step; this explains the lack of discrimination between hydrogen versus deuterium abstraction. In the absence of a radical stabilizing group, the mechanism displays a greater concerted character, as indicated by a KIE value much greater than unity (**707c**).

5.2.2.2. Thermal and Photochemical Radical Clock Experiments.: Further experimental investigations of the mechanism of the Schmittel reaction have been carried out using radical clock experiments (Scheme 174).^{226,227} Schmittel demonstrated thermal

and photochemical ring openings of diphenyl cyclopropane enyne–allene **712**. Because the ring opening of pendant cyclopropanes is generally accepted as evidence of a diradical intermediate, experimental observations of ring-opened products **710** and **713** support the presence of a stepwise mechanism.

5.2.2.3. Schmitt Cascades.: The Schmitt cyclization can be used as a powerful tool to create polycyclic aromatic compounds in a single step. Wang and coworkers engaged an Ireland–Claisen rearrangement to generate the corresponding enyne–allene from propargylic acetates (Scheme 175).²²⁸ The Schmitt cyclization of **714** results in the corresponding benzofulvene biradicals **717** and **719**, which undergo further cyclization to result in six-membered or four-membered rings **716** and **718**, respectively. In an additional report, Wang described access to polycyclic spirocyclic or highly twisted polycyclic molecules via an S_N1' reaction by treating the corresponding propargylic alcohol with thionyl chloride.²²⁹

The Schmitt cyclization enables the formation of fulvenyl diradical intermediates that can lead to diverse polycyclic compounds. Similar to suggestions for future explorations of the Myers–Saito reaction, the use of electrochemical methods to reduce or oxidize the diradical intermediate would unlock different reactivities and potentially provide shorter routes to target molecules useful for exploring bioactive chemical space. In addition, identifying new and mild procedures to prepare the enyne–allenes in situ is highly desirable and may find useful applications in biorthogonal chemistry.

5.3. Diradical Intermediates in Other Allene Reactions

Whereas there has been extensive work on thermal and photochemical [2 + 2] cycloadditions of allenes and enyne reactions involving diradical intermediates, there are other reactions of allenes proposed to proceed through similar species that are worth of mentioning. For example, Kamigata studied sulfur- and selenium-containing allenes under thermal²³⁰ and photochemical conditions.²³¹ Acyclic 1,3-bis(alkylthio)allenes **721** (R = H or Ph) gave several products under thermal conditions (Scheme 176). Path 1 illustrates the formation of methylenecyclobutanes **723–724** through an allene–allene [2 + 2] thermal dimerization that proceeds via bisallylic radical **722**. Path 2 provides an explanation for the formation of **727** and **729–730** and is proposed to proceed through diradical **725**. The addition of an α -thioradical on the ortho position of the aromatic ring of **725** gives **726**. A 1,5-hydrogen migration furnishes **727** and restores aromaticity. Thiophenes **729–730** are proposed to result from **725**, where radical recombination gives **728**; this then eliminates RCH_2SH (R = H, Ph) to deliver the major components of the mixture (**729–730**). Path 3 involves homolytic cleavage of the C–S bond of **721**, presumably due to the stability of the resulting benzylic and sulfur (**731**) radicals. Rearrangement of **731** to **732**, followed by H-atom abstraction and hydrolysis furnishes **736**, whereas the conversion of **731** to **733**, followed by H-atom abstraction, gives **734** in 5% yield.

The irradiation of 1,3-bis(alkylthio)allenes by Kamigata and coworkers furnished rearranged products **740/745** and **741/746** (Scheme 177). The mechanism is proposed to proceed through a diradical/carbene pathway (from **738/743** to **739/744**), as opposed to a photoinduced [1,3]-sigmatropic rearrangement. A 1,2-migration of **737/742**, followed by

carbene formation to **739/744** and subsequent rearrangement furnishes alkynes **740/745**. Monothiosubstituted compounds **741** and **746** result from the irradiation of **740/745** under the reaction conditions.

Under thermal conditions, *meso*-tetrathiocyclic bisallene **747** furnishes the tricyclic compound **749**, presumably via diradical intermediate **748** (Scheme 178). Allene dimerization becomes significant when the temperature exceeds 130 °C in refluxing xylene; under these conditions, **747** results in intermediate **748**, which closes to furnish dimethylenecyclobutane **749**. Under photochemical conditions, the rearranged products **750–751** are obtained, along with the stereoisomer of the starting material **752**. Presumably, **750–751** arise from the same pathway as was observed in the photochemical reaction of acyclic bisalkylthioallenes (Scheme 178).

Under thermal conditions, biseleniumalkylallenes display a different reactivities from their sulfur–chalcogen counterparts.²³² Kamigata postulated that this is due to the smaller bond dissociation energy (BDE) of the C–Se bond compared with that of the C–S bond. Running the reaction in the presence of galvinoxyl gave lower yields, providing support for a radical mechanism (Scheme 179). Route 1 is proposed to lead to **756**, which results from the dimerization of acyclic allene **753** to give bisallylic biradical intermediate **754**. The radical recombination of **754**, followed by the loss of diphenyl selenide from **755**, delivers **756**. Route 2 involves the sequential loss of two phenyl selenium radicals from **753** to give carbene **759**; dimerization of **759** furnishes **760–761**.

Under photochemical conditions, acyclic biselenium allenes primarily result in (*E*)- and (*Z*)-1,3,4,6-tetraphenyl-3-hexen-1,5-diynes **760–761** (Scheme 180; also see Scheme 179).²³³ These products evolve from the 1,2-photorearrangement of **762** to yield biradical intermediate **763**, which is in resonance with carbene **764** and ultimately undergoes 1,2-migration to **765**. Homolytic C–Se bond cleavage to **766**, followed by dimerization yields **767**, which loses RSe–SeR to deliver **760/761**. Carrying out the reaction under O₂ bubbling (Scheme 181) produced no **760/761**, giving **770** as the major product, supporting the reaction pathway outlined in Scheme 180.

Photochemical irradiation of cyclic bisallene **771** yields **760/761** (Scheme 182). In addition, **772** is obtained as a minor product, presumably via the homolytic cleavage of the C–Se bond in **771**, followed by the radical recombination of the selenium radicals. As in the case of cyclic sulfur bisallenes, the presence of the other stereoisomer of the starting material as *meso*-**771** suggests a photoinduced isomerization. The thermal pathway (Scheme 182, bottom) yields products **773–774** and **760–761** through the indicated mechanistic pathway.

Houk carried out computational analyses of the addition of butadiene and benzene (aromatic-containing diene) to propadiene (Scheme 183).²³⁴ Potential products include methylenecyclobutanes **783** from a formal [2 + 2] cycloaddition or cyclohexene **776** from a [4 + 2] cycloaddition. The formation of **776** could be explained by a concerted mechanism proceeding through **775** or by a stepwise cis-diradical pathway proceeding through **777/778**. Calculations indicate that both mechanisms (concerted and stepwise) involve the same transition state, computed to have a barrier of 27.7 kcal/mol. The transition state involved in

the formation of **781** was calculated to have an energy barrier of 28.1 kcal/mol, which can compete with the transition state leading to **775** or **777**.

Computational analysis indicates that the reaction of propadiene with benzene under thermal conditions likely occurs via a concerted pathway (Scheme 184). A stepwise pathway would entail the loss of aromaticity, which would counteract any favorable allylic radical stabilization in intermediate **785**. Accordingly, the transition state **784** for a stepwise pathway is calculated to be greater than that of the concerted transition state **789** (42.1 vs 37.1 kcal/mol, respectively). The concerted reaction goes through an aromatic transition state, which mitigates the disruption of the aromaticity of benzene. Despite the lower barrier for the concerted reaction (37.1 kcal/mol), the barrier is still higher than that of allene dimerization (32.9 kcal/mol) and thus allene dimerization would be expected to outcompete other reactions.²³⁵

Goré showed that reactions of α -allenic hydrazines **791a–c** give 3-pyrroline **798** or azetidine **795** via radicals **796** and **793**, respectively (Scheme 185).²³⁶ The ratio of **798**:**795** varies with temperature; at higher temperatures and long reaction times, **798** is the major product (45 vs 20 h). This led the authors to speculate that the formation of **795** is reversible at higher temperatures. Utilizing hydrazines **791a–c** resulted in different reactivities and different product ratios as the temperature was varied. Substituent effects, including the installation of a more basic terminal nitrogen of the hydrazine, result in a higher 3-pyrroline/azetidine ratio. Dimethylamine- and piperidine-containing hydrazines (**791a**) display enhanced reactivity when compared with a morpholine-containing hydrazine **791b**. An exception to this trend is the SAMP hydrazine **791c**, due to the coordination of the methoxy group to the lithium, which increases the basicity of the terminal nitrogen in **791c**. Additional tunability could be achieved by the selective positioning of radical stabilizing groups in the precursors to favor **792** or **796**.

In terms of the mechanism, the hydrazide **791** could undergo two possible pathways. At lower temperatures, the corresponding azetidine **795** is obtained, first through the loss of an electron, followed by 4-*exo-dig* cyclization at the central carbon to give stabilized allylic radical **793**. This radical is reduced to the corresponding anion **794**, whereas azetidine **795** is obtained via the protonation of **794**. When the reaction is carried out at higher temperatures, the formation of **795** is proposed to be reversible, giving 3-pyrroline as the major product. A separate reaction pathway is hypothesized to occur from **791**, where electron transfer to the allene results in intermediate **796**. The radical recombination of **796** yields the five-membered ring **797**. Protonation of the anion results in the corresponding 3-pyrroline **798**.

6. SYNTHESIS OF NATURAL PRODUCTS

The Hart group described a synthesis of pyrrolizidinones and indolizidinones utilizing α -acylamino radical additions to allenes **799–800**.²³⁷ The phenylselenyl lactams, arising from **799** and **800**, were converted to the indolizidinones and pyrrolizidinones **802–803** and **804–805**, respectively, in moderate yields (Scheme 186).

The pyrrolizidine alkaloid ($\pm$)-supinidine,^{238–241} which has reported antitumor properties, could be prepared from either **804** or **805**, as shown in Scheme 187. The conversion of **804** to the allylic acetate **806** was achieved in one step by SeO₂-mediated allylic oxidation. On the contrary, **805** was transformed to **806** via a sequence of four steps in a higher 41% yield, as compared with the 14% yield obtained utilizing **804** as the precursor.

In 1988, the Hart group published a synthesis of (+)-heliotridine **812** from (*S*)-3-acetoxysuccinimide **808**²⁴² (Scheme 188) by employing a protocol similar to that used for the preparation of ($\pm$)-supinidine.²³⁷ The key step in building the [3.3.0]-fused bicyclic ring system involved a *n*-Bu₃SnH-initiated free-radical cyclization of allene **809**, obtained from enantiomerically enriched **808** in good yield. The *exo*-cyclization product **810** was afforded in 40% yield following the radical cyclization step and was converted to the diacetate **811** in two additional steps. Lithium aluminum hydride reduction of **811** gave the pyrrolizidine alkaloid (+)-heliotridine in an overall 4.3% yield from **808**.

In 1993, the Meyers group published the first synthesis of ($\pm$)-7,8-epoxy-4-basmen-6-one **813**, a diterpenoid tobacco isolate that possesses a tricyclic ring system composed of three fused rings **A**, **B**, and **C**²⁴³ (Scheme 189). The key annulation step to form rings **A–C** involved an AIBN-mediated radical cyclization of the allene precursor **816**. The synthesis of **813** commenced with commercially available neryl acetone, which was converted to the alcohol **814** in quantitative yield. A sequence of nine steps furnished the allenyl macrocycle **815** in 20% overall yield from **814**. An additional four steps gave precursor **816** for the key radical cyclization.

Irradiating a mixture of the cyclization precursor **816**, *N*-methylcarbazole, and 1,4-cyclohexadiene in THF/H₂O for 5 h at 55 °C using Pyrex-filtered light from a medium-pressure mercury lamp yielded the isomeric tricyclic fused rings **817–818** in 51% yield. From a mechanistic perspective, the 5–8–5 tricyclic ring backbone is formed via two consecutive 5-*exo* cyclizations from intermediate **I** (Scheme 194). A 5-*exo-trig* cyclization of **I** was proposed to lead to **II**. Theoretical studies described by Houk and Spellmeyer²⁴⁴ support the observed regio- and chemoselectivity of this cyclization, indicating a 4.2 kcal/mol preference for this pathway over alternative cyclization pathways. The formation of radical intermediate **IV** was proposed to result from 5-*exo-dig* cyclization of intermediate **III** instead of **II**, as calculations predicted that it was energetically more favorable by ~4 kcal/mol. The isomeric mixture of **817–818** was subsequently heated in a 1:3 mixture (*v/v*) of thiophenol and heptane in the presence of a catalytic amount of AIBN to promote equilibration to deliver 91% of **817** as a single isomer. Intermediate **817** was then converted to ($\pm$)-7,8-epoxy-4-basmen-6-one **813** in an additional 12 steps in 18% overall yield.

In 1996, Chen and coworkers demonstrated a radical cyclization leading to the synthesis of ($\pm$)-chamigrene **824**, a spirocyclic sesquiterpene containing a spiro[5,5]undecane motif²⁴⁵ (Scheme 190). The α -allenic nitroketone radical precursor **820** was obtained in three steps from 1-methyl-4-nitrocyclohexene **819**, which itself was prepared via a known procedure. The treatment of **820** with *n*-Bu₃SnH and a catalytic amount of AIBN in refluxing benzene gave 37% of the 6-*exo-dig* cyclization product **821**, along with 26% of an enone byproduct

822. The reduction of the carbonyl group in **821** was achieved by dithiolation and a subsequent dethiolation employing sodium in liquid ammonia.

In 1999, Renaud and coworkers published a synthesis of (±)-botryodiplodin **829**, which is a mycotoxin that exhibits antibiotic and antileukemic activities²⁴⁶ by employing a Ueno–Stork reaction of allene **825**. This reaction involves a stereoselective radical cyclization of the α -bromoacetal moiety of an allene alcohol²⁴⁷ (Scheme 191). The stereoselectivity at C3 was controlled by the acetal center; however, the stereochemistry at C2 proved difficult to control. To overcome this stereoselectivity issue, the α -dibromoacetal **825** was employed to deliver **826** after the addition of the first equivalent of *n*-Bu₃SnH. The immediate addition of the bulky reductant TTMSS to **826** in situ yielded the all-*syn* product **827** in good yield. The *cis* stereoselectivity at C2 was attributed to the bulky reductant approaching from the face opposite to the C2 and C3 substituents. Hydrolysis of **827**, followed by Wacker oxidation, gave **829** as a mixture of anomers.

In 2003, Renaud and coworkers published the synthesis of enantiomerically pure (–)-botryodiplodin by utilizing (1*R*,2*S*)-2-phenylcyclohexanol as a chiral auxiliary.²⁴⁸ The enantio- and diastereomerically pure allene **832** was prepared in four steps from the allylated chiral auxiliary **831** (Scheme 192). The radical cyclization of **832**, followed by acetal hydrolysis and Wacker oxidation gave **830** in 15% yield.

In 2002, the Ley group published a synthesis of the framework of azadirachtin (Figure 2), a compound belonging to the C-*seco*-limonoid group of triterpenoids. Azadirachtin is a potent insect antifeedant, although its biochemical mode of action is not yet fully understood.²⁴⁹ Ley's strategy involved a highly diastereoselective Claisen rearrangement of a propargylic enol ether to build the C8–C14 (azadirachtin numbering) bond, whereas a radical cyclization of an allene was used to establish the bicyclo[3.2.1] ring system of the natural product.

In the synthesis, propargylic enol ether **835** was prepared from the pyran derivative **833** in eight steps in 31% overall yield (Scheme 193). After the extensive optimization of the conditions for the Claisen rearrangement, Ley discovered that the silyl deprotection of **834** to **835** afforded a better substrate for a microwave-assisted Claisen rearrangement. The irradiation of **835** with 15 consecutive 60 s pulses in 1,2-dichlorobenzene gave allene **836** in high yield. The radical cyclization of **836** first necessitated the protection of the hydroxyl groups at C1 and C3. However, TES protection at C3 failed due to the steric congestion at this site. The *bis*-xanthate **837** was designed as an alternative radical precursor and was obtained in good yield from **836**. Refluxing **837** in toluene in the presence of *n*-Bu₃SnH and AIBN exclusively gave an 81% yield of the *exo* cyclization product **838**. The absence of any *endo* cyclization product **839** was attributed to the steric inaccessibility of the tin hydride to form the tertiary radical center.

In 2008, Ley et al. completed the first total synthesis of azadirachtin.²⁵⁰ A different precursor (cf. **838** in Scheme 193) was used to construct the bicyclo[3.2.1] ring system, but the same strategy involving a radical cyclization of an allene was employed to convert **840** to **841** in high yield (Scheme 194).

In 2009, Hart et al. employed allene **851** as a radical acceptor in an attempt to develop a route to C₁₉ quassinoid polyandranes, such as **842–844**²⁵¹ (Scheme 195a). Previous attempts using the radical precursors **845** or **848** resulted in undesired byproducts **847**, **849**, and **850**. Products **847** and **850** were produced from the 1,6-hydrogen atom transfer of the vinyl radical intermediates **I** and **III**, whereas **849** was generated from the early quenching of the vinyl radical intermediate **II** by tin hydride (Scheme 195b). Allene **851** was considered to be an alternate substrate, as geometric constraints would forbid any 1,6-H transfer to form the undesired intermediate **853**. Indeed, the authors achieved a 95% yield of **852**, as demonstrated in Scheme 195c.

In 2015, Jahn et al. developed a radical cyclization approach to furnish diverse bridged diketopiperazines with variable ring sizes in good to excellent yield and with moderate to excellent *dr* from alkoxyamines;²⁵² one example is shown in Scheme 196a. Jahn applied this protocol to allene precursor **855** (Scheme 196b), prepared from a known dichloroacetamide **854** in three steps. The key bicyclo[4.2.2]piperazinedione ring system in **856** was furnished via an 8-*exo-trig* cyclization, where the carbon-centered radical regioselectively attacks the central allene carbon. Compound **856** was converted to **857** in 79% yield over two steps; **857** has been previously transformed to bicyclomycin in four additional steps by Williams.^{253,254}

7. CONCLUSIONS AND FUTURE PROSPECTS

The presence of two orthogonal double bonds in allenes imparts unique reactivity profiles to these unsaturated compounds, as compared with their alkene and alkyne counterparts. The rapid increase in the number of new synthetic methods available to prepare allenes bearing a diverse array of substitution patterns and structural complexities, often in an enantioenriched form, offers exciting opportunities to investigate the underexplored chemistry of these fascinating molecules. Within the context of allene reactivity, the addition of radicals has certainly been studied using a range of heteroatom- and carbon-based radical species for well over 50 years. Nonetheless, significant challenges remain in understanding the “rules” that govern the addition of radicals to allenes, despite the fact that our understanding of radical additions to alkenes and alkynes is fairly well-established. Several features of allenes contribute to this challenge, including the differing electron density distributions in allenes, especially between the two cumulated double bonds that are significantly affected by substituents installed directly (and even remote to) on the allene carbon(s). The orthogonality of the two π systems also presents difficulties in achieving predictable control over the regio-, site-, and stereoselectivities of allene functionalizations, in particular, in intermolecular reactions. This currently limits the synthetic utility of these building blocks in radical chemistry, and thus increasing our understanding of how to achieve both substrate and catalyst control over the selectivity is an enabling opportunity that will inspire the development of new methodologies with useful applications to complex and bioactive molecule synthesis.

In terms of what is known about intermolecular additions of halogen radicals to substituted allenes, addition typically occurs at the central carbon. However, little is known as to whether the nature of the solvent can alter the behavior of these reactions independent of substrate control; the advent of ionic liquids and supercritical solvents offers new

opportunities in this area. Further insight into reactivity patterns in the additions of halogens to allenes would also benefit from more careful kinetic and mechanistic studies employing a broader range of electronically and sterically distinct allenes now that the methodology is in place to secure such precursors in a convenient manner. Recent improvements in spectroscopic techniques to detect and interpret the behavior of radical intermediates as well as improved computational methods could also be brought to bear on updated versions of reactions that were carried out before these resources were available.

The ability to selectively control the addition of a carbon-based radical to an allene represents a powerful way to forge new C–C bonds while leaving significant functionality intact for further transformations. Thus far, reports surrounding the reactivity and selectivity of carbon-centered radicals show a heavy dependence on the substitution pattern of both the allene and the radical species. This is far from ideal, yet little has been done to date to explore whether the generation of carbon-based radicals using tunable, visible-light photocatalysts or electrochemical processes might offer more predictable control over the key C–C bond-forming process. These methods for generating radicals are certainly much milder than those traditionally used in these kinds of transformations. In addition, the ability to alter the lifetime of the intermediate carbon radical resulting from the addition to the allene could offer the chance to transfer axial chirality in the allene precursor to the product. In cases where stereochemical information from the allene substrate is lost due to the formation of achiral intermediates, a better understanding of the behavior of such reactive species could lead to asymmetric methods for the enantioselective construction of adjacent stereogenic carbons.

The introduction of heteroatoms into allenes by the addition of nitrogen-, phosphorus-, sulfur-, tin-, indium-, and selenium-based radicals is another powerful strategy to rapidly increase the structural complexity in products resulting from such reactions. Work thus far shows that heteroatom-based radicals prefer to attack at the central allene carbon, although changes in the substitution pattern of either reactant can change the product distribution. Nonetheless, the field requires that we explore a broader scope of substituted allenes to achieve a predictable and synthetically useful reactivity, particularly in intermolecular reactions. Easy access to silylated, borylated, and halogenated allenes offers potential ways to target the delivery of a heteroatom radicals to the distal allene double bond in intermolecular reactions. Intramolecular reactions largely depend on the tether length between the radical and the allene in the reported results, but the ability to flexibly control the ring size in these types of reactions through either substrate or catalyst control would be valuable. The identity of the radical could also be better understood, in particular, in the context of nitrogen radicals, which form extremely useful C–N bonds in reactions with allenes. This area might benefit greatly from the recent availability of photochemical and electrochemical methods to generate nitrogen radicals under mild and functional-group-tolerant conditions. Enantioselective methods to add nitrogen, phosphorus, and sulfur radicals to allenes could prove to be especially popular for rapid access to functionalized building blocks for bioactive chemical space.

Whereas there are some very nice examples showcasing the ability of tandem radical allene cyclizations to furnish complex molecular architectures, including application in the total

syntheses of natural products that include the pyrrolizidine alkaloids supinidine and heliotridine and (–)-botryodiplodin and, notably, Ley's first total synthesis of azadirachtin, we feel that the potential of such chemistry is greatly underexplored and will certainly benefit from advances in methodology.

In another class of reactions that potentially involve radical intermediates, cycloadditions of allenes with alkenes, alkynes, and other allenes have emerged as strategies for the rapid construction of polycyclic scaffolds. However, these reactions have not yet achieved broad synthetic utility and instead serve as valuable probes for mechanistic studies. Nonetheless, enyne–allene radical cyclizations are capable of generating significant molecular complexity through diradical intermediates that are of synthetic and biological interest. The key is to continue to explore allenes of diverse substitution patterns to identify transformations that are capable of participating in regio- and stereoselective reactions. Whereas this has been addressed to some extent in intramolecular reactions, many opportunities remain to address these challenges in intermolecular reactions. Whereas there are scattered reports of visible-light photo-catalysis involving allenes, further investigations in this area may prove fruitful, especially in the execution of tandem cyclizations to efficiently generate polycyclic scaffolds, ideally with excellent control over the stereochemical outcome of the reaction. All told, the field seems ripe for chemists to reinvestigate many old reactions involving the additions of radicals to allenes using modern catalysts, mild methods to generate radicals, the expanded range of readily available allenes, improved computational methods, and access to more advanced spectroscopic techniques for studying the behavior of radical intermediates.

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Jennifer M. Schomaker received her Ph.D. in 2006 from Michigan State University, working under the supervision of Prof. Babak Borhan. After completing an NIH postdoctoral

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Figure 1.
Cumulated π -bond system of allenes.

Figure 2.
Natural product azadirachtin.

Scheme 1.

Regio- and Stereoselectivity in Intermolecular Radical Addition to C1 or C3

Scheme 2.

Regio- and Stereoselectivity in Intermolecular Radical Addition to C2

Scheme 3.
Two Potential Reaction Pathways between Chlorine Radical and Propadiene

Scheme 4.

Cl Radical Addition to the C2 and C1/C3 Carbons of Propadiene in the Gas Phase

Scheme 5.
 Dichlorination of Aryl-Substituted Allenes **13** with 1-Chloro-1,2-benziodoxol-3-one

17a: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{D}$ **18**

17b: $\text{R}^1 = \text{R}^3 = \text{H}, \text{R}^2 = \text{R}^4 = \text{D}$

17a: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{D}$ **19**

17b: $\text{R}^1 = \text{R}^3 = \text{H}; \text{R}^2 = \text{R}^4 = \text{D}$

17c: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$

Scheme 6.

HBr/DBr Addition to Deuterated/Nondeuterated Propadienes

Scheme 7.
Equimolar HBr Addition to Propadiene in the Gas Phase

Conditions 20a(%) 21(%) 20b(%) 23(%)

-40 °C	63	13	24	trace
-70 °C	46	18	27	9
-70 °C ^a	33	24	30	13
-70 °C ^b	28	24	37	11

^aAIBN as the initiator ^bin 1 M propane

Scheme 8.

Equimolar HBr Addition to Propadiene in the Liquid Phase

Scheme 9.

HBr Addition to Excess Propadiene in the Liquid Phase

Scheme 10.
Rearrangements among Allylic, Vinylic, and Bridged Bromine Radical Intermediates

Scheme 11.

Proposed Mechanism for the Free-Radical Addition of HBr to Propadiene

17c: $R^1 = R^2 = H$: 98%

24: $R^1 = H, R^2 = Me$: 97%

25: $R^1 = R^2 = Me$: 89%

Scheme 12.

Free-Radical HBr Addition to Methyl-Substituted Allenes

Scheme 13.

Scope of Regioselective Radical Bromoallylation of Allenes 28

Scheme 14.
Proposed Mechanism of Regioselective Radical Bromoallylation of Allenes

Scheme 15.
Br-Radical-Mediated Three-Component Reaction for the Synthesis of 2-Bromo-1,7-dienes

Scheme 16.
Free-Radical Addition of CF_3I to Propadiene

^aHS = solvent (*iso*-octane)

Scheme 17.

Ratio of Rate Constants k_2/k_1 at 65 °C for Allenes and CF_3 Radical

Initiation: **Propagation:** **Termination:** **Scheme 18.**Proposed Mechanism of Free Radical Addition of CF₃I to Propadiene

Scheme 19.

Photoinitiated Radical Additions of Perfluoroalkyl iodides to Allenes

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R = P(O)Ph₂, P(O)(OEt)₂, CO₂Et, alkyl

R_F = (CF₂)₂Cl, (CF₂)₄Cl, (CF₂)₃CF₃, (CF₂)₇CF₃

Scheme 21.

Na₂S₂O₄-Initiated Radical Addition of Perfluoroalkyl iodides to Allenes with Electron-Withdrawing Groups

Scheme 22.

$\text{Na}_2\text{S}_2\text{O}_4$ -Initiated Radical Addition of Perfluoroalkyl iodides to 2,3-Allenols 44

Scheme 23. Cu(II)-Catalyzed formation of β -Trifluoromethyl Butenolides from 2,3-Allenoic Acids 46

(a) TEMPO trapping **(b) Enantioenriched allene** **(c) Reaction with 2,3-allenoate** **Scheme 24.**Evidence Supporting the Presence of a CF₃ Radical Intermediate

Pathway I: **Pathway II:**

Scheme 25.

Cu(II)-Catalyzed Formation of β -Trifluoromethyl Butenolides from 2,3-Allenolides

Scheme 26.

Cu(I)-Catalyzed Synthesis of Vinyl Trifluorides from Allenes with Togni Reagent II

Pathway I:Ar = *o*-I-C₆H₄ **Pathway II:** **Scheme 27.**

Cu(I)-Catalyzed Synthesis of Vinyl Trifluorides from Allenes with Togni Reagent II

R = *n*-C₅H₁₁, Cy, Ph, (CH₂)₂Ph,
n-Bu, *i*-Pr, (CH₂)₃OMe

13 examples
 47-75% yields
E:*Z* = 2:1-13:1

Scheme 28.

Cu(I)-Catalyzed Trifluoromethylazidation of Allenes With Togni's Reagent

$\text{R} = n\text{-C}_5\text{H}_{11}, (\text{CH}_2)_2\text{Ph},$
 $n\text{-Bu}, i\text{-Pr}$

8 examples
 70-90% yields
 $E:Z = 2:1\text{-}4:1$ (in DMSO) or 49-70% yields
 $E:Z = 3:1\text{-}9:1$ (in MeOH, at rt)

70b: 77%, $E:Z = 4:1$
 (in DMSO);
 70%, $E:Z = 9:1$
 (in MeOH)

70d: 80%, $E:Z = 3.5:1$
 (in DMSO);
 58%, $E:Z = 7:1$
 (in MeOH)

Scheme 29.

Cu(I)-Catalyzed Trifluoromethylthiocyanation of Allenes with Togni's Reagent

Scheme 30.
Proposed Pathway for Cu(I)-Catalyzed Trifluoromethylazidation and
Trifluoromethylthiocyanation of 1,1-Disubstituted Aryl Allenes with Togni's reagent

Scheme 31.

Cu(II)-Catalyzed Formation of CF_3 -Substituted Vinylic Cyclopropanes **75** from 2,3-Butadienyl Malonates **74** with Togni Reagent II

Formation of byproduct **76**:

Scheme 32.

Proposed Mechanism of Cu(II)-Catalyzed Formation of CF_3 -Substituted Vinylcyclopropanes **75** from 2,3-Butadienyl Malonates **74** with Togni Reagent II

Scheme 33.

Ru(II)-Catalyzed Formation of CF₃-Substituted Allyl Acetates from Allenes

Scheme 34.

Ru(II)-Catalyzed Formation of CF₃-Substituted Allyl Acetates from Allenes/Umemoto Reagent

(a) Reaction under N₂ vs. O₂ **(b) Proposed mechanism** **Scheme 36.**

Experimental Evidence and Proposed Mechanism for Ag(I)-Catalyzed Formation of α -CF₃ Acroleins from Allenes with Langlois Reagent

Scheme 37.
Measuring the Ratio of Rate Constants k_2/k_1

<u>Allene:</u>		k_2/k_1
17c: $R^1 = R^2 = R^3 = R^4 = H$		17.6 ± 0.2
26: $R^1 = R^2 = R^3 = H, R^4 = Me$		14.8 ± 2.0
88: $R^1 = R^2 = R^3 = H, R^4 = Et$		19.2
27: $R^1 = R^3 = Me, R^2 = R^4 = H$		13.8
89: $R^1 = R^2 = R^3 = R^4 = Ph$		52

Scheme 38.Selected Values of k_2/k_1 of Allenes at 65 °C

Scheme 39.
Free-Radical Addition of CH_3I to Propadiene

Scheme 40.

Free-Radical Additions of CF_3I , CH_3I , and CCl_3Br to Allenes

Selected experimental results **Scheme 41.**

Proposed Pathways of Free-Radical Addition of Bromomalonitrile to Propadiene

Scheme 42.

Free-Radical Addition of Samarium Ketyl to Methoxyallene

Scheme 43.

Mn(OAc)₃-Mediated Oxidative Free-Radical Reaction of Allenes with Malonate and Cyanoacetate

Scheme 44.

Mn(OAc)₃-Mediated Oxidative Free-Radical Reaction of Aryl-Substituted Allenes with Malonates

Scheme 45.

Proposed Mechanism of Mn(OAc)₃-Mediated Oxidative Free-Radical Reaction of Allenes with Dimethyl Malonate and Cyanoacetate

Mechanism for an alkene substrate:

Scheme 46.

Oxidative Radical Cyclization of Cyclic β -Keto Esters with Allene 115

Scope of allene:R¹, R² = H, alkyl, ArR³ = alkyl**Scope of amine:**R⁴ = Ar, R⁵ = alkyl, ArR⁶ = H, alkyl

16 examples, 12-67% yields

117:118 = 85:15-100:0*E:Z* (**117**) = 40:60-95:5 **117a**: 52%, *E:Z* = 50:50 **117b**: 47%, *E:Z* = 77:23 **117c**: 34%, *E:Z* = 40:60 **117d**: 12% (*E* only)**Scheme 47.**Ru(II)-Catalyzed α -Aminoalkyl Radical Addition to 2,3-Allenoates 116

Scheme 48. Proposed Mechanism of Ru(II)-Catalyzed α -Aminoalkyl Radical Addition to 2,3-Allenates

Scheme 49. Free-Radical Addition of Dialkyl *N*-Chloramines to Allenes 125

Scheme 50.

Nitro Radical Addition to Silyl Allenes and Conversion to Isooxazolidinone Derivatives

Scheme 51.

Chloronitration of Allenes 131 Using $\text{Fe}(\text{NO}_3)_3$ and FeCl_3

Scheme 52.

Proposed Mechanism for Nitroso Nitration and Chloronitration of Silyl Allenes

(a) Formation of allenamides:

R¹ = Ar; R² = alkyl, TMS, H

R³ = H, *n*-C₅H₁₁

(b) Proposed catalytic cycle:

Scheme 54.

Synthesis of Allenamides via Oxidative Coupling of Allenes and *N*-Fluoroaryl-sulfonimides

Scheme 55.
 Ag(I)-Catalyzed Aminofluorination of Allenes **144**

Scheme 56.
Phosphine Addition to Propadiene by UV Irradiation

Allene	R^1	R^2	R^4	R^3	Condition	Yield% ^a	Product Distribution
146a	H	$-(\text{CH}_2)_6-$	H	H	AIBN	100	147a only
146b	Me	Me	Me	Me	$h\nu$	55	148b only
146c	<i>n</i> -Bu	H	H	H	$h\nu$	96	147c ^b : 148c : 149c ^c = 80:5:15
146d	SnMe_3	H	H	H	$h\nu$	40	147d ^d : 148d : 149d ^c = 55:20:25
146e	OMe	H	H	H	AIBN	96	147e only ^e
146f	Ph	H	H	H	AIBN	95	147f ^f : 148f = 86:13
146g	<i>t</i> -Bu	H	H	H	AIBN	98	147g ^g : 148g : 149g ^h = 64:9:27

^aGLC yields ^b*E*:*Z* = 55:25 ^c*E* only ^d*E*:*Z* = 40:15 ^e*E*:*Z* = 61:39 ^f*E*:*Z* = 72:14
^g*E*:*Z* = 45:19 ^h*E*:*Z* = 20:7

Scheme 57.

Product Distribution of Diphenylphosphine Addition to Allenes **146**

(a) Selected results

RSO_2I	R	151(%)	152(%)	153(%)	154(%)
150b	Et	25	12	28	31
150c	<i>i</i> -Pr	4	33	52	17
150e	<i>p</i> -MeC ₆ H ₄	60	0	16	0

(b) Proposed mechanistic pathways

Scheme 58.

Free-Radical Addition of Sulfonyl Iodides to Propadiene

Radical intermediate for formation of 156:

Scheme 59.
Free-Radical Addition of Sulfonyl Iodides to Allenes

Scheme 60.
Free-Radical Addition of Tosyl Iodide to Allenes

Scheme 61.

Tosyl Iodide Addition to Optically Active Allenes 27 and 101

Scheme 62.

Radical Addition of *p*-Tsl/*p*-TsBr to Allenic Alcohols

Scheme 63.
Radical Addition of *p*-TsBr to Allenic Sulfonamides

Scheme 64.
 Radical Addition of *p*-TsBr to Monosubstituted Allenes

Scheme 65.

Radical Addition of p -TsBr to α -Allenic Alcohols and 1,4-Elimination of the Radical Adducts

^a1 equiv of CuCl instead of CuI. ^b0.7 equiv CuBr was used instead of CuI.

Proposed mechanism:

Scheme 66.

Cu(I)-Catalyzed Sulfur Iodide Addition to Allenes and a Proposed Mechanism

Scheme 67.

Arylsulfonylation of 2,3-Allenic Acids and a Proposed Mechanism

Scheme 68.

Regio- and Stereoselective Oxysulfonylation of Allenes 191 and 193

Scheme 69.

Proposed Mechanism for Oxysulfonylation of Allenes

Proposed mechanism:

Scheme 70.

Cu(I)-Catalyzed Cyclic Oxytrifluoromethylthiolation of 2,3-Allenic Acids 201

Scheme 71. Cu(II)-Catalyzed Bis-trifluoromethylthiolation of 2,3-Allenic Acids **205**

^aYields calculated based on the amount of Me₃SnH ^bE:Z = 38.6:16.3

^cE:Z = 10:3.5 ^dE:Z = 12.3:42.2

Scheme 72.

Free-Radical Addition of Me₃SnH to Allenes

Scheme 73.

Increased C2 Attack with Increasing Methyl Substitution on the Allene

***207-96** denotes product **207** formed from starting allene **96**, same for **208-96**

Scheme 74.

Intermediates **211** and **211'** Leading to the Formation of **207-96** and **208-96**

Scheme 75.

Intermediates **212** and **212'** Leading to the Formation of **208-26-(E)** and **208-26-(Z)**

***207-27** denotes product **207** formed from starting allene **27**

Scheme 76.

Intermediates **213** and **213'** leading to the formation of **207-27-(E)** and **207-27-(Z)**

Allene	R^1	R^2	215(%)	216(%)	217(%)	Ratio (C:T)
17c	H	H	40	24	0	24:40
214a	$n\text{-C}_{10}\text{H}_{21}$	H	E only, 5	51, $E:Z = 3:2$	10	61:5
214b	SiMe_2Ph	H	0	$E+Z$, 33	62	95:0
214c	$n\text{-C}_5\text{H}_{11}$	$n\text{-C}_5\text{H}_{11}$	0	81, $E:Z = 32:68$	0	81:0
101	$-(\text{CH}_2)_6-$		0	74	0	74:0

Scheme 77.

BEt₃-Induced Radical Addition of Ph₃SnH to Allenes

Scheme 78. BEt_3 -Induced Radical Addition of Ph_3GeH to Allenes

Selected results:

Condition (1): 1.2 equiv Me_3SnH , cat. AIBN, 80 °C, 20 h; (2): 1.2 equiv Me_3SnH , $h\nu$, 15 h

Scheme 79.

Free-Radical Addition of Me_3SnH to Allenes

Scheme 80.
Free-Radical addition of Bu_2SnIH to Allenes **221**

Generation of Bu₂SnIH: **Proposed mechanism:** **Scheme 81.**Proposed Mechanism for Bu₂SnIH Addition to Allenes

Scheme 82.
 O_2 -Initiated Radical Addition of Benzene Selenol to Allenes

Scheme 83.

Free-Radical Addition of Diphenyl Diselenide to Allenes

Scheme 84.

Photoinduced Thioselenation of Allenes 232 by Using the (PhS)₂–(PhSe)₂ Binary System

Scheme 85.

Photoinduced Dithiolation of 4,4-Dimethylpenta-1,2-diene 146g with a (PhS)₂–(PhTe)₂ Binary System

Scheme 86.
Selenophosphination of Allenes 236

Scheme 87.

Proposed Mechanism for Selenophosphination of Allenes

Scheme 88.

Visible-Light-Initiated Phenylchalcogenyl Oxygenation of Allenes

Scheme 90.

Proposed Mechanism of Photoinduced Chalcogenyl Oxyfunctionalization of Allene

Scheme 91.
 Hydroindation and Sequential Protonation of Allenes

electrolysis conditions: H-cell to $4\text{F}\cdot\text{mol}^{-1}$, carbon rod cathode $[-2.43\text{ V (vs. Ag/AgI)}]$, DMF, Et_4NOTs ($\sim 0.7\text{M}$)

Scheme 92.

Reductive Cyclization of Allenic Ketones by Electrolysis

Scheme 93. Annulation via a 5-*exo-dig* versus 5-*endo-dig* Pathway

* $\text{NaC}_{10}\text{H}_8$ = sodium naphthalenide

Scheme 94.
Dissolving Metal-Assisted Reductive Cyclizations of Allenic Ketones

Scheme 95. Photochemically Induced Reductive Cyclization of Allenic Ketones in the Presence of Et_3N

Conditions:

(1): 2 equiv SmI_2 , 2 equiv $t\text{-BuOH}$, THF, rt

(2): 2 equiv SmI_2 , MeOH

Scheme 96.

SmI_2 -Mediated Regioselective Reductive Cyclization of Ester-Substituted Allenic Aldehydes

Scheme 97.

SmI₂-Mediated Reductive Cyclization of Allenic Aldehydes and Ketones

Scheme 98.

Reductive Radical Cyclizations of Allenyl Lactones in the Presence of $\text{SmI}_2\text{-H}_2\text{O}$

Scheme 99.

Proposed Mechanism for Formation of Cycloheptan-1,4-diols and Hemiketals

Scheme 100. Reductive Cyclization Cascades of *cis*- and *trans*-Allenyllactones

Scheme 101.
 Reaction of Homoallenyl Iodides with $n\text{-Bu}_3\text{SnH}$

(1) mineral oil, 80 °C: **311:312** = 61:39

(2) hexane, rt: **311:312** = 47:53

(3) neat, rt: **311:312** = 1:99

Scheme 102.

Reactions Studying the Equilibrium between Homoallylic and Vinyl Cyclopropyl Radicals

Allene	n	X	Condition	Yield%	Product (ratio)
313a	1	Br	(1)	90	314:315 = 45:51
			(2)		314:315:316 = 39:42:17
313b	2	I	(1)	80	314:315:316:317 = 4:27:20:49
			(3)		316 = 100
313c	3	I	(1)	91	316:317:other ^a = 60:23:17
			(3)		316 = 100
313d	4	I	(1)	75	316:other ^b = 90:10

Condition: (1) PhH (2) neat, AIBN (3) neat

Scheme 103.

Cyclizations of Carbon-Centered Allenyl Radicals Generated from $n\text{-Bu}_3\text{SnH}$

Scheme 104. Potential Reaction Pathways and Product Distributions for *n*-Bu₃SnH Reduction of Allenes

$\text{R}^1 = \text{Cl, Me, Ph, etc.}$
 $\text{R}^2 = \text{H, etc.; X = Br, I}$
 $\text{Z} = \text{O, NTs}$

6 examples
66-82% yields

326a: 80%

326b: 78%

326c: 80%

Scheme 105.
 $n\text{-Bu}_3\text{SnH}$ -Mediated Radical Cyclization of *o*Haloaryl Allenylmethyl Ethers and Amines

Scheme 106.

Ueno–Stork-Type Radical Cyclization of Bromoacetal-Containing Allene 327

Allene	k	X	Y	Z	333(%)	<i>dr</i> (333)	334(%)
332a	0	H	H	H	36	-	23
332b	1	H	H	H	46	1:1.2	26
332c	1	Me	Me	H	45	1:2.5	8
332d	1	H	H	Me	47	1:1.1	10

(c) **Mechanism for formation of minor isomer:**

Scheme 107.

Photoinduced Radical Cyclizations of α -Iodoallenic Ketones

Scheme 108.
n-Bu₃SnH-Mediated Radical Cyclization of Allenamides

*Smaller value is underlined for convenience

*Unit: kcal/mol

(a) X = CH₂:

Allene	n	$\Delta G^\ddagger$ (P)	$\Delta G^\ddagger$ (C)	ΔG (P)	ΔG (C)
343a	1	<u>15.0</u>	17.9	4.3	<u>-16.6</u>
343b	2	19.6 ^a	<u>8.8</u>	3.7	<u>-39.8</u>
343c	3	<u>10.7</u> ^b	11.6 ^b	-15.8	<u>-42.7</u>

(b) X = NMe:

Allene	n	$\Delta G^\ddagger$ (P)	$\Delta G^\ddagger$ (C)	ΔG (P)	ΔG (C)
344a	2	26.1	<u>14.5</u>	13.7	<u>-31.5</u>
344b	3	<u>15.8</u> ^b	17.2 ^a	-4.1	<u>-32.3</u>

(c) X = O:

Allene	n	$\Delta G^\ddagger$ (P)	$\Delta G^\ddagger$ (C)	ΔG (P)	ΔG (C)
345a	2	17.6	<u>7.8</u>	4.5	<u>-40.7</u>
345b	3	<u>6.0</u> ^b	7.4 ^{a,b}	-14.8	<u>-42.6</u>

^aBoat TS ^bChair TS

Scheme 109.

Calculated $G^\ddagger$ and G for the Addition of C-, N-, and O-Centered Radicals to Allenes

Allene	n	$\Delta G^\ddagger$ (P)	ΔG_{intrin}	ΔG_{therm}	$\Delta G^\ddagger$ (C)	ΔG_{intrin}	ΔG_{therm}
343a	1	15.0	12.8	2.2	17.9	25.5	-7.6
343b	2	19.6	17.7	1.9	8.8	24.7	-15.9
343c	3	10.7	17.7	-7.0	11.6	29.0	-17.4

Scheme 110.

Intrinsic and Thermodynamic Barriers for Carbon-Centered Radical Cyclizations of Allenes

Scheme 111.
Radical Cyclization of Enantiopure and Racemic 2-Azetidinones Tethered to Bromovinyl
and Haloaryl Allenes

Scheme 112.

Ti(III)-Induced Intramolecular Radical Cyclizations of Epoxyallene Ethers and Amines

Scheme 113.

SmI₂-Mediated Radical Cyclization of Allenylanilines 354 and Allenyl Aryl Iodides 356

Scheme 114.
 $n\text{-Bu}_3\text{SnH}$ -Mediated Radical Cyclizations of Allenes 359

Scheme 115.

Heteroatom-Nucleophile-Induced Grob-Type Fragmentation and Intramolecular Oxidative Radical Cyclization of the Fragmentation Product 366

Scheme 116.

One-Pot Synthesis of α -O-, S-, and N-Substituted 4-Methylquinoline Derivatives 373

Scheme 117.

Mechanism for Cu(I)-Catalyzed Aerobic Oxidative Cyclization of *N*-Hydroxyaminoallenes
374

Scheme 118.

Prediction in the Regioselectivity of C-, N-, and O-Centered Radical Additions to Allenes

Type 1: **e.g.:** **Type 2:**

(only the first step
of the tandem
cyclization is shown)

e.g.: **Scheme 119.**

Simplified Schemes of Tandem Radical Cyclization Reactions Involving Allenes

Scheme 120.

Tandem Radical Cyclizations of Allenamides 383 and 389

Starting from 383: **Starting from 389:** **Scheme 121.**

Proposed Mechanisms for the Formation of 386–388 and 390

Scheme 122.
 Tandem Radical Addition/Cyclization of Allene-enes **393** and Dehydroiodination of Vinyl Iodides **394**

Scheme 123.

Phenanthrenes via Oxidative Cyclization of 2-Allenyl-1,1'-biphenyl **396** and α -Carbonyl Alkyl Bromide **397**

Scheme 124.

Mechanism for Oxidative Cyclization of 2-Allenyl-1,1'-biphenyl and α -Carbonyl Alkyl Bromide

Scheme 125.

Vinyl Sulfone Formation via Radical Addition/Cyclization of Tosyl Bromide to Allene-enes
405

Scheme 126.

Radical Addition/Cyclization of Tosyl Bromide to Allene-enes 407 and 409

Scheme 127. Radical Addition/Cyclization of *p*-TsBr to β -Allenyl Ketoximebenzoates 413

Scheme 128.

Proposed Mechanistic Pathways for Radical Intermediate 418

Scheme 129.*p*-Ts-Radical-Initiated Tandem Radical Addition/Cyclization Reactions of Bis(allenes) 419

Scheme 130.
Mechanism for Phenyl-Thiyl-Radical-Initiated Tandem Radical Addition/Cyclization of Allene-enes

Scheme 131.

Substrate Scope for Aryl-Thiyl-Radical-Initiated Tandem Addition/Cyclizations of Allene-
 enes

Selected examples ^aMajor isomer has -Me *cis* to -NHOMe group.**Proposed mechanism** **Scheme 132.***n*-Bu₃Sn-Radical-Initiated Tandem Addition/Cyclization of β -Allenyl *O*-Methyloximes **428**

Scheme 133.
n-Bu₃Sn-Radical-Initiated Tandem Addition/Cyclization of *N,N*-Dimethyl β -Allenyl Hydrazones

Scheme 134.*n*-Bu₃Sn-Radical-Initiated Cyclization of Allene-Tethered *O*-Benzyl Oximes 436

^aratio of *cis:trans*; Me and NHOBz *cis* in major isomer. ^b n -Bu₃SnH was used. ^cPh₃SnH was used.

^aratio of *cis:trans*; Me and NHOBz *cis* in major isomer.

R^1	R^2	444 (%)	445 (%)	446 (%)	447+448 (%)	R^1	R^2	444 (%)	445 (%)	446 (%)	447+448 (%)
H	Me	44(9:1 ^a)	19	0	0	Me	Et	0	0	42	48
Me	Me	0	0	82	<10	$-(CH_2)_5-$		0	0	17	43

^aratio of *cis:trans*; Me and NHOBz *cis* in major isomer.

Scheme 135.

n -Bu₃Sn-Radical-Initiated Cyclization of β -Allenylbenzoyloximes 443

Scheme 136.

n-Bu₃Sn-Radical-Initiated Tandem Addition/Cyclization of Allene-Tethered Hydrazones and Oximes

Scheme 137.

Ph₃Sn-Radical-Induced Cyclization of 2-Azetidinone-Tethered Allenynes

Scheme 138.

Tin-Radical-Promoted Cyclization of Bromovinyl and Halo-aryl Allenes 459–464

Scheme 139. Dibutylidotin-Radical-Induced Tandem Addition/Cyclization of Allene-ene **472**

Scheme 140.

Tris(trimethyl)silyl Radical Promoted Cyclization of Alkenyl Allenecyclopropanes **475** and **476**

Scheme 141.

Effect of Tether Length on Silyl-Radical-Promoted Cyclization of 484 and 486

Scheme 142. Indium Radical-Initiated Tandem Addition/Cyclization of Allene-enes **491**

Scheme 143.
Various Oligomeric Byproducts from Thermal Dimerization of Allenes

Scheme 144.
Plausible Diradical Intermediates and Resulting Dimers Formed via Allene Dimerization

Substrate	Condition	512 (%)	513 (%)	514 (%)	Condition
24	A	46.5	35.6	17.8	A: 151 °C, 0.3 h
511	B	46.7	36	17.3	B: 151 °C, 0.3 h
511 ^a	C	~53	~33	~14	C: 35 °C
511 ^a	D	~53	~32	~15	D: 300-nm filter, 34.5 °C

^aRatios were extrapolated.

Scheme 145.

Dimethylenecyclobutane Derivatives Obtained via a Presumed Diradical Intermediate

Scheme 146.
Pyrolysis of Bis(dideuteriomethylene)cyclobutane 515

Compound	T (°C)	% Conversion	526:527:528:529
520	207	28	20:14:33:33
520	300	>99	34:21:25:25
521	207	33	11:16:36:37
521	300	>99	26:20:22:28

Scheme 147.

Thermal Intramolecular Dimerization of Racemic and Meso Bisallenenes 520 and 521 at 1 mmHg

General reaction: **(a) Stepwise (diradical intermediate):**

i) via C2 attack

ii) via C1 attack

iii) via C3 attack

(b) Concerted

i) [p2s + p2a]

ii) [p2s + (p2s + p2s)]

Scheme 148.

Mechanistic Aspect of Thermal Allene–Alkene [2 + 2] Cycloadditions

Scheme 149.
Previous Evidence of Diradical Intermediate

Scheme 150.

Proposed Reaction Pathways for Allene/Alkene Cycloaddition under Thermal Conditions

Scheme 151.

Diradical Pathway for the Allene/Alkene [2 + 2] Cycloaddition To Furnish Methylenecyclobutanes

Scheme 152.

Product Distribution from Reaction of Allene with *N*-Phenylmaleimide

Scheme 153.

Formation of Products from Reaction of Diethyl Fumarate and Alkyl-Containing Allenes via Diradical Pathways

Scheme 154.

Evaluating Internal Rotation and Cleavage Properties of Diradical Intermediates in Allene–Alkene [2 + 2] Cycloadditions

Scheme 155.

Reaction of Methoxy- and Chloro-Substituted Allenes with 542

Scheme 156.

Intramolecular [2 + 2] Addition of an Alkene to a (Phenylsulfonyl)allene

Scheme 157.

Effect of Tether Variations on the Thermal Reaction of (Phenylsulfonyl)allenes

Scheme 158. Synthesis of Tricyclic β -Lactams from [2 + 2] Cycloaddition

Potential intermediates/Transition states

(a) Diradical (allylic and vinyl radical)

(b) Diradical (vinylic and vinyl radical)

(c) Concerted transition states

Scheme 159.

Potential Products of Intermolecular [2 + 2] Cycloaddition of Alkynes and Allenes

Scheme 160.

Competition Experiment Involving an Alkyne, Alkene, and Allene under Thermal Conditions

Scheme 161. Intramolecular [2 + 2] Reaction Pathways Involving the Distal π -Bond of the Allene

Scheme 162.

Investigating the Possibility of Diradical Intermediates Using Cyclopropyl Probes

Scheme 163.
 Intramolecular [2 + 2] Cycloaddition of Allenynes

Scheme 164. Intramolecular [2 + 2] of Diallene–Diyne To Result in Tricyclic β -Lactam Dimers

Scheme 165.

General Depiction of the Schmittel and Myers-Saito Cyclizations

Scheme 166.
Radical Trapping Experiments Using 1,4-CHD

Scheme 167.
 Cyclopropyl Trapping Experiments from the Dipolar and Diradical Pathways

Scheme 168.

Generation of a Variety of Allene Precursors from [2,3]-Sigmatropic Rearrangement

Scheme 169.
Various Enyne-Allene Substitution Patterns

(a) 1993, Wang et al.

(b) 1995, Grissom et al.

(c) 1999, Wang et al.

Scheme 170.

Radical Cascade Reactions Utilizing the Myers–Saito Cyclization

Scheme 171.
General Depiction of the Schmitt Pathway

Scheme 172.
Proposed Pathways for the Schmittel Cyclization

Scheme 173.

Intramolecular KIE Experiments for Investigating the Mechanism of the Schmitt
Cyclization

Scheme 174.

Thermal and Photochemical Investigation of the Schmittel Cyclization with Cyclopropanes

Scheme 175.
Synthesis of Polycyclic Molecules via Schmitt Cyclization

Scheme 176.

Potential Intermediates and Products from Thermal Reactions of Acyclic 1,3-Bis(alkylthio)allenes

Scheme 177.

Irradiation of 1,3-Bis(alkylthio)allenes

Scheme 178.

Reactions of Cyclic Bisalkylbissulfur Allene under Photochemical and Thermal Conditions

Scheme 179.

Reaction of Bisseleniumallenes under Thermal Chemical Conditions

Scheme 180.

Reaction of Bisseleniumalkylallenes under Photochemical Conditions

Scheme 181.
Support for a Radical Mechanism

(a) Photochemical **(b) Thermal** **Scheme 182.**

Thermal and Photochemical Reactions of Cyclic Bissulfur Allenes

Scheme 183.

Mechanistic Pathways for the Reaction of 1,3-Butadiene with Propadiene

Scheme 184.

Mechanistic Pathways for the Reaction of Propadiene with Benzene

Scheme 185.

Mechanistic Pathway and Ratio of Products from Cyclization of Allene Hydrazines

Scheme 186.
 $n\text{-Bu}_3\text{Sn}$ -Radical-Initiated Cyclization of Allenes

Scheme 187.
Synthesis of (±)-Supinidine from 804 and 805

Scheme 188. Synthesis of (+)-Heliotridine via $n\text{-Bu}_3\text{SnH}$ -Initiated Free-Radical Cyclization

Scheme 189.

Synthesis of (±)-7,8-Epoxy-4-basmen-6-one 813

Scheme 190.
Synthesis of (±)-α-Chamigrene

Scheme 191.
Renaud's Synthesis of (±)-Botryodiplodin

Scheme 192.
Renaud's Synthesis of (-)-Botryodiplodin

Scheme 193.

Claisen Rearrangement and Allene Radical Cyclization as an Approach to Azadirachtin

Scheme 194.

Radical Cyclization of Allene 840 for the Total Synthesis of Azadirachtin

Scheme 195.

Free-Radical Cyclizations of Alkynes and Allenes as Routes to the Synthesis of Polyandranes

Scheme 196.

Synthesis of Bridged Diketopiperazines and Applications to the Synthesis of Bicyclomycin