Notorious Radicals and Their Fate

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Received: 26 March 2020 Published: 10 April 2020

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Abstract

Organic chemistry has been an essential part of our civilization. In this article, we talk about one of the four intermediates in organic chemistry – "the radical". The evolution of radical from being termed as notorious to a versatile intermediate in organic transformations to generate complex molecular architectures and natural products has been discussed. We attempt to explain herein some basic aspects of radicals in the domain of organic synthesis through examples reported over the years from our laboratory.

Key words: Radicals, homolytic fission, vinylogous carbonates, intramolecular cyclization, Baldwin's rule

What alchemy was to the ancient civilization, chemistry is to the modern world! Organic chemistry has been a boon and has improved all facets of our lives, namely, agriculture, health, energy, textile and technology. For instance, eyesight is feasible due to a molecule present in our eyes, retinal, which undergoes structural change, in turn helping us in vision. Fragrance always has a significance, be it the smell of flowers such as roses, jasmine, or of fruits like oranges and lemons. The salivating truffle taste is due to a sulfur containing molecule whereas the vanillin gives the vanilla flavour we cherish in ice creams and cakes (figure 1).[1] Moreover, dyes such as Indigo, which has been a major part of our Indian history, is an organic molecule. All our five senses have been related to organic chemistry in one way or the other!

Numerous examples of organic compounds in nature make us believe that it is indeed possible to mimic it. To understand as well as replicate the structures and functions of nature,

organic chemistry and its tools have been studied and built over several years. The reactivity of organic molecules (mainly carbon containing compounds) can be ascertained if the intermediates can be studied broadly.

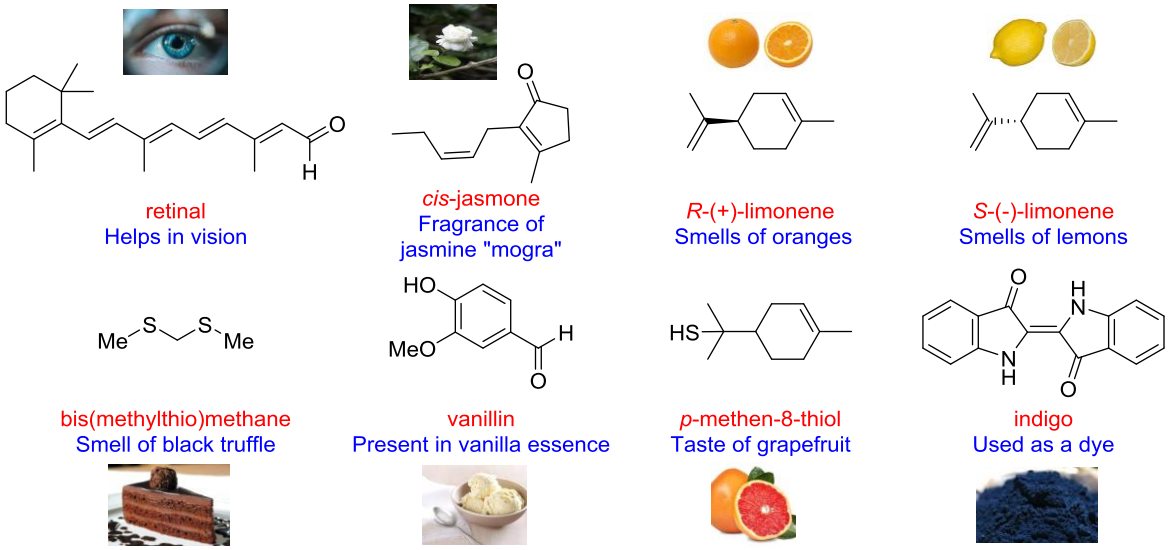


Figure 1: Organic molecules influencing our senses[1]

The primary intermediates in organic chemistry are cations, anions, radicals and carbenes (figure 2). They help in predicting and realizing synthesis of complex natural products, which are biologically significant. If you recall, in school, we are mainly taught about the ionic reactions, which involved the cations and the anions, and their reactivity and stability. They can be obtained by a heterolytic fission of a chemical bond, e.g. A in A–B allows B to take both the bonded pair of e⁻s, thus A becomes positively charged (cation) and B becomes negatively charged (anion). The 'book keeping' of electrons during the bond breaking process is denoted by a spear headed arrow.[2]

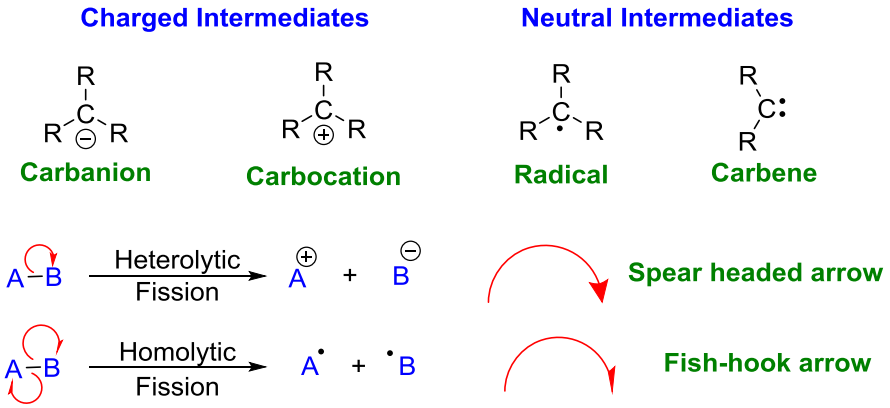


Figure 2: Reactive intermediates and their formation[2]

However, there is an alternative possibility for bond fission in which both A and B in A–B retain one e^- each. In this scenario, the intermediates $A^\bullet$ and $B^\bullet$ are both neutral and are called radicals. This homolytic fission is denoted by a 'fish-hook' arrow. Since their valency is incomplete, they look for options of completing it by a reaction, which many a times appears to be random. For several decades, the scientists thought that chemistry of radicals is quite mysterious! If looked at platonically, we may perceive them to be harmful. Free radicals are known to get generated in combustion of fuel in an engine. Did you know that melanin in our skin helps in preventing generation of free radicals by protecting us from UV rays of the sun? Do you know why green tea is considered good for weight loss? The current hypothesis is that it contains anti-oxidants, which have free radical scavenging capability. However, at school level, the knowledge of radicals that we got was of halogenation and ozone layer depletion. We studied that reactions of radicals are uncontrollable as they seem to be unstoppable until all the reactants are consumed. In fact, even in the early part of the 20th century, scientists largely focused on the ionic reactions (involving cations and anions) alone as they were far better controllable. Although, Gomberg was able to isolate triphenyl radical in 1900, it was not until 1930 that chemists could find enough evidence to accept that a trivalent carbon species existed.[3-4] Organic chemists had not taken appropriate risks for taming the notorious radicals. Perhaps, this was the time when the word "radical" got a negative connotation in English language! With the influx of courageous and innovative chemists came strategies with which the stability and reactivity of the radicals were studied. The initial breakthroughs on 'taming' radicals fruitfully were in the domain of polymer chemistry. Synthesis of polymers with different properties and hence diverse uses quickly caught the imagination of the industry in the middle of 20th century. Industrialization can be attributed to the progress in the synthesis of various polymers and textiles such as polystyrene, Teflon etc. *via* radical chemistry, in turn enabling the faith in these intermediates. Radicals became as important and sought out in the world of polymer chemistry as "Harry Potter" is to the wizarding world! Sustained efforts over the years on taming radicals to carry out well defined and controlled reactions finally yielded fruits, when organic chemists could tweak their substrates in such a manner that the radical reactions progressed only at the reactive centres and nowhere else. It was a great turning point and it led to 'mainstreaming' of this ephemeral intermediate. The developments in the understanding of the radical chemistry was so rapid that today, organic chemists confidently

plan the total synthesis of complex natural products using radical based reactions in key steps. But, it was not until the total synthesis of hirsutene by Curran in 1985 that we saw an efficient use of a cascade (a series of reactions, *vide infra*) radical cyclization.[5-15] Now, let us try to understand how and why radicals behave in a certain way and how they were tamed.

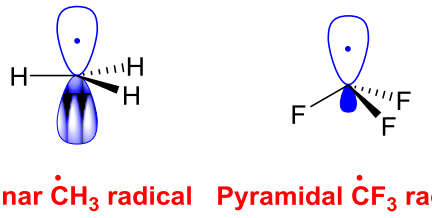
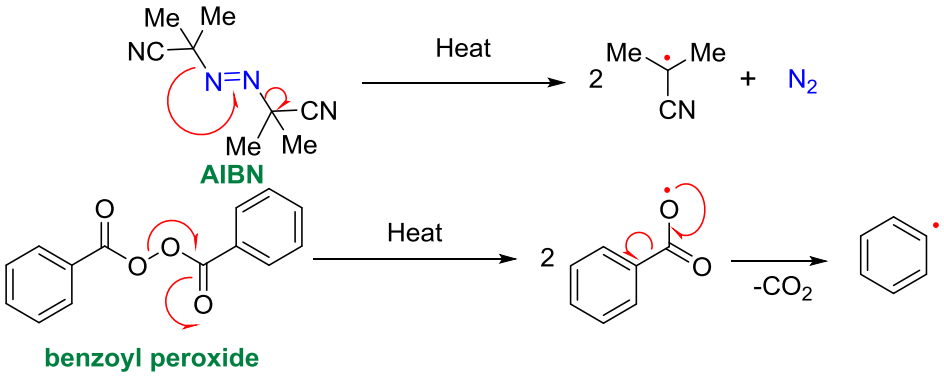


Figure 3: Structure of carbon centred radicals[1]

The radical, in specific, carbon radical is a species, which is trivalent and contains a single electron in the *p* orbital. It is electron deficient in nature. Its geometry is mostly planar but could occasionally be pyramidal due to certain substituents present on it (figure 3).[1]

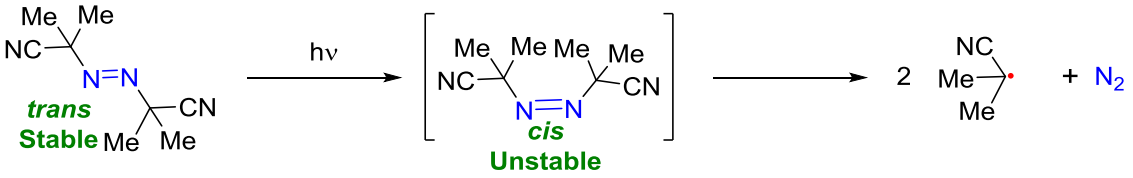


Scheme 1: Radical generation by thermolysis[2]

There are two ways of generating radicals by homolytic cleavage of covalent bonds:

1. **Thermolysis:** Most covalent bonds are strong and require high temperature (> 800 ^{o}C) to cleave them. But some molecules have weaker covalent bonds, which can be cleaved homolytically at <150 ^{o}C (Scheme 1), *e.g.* Azobisisobutyronitrile (AIBN), benzoyl peroxide, triethyl borane etc. In AIBN, generation of N_2 is the driving force for the homolytic C-N bond cleavage. On the other hand, in benzoyl peroxide, initial homolytic cleavage of O-O bond generates $PhCOO^{\bullet}$, which readily loses stable CO_2 leaving behind $Ph^{\bullet}$ radical.[2]
2. **Photolysis:** Weaker covalent bonds have the tendency to break when shown to light. For instance, AIBN produces radicals by converting into its *cis*-isomer, which is unstable and

hence cleaves C-N bond to generate radical and N_2. Expulsion of N_2 is entropically favoured process.[2]



Scheme 2: Radical generation by photolysis[2]

Thus, radical reactions can be initiated both by heat as well as light. Homolytic bond cleavage has been studied extensively and is dependent on the bond dissociation energy (energy required for the formation of that radical) (BDE).[16]

Bond	BDE (kcal/mol)	Bond	BDE (kcal/mol)	Bond	BDE (kcal/mol)
CH_3-H	105	F-H	136	PhS-H	83
CH_3CH_2-H	100	Cl-H	102	$(CH_3)_3Si$-H	93
$(CH_3)_2C$-H	98	Br-H	87	Bu_3Sn-H	78
$(CH_3)_3$-H	96	I-H	71	PhCOO-OOCPh	60
CH_2=CH-H	111	H_2NCH_2-H	84	$HOCH_2$-H	96
HC≡C-H	133	HO-H	119	H-H	104

Table 1: Bond dissociation energies (BDEs) of various molecules[16]

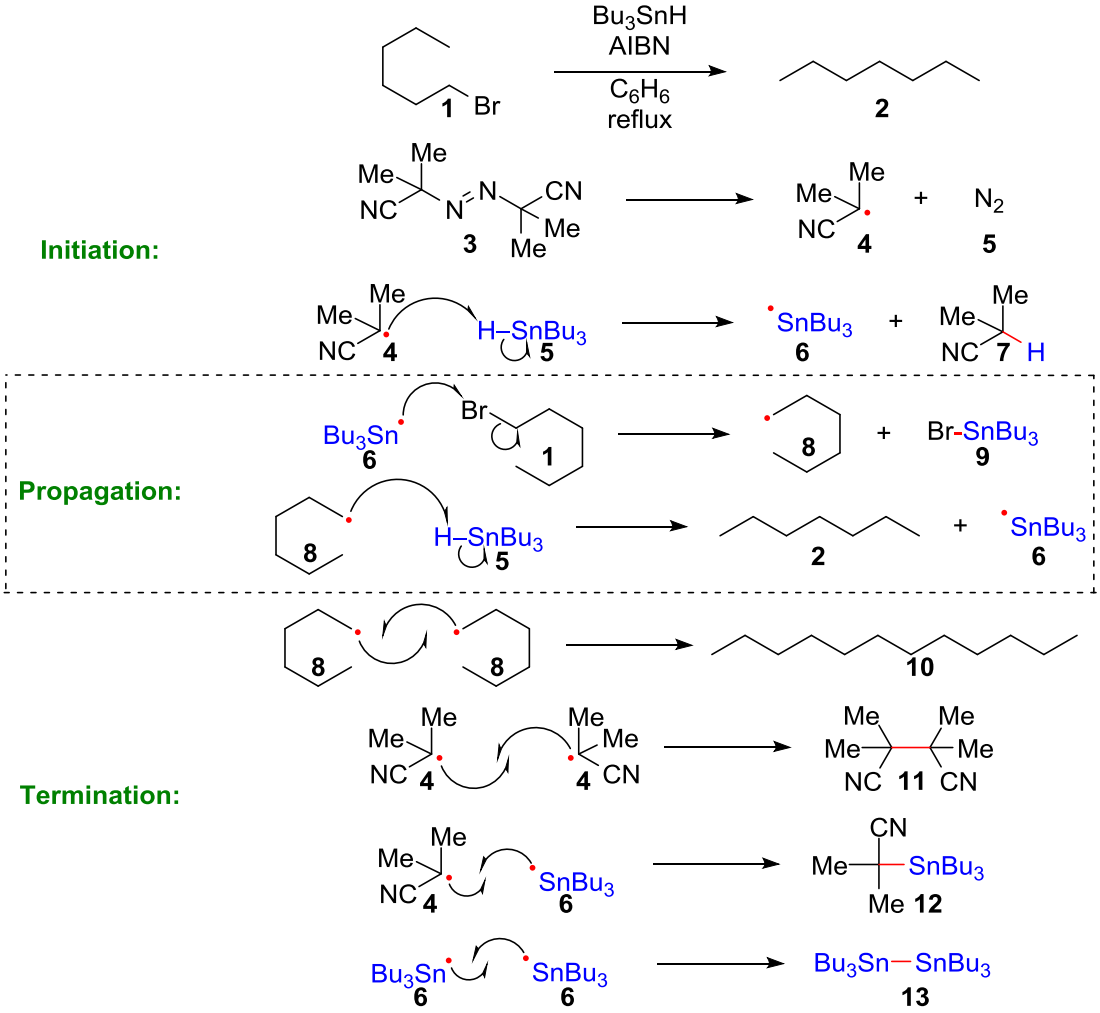
Table 1 shows the BDE of various radicals. If you observe closely, as the branching in carbon chain increases from methyl, ethyl, isopropyl to *tert*-butyl, the BDE slightly decreases – lower the BDE, easier cleavage. More the substitution on the radical carbon, more stable is the radical. This is similar to the property of cations (inductive effect and hyperconjugation). Allylic radical is more stable than vinylic (ethylene). Special mention must be made of PhS-H, Bu_3Sn-H and $[Ph(CO)O]_2$, which play key roles in most of the radical reactions, due to their low bond dissociation energy. As mentioned previously $[Ph(CO)O]_2$ undergoes

thermolysis or photolysis of O-O bond pretty easily and is one of the most frequently used initiators like AIBN.

A successful radical transformation can be attributed to the following steps *viz.*

a. Initiation
b. Propagation
c. Termination

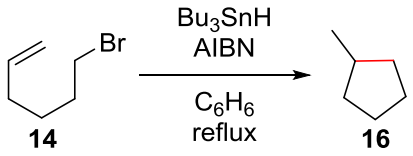
These processes are present in all the radical reactions, without any exceptions. Let's understand these steps with radical reaction of 1-bromohexane (**1**) using $^{n}Bu_3SnH$ and AIBN to furnish the *n*-hexane (**2**) as the product – a reduction reaction.



Scheme 3: Reduction of organic halide using radical reaction

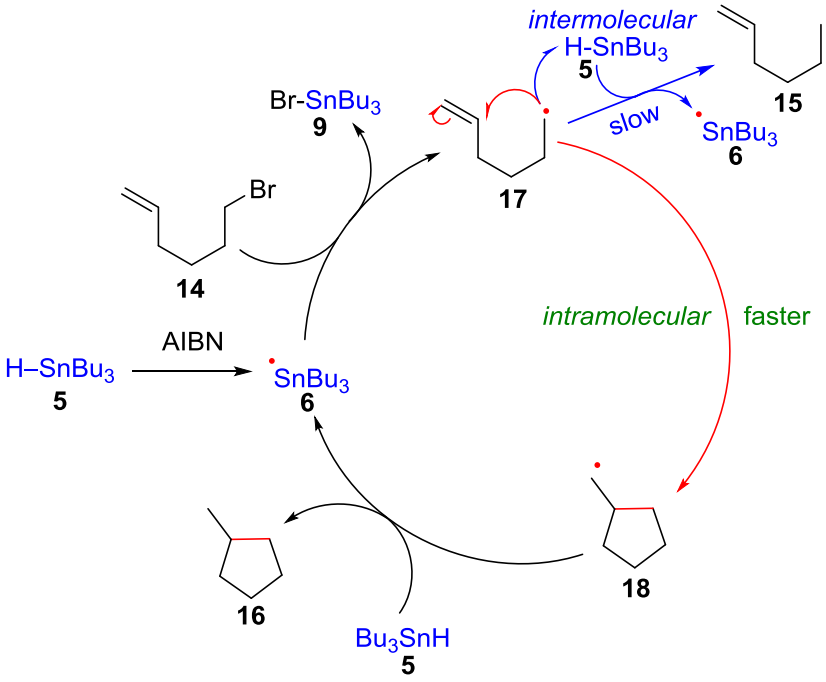
If you observe the temperature, benzene (C_6H_6) is being refluxed, which implies that the temperature is that of the boiling point of benzene i.e. 80 ^{o}C. AIBN (**3**) undergoes thermolysis at around 56 ^{o}C generating a rather unreactive radical $^{\bullet}C(CN)Me_2$ **4**. However, it can abstract

a weakly bonded hydrogen atom from $Bu_3Sn–H$ (**5**) to generate $Bu_3Sn^{\bullet}$ **6** (Scheme 3).After initiation, one must identify the next weak covalent bond, which in this case happens to be C–Br bond. Thus, the $Bu_3Sn^{\bullet}$ **6** starts a chain reaction, wherein it reacts with bromide **1** to generate hexanyl radical **8** along with Bu_3SnBr **9**. The hexanyl radical **8** abstracts a hydrogen from $Bu_3Sn–H$(**5**) enabling the regeneration of $Bu_3Sn^{\bullet}$**6** along with the hexane (**2**).These two steps keep repeating until all of the 1-bromohexane (**1**) has been consumed. This is called the propagation stage of the mechanism. Finally, various radical intermediates 'quench' by bonding with one another, known as the termination of the radical process.



Scheme 4: Intramolecular radical cyclization

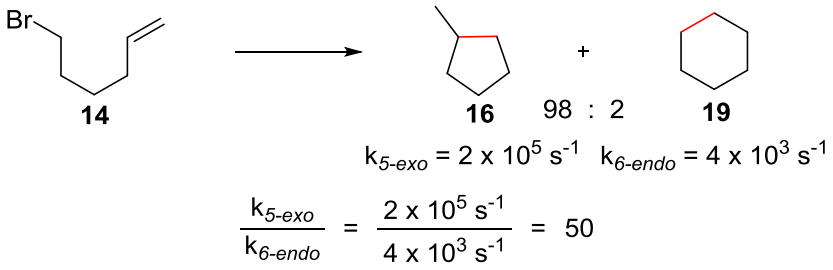
Consider the reaction of 6-bromohex-1-ene (**14**) under similar conditions i.e. using Bu_3SnH (**5**) and AIBN (**3**) in refluxing benzene (Scheme 4). Interestingly, while the difference between the two starting compounds is only that of an olefin, the outcomes change dramatically! What one observes in this reaction is not formation of the hex-1-ene (**15**) but methylcyclopentane (**16**) as the major product. So how do we rationalise the outcome of this reaction? Which step in the radical mechanism is different? Let us breakdown the steps again.



Scheme 5: Mechanism of intramolecular radical cyclization

As in the earlier case, the initiation step is the same. At the propagation stage, once the $Bu_3Sn^{\bullet}$ **6** reacts with the 6-bromohex-1-ene (**14**) to generate hex-1-enyl radical **17**, it undergoes a faster *intramolecular* (within the molecule) cyclization process to give cyclopentylmethyl radical **18** rather than the *intermolecular* hydrogen abstraction from Bu_3SnH (**5**) to furnish hex-1-ene (**15**) (Scheme 5). You would appreciate that an intramolecular process should in general faster due to proximity than an intermolecular reaction, which is diffusion controlled. Also note that a weaker π-bond is broken and a stronger σ-bond is formed during this radical cyclization step. Cyclopentylmethyl radical **18** then abstracts an H from Bu_3SnH (**5**) to furnish the product **16** and regenerates $Bu_3Sn^{\bullet}$ **6** (propagation).

But the story doesn't end here! On more careful analysis of the reaction, it was revealed that a very small quantity of cyclohexane **19** was also obtained along with the methylcyclopentane **16**, which is the major product. Arguably, cyclohexane **19** would be thermodynamically more stable product of the two (Scheme 6).[17]



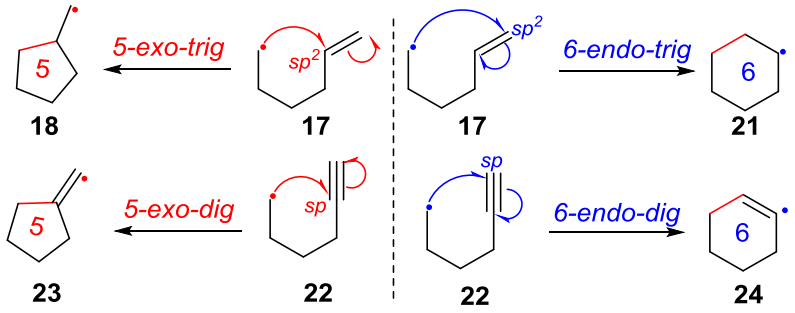
Scheme 6: Kinetics of radical cyclization reaction[17]

Measurement of rate of this reaction showed that methylcyclopentane formation is indeed 50 times faster than cyclohexane. Why is this so? Are there any principles, which govern this or related processes? Is this the only instance when selective formation of one ring over the other is seen? Baldwin observed that this phenomenon is not unique and this kind of selectivity for formation of one ring size over the other (here, five-membered ring formed easily as compared to six-membered ring) is quite common. While explaining this empirical observation of relative facility of ring forming reactions, he said, "The physical bases of the rules lie in the stereochemical requirements of the transition states for the various tetrahedral, trigonal, and digonal ring closure processes." While detailed discussion of these aspects would be out of the scope of the present article, these observations made by Baldwin way back in 1976, are still found to be useful by synthetic chemists, particularly in planning synthesis of cyclic compounds.[18]

An empirical basis to predict the relative facility of ring forming reactions are now referred to as Baldwin's rules. They are used for all *intramolecular* cyclizations – cationic, anionic or radical. The nomenclature of the rules captures three aspects related to the reaction, namely:

1. The size of the ring formed.
2. Whether the bond that broke is inside (*endo*) or outside (*exo*) the smallest ring formed.
3. The hybridization of the carbon being attacked – *sp* (*dig*onal), sp^2 (*trig*onal) or sp^3 (*tet*rahedral).

Now let us try to get the nomenclature for the radical cyclization of 6-bromohex-1-ene (**1**) to give methylcyclopentane (**16**) and cyclohexane (**19**) (*cf.* Scheme 6). As per Baldwin system, formation of methylcyclopentane involves a *5-exo-trig* radical cyclization. How do we arrive at this nomenclature?



Scheme 7: Nomenclature of Baldwin's Rules[18]

The cyclization of the hexenyl radical **17** involves formation of five membered ring – hence *5*. The hexenyl radical **17** undergoes *intramolecular* addition in such a way that the breaking bond is *exo*cyclic (i.e. outside the ring) to the ring that is formed – hence *exo*. The geometry (hybridization) of the carbon atom undergoing ring closure reaction is *tri*gonal (sp^2) – hence *trig* (Scheme 7). Now, can you guess what will be the nomenclature for cyclohexyl radical **21** formation process? Six-membered ring is formed, the breaking bond is inside the ring (*endo*cyclic) and the carbon atom undergoing ring closure is sp^2 hybridised i.e. has trigonal geometry – hence it will be a *6-endo-trig* radical cyclization.

What if we replace the olefin in the above example with the alkyne as in the case of radical **22** leading to radicals **23** or **24**? The reactions would be said to involve *5-exo-dig* (leading to methylenecyclopentenyl radical **23**) and *6-endo-dig* (leading to cyclohexenyl radical **24**) radical cyclization reactions, respectively.

The empirical rules provided by Baldwin are summarised in Table 2. To assess the favourable mode of cyclization, the boxes that are green and ticked are termed to be feasible, whereas, the boxes that are red and have a cross are known to be not feasible.

Ring Size	*endo*			*exo*		
	dig	***trig***	***tet***	***Dig***	***trig***	***tet***
3	✓	✗	✗	✓	✓	✓
4	✓	✗	✗	✓	✓	✓
5	✓	✗	✗	✗	✓	✓
6	✓	✓	✗	✗	✓	✓
7	✓	✓	✗	✗	✓	✓

Table 2: Baldwin's Rules for Ring Closure[1]

For example, a *4-exo-trig* cyclization would mean that a four-membered ring formation, with the bond that broke being outside the ring and sp^2 hybridization at the carbon centre on which the attack took place. According to Table 2, this cyclization is favourable, hence could occur.

For more than a decade, our group has been engaged in developing strategies for the synthesis of *oxa*- and *aza*-cycles using a functional group called *vinylogous* carbonates/carbamates. Since we would be using this term often, let us understand what we mean by *vinylogous*.

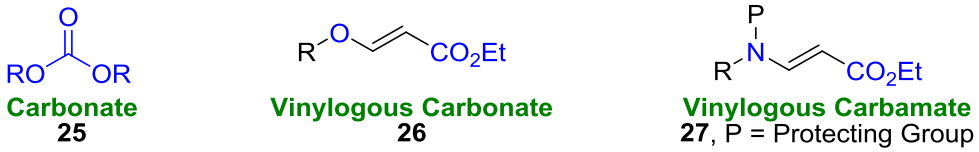
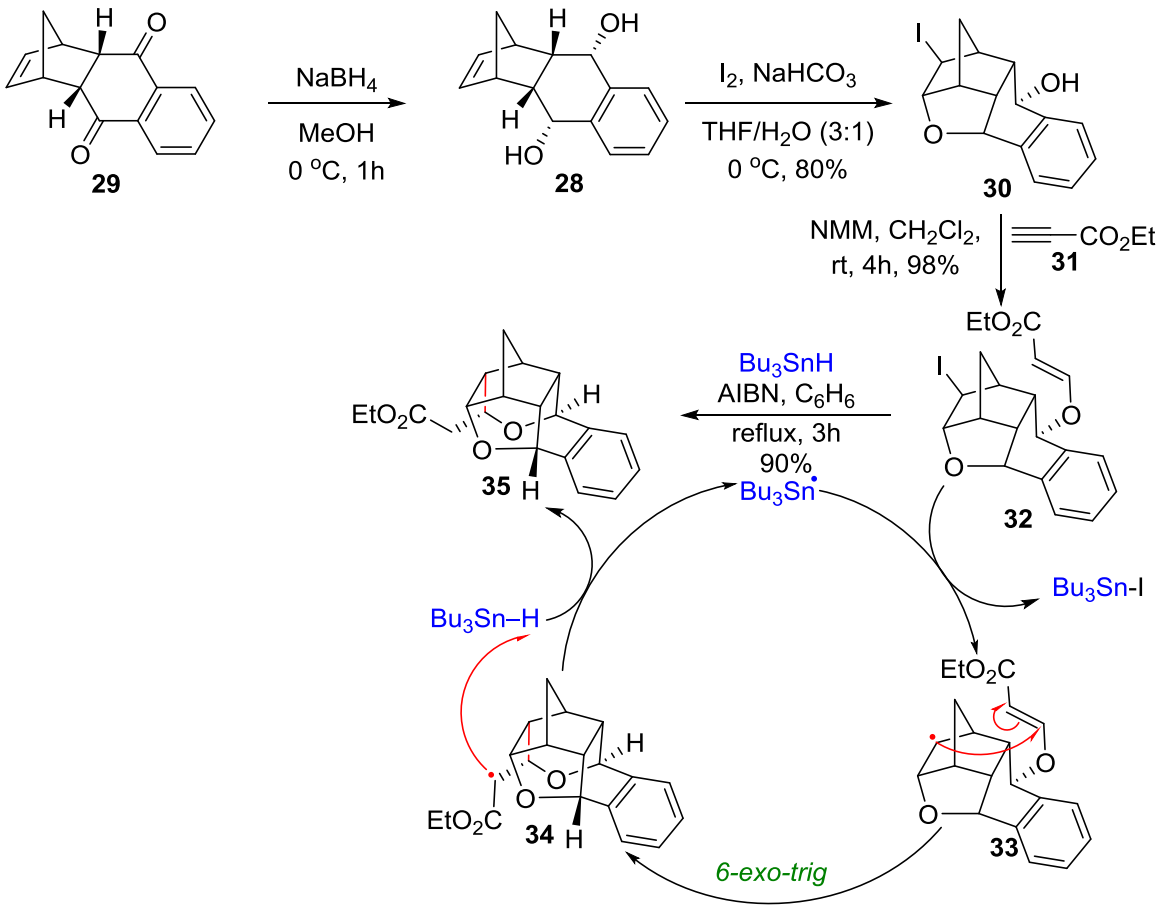


Figure 4: Carbonate and vinylogous carbonate/carbamate

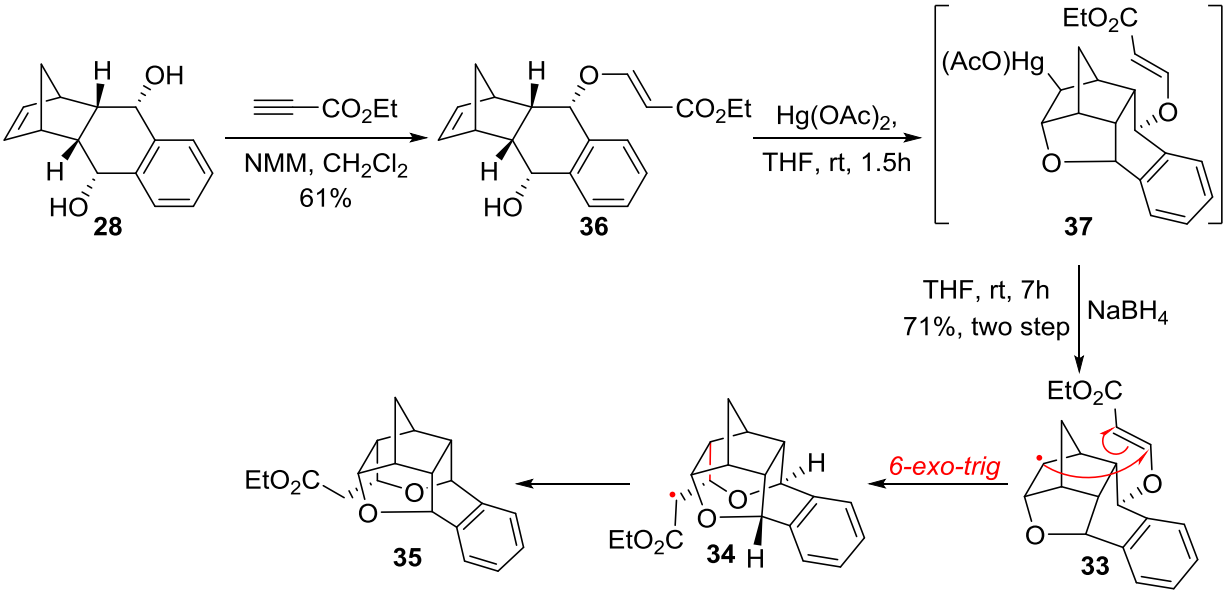
You already know that the functional group present in RO–CO–OR **25** is called as carbonate. Imagine a vinyl group inserted between oxygen and CO of the carbonate to give a compound like **26**. The functional group in this compound **26** would be referred to as vinylogous carbonate – recollect term '*homologous* series' for alkanes – you inserted a CH_2 to get higher alkane – so this is somewhat similar to that wherein we have inserted vinyl (CH=CH) group! In a similar manner the functional group in compound like **27** would be referred to as *vinylogous* carbamate. Of course, these compounds **26** and **27** can also be called as *β*-alkoxy acrylate and *β*-amino acrylate, respectively. The push-pull ability of this group is what

attracted us towards its reactivity as an acceptor and led us to explore its utility in radical reactions.

Oxa-bowls and cages are unnatural products with interesting structural features. Though symmetrical *oxa*-bowls and cages were synthesized easily, our objective was to synthesize the unsymmetrical *dioxa*-cages utilizing the radical cyclization strategy. We began with the synthesis of diol **28**, which was readily obtained by reduction of the Diels-Alder adduct **29**. Iodoetherification reaction on the diol **28** using iodine and aq. $NaHCO_3$ gave the iodo alcohol **30**. Reaction of the alcohol **30** with ethyl propiolate (**31**) in the presence of *N*-methyl morpholine (NMM) resulted in the formation of the vinylogous carbonate **32** *via oxa*-Michael addition of hydroxy group to ynoate moiety. Once the vinylogous carbonate **32** was available, it was subjected to radical cyclization conditions using Bu_3SnH and AIBN in refluxing benzene (Scheme 8). During the reaction, the C–I bond cleaves homolytically to give the radical **33**. This radical undergoes an *intramolecular 6-exo-trig* cyclization with vinylogous carbonate (*cf.* Baldwin's rules of cyclization, Table 1) to give new radical **34**. The radical **34** then abstracts a hydrogen from $^{n}Bu_3SnH$ (**5**) to give the *oxa*-bowl **35**, regenerating $^{n}Bu_3Sn^{\bullet}$ (propagation). The fate of the radical cyclization was determined by the topology of the substrate and hence, is extremely specific.[19]



Scheme 8: Synthesis of *oxa*-bowl *via* radical cyclization to vinylogous carbonate[19]

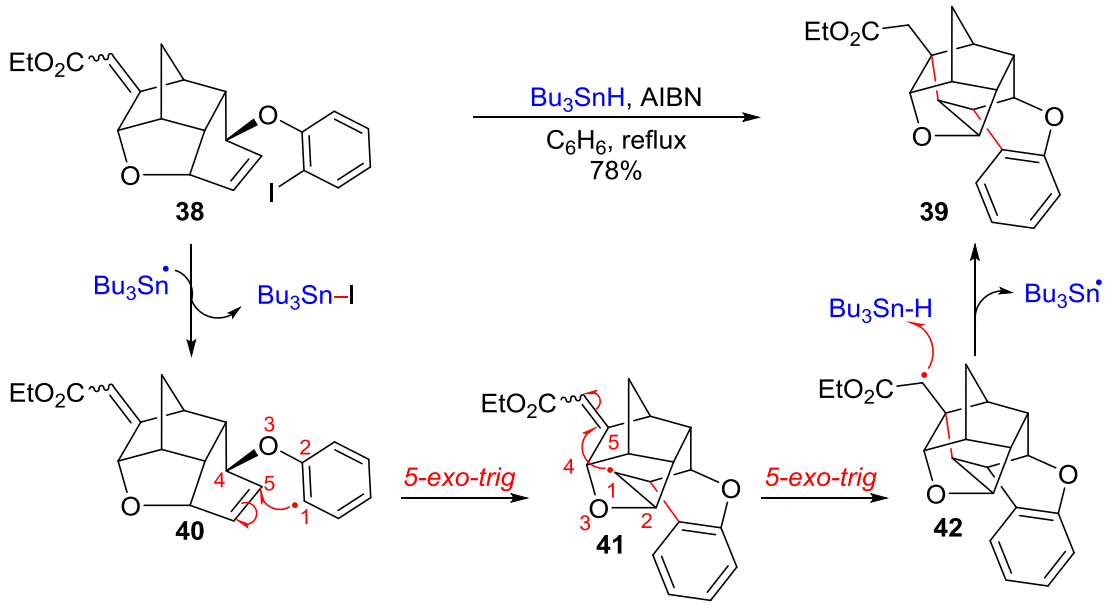


Scheme 9: Synthesis of *oxa*-bowl by oxy-mercuration-reduction[20-

As with other reactive intermediates, whatever be the method of its generation, once formed, the fate of the radical is the same. Thus, when the vinylogous carbonate **36** (generated from the diol **28** by reaction with ethyl propiolate) was subjected to treatment with [$Hg(OAc)_2$], it resulted in the formation of the intermediate **37** *via* oxy-mercuration (Scheme 9). When this intermediate is reacted sodium borohydride ($NaBH_4$), it generated radical **33**. This radical will undergo a *6-exo-trig* cyclization to furnish the di*oxa*-bowl **35**. This reaction in a way further supports that the mechanism of the reduction step of oxy-mercuration – reduction protocol for the synthesis of alcohols/ethers that you would have studied earlier, indeed involved a radical intermediate and not an ionic mechanism.[20]

At this juncture, we started wondering if it is necessary to generate radical from halide alone or one generated as the product of one cyclization can participate in another cyclization. In another words, can a radical cyclization be followed by another if one more olefin is situated correctly within the same molecule?

To test this idea, we synthesized ether **38** wherein an iodide is present on phenyl moiety along with two different types of olefins. When this iodide was subjected to radical cyclization using Bu_3SnH and AIBN in refluxing benzene, the dioxa-cage **39** was obtained as the product, which is devoid of both the olefins indicating that two cyclizations have indeed taken place. So how do we explain formation of the product?

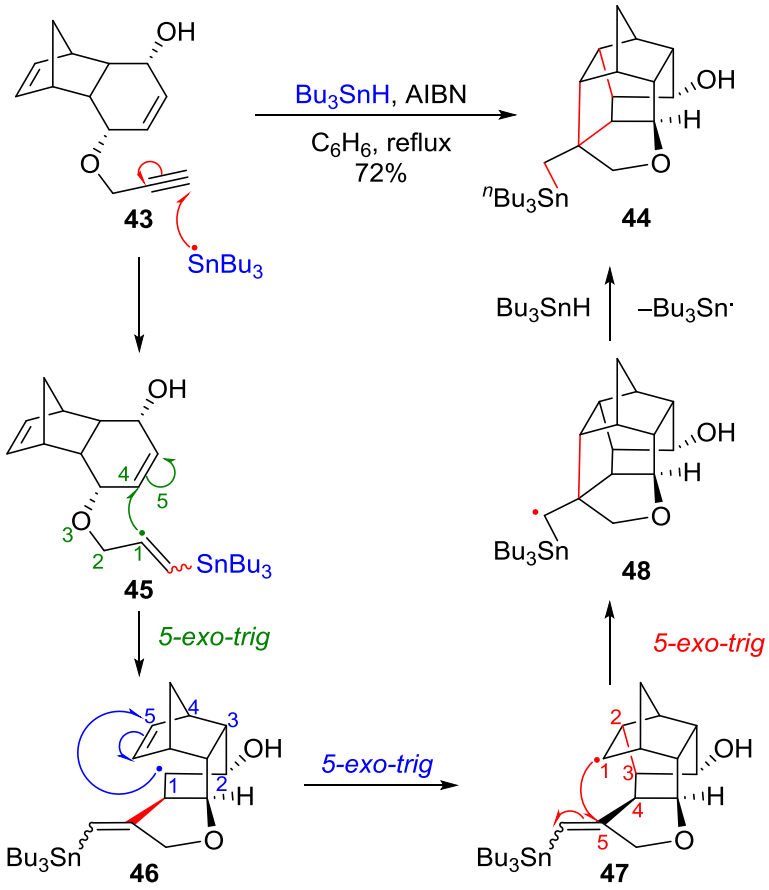


Scheme 10: Sequential radical cyclization for the synthesis of *oxa*-cage[21]

The $Bu_3Sn^{\bullet}$ cleaves the C–I bond to give transient radical **40**. It is in a suitable position to undergo a *5-exo-trig* cyclization with the C=C double bond present in the vicinity. Why did

aryl radical not cyclize on the olefin bearing ester, which arguably is better acceptor? Does it have to do with the relative ease of cyclization – a *5-exo-trig* cyclization is lot more facile than *7-exo-trig* cyclization – and it is a kinetic outcome? No, the reason is the topology of the molecule – the stereochemistry of the molecule precludes approach of the radical to the olefin bearing ester. The newly formed radical **41**, has the olefin bearing ester appropriately positioned for another *5-exo-trig* cyclization, which readily takes place to furnish the radical **42**. This intermediate is now reduced by the $Bu_3Sn–H$ in turn giving $Bu_3Sn^{\bullet}$, which propagates the reaction further (Scheme 10). This study helped us synthesize a unique framework, which would've been very difficult to synthesize otherwise.[21]

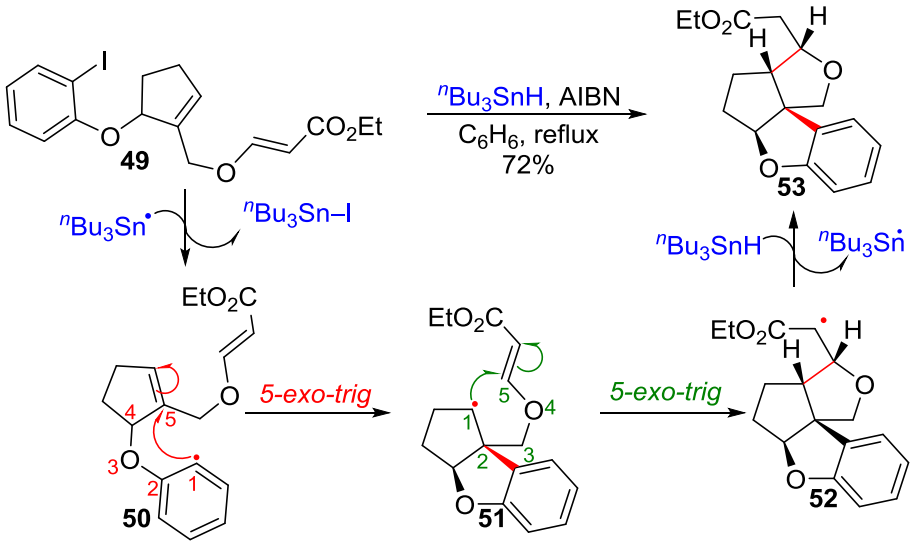
In the quest to dive deeper in the radical cyclization, we decided to move away from acrylates little bit and add more non-conjugated olefins instead in the molecule. Thus, we subjected propargyl ether **43**, which has an alkyne and two olefins, to radical cyclization conditions. The reaction indeed resulted in the consumption of starting material and resulted in the formation of a complex looking cage compound **44**. So how did this product form? It is appearent that lots of bond making/bond-making has taken place – most importantly, all the π-bonds in the starting compound have magically vanished! As you know, in science, there is no magic but only logic! So can we explain it logically?



Scheme 11: Tandem radical cyclization for the synthesis of *oxa*-cage[22]

Unlike previous cases, wherein tin radical would abstract an iodide, here due to absence of any C-X bond, the $^{n}Bu_3Sn^{\bullet}$ radical adds to weakest bond i.e. to the alkyne moiety generating a vinyl radical **45**. The vinyl radical **45** undegoes a very facile *5-exo-trig* radical cyclization to grenerate new radical intermediate **46**. Due to the topology of the molecule **46**, the radical entity comes in close proximity with the double bond located just above it. Not just that, but if the radical adds to olefin, it would result in a very facile *5-exo-trig* cycliazation! Naturally, this intramolecuar process takes place rather than its reduction with Bu_3SnH and thus, new radical **47** is generated. But the story does not end here! Note that an olefin is just located beneath the radical in the intermediate **47**. Can you count the location of the radical from the olefin if it was to undergo cyclization? In principle, you would get many answers, but as per Baldwin, one should remember to count the '*smallest ring so formed*'! So it is again a *5-exo-trig* radical cyclization that follows on the intermediate **47** resulting in the formation of the radical intermediate **48**. Finally, this radical abstracts hydrogen from Bu_3SnH to give the cage compound **44** – and not to forget regenerate $Bu_3Sn^{\bullet}$ to keep radical cyclization going (propagation) (Scheme 11)!

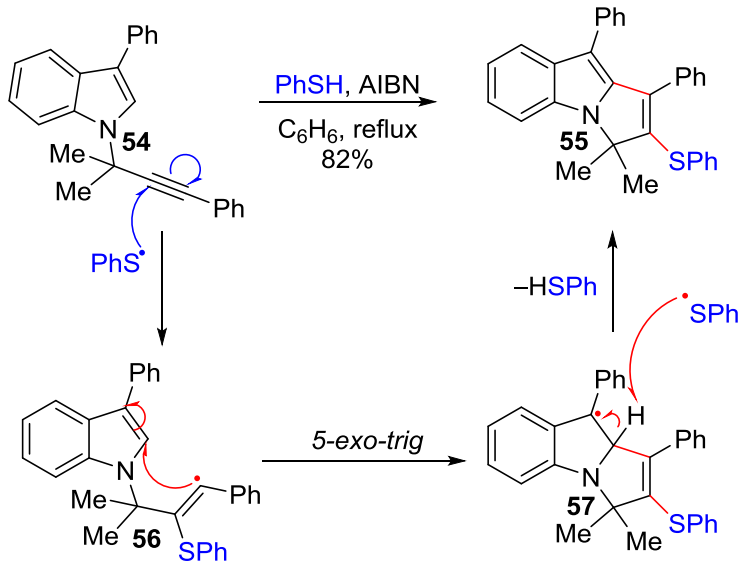
Can you count how many different steps were invovled in this process? Let's count: i. intermoelcular $^{n}Bu_3Sn^{\bullet}$ addition to alkyne; ii. *5-exo-trig* radical cyclization; iii. *5-exo-trig* radical cyclization; iv. *5-exo-trig* radical cyclization; v. intermoelcular hydrogen abstration. When a series of steps of such type occur one after the other in a reaction, it is termed as "*cascade reaction*" (*a.k.a. tandem reaction*). It is one of the unique transformations, wherein the successive cyclization is dependant on the outcome of the previous cyclization due to structural proximity of the reactive species.[22]



Scheme 12: Synthesis of angular triquinanes by tandem radical cyclization[23-24]

Another structurally interesting class of molecules that we were curious to synthesize were triquinanes. The idea of tandem/cascade radical cyclization was explored in the synthesis of linear triquianes in 1980's.[15] Many natural products bearing linearly or angularly-fused carbocyclic triquinane motifs from terpene family were isolated and synthesised using various methods. However, synthesis of heteroatom containing angular triquinanes had not been explored much. To proceed in this endeavour, we prepared *o*-iodophenyl cyclopentenyl vinylogous carbonate **49** and subjected it to radical conditions of Bu_3SnH/AIBN in benzene (Scheme 12). As you would have guessed by now, the initial step sill involve generation of $Bu_3Sn^{\bullet}$ radical, which in turn will furnish the phenyl radical **50**. This phenyl radical **51** adds to the cyclopentenyl double bond in a *5-exo-trig* manner forming a benzofuran skeleton **51** in a stereoselective manner. The radical **51** thus formed, undergoes one more *5-exo-trig* cyclization **52** – this time to vinylogous carbonate moiety, to stereoselectively form *dioxa*-triquinane **53** in good yield.[23-24]

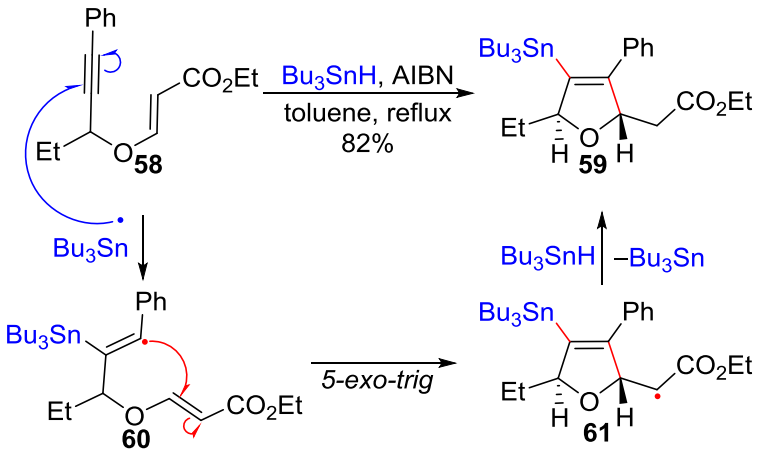
It may seem as if Bu_3SnH is the only reagent used for initiation of radicals. It is primarily so because in general, it does not react rapidly with the reactive intermediates generated, allowing them to participate in further cyclization processes as opposed to direct reduction. There are other reagents as well, which are used frequently while developing a successful radical cyclization, one such example being thiophenol (PhSH). As is visible from its BDE, thiophenol generates $H^{\bullet}$ and $PhS^{\bullet}$ quite easily.



Scheme 13: Synthesis of *N*-fused indole using radical cyclization[25]

Relying on this fact, we attempted a radical cyclization reaction on *N*-propargylated indole **54** using excess PhSH/AIBN rather than Bu_3SnH/AIBN. Interestingly, we observed formation of the *N*-fused indole **55** in good yield (Scheme 13). Initially formed $PhS^{\bullet}$ adds across the C≡C triple bond specifically, such that the vinyl radical **56** thus formed is stabilized by the Ph substituent. This vinyl radical **56** adds to the C=C double bond of the indole to give radical **57**. Unlike previous cases, here instead of reduction of the radical **57**, $PhS^{\bullet}$ abstracts a hydrogen atom from the carbon next to nitrogen and forms the product, *N*-fused indole **55**. The last step is attributed to ability of $PhS^{\bullet}$ to abstract a hydrogen easily as well as the fact that indole regains aromaticity if hydrogen is abstracted. [25]

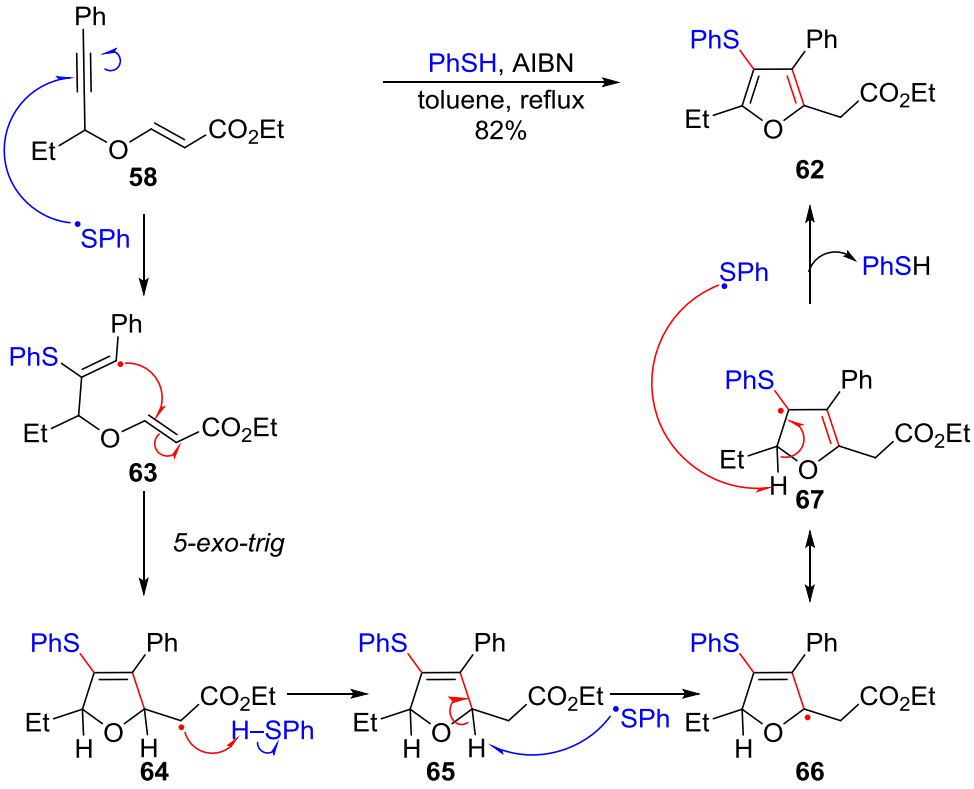
Till now, we came across radical cyclization wherein radicals were added onto isolated alkenes, vinylogous carbonates, alkynes or a heterocycle as in the case of indole. We planned synthesis of tetrahydrofuran **59** by addition of $Bu_3Sn^{\bullet}$ to propargyl vinylogous carbonate **58** (Scheme 14). Indeed, we observed synthesis of dihydrofuran by the addition of $Bu_3Sn^{\bullet}$ on the internal alkyne **58**, which in turn forms vinyl radical **60**.



Scheme 14: Synthesis of tetrasubstituted dihydrofuran by tributyltinhydride addition[26]

It then proceeds *via* a *5-exo-trig* cyclization to the vinylogous carbonate forming radical **61**, which is quenched by Bu_3SnH to give tetrasubstituted dihydrofuran **59** in good yield.

You may ask, when we add thiophenol PhSH to the same propargyl vinylogous carbonate **58**, will we get a molecule that is like dihydrofuran **59**? The only way to find the answer was to carry out an experiment. Interestingly, when we subjected vinylogous carbonate **58** to radical–



Scheme 15: Synthesis of tetrasubstituted furan by thiophenol addition[26]

cyclization with excess of PhSH/AIBN in refluxing toluene, we got tetrasubstituted furan **62**! So how did we get the furan? After carrying out mechanistic investigation, we got a fair idea as

to how reaction proceeds. To cut the long story short, let us very briefly explain what happened in this reaction. Addition of thiyl radical to alkyne gives radical intermediates **63**, which undergoes a *5-exo-trig* radical cyclization to furnish the radical **64**, which in turn undergoes reduction to form the dihydrofuran **65** (Scheme 15). However, the reaction does not stop here and the PhS$^{\bullet}$ picks up a hydrogen α to the oxygen and β to the ester, forming intermediate **66**. The intermediate **66** can be written as its resonance structure **67**. The PhS$^{\bullet}$ picks up another hydrogen, forming an aromatic molecule furan **62**.[26]

In conclusion, we have demonstrated over the years that tandem radical reactions of vinylogous carbonates have tremendous potential to be used in the synthesis of various types of complex heterocycles. It requires judicious planning, diligent execution and considerable effort – just like in the story of the thirsty crow and the scarce water in the clay pot! One by one, as the crow adds stone inside the pot, the water level keeps rising, ultimately making it reachable for it to drink and quench it's thirst. Radical reactions can be straightforward if thought out well and have helped in evolving the chemistry from something that was not dependable to the key reactions in the synthesis of complex molecules.

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