A Platinum Open Access Journal for Organic Chemistry

Review

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (2) 202312052

Recent applications of heteroatom-centered radicals as catalysts in organic synthesis

Yee Lin Phang, Feng-Lian Zhang* and Yi-Feng Wang*

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China
Email: zfl9@ustc.edu.cn; yfwangzj@ustc.edu.cn

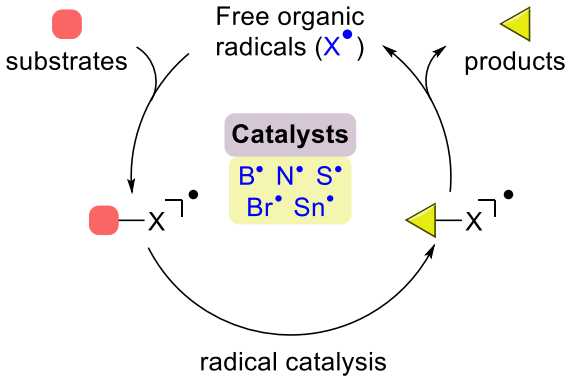
Dedicated to Professor Samir Z. Zard for his contribution to radical chemistry

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

Radical catalysis is an innovative synthetic approach employing the open shell reactive radical species as catalysts to facilitate chemical reactions. Generally, free organic radicals derived from elements like boron, nitrogen, sulfur, bromine and tin are utilized due to their reversibility in radical addition/elimination processes. Extensive efforts have been devoted to expanding the use of radical species as catalysts in [3+2] cycloaddition, oxidative cleavage of olefins, cyclopropanation, C-H functionalization, C-H amination, and other related transformations. This review summarizes the advancements in designing and generating active organic radicals, as well as their involvement in catalyzing intriguing organic reactions throughout the catalytic cycle.



Keywords: Organic radicals, homogenous catalysis, radical covalent catalysis, asymmetric

Table of Contents

1. Introduction

Catalysis is at the forefront of modern chemistry, serving as the linchpin for the development of efficient and sustainable chemical processes.[1-3] Within the realm of catalysis, three dominant categories have emerged: transition metal catalysis, organocatalysis and biocatalysis. Each of these approaches leverages distinct catalysts, such as transition metals, small organic molecules, and enzymes, to orchestrate chemical transformations.[4-7] Regardless of the catalyst employed, a delicate equilibrium must be maintained between reactivity and stability, crucial for driving organic reactions in a favourable direction while resisting catalyst deactivation.

Notably, in all three catalytic systems, certain reactions involve the use of radical intermediates. In such cases, the catalyst can either initiate radical formation or interact with radicals produced from other reactions, thereby facilitating additional transformations. In recent years, the progress in photoredox and electrochemical catalysis has ushered in a new era of radical intermediates in organic reactions, where light or electricity was converted into chemical energy to promote single electron transfer (SET) events in organic molecules.[8-10]

However, amid these catalytic systems, one intriguing challenge has emerged—the utilization of free organic radicals as catalysts. These radical species, inherently kinetic unstable due to their unsatisfied valency, are prone to side reactions or self-termination, posing obstacles to efficient catalytic turnover. Additionally, their generally high reactivity and low activation barriers often result in poor selectivity in organic reactions.

Yet, a glimmer of promise lies in the realm of heteroatom-centered free radicals, including those derived from boron, nitrogen, sulfur, bromine and tin compounds. These radicals have demonstrated the capacity to act as catalysts through unique mechanistic pathways, distinct from transition metal, organocatalytic, and biocatalytic routes. They exhibit unpaired electron processes that can surmount steric and electronic constraints, enabling one or multiple bond formations in a time-efficient “one-pot” manner.[11] These radicals also exhibit high functional group tolerance, minimizing the need for protecting group installation.

In heteroatom-centered radical-catalysed reactions, a transiently stable yet reactive radical is firstly generated through bond homolysis, hydrogen atom abstraction or photocatalysis (**Error! Reference source not found.**). This radical species can reversibly add to a molecule, creating new radical intermediate that may undergo various transformations before ultimately delivering the product while regenerating the radical, thus completing a catalytic cycle. This reversibility of radical addition and elimination forms the crux of a complete radical catalytic cycle. Notably, the radical intermediates could undergo intermolecular cyclization or addition to unsaturated bonds, leading to the propagation of radical processes in single-step or cascade transformations

like cycloaddition, cyclopropanation, or C(sp^3)-H functionalization, enabling the modular assembly of complex structures. There has also been a growing emphasis on the stereoselective catalysis of radical reactions, considering that chirality is commonly lost during radical formation.

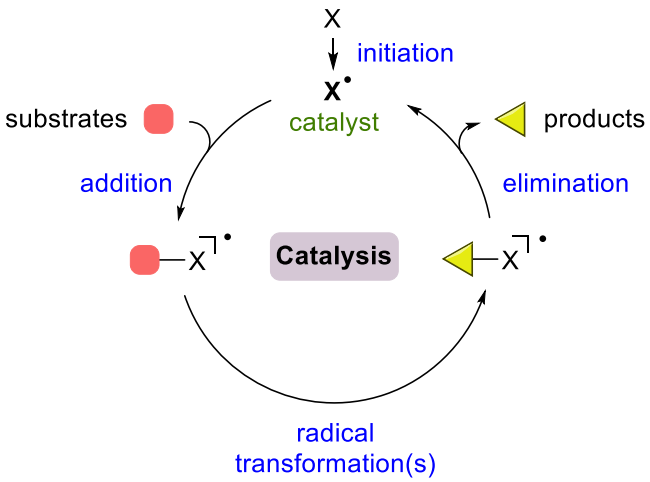


Figure 1. Heteroatom-centered organic radicals in catalysis

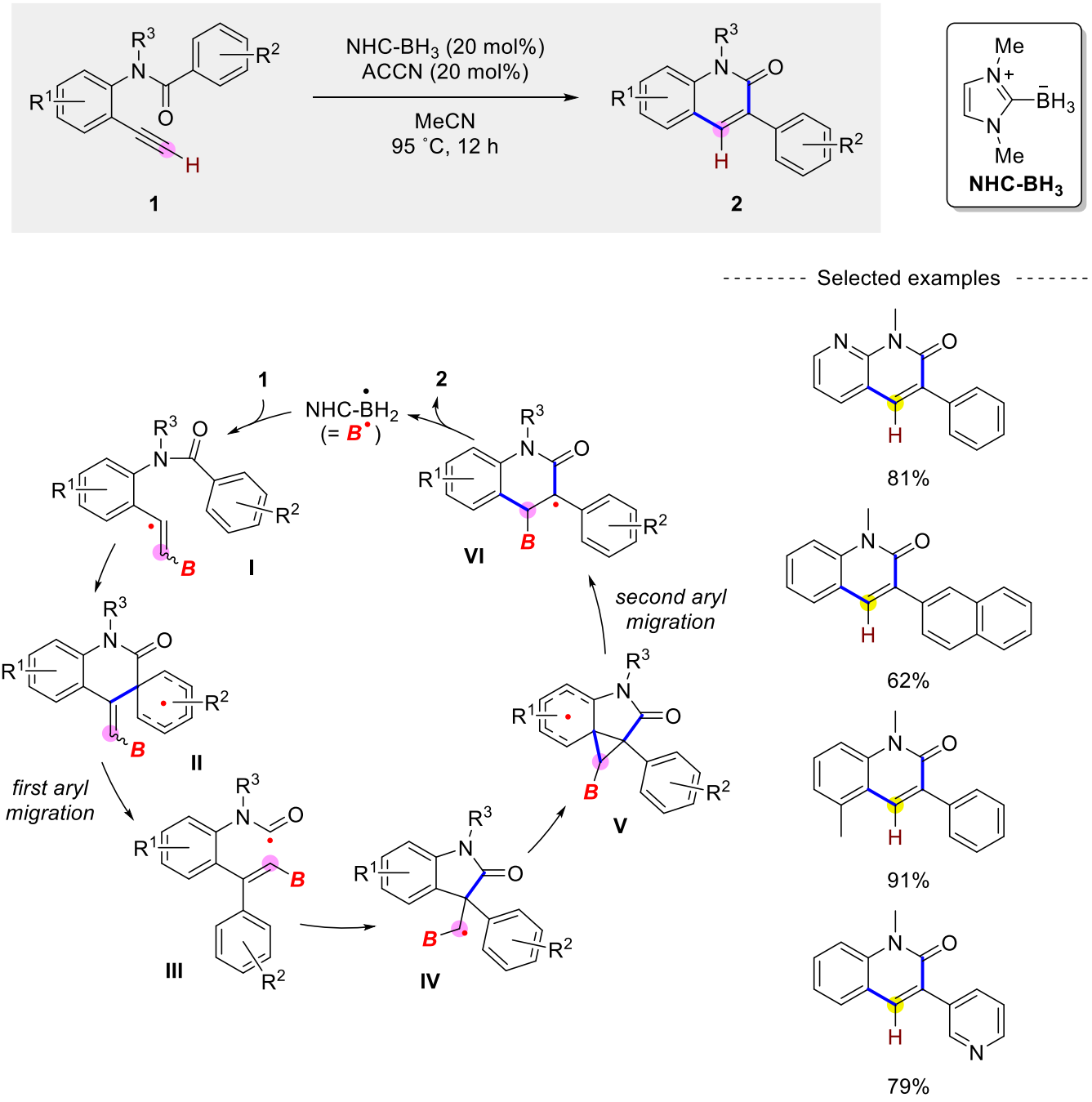
This review delves into the recent developments in the field of radical catalysis, focusing on free organic radicals, particularly those centered around main-group elements such as boron, nitrogen, sulfur, bromine and tin. In addition to those main group element radical catalysts, transition metals such as cobalt,[12-13] titanium,[14-20] samarium,[21-23] and bismuth[24] demonstrate similar role to catalyse radical reactions. For instance, the Lin group utilizes titanium complexes for radical redox relay catalysis[25-28] while the Zhang group employs cobalt(II) complexes of porphyrins for metalloradical catalysis.[29-39] Nevertheless, the transition metal-catalysed radical reaction is beyond the scope of this article, and it could be referred to several published review papers.[13, 40-45] This review organizes the developments of heteroatom-centered radical catalysis in chronological order, highlighting the recent advances and burgeoning interest in this captivating field. For other related reviews relevant to radical covalent catalysis,[46] bromine-[47] or nitrogen-centered[48] radicals, readers are directed to the cited sources.

2. Boron Radicals

Over the past decades, studies on the chemistry of boron-centred radicals have emerged rapidly especially with the development of *N*-heterocyclic carbene (NHC)- and pyridine-boryl radicals.[49-52] Studies have shown that the addition of boryl radical to unsaturated bonds is a reversible process and such reaction is driven forward when the resulting radical is stabilized by adjacent group such as the carbonyl and aryl.[53-55] After cascade of molecular transformations mediated by radical process, β-elimination took place to regenerate the radical from β-boryl alkyl radical. Hence, with proper design of substrates, an elegant catalytic cycle could be realized through the reversible transfer of boryl radical species.

In 2019, our group discovered that the *N*-(2-ethynylaryl)arylamides **1** were cycloisomerized to quinolinones **2** under mild reaction conditions in the presence of NHC-boryl radical catalyst.[55] Mechanistic and computational studies support the mechanism illustrated in Scheme 1. The radical initiator 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) abstracts a hydrogen atom from NHC-BH_3 to deliver NHC-boryl radical that adds to the starting material

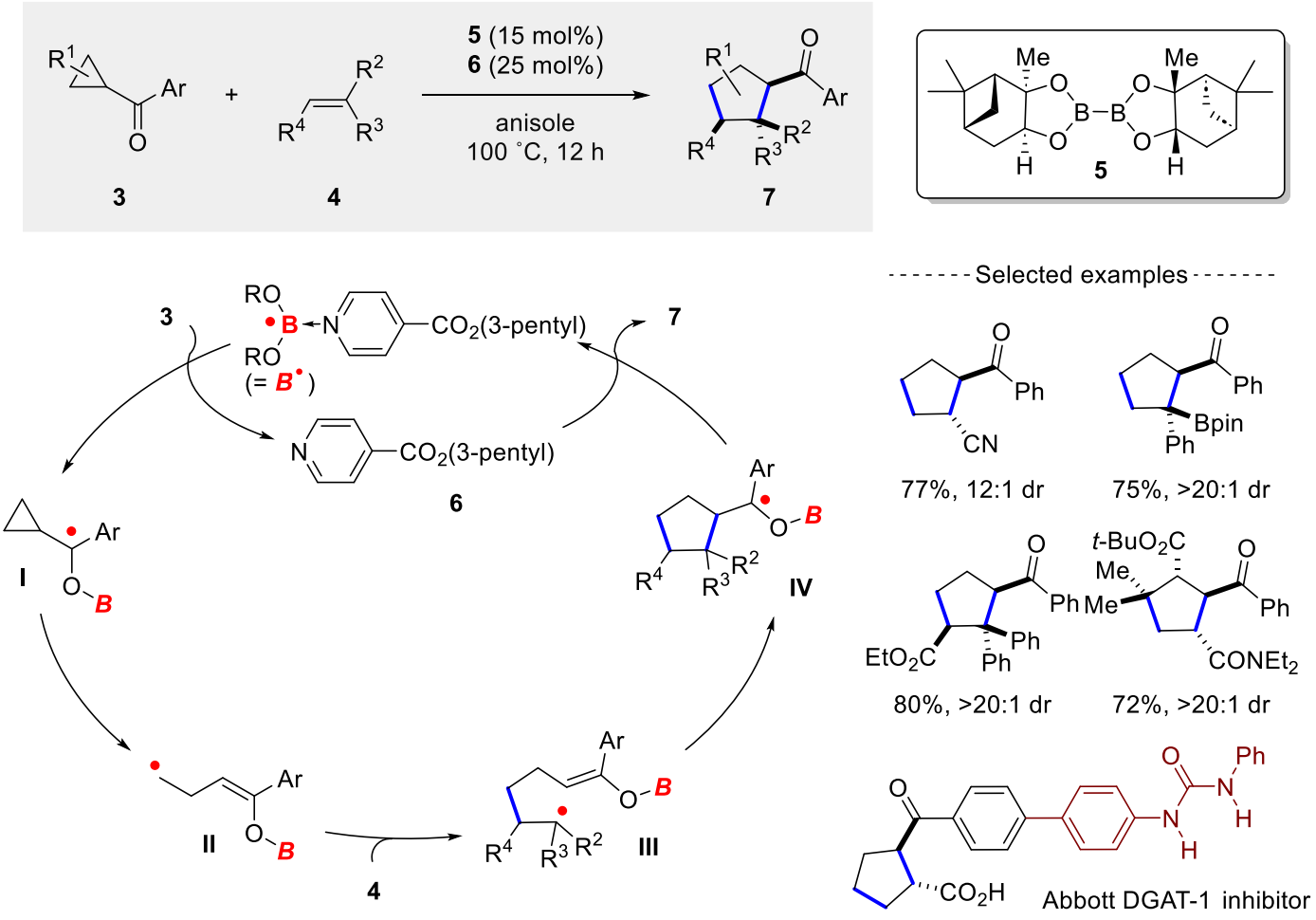
1 to afford an alkenyl radical **I**. Intramolecular radical cyclization to benzamide **II** is followed by C-C bond cleavage to achieve the first aryl migration, delivering acyl radical **III**. This intermediate radical is calculated to undergo 5-*exo-trig* cyclization with low activation barrier (2.1 kcal/mol) and is exergonic by 16.6 kcal/mol, resulting in α-boryl alkyl radical **IV**. A second aryl migration then precedes the final β-fragmentation to provide product **2** and regenerate the NHC-boryl radical.



Scheme 1. NHC-boryl radical-catalysed cycloisomerization of *N*-(2-ethynylaryl)arylamides

In 2022, Xu and Li reported a method for the synthesis of highly substituted cyclopentanes **7** via radical relay catalysis of aryl cyclopropyl ketones **3** and alkenes **4** (Scheme 2).[56] This reaction features a dual catalytic system whereby electron-poor pyridine acts as a co-catalyst for the formation and transfer of pinacolato boryl

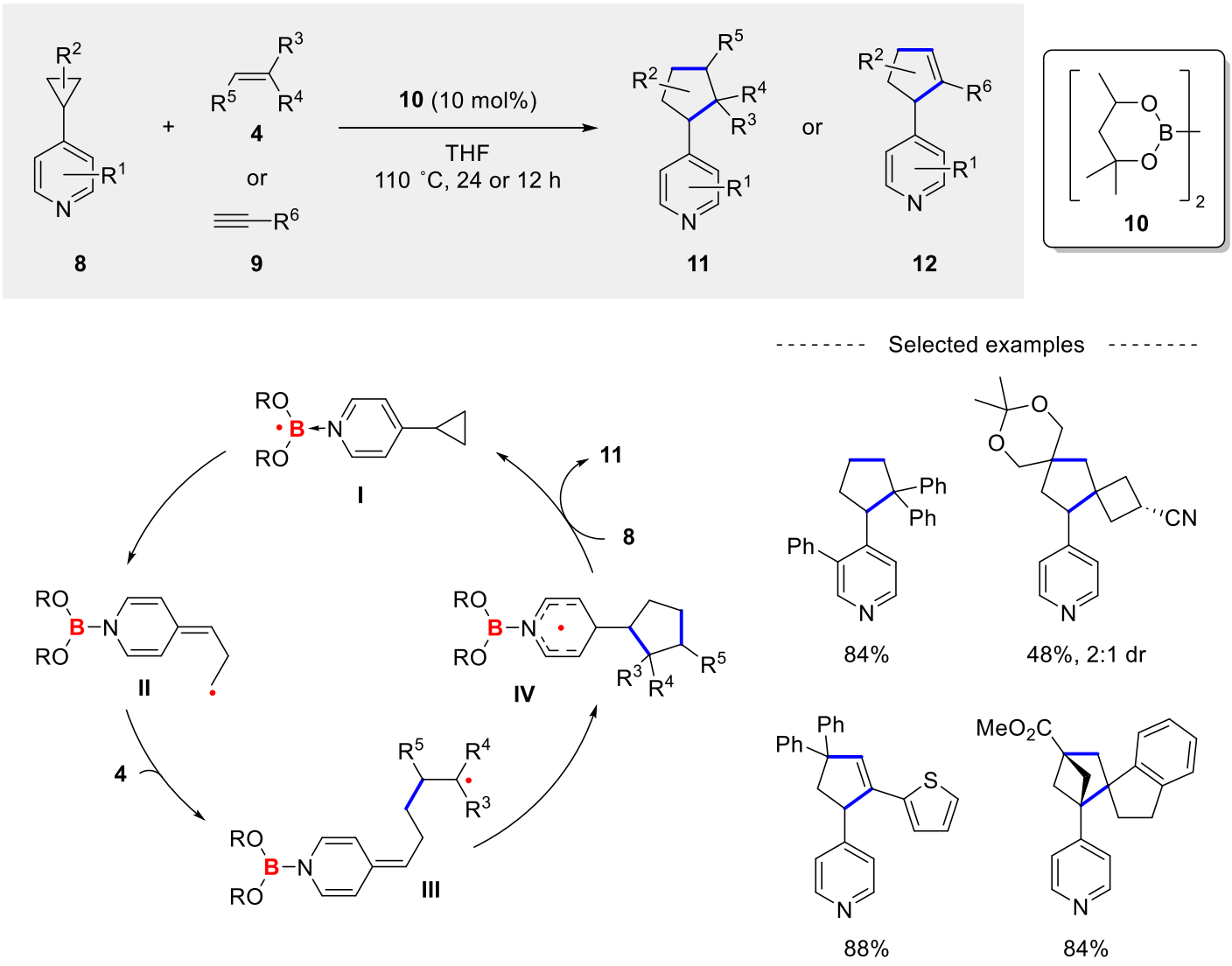
radical. Homolytic cleavage of tetraalkoxydiboron(4) compound **5** generates a boronyl radical which complexes with 3-pentyl isonicotinate (**6**) to form a stabilized radical complex. Addition of this boronyl radical to the carbonyl oxygen of **3** affords a benzylic ketyl radical **I** while at the same time liberates the pyridine **6**. Further cyclopropane opening/radical addition to alkene **4**/5-*exo-trig* ring-closing tandem reactions produce a new benzylic ketyl radical **IV**. At this stage, pyridine **6** mediates the release of boronyl radical by complexing with it, delivering the desired product **7** with high to excellent yield and diastereoselectivity. This protocol is applicable to both polysubstituted cyclopropanes and alkenes, emphasizing its broad substrate scope with 65 examples shown. Furthermore, the synthesis of key intermediate that allows access to glycerolacyltransferase (DGAT-1) inhibitor, a selective anti-obesity drug by Abbott, was achieved through this methodology.



Scheme 2. [3+2] cycloaddition of cyclopropanes and alkenes via diboron(4)/pyridine co-catalysis

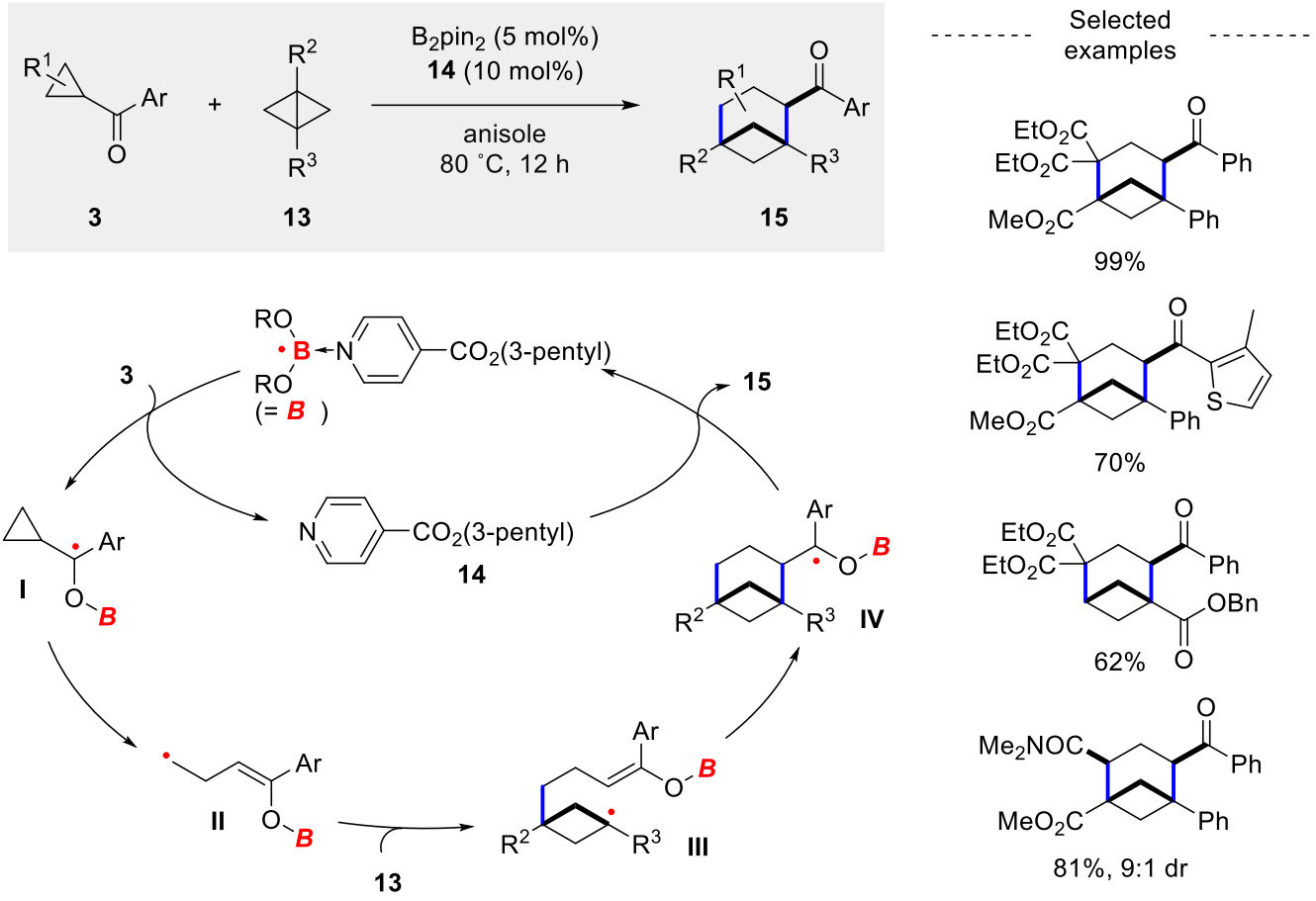
The pyridine co-catalysed [3+2] cycloaddition was further improved by Li and co-workers in the same year.[57] Here, the pyridine moiety complexes with boronyl radical and serves as a medium for radical transmission via dearomatization and rearomatization processes. Mechanistic studies and computational results showed the reaction commences with the complexation of 4-pyridinyl cyclopropanes **8** to boronyl radical derived from **10** (Scheme 3). The resulting boronyl radical complex **I** then undergoes cyclopropane ring opening by dearomatization of pyridine to yield intermediate **II**. Subsequent radical addition to alkene **4** or alkyne **9**, followed by intramolecular cyclization forge the cyclopentane or cyclopentene ring **IV**. Reaction with another molecule of starting material **8** allows rearomatization of pyridine to deliver **11** or **12** and regenerates pyridine-complexed boronyl radical **I**. Aside from the highly substituted cyclopentanes and cyclopentenes, this reaction

is also applicable to the synthesis of bicyclo[2.1.1]hexanes with 4-pyridinyl bicyclo[1.1.0]butanes as substrates. This reaction disclosed a radical transmission approach for reactions where the radical initiation site lies distantly from the reaction site.



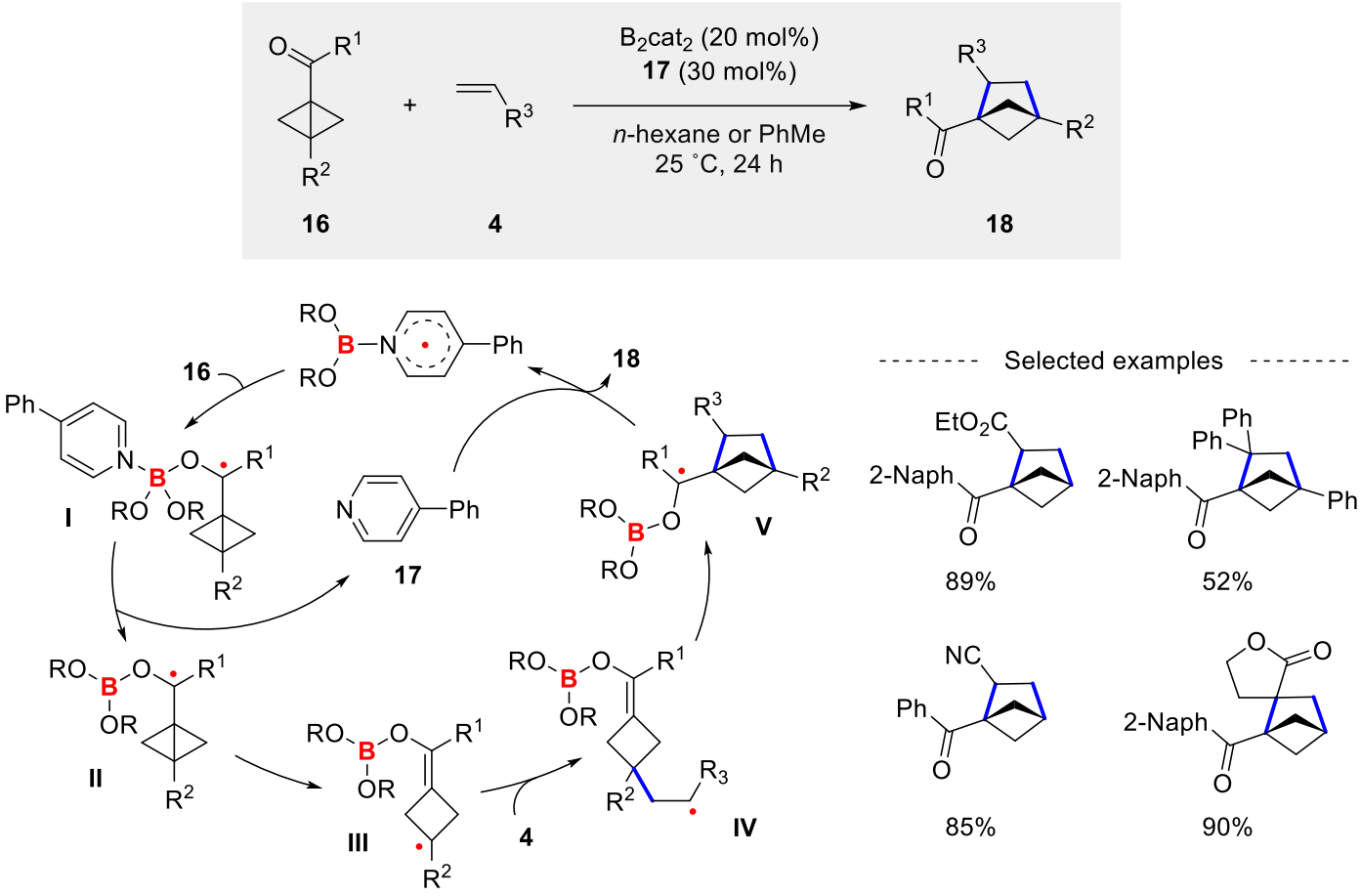
Scheme 3. [3+2] cycloaddition of 4-pyridinyl cyclopropanes with alkenes or alkynes

The same group again utilized the diboron(4)/pyridine co-catalysis strategy on the [2σ+2σ] radical cycloaddition of cyclopropanes **3** and bicyclo[1.1.0]butanes **13** to form multisubstituted bicyclo[3.1.1]heptane products **15** (Scheme 4).[58] Similarly, B-B homolytic cleavage of B_2pin_2 followed by coordination to pyridine deliver the pyridine-stabilized boronyl radical that adds to the carbonyl oxygen group to afford benzylic ketyl radical **I**. After cyclopropane ring opening, intermolecular radical addition of **13** releases ring strain of the two *cis*-fused cyclopropanes, giving cyclobutyl radical **III** which undergoes 6-*exo*-*trig* ring-closing. The resulting benzylic ketyl radical **IV** yields the desired product **15** while the boryl radical recomplexes with pyridine **14** to regenerate the catalyst.



Scheme 4. [2σ+2σ] cycloaddition of cyclopropanes and bicyclo[1.1.0]butanes via diboron(4)/pyridine co-catalysis

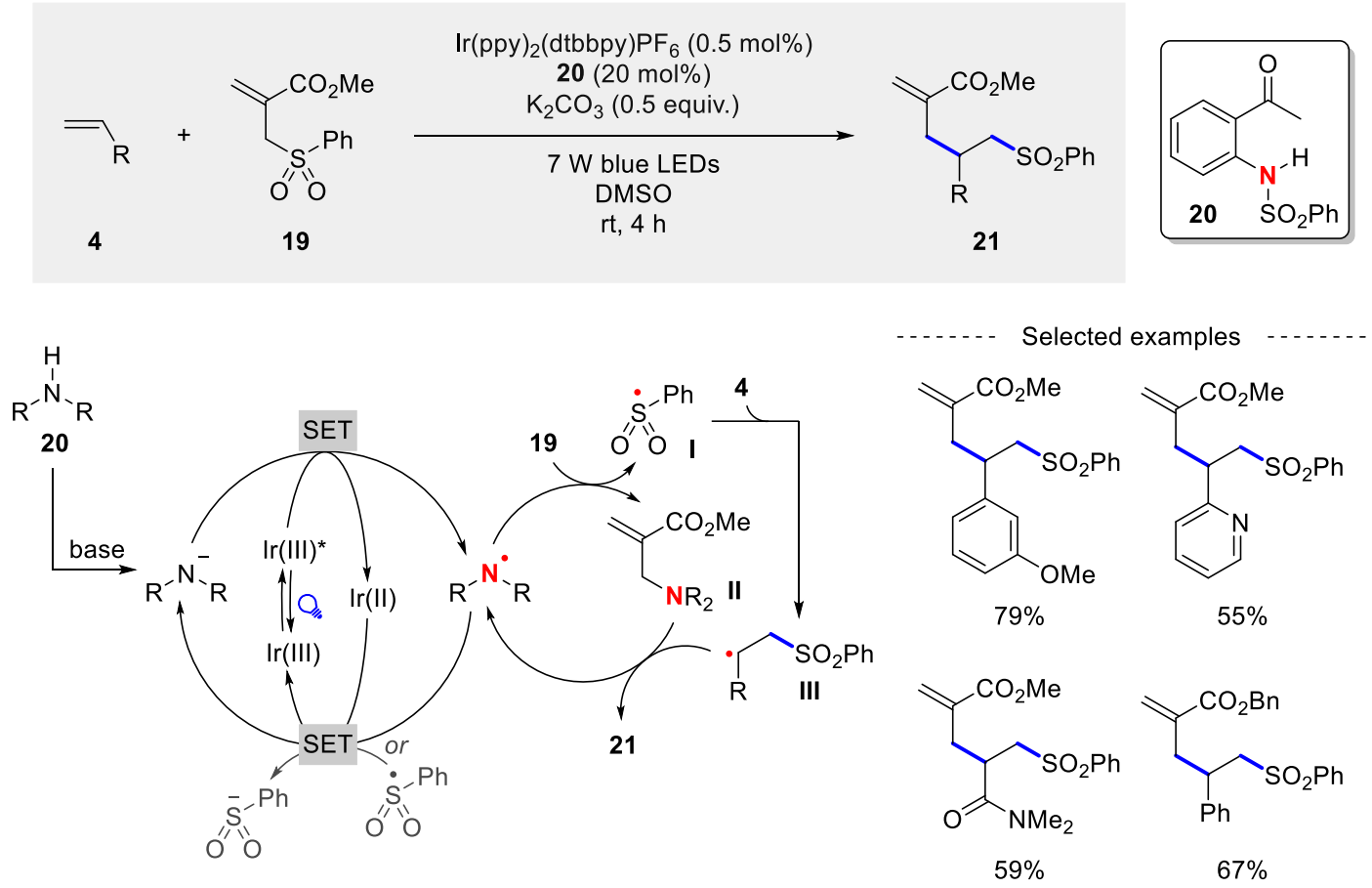
In 2023, the Wang group reported a [2π+2σ] cycloaddition of bicyclo[1.1.0]butanes **16** with alkenes **4** that utilize the similar pyridine-boryl radical catalysis strategy (Scheme 5).[59] The coordination of 4-phenyl pyridine (**17**) on boryl radical, generated from homolytic cleavage of B_2cat_2, delivers the active pyridine-boronyl radical species. Radical addition on the carbonyl group of **16** followed by pyridine dissociation affords ketyl radical **II** that promotes the fragmentation of bicyclo[1.1.0]butane ring. The resulting radical **III** then traps a molecule of alkene **4** and undergoes an intramolecular cyclization to deliver **V** via the radical rebound step. Finally, the release of product **18** was assisted by coordination of 4-phenyl pyridine on boryl radical to regenerate the active catalytic species.



Scheme 5. [2π+2σ] cycloaddition of bicyclo[1.1.0]butanes and alkenes via pyridine/boronyl catalysis

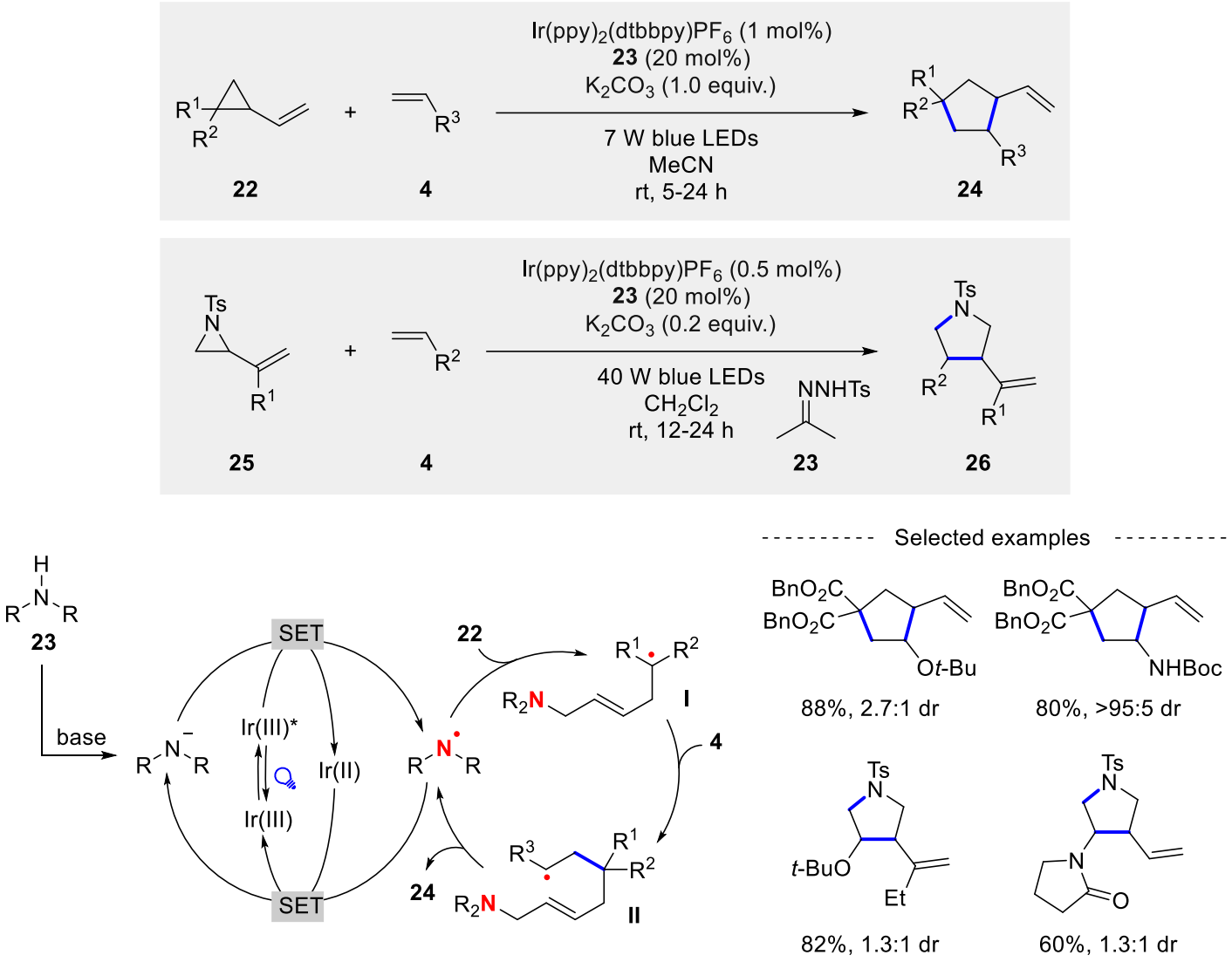
3. Nitrogen Radicals

Stimulated by the research interest on neutral nitrogen-centred radicals, the Chen and Xiao research team disclosed an unprecedented intermolecular alkene bifunctionalization reaction that was realized through *in situ*-generated radical species from photocatalysis.[60] The proposed mechanism of this transformation is illustrated in Scheme 6. The reaction is initiated by base-mediated deprotonation of *N*-(2-acetylphenyl) benzenesulfonamide (**20**) to generate the corresponding anion, which upon SET oxidation, gives access to neutral nitrogen radical. Radical addition to allyl sulfone **19** produces an *N*-sulfonamide intermediate **II** and a sulfonyl radical **I**. The latter adds to alkene **4**, releases a secondary carbon radical **III** that traps the *N*-sulfonamide **II** to deliver desired product **21** and the nitrogen radical. Another SET process on Ir(II) could reconvert nitrogen radical or sulfonyl radical to the corresponding anion.



Scheme 6. Photoredox- and nitrogen radical-catalysed alkene bifunctionalization

Later, this photogenerated neutral nitrogen radical was further applied by the same team in the [3+2] cycloaddition of vinylcyclopropanes **22** and *N*-tosyl vinylaziridines **25** with alkenes **4** to afford vinylcyclopentanes **24** and pyrrolidines **26**, respectively (Scheme 7).[61] In the reaction, an easily accessible hydrazone **23** was used as the catalyst to facilitate the transformation, offering an alternative precursor of neutral nitrogen radical.

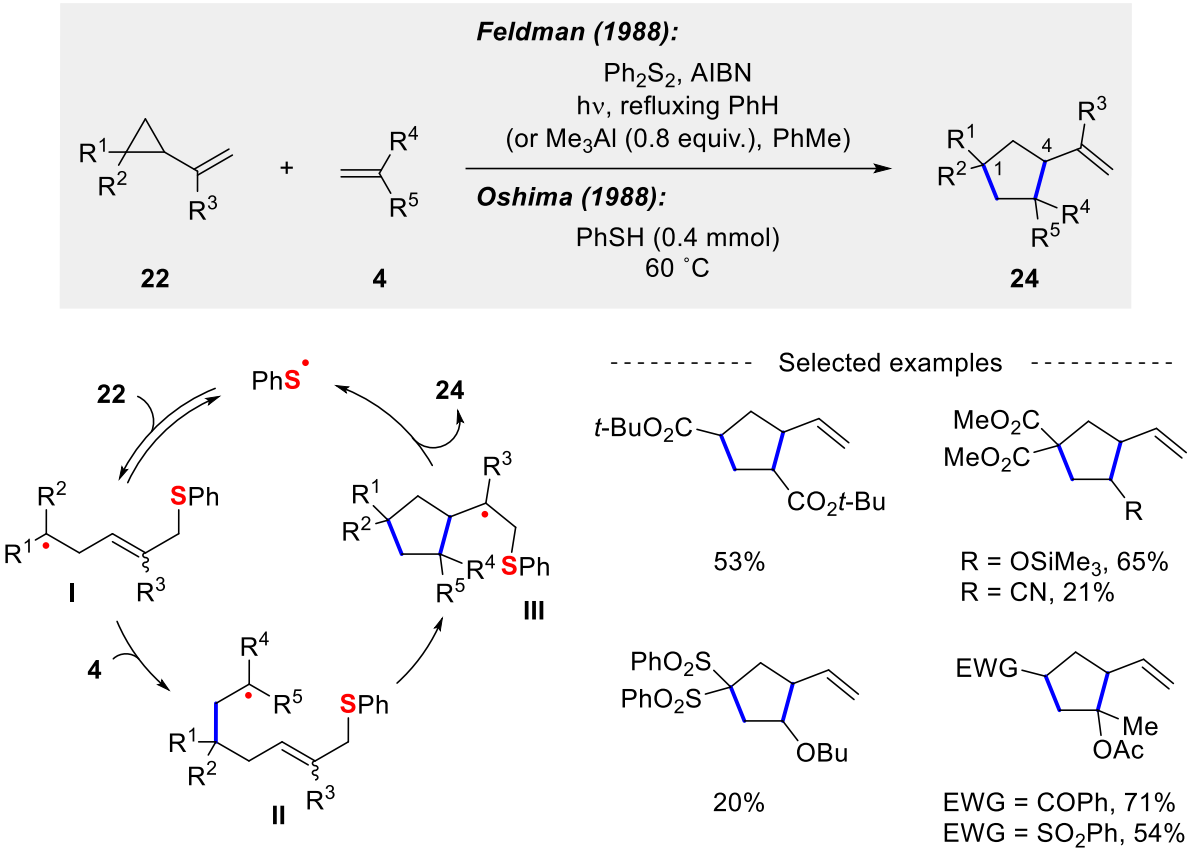


Scheme 7. [3+2] Cyclization of vinylcyclopropanes and *N*-tosyl vinylaziridines with alkenes

4. Sulfur Radicals

Among the manifold reactions catalysed by a radical species, [3+2] cyclization between a vinylcyclopropane and a functionalized alkene is the most prevalent transformation that has been observed thus far. This pioneer work was independently disclosed by the groups of Feldman[62] and Oshima[63] in 1988 (Scheme 8). They demonstrated that a phenylthiyl radical could catalyse the addition of substituted alkenes **4** to vinylcyclopropanes **22** to afford vinylcyclopentanes **24**. This reaction proceeds through a radical addition onto the double bond of vinylcyclopropane **22**, followed by ring opening to afford homoallylic radical **I**. Then, a second radical addition with **4** takes place to yield **II** that affords the corresponding cyclopentanyl carbinyl radical **III** after cyclization. Finally, elimination of phenylthiyl radical affords the final product **24**. With vinylcyclopropyl esters as substrates, vinylcyclopentanes **24** were obtained in a favoured 1,4-*syn* configuration (where R^2 = H), especially under low temperature and in the presence of Lewis acid.[64] Building on the reported reaction, Feldman extended this strategy to a series of work whereby the functionalized alkenes were substituted with alkynes[65] and oxygen[66] to give vinylcyclopentenes or 1,2-dioxolanes, respectively. In addition, aryl vinyl oxiranes[67] and 2,2-

dihalovinylcyclopropanes[68] may also act as the vinylcyclopropane analogues to furnish tetrahydrofurans and 1,1-dihalo-3-vinylcyclopentanes, respectively.

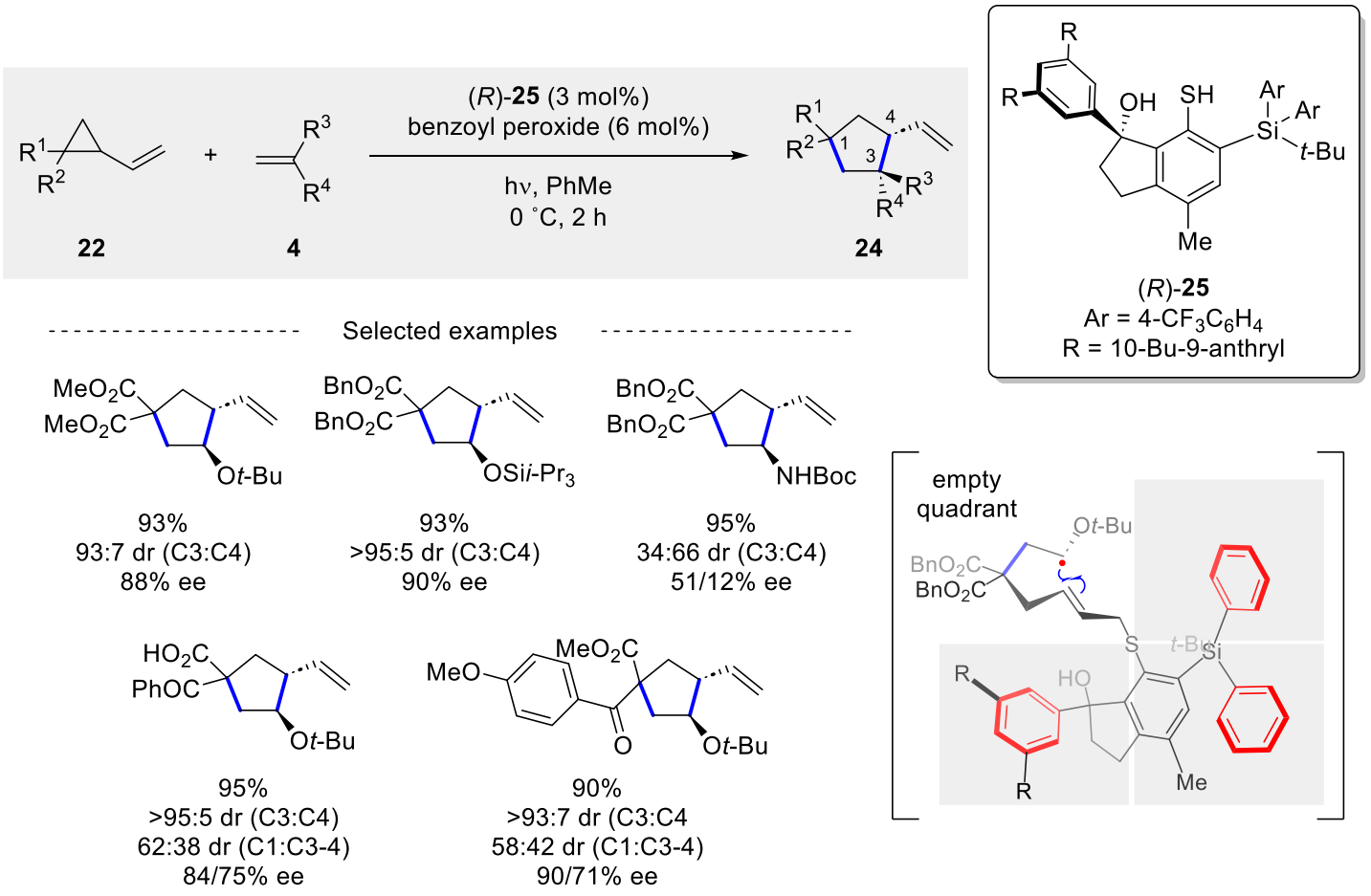


Scheme 8. Addition of functionalized alkenes to vinylcyclopropanes to afford vinylcyclopentanes

Since chirality is one of nature's indispensable elements, advances of radical chemistry in racemic synthesis fall far short of meeting the needs of asymmetric synthesis in real-world applications. The longstanding challenge in achieving enantioselective control of radical reactions stems from their lack of stereospecificity, as the chiral information is often lost upon formation of planar radical species.[69-70] To address this challenge, chemists have devised various approaches to achieve enantioselective radical catalysis. One of the pioneering contributions was reported by Roberts during the introduction of concept “polarity-reversal catalysis” whereby a chiral thiol catalyst was used for enantioselective hydrogen atom transfer (HAT) in a two-step polarity-matched process.[71] In addition, other approaches include the incorporation of chirality-inducing group on the radical species, the molecular substrates, or the transition metals that act as either of the first two.[70] The chirality on the radical approach has been receiving intense focus and indeed this is demonstrated throughout the enantioselective radical reactions in this paper.

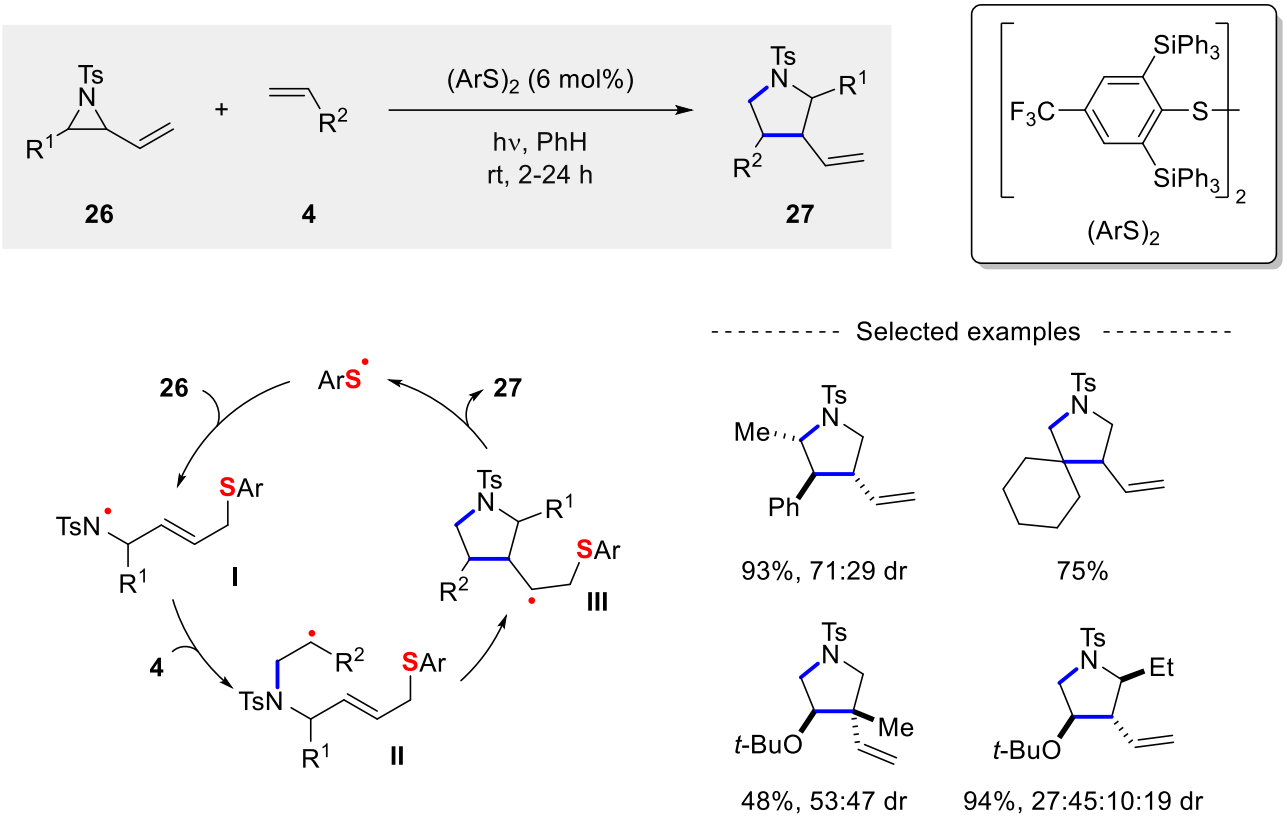
In 2014, the group of Maruoka first envisioned that a chiral thiyl radical catalyst could facilitate the diastereo- and enantioselective radical [3+2] cyclization of vinylcyclopropanes **22** and alkenes **4** (Scheme 9).[72] Building on the systematic studies conducted on binaphthyl-based catalyst, the authors redesigned an unprecedented chiral thiol (*R*)-**25** that bears an indanol scaffold to improve the enantioselectivity of the reaction. The two aryl groups attached on the silyl atom and one aryl moiety on quaternary carbon block the three quadrants around sulfur atom, leaving a chiral pocket for chemical reactions to take place. The bulky 10-

butyl-9-anthryl group on the C-3 and C-5 positions of aryl is crucial for enantioselective control. High diastereoselective (C3:C4) and enantioselective controls were achieved from this methodology.



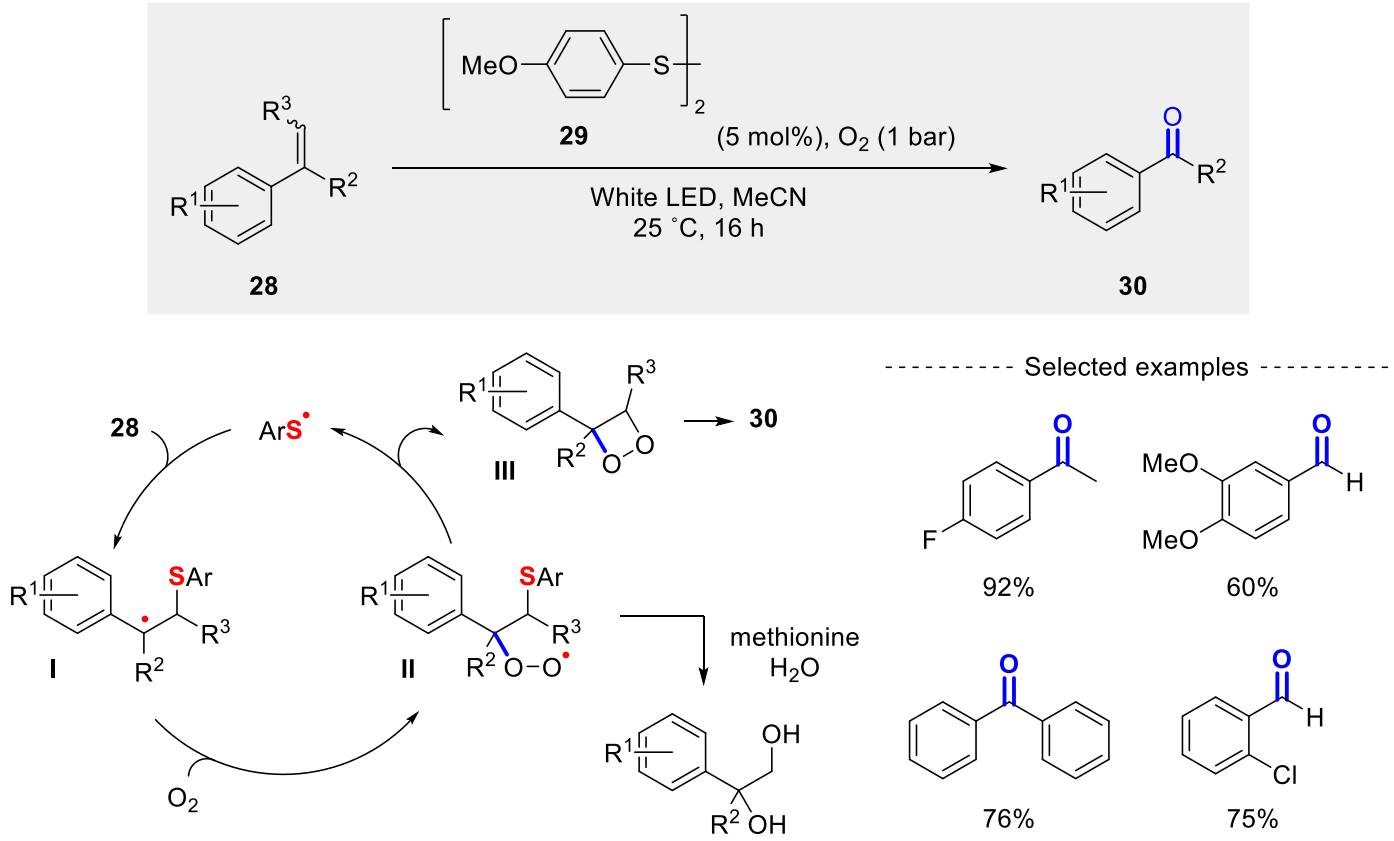
Scheme 9. Enantioselective radical cyclization of vinylcyclopropanes and alkenes

Many years later, in 2016, Maruoka and co-workers reported a thiyl radical-catalysed [3+2] cyclization of *N*-tosyl vinylaziridines **26** and alkenes **4** to access substituted pyrrolidines **27** (Scheme 10).[73] Similarly, the suggested mechanism comprises a thiyl radical addition to the double bond of vinylaziridine. The preliminary experiment suggested that this thiyl radical could also react with the simple alkene **4**, generating a carbon radical that is prompted to second thiyl radical addition, thereby deactivating the catalyst. As proposed by the authors, a solution to this hurdle relied on the use of bulky thiyl radical that may prevent the second addition. Moreover, unlike the Feldman's synthesis of tetrahydrofuran where carbon-carbon bond cleavage predominates due to the aromatic substituent on vinyl oxirane,[67] carbon-nitrogen bond cleavage was observed in this study. Alkene **4** addition, cyclization and subsequent radical elimination eventually lead to the isolated product **27**.



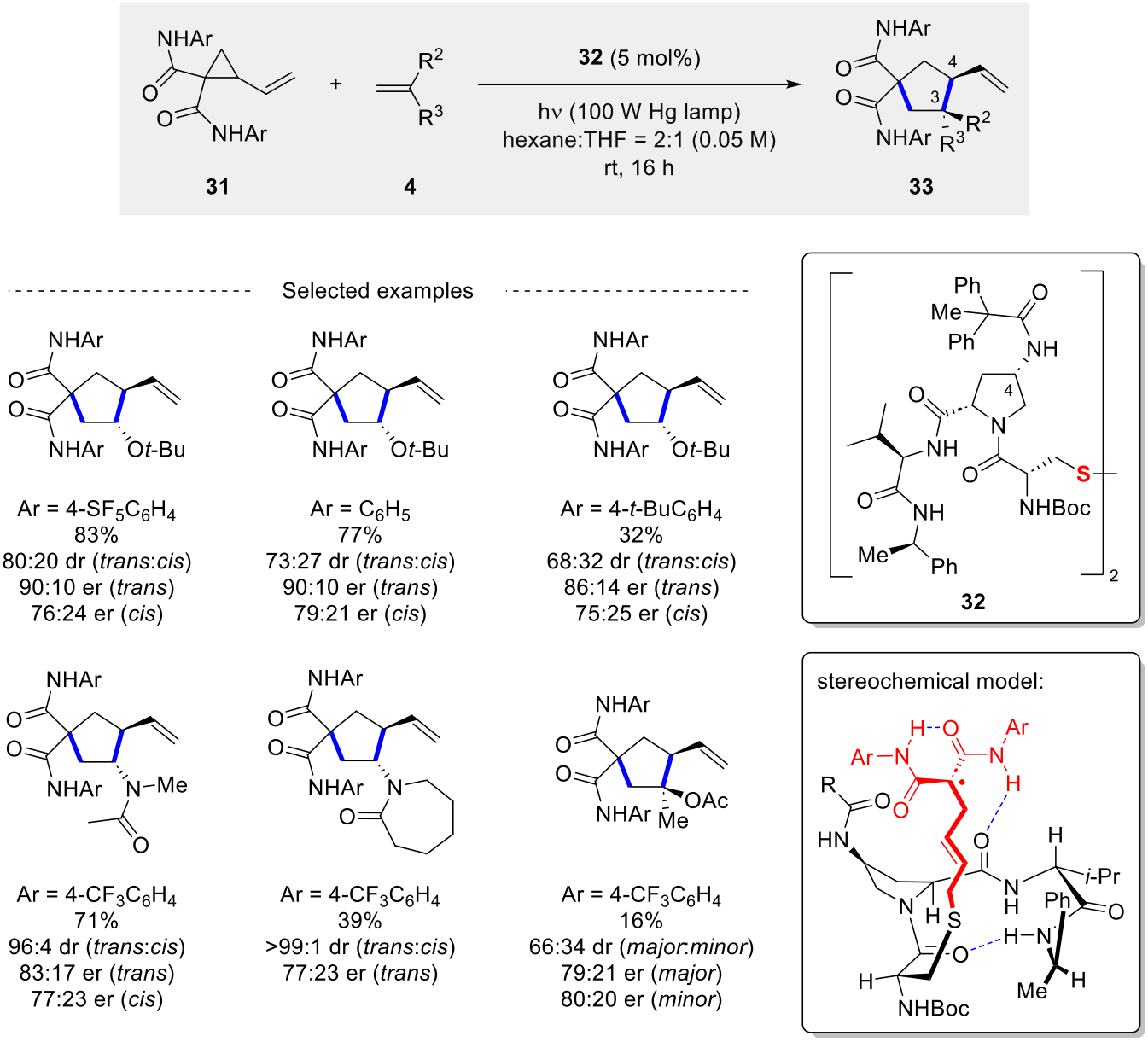
Scheme 10. Synthesis of pyrrolidines via addition of alkenes to *N*-tosyl vinylaziridines

In 2017, the Wang group demonstrated that bis(4-methoxyphenyl) disulfide (**29**) catalyzes the oxidative cleavage of aromatic olefins **28** to form ketones or aldehydes **30** in the presence of visible light (Scheme 11).[74] Remarkably, homolytic cleavage of common aromatic disulfide normally does not occur under LED light. However, in this study, disulfide forms a charge-transfer complex with aromatic olefin to facilitate the photolytic cleavage of the S-S bond. Addition of the resulting thiyl radical to olefin **28** produces a new radical **I** at the benzylic position, which then traps a molecule of oxygen to deliver dioxetane **III** after abstraction and substitution of the thiyl radical. Spontaneous cleavage of dioxetane then affords ketone **30**. Notably, the formation of dioxetane intermediate via a rare bimolecular homolytic substitution (S_H2) on a saturated carbon (**II** to **III**) was not directly observed in this work; instead, methionine and water were added as trapping reagents to deliver diol. In the view of the authors of this review article, the proposed formation of dioxetane through an S_H2 mechanism may need to be further investigated.



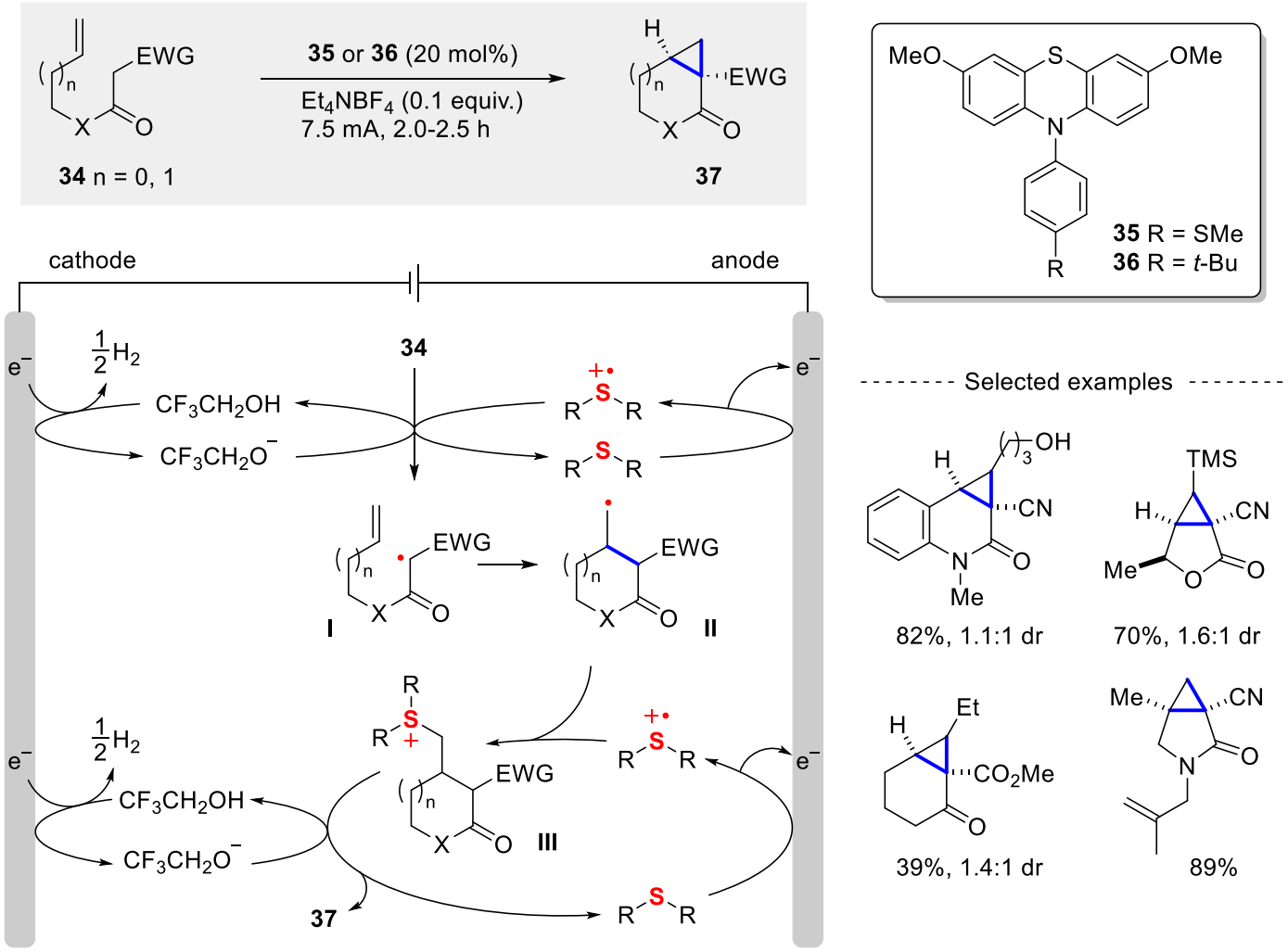
Scheme 11. Oxidative cleavage of olefins via photocatalysis

With disulfide-bridged peptide as precatalyst, Miller and co-workers also achieved a radical-catalysed [3+2] cycloaddition of diamide-functionalized vinylcyclopropanes **31** and electron-rich alkenes **4**, delivering cyclopentanes **33** with high enantioselectivity and 3,4-*trans* selectivity (Scheme 12).[75] During the process, the peptide backbone of the catalyst **32** interacts with the substrate via hydrogen bonding, and the steric profile of the amide moiety at C-4 position of proline was found to promote the enantioselective control of this reaction.



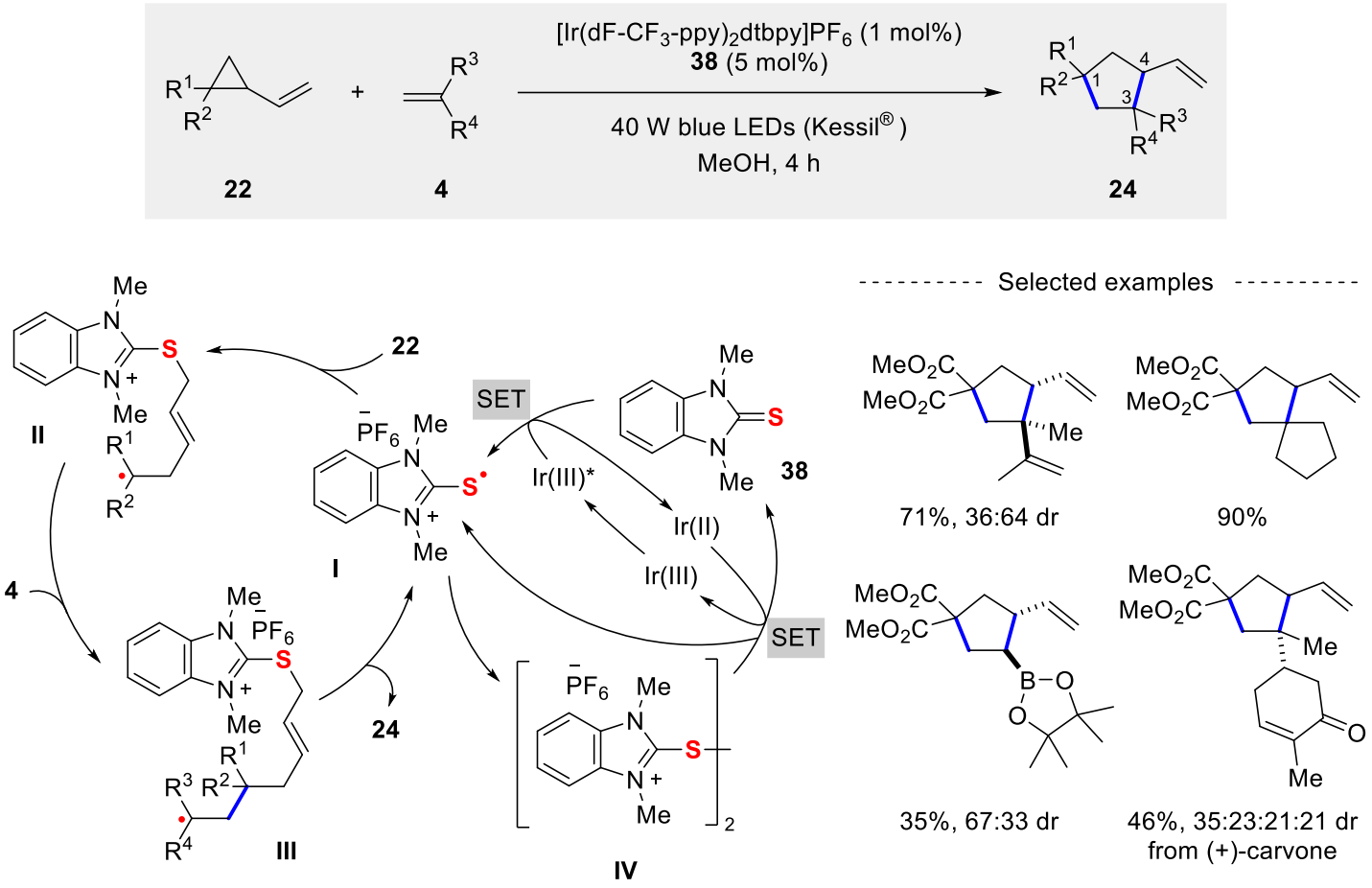
Scheme 12 Cysteine-derived thiyl radical-catalysed cycloaddition of vinylcyclopropanes and alkenes

In 2022, Xu and co-workers reported a radical-polar crossover process through electrocatalytic reaction.[76] They described a complex electrochemical dehydrogenative annulation reaction for the preparation of cyclopropane-fused rings from the active methylene starting materials. As depicted in Scheme 13, this transformation is initiated by the transfer of a single electron from phenothiazine catalyst to anode to afford the stable phenothiazine radical cation. The resulting radical cation would in turn catalyse the oxidation of methylene **34** to carbon radical intermediate **I**, with $CF_3CH_2O^-$ acting as the proton acceptor. Then, radical 6-*exo*-*trig* cyclization and radical-radical cross coupling with another phenothiazone radical cation deliver a sulfonium ion **III**, which subsequently undergoes an intramolecular nucleophilic substitution with the aid of $CF_3CH_2O^-$ ion, eventually forming the cyclopropane ring while regenerating the phenothiazine radical. During the whole electrocatalytic process, hydrogen is emitted to regain the alkoxide ion. This method demonstrates a broad substrate scope and excellent scalability.



Scheme 13. Cyclopropanation of methylene compounds

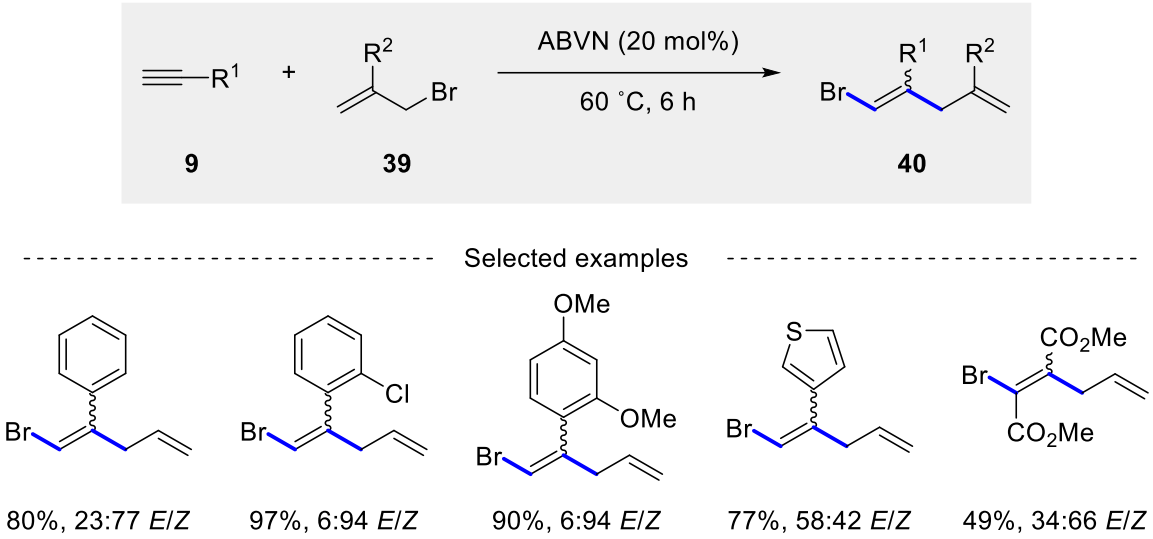
In addition to electrocatalytic strategy, recent advances in the photoredox catalysis offers a new avenue for innovative organic transformations. In 2022, the group of Merad has developed a photoredox and radical covalent dual-catalysis system to achieve the [3+2] cyclization of cyclopropanes and alkenes (Scheme 14).[77] This reaction was operated with a newly designed benzimidazole-derived thiourea precatalyst that offers high structural diversity compared to the catalysts used in the aforementioned approaches. The reaction also features mild reaction conditions and high functional group tolerance. Mechanistically, single electron oxidation of *N*,*N*,*N*,*N*-tetrasubstituted thiourea **38** by the photocatalyst [Ir(dF-CF_3-ppy)$_2$dtbpy]PF_6 forms isothiouronyl radical cation **I**, which is prone to undergo sequential ring opening/radical addition/cyclization/elimination processes, affording vinylcyclopentane **24** in a preferred 3,4-*trans* relationship. The regenerated radical **I** then reenters the photoredox catalytic cycle to give the dimerized intermediate **IV** which in turn be reduced by Ir(II) to deliver **38** and **I**, allowing a new cycle to begin.



Scheme 14. [3+2] radical cyclization via photoredox and radical covalent catalysis

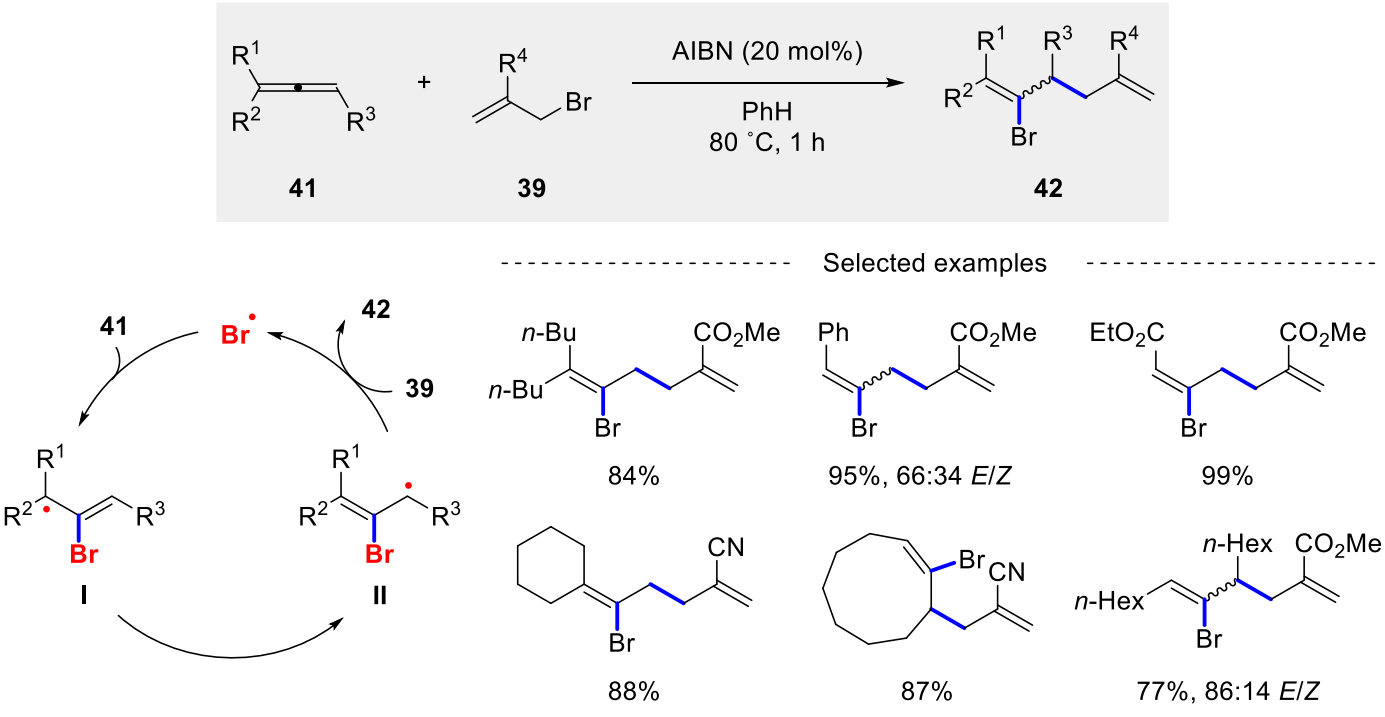
5. Bromine Atoms

Over the years, the Ryu group has been actively working on bromine radical-mediated bromoallylation of various unsaturated compounds.[78] In 2010, the Ryu group disclosed that bromoallylation of acetylenes **9** could be realized by *in situ* generated bromine radical to afford 1-bromo-1,4-dienes **40** (Scheme 15).[79] In their study, 2,2'-azobis(2,4-dimethylvaleronitrile) (ABVN) was used as the radical initiator to release bromine radical from substrate **39**. This bromine radical regioselectively adds to the terminus of alkyne, providing an alkenyl radical that reacts with **39** via bimolecular homolytic conjugate substitution (S_H2' reaction). The resulting product **40** exists majorly as *Z* isomer as the attack of allyl bromide prefers to be carried out in a less-sterically hindered environment. The bromide **40** could later be subjected to palladium-catalysed reactions such as carbonylation, reduction, Sonogashira reaction and Suzuki-Miyaura coupling for further modifications.



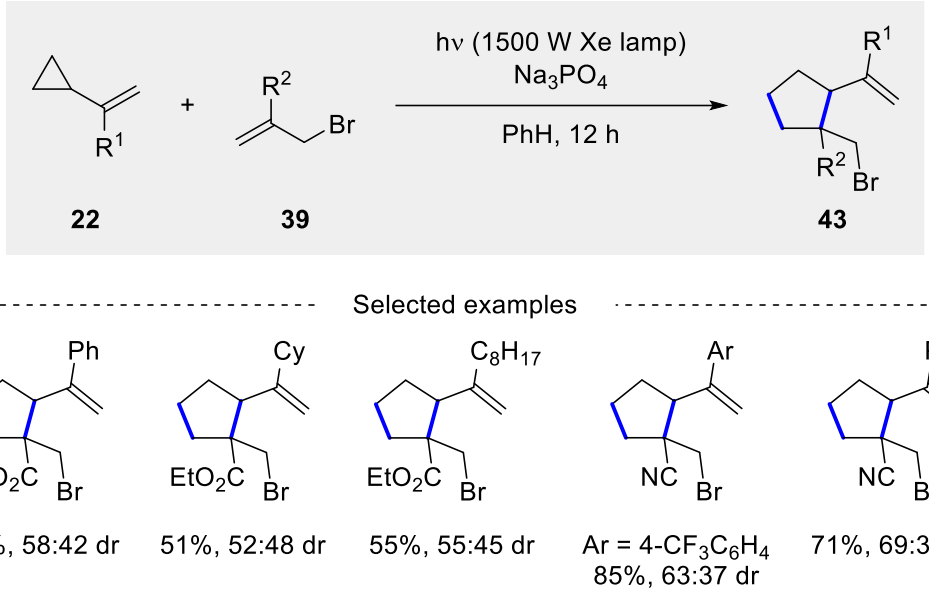
Scheme 15. Regioselective radical bromoallylation of acetylenes

This radical bromoallylation strategy was also applied by Ryu's research team to allenes **41** to deliver 2-bromo-substituted 1,5-dienes **42** where the bromine radicals regioselectively add to the centre carbon of allenes (Scheme 16).[80] The resulting allyl radical **I** isomerizes into radical **II** before reacting with allyl bromide **39** to give **42**. In this case, preference towards the formation of *E* isomers was observed and it was postulated that there is steric repulsion between the bromine and the substituents on allene. Later, the Ryu group also extended this synthetic strategy by substituting allene substrates **41** with alkylidenecyclopropanes[81] and alkenes.[82] Notably, the allyl radical **II** may also trap a molecule of electron-deficient alkene to propagate the chain before it reacts with **39**, yielding 2-bromo-1,7-dienes.[83] A similar three component reaction of alkylidenecyclopropanes, carbon monoxide and allylic bromides was also reported by the same team for the synthesis of 2-bromo-substituted 1,7-dien-5-ones.[81]



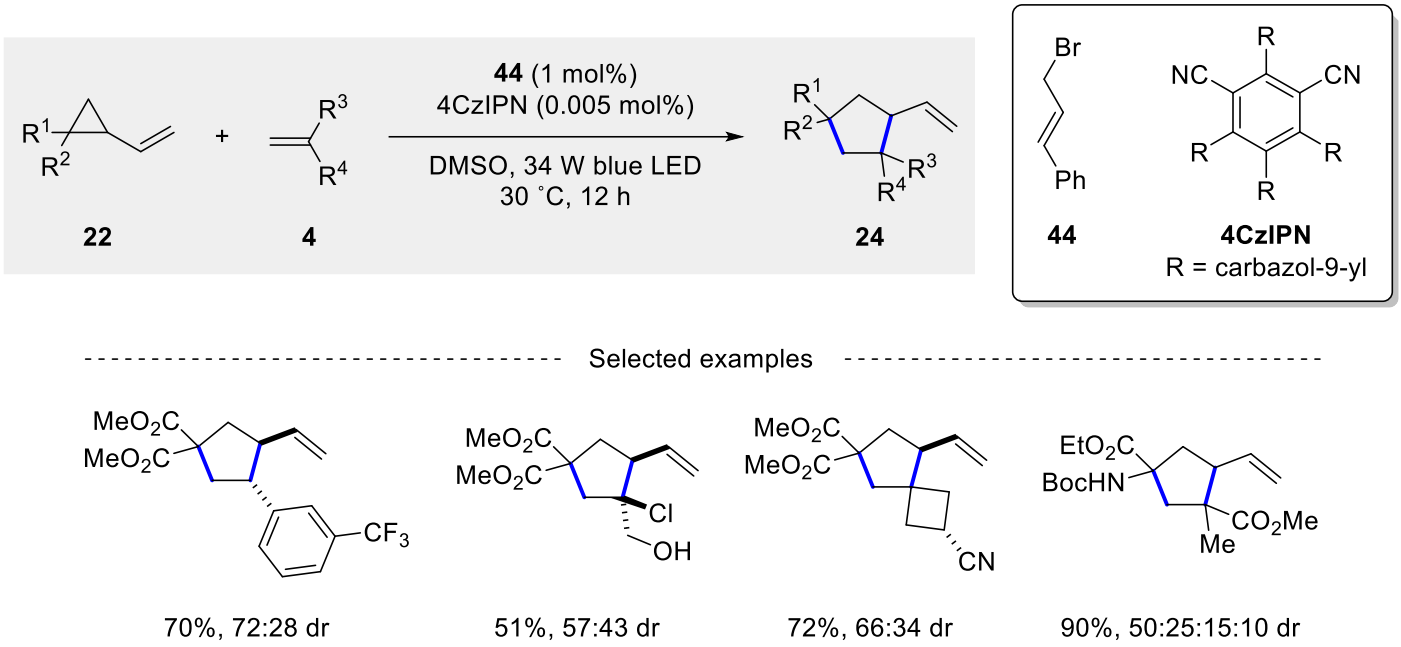
Scheme 16. Regioselective radical bromoallylation of allenes

The radical [3+2] annulation could also be achieved via bromine radical catalysis. This reaction was reported by Ryu in 2019 where 2-bromomethyl alkenylcyclopentanes **43** were synthesized from vinylcyclopropanes **22** and allyl bromides **39** (Scheme 17).[84] The reaction was carried out in simple reaction conditions where photoirradiation takes place to form bromine radical via C-Br homolysis, and the addition of Na_3PO_4 as base to inhibit the formation of by-products from starting materials **22** and HBr.



Scheme 17. [3+2] Cycloaddition of vinylcyclopropanes and allyl bromides

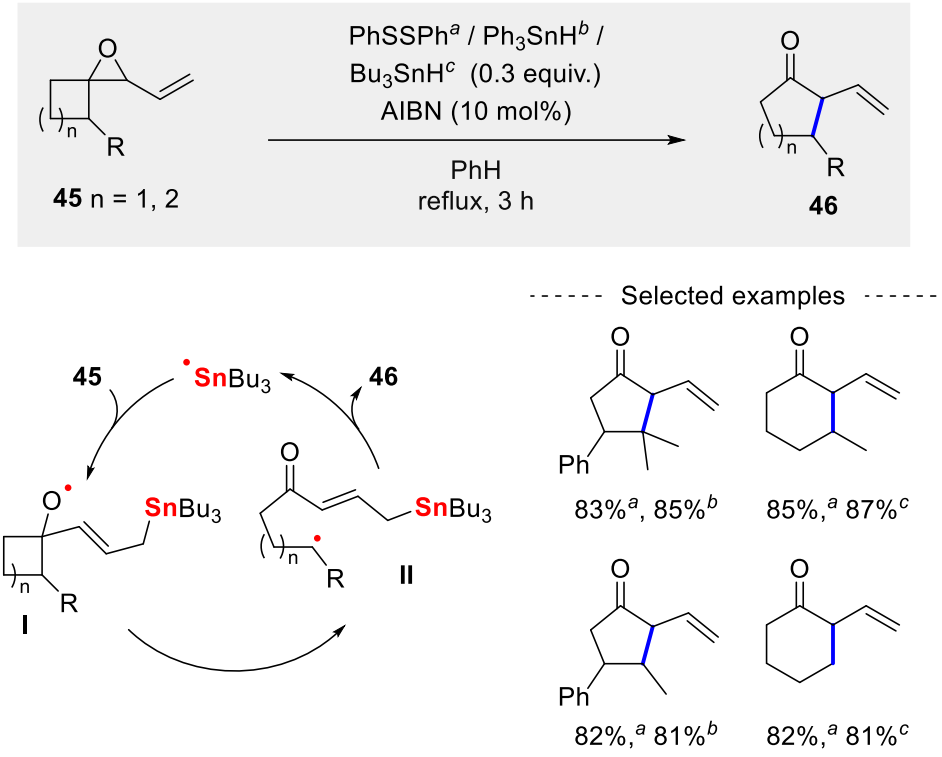
Recognizing that the field of energy transfer catalysis is underexploited compared to electron transfer catalysis (that is, the photoredox catalysis), Miyake and co-workers devised a protocol to facilitate [3+2] cycloaddition of vinylcyclopropanes **22** and alkenes **4** using energy transfer photosensitization strategy (Scheme 18).[85] In their reaction, parts per million level (0.005 mol%) of carbazole–cyanobenzene donor–acceptor fluorophore 4CzIPN is excited by visible light and this excited state energy is then transferred to cinnamyl bromide (**44**) to release bromine radical after β-fragmentation.[86-87] Subsequently, radical addition to the double bond of vinylcyclopropane is followed by ring opening. The resulting radical intermediate then adds to alkene **4** to propagate the radical chain which further undergoes intramolecular cyclization and radical elimination, completing the catalytic cycle.



Scheme 18. [3+2] Cycloaddition of vinylcyclopropanes and alkenes via energy transfer catalysis

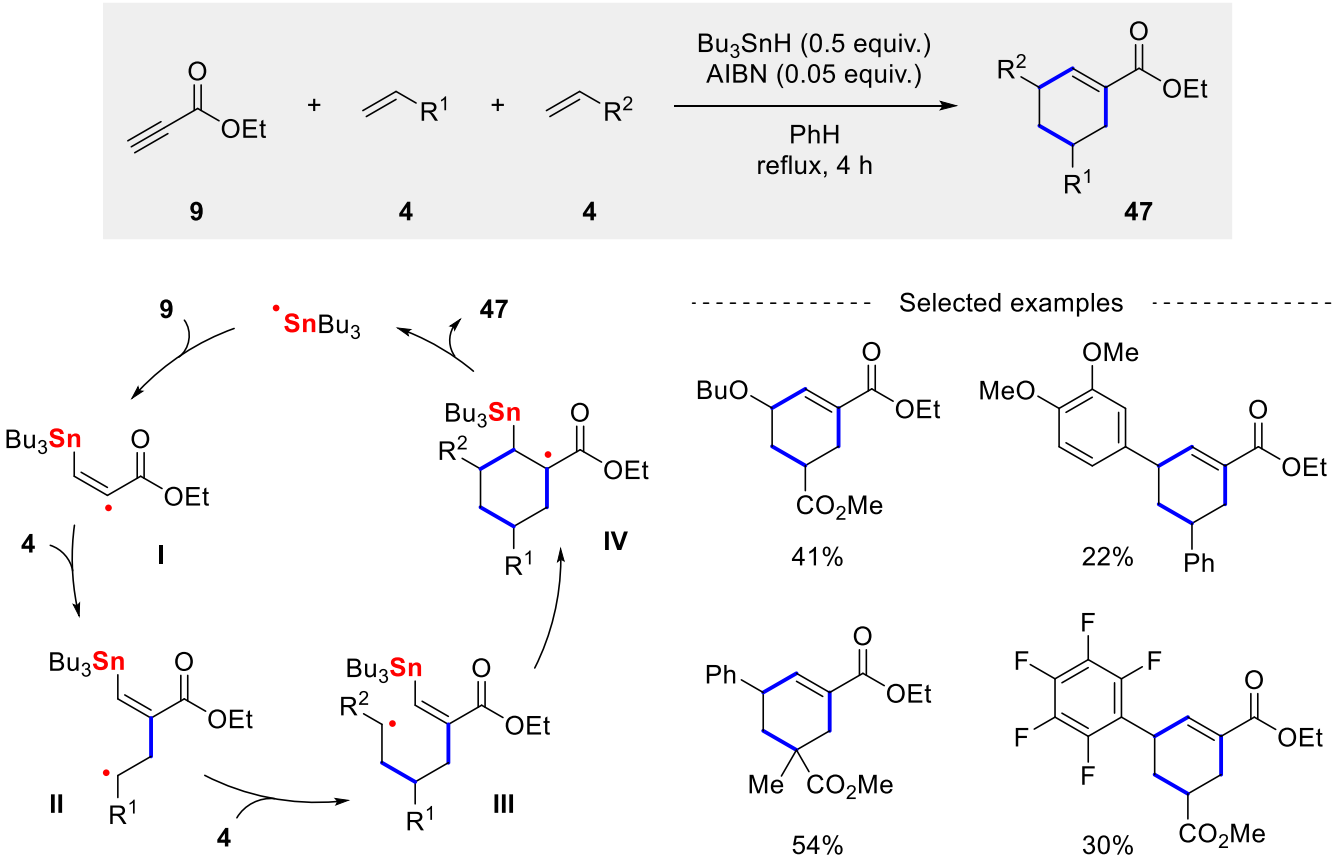
6. Tin (or Stannyl) Radicals

Organotin hydride is a common reagent used in the radical chain reaction as it can easily be initiated in the presence of azobisisobutyronitrile (AIBN) or light irradiation. Nonetheless, concern on its toxicity limits its application and stimulates the development of its alternatives.[88] Over the years, the role of tin radical as catalyst in an organic reaction has been investigated occasionally. In 1991, the Kim group reported a tributyltin radical-catalysed ring expansion of vinyl spiro epoxides **45** to generate cyclopentanones or cyclohexanones **46** (Scheme 19).[89] The process involves the radical addition to the vinyl moiety followed by C–O bond cleavage to yield alkoxy radical **I**. Subsequently, β-cleavage delivers a carbon radical **II** that produces product **46** after the elimination of tributyltin radical. Remarkably, addition of a catalytic amount of phenylthiyl radical could hinder the undesired side reaction in which the conjugate addition of carbon radical **II** takes place, followed by hydrogen atom abstraction to produce stannylated cyclohexanone in low yield. This reaction could also be carried out with diphenyl disulfide instead of the stannates.



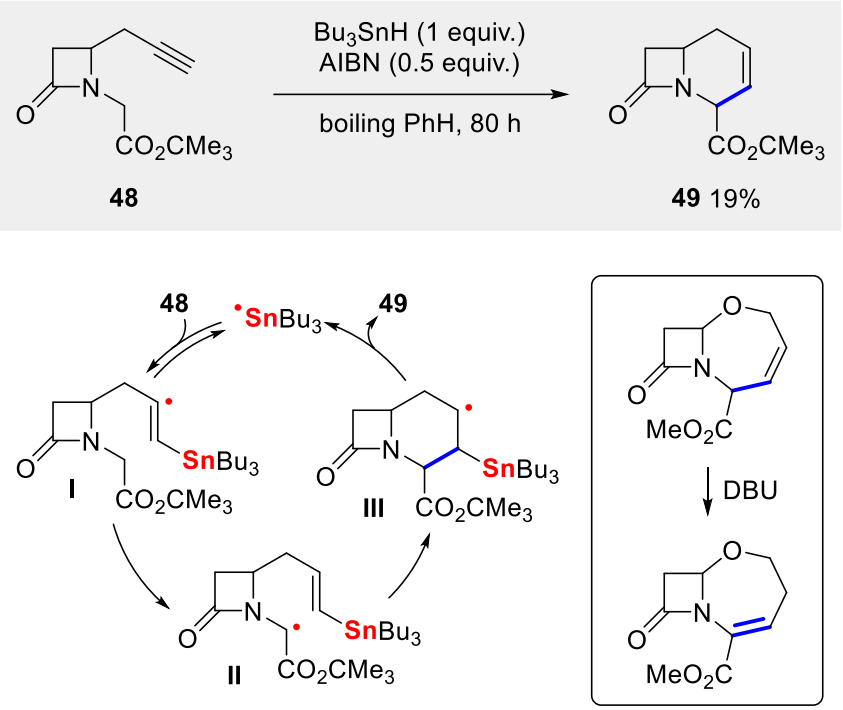
Scheme 19. Ring expansion of vinyl epoxides

Similar to alkenes, tributyltin radical could be added to alkynes for further transformations. In 1993, the group of Lee reported a three-component [2+2+2] cycloaddition involving a molecule of ethyl propiolate (**9**) and two molecules of alkenes **4** to access the substituted cyclohexenecarboxylate derivatives **47** (Scheme 20).[90] In the study of this reaction, alkenes with different electronic properties were subjected to the reaction conditions. Mechanistically, reaction of tributyltin hydride with AIBN generates a tributyltin radical, which then adds to the terminus carbon of ethyl propiolate (**9**) to form a reactive alkenyl radical species **I**. This radical is postulated to possess moderate nucleophilicity, preferably undergoes radical conjugate addition with electron-deficient alkenes **4**. The resulting radical intermediate **II** exhibits relative electrophilicity and reacts with electron-rich alkenes **4** through a second radical conjugate addition, yielding species **III**. Subsequent ring closure, followed by β-elimination releases the cyclization product **47** while regenerating the stannyl radical. Despite the successful synthesis of desired product, an inseparable mixture of regio- and diastereomers were obtained.



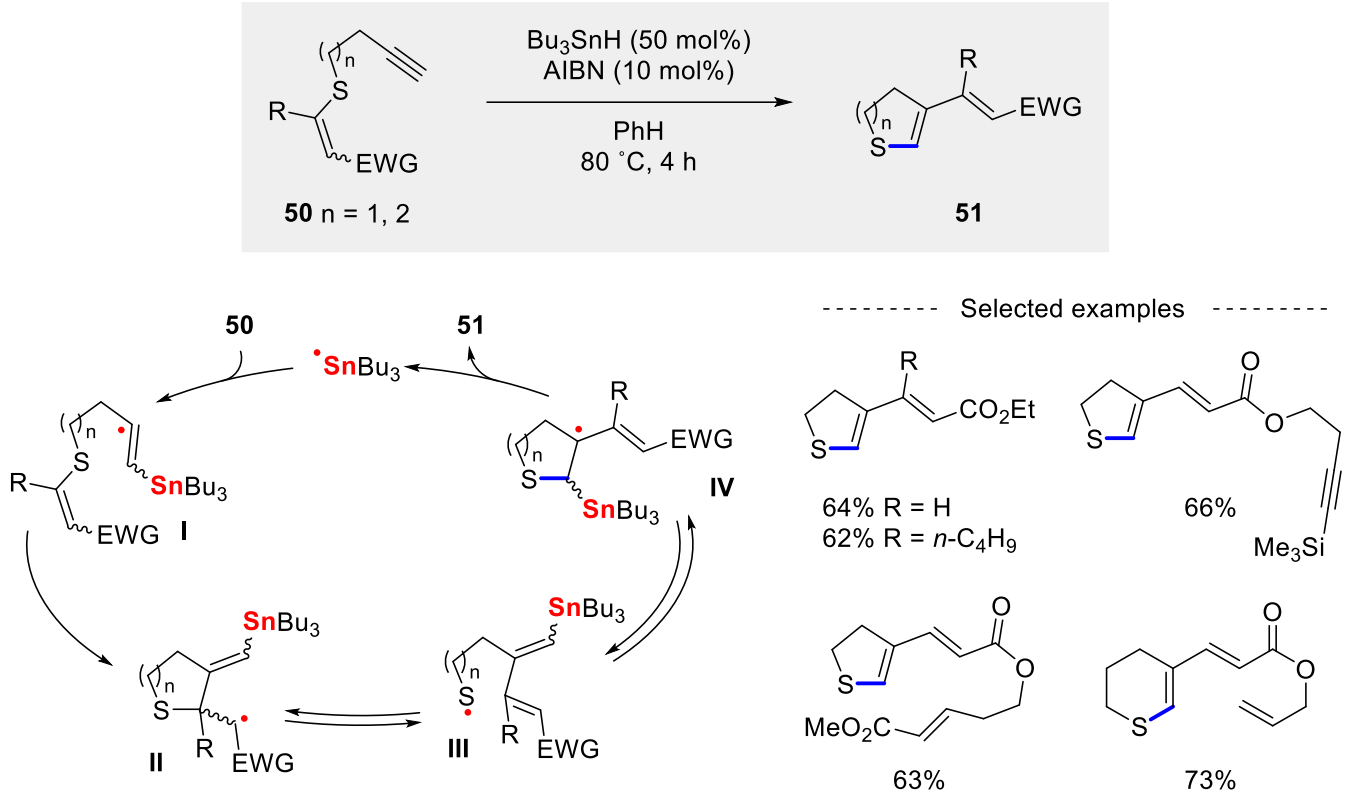
Scheme 20. Synthesis of cyclohexenecarboxylates via [2+2+2] cycloaddition of propiolate and alkenes

In 1993, Bachi and co-worker disclosed the addition of tributyltin radical to the triple bond of alkynyl-β-lactams **48** (Scheme 21).[91] The resulting alkenyl radical **I** is unstable and prone to β-elimination to recover the starting material. Nevertheless, a small amount of this intermediate undergoes intramolecular HAT to afford stabilized radical **II**, which can then yield the final product **49** via cyclization and β-elimination. As the hydrogen transfer step is inefficient, the product was obtained in low yield as expected. This method was also applied to synthesize β-lactam-fused 1,3-oxazepanes.



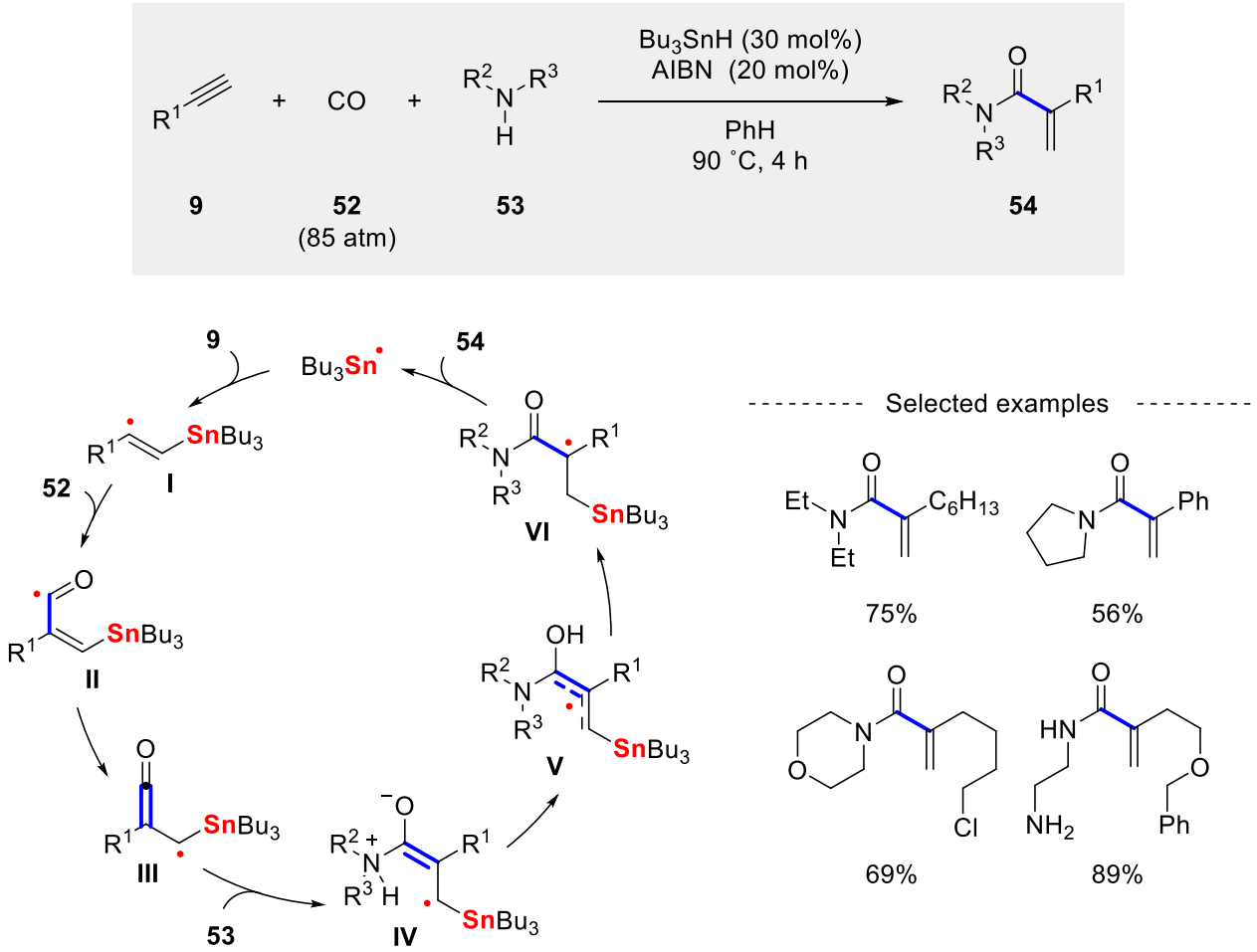
Scheme 21. Synthesis of bicyclic β-lactams via intramolecular radical cyclization

In 1997, Journet and co-workers developed a double radical cyclization/β-fragmentation sequence for the preparation of 3-vinyldihydrothiophene and dihydrothiopyran derivatives **50** from acyclic ω-yne vinyl sulfides **50** (Scheme 22).[92] Similar to the previous scheme, radical addition of the tributyltin radical to an terminal alkyne affords an alkenyl radical **I**, which subsequently undergoes 5- or 6-*exo-trig* cyclization. The resulting ring intermediate **II** is susceptible to β-fragmentation, generating a thiyl radical **III** that adds to the other double bond via 5- or 6-*endo-trig* cyclization. Finally, β-fragmentation again takes place to regenerate the tributyltin radical and afford the isolated product **51**.



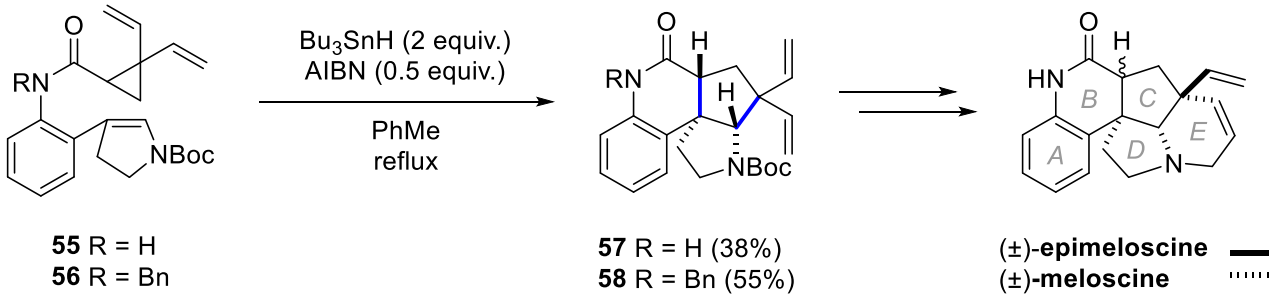
Scheme 22. Double radical cyclization/β-fragmentation of acyclic ω-yne vinyl sulfides

Building on series of work where radical carbonylation was applied for the synthesis of five- and six-membered lactams,[93-96] the Ryu group disclosed that α-methylene amides can be prepared by stannyl radical-catalysed carbonylation of 1-alkynes **9**, carbon monoxide and secondary amines **53**, in year 2005 (Scheme 23).[97-98] In the process, addition of tributyltin radical to terminus of alkyne **9** generates vinyl radical **I**. Subsequent carbon monoxide addition delivers acyl radical **II** which may isomerize into α-ketenyl radical **III**. The nucleophilic attack of aliphatic amine **53** on the center carbon of ketene affords allyl radical **IV**. This radical is then transformed into **V** and undergoes 1,4-HAT and β-elimination to give product **54** and the radical catalyst. This report demonstrates a new perspective in the application of radical catalysis especially when a multicomponent reaction may be realised through appropriate control of polarity.



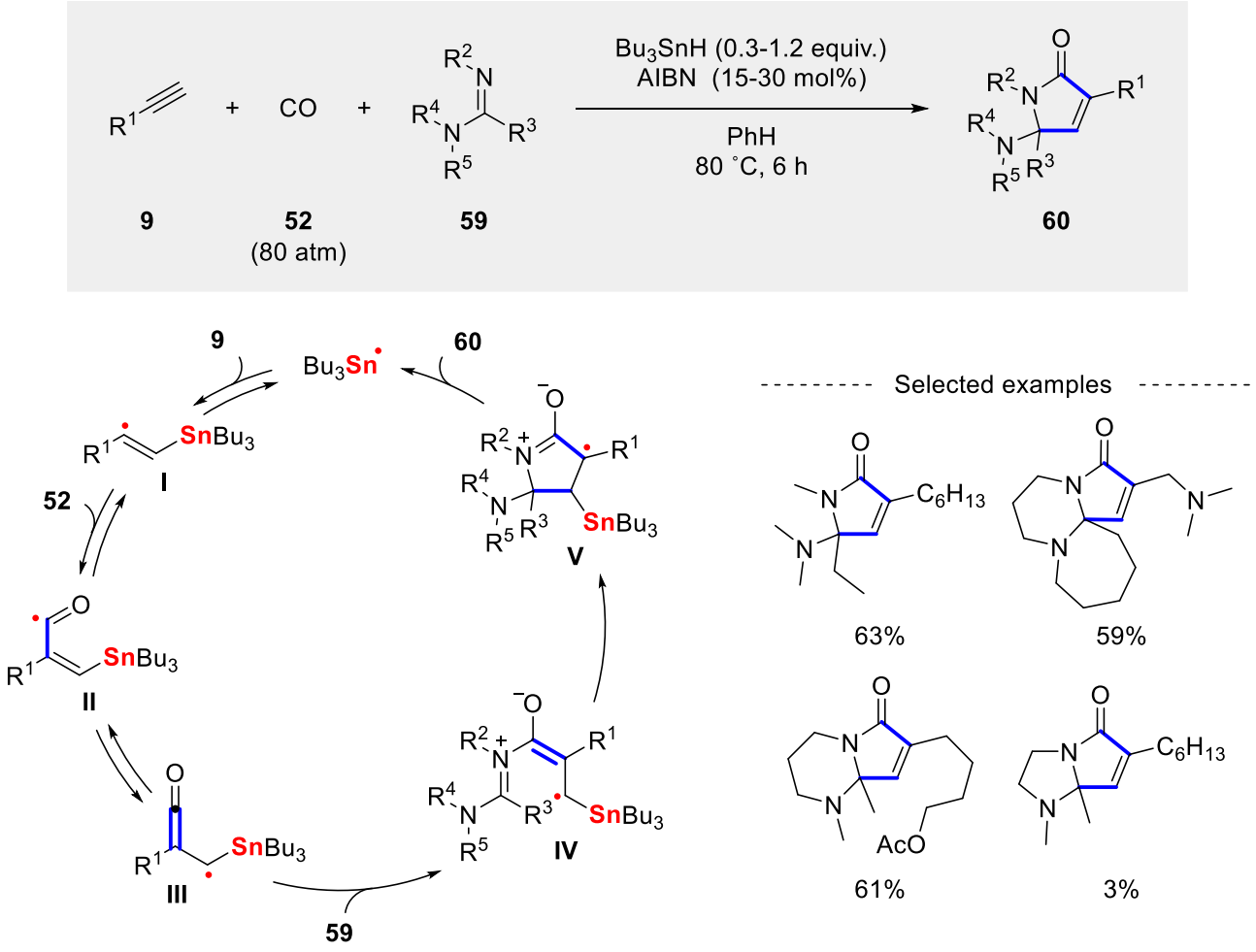
Scheme 23. Radical carbonylation for the synthesis of α-methylene amides

As tin radical has demonstrated its effectiveness in promoting radical cyclization, its application on total synthesis was illustrated by Curran and his team in 2011, where they applied the radical-catalysed [3+2] annulation reaction in the synthesis of natural product known as meloscine (Scheme 24).[99] The reaction proceeds through radical addition on the double bond of divinyl cyclopropane **55** or **56**, followed by cyclopropane fragmentation/double cyclization/β-elimination cascades, forming two new bonds that completed the construction of tetracyclic ring **57** or **58**. Eventually, **57** proceeds with further transformations to deliver epimeloscine, which gives meloscine upon epimerization. Three years after this study, Curran and LaPorte also demonstrated that this methodology could be used to prepare meloscine analogues with five- to seven-membered D rings.[100]



Scheme 24. Synthesis of meloscine via radical [3+2] cyclization

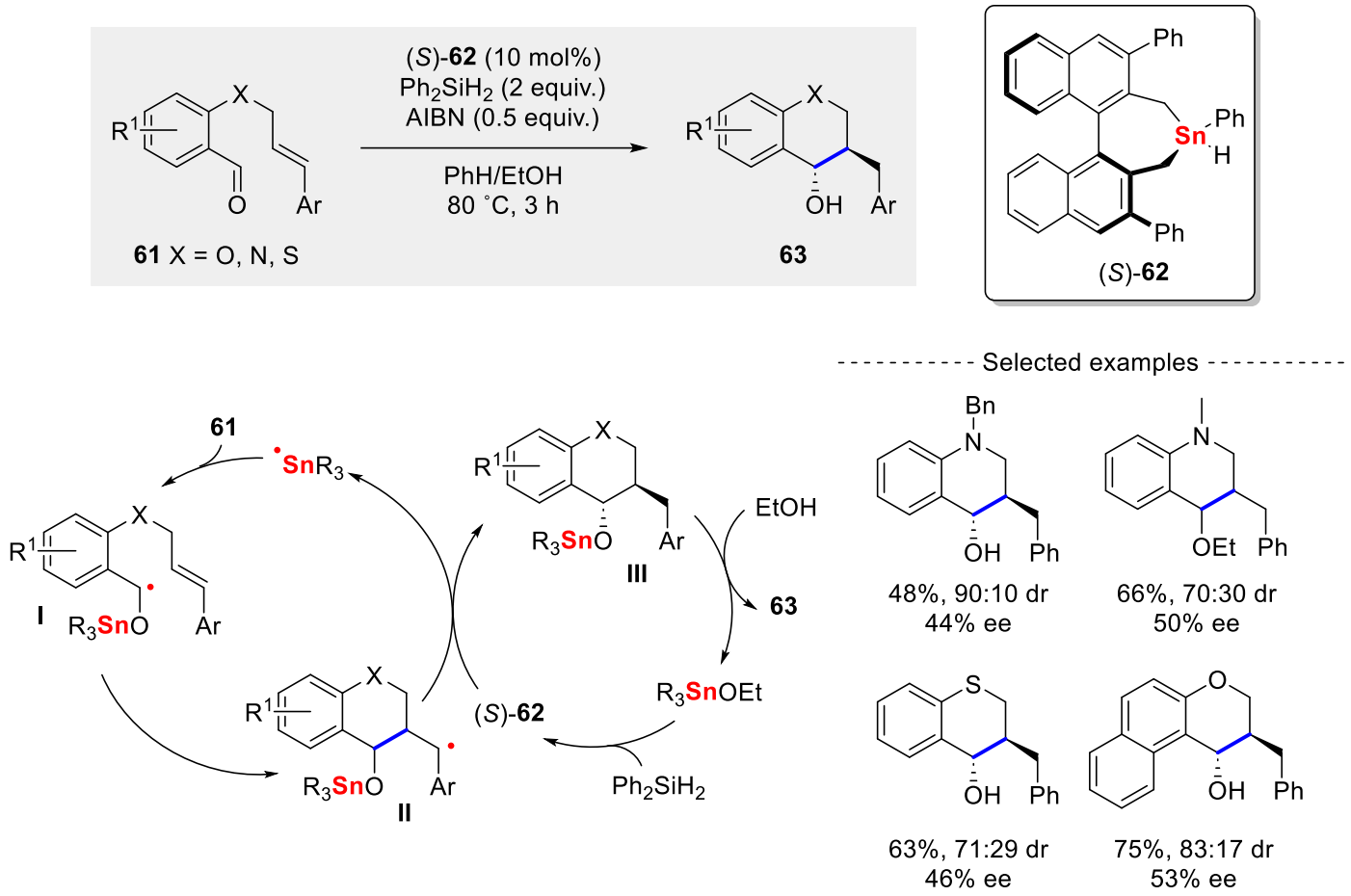
In 2013, the Ryu group applied the tributyltin radical catalysis into three-component cycloaddition of acetylenes, carbon monoxide, and amidines for the synthesis of α,β-unsaturated five-membered lactams (Scheme 25).[101] The reaction tolerates both acyclic and cyclic amidines, allowing the formation of monocyclic, bicyclic and tricyclic lactams. This reaction was proposed to proceed through radical addition to acetylene **9** to form β-stannylated vinyl radical **I**. The coupling of this resulting radical with carbon monoxide (**52**) yielded α,β-unsaturated acyl radical **II** that isomerizes into α-ketenyl radical **III**. After that, an intermolecular nucleophilic attack of amidine **59** onto the α-ketenyl radical delivers a stabilized radical intermediate **IV** that could easily cyclize to form the desired β-lactam **60** after radical elimination. Later in 2019, the same group has also reported a similar [2+2+1] cycloaddition reaction with aromatic imines in place of amidines **59** as the coupling partner to deliver the unsaturated lactam products.[102]



Scheme 25. Synthesis of α,β-unsaturated five-membered lactams via [2+2+1] cycloaddition

Apart from the typical reactions where radical adds to the terminus of alkenes or alkynes, Maruoka and co-workers introduced an enantioselective radical cyclization of aldehydes through chiral organotin hydride catalysis (Scheme 26).[103] The proposed mechanism suggested that the addition of chiral organotin radical to carbonyl oxygen of **61** first generates an *O*-stannyl ketyl radical **I**. This intermediate undergoes cyclization and abstracts a hydrogen atom from the chiral catalyst (*S*)-**62** to regenerate the radical while affording organotin alkoxide **III**. Reaction of organotin alkoxide with ethanol then provides the final product **63** and tin ethoxide, with the latter be reduced by Ph_2SiH_2 to redeliver (*S*)-**62**. The related reduction of the stannane reagent by

stoichiometric reductants such as poly(hydromethylsiloxane),[104] sodium borohydride,[105] or sodium cyanoborohydride[106] has also been well reported previously.



Scheme 26. Enantioselective radical cyclization of aldehydes

7. Conclusions

Radical catalysis provides ample opportunities to perform cascade reactions that allow rapid construction of one or multiple chemical bonds in a single step. Overcoming the issues of reactivity, regioselectivity or even stereoselectivity control, incredible progresses in the field of radical-catalysed organic reactions have been revealed in the past decades, as summarized in this paper. The pioneer work of radical catalysis involved [3+2] annulation of cyclopropanes with alkenes to afford cyclopentanes. Throughout years of study, this organic transformation has been realized by sulfur, tin, boron, nitrogen, and bromine radicals. The method to furnish these radicals also expands from simple bond homolysis under ultraviolet light or in presence of radical initiator, to photoredox catalysis and photochemical sensitization. Meanwhile, new approach such as metalloradical catalysis opens up new avenues for innovative protocols. Reactions like intramolecular cyclization, oxidative cleavage of olefin, cyclopropanation and [2+2+1] cycloaddition have all been accomplished through radical catalysis, clarifying its value for further development.

Despite these remarkable advances, it could be foreseen that several areas and directions are more likely to receive attention for future research: (1) Achieving control over enantioselectivity and diastereoselectivity in

free radical reactions continues to be a substantial hurdle. The existing solutions to overcome this issue involve carefully designing radicals to manipulate their steric and electronic properties. However, the development of general radical precursors that can tolerate diverse functional groups and reaction types still poses a demanding task, necessitating substantial dedication and effort; (2) The radical catalysis strategy is mainly applied on [3+2] cycloaddition of vinylcyclopropanes and alkenes. Other ingenious methodology to expand the scope of radical catalysis is awaiting further exploration; (3) Continued development of main-group element-based radicals is expected, especially the sulfur, boron, and nitrogen radicals. The toxicity of tin radicals hinders their use and a growing interest to search for their alternatives could be observed in near future. (4) Scale-up application of the designed methodology in the total synthesis of bioactive molecules.

We hope this review helps to direct more attention to radical catalysis and we look forward to seeing how this fascinating field continues to evolve and make creative advancements in the near future.

Acknowledgements

We thank the National Natural Science Foundation of China (21971226 and 22171253) and the Fundamental Research Funds for the Central Universities (WK2060000017) for financial support.

References

1. Anastas, P. T.; Bartlett, L. B.; Kirchhoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11-22. https://doi.org/10.1016/S0920-5861(99)00222-9
2. Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686-694. https://doi.org/10.1021/ar010065m
3. Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825-1864. https://doi.org/10.1002/adsc.201100488
4. Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, *2010*, 2999-3025. https://doi.org/10.1002/ejoc.201000004
5. Zhou, J. *Chem. Asian J.* **2010**, *5*, 422-434. https://doi.org/10.1002/asia.200900458
6. Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. *Acc. Chem. Res.* **2014**, *47*, 2365-2377. https://doi.org/10.1021/ar500101a
7. Rudroff, F.; Mihovilovic, M. D.; Gröger, H.; Snajdrova, R.; Iding, H.; Bornscheuer, U. T. *Nat. Catal.* **2018**, *1*, 12-22. https://doi.org/10.1038/s41929-017-0010-4
8. Lang, X.; Zhao, J.; Chen, X. *Chem. Soc. Rev.* **2016**, *45*, 3026-3038. https://doi.org/10.1039/C5CS00659G
9. Lu, J.; Wang, Y.; McCallum, T.; Fu, N. *iScience* **2020**, *23*, 101796. https://doi.org/10.1016/j.isci.2020.101796
10. Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y. *Chem. Rev.* **2021**, *122*, 1485-1542. https://doi.org/10.1021/acs.chemrev.1c00383
11. Gilbert, B. C.; Parsons, A. F. *J. Chem. Soc. Perkin Trans. 2* **2002**, 367-387. https://doi.org/10.1039/b102044g
12. Epping, R. F. J.; Hoeksma, M. M.; Bobylev, E. O.; Mathew, S.; de Bruin, B. *Nat. Chem.* **2022**, *14*, 550-557. https://doi.org/10.1038/s41557-022-00905-4

13. Wang, X.; Zhang, X. P. in *Transition Metal-Catalyzed Carbene Transformations* (Eds.: J. Wang, C.-M. Che, M. P. Doyle), Wiley-VCH, Weinheim, Germany, **2022**, pp. 25-66.
https://doi.org/10.1002/9783527829170
14. Gansauer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A. 2nd, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 4739-4742.
https://doi.org/10.1002/anie.201200431
15. Gansauer, A.; Hildebrandt, S.; Michelmann, A.; Dahmen, T.; von Laufenberg, D.; Kube, C.; Fianu, G. D.; Flowers, R. A. 2nd, *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 7003-7006.
https://doi.org/10.1002/anie.201501955
16. Gansauer, A.; von Laufenberg, D.; Kube, C.; Dahmen, T.; Michelmann, A.; Behlendorf, M.; Sure, R.; Seddiqzai, M.; Grimme, S.; Sadasivam, D. V.; Fianu, G. D.; Flowers, R. A. 2nd, *Chemistry* **2015**, *21*, 280-289.
https://doi.org/10.1002/chem.201404404
17. Hildebrandt, S.; Gansauer, A. *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 9719-9722.
https://doi.org/10.1002/anie.201603985
18. Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 12141-12144.
https://doi.org/10.1021/jacs.7b06723
19. Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2018**, *140*, 3514-3517.
https://doi.org/10.1021/jacs.7b13710
20. Mühlhaus, F.; Weißbarth, H.; Dahmen, T.; Schnakenburg, G.; Gansäuer, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 14208-14212.
https://doi.org/10.1002/anie.201908860
21. Huang, H.-M.; McDouall, J. J. W.; Procter, D. J. *Nat. Catal.* **2019**, *2*, 211-218.
https://doi.org/10.1038/s41929-018-0219-x
22. Huang, H.-M.; He, Q.; Procter, D. J. *Synlett* **2020**, *31*, 45-50.
https://doi.org/10.1055/s-0039-1690196
23. Agasti, S.; Beattie, N. A.; McDouall, J. J. W.; Procter, D. J. *J. Am. Chem. Soc.* **2021**, *143*, 3655-3661.
https://doi.org/10.1021/jacs.1c01356
24. Ramler, J.; Krummenacher, I.; Lichtenberg, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 12924-12929.
https://doi.org/10.1002/anie.201904365
25. Ye, K.-Y.; McCallum, T.; Lin, S. *J. Am. Chem. Soc.* **2019**, *141*, 9548-9554.
https://doi.org/10.1021/jacs.9b04993
26. Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 12141-12144.
https://doi.org/10.1021/jacs.7b06723
27. Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2018**, *140*, 3514-3517.
https://doi.org/10.1021/jacs.7b13710
28. Wood, D. P.; Guan, W.; Lin, S. *Synthesis* **2021**, *53*, 4213-4220.
https://doi.org/10.1055/s-0037-1610779
29. Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796-12799.
https://doi.org/10.1021/ja1056246
30. Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; Lopez de Mesa, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292-15295.
https://doi.org/10.1021/ja2062506
31. Cui, X.; Xu, X.; Jin, L.-M.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2015**, *6*, 1219-1224.
https://doi.org/10.1039/C4SC02610A
32. Jiang, H.; Lang, K.; Lu, H.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2017**, *139*, 9164-9167.
https://doi.org/10.1021/jacs.7b05778
33. Li, C.; Lang, K.; Lu, H.; Hu, Y.; Cui, X.; Wojtas, L.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 16837-16841.
https://doi.org/10.1002/anie.201808923
34. Wang, Y.; Wen, X.; Cui, X.; Zhang, X. P. *J. Am. Chem. Soc.* **2018**, *140*, 4792-4796.
https://doi.org/10.1021/jacs.8b01662

35. Wen, X.; Wang, Y.; Zhang, X. P. *Chem. Sci.* **2018**, *9*, 5082-5086.
https://doi.org/10.1039/C8SC01476K
36. Hu, Y.; Lang, K.; Li, C.; Gill, J. B.; Kim, I.; Lu, H.; Fields, K. B.; Marshall, M.; Cheng, Q.; Cui, X.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2019**, *141*, 18160-18169.
https://doi.org/10.1021/jacs.9b08894
37. Lang, K.; Li, C.; Kim, I.; Zhang, X. P. *J. Am. Chem. Soc.* **2020**, *142*, 20902-20911.
https://doi.org/10.1021/jacs.0c11103
38. Zhang, C.; Wang, D.-S.; Lee, W.-C. C.; McKillop, A. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2021**, *143*, 11130-11140.
https://doi.org/10.1021/jacs.1c04719
39. Xu, P.; Xie, J.; Wang, D.-S.; Zhang, X. P. *Nat. Chem.* **2023**, 1-10.

40. Jahn, U. in *Radicals in Synthesis III* (Eds.: M. Heinrich, A. Gansäuer), Springer, Berlin, Heidelberg, **2012**, pp. 121-189.

41. Jahn, U. in *Radicals in Synthesis III* (Eds.: M. Heinrich, A. Gansäuer), Springer, Berlin, Heidelberg, **2012**, pp. 191-322.

42. Jahn, U. in *Radicals in Synthesis III* (Eds.: M. Heinrich, A. Gansäuer), Springer, Berlin, Heidelberg, **2012**, pp. 323-451.

43. Wang, K.; Kong, W. *Chinese J. Chem* **2018**, *36*, 247-256.
https://doi.org/10.1002/cjoc.201700745
44. Huang, H.-M.; Bellotti, P.; Glorius, F. *Chem. Soc. Rev.* **2020**, *49*, 6186-6197.
https://doi.org/10.1039/D0CS00262C
45. Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M. *Chem. Rev.* **2022**, *122*, 5842-5976.
https://doi.org/10.1021/acs.chemrev.1c00582
46. Xiao, W.; Wu, J. *ChemCatChem* **2023**, *15*.
https://doi.org/10.1002/cctc.202300541
47. Sumino, S.; Ryu, I. *Synlett* **2023**.

48. Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.; Xiao, W.-J.; Chen, J.-R. *Acc. Chem. Res.* **2020**, *53*, 1066-1083.
https://doi.org/10.1021/acs.accounts.0c00090
49. Ueng, S. H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacote, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256-11262.
https://doi.org/10.1021/ja904103x
50. Taniguchi, T. *Eur. J. Org. Chem.* **2019**, *2019*, 6308-6319.
https://doi.org/10.1002/ejoc.201901010
51. Taniguchi, T. *Chem. Soc. Rev.* **2021**, *50*, 8995-9021.
https://doi.org/10.1039/D1CS00385B
52. Peng, T. Y.; Zhang, F. L.; Wang, Y. F. *Acc. Chem. Res.* **2023**, *56*, 169-186.
https://doi.org/10.1021/acs.accounts.2c00752
53. Walton, J. C.; Brahmi, M. M.; Fensterbank, L.; Lacote, E.; Malacria, M.; Chu, Q.; Ueng, S. H.; Solovyev, A.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 2350-2358.
https://doi.org/10.1021/ja909502q
54. Qi, J.; Zhang, F. L.; Huang, Y. S.; Xu, A. Q.; Ren, S. C.; Yi, Z. Y.; Wang, Y. F. *Org. Lett.* **2018**, *20*, 2360-2364.
https://doi.org/10.1021/acs.orglett.8b00694
55. Xu, A.-Q.; Zhang, F.-L.; Ye, T.; Yu, Z.-X.; Wang, Y.-F. *CCS Chem.* **2019**, *1*, 504-512.
https://doi.org/10.31635/ccschem.019.20190025

56. Ding, Z.; Liu, Z.; Wang, Z.; Yu, T.; Xu, M.; Wen, J.; Yang, K.; Zhang, H.; Xu, L.; Li, P. *J. Am. Chem. Soc.* **2022**, *144*, 8870-8882.
https://doi.org/10.1021/jacs.2c03673
57. Xu, M.; Wang, Z.; Sun, Z.; Ouyang, Y.; Ding, Z.; Yu, T.; Xu, L.; Li, P. *Angew. Chem. Int. Ed. Engl.* **2022**, *61*, e202214507.
https://doi.org/10.1002/anie.202214507
58. Yu, T.; Yang, J.; Wang, Z.; Ding, Z.; Xu, M.; Wen, J.; Xu, L.; Li, P. *J. Am. Chem. Soc.* **2023**, *145*, 4304–4310
https://doi.org/10.1021/jacs.2c13740
59. Liu, Y.; Lin, S.; Li, Y.; Xue, J.-H.; Li, Q.; Wang, H. *ACS Catal.* **2023**, *13*, 5096-5103.
https://doi.org/10.1021/acscatal.3c00305
60. Zhao, Q.-Q.; Chen, J.; Zhou, X.-S.; Yu, X.-Y.; Chen, J.-R.; Xiao, W.-J. *Chem. Eur. J.* **2019**, *25*, 8024-8029.
https://doi.org/10.1002/chem.201901665
61. Zhao, Q.-Q.; Zhou, X.-S.; Xu, S.-H.; Wu, Y.-L.; Xiao, W.-J.; Chen, J.-R. *Org. Lett.* **2020**, *22*, 2470-2475.
https://doi.org/10.1021/acs.orglett.0c00712
62. Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300-3302.
https://doi.org/10.1021/ja00218a050
63. Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135-5138.
https://doi.org/10.1016/S0040-4039(00)80701-7
64. Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100-110.
https://doi.org/10.1021/jo00027a020
65. Feldman, K. S.; Ruckle, R. E.; Romanelli, A. L. *Tetrahedron Lett.* **1989**, *30*, 5845-5848.
https://doi.org/10.1016/S0040-4039(01)93486-0
66. Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878-4886.
https://doi.org/10.1021/ja00195a047
67. Feldman, K. S.; Fisher, T. E. *Tetrahedron* **1989**, *45*, 2969-2977.
https://doi.org/10.1016/S0040-4020(01)80124-1
68. Feldman, K. S.; Berven, H. M.; Weinreb, P. H. *J. Am. Chem. Soc.* **1993**, *115*, 11364-11369.
https://doi.org/10.1021/ja00077a040
69. Curran, D. P.; Porter, N. A.; Giese, B. in *Stereochemistry of Radical Reactions* (Eds.: D. P. Curran, N. A. Porter, B. Giese), **1995**, pp. 1-22.
https://doi.org/10.1002/9783527615230
70. Nagib, D. A. *Chem. Rev.* **2022**, *122*, 15989-15992.
https://doi.org/10.1021/acs.chemrev.2c00622
71. Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25-35.
https://doi.org/10.1039/a804291h
72. Hashimoto, T.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2014**, *6*, 702-705.
https://doi.org/10.1038/nchem.1998
73. Hashimoto, T.; Takino, K.; Hato, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 8081-8085.
https://doi.org/10.1002/anie.201602723
74. Deng, Y.; Wei, X.-J.; Wang, H.; Sun, Y.; Noël, T.; Wang, X. *Angew. Chem. Int. Ed.* **2017**, *56*, 832-836.
https://doi.org/10.1002/anie.201607948
75. Ryss, J. M.; Turek, A. K.; Miller, S. J. *Org. Lett.* **2018**, *20*, 1621-1625.
https://doi.org/10.1021/acs.orglett.8b00364
76. Jie, L.-H.; Guo, B.; Song, J.; Xu, H.-C. *J. Am. Chem. Soc.* **2022**, *144*, 2343-2350.
https://doi.org/10.1021/jacs.1c12762
77. Archer, G.; Cavalere, P.; Medebielle, M.; Merad, J. *Angew. Chem. Int. Ed. Engl.* **2022**, *61*, e202205596.
https://doi.org/10.1002/anie.202205596
78. Sumino, S.; Ryu, I. *Synlett* **2023**, *34*, 1001-1011.

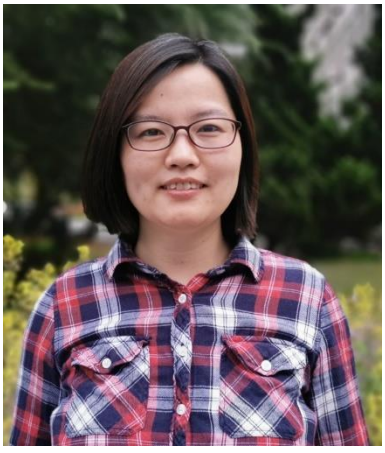
79. Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 4006-4009.
https://doi.org/10.1021/ol1016096
80. Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864-3867.

https://doi.org/10.1021/ol201395p
81. Kippo, T.; Hamaoka, K.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 632-635.
https://doi.org/10.1021/ja311821h
82. Kippo, T.; Hamaoka, K.; Ueda, M.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2017**, *19*, 5198-5200.
https://doi.org/10.1021/acs.orglett.7b02471
83. Kippo, T.; Ryu, I. *Chem. Commun.* **2014**, *50*, 5993-5996.
https://doi.org/10.1039/C4CC01597E
84. Fukuyama, T.; Kippo, T.; Hamaoka, K.; Ryu, I. *Sci. China Chem.* **2019**, *62*, 1525-1528.
https://doi.org/10.1007/s11426-019-9595-0
85. Chen, D.-F.; Chrisman, C. H.; Miyake, G. M. *ACS Catal.* **2020**, *10*, 2609-2614.
https://doi.org/10.1021/acscatal.0c00281
86. Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190-7202.
https://doi.org/10.1039/C8CS00054A
87. Lu, J.; Pattengale, B.; Liu, Q.; Yang, S.; Shi, W.; Li, S.; Huang, J.; Zhang, J. *J. Am. Chem. Soc.* **2018**, *140*, 13719-13725.
https://doi.org/10.1021/jacs.8b07271
88. Boyer, I. J. *Toxicology* **1989**, *55*, 253-298.
https://doi.org/10.1016/0300-483X(89)90018-8
89. Kim, S.; Lee, S. *Tetrahedron Lett.* **1991**, *32*, 6575-6578.
https://doi.org/10.1016/0040-4039(91)80225-U
90. Lee, E.; Hur, C. U.; Rhee, Y. H.; Park, Y. C.; Kim, S. Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1466-1468.
https://doi.org/10.1039/C39930001466
91. Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581-5582.
https://doi.org/10.1021/jo00073a005
92. Journet, M.; Rouillard, A.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **1997**, *62*, 8630-8631.
https://doi.org/10.1021/jo971787n
93. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838-5839.
https://doi.org/10.1021/ja980731n
94. Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262-4267.
https://doi.org/10.1039/B309944J
95. Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632-5633.
https://doi.org/10.1021/ja034896u
96. Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2004**, 2482-2483.
https://doi.org/10.1039/B408746A
97. Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem.* **2005**, *117*, 1099-1102.
https://doi.org/10.1002/ange.200461954
98. Matsubara, H.; Kawamoto, T.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2018**, *51*, 2023-2035.
https://doi.org/10.1021/acs.accounts.8b00278
99. Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 10376-10378.
https://doi.org/10.1021/ja2042854
100. Zhang, H.; Jeon, K. O.; Hay, E. B.; Geib, S. J.; Curran, D. P.; LaPorte, M. G. *Org. Lett.* **2014**, *16*, 94-97.
https://doi.org/10.1021/ol403078e
101. Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 1006-1008.
https://doi.org/10.1021/ja312654q
102. Fukuyama, T.; Okada, T.; Nakashima, N.; Ryu, I. *Helv. Chim. Acta* **2019**, *102*, e1900186.
https://doi.org/10.1002/hlca.201900186
103. Shirakawa, S.; Usui, A.; Kan, S. B. J.; Maruoka, K. *Asian J. Org. Chem.* **2013**, *2*, 916-919.
https://doi.org/10.1002/ajoc.201300138
104. Grady, G. L.; Kuivila, H. G. *J. Org. Chem.* **1969**, *34*, 2014-2016.
https://doi.org/10.1021/jo01258a124

105. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554-2555.
https://doi.org/10.1021/jo00905a039
106. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **2002**, *108*, 303-304.
https://doi.org/10.1021/ja00262a024

Authors' Biographies

Yee Lin Phang received her Bachelor of Pharmacy (Hons) degree from International Medical University, Malaysia in 2018. In 2022, she obtained her Master of Science in Chinese Materia Medica at Shanghai University of Traditional Chinese Medicine, Shanghai, P. R. of China under the supervision of Prof. Hongxi Xu and Prof. Changwu Zheng. Currently, she is a PhD candidate major in Organic Chemistry under the supervision of Prof. Yi-Feng Wang and Assoc. Prof. Feng-Lian Zhang at the University of Science and Technology of China, Hefei, P. R. of China. Her research interest lies on the reactivity and application of Lewis-base boryl radicals.



Feng-Lian Zhang, is an associate professor of Organic Chemistry at the Department of Chemistry, University of Science and Technology of China. She received her B.Sc. from Nankai University (P. R. of China) in 2011 and obtained her Ph.D. from Nanyang Technological University Singapore under the supervision of Prof. Shunsuke Chiba in 2016. After that she worked as a postdoctoral researcher at USTC (2016–2019), where she is now an associate professor. Her current focus is organoboron chemistry, including methodology development and mechanistic investigation through computational studies.

Yi-Feng Wang, is a professor of Organic Chemistry at the Department of Chemistry, University of Science and Technology of China. He received his Ph.D. in 2011 at the Nanyang Technological University, Singapore under the supervision of Profs. Koichi Narasaka and Shunsuke Chiba. He continued to work with Prof. Chiba as a research fellow (2011–2015) and was appointed as a Lee Kuan Yew Postdoctoral Fellow during 2012–2014. In 2015, he started his independent research work at USTC as a full professor. His research interests include radical chemistry, organoboron chemistry, and the synthesis of bioactive molecules.

