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# Catalytic Radical Domino Reactions in Organic Synthesis

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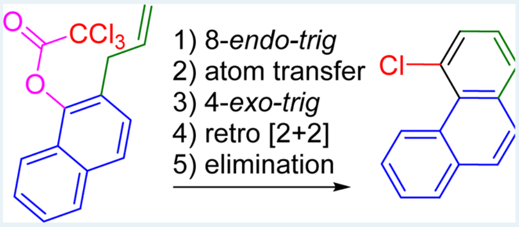
**ABSTRACT:** Catalytic radical-based domino reactions represent important advances in synthetic organic chemistry. Their development benefits synthesis by providing atom- and step-economical methods to complex molecules. Intricate combinations of radical, cationic, anionic, oxidative/reductive, and transition metal mechanistic steps result in cyclizations, additions, fragmentations, ring-expansions, and rearrangements. This Perspective summarizes recent developments in the field of catalytic domino processes.



**KEYWORDS:** *radical, domino, cascade, tandem, transition metal, photoredox*

## INTRODUCTION

Synthetic organic chemists continuously pursue new reactions and chemoselective transformations under mild conditions. To this end, new methods for the facile and efficient installation of complexity in small molecules are in constant development. The ideal transformation is an efficient single reaction with one set of reagents that yields a desired product. Great efforts have been made to develop efficient, single-step transformations, which result in the formation and fragmentation of multiple bonds in a stepwise fashion. These reactions have been termed domino, cascade, or tandem processes.[1]

A domino reaction is a transformation that installs two or more bonds under identical conditions. The advantages of methods that construct complex molecules in a single reaction are self-evident, providing both atom[2] and step economy.[3] Tietze has described at length the factors that define a domino reaction.[1f] First, all reactants and reagents must be added at the beginning of the process without further addition. Next, two or more bonds must be formed or, in some cases, broken. Each bond-forming step must happen sequentially, resulting in a "time-resolved succession of steps" that occur linearly from the point of view of a reaction mechanism.[1b] The steps within the mechanism can be classified as cationic, anionic, pericyclic, photochemical, transition-metal mediated, oxidative or reductive, enzymatic, or radical.

Historically, organic radicals were deemed uncontrollable and unselective, except under tightly managed reaction conditions. However, great mechanistic efforts have been applied to gain insight into the reactivity of the free radical to understand how best to apply this reactive intermediate. As a result, radical-mediated processes provide nonpolar access to the formation of carbon−carbon and carbon−heteroatom bonds.[4] Traditional radical domino reactions are thought of as a series of rapid intramolecular cyclizations of pendant olefins and alkynes. However, radical-based domino processes have emerged that undergo additions, fragmentations, ring-expansions, and rearrangements under a variety of conditions.

Many radical transformations that proceed through atom transfer are initiated by the addition of stoichiometric stannanes, silanes, or peroxides. In addition, these reactions typically require the use, albeit a substoichiometric amount, of an unstable initiator.[5] Redox-mediated transformations usually require 1 or more equivalents of metal oxidant or reductant.[6] Both of these methods are routinely utilized in organic synthesis; however, radical transformations that utilize a catalytic electron transfer agent alleviate the need for stoichiometric metals or harsh atom abstractors. Significant efforts have been focused toward the development of catalytic radical reactions using redox-active transition metals[7] and photoactive catalysts.[8]

This Perspective outlines recent efforts to apply catalytic electron transfer agents toward the development of radical domino reactions. The selection of transformations within highlights the diverse number of methods available to synthetic chemists. Many examples of catalytic radical-mediated processes exist, but we seek to display those that form/break two or more bonds prior to the generation of the final product. These examples were chosen because a radical participates in at least the first bond-forming step and one or more subsequent steps result from this initial transformation.

## TRANSITION METAL-MEDIATED DOMINO REACTIONS

The seminal works of Kharash,[9] Kochi,[10] and Minisci[11] clearly demonstrated that carbon radicals could be formed in the presence of a transition metal catalyst. Since their efforts, a great number of transformations have been reported in the literature.[7,12] These methods employ copper, manganese, iron, cobalt, titanium, and ruthenium catalysts to perform atom transfer as well as single electron reductions and oxidations. In recent years, radical domino reactions utilizing transition metal complexes have garnered considerable attention. These systems combine traditional radical transformations with cationic, anionic, oxidative, reductive, or pericyclic steps to provide access to fragmentations, rearrangements, and complex ring systems.

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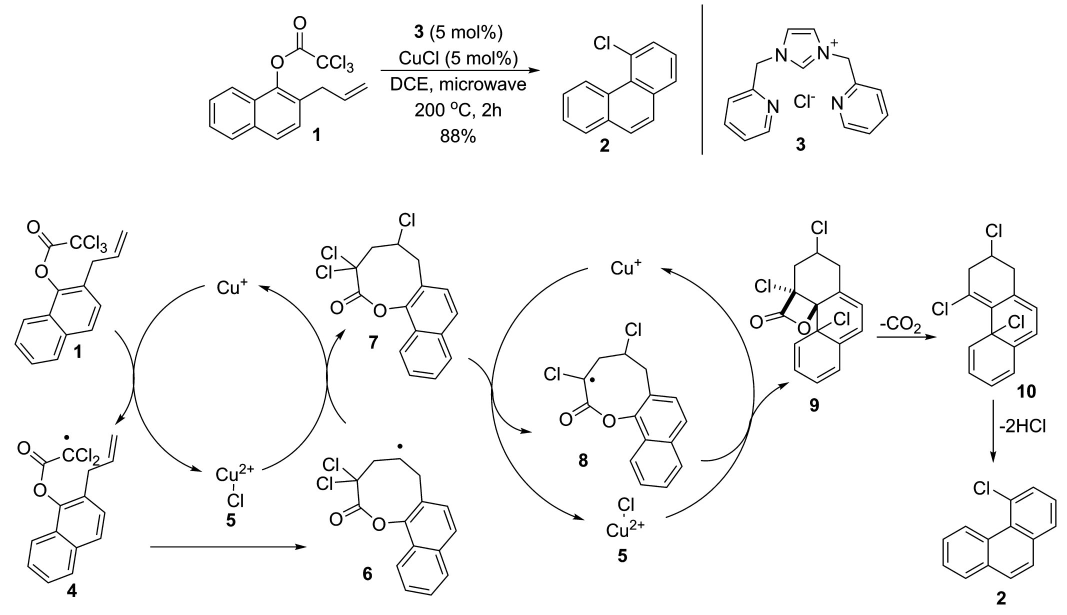

**Figure 1.** Cu-mediated domino benzannulation of **1** and mechanism.

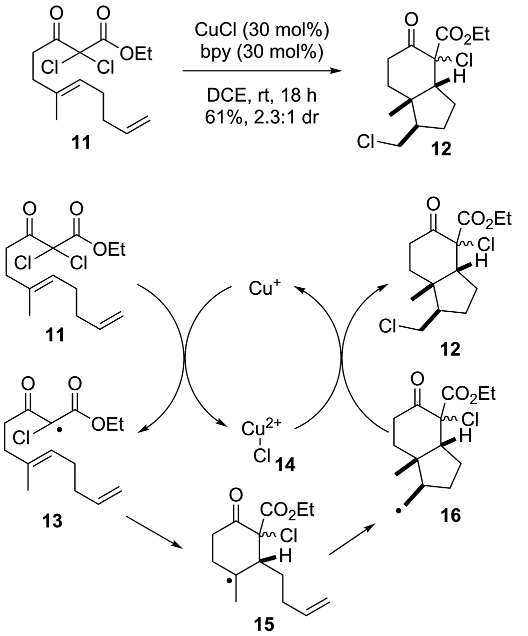

**Figure 2.** Cu-mediated ATRC of **11** and mechanism.

Cu-mediated atom transfer radical cyclizations (ATRC) have been developed extensively over the years.[7] In 2007, Quayle and co-workers continued their development of Cu-mediated ATRC reactions with trichloroacetates.[13] They observed that microwave irradiation at 200 °C supplemented the ATRC reaction of **1**, resulting in a domino benzannulation to form chloronaphthalenes (Figure 1). The authors propose a radical/radical/pericyclic/anionic domino process. Beginning with a Cu(I)-mediated chlorine atom transfer from **1**, dichlororadical **4** and Cu(II) complex **5** are formed at the onset. Radical **4** then undergoes a preferred 8-endo-trig cyclization[14] to yield radical **6**, which is then chlorinated by **5** to form lactone **7**. Quayle et al. detected no annulation when **7**, easily accessible via conventional heating, was irradiated for 2 h in the absence of other reagents. Compound **2** was observed only in the presence of CuCl and **3**. As a result, they proposed that **7** reacts with a second Cu complex to yield radical **8** and chloro complex **5**. This radical then undergoes a reversible 4-exo-trig cyclization, which is facilitated by chlorine atom transfer from **5**, to form spirolactone **9**. Retro [2 + 2] cyclization, driven by elimination of $CO_2$, converts **9** to **10**, which, upon the elimination of 2 equiv of HCl, yields 4-chlorophenanthrene (**2**).

In 2006, Yang et al. found that ATRC reactions of $\alpha,\alpha'$-dichloro-$\beta$-ketoesters could be facilitated by 30 mol % CuCl in the presence of chiral, bidentate amine ligands (Figure 2).[15] However, when the system was extended beyond the formation of a single C–C bond, use of 2,2′-bipyridine (bpy) provided optimal reactivity. The domino bicyclization occurs through a radical/radical process initiated by removal of a chlorine atom from **11** by Cu(I). Radical **13** then undergoes a 6-endo-trig cyclization to form **15**, which is then trapped by a rapid 5-exo-trig cyclization to yield primary radical **16**. The primary radical then reacts with Cu(II) complex **14** to form **12** in a 61% yield as a 2.3:1 ratio of diastereomers and turnover the catalyst.

Pérez, Belderraín, and Muñoz-Molina developed a diastereoselective Cu-catalyzed ATRC domino reaction (Figure 3).[16] In addition, they found that when Mg was added as a reducing agent, they observed improved yields. This radical/radical process is initiated by abstraction of a chlorine atom from $CCl_4$. The resulting trichloromethyl radical then adds to one of the allyl groups of **17** to form radical **19**. This product radical then undergoes a rapid 5-exo-trig cyclization, followed by chlorine atom transfer to provide **18** in a 99% yield and turn over the catalyst. Pintauer and co-workers found that the turnover efficiency of this Cu-mediated reaction could be greatly enhanced to where only 0.01 mol % catalyst is required with tris(2-pyridylmethyl)amine as a ligand and substoichiometric amounts of either a diazo initiator[17] or ascorbic acid[18] as reducing agents.

In their seminal work, Mori and Ban first demonstrated the ability of low-valent Pd to mediate ATRC processes of $\alpha$-haloamides.[19] In recent years, chemists have combined catalytic single-electron reductions with carbonylations. Ryu, Komatsu, and co-workers found that when **21** was exposed to light under 40 atm of CO and a catalytic amount of $Pd(PPh_3)_4$, $\gamma$-ketoester **22** was formed (Figure 4).[20] They propose a

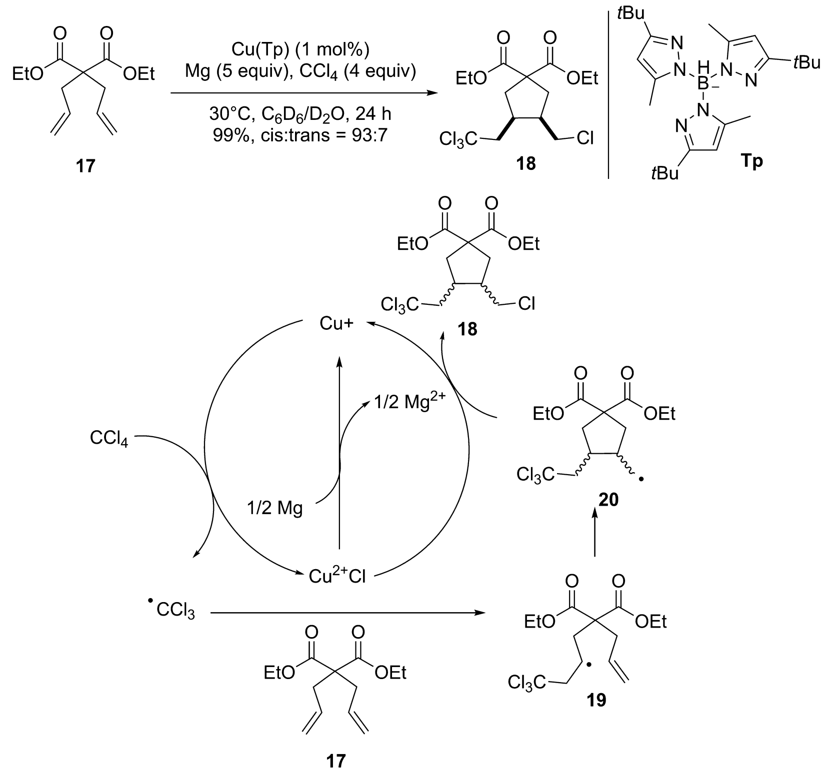

**Figure 3.** Cu-mediated radical addition/cyclization of **17** and mechanism.

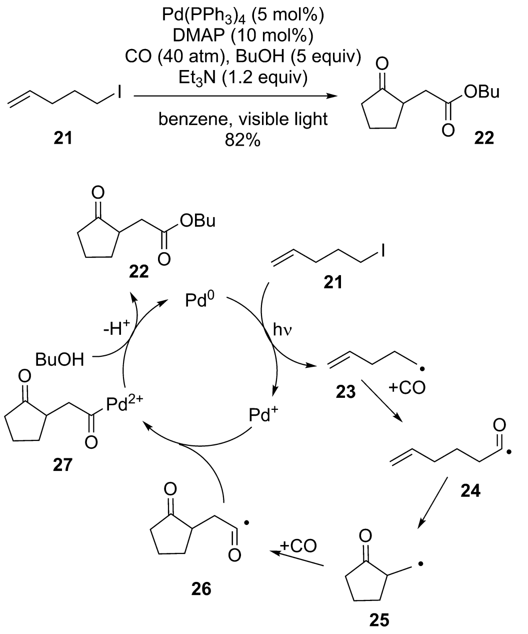

**Figure 4.** Pd-mediated radical cyclization and carbonylation of **21** and mechanism.

radical/radical/radical/reduction process. Under irradiation, an iodine atom is removed from **21** by Pd(0) to form primary radical **23**. This radical adds to CO, forming **24**, and then undergoes a rapid 5-exo-trig cyclization, yielding radical **25**. The resulting $\beta$-keto radical then attacks another equivalent of CO to form **26**, which is reduced by Pd(I) to form organopalladium(II) complex **27**. Addition of butanol and reductive elimination yields **22** and turns over the catalyst. They later found that when $H_2O$ and a boronic acid (**28**) were substituted

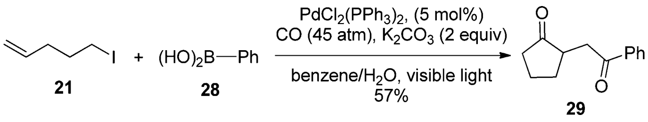

**Figure 5.** Pd-mediated radical cyclization, carbonylation, and arylation of **21**.

for the alcohol, transmetalation and reductive elimination resulted in the formation of diketone **29** (Figure 5).[21]

Continuing their work on radical carbonylations, Ryu and co-workers designed a method for the formation of lactones (**32**) from their conditions (Figure 6).[22] When irradiated with light, this radical/radical/reduction process begins with the abstraction of an iodine atom from **30** to form radical **33**. This primary radical then adds to olefin **31** to form **34**, which can add to an equivalent of CO to form keto-radical **35**. Reduction of this intermediate results in the formation of organopalladium(II) complex **36**. Addition of the pendant hydroxyl group and reductive elimination regenerates the catalyst and forms lactone **32** in a 77% yield.

Similarly, Alexanian and Bloom found that an analogous transformation could be mediated by low-valent palladium in the absence of light.[23] Alkyl iodide **37** participates in a carbonylative Heck reaction at elevated temperatures in toluene to give spirocyclopentanone **38** (Figure 7). This radical/radical/oxidative process begins with removal of an iodine atom from **37** to form primary radical **39**. Similar to the mechanism in Figure 4, radical addition to CO provides access to a rapid 5-exo-trig cyclization, yielding tertiary radical **41**. Single electron oxidation by Pd(I) yields tertiary cation **42**, which can undergo facile deprotonation at the newly formed $\alpha$-position of **38**.

Oshima and co-workers developed a Co-mediated process that is initiated by atom transfer.[24] They observed that when **43** and **44** were combined in the presence of trimethylsilylmethylmagnesium chloride and a catalytic amount of $CoCl_2$

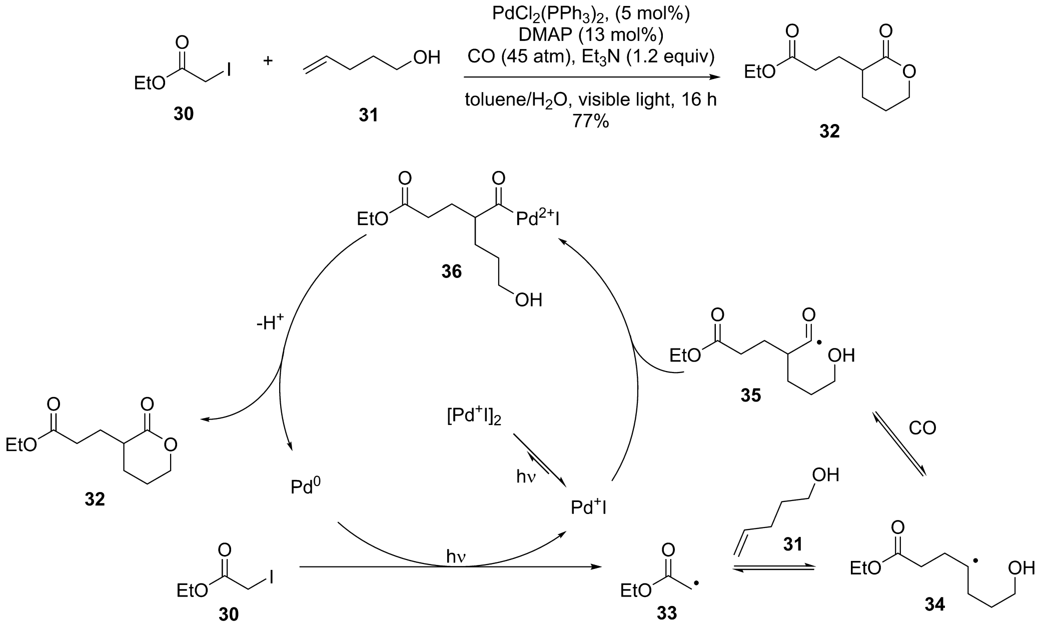

**Figure 6.** Pd-mediated radical addition and carbonylation of **30** and mechanism.

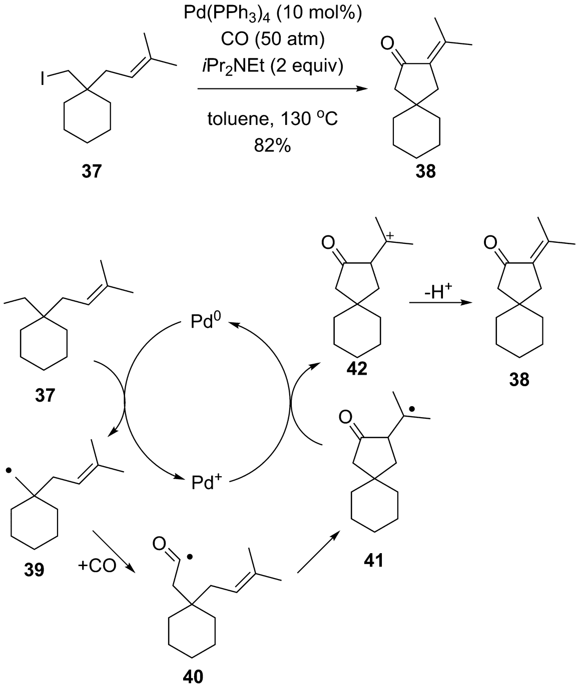

**Figure 7.** Pd-catalyzed radical cyclization and carbonylation of **37** and mechanism.

ligated by 1,6-bis(diphenylphosphino)hexane (dpph), silane **45** was produced in excellent yield (Figure 8). This transformation provides insight into the mechanism. Furan **48** was produced via a radical/radical/reduction/Tsuji–Trost allylation process. A bromine atom is removed from **43** by Co(0) to form primary radical **46** and Co(I) complex **47**. This primary radical undergoes rapid 5-exo-trig cyclization to form **48**, which then adds to butadiene **44**. Allylic radical **49** is then reduced by **47** to form complex **50**. The metal center of **50** is then alkylated by the Grignard reagent to form **51**, which undergoes reductive elimination to form furan **45** and regenerate the catalyst.

Fu and Cardenas independently developed Ni-catalyzed cross-coupling methods initiated by atom transfer. Initially, Fu et al. demonstrated that both Ni-catalyzed Stille cross-couplings[25] and Suzuki cross-couplings[26] of secondary alkyl halides began via low-valent Ni-mediated radical formation (Figure 9). Later, Cardenas et al. demonstrated the same radical process for Ni-catalyzed Negishi cross-coupling of secondary alkyl halides.[27] These three methods proceed through similar radical/reduction/anionic domino sequences. Initially, a halogen atom is removed from alkyl halide **59** to form secondary radical **60** and Ni(I) complex **61**. The secondary radical undergoes rapid 5-exo-trig cyclization to form primary radical **62**, which is then reduced by **61** to form organonickel **63**. This complex undergoes transmetalation with agent **64** to form organonickel **65**. Upon reductive elimination, Ni(0) is regenerated, yielding **66**.

In addition to atom transfer reactions, radical-mediated domino reactions can be initiated with single electron reductions. In 2012, Barrero, Moral, and co-workers applied a radical/radical/oxidation domino process to the total synthesis of (+)-*seco*-C-oleanane (**68A**) (Figure 10).[28] Most notable about this synthesis is that performing this reaction with a substoichiometric amount of $Cp_2TiCl_2$ improved the efficiency of the desired 6-endo-trig/6-endo-trig bicyclization process over the use of stoichiometric Ti reductant. The authors propose that this process begins with single electron reduction and ring-opening of epoxide **67** to give tertiary radical **69**. This radical then undergoes two consecutive 6-endo-trig radical cyclizations to form radical **71**. Hydrogen atom abstraction of hydrogen atoms A or B (Figure 10) followed by TMS-protection, yields TMS-protected **TMS-68A** as well as TMS protected *β-seco*-amyrin (**TMS-68B**).

Similar to the reductive capabilities of Ti(III), Aubé et al. utilized the reducing power of Cu(I) to ring-open chiral oxaziridines to form nitrogen-centered radicals (Figure 11).[29] They observed that when oxaziridine **72** was refluxed in THF in the presence of $[Cu(PPh_3)Cl]_4$, pyrroline **73** was formed in 66% yield with >95% ee. This radical rearrangement potentially occurs through a radical/radical/oxidation/pericyclic domino process. At the onset, Cu(I) reduces oxaziridine **72**, which ring-opens to form nitrogen-centered radical **74**. Rapid 5-exo-trig

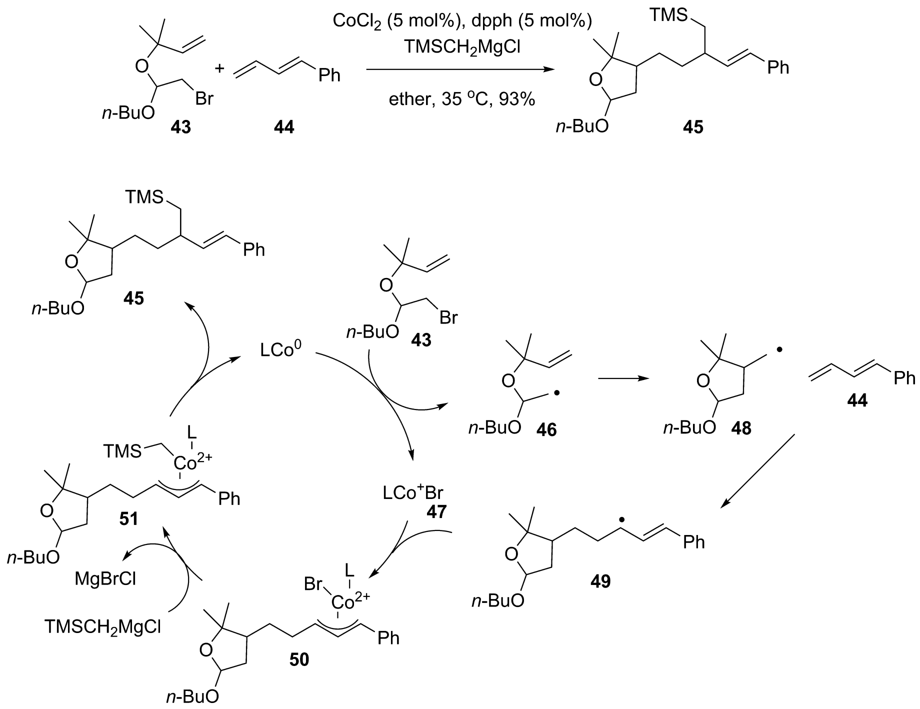

Figure 8. Co-catalyzed radical cyclization/Tsuji−Trost allylation of 43 and mechanism.

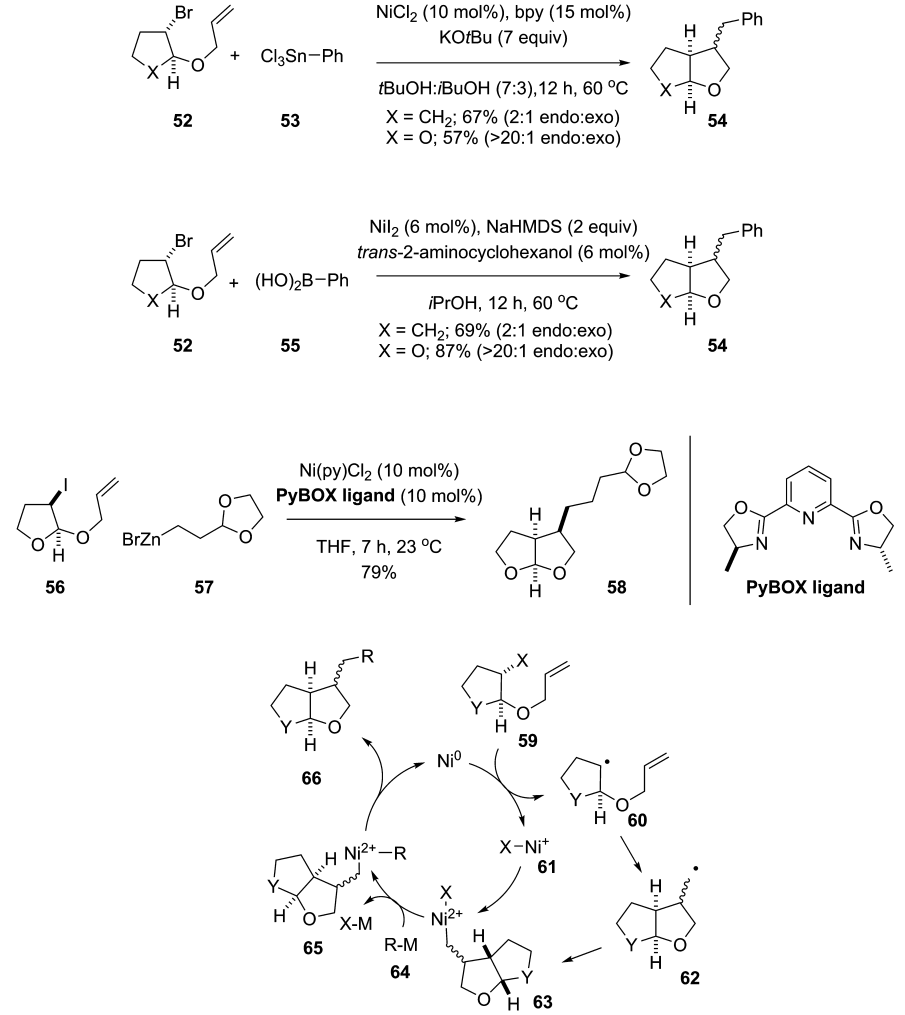

Figure 9. Ni-catalyzed radical cyclization−Stille coupling of 52, Ni-catalyzed radical cyclization−Suzuki coupling of 52, and Ni-catalyzed radical cyclization−Negishi coupling of 56 and their mechanism.

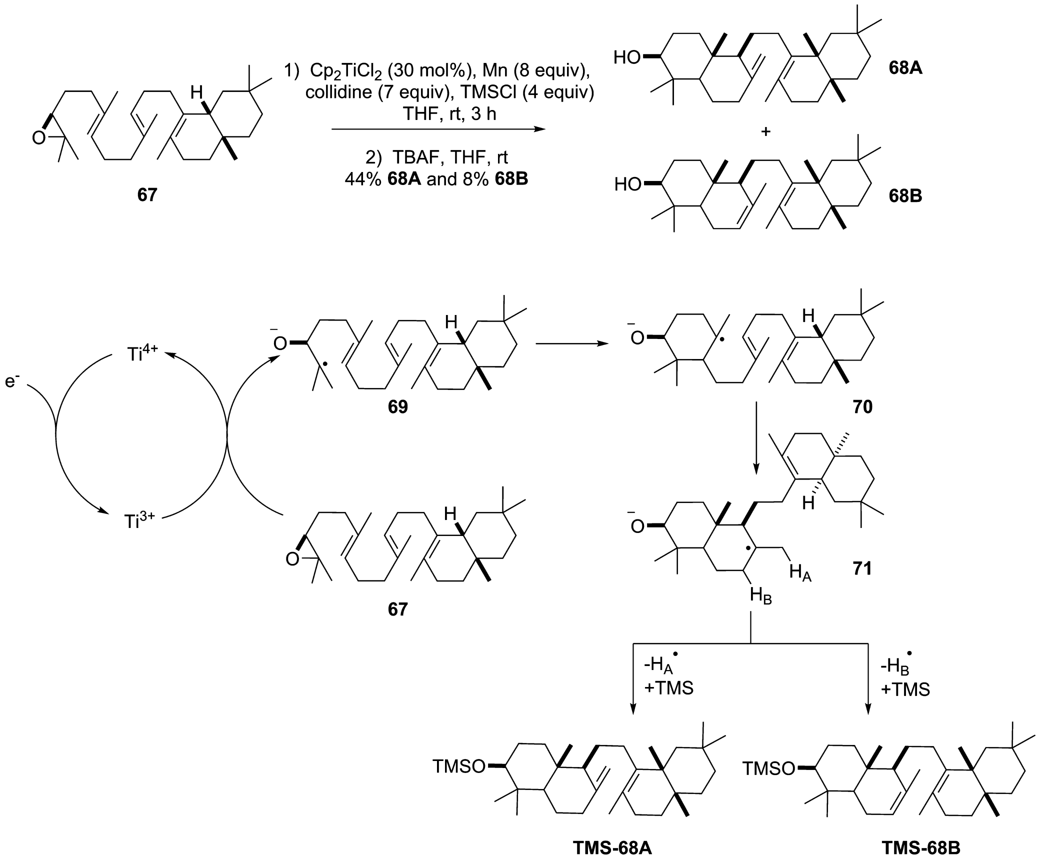

**Figure 10.** Ti-catalyzed reductive polyene cyclization of **67** and mechanism.

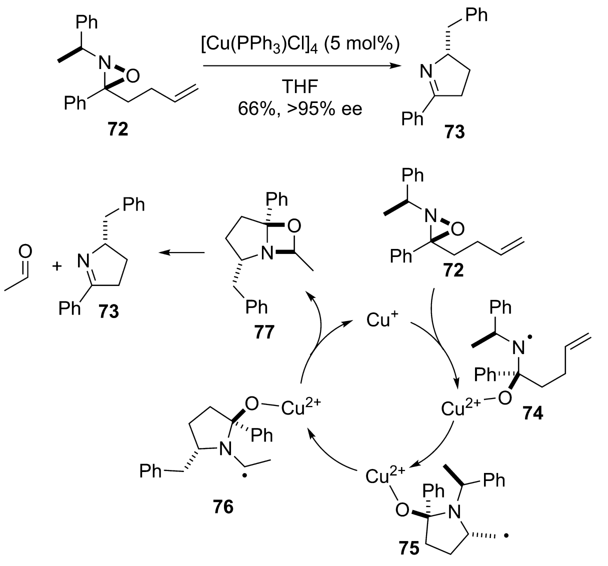

**Figure 11.** Cu-catalyzed redox neutral rearrangement of **72** and mechanism.

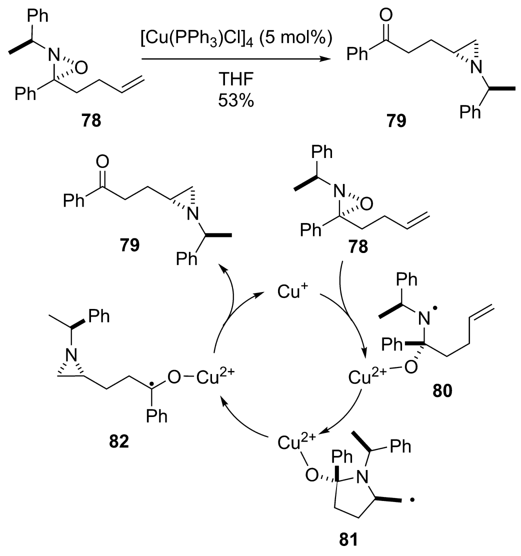

**Figure 12.** Cu-catalyzed redox neutral rearrangement of **78** and mechanism.

cyclization of **74** results in pyrrolidine radical **75**. The authors then propose that radical **76** is formed when **75** undergoes 1,4-aryl migration via ipso attack on the aryl ring. Finally, Cu(I) and acetaldehyde are eliminated to form pyrroline **73**. Although not proposed by the authors, this rearrangement/elimination may be initiated by single-electron oxidation of the alkoxide to form an oxygen-centered radical and regenerate the catalyst. Intramolecular radical coupling results in the formation of **77**, which can undergo a retro [2 + 2] cyclization to form pyrroline **73**.

Conversely, when the oxaziridine diastereomer **78** was exposed to the same conditions, a radical/radical domino process was observed that results in rearrangement to aziridine **79** (Figure 12), initiated by a Cu-mediated ring-opening of **78**. An analogous 5-exo-trig cyclization of **80** leads to pyrrolidine radical **81**; however, they propose that the transition state that would result in phenyl transfer is disfavored because of the steric constraints

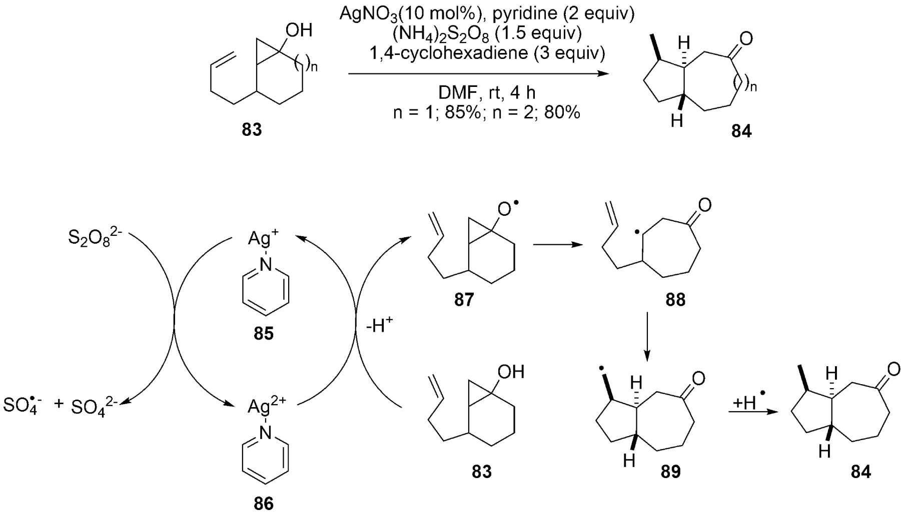

**Figure 13.** Ag-catalyzed oxidative fragmentation/cyclization of **83** and mechanism.

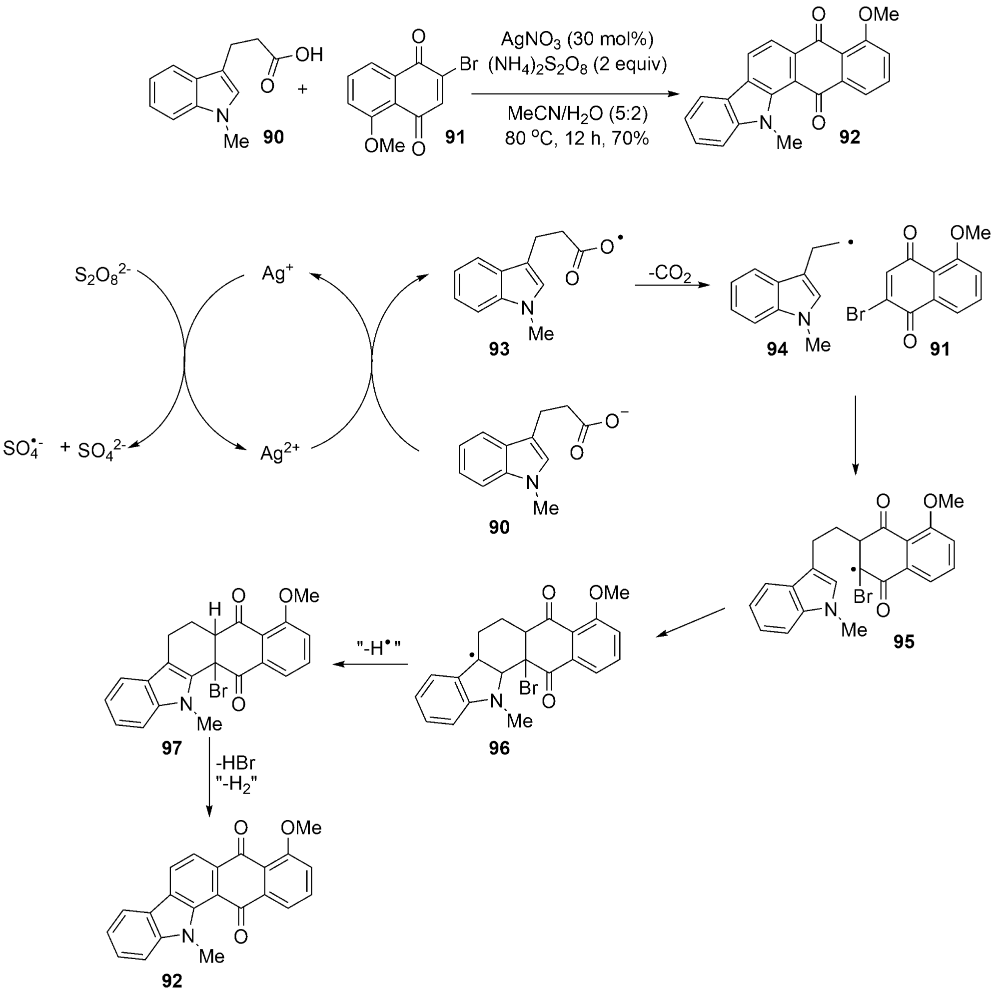

**Figure 14.** Ag-catalyzed Minisci/cyclization of **90** and **91** and mechanism.

of this diastereomer. As a result, intramolecular radical addition to the nitrogen simultaneously forms an aziridine moiety and ring-opens the pyrrolidine, resulting in benzylic radical **82**. Single-electron oxidation by Cu(II) regenerates the catalyst and yields **79**.

Ag(II) is a powerful oxidant that is easily generated by the combination of Ag(I) and persulfate, which has been utilized by chemists for decades.[30] A considerable wealth of mechanistic and kinetic information has been compiled over the years, and chemists use these data to develop new transformations. In 2006, Narasaka and co-workers applied this oxidative system to the single electron-mediated ring-opening of cyclopropanols (Figure 13).[31] Notably, this method provided diminished yields

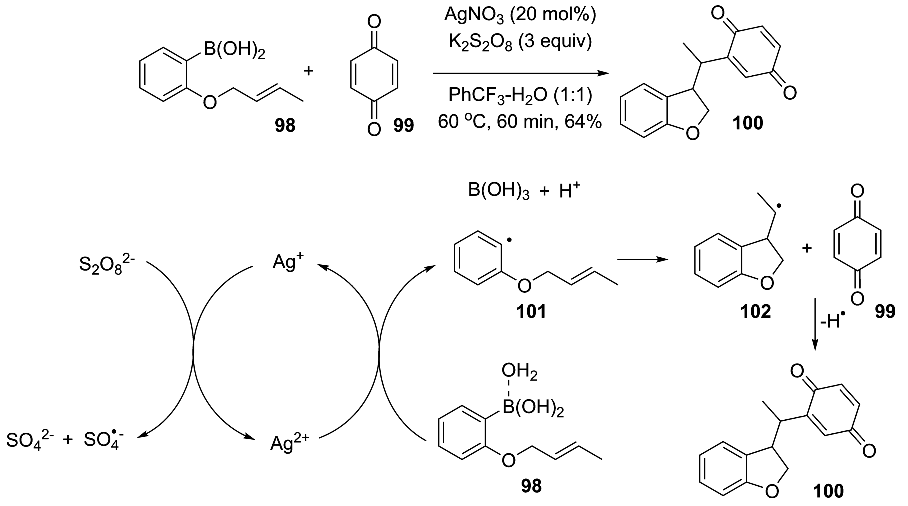

**Figure 15.** Ag-catalyzed oxidative cyclization of **98** and addition to **99** and mechanism.

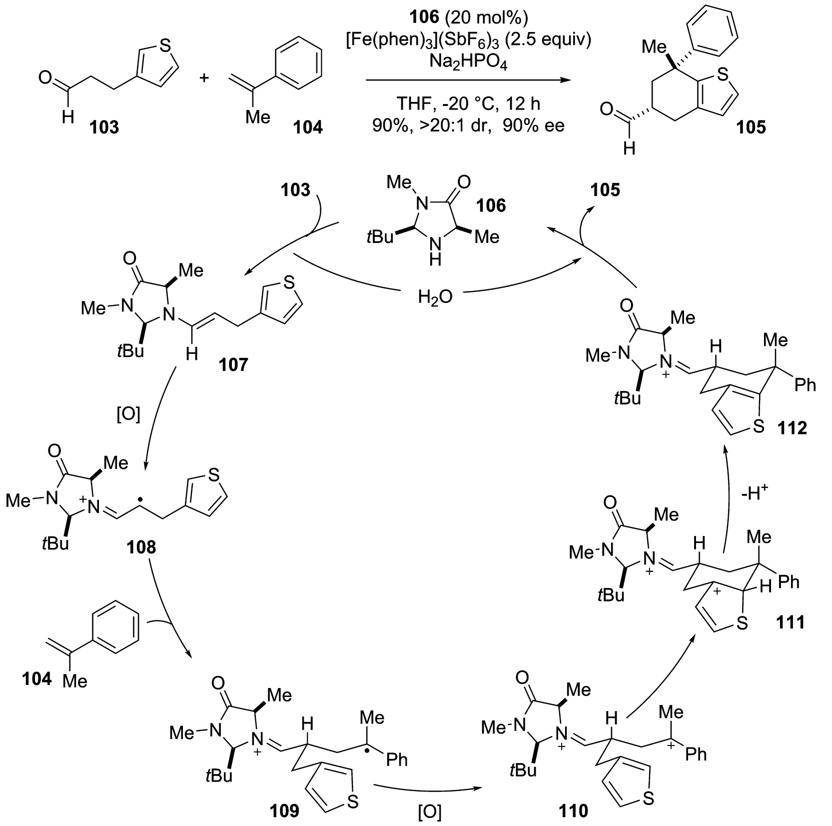

**Figure 16.** Fe(III)-mediated organo-SOMO cycloaddition of **103** and **104** with mechanism.

when performed in the absence of pyridine. The improvement is attributed to coordination of pyridine to Ag(I), activating the metal toward oxidation by persulfate.[32] Attachment of a pendant olefin to the cyclopropanol provided access to **84**. This reaction occurs via a radical/radical domino process. Ag complex **85** is oxidized by persulfate to Ag(II) complex **86**, which is capable of oxidizing cyclopropanol **83** to an alkoxy radical. This radical then undergoes a retro 3-exo-trig cyclization to form heptanone radical **88**. A 5-exo-trig cyclization forms primary radical **89**, which abstracts a hydrogen atom from 1,4-cyclohexadiene to form **84**.

Yao, Hu, Zhang, and co-workers utilized the Minisci reaction[33] to generate fused pentacycles (**92**) from indolylpropanoic acids (**90**) and quinones (**91**) (Figure 14).[34] These carbazoles are formed via a radical/radical/radical/oxidation/anionic/oxidation domino process. This transformation begins by oxidation of Ag(I) to Ag(II), which then oxidizes **90** to a carboxyl radical (**93**). Elimination of $CO_2$ leads to primary radical **94**, which adds to quinone **91**. Radical **95** then undergoes a 6-endo-trig cyclization with the pendant indole to complete the pentacyclic framework. Next, tertiary radical **96** is converted to **97** via one of three pathways: (1) hydrogen atom abstraction; (2) oxidation to the cation and then deprotonation; or (3) deprotonation to the radical anion, followed by oxidation. The central ring of the pentacycle is then aromatized via elimination of HBr and oxidation to yield **92**.

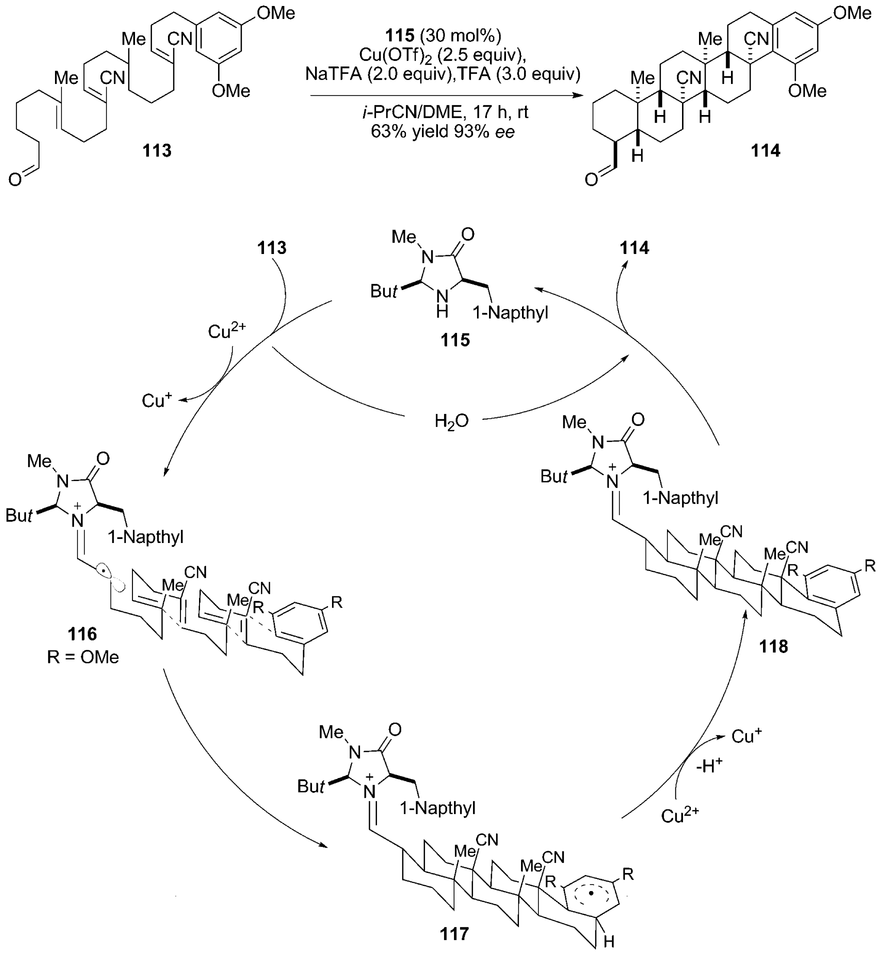

**Figure 17.** Cu(II)-mediated organo-SOMO polyene cyclization of **113** and mechanism.

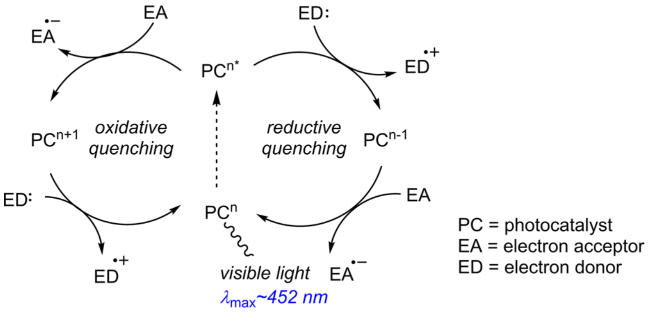

**Figure 18.** General photoredox paradigm.

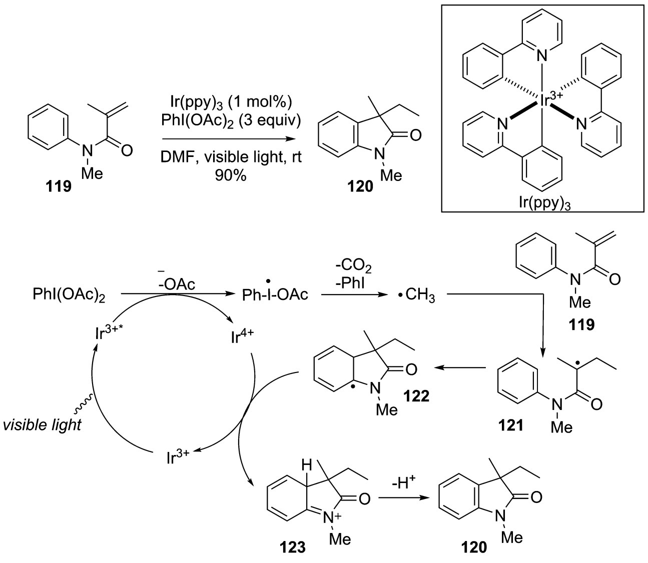

**Figure 19.** Visible light-mediated methyl transfer to **119** and cyclization and mechanism.

In 2010, Baran and co-workers developed an intermolecular Minisci reaction for boronic acids.[35] A year later, they demonstrated an intramolecular variant that could utilize either boronic acids or trifluoroborates (Figure 15).[36] Utilizing quinones as radicophiles, the Baran group was able to perform a radical/radical domino reaction to yield **100**. In this process, Ag(II) is generated via a persulfate-mediated single electron oxidation. Then, Ag(II) oxidizes quaternized **98**[37] to form aryl radical **101**, which cyclizes to secondary radical **102**. Quinone **99** then adds to the radical and forms **100** after hydrogen atom abstraction.

MacMillan et al. devised a series of domino reactions by combining the properties of the SOMO-activated addition of styrene[38] and the intramolecular arylation.[39] In the original styrene approach, the product was formed by internal ligand transfer of a nitrate from ceric ammonium nitrate to a benzylic cation. MacMillan and co-workers utilized this electrophilic intermediate for follow-up nucleophilic attack from aromatic rings and pendant, protected amines.[40] Application of these nucleophiles provides access to multicyclic ring systems containing substituted benzenes, such as **105** (Figure 16)

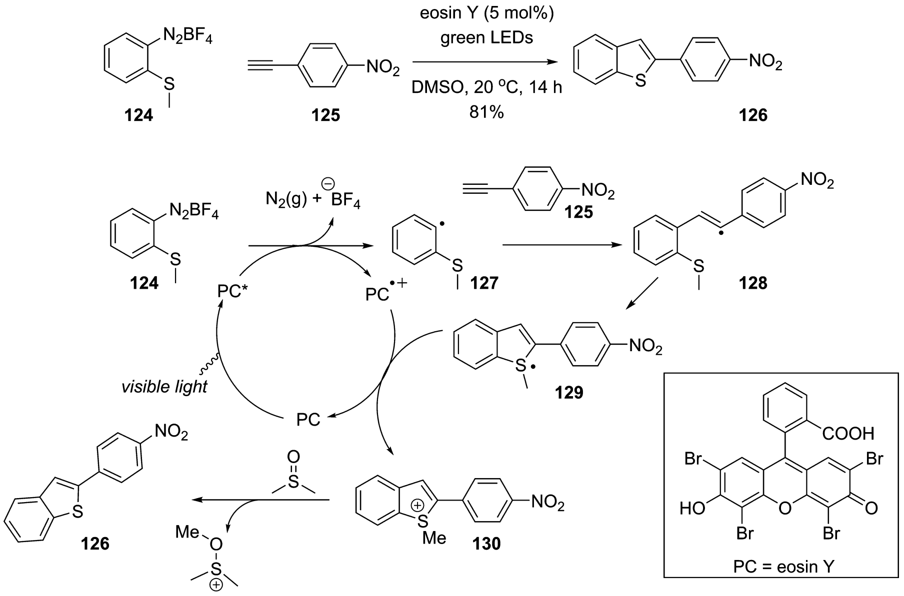

**Figure 20.** Visible-light-mediated reduction/addition/cyclization of **124** and **125** and mechanism.

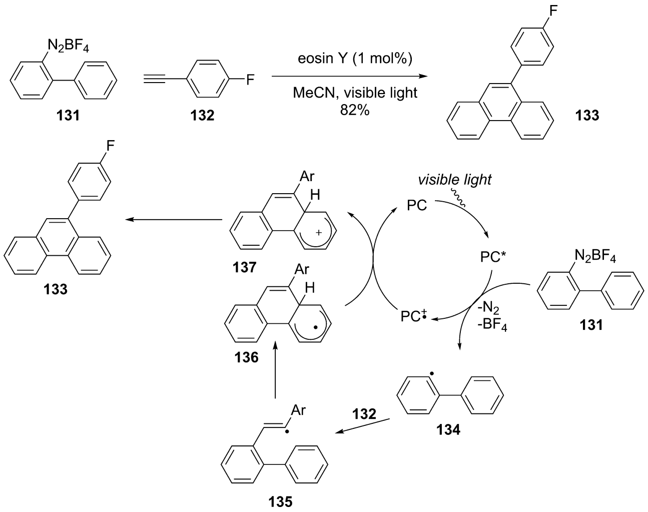

**Figure 21.** Visible-light-mediated reductive benzannulation of **131** and **132** and mechanism.

or pyrrolidines. These cyclizations proceed through a radical/oxidation/cationic domino mechanism. First, condensation of aldehyde **103** and catalyst **106** forms electron-rich enamine **107**, which is then oxidized by Fe(III) to yield radical cation **108**. Addition of radicophile **104** to **108** yields product radical cation **109**. A secondary Fe(III)-mediated oxidation forms dication **110**, which then undergoes an intramolecular Friedel–Crafts alkylation, proton transfer, and hydrolysis to form **105** and regenerate the catalyst.

The MacMillan group further extended the reactivity of the radical intermediate through unsaturations in polyenes to form multiple fused six-membered rings in one reaction with high enantioselectivity (Figure 17).[41] Reaction of **113** in the presence of catalyst **115** and Cu(II) as an oxidant formed hexacyclic **114** in 63% yield and 93% ee. This domino reaction undergoes four consecutive 6-endo-trig cyclizations. The mechanism is initiated by condensation of **113** with **115** to form an enamine, which is oxidized by Cu(II) to form distonic radical cation **116**. This radical cation then undergoes rapid and successive 6-endo-trig cyclization, terminating in the formation of conjugated radical **117**. Oxidation and elimination of a proton yield iminium **118**, which, upon hydrolysis, releases catalyst **115** and forms **114**.

## ■ DOMINO REACTIONS MEDIATED BY PHOTOREDOX CATALYSIS

Visible light photoredox catalysis has established itself as a powerful technique for enacting free radical transformations.[8,42] Typical photocatalysts are transition metal complexes or organic dyes that, upon photoexcitation by visible light to an excited triplet state, can proceed through oxidative or reductive quenching pathways to enact single electron transfers (Figure 18). It is emerging as a versatile and advantageous technique for mediating free radical reactions for several reasons. First, photoredox catalysts are activated by visible light, and unlike a traditional photochemical apparatus, reactions are conducted in typical borosilicate glassware with simple light fixtures. Second, the stoichiometric electron carrier is typically an inexpensive amine, as opposed to stannanes or silanes found in traditional radical processes. Finally, reactions are very robust, with typical transformations proceeding efficiently at low catalyst loadings.

In 2013, Zhu and co-workers developed a visible light-mediated, room temperature, decarboxylation/aromatic substitution of aniline **119** to oxindole **120** (Figure 19) via a radical/radical/cation domino process.[43] In this transformation, the excited state of $Ir(ppy)_3$ is oxidatively quenched by iodosobenzene diacetate (PIDA). The PIDA radical then fragments into iodobenzene, $CO_2$, and a methyl radical, which adds to **119**. Intramolecular cyclization to the arene installs the quaternary center in **122**. Thereafter, oxidation to the resonance-stabilized cation followed by deprotonation leads to aromatization of the 3-disubstituted product.

In 2012, König and co-workers developed an eosin Y-catalyzed synthesis of benzothiophene derivatives (**126**) (Figure 20).[44] This method utilizes a radical/radical/oxidative/cation domino reaction to access these heteroarenes. Starting from the *o*-methylthiobenzenediazonium salt **124**, visible light irradiation excites the photocatalyst to the triplet state, which is oxidatively quenched by the diazonium salt to release $N_2$ gas and aryl

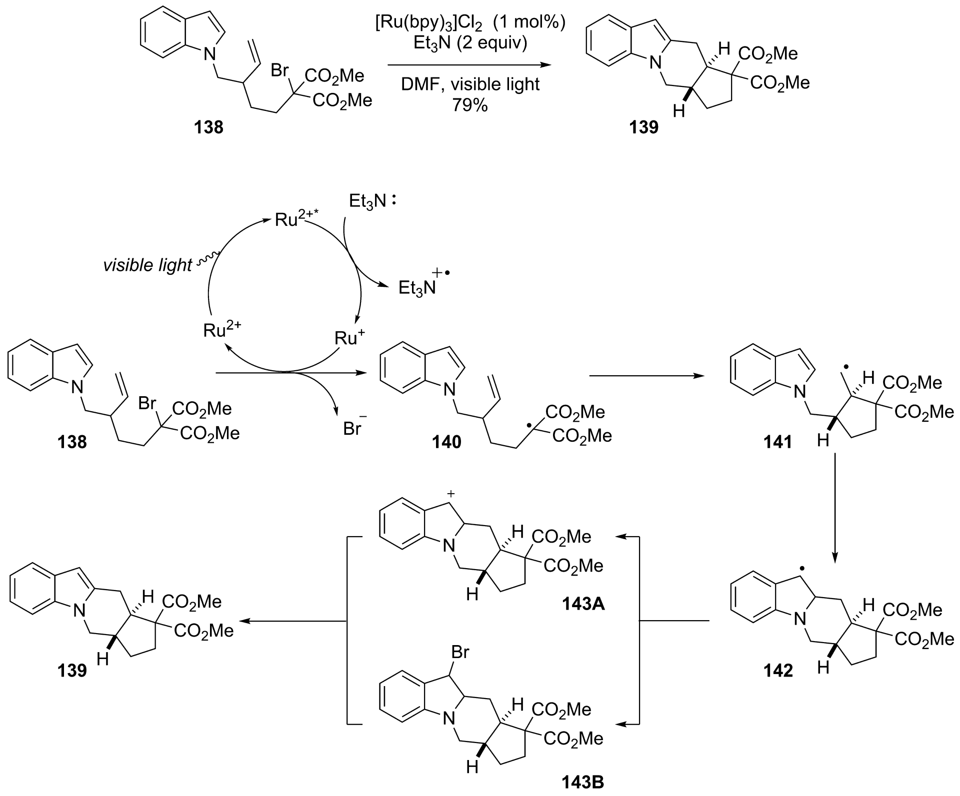

Figure 22. Visible-light-mediated ATRC of **138** and mechanism.

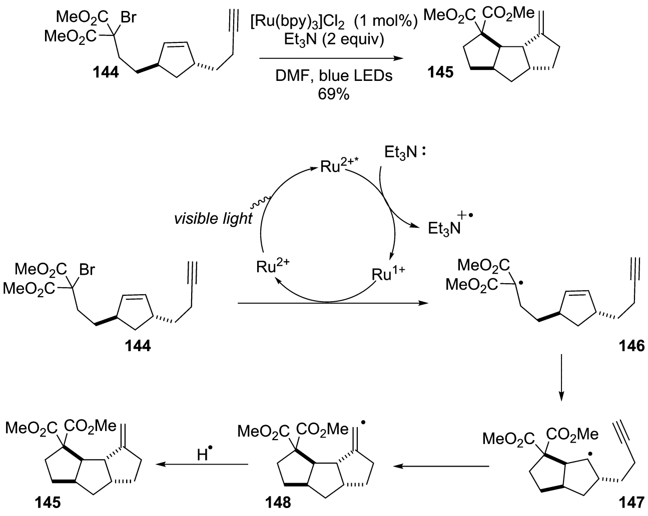

Figure 23. Visible-light-mediated radical cyclization of **144** and mechanism.

radical **127**. In the presence of *p*-nitro phenyl acetylene (**125**), radical addition yields vinyl radical **128**. Addition to sulfur followed by oxidation forms thionium **130**. Methyl transfer results in formation of **126**.

In a recent report by Zhou and co-workers, eosin Y induced a [4 + 2] benzannulation of biaryldiazonium salts with alkynes (Figure 21).[45] This radical/radical/cation domino reaction produced a variety of 9- and 9,10-disubstituted phenanthrenes. Irradiation with visible light excites eosin Y from the ground state. A single electron transfer from the excited photocatalyst to aryl diazonium **131** results in the radical cation of the catalyst and aryl radical **134**. Radical addition to alkyne **132** affords vinyl radical **135**. Intramolecular cyclization followed by single electron oxidation yields the carbocation **137** and the regenerated catalyst. Finally, deprotonation of **137** results in the desired phenanthrene **133**.

The Stephenson group reported a tin-free reductive dehalogenation reaction utilizing a visible-light-activated photocatalyst in 2009.[46] This method, which formed a radical intermediate, was applied to the functionalization of indoles and pyrroles (Figure 22).[47] Utilizing the radical generated from C−Br cleavage, a radical/radical/oxidation process yielded tetracyclic indole **139**. The proposed mechanism begins with irradiation of the photocatalyst with visible light to afford an electron-accepting excited state that is reductively quenched by triethylamine to form a triethylamine radical cation and Ru(I). Reduction of the C−Br bond of **138** affords tertiary radical **140**, which undergoes successive 5-exo-trig and 6-exo-trig cyclizations to form radical **142**. The indole radical is then rearomatized, affording the tetracyclic product **139**.

Inspired by the work of Curran[48] and Tanabe,[49] Stephenson and co-workers continued to develop radical/radical domino reactions onto unactivated π-systems.[50] The reaction led to a variety of products, including 5- and 6-membered rings as well as fused and spiro products (Figure 23). When applied to this domino system, photoexcitation of the metal catalyst and reductive quenching affords the active single electron reductant Ru(I). The electron-rich catalyst then reduces the C−Br bond of **144** to yield the regenerated Ru(II) and radical **146**. This radical then undergoes two successive 5-exo-trig cyclizations to form vinyl radical **148**. Finally, the carbon radical abstracts a hydrogen atom to form tricyclic product **145** in a 69% yield.

Following the development of a general cyclization strategy, the Stephenson group applied this concept to the formation of tricyclic pyrrolidinones (Figure 24).[51] The system proceeds through either a radical/radical/pericyclic or a radical/radical/

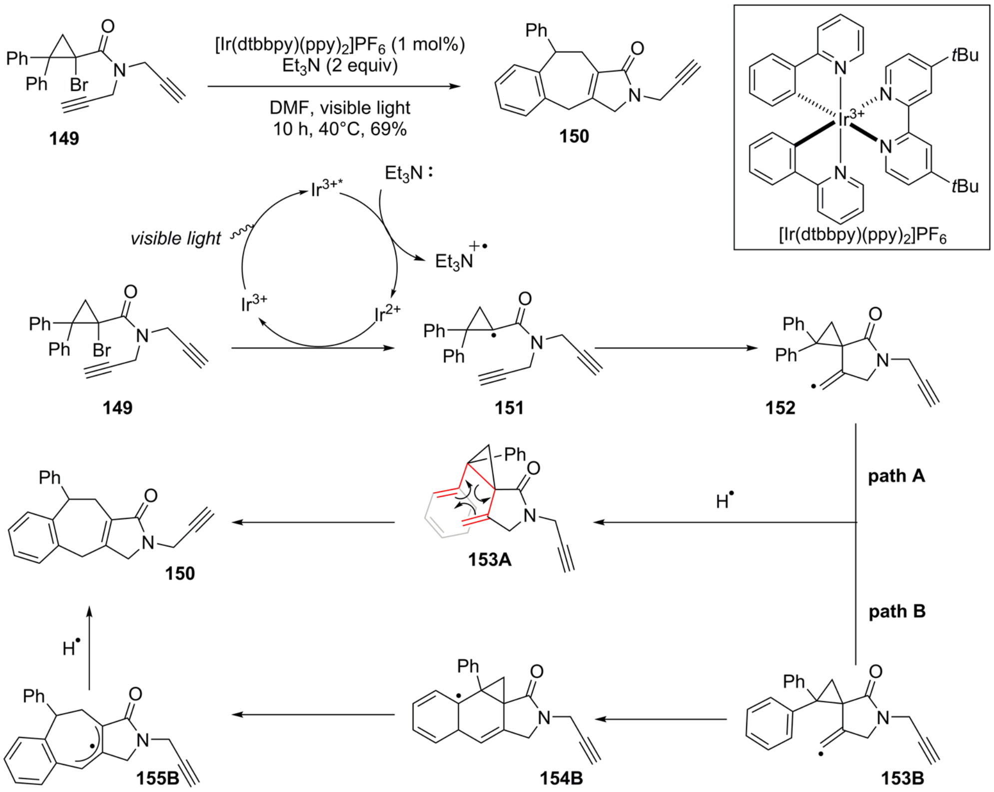

Figure 24. Visible light-mediated radical cyclization/fragmentation of **149** and mechanism.

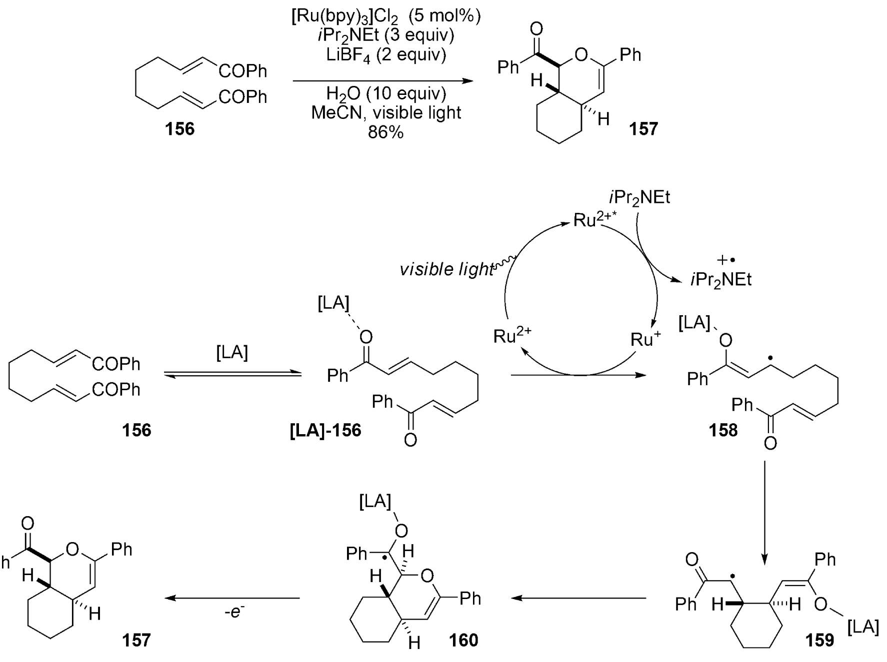

Figure 25. Visible-light-mediated, redox-neutral bicyclization of **156** and mechanism.

radical domino mechanism. The reaction, outlined in Figure 24, begins with the reductive quenching of photoexcited Ir(III) by $Et_3N$ to form an Ir(II) complex. Single-electron transfer to **149** provides $\alpha$-radical **151**, which quickly undergoes a 5-exo-dig cyclization with the pendant alkyne to form lactam **152**. At this point, the mechanism is less clear. In path A, **152** can undergo hydrogen atom abstraction, followed by a thermal sigmatropic rearrangement that is driven by strain release of the cyclopropyl ring to yield **150**. Alternatively, radical **152** can undergo an additional cyclization onto the aromatic ring, followed by $\beta$-scission to form radical **154B** (path B). Then, isomerization and hydrogen atom abstraction may lead to product **150**. Interestingly, trace quantities of **153A** were isolated from the reaction mixture. To provide further mechanistic insight, intermediate **153A** was heated at 40 °C in DMF in the absence of other redox conditions. The desired fused pyrrolidinone (**150**) was the only observed product, suggesting that path A is the likely route.

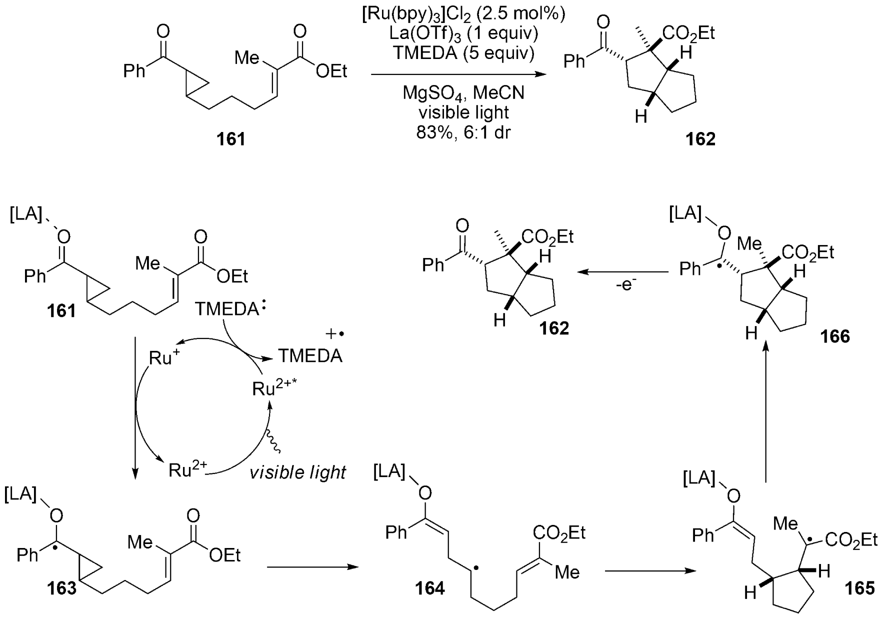

**Figure 26.** Visible-light-mediated, redox-neutral fragmentation/bicyclization of **161** and mechanism.

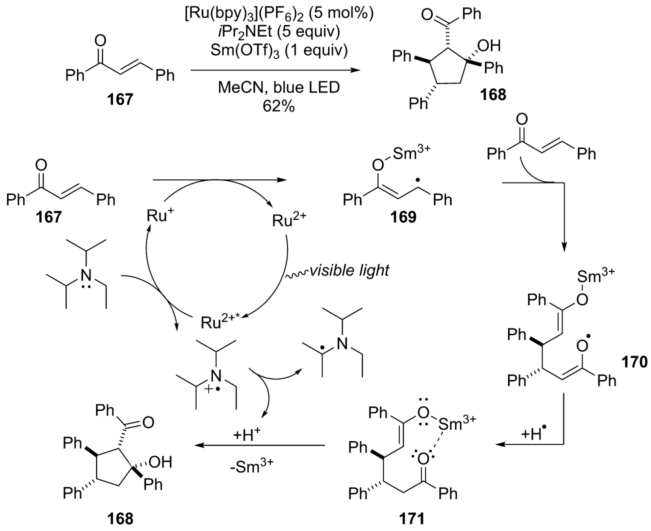

**Figure 27.** Visible-light-mediated, redox-neutral dimerization/cyclization of **167** and mechanism.

In 2008, the Yoon group developed a photocatalytic [2 + 2] reductive cyclization of a (bis)enone bearing a three-carbon tether.[52] Later, the authors observed that when the bis(enone) tether was expanded by the addition of a methylene unit under the same conditions, the expected products were not formed, and the observed products included dihydropyran **157** (Figure 25).[53] Intrigued by this observation, the authors optimized a photocatalytic radical/radical reaction to access dihydropyrans. The proposed mechanism involves reductive quenching of the excited state of the ruthenium catalyst, followed by single-electron reduction of Li-activated (bis)enone (**LA-156**) to form radical **158**. This allylic radical then undergoes a 6-exo-trig cyclization to form *α*-radical **159**. Enolate attack on the *α*-radical leads to ketyl **160**, which is then oxidized to form desired tetrahydropyran **157** in high yield (86%).

Continuing their efforts to combine Lewis acid activation with photoredox catalysis, the Yoon group reported a photocatalytic [3 + 2] cycloaddition of activated cyclopropanes with olefins (Figure 26).[54] This radical/radical/radical domino process results in the formation of fused cyclopentane rings. Single electron reduction of LA-activated **161** by the photocatalyst results in ketyl radical anion formation (**163**). The subsequent retro 3-exo-trig cyclization drives the reaction forward to allyl radical **164**. Facile 5-exo-trig cyclization onto the pendant olefin forms tertiary radical intermediate **165**. Finally, ring closure via another 5-exo-trig cyclization and single electron oxidation affords fused [3.3.0] product **162** in a 6:1 diastereomeric ratio.

In 2012, Zhao and co-workers showcased a visible-light-initiated reductive coupling/aldol cyclization of chalcones (Figure 27).[55] During preliminary studies, the expected [2 + 2] cyclobutane product was not observed. Rather, exposure of chalcone **167** to photoredox conditions resulted in a complex mixture of products, which included cyclic dimer **168** in 24% yield. A Lewis acid screen demonstrated $Sm(OTf)_3$ as an effective additive to activate the carbonyl of **167**. Single electron reduction of **167** coordinated to Sm(III) generates reactive *β*-radical intermediate **169** which adds to another equivalent of **167** to form **170**. Hydrogen atom abstraction forms enolate **171**, which is subsequently protonated and undergoes an intramolecular aldol addition to form **168** in 62% yield.

## ■ CONCLUSION

These transition metal- and visible-light-mediated radical processes demonstrate the efforts of the synthetic organic community to develop new and efficient methods for the generation of complex molecules in both an atom- and step-economical fashion. Both transition metal and photoredox domino processes garner access to a wide variety of products. Although the mechanisms illustrated here show clear, succinct catalytic systems, it is also possible for these reactions to operate additionally through short-chain propagation. However, in all of the systems presented, a catalyst is required, at a minimum, for initiation. Further studies of the discrete interactions of each system might shed insight onto which mechanistic pathway is dominant. These data could provide important details necessary to expand the selection of complex transformations in this area.

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### Notes

The authors declare no competing financial interest.

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