Review

Radical Cyclization-initiated Difunctionalization Reactions of Alkenes and Alkynes

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Review

Radical Cyclization-Initiated Difunctionalization Reactions of Alkenes and Alkynes

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Abstract: Radical reactions are powerful in the synthesis of diverse molecular scaffolds bearing functional groups. In pervious review articles, we have presented 1,2-difunctionalizations, remote 1,3-, 1,4-, 1,5-, 1,6- and 1,7-difunctionalizations, and addition followed by cyclization reactions. Presents in this paper are radical cyclization followed by the second functionalization reactions. The second functionalization could be realized by atom transfer reactions, radical or transition metal-assisted coupling reactions, and reactions with neutral molecules, cationic and anionic species.

Keywords: radical; difunctionalization; atom transfer; cyclization; coupling; addition

1. Introduction

Feasible radical transformations including addition, cyclization, coupling, atom or group transfer, rearrangement, and fragmentation reactions have made radical reactions a powerful tool for making carbon-carbon and carbon-heteroatom bonds [1,2]. The recent development on radical cyclative functionalization [3,4], radical-enabled bicyclization [5], photoredox reactions [6–8], mechanoredox reactions [9], electrochemical reactions [10], and transition metal-assisted radical reactions [11–14] have empowered the utility of synthetic radicals. It is a unique feature that radical reactions could be performed in a cascade sequence for the assembling of complex molecular scaffolds with multiple functional groups in regio- and diastereoselective manners. Other than the cascade reaction sequence, the final radical intermediates could be trapped by radicals or other active species to introduce new functional groups. This process makes the radical reactions even more attractive.

Radical difunctionalization is an attractive topic due to its advantages of synthetic efficiency and product structure diversity. There are numbers of reviews on this topic [15–25]. In our recent review articles, we have highlighted 1,2-difunctionalization of alkenes and alkynes (Scheme 1, I) [26], remote 1,3-, 1,4-, 1,5-, 1,6- and 1,7-difunctionalization of alkenes and alkynes (Scheme 1, II) [27], and addition/cyclization sequence of dienes, enynes and related compounds (Scheme 1, III) [28]. Presented in this paper are radical cyclization-initiated reactions followed by the second functionalization for the synthesis of cyclic compounds (Scheme 1, IV). The second functionalization reactions could be accomplished by atom transfer reactions, radical or transition metal coupling reactions, and reactions involving neutral molecules, cationic and anionic species (Scheme 2). In the reaction process, radical cyclization is considered as the first functionalization, while the introduction of X or Y groups are the second functionalization.

It is noteworthy that the reactions covered in this paper involve only a single cyclization. More sophistic double or multiple cyclization reactions are not included in this paper.

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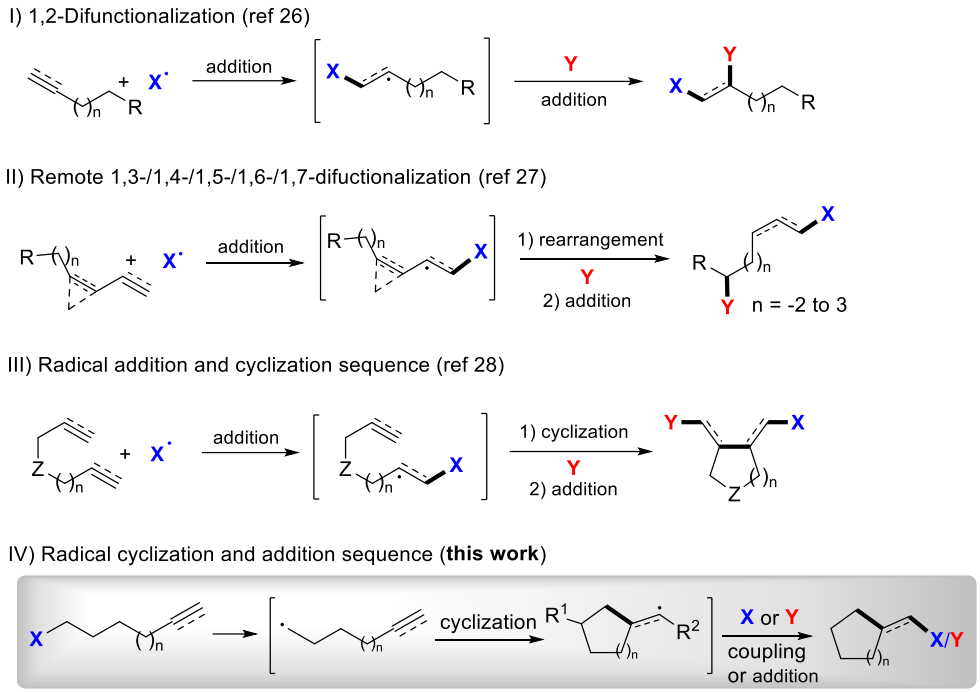
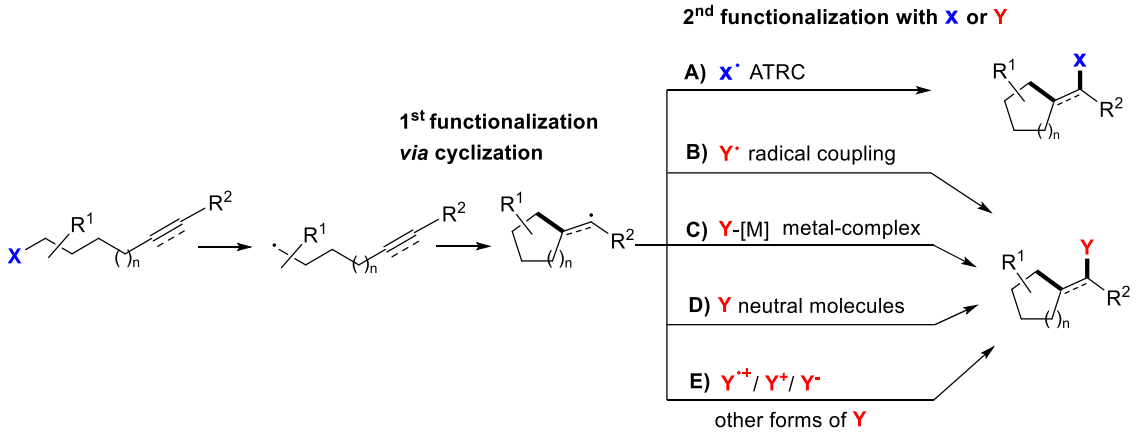


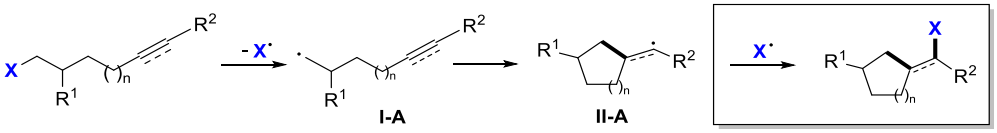
Scheme 1. Different kinds of radical difunctionalization reactions.



Scheme 2. Radical cyclization followed by the 2nd functionalization with **X** or **Y**.

2. Second Functionalization with X *via* Atom-Transfer Radical Cyclization

In atom-transfer radical cyclization (ATRC) reactions, radicals **I-A** generated from the homolytic cleavage of X–C bond undergo cyclization to form radicals **II-A** followed by coupling with radical X for the second functionalization to give products (Scheme 3). A majority of radical cyclization-initiated difunctionalization are ATRC reactions. The common X groups could be I, Br and Cl atoms, or carbonate, pyridinyl, xanthyl, and (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO)-related groups. The reactions presented in this section are classified based on the substrates which include halo-alkenes or -alkynes, *N*-allyl-haloacetamides, *N*-allyl-haloamines, *O*-allyl-halo ethers, *O*-allyl-halo-hemiacetal acetates and other related compounds.



Scheme 3. Atom-transfer radical cyclization (ATRC) reaction.

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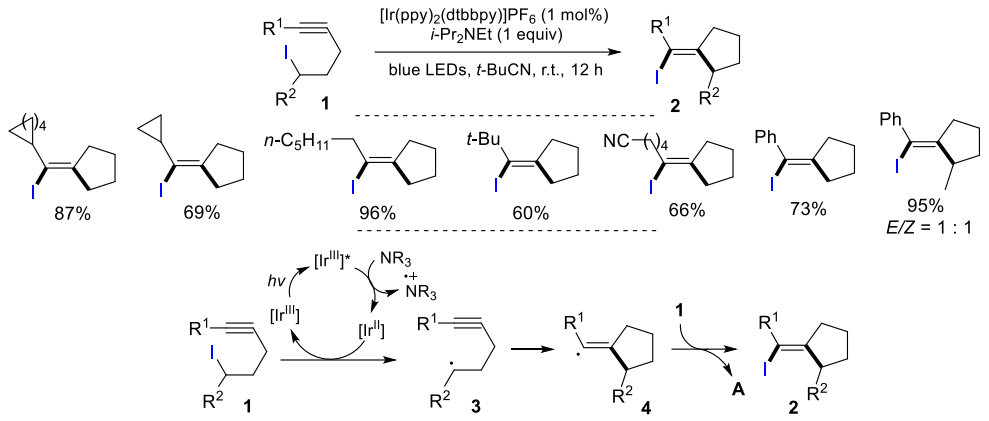
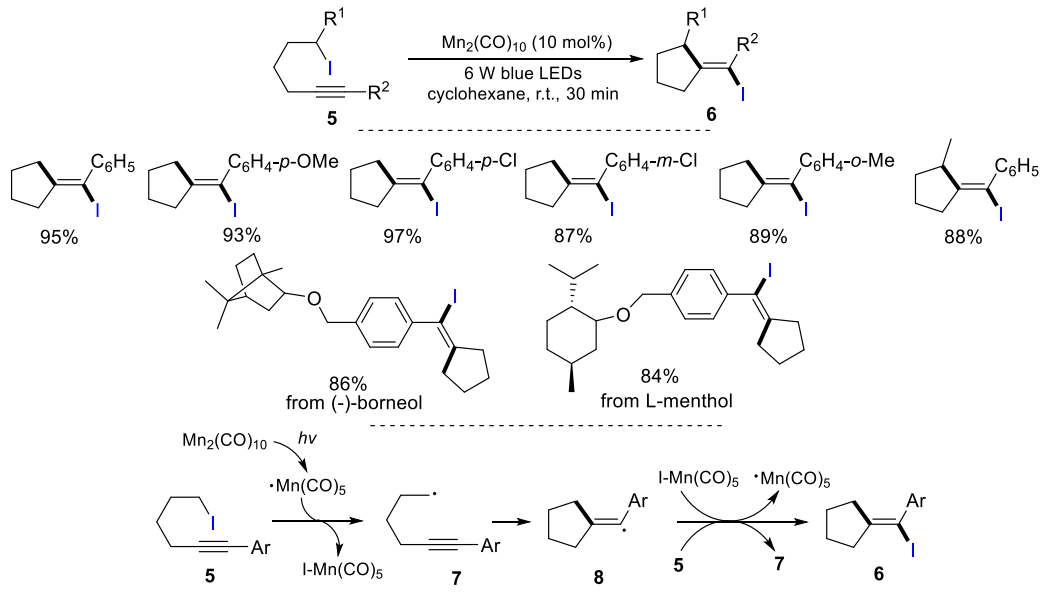
2.1. Halo Alkenes or Alkynes as Substrates

The iodine atom is a good transfer group for ATRC. In 2017, Martin and coworkers developed a visible light-promoted ATRC reactions of unactivated alkyl iodides for the synthesis of (iodomethylene)cyclopentanes. The reaction was carried out using alkyl iodides 1 in the presence of $[Ir(ppy)_2(dtbbpy)]PF_6$ and *i*-Pr_2NEt in *t*-BuCN under blue LEDs irradiation at room temperature for 12 h to give products (iodomethylene)cyclopentanes 2 in good to excellent yields (Scheme 4) [29]. The suggested reaction mechanism indicates that radicals 3 generated *via* a SET process of alkyl iodides 1 with $[Ir^{II}]$ undergo a 5-*exo* cyclization to give radicals 4 and then lead to the formation of products 2 after trapping the iodine radical from alkyl iodides 1.



Scheme 4. Synthesis of (iodomethylene)cyclopentanes.

In 2019, Zhang and coworkers reported a visible-light-induced and ATRC reaction of alkyl iodides for the synthesis of cyclic alkenyl iodides (Scheme 5) [30]. The $Mn_2(CO)_{10}$-catalyzed reaction of alkyl iodides 5 under the irradiation of blue LEDs in cyclohexane at room temperature gave products 6 in moderate to excellent yields. The reactions of natural products such as (−)-borneol and L-menthol also afforded the corresponding products in excellent yields. The reaction mechanism suggested that the $Mn(CO)_5$ radical is generated by the photo-induced Mn−Mn bond homolysis of $Mn_2(CO)_{10}$. The reaction of alkyl iodides 5 with the $Mn(CO)_5$ radical affords radicals 7 which undergo 5-*exo* cyclization to form radicals 8 followed by iodine atom transfer from 5 to give products 6.



Scheme 5. Synthesis of iodocyclic alkenyl iodides.

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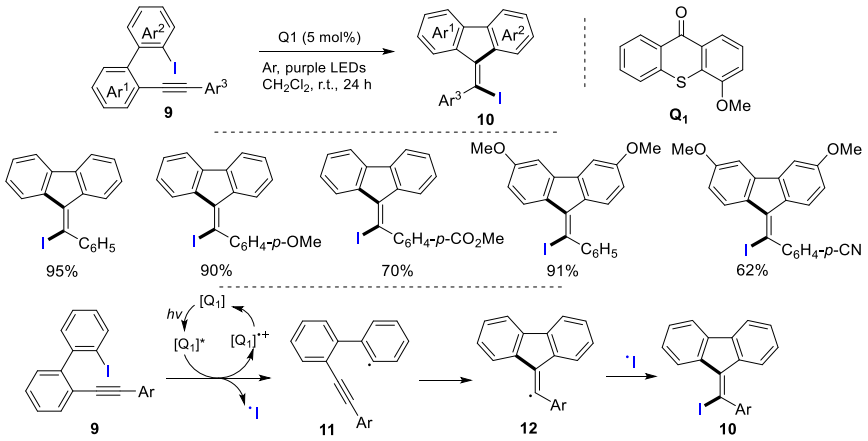
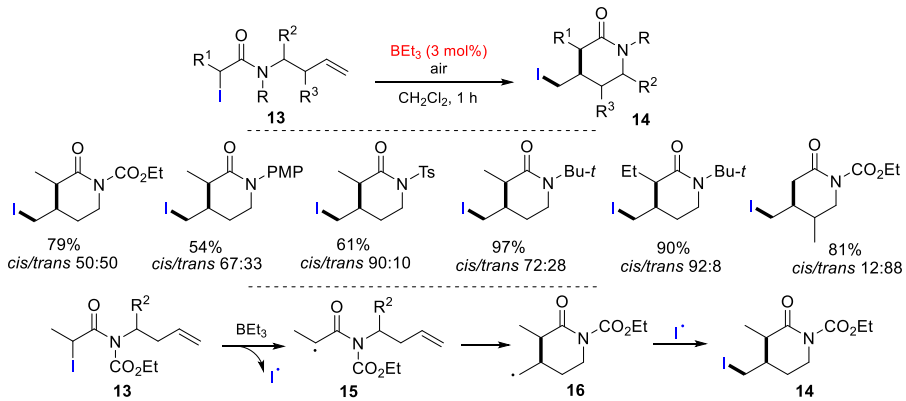
Other than alkyliodo group, aryliodo groups are also good for ATRC. Guo and coworkers, in 2019, introduced a photo-induced ATRC reaction of aryl iodide for the synthesis of iodine-substituted fluorene derivatives. The reaction of aryl iodide **9** with photosensitizer thioxanthone (**Q**$_1$) under the irradiation of purple LEDs in CH_2Cl_2 at room temperature gave products **10** in good to excellent yields (Scheme 6) [31]. The reaction process involves the formation of triplet **9** *via* SET reduction of the photoexcited state [**Q**$_1$]* species to [**Q**$_1$]$^{\bullet+}$. The Ar–I bond cleavage of triplet **9** produces aryl radicals **11** and the iodine radical. Subsequential radical cyclization to form **12** followed by the iodine radical coupling afford products **10**.



Scheme 6. Synthesis of iodo-substituted fluorene derivatives.

2.2. N-Allyl-haloacetamides as Substrates

A BEt_3/O_2-initiated iodine-atom-transfer radical cyclization of *N*-(but-3-en-1-yl)-*N*-(tert-butyl)-2-iodoalkanamides for the synthesis of iodine substituted *δ*-lactams has been reported by Li, Liu and their coworkers in 2016. The reaction of *N*-(but-3-en-1-yl)-*N*-(tert-butyl)-2-iodoalkanamides **13** in the presence of BEt_3 and air for 1 h afforded products **14** in good yields (Scheme 7) [32]. In this reaction process, radicals **15** formed *via* the abstraction of iodine atom of **13** by BEt_3 undergo the 6-*exo* cyclization to give radicals **16** followed by coupling with iodine radical to form products **14**.



Scheme 7. Synthesis of iodinated lactams.

In 2020, Bolm and co-workers reported a mechanochemical reaction of *N*-allyl-2-bromo-propanamides for the synthesis of brominated lactams. The reaction of *N*-allyl-2-bromo-propanamides **17** in the presence of the mineral covellite and tris[2-(dimethyl-amino)ethyl]amine (Me_6TREN) under mechanochemical conditions in ball mills gave **18** in good to excellent yields (Scheme 8) [33]. The reaction of *N*-allyl-2-bromo-propanamides **17** and [Cu^IL] afford radicals **19**

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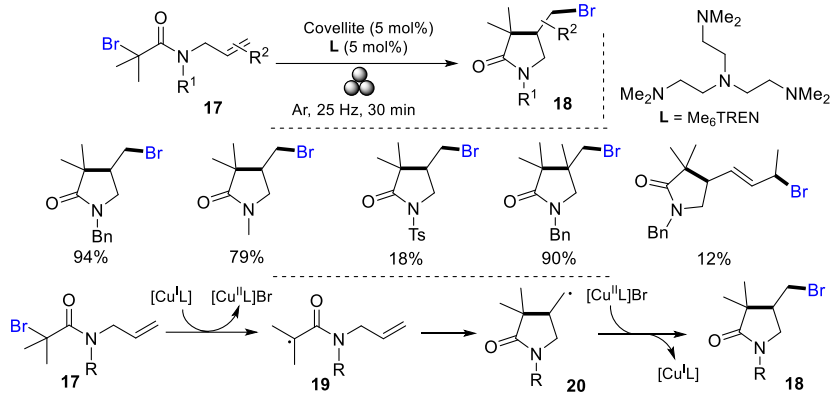
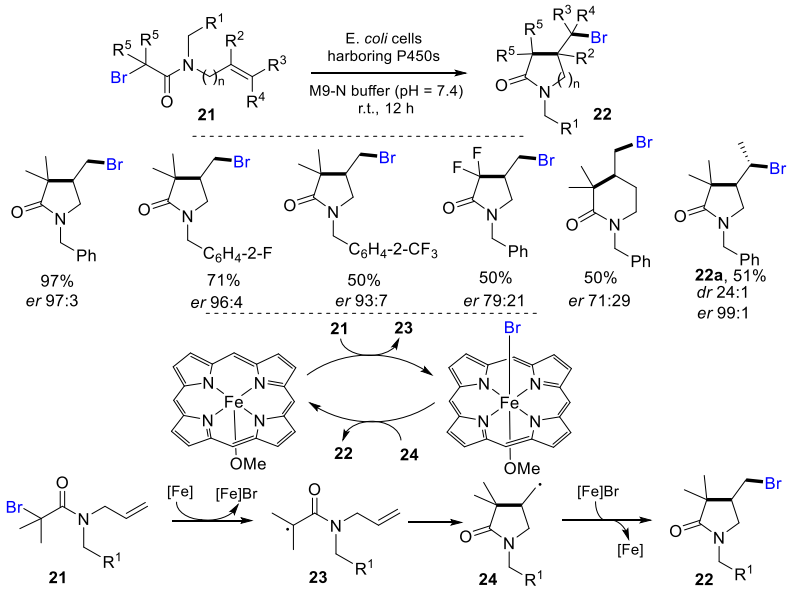
which undergo 5-*exo* cyclization to give radicals **20** followed by bromide atom transfer from [Cu^{II}L]Br to close the catalytic cycle and form products **18**. In another paper, Bolm and co-workers conducted similar reactions but modified the reaction conditions by using $Cu(OTf)_2$, tris(2-pyridylmethyl)amine (TPMA) and *tet*-$BaTiO_3$ to give brominated lactams in good yields [34].



Scheme 8. Synthesis of brominated lactams.

In 2021, Yang and coworkers developed cytochromes P450 metalloenzyme-catalyzed radical cyclization reactions of bromo-propanamides for the synthesis of nitrogen-heterocycles. The reaction of 2-bromo-propanamides **21** in the presence of whole-cell biotransformation E. *coli* cells resuspended in M9-N buffer (pH = 7.4) at room temperature gave products **22** in good yields (Scheme 9) [35]. γ-Lactam product **22a** was obtained in good a diastereomeric ratio of 24:1 which is better than the traditional $Cu(OTf)_2$/TPMA catalysis of 64 : 36 diastereomeric ratio [34]. In this metalloenzymatic reaction process, radicals **23** formed by the reaction of *N*-allyl-2-bromo-propanamides **21** and [Fe] undergo 5-*exo* cyclization to give radicals **24** which abstract Br from [Fe]Br to give products **22.**



Scheme 9. Metalloenzyme-catalyzed reactions for making brominated γ-lactams.

Nishikata and coworkers, in 2021, reported a photo-induced radical reaction of *N*-allyl-α-haloamides for the synthesis of γ-lactams. The reaction of *N*-allyl-α-haloamides **25** in the presence of *N*-Ph-phenothiazine (PTH) and $MgBr_2$ in DMSO under the irradiation of 365 nm LEDs at room temperature for 24 h gave products **26** in good to excellent yields (Scheme 10) [36]. The reaction first generates radicals **27** from the reaction of *N*-allyl amide **25** with PTH under the irradiation of LEDs.

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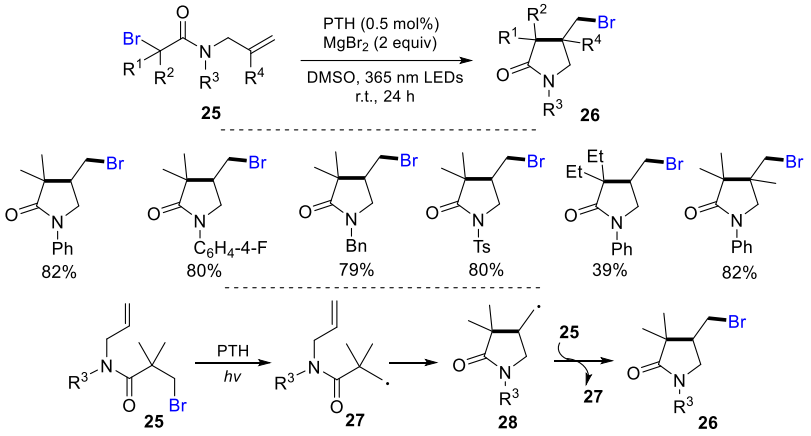
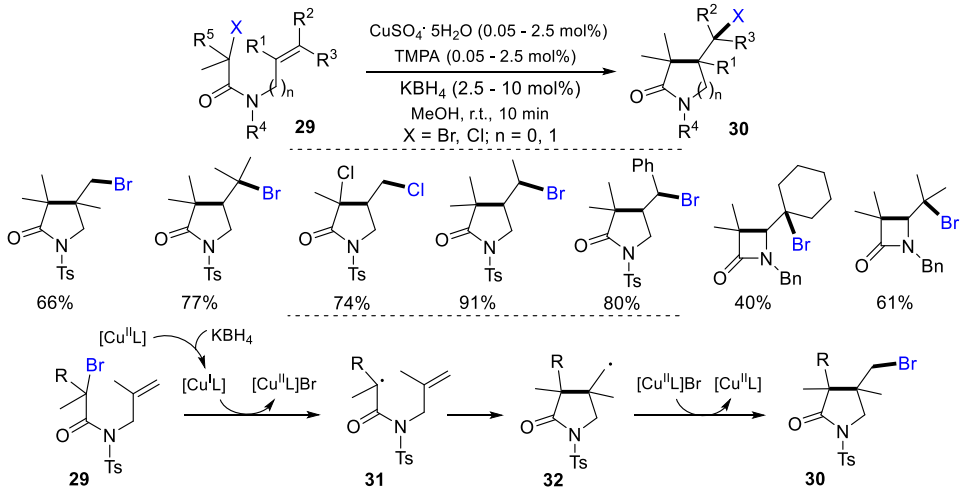
The cyclization of radicals **27** gives radicals **28** which trap the Br radical from *N*-allyl amides **25** to give products **26**.



Scheme 10. Preparation of brominated γ-lactams.

N-Allyl-haloacetamides are another class of substrate for ATRC to make *N*-containing heterocyclic compounds. Since the halogen atoms are at the α-position of carbonyl which are more reactive, not only the iodo and bromo atoms, chloro atom is also good for the ATRC. Clark and coworkers reported a Cu-catalyzed ATRC reaction of halo-olefins for the synthesis of nitrogen-heterocycles in 2012. The reaction of *N*-allyl-haloacetamides **29** in the presence of $CuSO_4{\cdot}5H_2O$, TPMA and borohydride salts at room temperature for 10 min gave products **30** in good yields (Scheme 11) [37]. The mechanism suggested that [Cu^{I}L] produced from the reduction of [Cu^{II}L] with KBH_4 reacts with **29** to form radicals **31** followed by the cyclization to give radicals **32**. Final products **30** are obtained from the reaction of radicals **32** and [Cu^{II}LBr] along with the regeneration of [Cu^{II}L].



Scheme 11. Synthesis of hologenated nitrogen-heterocycles.

Pellizzoni and coworkers reported a myoglobin-catalyzed reaction of *N*-allyl-α-haloamides for the synthesis of γ-lactams in 2022. The reaction of *N*-allyl-α-haloamides **33** in the presence of Mb H93S (as purified protein and in whole bacterial cells), sodium ascorbate, and sodium phosphate buffer (pH = 7.4) produced products **34** in good yields (Scheme 12) [38]. Initial radicals **35** produced by the reaction of *N*-allyl-2-bromo-propanamide **33** and [Fe^{II}] of Mb H93S undergo a 5-*exo* cyclization to give radicals **36** followed by coupling with Br radical from [Fe^{III}]Br to give products **34**.

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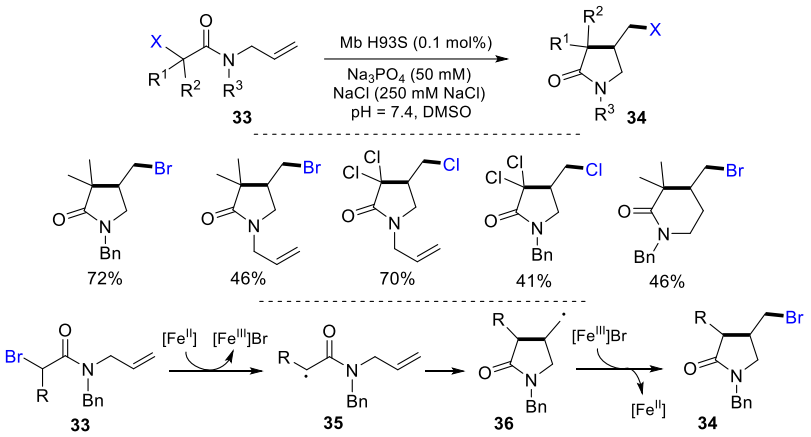
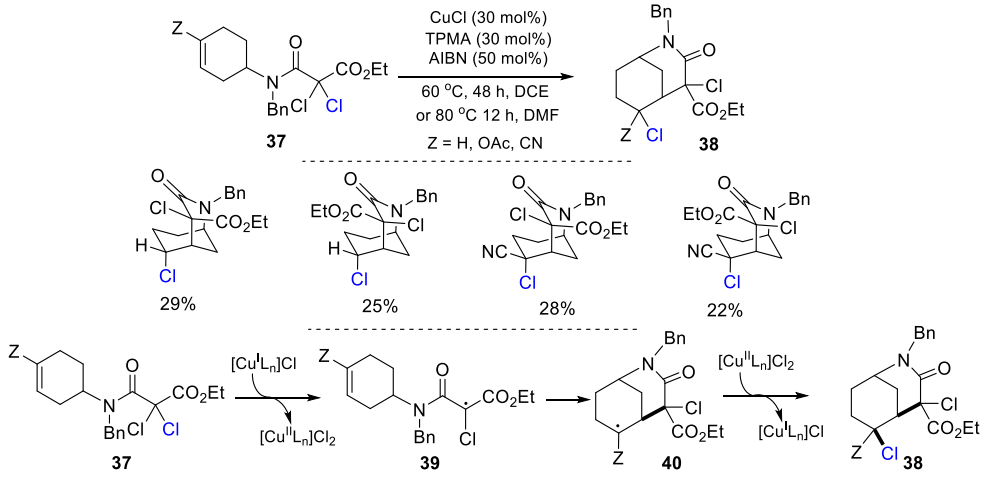


Scheme 12. Synthesis of brominated γ-lactams.

Diaba, Bonjoch and coworkers, in 2014, reported a Cu-mediated ATRC reaction of aminotethered dichloromalonamides for the synthesis of 2-azabicyclo[3.3.1]nonanes. The reaction of aminotethered dichloromalonamides **37** (such as carbamoyldichloroacetate-tethered alkenes and α,β-unsaturated nitriles) in the presence of CuCl, TPMA and AIBN in DCE at 60 °C for 48 h or in DMF at 80 °C for 12 h afforded products **38** in good yields (Scheme 13) [39]. Radicals **39** generated from the reaction of **37** and $[Cu^{I}L_n]Cl$ undergoes a 6-*exo* cyclization to give radicals **40** which then trap the Cl radical from $[Cu^{II}L_n]Cl_2$ to give products **38** along with the regeneration of $[Cu^{I}L_n]Cl$.



Scheme 13. Synthesis of chlorinated nitrogen-heterocycles.

In 2014, Ghelfi and coworkers developed a Cu-catalyzed ATRC reaction of dichloromalonamides for the synthesis of nitrogen-heterocycles. The reaction of *N*-allyl-*N*-tosyl-2,2-dichlorobutanamides **41** in a mixture of AcOEt/EtOH and in the presence of CuCl/TPMA/ascorbic acid/Na_2CO_3 gave *N*-arylsulfonyl-halo-γ-lactams **42** in good to excellent yields (Scheme 14) [40]. 3-Pirrolin-2-one **43** could be generated after the deprotection of the *N*-tosyl-halo-γ-lactam **42**. The reaction mechanism suggested that radicals **44** generated from the reaction of **41** and $[Cu^{I}L_n]Cl$, undergo a 5-*exo* cyclization to give radicals **45** which then react with $[Cu^{II}L_n]Cl_2$ to afford products **42** and $[Cu^{I}L_n]Cl$.

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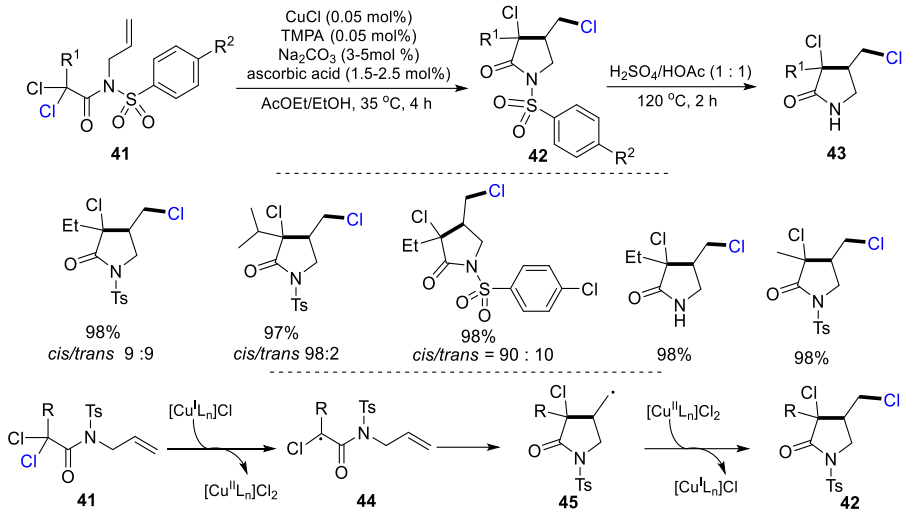
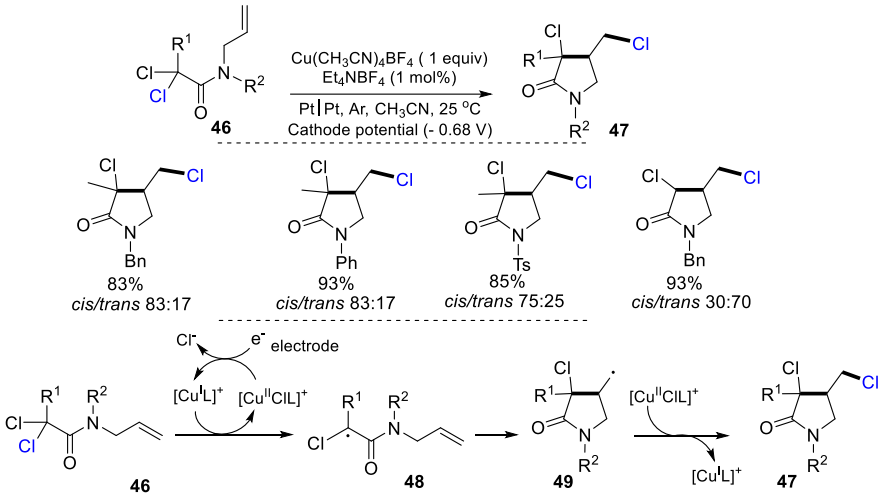


Scheme 14. Synthesis of chlorinated nitrogen-heterocycles.

In 2015, Isse & Gennaro and their coworkers reported an electrochemical reaction of *N*-allyl-*α*,*α*-dichloroamides for the synthesis of halogenated nitrogen-heterocycles. The reaction of *N*-allyl-*α*,*α*-dichloroamides **46** was carried out in a cell assembled with a Pt gauze cathode and a Pt plate anode with the appropriate cathode potential value (often - 0.68 V *vs*. SCE). In the presence of $Cu(CH_3CN)_4BF_4$, TPMA, and Et_4NBF_4 in CH_3CN at 25 ℃ under argon, the reaction gave products **47** in good to excellent yields (Scheme 15) [41]. In this reaction process, $[Cu^{I}L]^+$ produced from the reduction of $[Cu^{II}L]^+$ at the electrode surface reacts with *N*-allyl-*α*,*α*-dichloroamides **46** to form radicals **48** which then undergo cyclization to form radicals **49** followed by the reaction with $[ClCu^{II}L]^+$ to give products **47**.



Scheme 15. Synthesis of chlorinated nitrogen-heterocycles.

In 2016, Soni and Ram developed a Cu-catalyzed radical cyclization reactions of *N*-allyl-*N*′′-trichloro-acetylhydrazines for the synthesis of heterocyclic molecules containing two N-atoms. The reaction of *N*-allyl-*N*′′-trichloroacetylhydrazines **50** in the presence of CuCl and pentamethyldiethylenetriamine (PMDETA) with DCE as solvent at refluxing for 2 h afforded a mixture of chlorinated tetrahydro-pyridazin-3-ones **51** and 1,2-diazepan-3-ones **52** in good yields (Scheme 16) [42]. Two different products were separated based on their solubility in *n*-hexane. The reaction of **50** with $CuCl_2$ first generates dichlorocarbon radical **53** *via* the abstraction of a chlorine atom by CuCl/PMDETA. Radicals **53** undergo a more favorable 6-*exo* cyclization to give radicals **54** followed by reaction with $[Cu^{II}L]Cl_2$ to give 6-membered products **51**. Radicals **53** could also undergo

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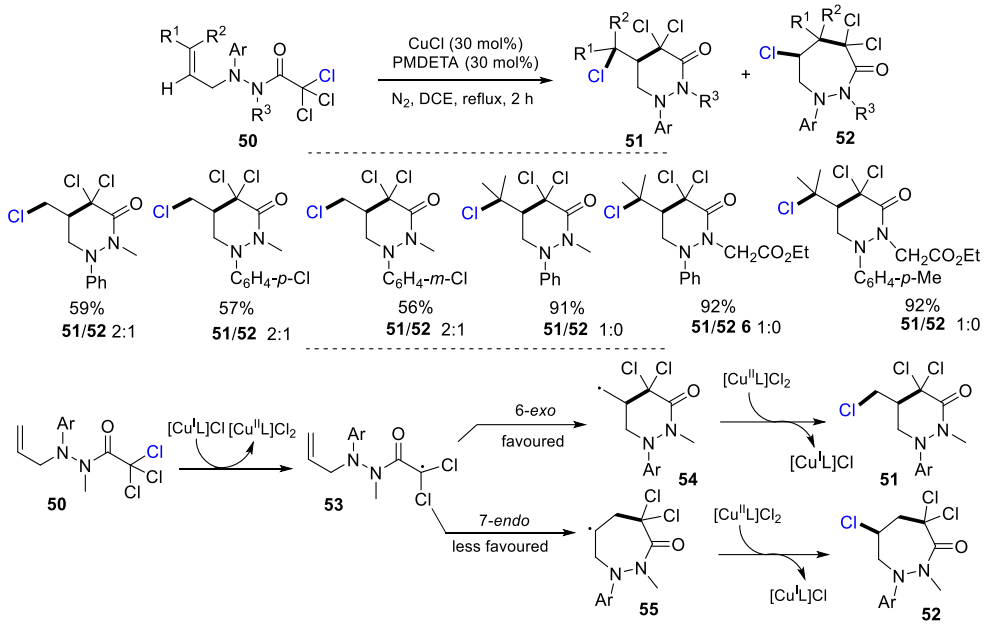
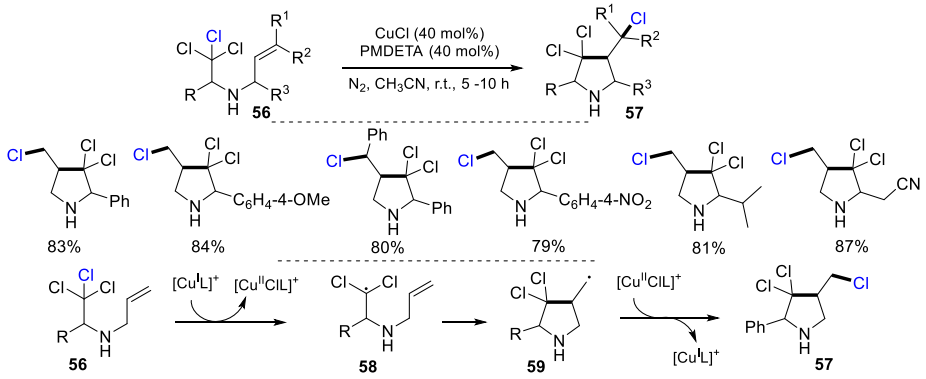
less favorable 7-*endo* cyclization to form radicals **55** and then lead to the formation of 7-membered products **52**.



Scheme 16. Synthesis of 6- and 7-membered nitrogen-heterocycles.

2.3. N-Allyl-Haloamines as Substrates

N-Allyl-haloamines could be employed as substrates for ATRC to make *N*-containing heterocyclic compounds. A Cu-catalyzed radical cyclization reactions of *β*-haloethylallyl- amines for the synthesis of substituted 2,4-*trans*-(*N*H)-pyrrolidines was reported by Gupta and coworkers in 2016. The reaction of 2,2,2-trichloro-ethylallyl-*N*H-amines **56** with CuCl and PMDETA with CH_3CN as solvent at 0 °C gave products **57** in high yields (Scheme 17) [43]. The radicals **58** generated form Cl atom transfer of **56** cyclized to form radicals **59** followed by the reaction with $[ClCu^{II}L]^+$ to give products **57**.



Scheme 17. Synthesis of nitrogen-heterocycles.

An Fe-catalyzed radical reaction of chloromethyl-1,6-dienes/1,6-enyne for the synthesis of nitrogen-heterocycles a protocol of Fe-catalyzed radical cyclization reactions of chloromethyl-1,6-dienes/1,6-enyne for the synthesis of nitrogen-heterocycles was reported by Tong and coworkers in 2017. The reaction of chloromethyl-1,6-dienes/1,6-enyne **60** or **61** using DPPF [1,1′-bis(diphenylphosphino)-ferrocene] as a catalyst and $PhCF_3$ as a solvent at 120 °C for 24 h gave products **62** or **63** in good yields (Scheme 18) [44]. In this reaction process, abstraction of a chlorine

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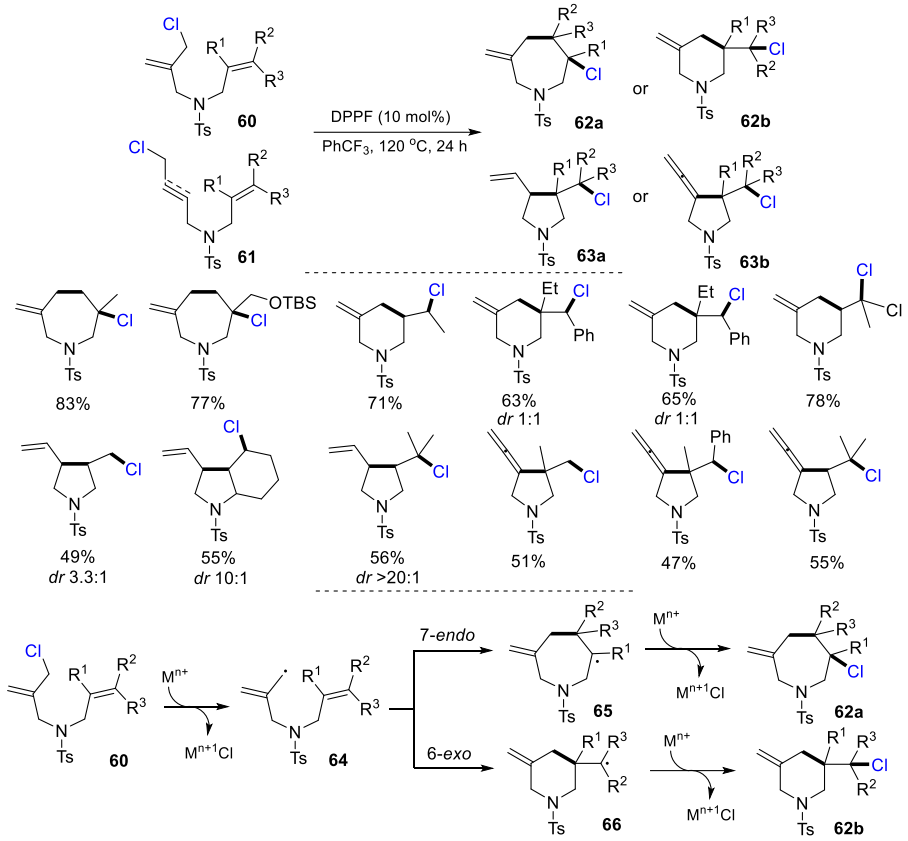
atom from substrates **60** by DPPF lead to the formation of radicals **64** which undergo a 7-*endo* cyclization to form radicals **65**, or a 6-*exo* cyclization to give radicals **66**. The reaction of radicals **65** or **66** with $M^{n+1}Cl$ afford products **62a** or **62b**.



Scheme 18. Synthesis of chlorinated heterocycles.

Sadanandan and Gupta, in 2020, developed a Cu-catalyzed radical reactions of trichloroethyl allylamines for the synthesis of nitrogen-heterocycles. The reaction of trichloroethyl allylamines **67** in the presence of CuCl/PMDETA at 0 °C in MeCN under N_2 atmosphere gave products **68** in good yields (Scheme 19) [45]. While the reaction of allylamines **69** in refluxing DCE/MeCN under N_2 atmosphere afforded a mixture of products **70** and **70′**. In the reaction process, radicals **71** formed from **67** *via* the abstraction of a Cl atom from CuCl undergo a 5-*exo* cyclization to give radicals **72** which then lead to the formation of products **68** after coupling with $[Cu^{II}L]Cl_2$.

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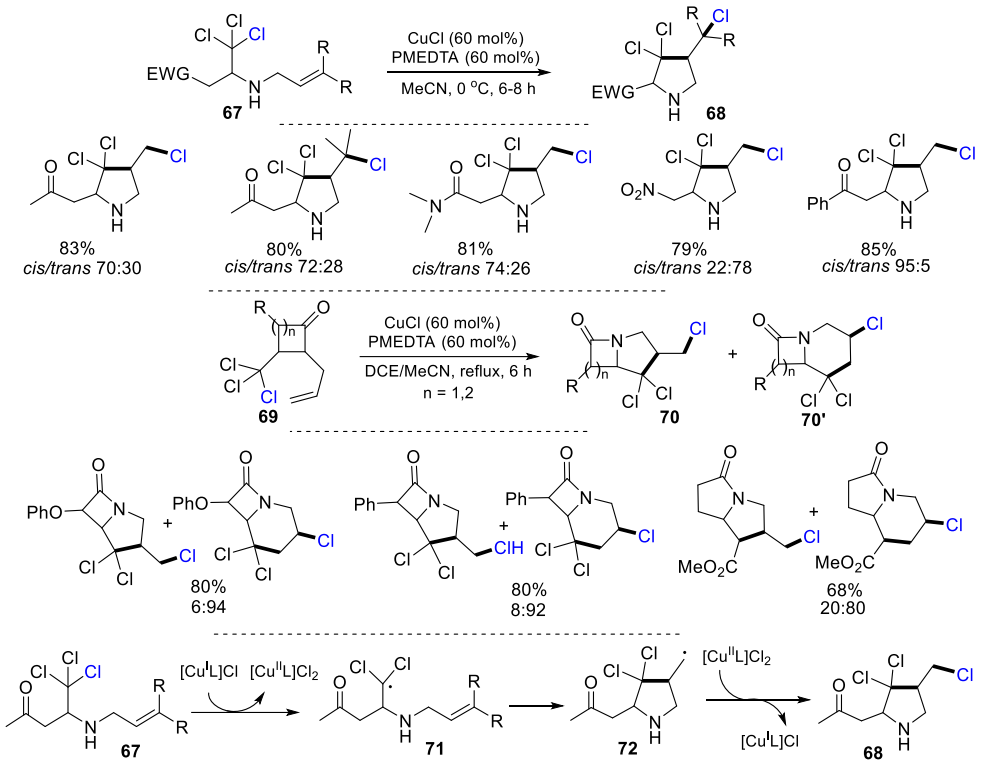
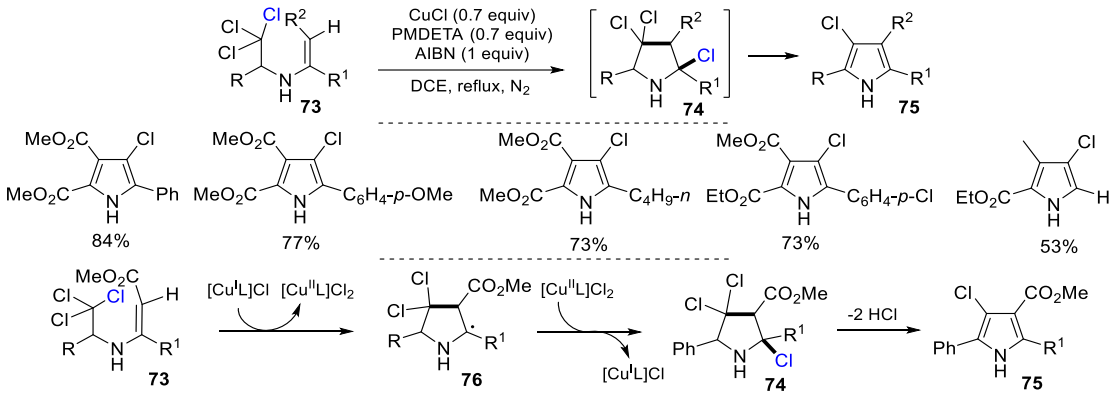


Scheme 19. Synthesis of chlorinated heterocycles.

In 2019, Gupta and coworkers reported a Cu-catalyzed radical reaction of trichloroethyl-*N*H-enamine for the synthesis of multi-functionalized pyrroles. The reaction of trichloroethyl-*N*H-enamines **73** with CuCl, PMDETA and AIBN in refluxing DCE afforded products **75** in good yields (Scheme 20) [46]. The initial radicals formed *via* the abstraction of a Cl atom of **73** by CuCl/PMDETA undergo a 5-*endo* cyclization to give radicals **76** followed by the Cl atom tranfer from $[Cu^{II}L]Cl_2$ to give products **74.** Sequential dehydrochlorinative aromatization of **74** leads to the substituted pyrroles **75**.



Scheme 20. Synthesis of chlorinated tetrhydropyrroles and substituted pyrroles.

2.4. O-Allyl-Halo Ethers as Substrates

There are several examples of using *O*-allyl-halo ethers as starting materials for ATRC to make *O*-containing heterocyclic compounds. Yu and Yang, in 2022, introduced a Cu-catalyzed radical reaction of unsaturated iodides for the synthesis of iodine substituted heterocycles. The reaction of 2-allyloxy-3-iodotetrahydropyrans or tetrahydrofurans **77** in the presence of $[Cu^{I}(N\text{^}N)(P\text{^}P)]PF_6$ complexes under the irradiation of blue LEDs in a mixture of CH_3CN and H_2O or in pure water

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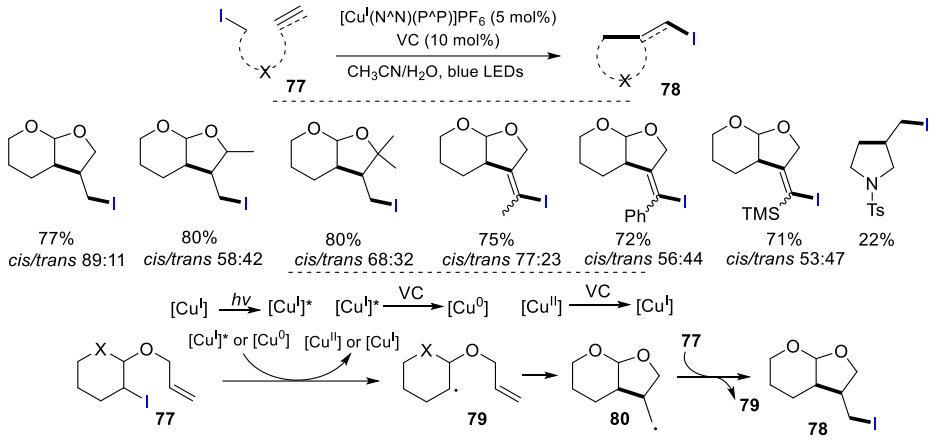
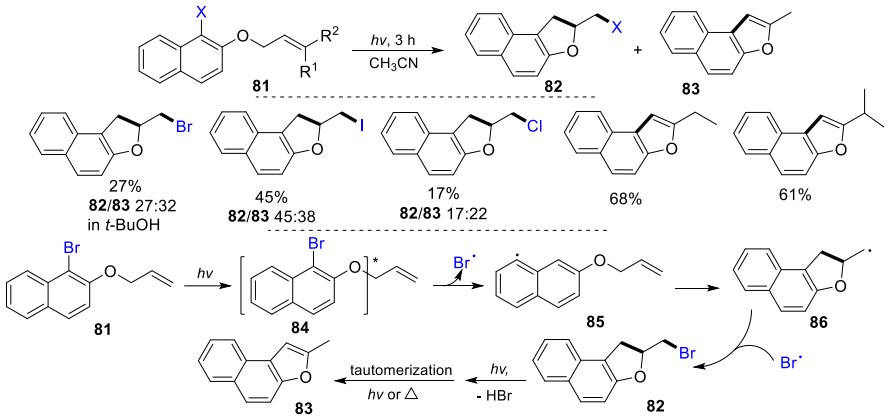
afforded products **78** in good yields (Scheme 21) [47]. The initial radicals **79** produced from the reaction of **77** under either the photo-excited $[Cu^{I}]^{*}$ or the *in situ* generated $[Cu^{0}]$ species from $[Cu^{I}]^{*}$ undergo cyclization to form radicals **80** followed by iodine transfer to give products **78**.



Scheme 21. Synthesis of iodine-substituted heterocycles.

Yoshimi and co-workers, in 2014, reported a photo-induced radical reaction of allyl bromonaphthyl ethers for the synthesis of naphtho[*b*]furans. The reaction of allyl halo-naphthyl ethers **81** in CH_3CN (or *t*-BuOH) under the irradiation of a 100 W high-pressure mercury lamp with a Pyrex glass filter (>280 nm) at room temperature for 3 h to give 2-halomethyl substituted naphthodihydrofuran **82** and naphtho[*b*]furans **83** in good yields (Scheme 22) [48]. The reaction involves the formation of triplet states of **84*** from **81** under photo irradiation followed by homolytic C–X bond cleavage to give radicals **85** and Br radical. The 5-*exo* cyclization of radicals **85** gives radicals **86** and Br radical trapping gives brominated products **82** which could undergo further transformations of dehydrobromination and tautomerization to give **83**.



Scheme 22. Synthesis of brominated naphtho[*b*]furans.

In 2016, Soni and coworkers reported a Cu-catalyzed cyclization reactions of 2,2,2-trichloroethyl vinyl ethers for the synthesis of highly substituted 2,3-difunctionalized-4-chlorofurans. The reaction of 2,2,2-trichloroethyl vinyl ethers **87** in the presence of CuCl, and tetramethylethylenediamine (TMEDA) or PMDETA using benzene as solvent at reflux for 12–32 h gave products **89** in good yields (Scheme 23) [49]. Radicals **90**, generated from 2,2,2-trichloroethyl vinyl ethers **87** *via* abstraction of a chlorine atom by CuCl/PMDETA, undergo 5-*endo* cyclization to give radicals **91** which then lead to the formation of products **88** after trapping the Cl radical from $[Cu^{II}L]Cl_2$. Further transformation of **88** *via* aromative dehydrochlorination give substituted furans **89**.

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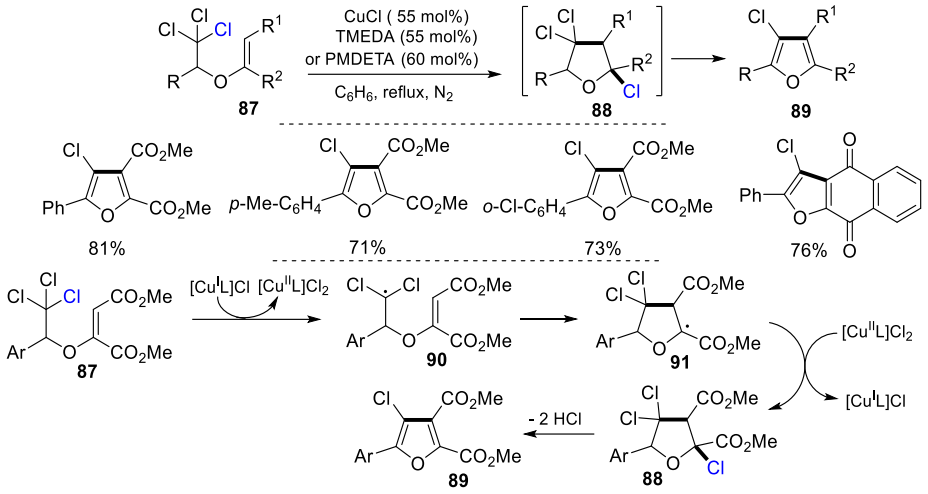
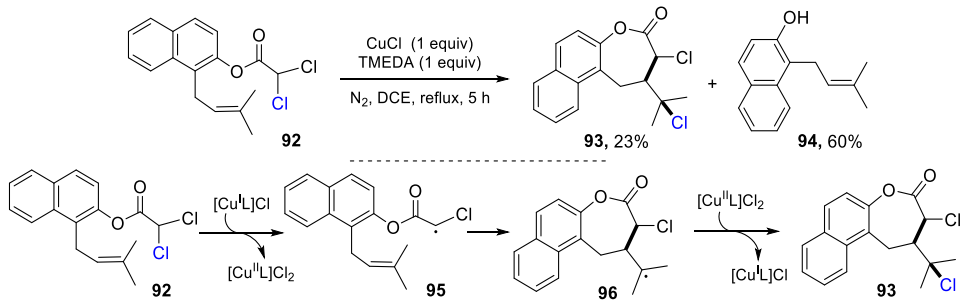


Scheme 23. Synthesis of substituted tetrhydrofuranes and furans.

In 2018, the Tittal group reported a Cu-catalysed radical reaction of 1-(3-methyl-but-2-enyl)-naphthalen-2-yl ester for the synthesis of 7-member lactones. The reaction of 1-(3-methyl-but-2-enyl)-naphthalen-2-yl ester **92** in the presence of CuCl/TMEDA in refluxing DCE for 5 h gave product **93** in 25% yield along with 1-(3-methyl-but-2-enyl)-naphthalen-2-ol **94** in 60 % yield (Scheme 24) [50]. The initial radical **95** generated after the abstraction of a chlorine atom from **92** with [Cu^{I}L]Cl undergoes 7-*exo* cyclization to give the radical **96** followed trapping Cl radical from [Cu^{II}L]Cl$_2$ to give product **93**.



Scheme 24. Synthesis of chlorinated 7-membered lactone.

2.5. O-Allyl-Halo-Hemiacetal Acetates as Substrates

The use of *O*- or *S*-allyl-halo-hemiacetal acetates as substrates for ATRC could lead to the formation of cyclic hemiacetal compounds. In 2014, Roncaglia and coworkers introduced a Cu-catalyzed reaction of *O*-allyl-2,2-dichlorohemiacetal acetates for the construction of cyclic acetals and *γ*-lactones. The reaction of *O*-allyl-2,2-dichlorohemiacetal acetates **97** with CuCl and PMDETA in toluene at 80 °C for 18 h afforded cyclic acetals **98** in good to excellent yields (Scheme 25) [51]. The initial radicals **100** generated from the reaction of **97** and [Cu^{I}L$_n$]Cl undergo cyclization to give radicals **101** which couple with the Cl radical from [Cu^{II}L$_n$]Cl$_2$ to give of cyclic acetals **98**. The cyclic acetals **98** could be readily hydrolyzed and oxidized to form *γ*-lactones **99**.

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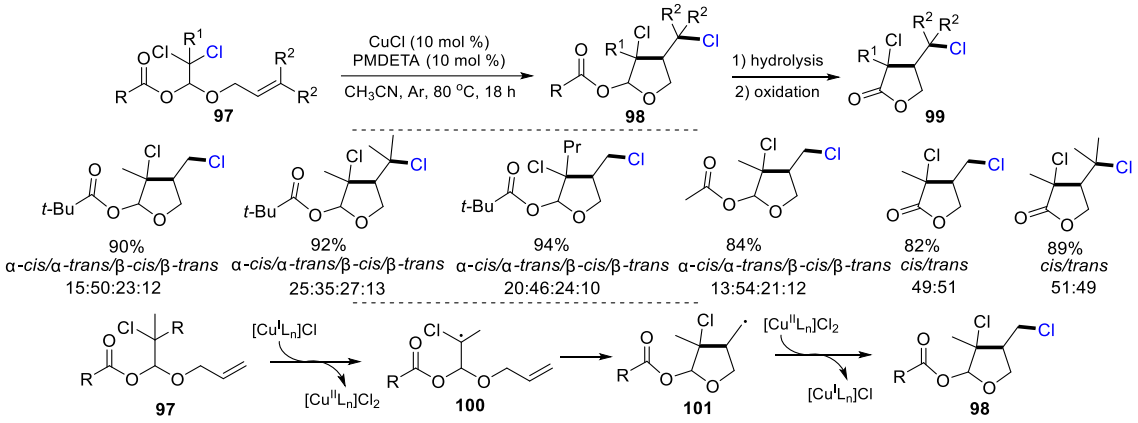
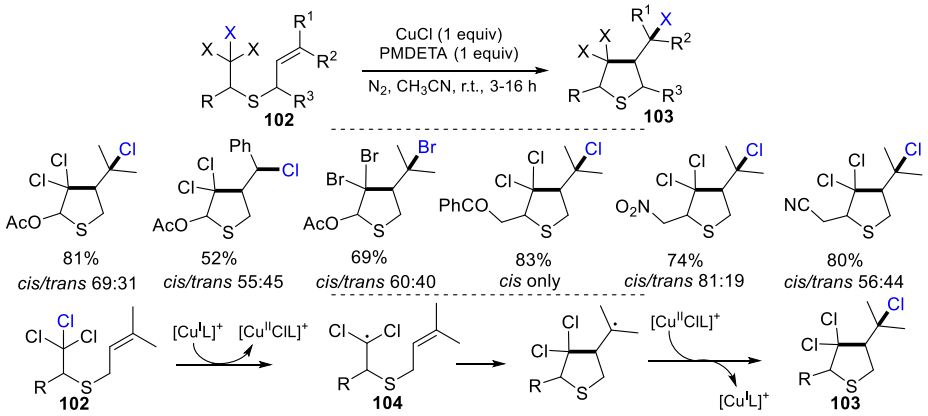


Scheme 25. Synthesis chlorinated cyclic acetals and *γ*-lactones.

In 2016, Gupta, Soni and their coworkers reported a Cu-promoted radical reaction of 2,2,2-trihaloethylallyl sulfides for the synthesis of highly substituted tetrahydrothiophenes. The reaction of 2,2,2-trihaloethylallyl sulfides **102** with CuCl/PMDETA in CH_3CN at room temperature gave products **103** in good to high yields (Scheme 26) [52]. Initial radicals **104** generated form the reaction of 2,2,2-trihaloethylallyl sulfides **102** with $[Cu^{I}L]^{+}$ undergo 5-*exo* cyclization followed by the reaction with $[ClCu^{II}L]^{+}$ to give products **103**.



Scheme 26. Synthesis of tetrahydrothiophenes.

In 2017, Gupta and coworkers reported a Cu-catalyzed radical cyclization reaction of unsaturated carbohydrate-derived chloroacetals for the synthesis of chlorinated perhydrofuro[2,3-*b*]pyrans. The reaction of chloroacetals **105** with CuCl/2,2′-bipyridine with refluxing CH_2Cl_2 under N_2 atmosphere for 4 h to give products **106** in good yields (Scheme 27) [53]. The initial radicals **107** generated from **105** *via* abstraction of a chlorine atom from $[Cu^{I}L]Cl$ undergo 5-*exo* cyclization to give radicals **108** which then reacts with $[Cu^{II}L]Cl_2$ to form products **106**.

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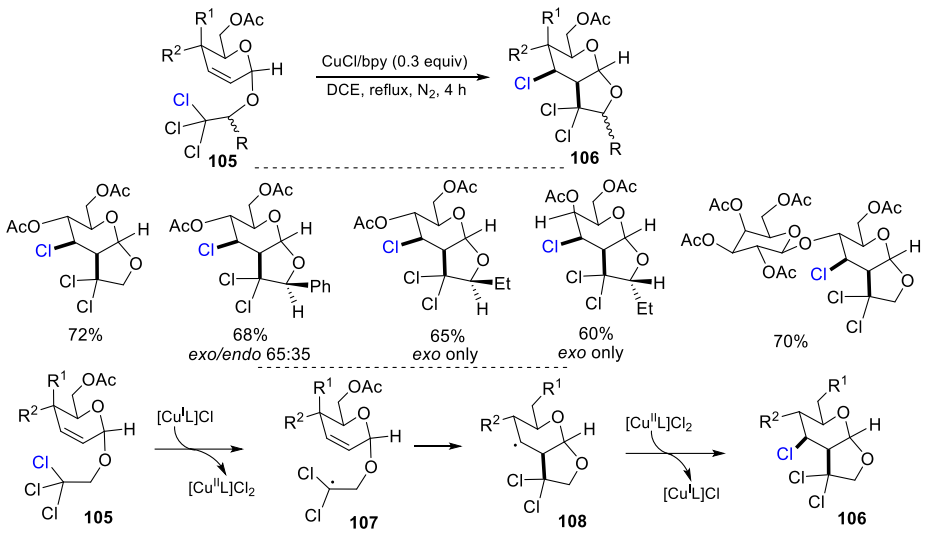
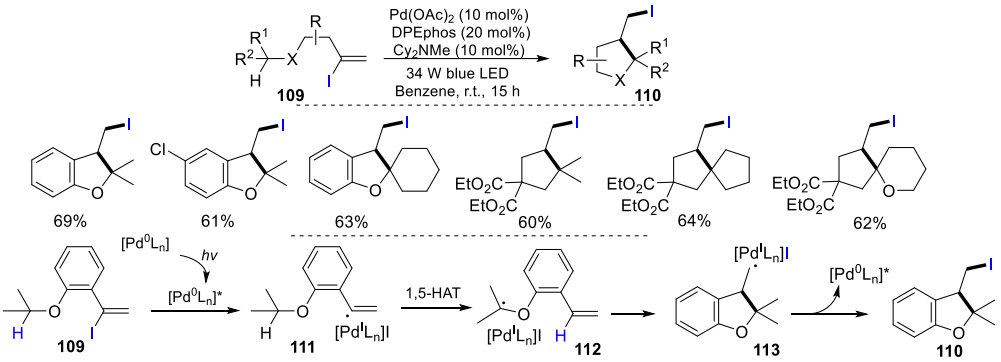


Scheme 27. Synthesis of chlorinated perhydrofuro[2,3-*b*]pyrans.

2.6. Other Vinyl Derivatives as Substrates

Presented in this section are the ATRC reactions using the substrates which are not included in the previous sections. The atoms transfer groups X could be unique carbonate, pyridinyl, xanthyl, and TEMPO-related groups. Similar to the halogen atoms, these groups are good for homolytic cleavage to generate radicals for ATRC reactions. Gevorgyan and coworkers in 2018 reported a Pd-catalyzed radical reaction of iodovinyl derivatives for the synthesis of cyclic compounders. The reaction of iodovinyl derivatives **109** in the presence of $Pd(OAc)_2$, DPEphos and Cy_2NMe under the irradiation of 34 W blue LEDs in benzene afforded products **110** in good to excellent yields (Scheme 28) [54]. The reaction first generates Pd-radical intermediates **111** *via* a SET process of vinyl iodides **109** with the active $[Pd^0L_n]^*$. After 1,5-HAT (hydrogen atom transfer) of **111** to form **112** followed by a 5-*exo* cyclization give radicals **113** which then undergo reductive elimination of $[Pd^0L_n]^*$ to give products **110**.



Scheme 28. Synthesis of cyclic compounders.

A unique ATRC reaction involving pyridinyl group was reported by Hong and coworkers in 2019. They developed a visible-light-induced radical reaction of *N*-alkenyloxypyridinium salts for the synthesis of pyridine-tethered tetrahydrofurans. The reaction of *N*-alkenyloxypyridinium salts **114** in the presence of 3-phosphonated quinolinone (**Q2**) and $NaHCO_3$ under the irradiation of blue LEDs at room temperature gave products **115** in good yields (Scheme 29) [55]. The initial alkoxy radicals **116** generated from *N*-alkoxypyridinium salts **114** *via* the reaction with photoexcited state $[\mathbf{Q_2}]^*$ undergo 5-*exo* cyclization to give radicals **117**. Reaction of **117** with substrates **114** for the

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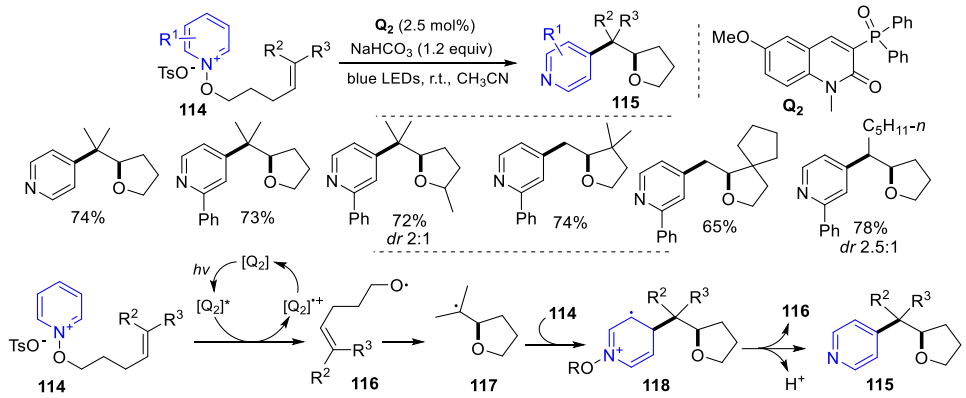
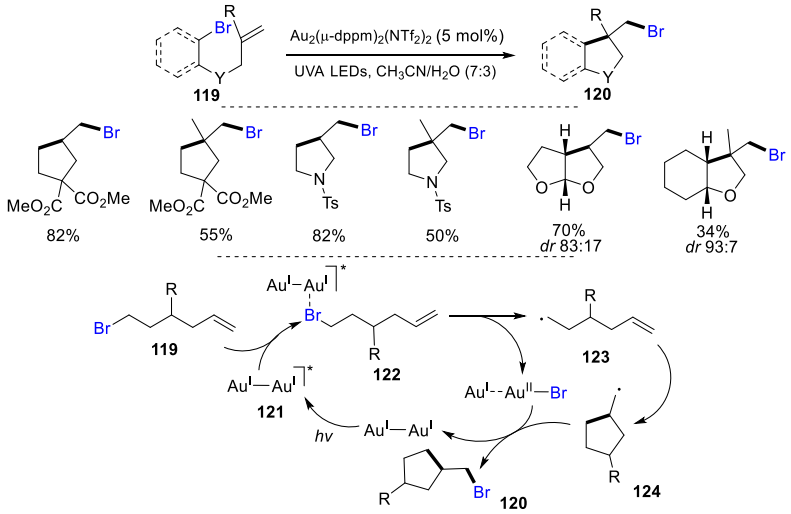
addition of addition of the pyridyl group to form radicals **118** followed by the N–O bond cleavage lead to the formation of products **115**.



Scheme 29. Synthesis of pyridine-tethered tetrahydrofurans.

In 2020, Barriault and coworkers reported a photo-induced radical reaction of bromoalkanes for the synthesis of cyclic compounders. The reaction of unactivated bromoalkanes **119** in the presence of $Au_2(\mu\text{-dppm})_2(NTf_2)_2$ under the irradiation of UVA LEDs in CH_3CN/H_2O produced products **120** in good yields (Scheme 30) [56]. In the reaction process, bromoalkenes **119** react with $[Au^I–Au^I]^*$ species **121** to form intermediates **122** followed by C–Br bond cleaving to give radicals **123** and 5-*exo* cyclization to form radicals **124**, and finally to form products **120** after Br atom abstraction from radicals **124**.



Scheme 30. Synthesis of brominated cyclic compounders.

A Cu-catalyzed radical reaction of allyl bicyclic *β*-lactam for the synthesis of tricyclic *β*-lactams has been reported by Dawra and coworkers in 2020. The reaction of allyl bicyclic *β*-lactam **125** under the catalysis of CuCl/PMDETA in DCE at room temperature gave products **126** or **127** in good to excellent yields (Scheme 31) [57]. Between two alkenyl groups (*S*-allyl and *N*-allyl) the competitive experiments revealed that the ATRC is more favorable to the *S*-allyl group than the *N*-allyl group. It was suggested that radicals **128** formed *via* the abstraction of a Cl atom of **125** by CuCl/PMDETA undergo a 5-*exo* cyclization to give radicals **129** which then react with $[Cu^{II}L]Cl_2$ to give products **126**.

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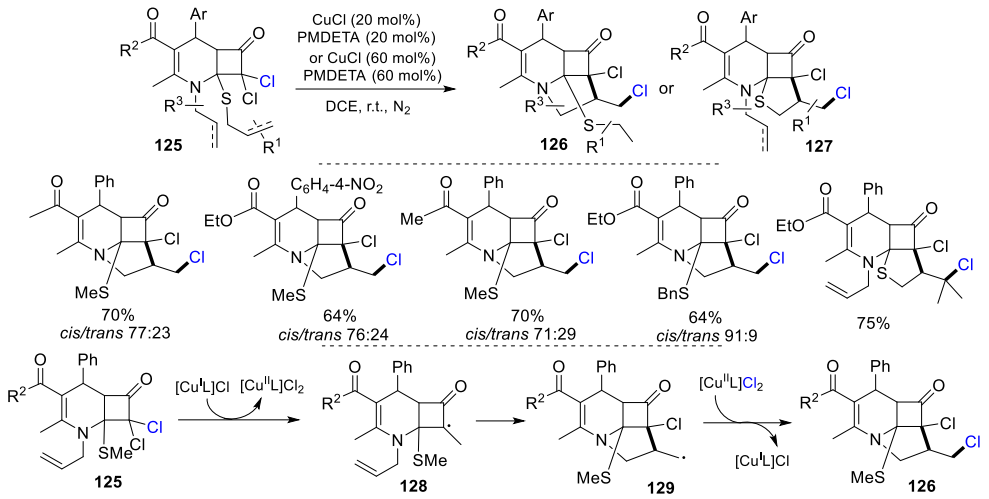
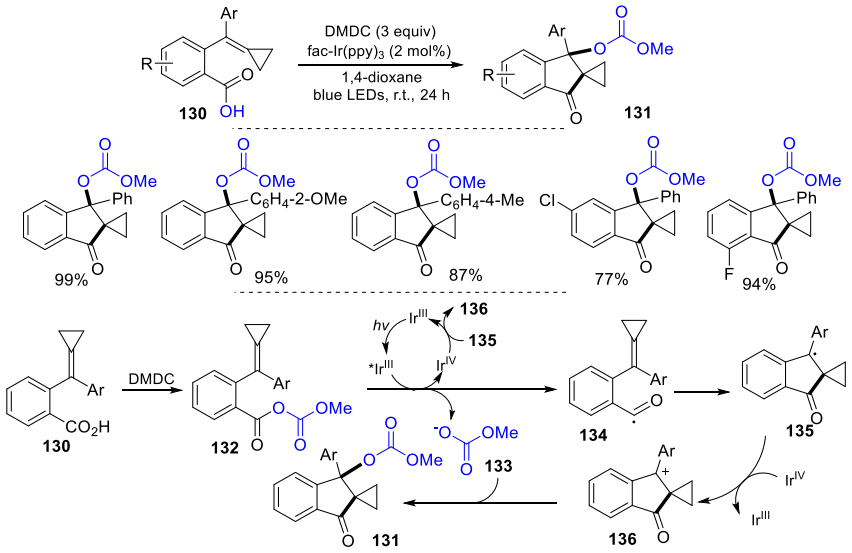


Scheme 31. Synthesis of tricyclic *β*-lactams.

Shi and coworkers in 2021 introduced an interesting ATRC reaction involving carbonate radical transformation. The photo-induced radical reaction of methylenecyclopropanes tethered with carboxylic acid for the synthesis of spiro[cyclopropane-1,2-indan]ones. The reaction of carboxylic acids tethered methylenecyclopropanes **130** and dimethyl dicarbonate (DMDC) in the presence of *fac*-Ir(ppy)$_3$ under 5 w blue LEDs in 1,4-dioxane at room temperature gave products **131** were obtained in excellent yields (Scheme 32) [58]. In the reaction process, carbonates **132** generated *in situ* from the reaction of carboxylic acid **130** and DMDC first form radical anions and then undergoes fragmentation of methyl carbonate **133** to give acyl radicals **134** followed by a 5-*exo* cyclization to form radicals **135**. Sequential oxidation of **135** to cations **136** and nucleophilic attack by cation **133** give products **131**.



Scheme 32. Synthesis of methyl carbonated spiro[cyclopropane-1,2-indan]ones.

Jahn and co-workers reported a TEMPO-related ATRC of *α,γ*-dioxygenated amides for the synthesis of *γ*-lactams. The reaction of *α,γ*-dioxygenated amides **137** in *t*-BuOH under the irradiation of microwave at 150 °C for 1 h followed by the treatment with TBAF in THF gave products **138** in good to excellent yields (Scheme 33) [59]. The reaction mechanism suggests that radicals **139** generated from *N*-allyl amides **137** undergo a 5-*exo* cyclization to give radicals **140** which then couple with OTMP radical to form **141** and then products **138** after OTMS deprotection.

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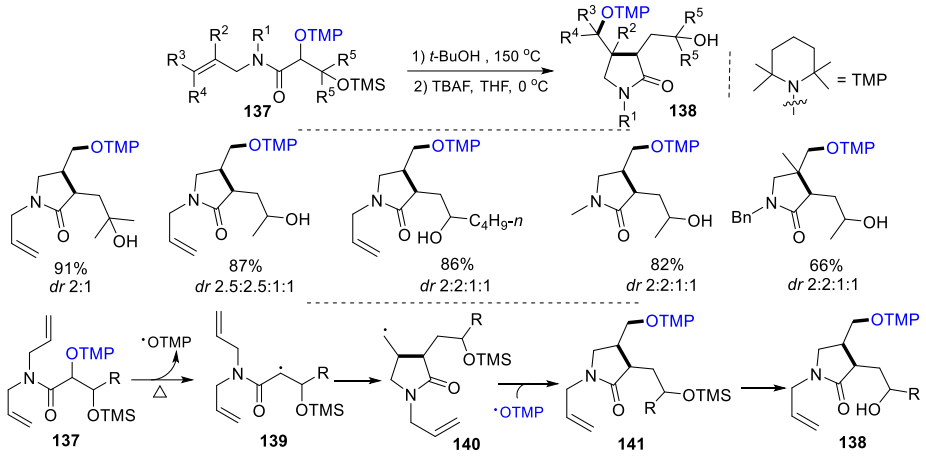
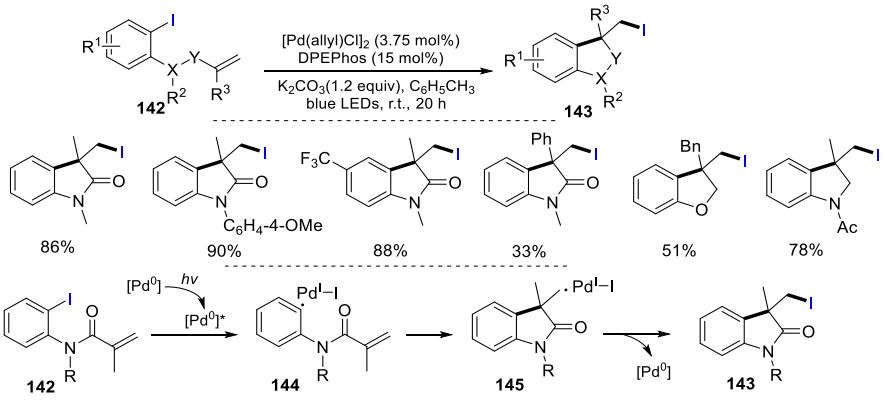


Scheme 33. Synthesis of OTMP-functionalized γ-lactams.

Marchese and coworkers, in 2022, developed a photo-induced radical reaction of allyl 2-iodobenzenes for the synthesis of iodinated heterocyclic compounds. The reaction of allyl 2-iodobenzenes **142** in the presence of $[Pd(allyl)Cl]_2$, DPEPhos and K_2CO_3 in toluene under the irradiation of blue LEDs gave products **143** in good yields (Scheme 34) [60]. The initial radicals **144** by photo reaction of **142** with $[Pd^0]^*$ undergo a 5-*exo* cyclization to form **145** followed by iodine transfer to give product **143**.



Scheme 34. Synthesis of nitrogen-heterocycles.

Chen & Wang and coworkers, in 2022, introduced a xanthate-involved ATRC reaction of unactivated olefins for the synthesis of various nitrogen-heterocycles such as γ-lactams, δ-lactams, pyrrolidines, indolones, quinolinones, and fused polycyclic compounds. The reaction of *N*-xanthylamides **146** in CH_2Cl_2 under the irradiation of 24 W 400 nm LEDs at room temperature gave products **147** or **148** in good to excellent yields (Scheme 35) [61]. It was worth mentioning that the xanthate-transfer reaction proceeded without photo-catalyst and additive. A reaction mechanism suggested visible light-induced N−S bond homolysis of substrates **146** gives xanthate radical **149** and amidyl radicals **150**. The 5-*exo* or 6-*endo* cyclization of **150** gives radicals **151** and **152**, respectively. Finally, the coupling of **151** or **152** with xanthates **146** affords products **147** or **148**.

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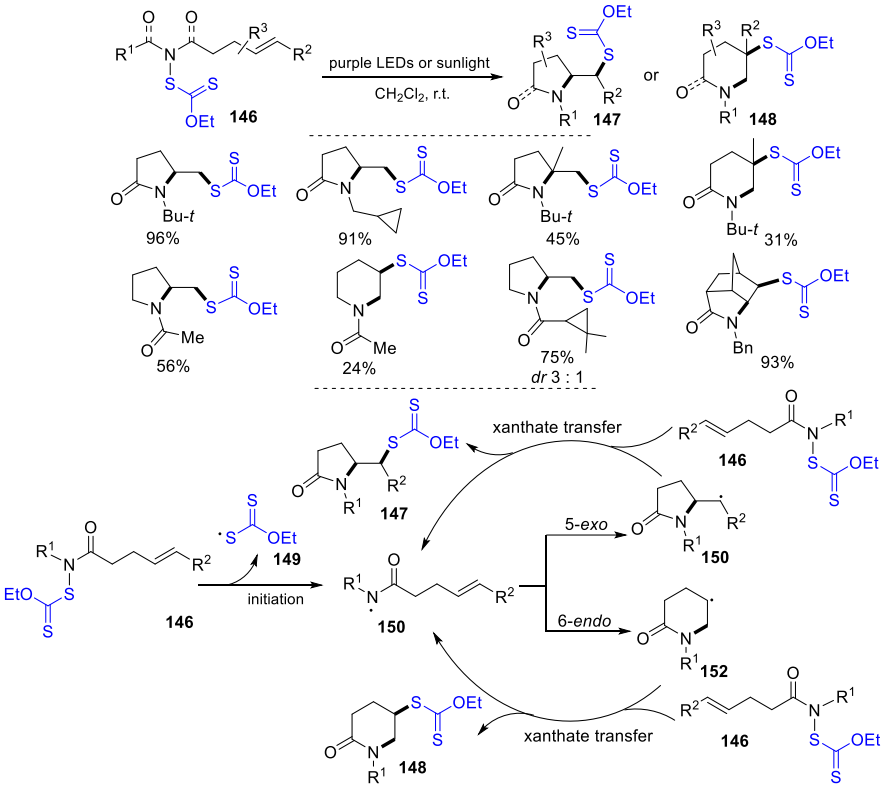
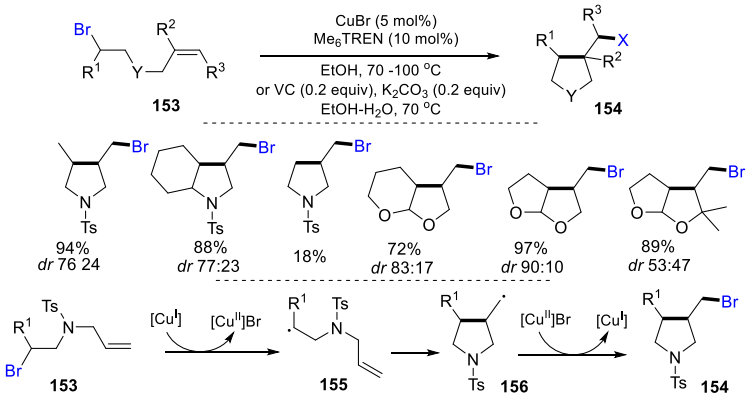


Scheme 35. Synthesis of nitrogen-heterocycles.

Yu and coworkers developed a Cu-catalyzed radical reaction of unactivated alkyl bromides for the synthesis of five-membered heterocyclic rings in 2023. The reaction of unactivated alkyl bromides **153** in the presence of CuBr and Me$_6$TREN gave products **154** in good to excellent yields (Scheme 36) [62]. It was suggested that radicals **155** produced from the reaction of alkyl bromides **153** and [Cu^{I}] undergo a 5-*exo* cyclization to give radicals **156** then lead to the formation of products **154** after coupling with [Cu^{II}]Br.



Scheme 36. Synthesis of heterocycles.

3. Second Functionalization with Y *via* Radical Coupling

Presented in this section are the reactions in which the second functionalization is accomplished by coupling with radical Y (Scheme 37). Different from the ATRC in which the X radical is from the same substrate for cyclization, the Y radical is generated from a different substrate. As shown in Scheme 37, radicals I-B generated from the homolytic cleavage of X–C bond undergoes cyclization to form radicals II-B followed by coupling with radical Y generated from a different reactant to give the

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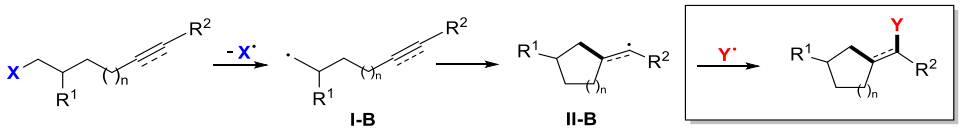
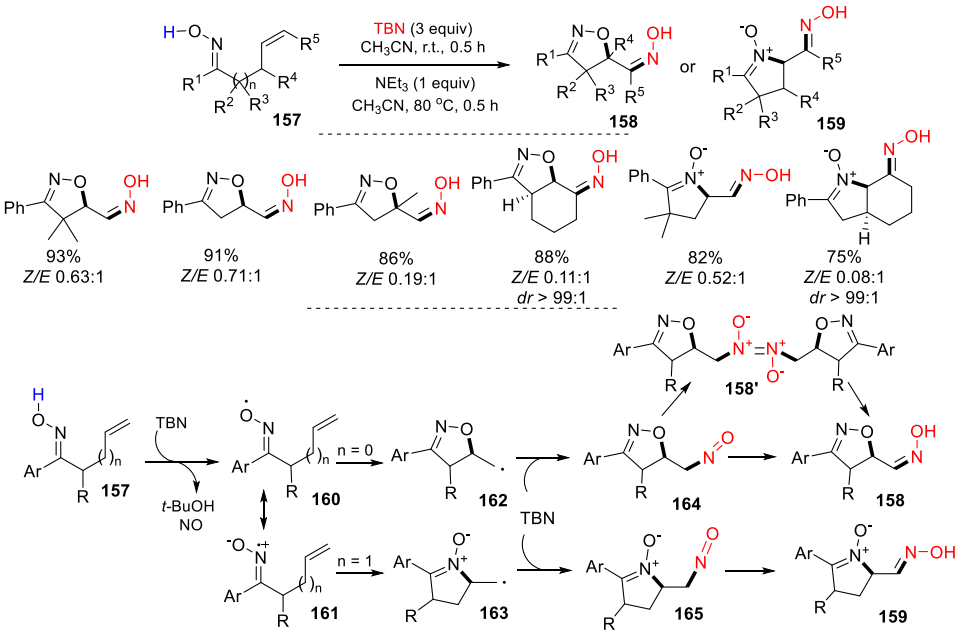
products. The reactions presented in this section are classified based on the substrates including alkenyl oximes, amino-substituted alkenes, alkynes, and allenes, halo-substituted alkenes, alkynes and allenes and other alkenes and allenes were used as substrates. There is a wide range of Y radicals could be used for the second functionalization. The Y groups presented in this section include halogen atoms and NO, CF_3, Bpin, 2-azaallyl, lauroyl, alkenyl, N_3, arylthiomethyl, ketyl, and TEMPO-related groups.



Scheme 37. The second functionalization *via* radical coupling.

3.1. Alkenyl Oximes as Substrates

There are several examples of using alkenyl oximes as substrates for the generation of the iminoxyl radicals for cyclization and sequential difunctionalization reactions. Han and coworkers, in 2014, reported a radical cyclization reaction of unsaturated ketoximes for the synthesis of heterocyclic compounds. The reaction of ketoximes 157 in the presence of *tert*-butyl nitrite (TBN) in CH_3CN at room temperature for 0.5 h, followed by the addition of NEt_3 and heating at 80 °C for 0.5 h to give oxime featured 4,5-dihydroisoxazoles 158 or cyclic nitrones 159 in good to excellent yields (Scheme 38) [63]. In this reaction, TBN is used as the iminoxyl radical initiator and the carbon radical trap. Initially, the reaction of ketoximes 157 with TBN generates unsaturated iminoxyl radicals (*O*-atom radical 160 and *N*-atom radical 161) which undergo 5-*exo* cyclization to form radicals 162 (n = 0) and 163 (n = 1), respectively. Radical trapping of 162 or 163 with TBN affords intermediates 164 or 165 which could be further converted to products 158 or 159. The dimerized 158′ generated from intermediates 164 was isolated and its structure was confirmed by a single-crystal X-ray diffraction study.



Scheme 38. Synthesis of heterocyclic compounds.

Zhang and coworkers, in 2018, reported a Ru-catalyzed radical reaction of alkenyl oximes for the synthesis of 5-cyanated isoxazolines. The reaction of alkenyl oximes **166** and TBN catalyzed with $RuCl_2$(*p*-cymene)]$_2$ and $MgSO_4$ in CH_3CN at room temperature for 4 h gave 5-cyanated isoxazolines

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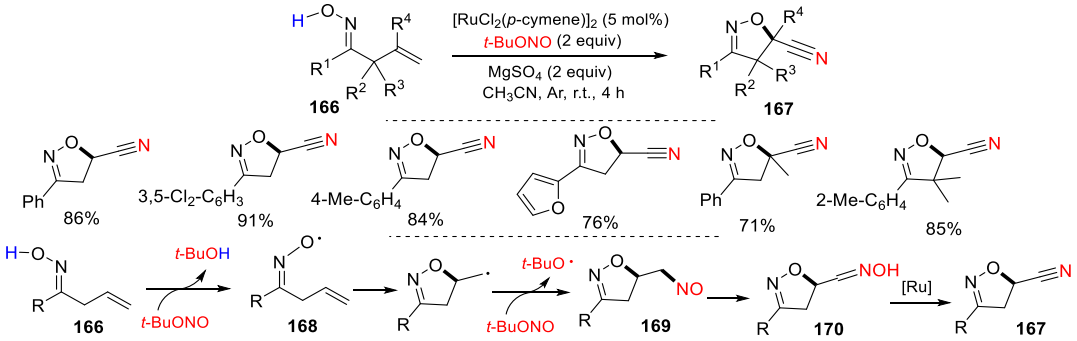
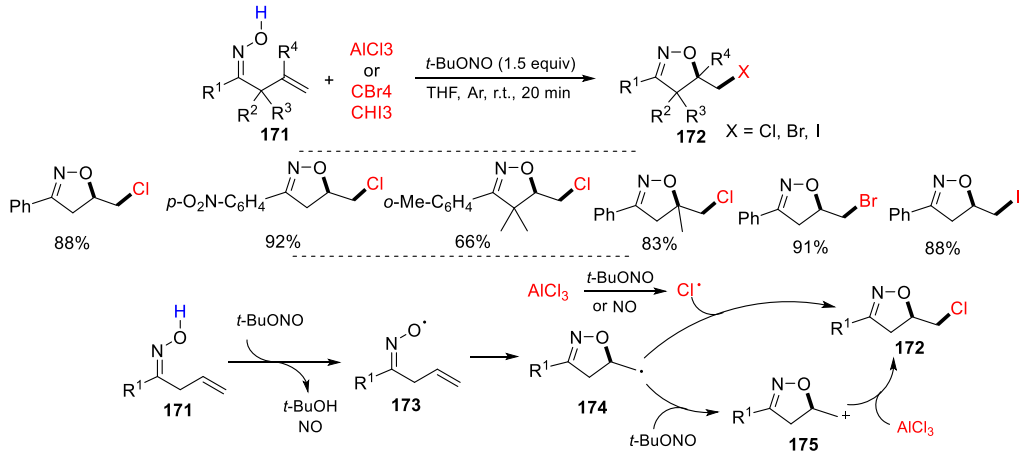
167 in good to high yields (Scheme 39) [64]. In the reaction process, TBN acts as an oxidant and a nitrogen source to avoid the use of toxic radical initiators or cyanide reagents. The initial oxime radicals **168** produced *via* oxidization of alkenyl oximes **166** with TBN undergo 5-*exo* cyclization followed by the coupling with *t*-BuO radical to give intermediates **169** which could be tautomerized to form intermediates **170**. Ru-Catalyzed reduction of **170** gives final products **167**.



Scheme 39. Synthesis of 5-cyanated isoxazolines.

In 2016, Kang and coworkers introduced a similar radical reaction of alkenyl oximes for the synthesis of halo-isoxazolines. The reaction of alkenyl oximes **171** with TBN as a dual oxidant and $AlCl_3$, CBr_4 or CHI_3 as a chlorine source in THF/H_2O for 20 min gave halo-isoxazolines **172** in moderate to good yields (Scheme 40) [65]. In this reaction, the oximes **171** were oxidized by TBN to yield the iminoxyl radicals **173** with the generation of NO and *tert*-butanol, followed by 5-*exo* cyclization to give the radical intermediates **174**. Simultaneously, TBN oxidizes the Cl-anion to the chlorine radical. Next, the final products **172** were obtained from radicals **174** by combining with the chlorine radical. Otherwise, the cations **175** were formed by oxidization of TBN, followed by reaction with Cl-anion to access the products **172**.



Scheme 40. Synthesis of halo-isoxazolines.

In 2017, Hu and coworkers developed Cu-catalyzed radical reaction of allylic oximes for the synthesis of trifluoromethylated isoxazolines. The reaction of allylic oximes **176** and $TMSCF_3$ in the presence of trichloroisocyanuric acid (TCCA), CuOAc, 1,10-phenanthroline and CsF in CH_3CN at room temperature for 1–10 h to afford products **177** in good to excellent yields (Scheme 41) [66]. In the reaction process, radicals **178** generated from TCCA abstract H atom from allylic oximes **176** to form radicals **179** which undergo 5-*exo* cyclization to give radical **180**. The trapping of CF_3 radical derived from $TMSCF_3$ with **180** generate trifluoromethylated isoxazolines **177**.

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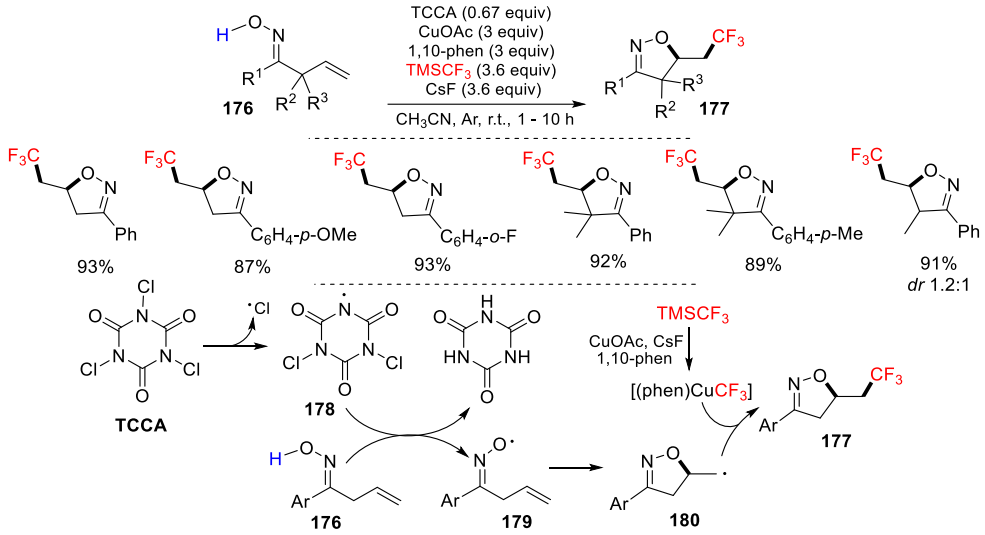
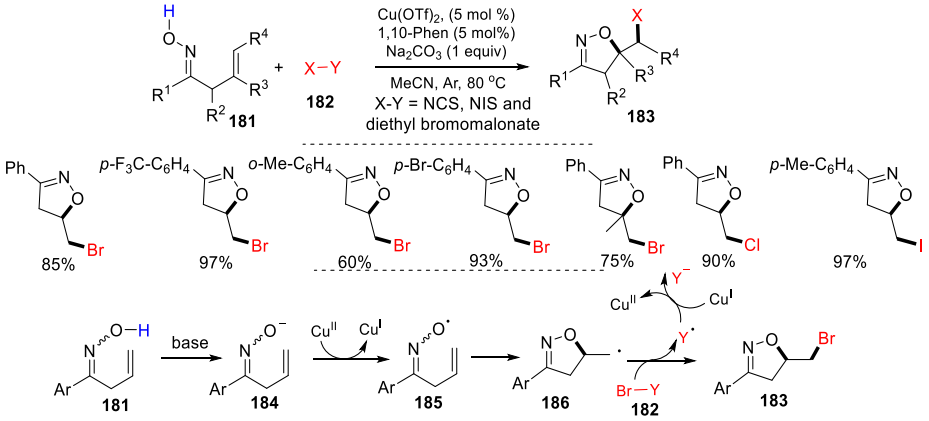


Scheme 41. Synthesis of trifluoromethylated isoxazolines.

In 2019, Xu & Li and coworkers reported a Cu-catalyzed radical reaction of unsaturated ketoximes for the synthesis of 5-halomethyl isoxazolines. The reaction of ketoximes **181** and halo reagents **182** (such as diethyl bromomalonate, *N*-chlorosuccinimide, and *N*-iodosuccinimide) in the presence of $Cu(OTf)_2$, 1,10-phenanthroline (1,10-Phen) and Na_2CO_3 in CH_3CN at 80 °C for 0.5 h to produce 5-halomethyl isoxazolines **183** in good to excellent yields (Scheme 42) [67]. The iminoxyl anions **184** formed by the deprotonation of ketoximes **181** with a base undergo SET with Cu^{II} to generate iminoxyl radicals **185**. Then radical cyclization of **185** to form **186** followed by halogen atom transfer with Br–Y **182** to generate desired products **183**.



Scheme 42. Synthesis of isoxazoline derivatives.

3.2. Amino-Substituted Alkenes, Alkynes, and Allenes as Substrates

Amino-substituted alkenes, alkynes, and allenes could be used as the substrates to generate N-radicals for cyclative difunctionalization reactions. In 2013, Chemler and coworkers introduced a Cu-catalyzed enantioselective radical reaction of alkenyl sulfonamides for the synthesis of chiral indolines and pyrrolidines. The aminooxygenation reaction of alkenyl sulfonamides **187** with the use of TEMPO as the oxygen source and under the catalysis of $Cu(OTf)_2$ and (*R*,*R*)-Ph-Box in $PhCF_3$ gave desired products **188** in good to excellent yields and high enantioselectivity (Scheme 43) [68]. The reaction kinetics showed a first-order dependence in the sulfonamide substrate and the Cu–bis(oxazoline) complex and zero order in TEMPO. In the reaction process, (*R*,*R*)-Ph-Box)-/$Cu(OTf)_2$ complex **189** reacts with **187** to produce N–Cu^{II} intermediates **190** which then leads to the formation of **191**. Homolysis of **191** to give **192** followed by trapping with TEMPO affords products

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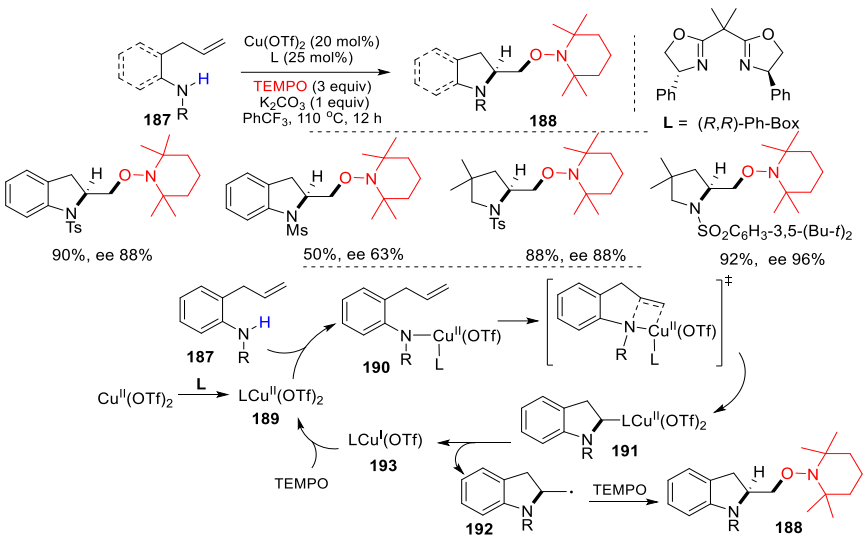
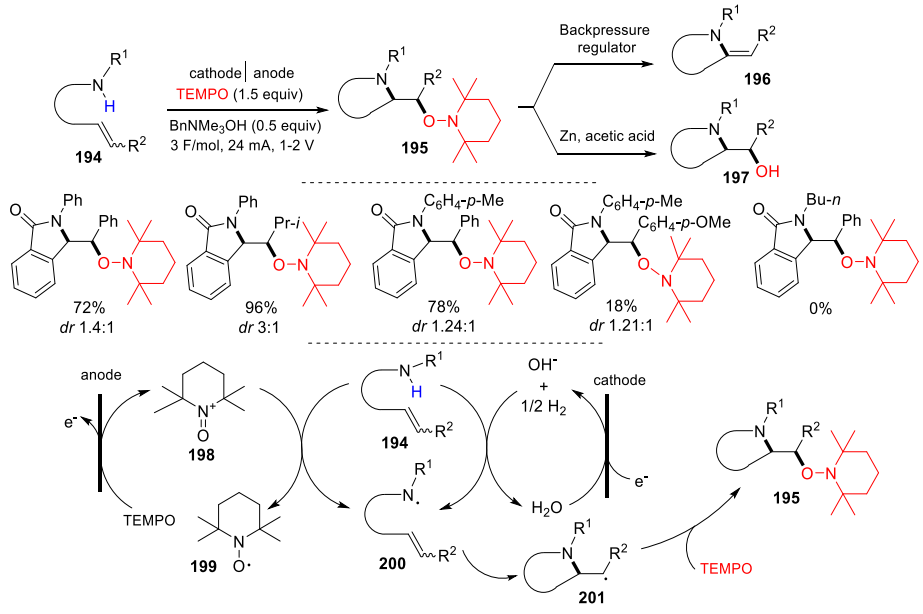
188. The reactive Cu^{II} species **189** is regenerated by oxidization of the Cu^{I} species **193** with TEMPO to complete the catalytic cycle.



Scheme 43. Synthesis of TEMPO-functionalized chiral indolines and pyrrolidines.

Wirth and coworker reported an electrochemical flow reaction of carbamates for the synthesis of isoindolinone derivatives in 2017. The reaction of carbamates **194** and TEMPO using benzyltrimethylammonium hydroxide ($[BnNMe_3]^+OH^-$) as the supporting electrolyte in an electrochemical flow micro-reactor under the optimized reaction conditions (3 F mol^{-1}, 24 mA, 1–2 V) to give products **195** in good yields (Scheme 44) [69]. The isoindolinone products **195** could be used for following two subsequent functionalization: 1) elimination of the TEMPO moiety with Backpressure regulator to yield alkenes **196**, and 2) reduction of the N–O bond with Zn and acetic acid to yield corresponding alcohols **197**. In this reaction process, the TEMPO cation **198** reacts with carbamates **194** generates TEMPO radical **199** and nitrogen radicals **200**. Cyclization of radicals **200** to form **201** followed by a radical trapping with TEMPO gives products **195**.



Scheme 44. Synthesis of TEMPO-functionalized isoindolinone derivatives.

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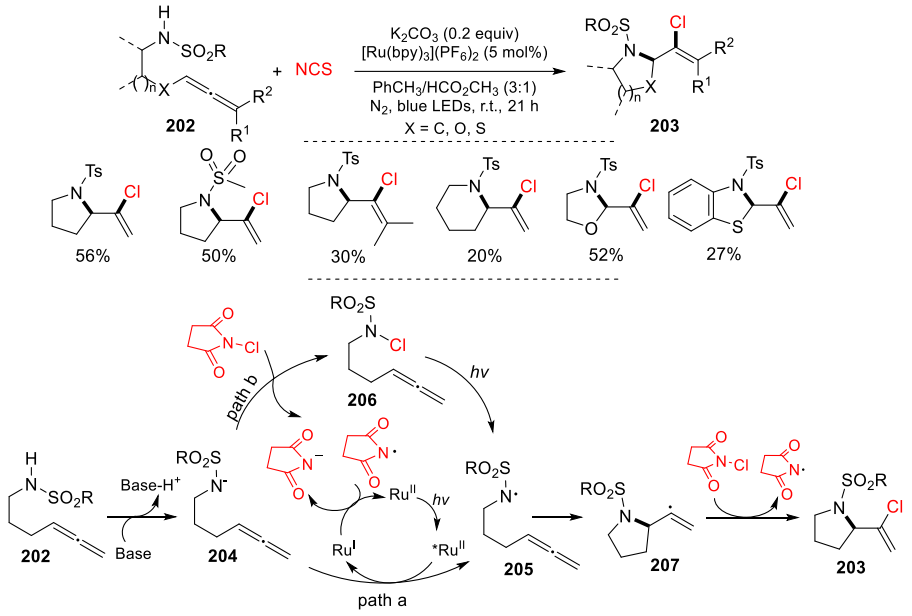
In 2023, Renzi and coworkers reported a photo-induced radical reaction of *N*-(allenyl)sulfonylamides for the synthesis of 2-(1-chlorovinyl)pyrrolidines. The blue LEDs irradiated reactions of *N*-(allenyl)sulfonylamides **202**, *N*-chlorosuccinimide (NCS) and K_2CO_3 under the catalysis of $[Ru(bpy)_3](PF_6)_2$ using anhydrous $PhCH_3$ and HCO_2CH_3 as a co-solvent for 21 h gave products 2-(1-chlorovinyl)pyrrolidines **203** in good yields (Scheme 45) [70]. After the initial deprotonation of allenes **202** with a base to form **204**, there are two different pathways for the formation of radicals N-centered radicals **205**. In the path a, radicals **205** are generated from the oxidation of **204** with photoexcited state of the Ru-catalyst. In the path b, reaction of **204** with NCS to form **206** followed by the photodissociation of Cl to give **205**. The 5-*exo* radical cyclization of radical **205** affords vinyl radical **207** followed by radical trapping to give final 2-(1-chlorovinyl)pyrrolidines **203**.



Scheme 45. Synthesis of 2-(1-chlorovinyl)pyrrolidines.

3.3. Halo-Substituted Alkenes, Alkynes and Allenes as Substrates

Halogenated alkenes, alkynes and allenes as substrates are good substrates to generate carbon radicals for cyclative difunctionalization reactions. Liang and coworkers, in 2020, introduced a visible-light-induced radical reaction of alkyl bromides or alkyl iodine for the synthesis of heterocyclic compounds. The reaction of alkyl bromides or iodines **208** and KI with $Pd(PPh_3)_4$ as a photo-catalyst and potassium carbonate as a base under the irradiation of blue LEDs to give heterocyclic compounds **209** in moderate yields (Scheme 46) [71]. Under the conditions of using $Pd(PhCN)_2Cl_2$ as a catalyst and potassium carbonate as a base, the reaction with diboron reagents gave borylated products **210** in moderate yields. In the reaction process for products **209**, the $[Pd^0]^*$-promoted the homolytic cleavage of the aryl C−Br bond of **208** yields radicals **211** which undergo 5-*exo* cyclization to form radicals **212** followed by iodiozation with $[Pd^I]I$ to give products **209**. For the borylation reaction, recombination of radicals **212** with $[Pd^I]Br$ gives Pd-complexes **213** which undergo transmetalation with bis(pinacolato)diboron to form Pd-complexes **214**. Finally, the reductive elimination of Pd-cat of **214** affords borylated products **210**.

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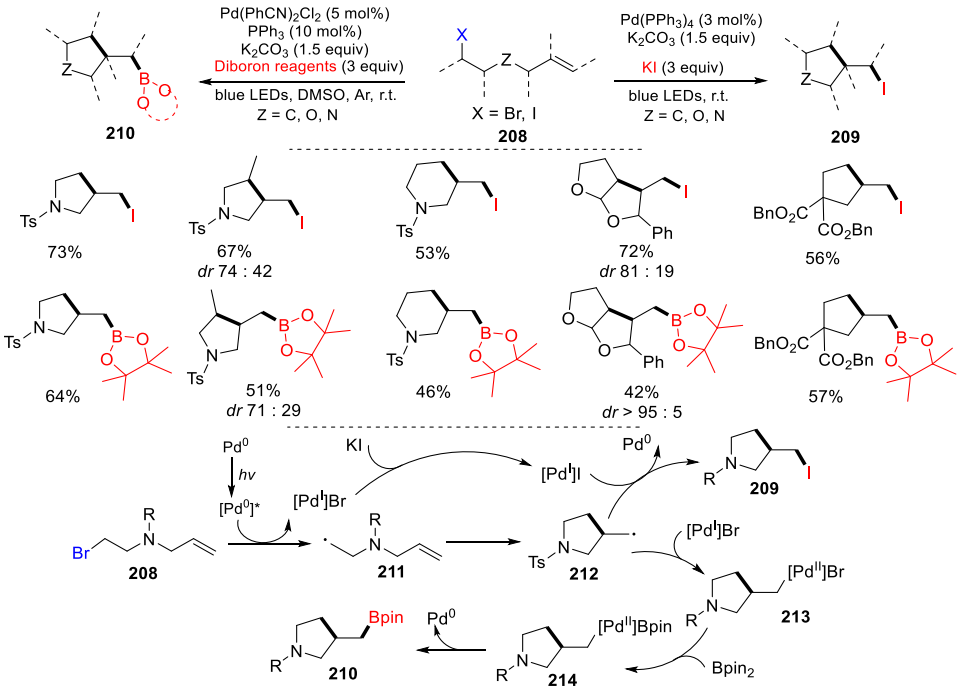
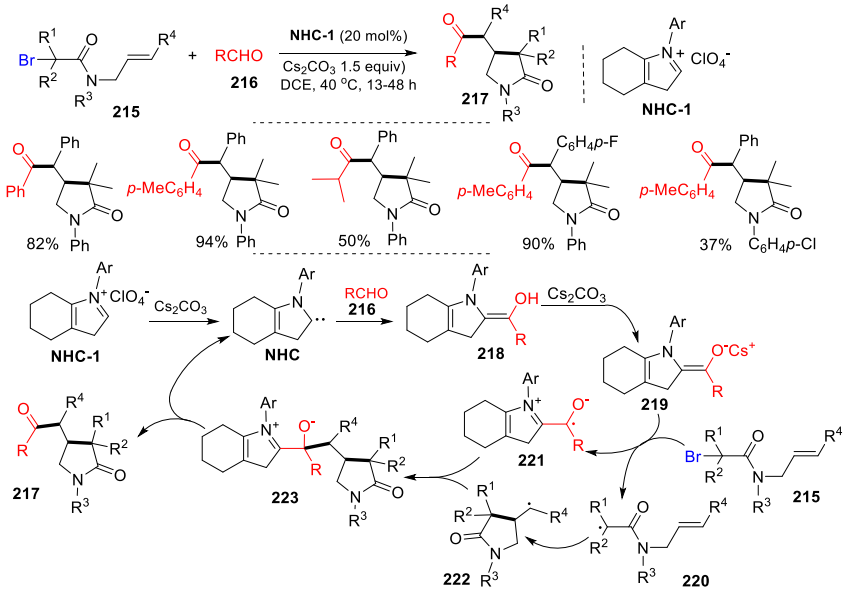


Scheme 46. Synthesis of heterocyclic compounds.

In 2023, Yao and coworkers reported an N-heterocyclic carbene (NHC)-catalyzed radical reaction of *α*-bromo-*N*-cinnamylamides for the synthesis of 2-pyrrolidinone derivatives. The reaction of *α*-bromo-*N*-cinnamylamides **215** and aldehydes **216** in the presence of **NHC** precursor **NHC-1** and Cs_2CO_3 in DCE at 40 °C for 13–48 h yielded 2-pyrrolidinone derivatives **217** in good to excellent yields (Scheme 47) [72]. The **NHC** catalyst generated by the reaction of catalyst precursor **NHC-1** with Cs_2CO_3 couples with aldehyde **216** to form intermediates **218** which are then deprotonated with Cs_2CO_3 to give enolate intermediates **219**. A process of SET of *α*-bromo-*N*-cinnamylamides **215** with **219** produces the radical zwitterionic intermediates **220** and radical intermediates **221**. The 5-*exo* cyclization of the radicals **220** gives **222** followed by radical coupling with the radicals **221** to provide **223** and the last step of **NHC** catalyst elimination to give products **217**.



Scheme 47. Synthesis of 2-pyrrolidinone derivatives.

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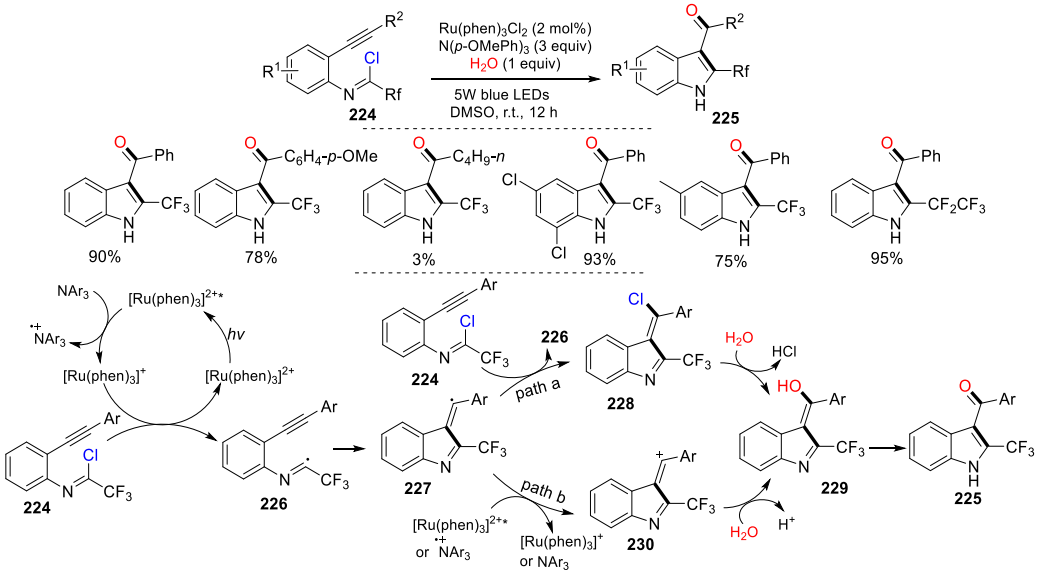
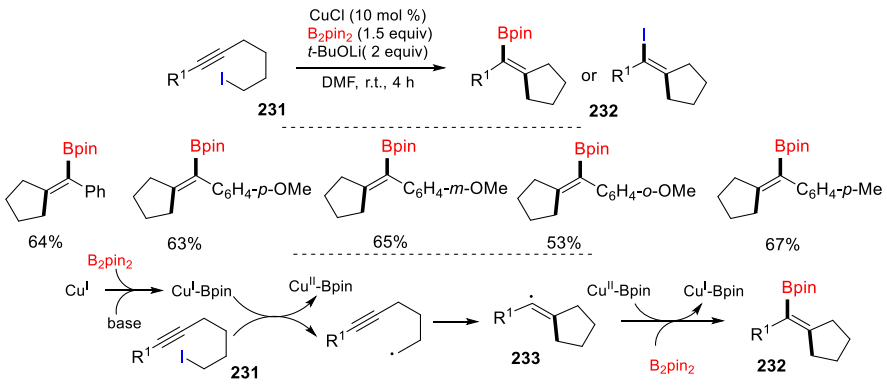
Zhou and coworkers, in 2015, reported a visible-light induced radical reaction of trifluoroacetimidoyl chlorides for the synthesis of 2-trifluoromethyl-3-acylindoles. The reaction of trifluoroacetimidoyl chlorides **224** in the presence of $Ru(phen)_3Cl_2$, (*p*-OMe-Ph)$_3$N (Ar_3N), and H_2O in DMSO under the irradiation of 5 W blue LEDs at room temperature gave products **225** in good to excellent yields (Scheme 48) [73]. The reaction mechanism suggested that imidoyl radicals **226** produced by the C–Cl bond cleavage of trifluoroacetimidoyl chlorides **224** undergo a 5-*exo* cyclization to form vinyl radicals **227** which then go through two different pathways to generate 2-CF_3 indoles **225**. For the favorable pathway (path a), the reaction of vinyl radicals **227** and trifluoroacetimidoyl chlorides **224** afford vinyl chlorides **228** followed by hydrolysis to give enols **229** and then isomerization to give **225**. While in the less favorable pathway (path b), vinyl cations **230** are formed by the oxidation of radicals **227** with excited $[Ru(phen)_3]^{2+*}$ or Ar_3N radical cation followed by trapping with H_2O to yield enols **229** and then products **225** after isomerization.



Scheme 48. Synthesis of 2-trifluoromethyl-3-acylindoles.

In 2018, Zhao and coworkers introduced a Cu-catalyzed radical reaction of acetylenic iodides for the synthesis of functionalized exocyclic alkenes. The reaction of acetylenic iodides **231** and B_2pin_2 in the presence of CuCl and *t*-BuOLi in DMF at room temperature for 4 h gave products **232** were obtained in good yields (Scheme 49) [74]. The reaction mechanism suggested that the reaction of acetylenic halides **231** with Cu^I–Bpin followed by a 5-*exo* cyclization afford intermediates **233** which then react with the Cu^{II} species to give borylated products **232**.



Scheme 49. Synthesis of exocyclic alkenes.

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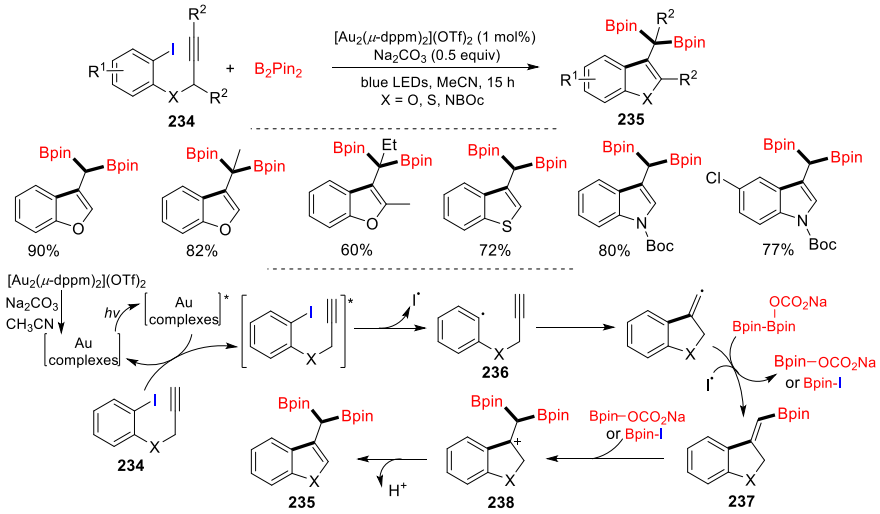
A visible-light-induced radical reacation of aryl iodides for the synthesis of benzofuran-, indole-, and benzothiophene-based benzylic *gem*-diboronates was reported by the Hashmi group in 2020. The reaction of aryl iodides **234** and B_2Pin_2 under the irradiation of blue LEDs in the presence of $[Au_2(\mu\text{-dppm})_2](OTf)_2$ and Na_2CO_3 in MeCN for 15 h afforded products **235** in good to excellent yields (Scheme 50) [75]. The photoactivated Au-complex promotes the homolytic cleavage of the C–I bond of aryl iodide **234** to give aryl radicals **236** which undergo 5-*exo* cyclization followed by radical trapping to give viny boronates **237**. Formation of benzyl cations **238** by electrophilic borylation of boronates **237** with Bpin–I or Bpin–OCO_2Na followed by rapid *β*-H elimination afford to the formation of products **235**.



Scheme 50. Synthesis of *gem*-diboronated heterocyclic compounds.

The Guo group reported a visible-light-induced radical reaction of alkyne-containing aryl iodides for the synthesis of 1,4-dicarbonyl compounds. The reaction of alkyne-containing aryl iodides **239**, TEMPO and 4-methoxythioxanthone under the irradiation of purple LEDs using acetone/DCM as solvent gave products **240** in good to excellent yields (Scheme 51) [76]. Under the irradiation of purple LEDs, the photosensitizer 4-methoxythioxanthone converts substrates **239** to triplet state **239*** to form aryl radicals for 5-*exo* cyclization followed by trapping with TEMPO to afford intermediates **241**. The photo-excited triplet state intermediates **241*** undergo a single-electron reduction and coupling with I^- to give intermediates **242** followed by removing of iodine radical and biradical coupling to provide 1,4-dicarbonyl compounds **240**.

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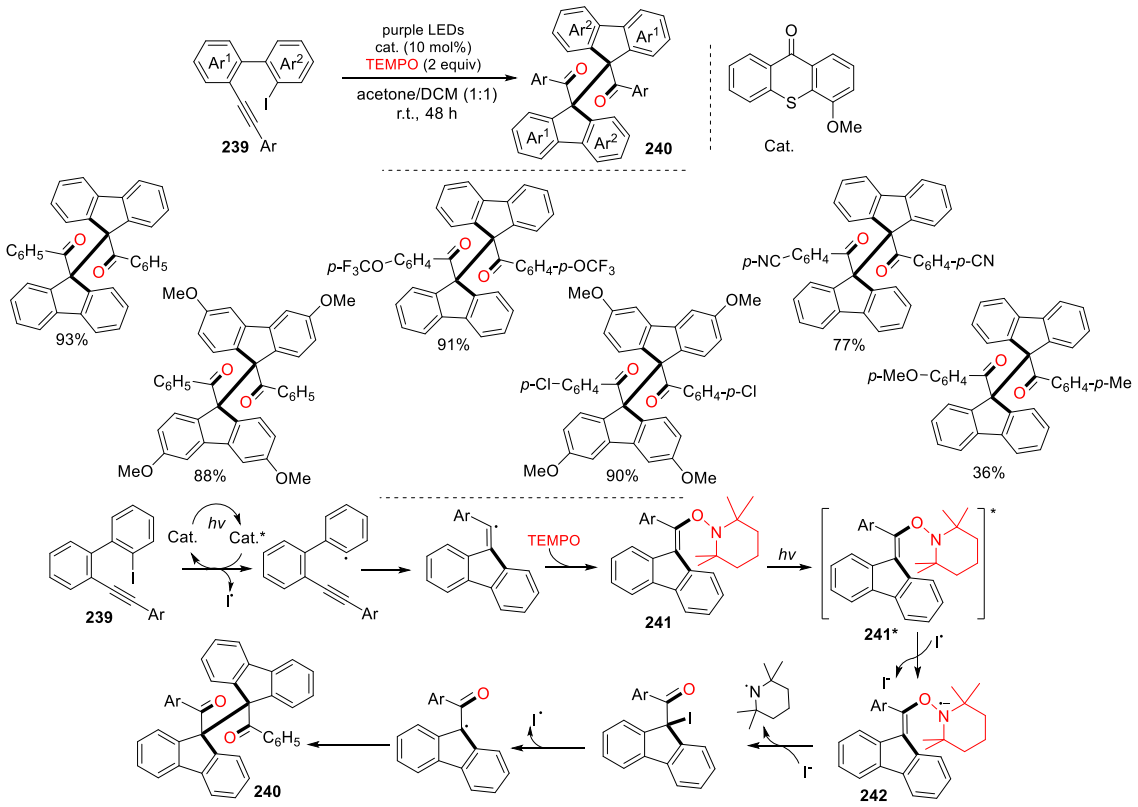
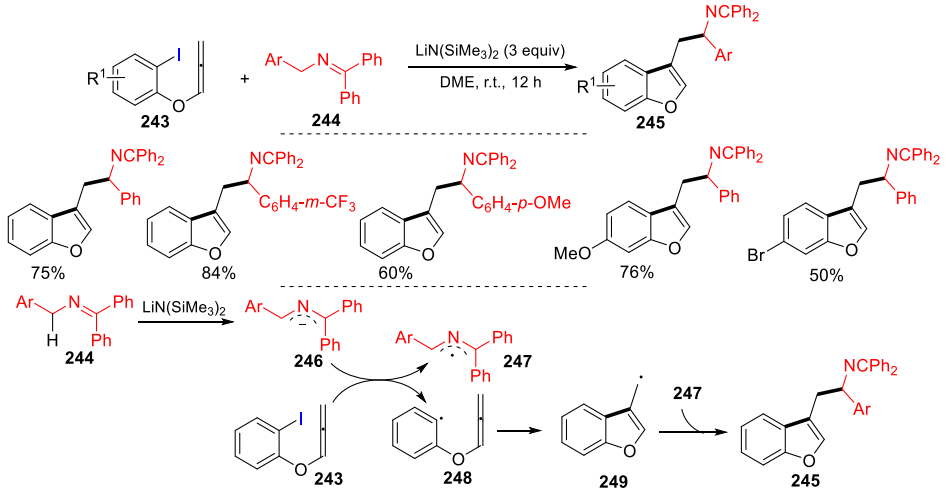


Scheme 51. Synthesis of 1,4-dicarbonyl compounds.

A radical reaction of 2-iodoaryl-allenyl ethers for the synthesis of benzofuran derivatives was reported by the Walsh group in 2019. The reaction of 2-iodoaryl-allenyl ethers **243** and ketimines **244** in the presence of $LiN(SiMe_3)_2$ in DME for 12 h to give products **245** in good to excellent yields (Scheme 52) [77]. In the reaction process, 2-Azaallyl anions **246** generated from ketimines **244** serves as "super electron donor" (SED). The SET of **246** to aryl iodides **243** generates aryl radicals **248** which undergo 5-*exo* cyclization to form 2-azaallyl radicals **249** followed by trapping with radicals **247** to afford products **245**. The same group extended the scope of this reaction using 2-iodobenzyl allenyl ethers **250** as substrates for the synthesis of substituted isochromenes **251** (Scheme 53) [78].



Scheme 52. Synthesis of substituted benzofurans.

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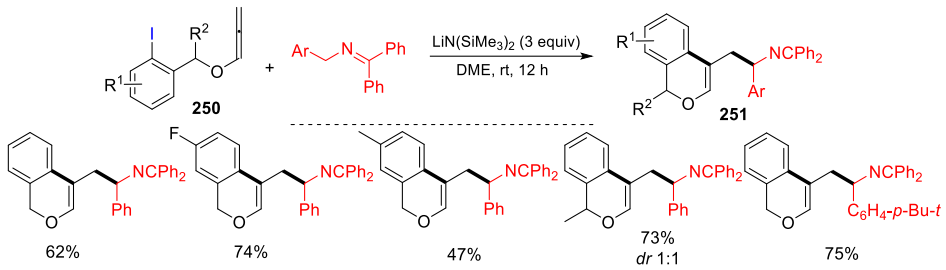
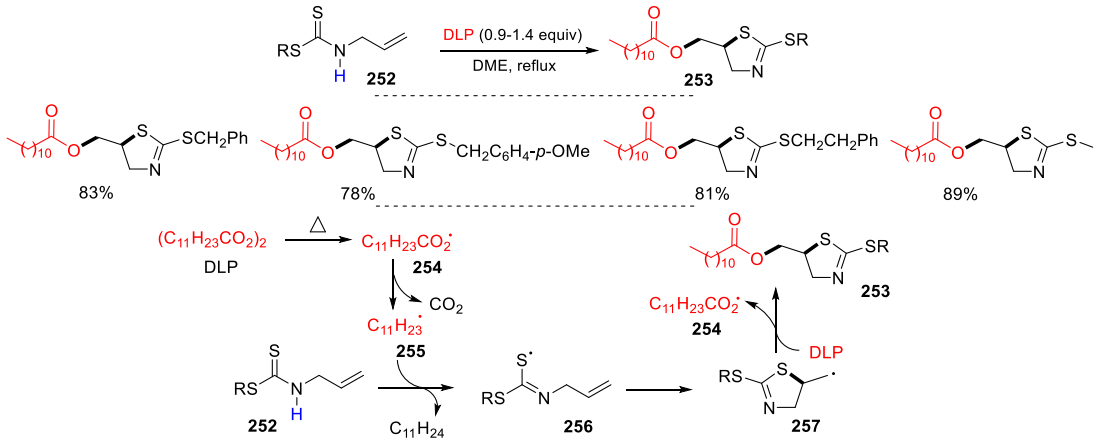


Scheme 53. Synthesis of substituted isochromenes.

3.4. Other Functionalized Alkenes and Allenes as Substrates

Other than the substrates presented above, compounds used for the formation of initial radicals could be used as the source for the second functionalization. Xu and Kakaei in 2013 reported a radical reaction of alkyl *N*-allylcarbamodithioates for the synthesis of (2-alkylthiothiazolin-5-yl)methyl dodecanoates. The reaction of alkyl *N*-allylcarbamodithioates **252** and dilauroyl peroxide (DLP) in refluxing DME for 4–7 h gave products **253** in good yields (Scheme 54) [79]. The heating of DLP gives lauroyl radical **254** followed by decarboxylation to form **255** undecyl radical **255**. H-abstraction of **255** from *N*-allylcarbamodithioates **252** generates thiyl radicals **256** which undergo 5-*exo* cyclization to yield (2-alkylthiothiazolin-5-yl)-methyl radicals **257**. Final products (2-alkylthiothiazolin-5-yl)methyl dodecanoates **253** are obtained from the reaction of radicals **257** with DLP along with regeneration of the lauroyl radical **254**.



Scheme 54. Synthesis of (2-alkylthiothiazolin-5-yl)methyl dodecanoates.

In 2020, Riant and coworkers reported a radical electrocyclization of potassium 3-(diallylamino)-3-oxopropanoate for the synthesis of 4-substituted pyrrolidin-2-ones. In Teflon half-cells equipped with platinum plated electrodes, the reaction of potassium 3-(diallylamino)-3-oxopropanoates **258** in the presence of KOH and RCOOH with MeOH as solvent gave 4-substituted pyrrolidin-2-ones **259** in good yields (Scheme 55a) [80]. The application of this method for continuous flow electrochemical reaction in a loop-reactor setup (equipped with a 5 mL container) allowed for an excellent productivity of 0.40 g/(h·mL) and afforded 2-pyrrolidinone **259a** in 81% yield (Scheme 55b) [81]. The product could be used for the synthesis of Brivaracetam in 23% yield. For the synthesis of **259**, radicals **260** generated *via* Kolbe decarboxylation of **258** undergo 5-*exo* cyclization followed by a coupling of Et radical with **261** to give the final products.

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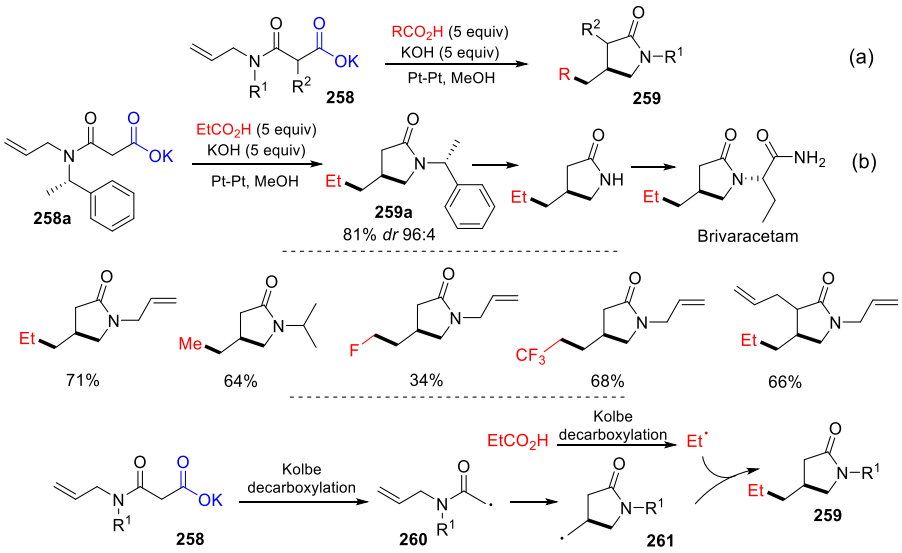
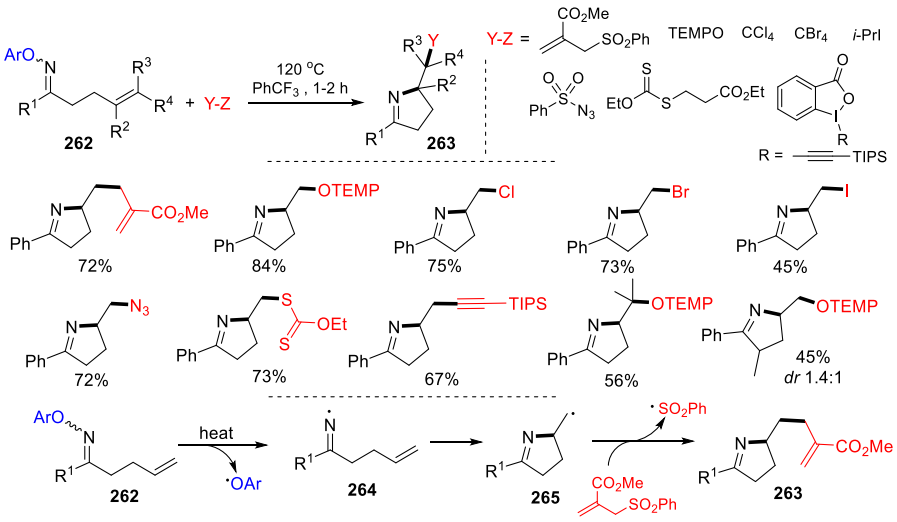


Scheme 55. Synthesis of 4-substituted pyrrolidin-2-ones.

In 2022, Castle and coworkers developed a protocol of thermal and microwave-promoted radical cyclization of *O*-aryloximes for the synthesis of functionalized pyrrolines. The reaction was carried out using *O*-aryloximes **262** and the radical traps Y−Z in $PhCF_3$ at 120 °C for 1–2 h, and the products functionalized pyrrolines **263** were obtained in good yields (Scheme 56) [82]. The reactions could be triggered by either microwave irradiation or conventional heating in an oil bath. Initially, the iminyl radicals **264** are generated by direct homolysis of the weak N−O bond of *O*-aryloximes **262**, which could be promoted by either microwave irradiation or conventional heating. Subsequently, radicals **265** are formed by a 5-*exo* radical cyclization of radicals **264**, followed by radical trapping to give the final functionalized pyrrolines **263**.



Scheme 56. Radical spirocyclization for preparation of spirocycle.

In 2022, Chemler and coworkers reported a Cu-catalyzed radical reaction of alkenols for the synthesis of arylthiomethyl-substituted cyclic ethers. The reaction of alkenols **266** and diarly disulfides in the presence of $Cu(OTf)_2$, (*S*,*S*)-*t*-Bu-Box, MnO_2 and K_2CO_3 in $PhCF_3$ at 120 °C for 14 h afforded arylthiomethyl substituted cyclic ethers **267** in moderate to good yields and high enantioselectivity (Scheme 57) [83]. The reaction mechanism suggested the enantioselective route (path a) is lower in energy than the competing racemic route (path b). First, C−O bond formation *via* enantioselective oxycupration of **266** affords intermediate **268** followed by C−[Cu] homolysis to give

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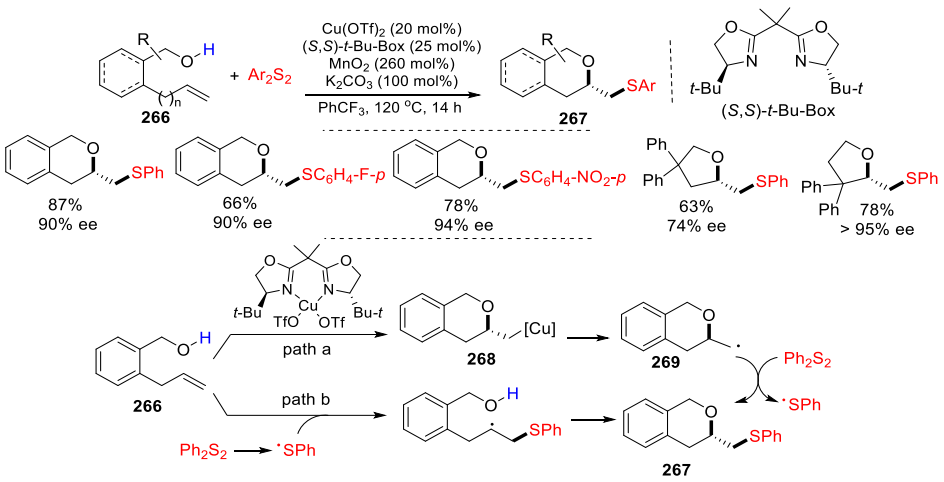
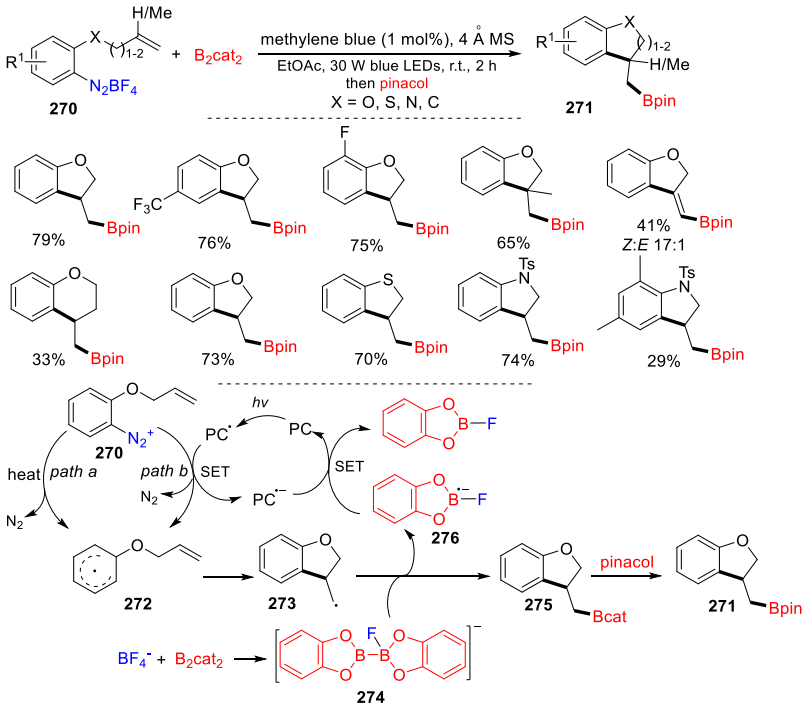
radical intermediate **269**. The formation of C–S bond *via* coupling of **269** with PhS radical gives oxysulfenylated product **267**.



Scheme 57. Asymmetric synthesis of arylthiomethylated cyclic ethers.

A photo-promoted radical cyclization of alkenes for the synthesis of benzocyclic boronates was reported by the Li group in 2023. The reaction of allyl aryldiazonium salts **270** and bis(catecholato)diboron (B_2cat_2) using methylene blue as catalyst under the irradiation of 30 W blue LEDs in dimethylacetamide (DMA) for 2 h at room temperature followed by the treatment with pinacol to give benzocyclic boronates **271** in good yields (Scheme 58) [84]. The reaction mechanism suggested that an aryl radical **272** is produced from the diazonium salt **270** either by heated (path a) or through SET by an excited photocatalyst (path b). The 5-*exo* cyclization of **272** forms benzocyclic alkyl radical **273** followed by the boron-transfer with **274** to give the borylated product **275** and the radical anion **276**. Alcohol exchange between **275** and pinacol gives final product **271**.



Scheme 58. Synthesis of benzocyclic boronates.

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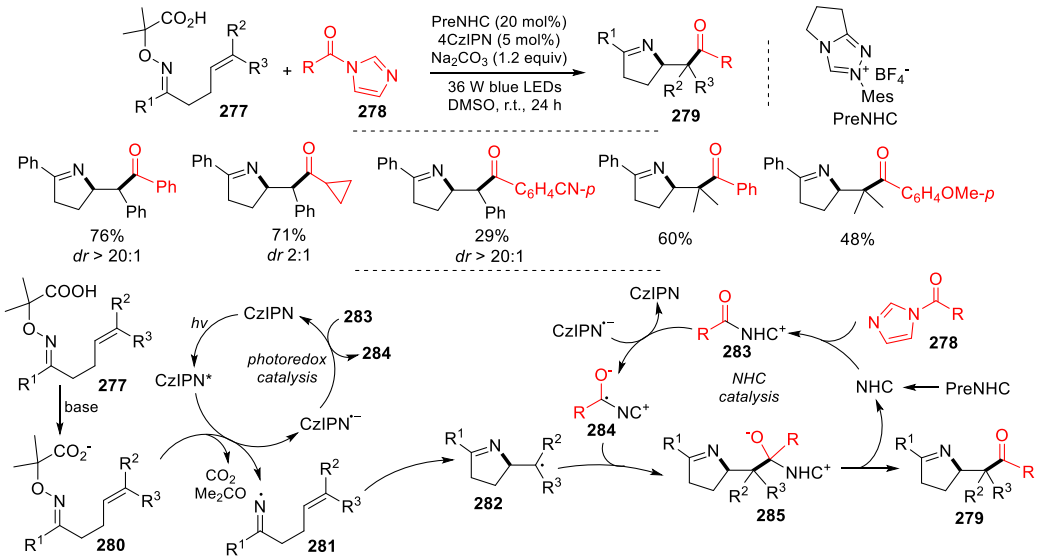
In 2023, Ye and coworkers developed a protocol of photoredox N-heterocyclic carbene catalyzed radical cyclization of alkene-tethered *α*-imino-oxy acids for the synthesis of substituted 3,4-dihydro-2*H*-pyrroles. The reaction was carried out using alkene-tethered *α*-imino-oxy acids **277** and acyl imidazoles **278** with *N*-Mes-substituted triazolium (preNHC, Mes = 2,4,6-trimethylphenyl) as the catalyst and 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as photocatalyst in the presence of Na_2CO_3 in DMSO under irradiation of blue LEDs at room temperature for 24 h, and the products substituted 3,4-dihydro-2*H*-pyrroles **279** were obtained in moderate to good yields and with good to high diastereoselectivities (Scheme 59) [85]. Initially, the iminyl radical intermediates **281** were generated *via* oxidization of the carboxylate anions **280** of *α*-imino-oxy acids **277** with the excited photosensitizer 4CzIPN*, followed by 5-*exo* cyclization to give the dihydropyrrole-derived C-radicals **282**. In the meantime, the acyl azoliums **283** were formed *via* addition of acyl imidazoles **278** with *in situ* generated free NHC, followed by reduction with 4CzIPN$^{\bullet-}$ to give the ketyl radicals **284** and 4CzIPN. Next, the intermediate adducts **285** were provided by radical coupling of the radicals **282** with the radicals **284**, followed by fragmentation to deliver the final iminoacylation products **279** and release the **NHC** catalyst for the catalytic cycle.



Scheme 59. Synthesis of substituted 3,4-dihydro-2*H*-pyrroles.

In 2021, Schomaker and coworkers developed a protocol of photo-promoted radical cyclization of allenes for the synthesis of pyrrolidin-2-one derivatives. The reaction was carried out using allenes **286** and TEMPO in the presence of K_2CO_3 under the irradiation of blue LEDs with MeCN as solvent, and the products pyrrolidin-2-one derivatives **287**, **288** and **289** were obtained in moderate yields (Scheme 60) [86]. Initially, radical **290** was generated from allene **286** under irradiation of visible light, followed by 5-*exo* cyclization to give radical **291**. Then, product **288** was formed *via* radical trapping, followed by H exchange to give the enone **289**. Meanwhile, the O-centered radical **292** was produced by radical hemolysis of **288**, followed by electron transfer to give the C-centered radical **293**. Finally, product **287** was obtained by radical trapping of radical **293**.

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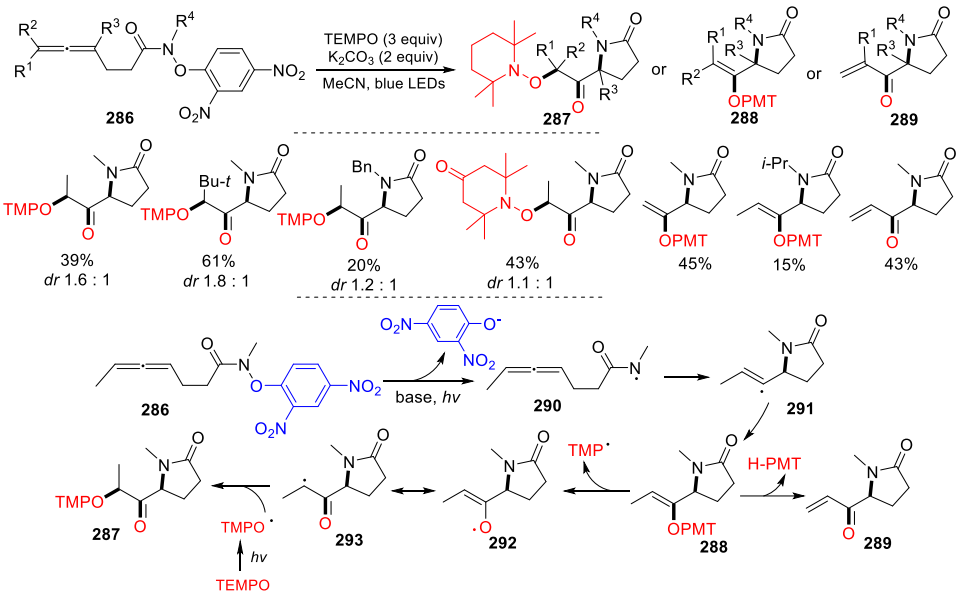
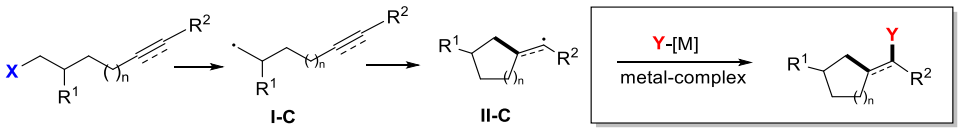


Scheme 60. Synthesis of pyrrolidin-2-one derivatives.

4. Second Functionalization with Metal Complexes

Presented in this section are examples of using metal complexes for the second functionalization (Scheme 61). Other than Cu-complexes, Pd-, Ni-, and Co-complexes have been developed for the coupling reactions.



Scheme 61. Second functionalization with metal complexes.

Chemler and coworker reported a protocol of Cu-catalyzed radical reaction of alkyne tethered Cbz-protected hydroxylamines for the synthesis of functionalized isoxazolidines in 2017. The reaction of alkyne tethered Cbz-protected hydroxylamines **294** and amine sources in the presence of Cu(2-ehtylhexanote)$_2$, 2,6-di-*t*-Bu-4-Me-pyridine, MnO_2 and 4Å M.S. in DCE at 85 °C for 24 h gave isoxazolidines **295** in good yields (Scheme 62) [87]. It should be mentioned that sulfonamides, anilines, piperidine, morpholine and benzamide could be served as the external amines source. A reaction mechanism suggested that the reactions of **294** with Cu^{II} lead to the formation of Cu^{II}-complexes **296** for 5-*exo* cyliczation to form intermediates **297** and then **298** after the homolysis of the C–Cu^{II} bond. The reactions of **298** with Cu^{II} and amine give Cu^{II}-complex **299** which then lead to the formation of isoxazolidines **295** after reductive elimination of the Cu^{I} catalyst.

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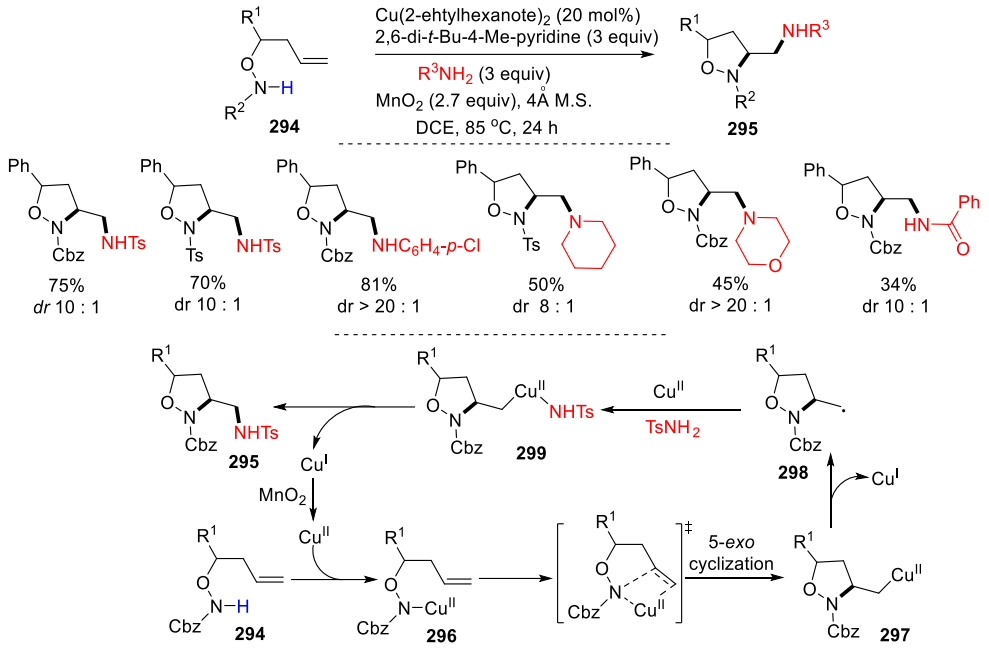
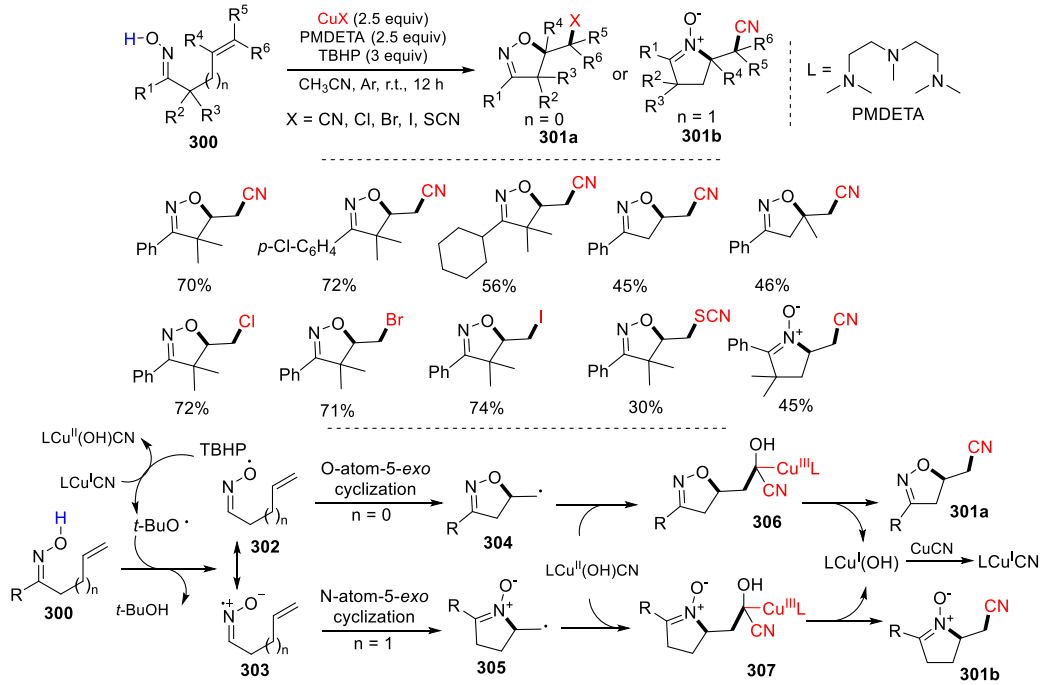


Scheme 62. Radical cyclization for preparation of isoxazolidines.

Han and coworkers, in 2017, reported a radical reaction of unsaturated ketoximes for the synthesis of isoxazolines and cyclic nitrones. The reaction of unsaturated ketoximes **300** in the presence of *tert*-butyl hydroperoxide (TBHP), Cu-X and PMDETA in CH_3CN at room temperature for 12 h gave **301** in good yields (Scheme 63) [88]. In the reaction process, *t*-BuO radical derived from TBHP reacts with oximes **300** to form iminoxyl radicals which have resonance structures **302** and **303**. Radicals **302** or **303** undergo O-radical 5-*exo* cyclization (n=0) or N-radical 5-*exo* cyclization (n=1) to form radicals **304** or **305** which then interact with **L**Cu^{II}(OH)CN to generate Cu^{III} species **306** or **307**. Finally, products **301a** or **301b** are obtained by reductive elimination of Cu^{III} from **306** or **307** and the **L**Cu^{I}CN species is regenerated.



Scheme 63. Synthesis of isoxazolines and cyclic nitrones.

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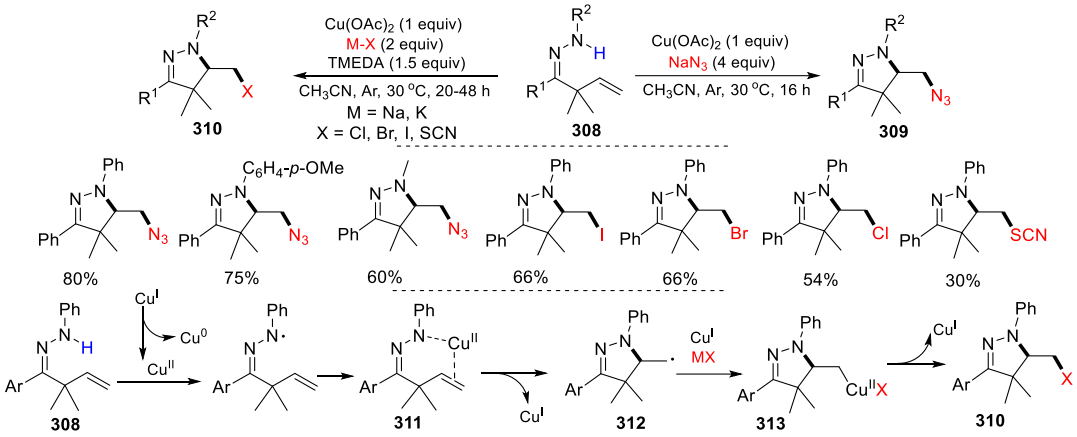
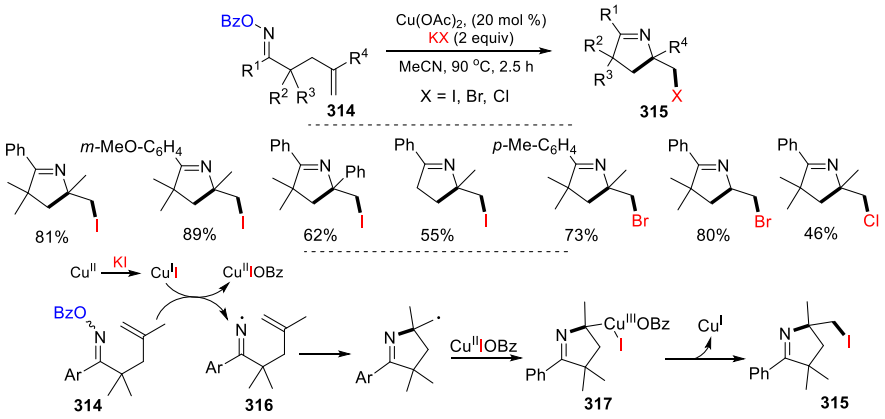
A Cu-mediated radical reaction of *β*,*γ*-unsaturated hydrazones for the synthesis of functionalized pyrazolines was reported by Li and coworkers in 2018. The reaction of *β*,*γ*-unsaturated hydrazones **308** and M–X (M = Na, K; X = N_3, Cl, Br, I, SCN) and $Cu(OAc)_2$ in CH_3CN provided products **309** or **310** in good to high yields (Scheme 64) [89]. In the reaction process, HAT of *β*,*γ*-unsaturated hydrazones **308** generates N-radicals which coordinate with Cu^{II} to form complexes **311**. Reductive elimination of Cu^{II} followed by a radical cyclization give radicals **312** which couple with Cu^{I} and M–X to provide Cu^{II} complex **313** and then products **310** after reductive elimination of the Cu^{I} catalyst.



Scheme 64. Synthesis of functionalized pyrazolines.

Zhu and coworkers, in 2019, introduced a Cu-catalyzed radical reaction of unsaturated oxime esters for the synthesis of 2-halomethyl pyrrolines. The reaction of *γ*, *δ*-unsaturated oxime esters **314** and halide salts (such as KI, KBr and KCl) and $Cu(OAc)_2$ in CH_3CN at 120 °C for 2.5 h gave 2-halomethyl pyrrolines **315** in good yields (Scheme 65) [90]. The reaction mechanism suggested that iminoxyl radicals **316** generated from oxime esters **314** undergo 5-*exo* cyclization followed by coordinate with Cu^{II}IOBz to form complexes **317** followed by reductive elimination to afford products **315**.



Scheme 65. Synthesis of pyrrolines derivatives.

In 2019, Yoshikai and coworkers reported a Co–N-heterocyclic carbene catalyzed radical reaction of tosylamide-tethered bromo-alkenes for the synthesis of 3-(arylmethyl)pyrrolidine derivatives. The reaction of tosylamide-tethered bromoalkenes **318** and aryl N–H imines **319** in the presence of $CoBr_2$, NHCs bearing cyclohexylethyl groups (**L**) and *t*-$BuCH_2MgBr$ in THF for 12 h afforded products **320** in good yields (Scheme 66) [91]. In the reaction process, *t*-$BuCH_2Co^{I}$ **321** is generated from the reaction of $Co^{I}L_nBr_2$ and the Grignard reagent *t*-$BuCH_2MgBr$. It then reacts with

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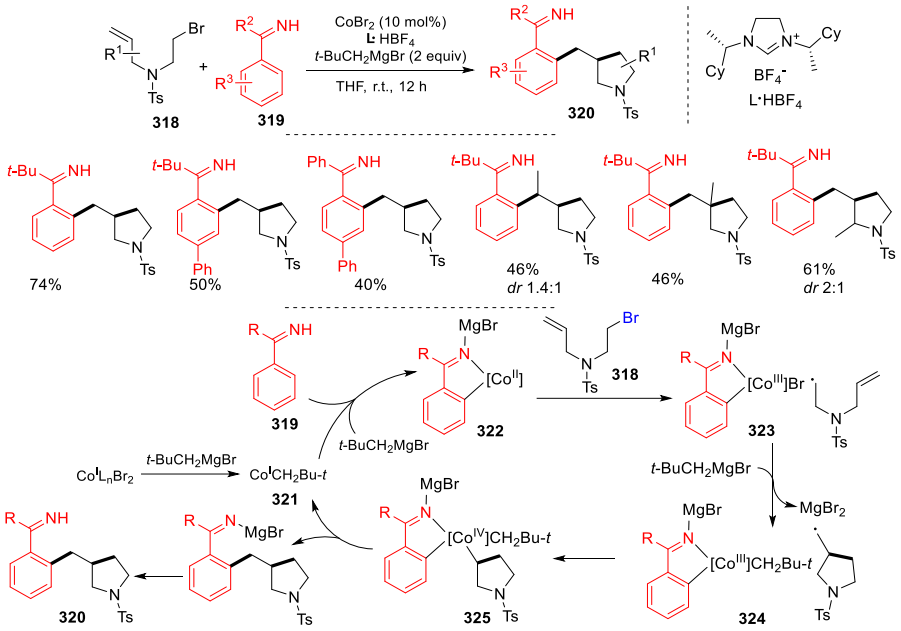
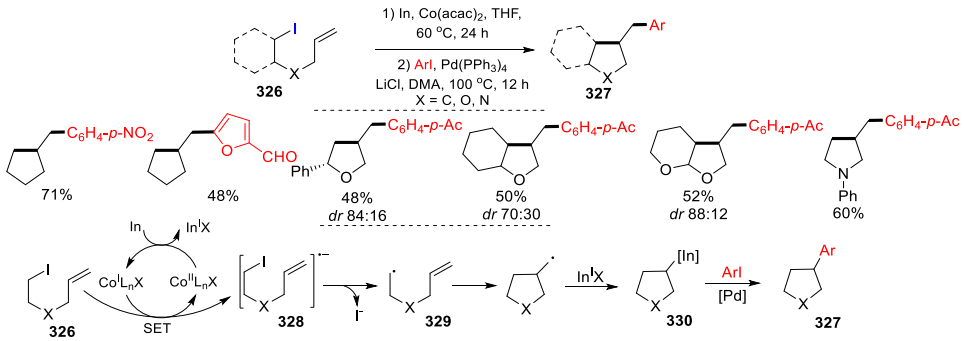
N–H imines **319** and *t*-BuCH$_2$MgBr to give Co^{II} complexes **322** and then reacts with bromoalkene **318** to form complex pairs **323** which undergo 5-*exo* cyclization and transmetalation with the Grignard reagent to give radical complex pairs **324** and then **325**. Products **320** are generated from **325** after reductive elimination of Co catalyst and hydrolysis of the MgBr moiety.



Scheme 66. Synthesis of pyrrolidine derivatives.

In 2020, Shen, Han and their coworkers reported a metal-catalyzed radical reaction of iodoalkyl-tethered unactivated alkenes for the synthesis of a wide variety of cyclic compounds, including substituted cyclopentanes, furans, pyrrolidines, octahydro-1*H*-indenes, octahydro-benzofurans, hexahydro-4*H*-furo[2,3-*b*]pyrans, and hexahydro-furo[2,3-*b*]furans. The reaction of iodoalkyl-tethered alkenes **326** in the presence of In powder and Co(acac)$_2$ at 60 °C for 24 h in THF followed by the treatment with ArI in the presence of Pd(PhPh$_3$)$_4$ and LiCl in DMA at 100 °C for 12 h gave products **327** in moderate to good yields (Scheme 67) [92]. The reaction mechanism suggested that Co^{I}L$_n$X converts olefin-tethered alkyl iodides **326** to alkyl radical anions **328** and then alkyl radical **329** after elimination of iodine anion. Cyclization of radicals **329** followed by radical trapping with In^{I}X give alkyl indium reagent **330** which then undergo Pd-catalyzed cross-coupling with aryl iodides to form products **327**.



Scheme 67. Radical cyclization for preparation of cyclic compounds.

Zhu and coworkers reported a metal-catalyzed radical reaction of unactivated alkenes for the synthesis of SCN-substituted pyrazolines. The reaction of alkenes **331**, NH$_4$SCN, Co(acac)$_2$, K$_2$S$_2$O$_8$, and NaHCO$_3$ in DMSO at room temperature for 12 h gave products **332** in good to excellent yields

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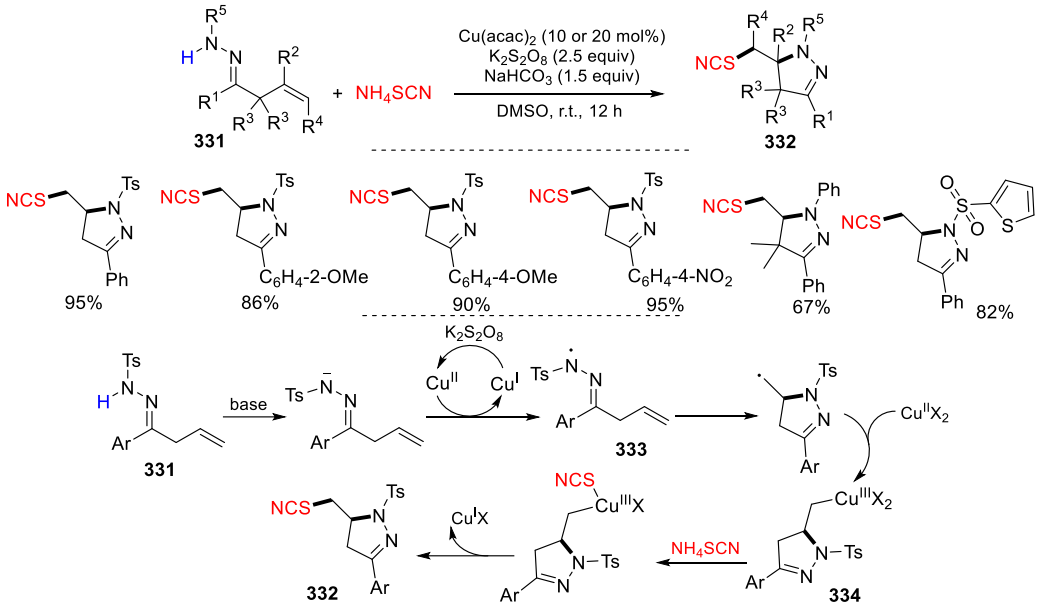
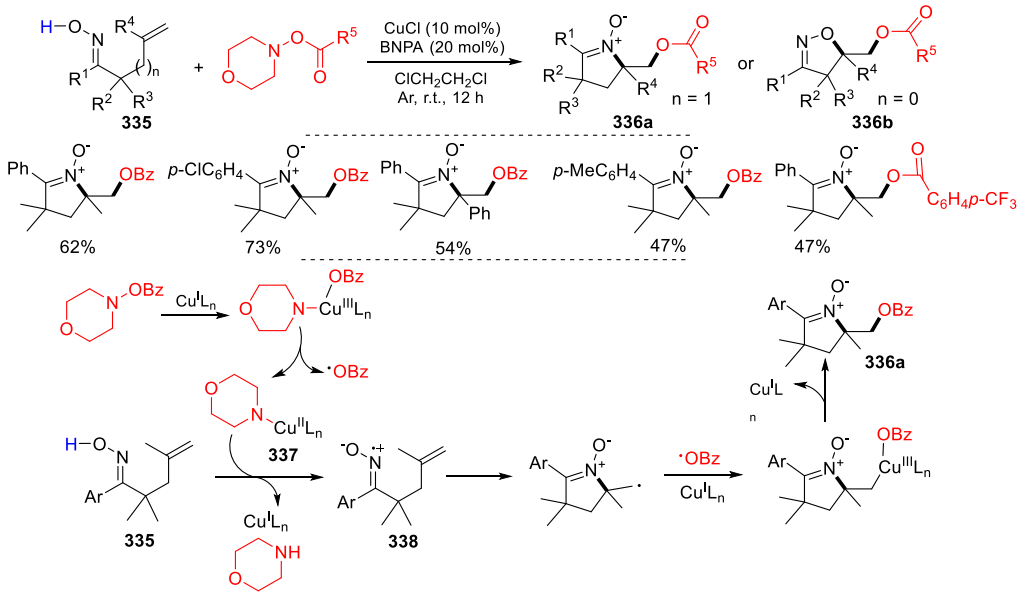
(Scheme 68) [93]. In the reaction process, ketoximes **331** are deprotonated with a base and oxidized by Cu^{II} to iminoxyl radicals **333** for 5-*exo* cyclization followed by the reaction with $Cu^{II}X_2$ to form the Cu^{III} complexes **334**. The reactions of **334** with NH_4SCN followed by reductive elimination afford products **332**.



Scheme 68. Synthesis of SCN-containing pyrazolines.

Wang and coworkers reported a Cu-catalyzed radical reaction of unsaturated ketoximes for the synthesis of cyclic nitrone products in 2021. The reaction of ketoximes **335** and morpholino benzoates in the presence of CuCl and 1,1-binaphthyl-2,2-diyl hydrogen-phosphate (BNPA) with $ClCH_2CH_2Cl$ as solvent, and the cyclic nitrone gave products **336** in good yields (Scheme 69) [94]. In the synthesis of **336a**, Cu^{II} complex **337** generated from morpholino benzoate and $Cu^{I}Ln$ reacts with ketoximes **335** (n=1) to form radicals **338** *via* oxidative SET. Cyclization of **338** followed by coupling with OBz radical and then reductive elimination give final products **336a**.



Scheme 69. Radical cyclization for preparation of cyclic nitrones.

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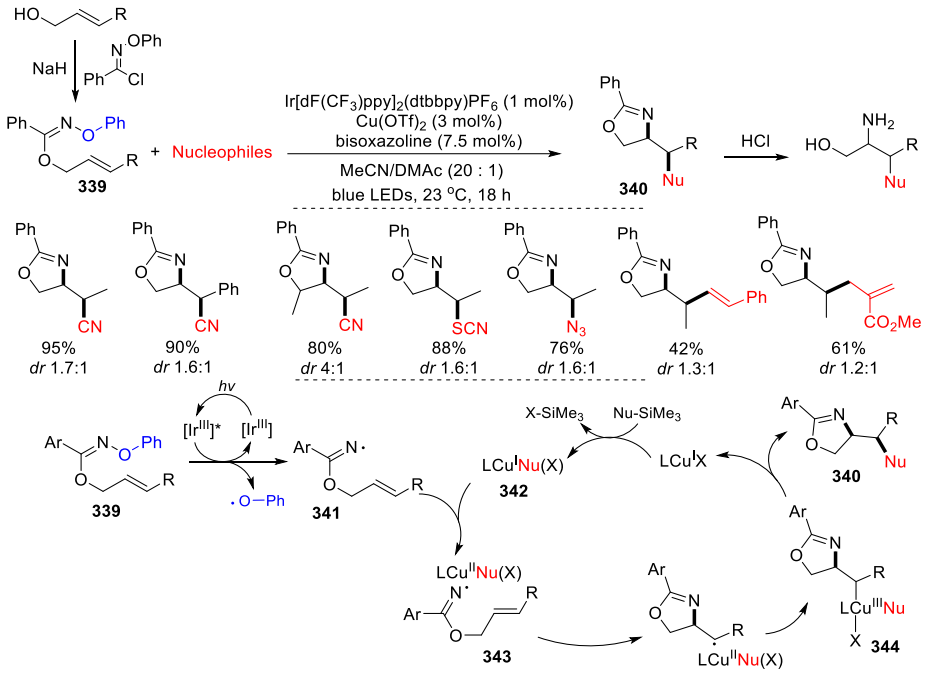
An Ir and Cu dual-catalysts-promoted photo reaction of oxime of allyl alcohols for the synthesis of functionalized oxazolines was developed by the Nagib group in 2021. The reaction of oxime of allyl alcohols **339** under the photo catalysis with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $Cu(OTf)_2$ in the presence of bisoxazoline and nucleophiles such as CN, SCN, N_3, vinyl, allyl and under the irradiation of blue LEDs for 18 h in 20:1 MeCN/DMAc gave functionalized oxazolines **340** in moderate to good yields (Scheme 70) [95]. The functional oxazolines **340** could be hydrolyzed with HCl to *β*-amino-*γ*-cyano alcohols. A dual catalytic mechanism was proposed for this reaction. Oxime of allyl alcohols **339** derived from allyl alcohols under $[Ir^{III}]^*$-catalyzed homolysis to form radicals **341** which react with $LCu^{I}Nu(X)$ **342** to give Cu^{II} complex **343**. The 5-*exo* cyclization of N-centered radicals **343** followed by radical trapping give Cu^{III} species **344**, next and then products **340** after reductive elimination of the Cu^{I} catalyst.



Scheme 70. Synthesis of functionalized oxazolines.

A Pd-catalyzed radical reaction of *N*-(2-bromobenzoyl)indoles for the synthesis of 2,3-disubstituted indolines was introduced by the Sharma group in 2020 (Scheme 71) [96]. The reaction of *N*-(2-bromobenzoyl)indoles **345** and styrenes with $Pd(PPh_3)_4$, Xantphos and Cy_2NMe in *N*-methyl-2-pyrrolidone (NMP)/DCE under the irradiation of blue LEDs for 24 h gave 2,3-disubstituted indoline derivatives **346** in moderate to good yields and good to excellent diastereoselectivities. The proposed mechanism indicated that aryl radicals **347** produced *via* a SET reduction of aryl bromides **345** undergo 5-*exo* radical cyclization followed by the addition to styrenes to give hybrid alkyl $[Pd^{I}]$ radicals **348** which have equilibrium structures **349** which undergo *β*-H elimination to give products **346**.

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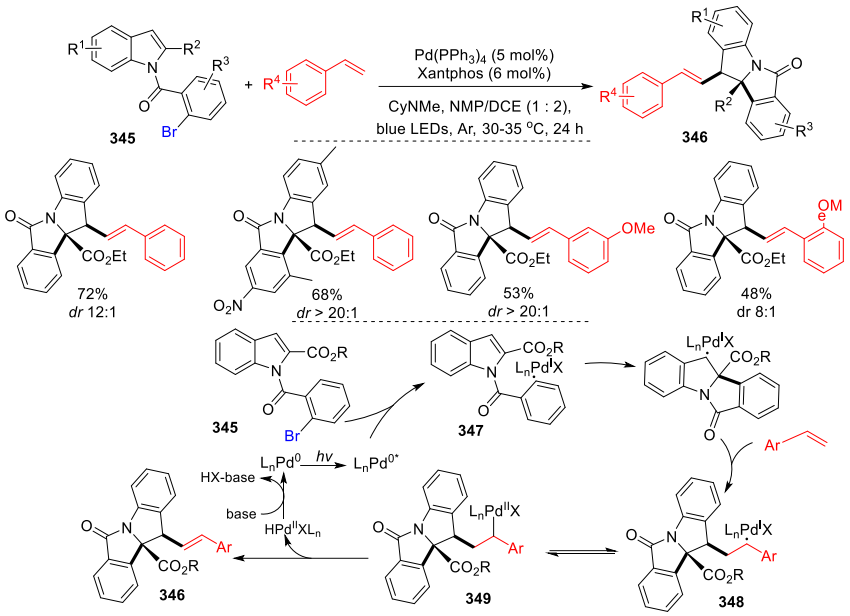
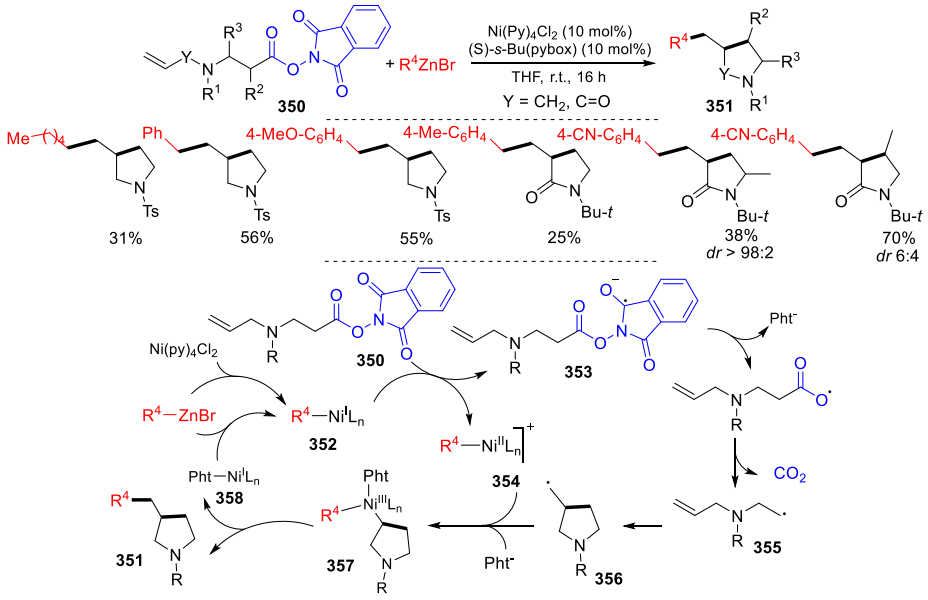


Scheme 71. Synthesis of indoline derivatives.

In 2022, Cárdenas and coworkers reported a Ni-catalyzed radical reaction of allylamines and acryl-amides containing an active ester group for the synthesis of nitrogen-heterocycles. The reaction of allylamines or acryl-amides **350**, alkylzinc or arylzinc bromides, $Ni(py)_4Cl_2$ and (*S*)-*s*-Bu(pybox) in THF at room temperature for 16 h afforded pyrrolidines and pyrrolidinones **351** were obtained in good yields (Scheme 72) [97]. In this reaction, $[RNi^{I}L_n]$ complexes **352** produced by the reaction of $Ni(py)_4Cl_2$ and RZnBr undergo SET with esters **350** to form radical anions **353** and $[RNi^{I}L_n]^+$ complexes **354**. Homolytic N–O cleavage of radical anions **353** followed by decarboxylation give radicals **355** which undergo 5-*exo* cyclization to form **356** which then forming $[Ni^{III}]$ complexes **357** by reacting with **354** and Pht^-. Products **351** are obtained by reductive elimination of complexes **357** while the $[Ni^{I}]$ complex **358** could react with RZnBr to regenerate the $[RNi^{I}L_n]$ complexes **352** for the catalytic cycle.



Scheme 72. Synthesis of functionalized pyrrolidines and pyrrolidinones.

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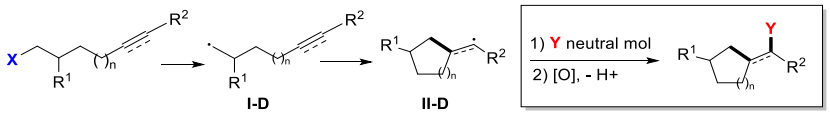
5. Second Functionalization with Y of Neutral Molecules

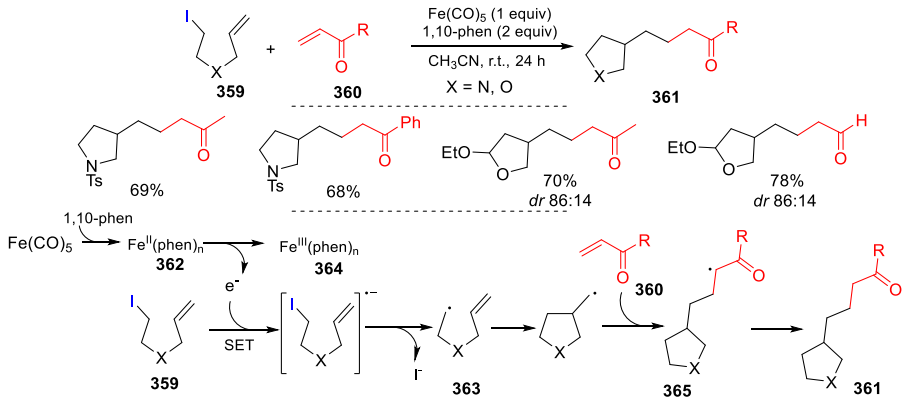
Presented in this section are the reactions in which the second functionalization is accomplished by reacting with neutral molecules Y followed by a reduction of the resulted radicals to anions and then deprotonation to give the final products (Scheme 73). Alkenes, alkynes, arenes, molecular oxygen (O_2), sulfur dioxide (SO_2), 2-isocyanobiaryl, CO, $B_2(OH)_4$, and glycine derivatives could serve as the neutral molecules for the second functionalization reactions.



Scheme 73. Second functionalization with Y from neutral molecules.

5.1. Alkenes, Alkynes and Arenes as Y

There are several examples of using alkenes, alkynes and arenes for the second functionalization reactions. In 2016, Kang and coworkers reported a radical reaction of ω-iodoalkenes for the synthesis of heterocyclic compounds. The reaction of ω-iodoalkenes **359** and α,β-unsaturated carbonyl compounds **360** in the presence of $Fe(CO)_5$ and 1,10-phenanthroline monohydrate in CH_3CN for 24 h gave products **361** in good to excellent yields (Scheme 74) [98]. A proposed reaction mechanism suggested that complex **362** was generated from $Fe(CO)_5$ and phenanthroline reacts with alkyl iodides **359** to form alkyl radical intermediates **363** which undergo 5-*exo* cyclization followed by radical addition to the β-C in the α,β-unsaturated carbonyl compound **360** to yield α-carbonyl radicals **365** and then products **361**.



Scheme 74. Synthesis of heterocyclic compounds.

A Cu-catalyzed asymmetric reaction of 2-vinylbenzyl alcohols for the synthesis of phthalans was reported by Chemler and Chen in 2018. The reaction of 2-vinylbenzyl alcohols **366** and 1,1-diarylethylene in the presence of $Cu(OTf)_2$, (*S*,*S*)-*t*-Bu-Box, K_2CO_3, and MnO_2 in $PhCF_3$ at 120 °C for 24 h gave phthalan products **367** in good to high yields and enantioselectivity (Scheme 75) [99]. Radicals **368** generated from benzylalcohols **366** coordinate with Cu^{II} to give intermediates **369** and lead to the formation of radicals **370** after a 5-*exo* cyclization. The addition of **370** to arylethylenes gives benzylic radicals **371** followed by oxidation and H-elimiation to afford products **367**.

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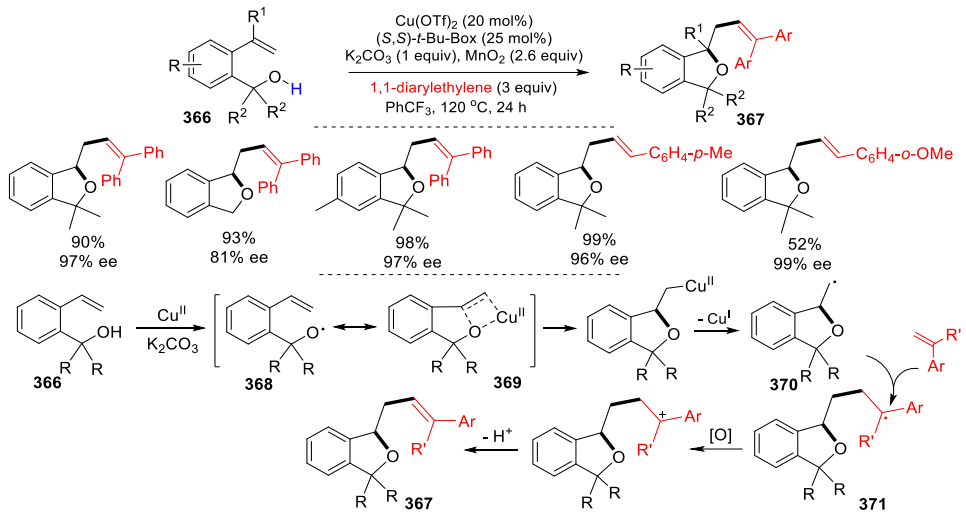
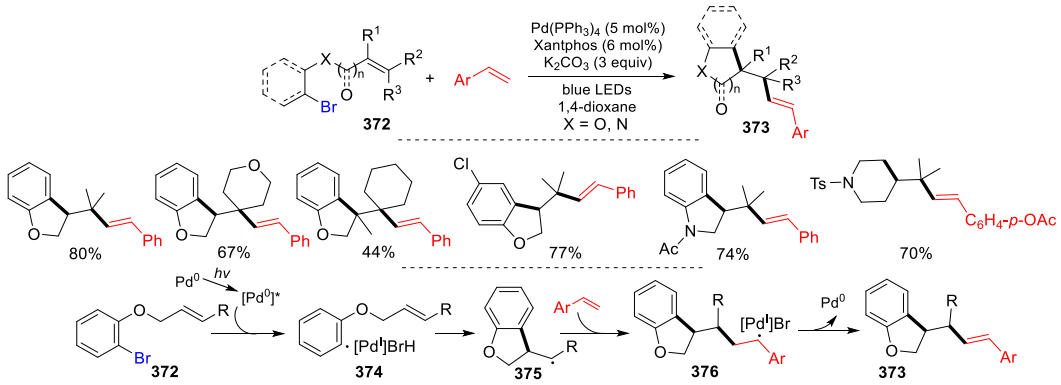


Scheme 75. Synthesis of phthalans.

Glorius and coworkers, in 2020, reported a visible-light-induced radical reaction of prenylated 2-bromophenols for the synthesis of substituted dihydrobenzofurans. The reaction of 2-bromophenols **372** and styrenes with $Pd(PPh_3)_4$ as photo-catalyst, xantphos as an ancillary ligand, and potassium carbonate as a base, and 1,4-dioxane as a solvent and under irradiation of blue LEDs gave products **373** in good to excellent yields (Scheme 76) [100]. In the reaction process, photo-the photo-excited $[Pd^0]^*$ induces the homolytic cleavage of aryl C–Br bond of **372** to form radicals **374** for the subsequential 5-*exo* cyclization to give radical intermediates **375**. The addition of radicals **375** to styrene derivatives followed by substituted dihydrobenzofurans **373** was obtained *via* β-H elimination of the intermediates **376**, and the photo-catalyst Pd^0 was regenerated for the catalytic cycle.



Scheme 76. Synthesis of substituted dihydrobenzofurans.

In 2021, Gryko and coworkers introduced a vitamin B_{12}-catalyzed radical reaction of bromoalkenes for the synthesis of substituted pyrrolidines and piperidines. Under the irradiation of blue LEDs, the vitamin B_{12}-catalyzed reaction of bromoalkenes **377** and electrophilic olefins in the presence of Zn and NH_4Cl in MeOH for only 15 min afforded substituted pyrrolidines **378** or piperidines **379** in decent yields (Scheme 77) [101]. The reaction of **377** with Co^I which is derived from vitamin B_{12} leads to the formation of radicals **380** for 5-*exo* cyclization to form radicals **381**. Addition of radicals **381** to an electron-deficient olefin followed by a single electron reduction with the Zn affords pyrrolidines **378**.

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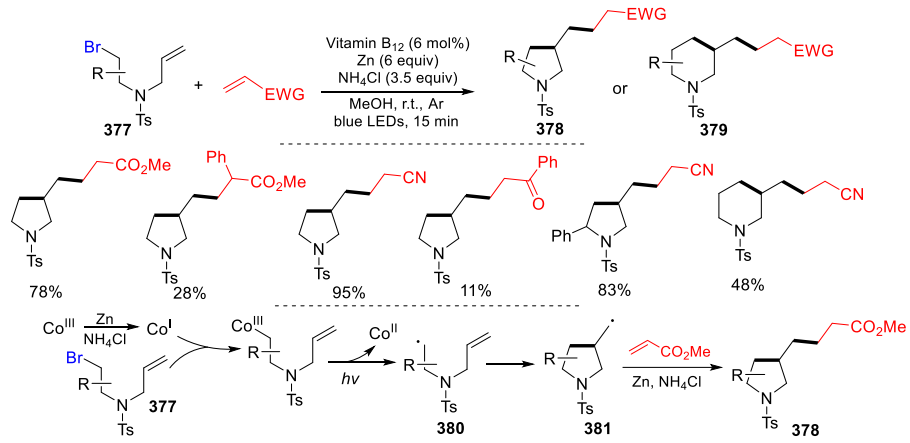
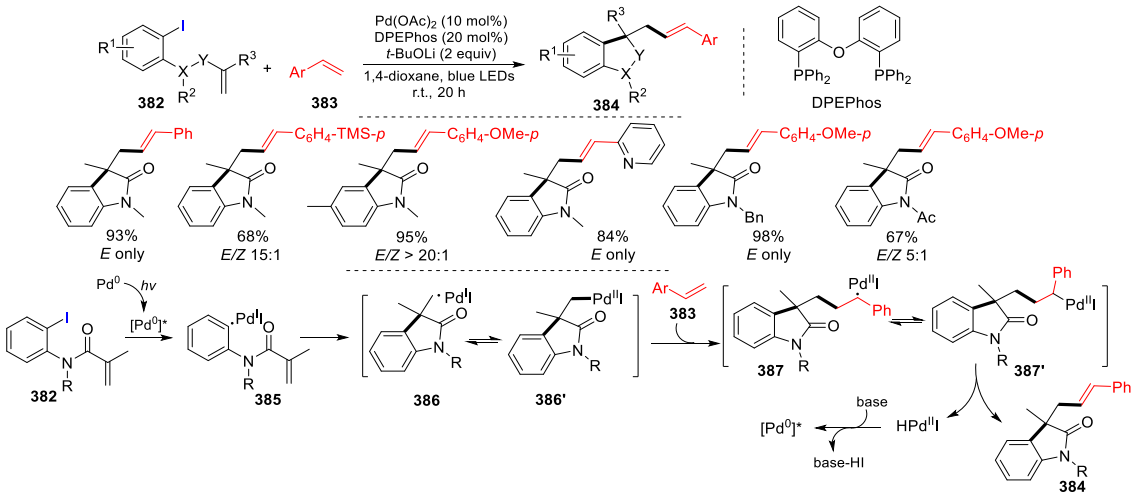


Scheme 77. Synthesis of functional pyrrolidines and piperidines.

A photo and Pd-catalyzed radical cyclization of *N*-(2-iodo-aryl) acrylamides for the synthesis of diverse oxindole scaffolds was reported by Chen, Teng and their coworkers in 2023. The reaction of *N*-(2-iodo-aryl) acrylamides **382** and vinyl arenes **383** in the presence of $Pd(OAc)_2$, DPEPhos and *t*-BuOLi in 1,4-dioxane under the irradiation of blue LEDs at room temperature for 20 h gave oxindole products **384** in good to excellent yields (Scheme 78) [102]. The proposed reaction mechanism suggested the visible light-excited $[Pd^0]^*$ reacts with **382** provides aryl hybrid Pd-radical intermediates **385** which lead to the formation of alkyl hybrid Pd-radical species **386** and **386′** after 5-*exo* cyclization. The reaction of styrene **383** with **386′** to form **387** and **387′** followed by *β*-H elimination to afford products **384**.



Scheme 78. Synthesis of functionalized oxindoles.

Han and coworkers introduced a radical reaction of *β*,*γ*-unsaturated hydrazones for the synthesis of pyrazoline-functionalized oxindoles in 2015. The reaction of *β*,*γ*-unsaturated hydrazones **388** and *N*-aryl acrylamides **389** in the presence of DTBP (*di-tert*-butyl peroxide) under the solvent-free conditions at 100 °C for 72 h gave products **390** in good to excellent yields (Scheme 79) [103]. The *t*-BuO radical derived from DTBP abstracts H from *β*,*γ*-unsaturated hydrazones **388** to give radicals **391** followed by cyclization to form radicals **392**. Addition of **392** to *N*-aryl acrylamides **389** to form radicals **393** followed by the second cyclization and oxidative aromatization with DTBP yield pyrazoline-functionalized oxindoles **390**. The same group extended the scope for the reaction of unsaturated ketoximes for the synthesis of isoxazoline-functionalized oxindoles and dihydroquinolinones. The reaction of unsaturated ketoximes **395** and *N*-arylpropiolamides or *N*-

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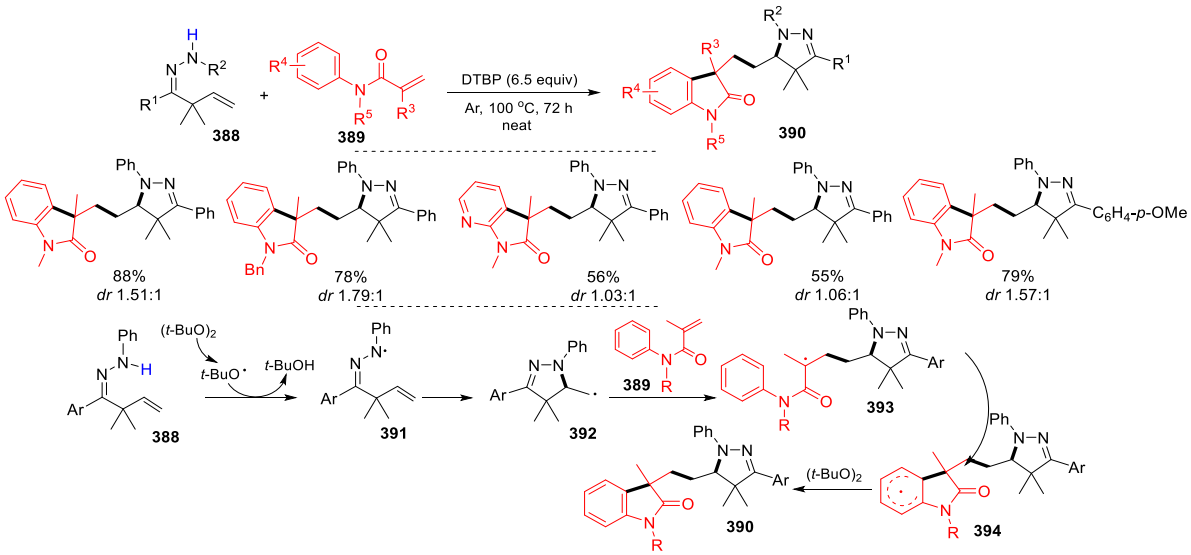
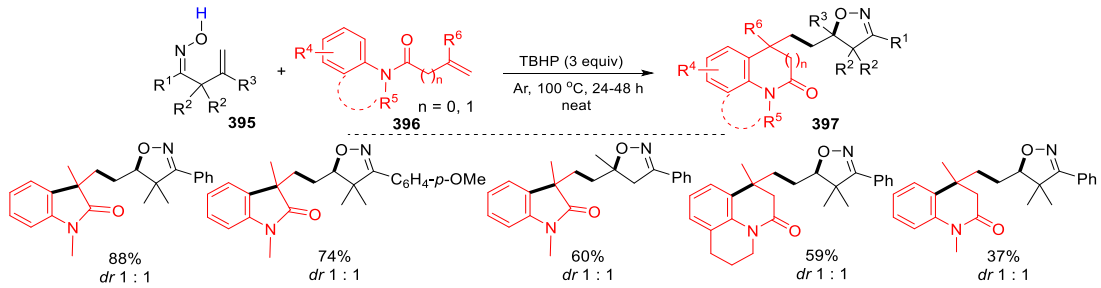
arylacrylamides **396** in the presence of TBHP at 100 °C for 24–48 h gave products **397** in good to excellent yields (Scheme 80) [104].



Scheme 79. Synthesis of pyrazoline-functionalized oxindoles.



Scheme 80. Synthesis of isoxazoline-bearing oxindoles and dihydroquinolinones.

Han and coworkers reported a Cu-catalyzed reaction of unsaturated ketoximes for the synthesis of alkynylated isoxazolines and cyclic nitrones. The reaction of unsaturated ketoximes **398** and ethynylbenziodoxolones (EBX) **399** in the presence of $Cu(OTf)_2$ in DCE under Ar at 100 °C for 1 h gave products **400** in moderate to good yields (Scheme 81) [105]. In the reaction process, Cu^{II} catalysis converts ketoximes **398** to iminoxyl radicals which have resonance structures **401** and **402**. Subsequential O-/N-atom 5-*exo* cyclizations of **401** and **402** yield radical intermediates **403** and **404**, respectively. Additions of **403** or **404** at alkyne moiety of EBX **399** followed by the Cu^{I}-assisted elimination of 2-iodobenzoate give products **400a** or **400b**.

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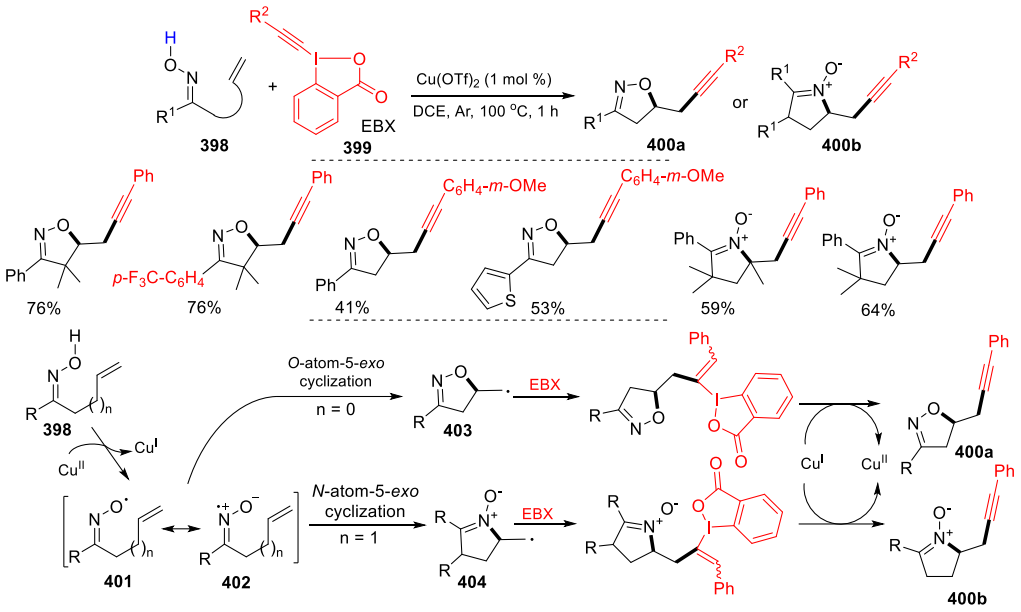
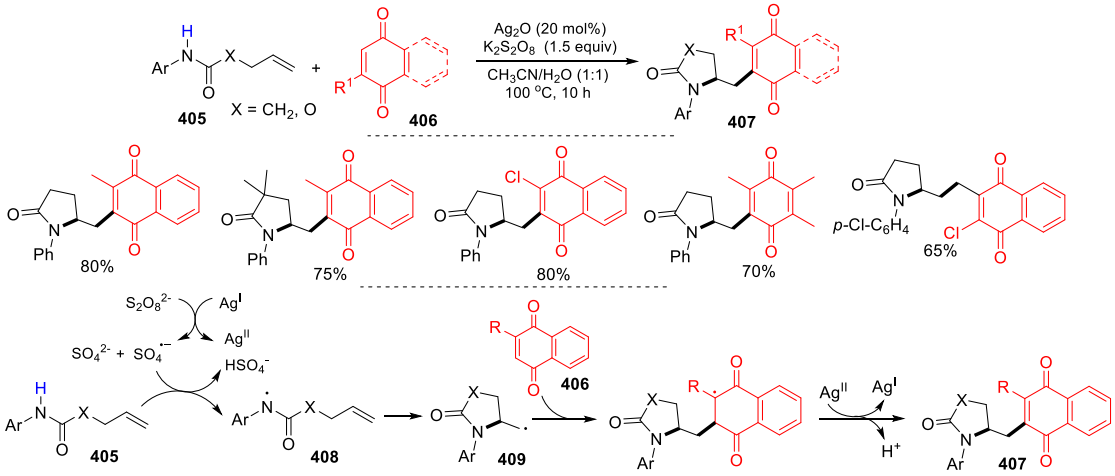


Scheme 81. Synthesis of isoxazolines and cyclic nitrones.

An Ag-catalyzed radical reaction of unactivated olefins for the synthesis of substituted quinone was reported by Li and coworkers in 2022. The reaction of unactivated olefins **405** (such as *N*-aryl-4-pentenamides and *N*-aryl allyl carbamates) and quinones **406** in the presence of Ag_2O and $K_2S_2O_8$ in CH_3CN/H_2O at 100 °C for 10 h gave substituted quinone products **407** in good to excellent yields (Scheme 82) [106]. Amidyl radicals **408** generated *via* H-abstraction of *N*-aryl-4-pentenamides **405** *by* $SO_4^{\bullet-}$ radical undergo 5-*exo* cyclization to give radicals **409** which then add to menadionse **406** followed by an Ag^{II}-induced HAT to give products **407**.



Scheme 82. Synthesis of substituted quinones.

In 2023, Chen, Huang and their coworkers reported a photo-induced radical reaction of *N*-allyl-2-bromo-2,2-difluoroacetamides for the synthesis of *α,α*-difluoro-*g*-lactam-fused quinoxalin-2(1*H*)-ones and coumarins. The reaction of *N*-allyl-2-bromo-2,2-difluoroacetamides **410** and quinoxalin-2(1*H*)-ones **411** or coumarins **411′** in the presence of PMDETA and LiOH in CH_3CN under the irradiation of 24 W blue LEDs for 36 h gave *α,α*-difluoro-*g*-lactam-fused quinoxalin-2(1*H*)-ones or coumarins **412** in moderate to excellent yields (Scheme 83) [107]. In this reaction process PMDETA plays a dual role as an electron donor and hydrogen atom transfer reagent. The EDA (electron donor

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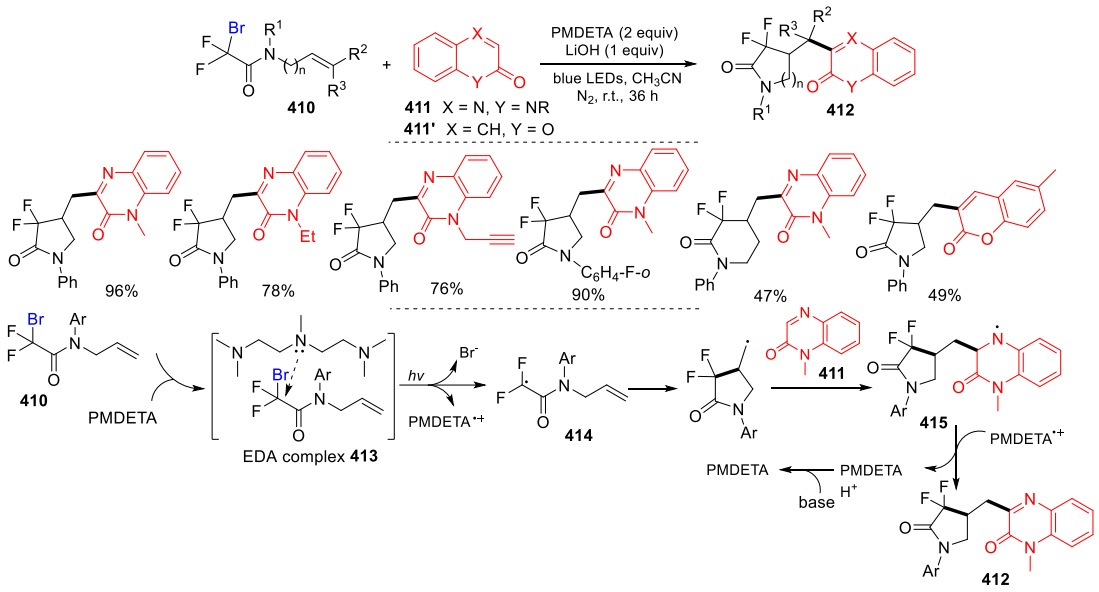
acceptor) complexes **413** generated from **410** and PMDETA lead to the formation of difluoroalkyl radicals **414** after SET under the irradiation of blue LEDs. The 5-*exo* cyclization of radicals **414** followed by radical addition to quinoxalin-2(1*H*)-one **411** afford intermediates **415** which undergo H-abstraction with PMDETA$^{\bullet+}$ to afford products **412**.



Scheme 83. Synthesis of *α,α*-difluoro-*g*-lactam-fused heterocyclic compounds.

5.2. O_2 as Y

Using molecular oxygen for the second functionalization could introduce a hydroxy or carbonyl group to the products. Han and coworkers in 2017 reported a Cu-catalyzed radical reaction of oxime-tethered alkynes for the synthesis of hydroxylated isoxazolines and dihydropyrrole oxides. The reaction of oxime-tethered alkynes **416** with O_2 in the presence of $CuBr_2$/toluene or $Cu(OAc)_2$/CH_3CN gave products **417** or **418** in good yields (Scheme 84) [108]. The iminoxyl O-radicals **419** generated *via* SET between Cu^{II} and oximes **416** have a resonance N-radicals **420** structure. Cyclization of **419** or **420** afford alkenyl radicals **421** or **422** followed by trapping of O_2 to yield the alkoxy radicals **423** or **424** after cyclization of peroxy radicals followed by the O–O bond cleavage. Products **417** and **419** are generated from the hydrogen abstraction of **423** and **424**, respectively. A related reaction of unsaturated oximes for the synthesis of hydroxylated dihydropyrrole oxides was reported by Li's group. The reaction of unsaturated oximes **425** and O_2 in the presence of CuBr/DMSO and DABSO in EtOH at 50 °C for 12–24 h gave hydroxylated dihydropyrrole oxides **426** in good yields (Scheme 85) [109].

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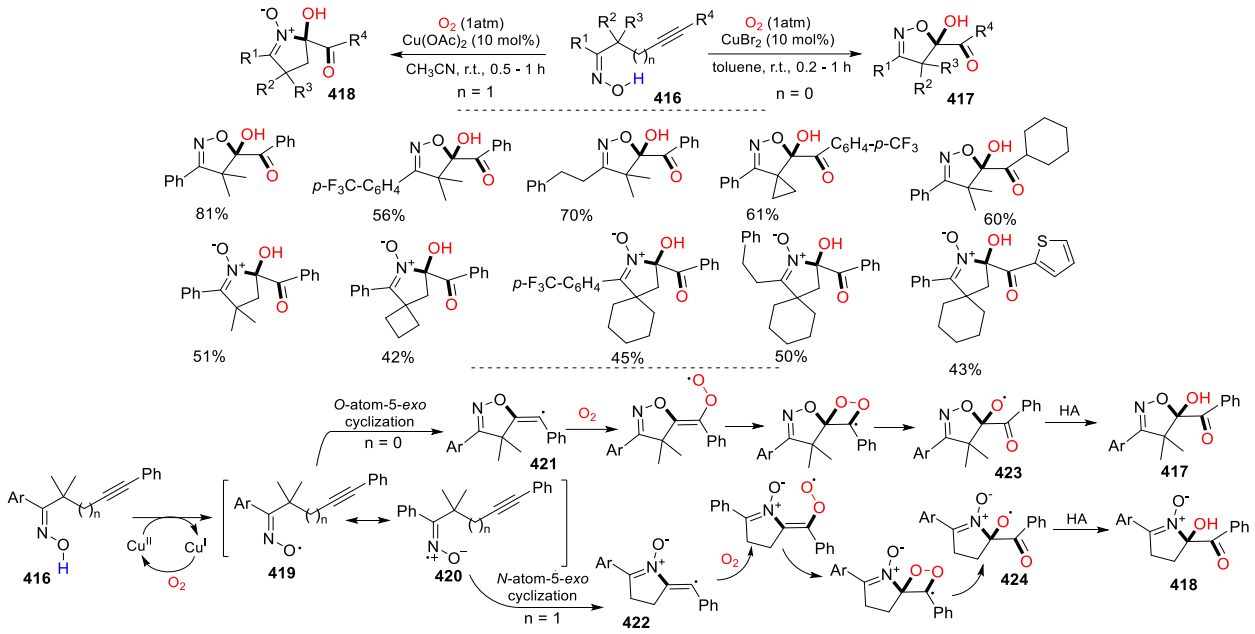
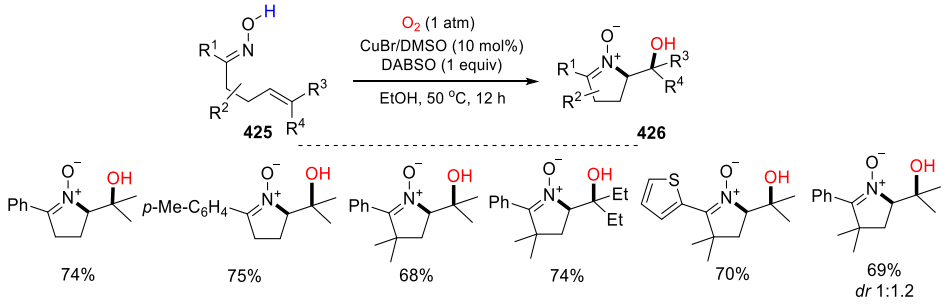


Scheme 84. Synthesis of hydroxylated isoxazolines and dihydropyrrole oxides.



Scheme 85. Synthesis of cyclic nitrones.

A visible-light-induced radical reaction of *β,γ*-unsaturated oximes for the synthesis of isoxazolines by Yu, Chen and coworkers in 2022. The reaction of *β,γ*-unsaturated oximes **427** using graphitic carbon nitride (*g*-C_3N_4) as photocatalyst in the presence of $NaHCO_3$ in CH_3CN/H_2O under the irradiation of 10 W blue LEDs for 36 h gave OH-decorated isoxazolines **428** in moderate to good yields (Scheme 86) [110]. In the reaction process, the photo irradiation of the semiconductor *g*-C_3N_4 generates an electron and a hole followed by a single-electron oxidation of the hole in the valence band with water forms hydroxyl radical and proton, while the single-electron reduction of the electron in the conduction band and the O_2 in air gives superoxide anion and water. The superoxide radical anion is protonated to produce H_2O_2 which then converts to a HO radical. Intermediates **429** produced by the reaction of allyl oximes **427** with base undergo SET to the hole to generate radical intermediates **430** and then radicals **431** after cyclization. The coupling of HO radical and **431** gives final products **428**.

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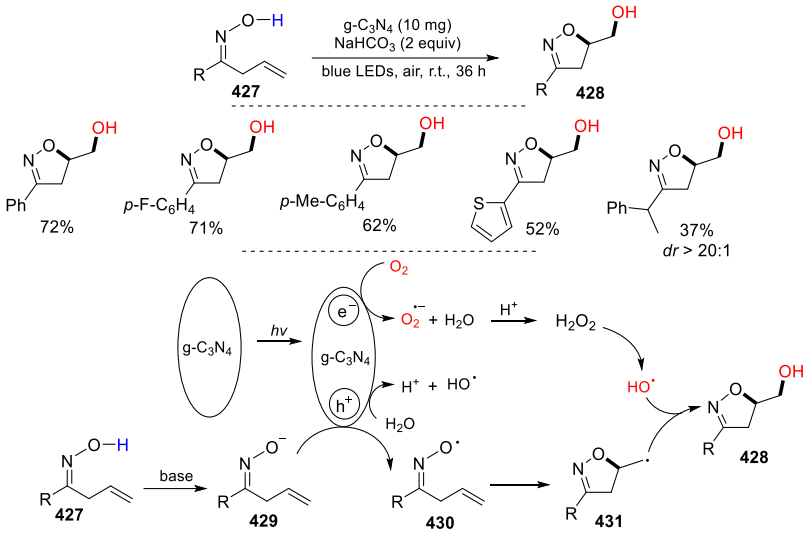
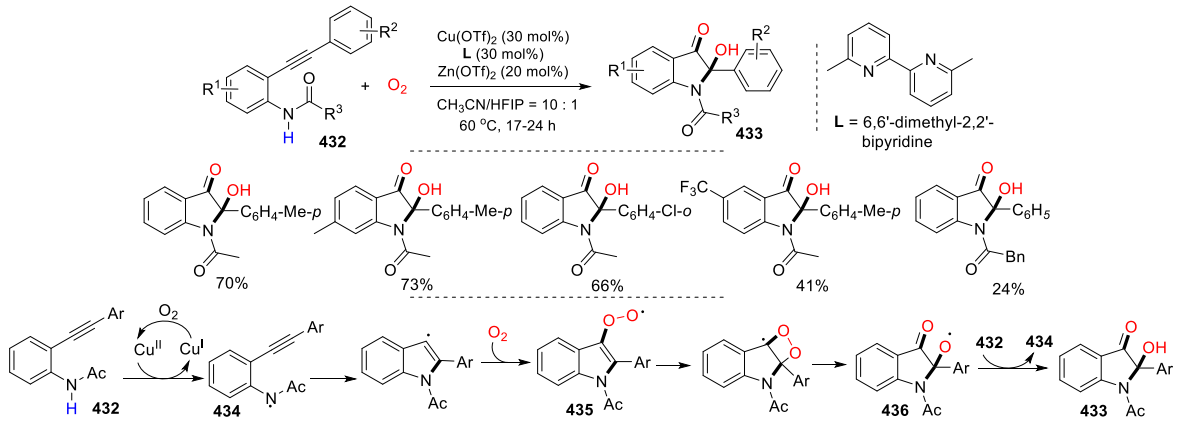


Scheme 86. Synthesis of isoxazolines.

A Cu-catalyzed reaction of 2-arylethynylanilines for the synthesis of substituted 2-hydroxy-2-indol-3-ones was reported by Wu, Chen and their coworkers in 2023. The reaction of 2-arylethynylanilines **432** and O_2 in the presence of $Cu(OTf)_2$, $Zn(OTf)_2$ and 6,6'-dimethyl-2,2'-bipyridine CH_3CN/HFIP (hexafluoro-iso-propanol) at 60 °C for 17–24 h afforded substituted 2-hydroxy-2-indol-3-ones **433** in good yields (Scheme 87) [111]. This reaction could be carried out at a gram-scale under the standard conditions to give product **433a** in 69% yield. In the reaction process, the *N*-center radicals **434** generated *via* H-abstraction from 2-arylethynylanilines **432** undergo 5-*endo* cyclization followed by reaction with O_2 to form peroxic species **435** for radical cyclization and subsequential O–O bond cleavage to form radicals **436**. H-abstraction of **436** from substrates **432** gives products **433** while radicals **434** are regenerated for the reaction cycle.



Scheme 87. Synthesis of 2-hydroxy-2-indol-3-ones.

A radical reaction of unsaturated hydrazones/ketoximes for the synthesis of heterocyclic compounds such as pyridazin-4(1*H*)-ones or oxazin-4(1*H*)-ones was reported by Jiang and coworkers in 2023. The reaction of *β*,*γ*-unsaturated hydrazones **437a** or ketoximes **437b** and diazonium tetrafluoroborates in the presence of Et_3N and O_2 in DCE at −20 °C for 24 h gave pyridazin-4(1*H*)-ones **438a** or oxazin-4(1*H*)-ones **438b** in good to excellent yields (Scheme 88) [112]. In the synthesis of **438a**, anionic intermediates generated from hydrazones **437a** *via* deprotonation of NHTs with Et_3N are oxidized by O_2 to form *N*-centered radicals **439** followed by 6-*endo* cyclization and capture with O_2 to form hydroperoxide radicals **440**. 1,4-HAT of **440** gives C-radicals followed by the cleavage of

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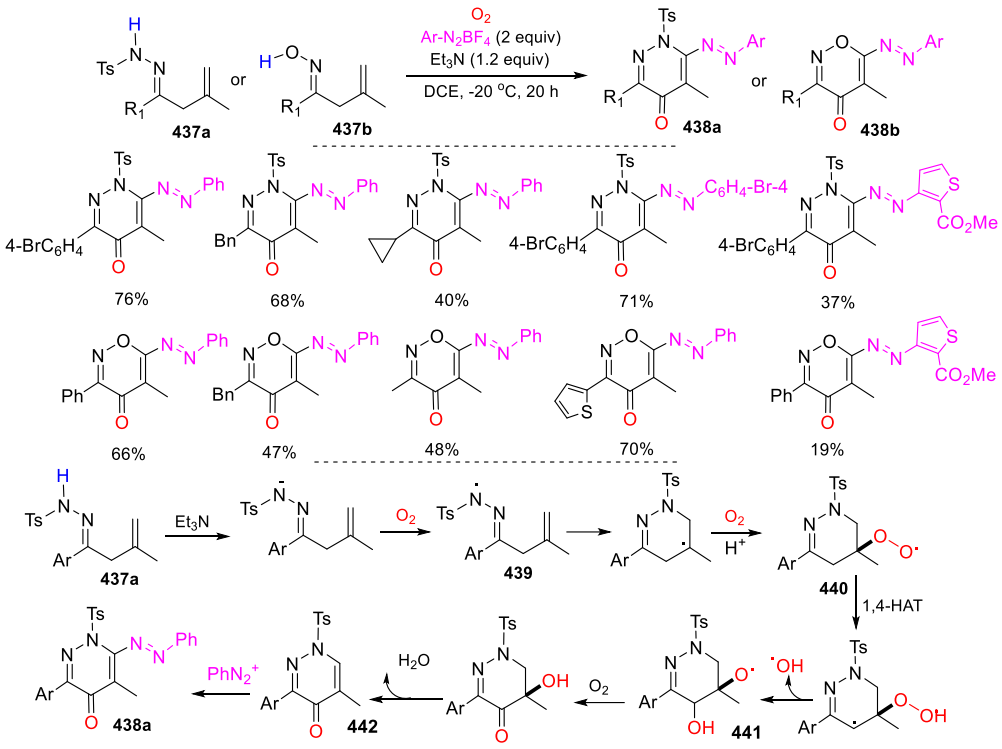
the O–O bond to give radicals **441** which are oxidized and followed dehydration to form **442** and react with aryldiazonium species to give products **438a**.



Scheme 88. Synthesis of substituted pyridazin-4(1*H*)-ones and oxazin-4(1*H*)-ones.

5.3. SO_2 from DABSO as Y

Similar to the molecular oxygen, SO_2 from DABSO (1,4-diazoniabicyclo[2.2.2]-octane-1,4-disulfinate) could be used for the reactant for the second functionalization to introduce sulfonyl group to the products. Ye and coworkers in 2023 developed a visible light induced photocatalyst-free reaction of *N*-allylbromodifluoroacetamides for the synthesis of difluoroamidosulfonylated quinolones. The reaction of *N*-allylbromodifluoroacetamides **443**, *N*-propargylamine **444** and DABSO under the irradiation of 40 W blue LEDs for 18 h in DMA at room temperature gave difluoroamidosulfonylated quinolines **445** in moderate to good yields (Scheme 89) [113]. In the reaction process, EDA complexes **446** generated from *N*-allylbromodifluoroacetamides **443** and DABSO under SET afford difluoroalkyl radicals **447** for 5-*exo* cyclization followed by the reaction with SO_2 to give difluoroamidosulfonyl radicals **448** which then react with *N*-propargylamines **444** to form vinyl radicals **449** followed by radical cyclization and deprotonative aromatization to afford products **445**.

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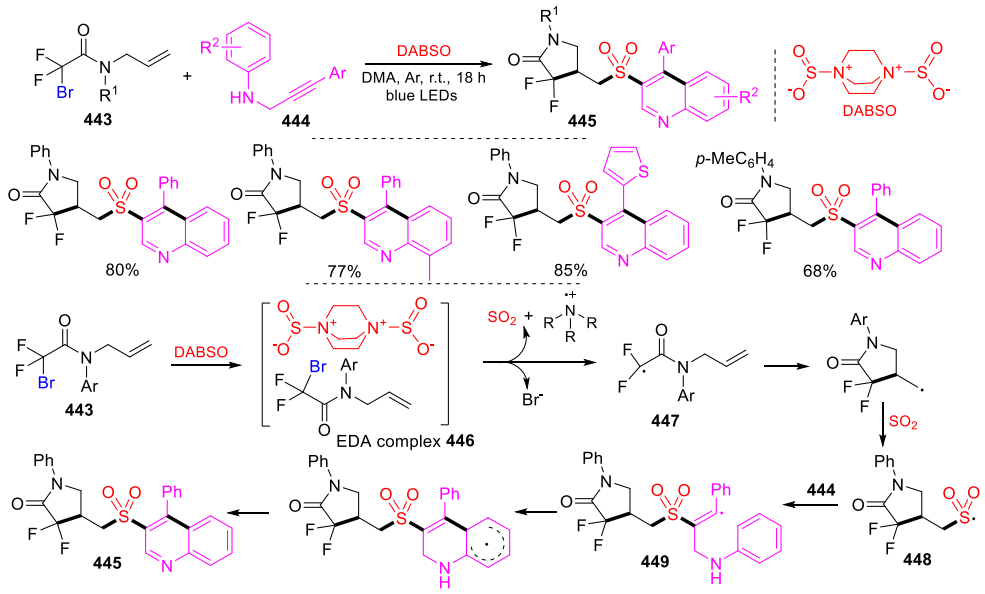
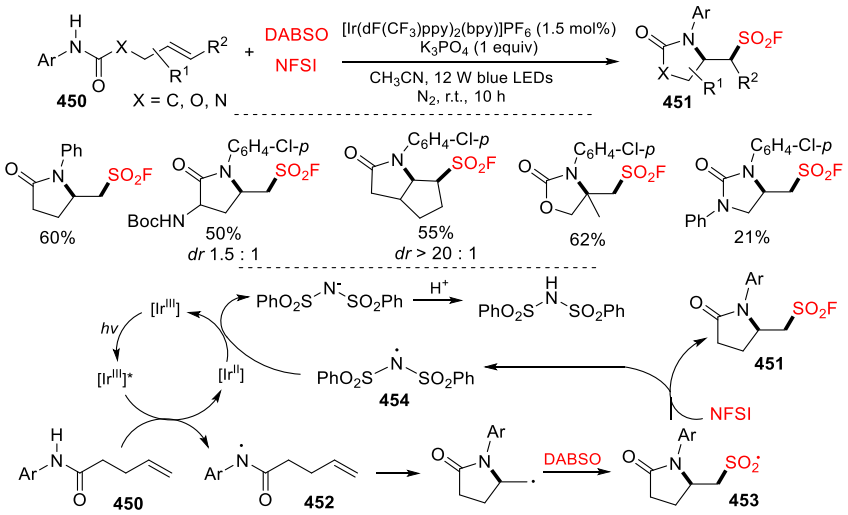


Scheme 89. Synthesis of difluoroamidosulfonylated quinolines.

In 2021, Weng and coworkers reported a photoredox-catalyzed reaction of unactivated olefins for the synthesis of SO_2F-attached 5-membered heterocyclic compounds. The reaction of unactivated olefins **450** such as *N*-phenyl pent-4-enamide, DABSO and *N*-fluorobenzenesulfonimide (NFSI) in the presence of $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ and K_3PO_4 in CH_3CN under the irradiation of blue LEDs for 10 h gave products **451** in good to excellent yields (Scheme 90) [114]. Amidyl radicals **452** generated from *N*-phenyl pent-4-enamides **450** *via* SET with $[Ir^{III}]^*$ undergo 5-*exo* cyclization followed by radical trapping with SO_2 of DABSO to give alkylsulfonyl radicals **453** which trap the fluorine atom from NFSI to give products **451** and meanwhile the $(PhSO_2)_2N$ radical **454** is generated which is converted to $(PhSO_2)_2NH$ after oxidation of $[Ir^{II}]$ to $[Ir^{III}]$. Wang and coworkers reported a similar reaction of unsaturated hydrazones for the synthesis of SO_2F- functionalized pyrazolines. The reaction of β,γ-unsaturated hydrazones **455**, DABSO and NFSI in the presence of 2,4,6-collidine, EtOH under Ar at 25 °C for 24 h gave products **456** in good to excellent yields (Scheme 91) [115]. Products **456** could be further transformed to sulfonate esters and amides.



Scheme 90. Synthesis of SO_2F-functionalized heterocyclic compounds.

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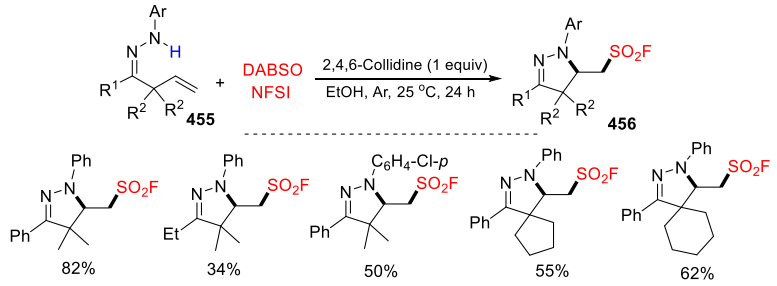
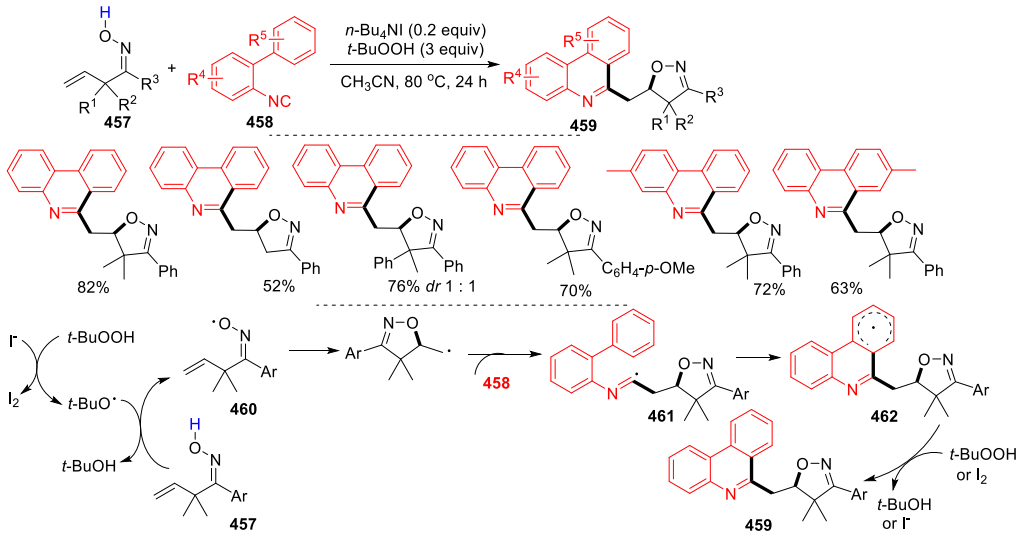


Scheme 91. Synthesis of SO_2F-functionalized pyrazolines.

5.4. Y from Other Neutral Molecules

Other than alkenes, molecular oxygen and SO_2 described above, isocyanides, imines, CO, and $B_2(OH)_4$ could be used for the second functionalization reactions. The Han group reported a radical reaction of *β*,*γ*-unsaturated ketoximes for the synthesis of isoxazoline functionalized phenanthridines in 2014. The reaction of *β*,*γ*-unsaturated ketoximes **457** and 2-arylphenylisonitriles **458** in the presence of *t*-BuOOH and *n*-Bu_4NI in CH_3CN at 80 °C for 24 h gave products **459** in good yields (Scheme 92) [116]. In the reaction process, *t*-BuO radical and I_2 are produced by the reaction of *t*-BuOOH with *n*-Bu_4NI followed by H-abstraction with oxime **457** to yield iminoxyl radicals **460** for 5-*exo* cyclization to form radicals which then add to 2-isocyanobiaryl **458** to yield imidoyl radicals **461** for cyclization to the adjacent phenyl ring to form radicals **462** which undergo oxidative aromatization with I_2 or TBHP to afford products **459**.



Scheme 92. Synthesis of isoxazoline functionalized phenanthridines.

In 2018, Polyzos and coworkers reported a continuous-flow reaction of alkenyl-tethered arenediazonium salts for the synthesis of 2,3-dihydrobenzofurans. The flow reaction of alkenyl-tethered arenediazonium salts **463**, CO and ROH in the presence of $[Ir(dtbbpy)(ppy)_2]PF_6$ in CH_3CN under the irradiation of blue LEDs gave products **464**. The reaction can be completed in a short time of 200 seconds and is scalable (Scheme 93) [117]. In the reaction process, photo-exited catalyst PC^* promoted the reaction of diazonium tetrafluoroborates **463** to form radicals **465** which undergo 5-*exo* cyclization to form radicals which then trap CO to give acyl radicals **466** which are oxidized with $PC^{\bullet+}$ to **467** and then react with ROH and BF_4^- to afford products **464**.

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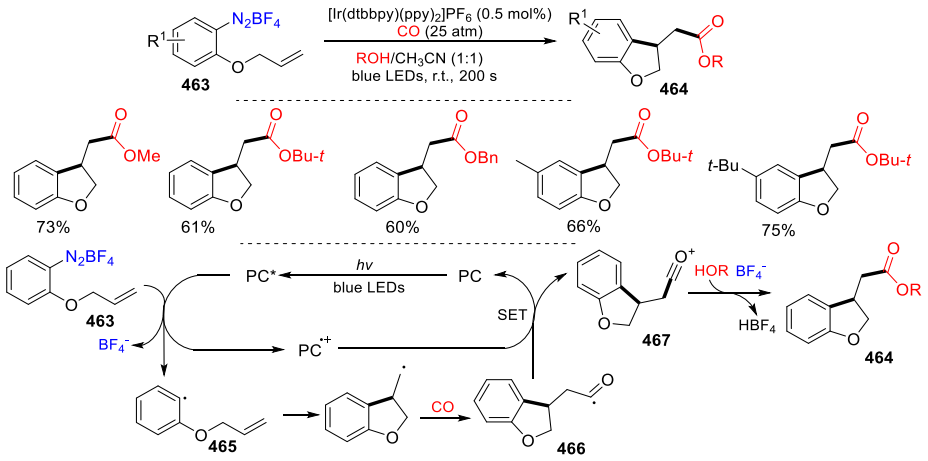
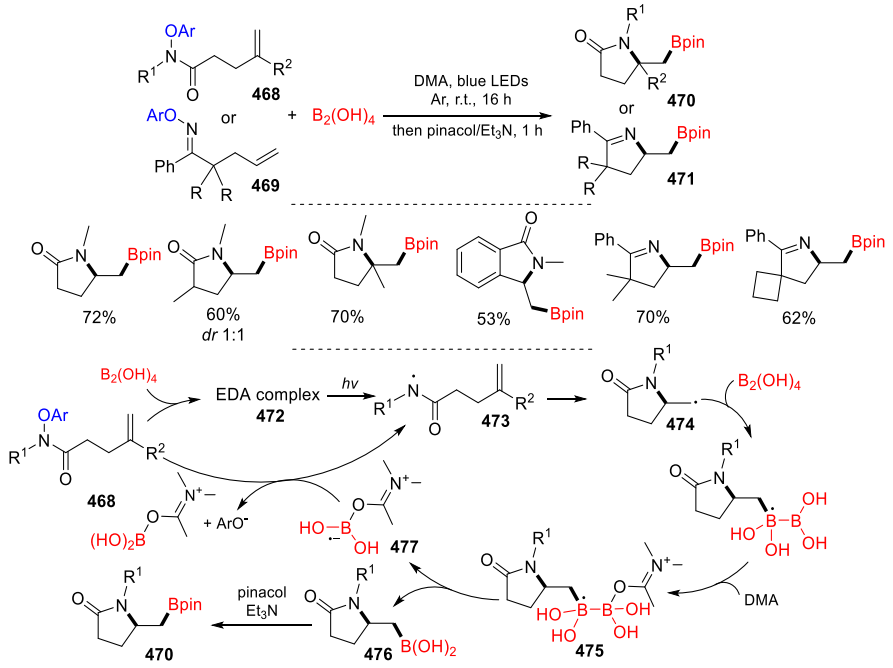


Scheme 93. Synthesis of 2,3-dihydrobenzofurans derivatives.

Studer and coworkers reported a radical reaction of unactivated alkenes for the synthesis of cyclic 1,2-aminoboronic esters. The reaction of unsaturated aryloxy-amides **468** or ketoximes **469** and $B_2(OH)_4$ under the irradiation of blue LEDs with dimethylacetamide (DMA) as a solvent gave cyclic boronic esters **470** or **471** in good yields (Scheme 94) [118]. The proposed mechanism suggested that EDA complexes **472** generated from the reaction of **468** and $B_2(OH)_4$ are converted to radicals **473** under the photo conditions and then undergo 5-*exo* cyclization to form radicals **474**. The reactions of **474** with $B_2(OH)_4$ and then with DMA produce radicals **475** followed by the homolysis of weak B–B bond to give boronic acids **476** along with the DMA-stabilized B-centered radical **477**. The reactions of boronic acids **476** with pinacol and Et_3N give cyclic boronic esters **470**.



Scheme 94. Synthesis of cyclic 1,2-aminoboronic esters.

In 2023, Gong & Lu and coworkers reported a Fe-catalyzed radical reaction of unsaturated oxime esters for the synthesis of pyrroline-containing amino acids derivatives. The reaction of γ,δ-unsaturated oxime esters **478** and glycine derivatives **479** in the presence of $Fe(OAc)_2$ and 3,4,7,8-tetramethyl-1,10-phenanthroline (L) in EtOAc/DMA at 78–80 °C for 5–7 h gave pyrroline-containing amino acids derivatives **480** in good to excellent yields (Scheme 95) [119]. The iminyl radicals **481**

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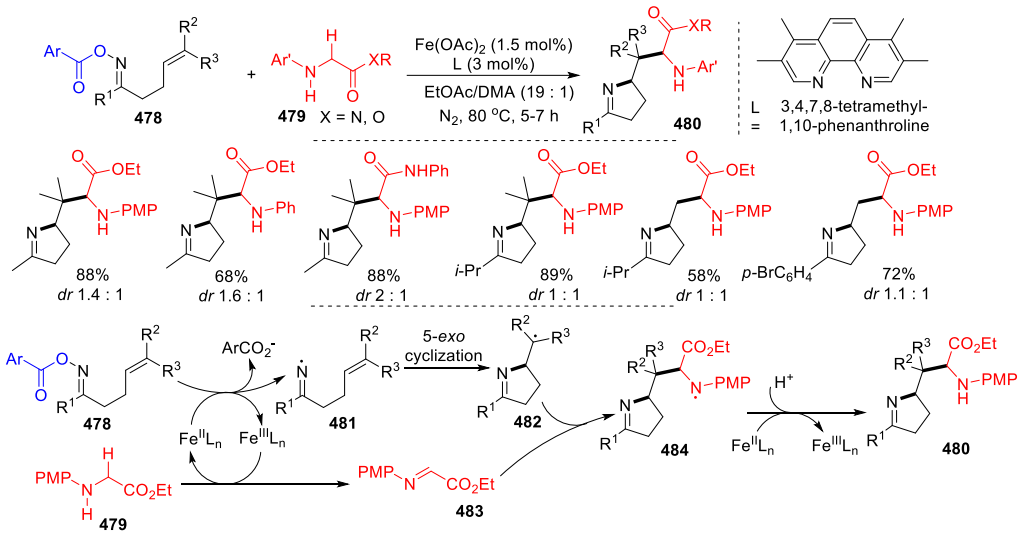
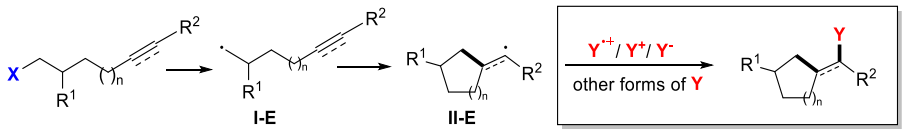
generated *via* the reductive cleave of the N–O bond of oxime ester **478** undergo 5-*exo* cyclization to give alkyl radicals **482** and then react with imines **483** generated from **479** to give N-centered radicals **484**. Final products **480** are obtained *via* SET of $Fe^{II}L_n$ to radicals **484**.



Scheme 95. Synthesis of heterocyclic compounds.

6. Second Functionalization with Other Forms of Y ($Y^{\bullet+}$, Y^+, and Y^-)

In the cyclative radical difunctionalization reactions, the cyclized radicals could be converted to cations, anions or other reactive species for the second functionalization with the right counterparts. Presented in this section are the reactions using $Y^{\bullet+}$, Y^+ and Y^- for the second functionalization reactions (Scheme 96).



Scheme 96. Second functionalization with other forms of Y.

In 2022, Zhou, Sun and their coworkers reported a photo-promoted radical reaction of bromodifluoroacetamides with quinoxalin-2(1*H*)-ones for the synthesis of *α*,*α*-difluoro-*γ*-lactam-fused quinoxalin-2(1*H*)-ones (Scheme 97) [120]. The reaction of bromodifluoroacetamides **485**, quinoxalin-2(1*H*)-ones, 4CzIPN, and DBU in EtOH and under the irradiation of blue LEDs for 24 h gave *α*,*α*-difluoro-*γ*-lactam-fused quinoxalin-2(1*H*)-ones **486** in moderate to good yields. In this reaction, excited-state $4CzIPN^*$ reacts with quinoxalin-2(1*H*)-one to form radical cation **487** and $4CzIPN^-$, and the later one reacts with bromodifluoroacetamides **485** to give difluoroalkyl radicals **488**. Radicals **489** generated from 5-*exo* cyclization of radicals **488** are attacked by **487** to give intermediates **490** and then products **486** after deprotonation with a base.

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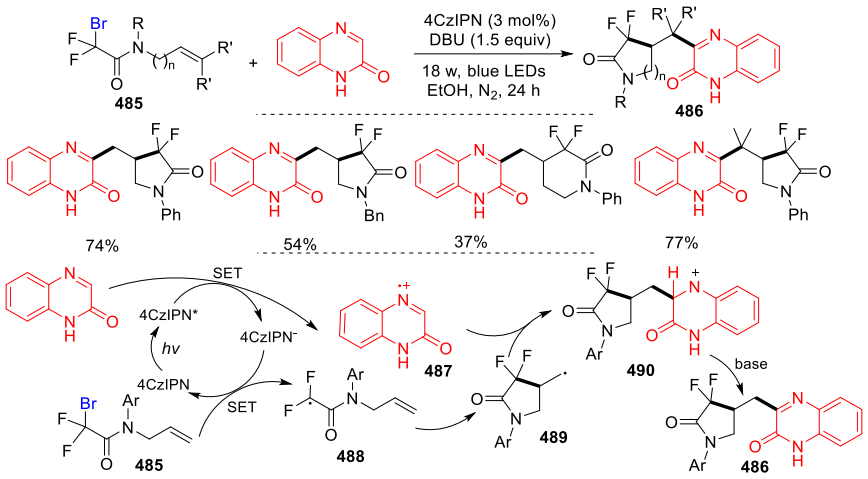
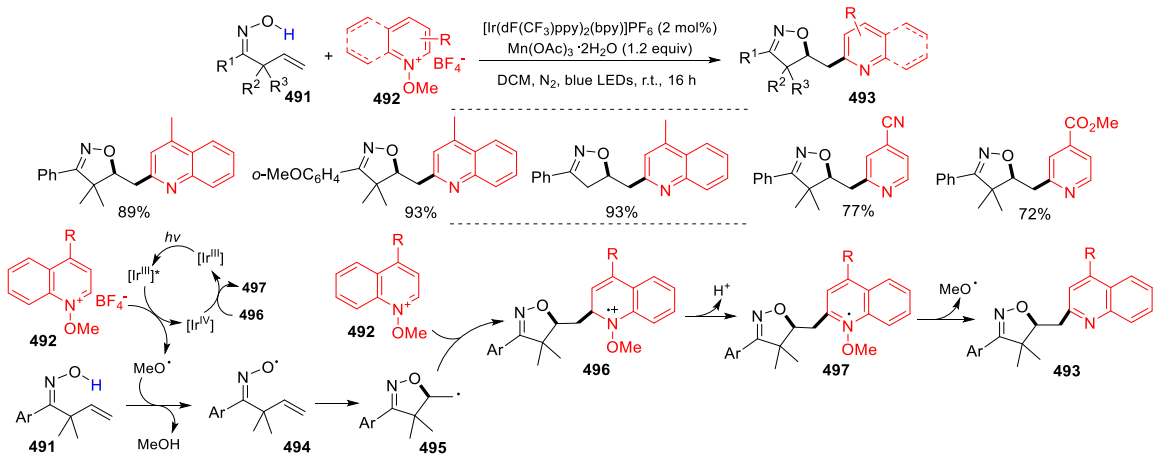


Scheme 97. Synthesis of difluorolactam-attached quinoxalin-2(1*H*)-ones.

He, Banwell and their coworkers, in 2023, introduced a visible light-mediated radical reaction of unsaturated oximes for the synthesis of methylene-bridged bis-heterocyclic compounds. The reaction of *β*,*γ*-unsaturated oximes **491**, *N*-methoxy quinolinium salts **492**, and $Mn(OAc)_3{\cdot}2H_2O$ with $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ as a photocatalyst under the irradiation of blue LEDs for 16 h gave dihydroisoxazoline-attached pyridines or quinolone **493** in good to excellent yields (Scheme 98) [121]. In the reaction process, methoxy radical generated from pyridinium salts **492** abstract a H atom from oximes **491** to form O-centered iminoxyl radical **494** which then undergo 5-*exo* cyclization to form radical **495**. The reaction of radical **495** and **492** to give radical cation **496** and then **497** after deprotonation. The demethylation *via* homolytic N–O bond cleavage afford oxazoline-attached quinolines **493**. In the meantime, the methoxy radical is regenerated to complete the radical-chain process.



Scheme 98. Synthesis of oxazoline-attached quinolines and pyridines.

In 2014, Moeller and coworker reported a radical reaction of *O*-benzyl hydroxamates or *N*-phenyl amides for the synthesis of five and six-membered lactams. In an electrolysis cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum wire cathode, the reaction of electron-rich olefins such as *O*-benzyl hydroxamates or *N*-phenyl amides **498** in MeOH as a solution, Et_4NOTs as the electrolyte, and LiOMe as a base, lactam products were obtained **499** in good yields (Scheme 99) [122]. In the synthesis of six-membered lactams, amidyl radicals **500** generated anodically from *O*-benzyl hydroxamates **498** undergo a 6-*exo* cyclization to give radicals **501** which are oxidized to cations **502** followed by MeOH trapping to access give final products **499**.

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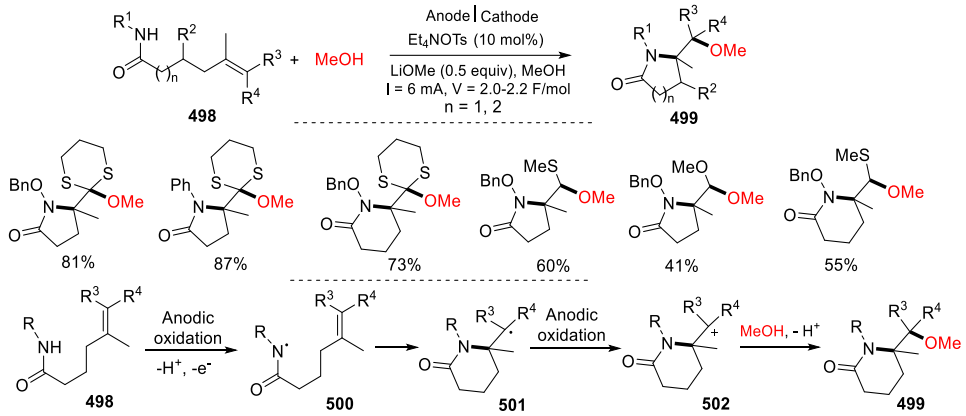
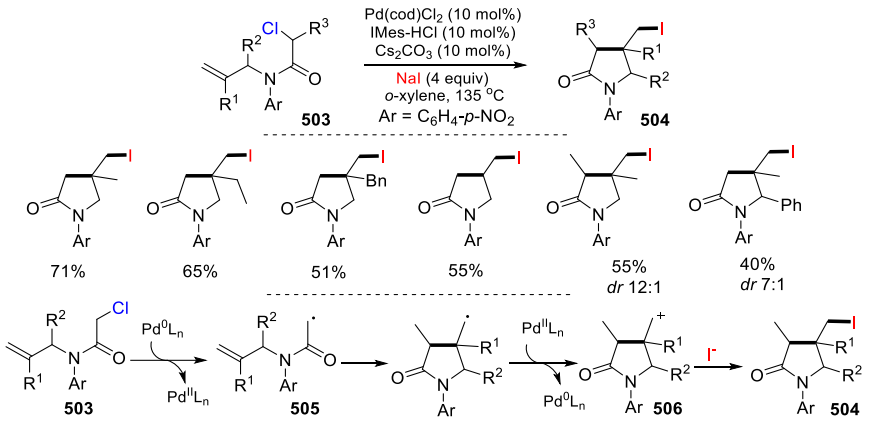


Scheme 99. Synthesis of functionalized five- and six-membered lactams.

Tong and coworkers, in 2015, reported a Pd-catalyzed radical reaction of *N*-allyl-*α*-chloroamides for the synthesis of substituted *γ*-lactams. The reaction of *N*-allyl-*α*-chloroamides **503** in the presence of Pd(cod)Cl_2 catalyst, *N*-heterocyclic carbene (IMes) ligand, NaI additive, and Cs_2CO_3 base in *o*-xylene at 135 °C gave *β*-iodomethyl *γ*-lactam **504** in moderate to good yields and good stereoselectivity (Scheme 100) [123]. The reaction mechanism suggested radicals **505** produced from chloroamides **503** undergo 5-*exo* cyclization followed by single-electron oxidation with $Pd^{II}L_n$ to give cations **506** and then lead to the formation of products **504** after reaction with NaI.



Scheme 100. Synthesis iodosubstituted *γ*-lactams.

An electrochemical dearomative spirocyclization reaction of *N*-acyl thiophene-2-sulfonamides for the synthesis of spirocycles was reported by Ye in 2022. The reaction of *N*-acyl thiophene-2-sulfonamides **507**, Bu_4NOAc and HOAc in an undivided cell (carbon anode, Pt cathode) for 2.5 h gave dearomative spirocycles **508** in good yields (Scheme 101) [124]. It is a regio-specific radical spirocyclization of C2-tethered thiophenes. The complexes **509** produced from *N*-sulfonyl-benzamide **507** undergo electrochemical proton-coupled electron transfer (PCET) to yield the amidyl radicals **510** which could be resonanced to O-centered radicals **511**. The 5-*exo* spirocyclization of radicals **511** followed by oxidation to thiocarbenium ions **512** and then nucleophilic intercept to yield dearomative spirocycles **508**.

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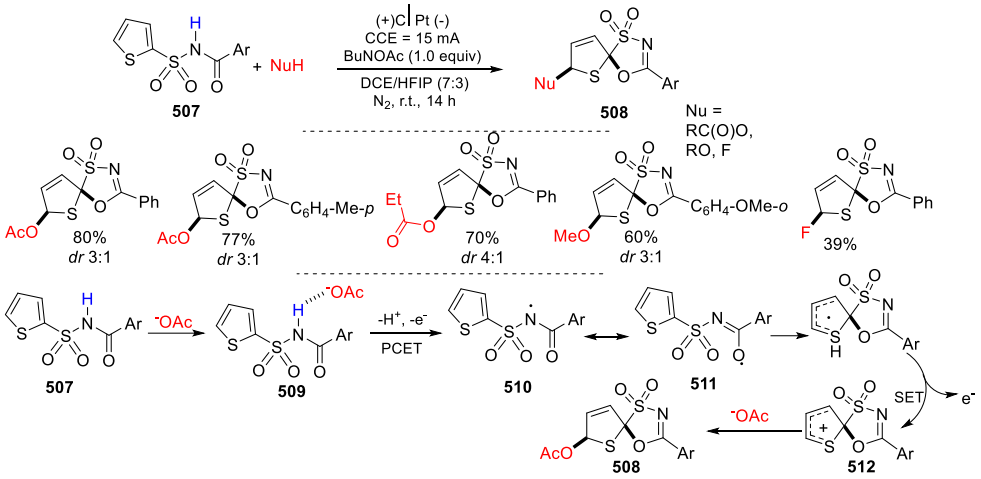
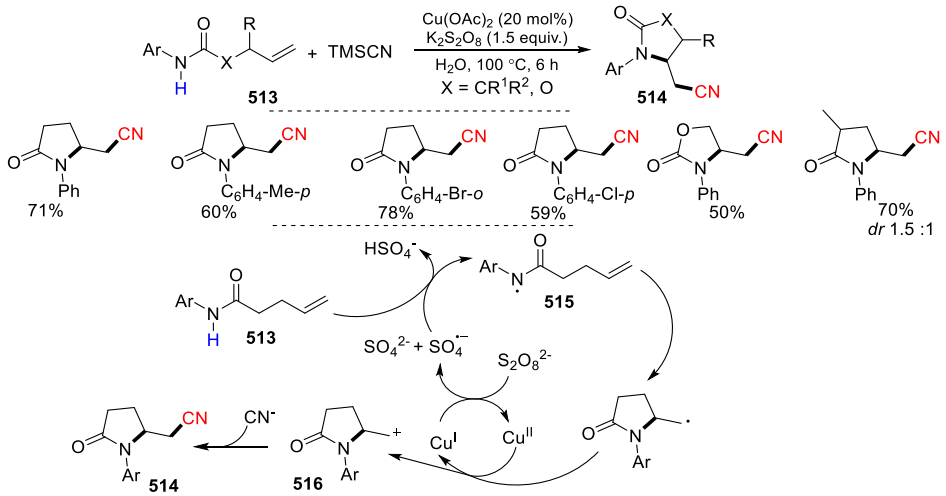


Scheme 101. Synthesis of dearomative spirocycles.

In 2023, Li & Fang and coworkers introduced a Cu-catalyzed radical reaction of *N*-aryl-4-pentenamides for the synthesis of cyano-substituted *γ*-lactams. The reaction of *N*-aryl-4-pentenamides **513**, TMSCN, $Cu(OAc)_2$ and $K_2S_2O_8$ at 100 °C gave cyano-substituted *γ*-lactams **514** in moderate to good yields (Scheme 102) [125]. The reaction mechanism suggested that amidyl radicals **515** generated from **513** *via* HAT with SO_4 radical anion undergo 5-*exo* cyclization followed by oxidization with Cu^{II} to give cations **516**. Meanwhile, Cu^{II} is reproduced for catalytic cycle with the aid of persulfate. Products **514** are obtained by the reaction of cations **516** and cyano anion.



Scheme 102. Synthesis of cyano-substituted *γ*-lactams.

An electrochemical reaction of *N*-propargylbenzamides for the synthesis of oxazole ketals was developed by the Xiao group in 2023. The reaction of *N*-propargylbenzamides **517** and *n*-Bu_4NPF_6 in an undivided cell with graphite rod anode and platinum plate cathode for 5 h produced oxazole ketals **518** in moderate to good yields (Scheme 103) [126]. In this reaction, anions generated from the deprotonation of **517** with MeO^- undergo anodic oxidation to give *N*-centered radicals **519** which have *O*-centered radicals **520** as the resonance structures. Cyclization of radicals **520** followed by anodic oxidation generate cations **521** which then react with MeO^- to form **522** and rearranged to compounds **523**. Deprotonation of **523** with MeO^- followed by single electron oxidation give radicals **524** and then oxazole ketals **518** after anode oxidation and nucleophilic substitution with MeO^-.

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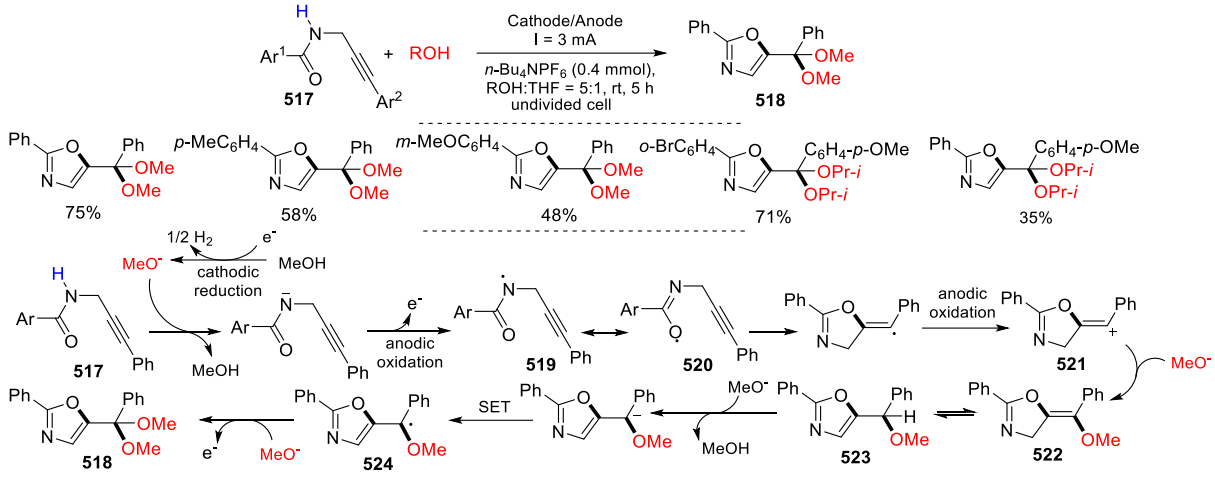

Scheme 103. Radical cyclization for preparation of heterocyclic compounds.

7. Conclusions

Presented in this article are the radical difunctionalization reactions which are initiated with radical cyclization followed by a second functionalization. It is a new addition of our previous reviews on radical 1,2-difunctionalization, remote 1,3-, 1,4-, 1,5-, 1,6- and 1,7-difunctionalization, and addition followed by cyclization difunctionalization reactions. For the current topic, the initial cyclization could result a wide range of cyclics and heterocyclics with variable ring size, while the second functionalization decorates the ring by atom transfer, radical or transition metal coupling, reacting with neutral molecules or with cationic and anionic species. A great number of choices of the second functionalization increase the diversity of the groups incorporated into the ring. The future work on the cyclative difunctionalization reactions could be directed to the development of new substrates for generating the initiate radicals for the cyclization. It is also important to develop new processes and reactants for the second functionalization. The recent advances on photoredox reactions, electrochemical reactions, and transition metal-catalyzed coupling reactions provide ample opportunities for both the formation of initial radicals and for the second radical functionalization. The synthetically efficient and operationally simple radical cyclative difunctionalization reactions can be further explored and fully utilized in the synthesis of unique compounds with potential biological and functional material applications.

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Graphical Abstract